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Integrative Network Pharmacology Study of *Cordyceps militaris* Compounds for Prostate Cancer Treatment

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Abstract

Prostate cancer remains one of the leading causes of cancer-related mortality in men, while adverse effects and the development of drug resistance often limit current therapeutic strategies. Natural products have gained increasing attention as potential sources of novel anticancer agents due to their multitarget properties and relatively low toxicity. *Cordyceps militaris*, a medicinal fungus rich in bioactive compounds, has been reported to exhibit anticancer activity; however, its compound-target interactions in prostate cancer have not been comprehensively elucidated. This study aimed to explore the interactions between *C. militaris* bioactive compounds and prostate cancer-associated targets using a pharmacology network-based in silico approach. A total of 50 bioactive compounds were collected from metabolite profiling studies, of which 19 compounds were selected based on high predicted TP53 expression enhancer activity (Pa ≥ 0.7) using WAY2DRUG PASS analysis. Protein targets were predicted using SwissTargetPrediction and the Similarity Ensemble Approach, and then intersected with prostate cancer-associated proteins retrieved from GEPIA2, GeneCards, and OMIM, yielding 499 overlapping targets. Protein interaction network analysis was performed using STRING and visualized in Cytoscape, enabling the identification of key hub proteins based on the applied parameters, highlighting ten key proteins, including SRC, ESR1, MAPK1, AKT1, HSP90AA1, MAPK3, HSP90AB1, EGFR, GRB2, and PRKACA, within the interaction network. Pathway enrichment analysis indicated that these targets were predominantly involved in cancer-associated signaling pathways, such as the EGFR tyrosine kinase inhibitor resistance pathway. Furthermore, the results revealed that the selected compounds interact with these key prostate cancer-associated proteins. Pharmacokinetic and toxicity evaluation predicted favorable drug-likeness and acceptable safety profiles for selected compounds. Overall, this study highlights the potential of *C. militaris* bioactive compounds as promising alternative for prostate cancer through multitarget modulation of clinically relevant signaling pathways. Further experimental validation is still required to confirm these findings.

1. Introduction

Prostate cancer is one of the most common malignancies and remains a leading cause of cancer-related mortality [1]. Adenocarcinoma is the most common histological subtype of malignancy [2, 3]. Prostate cancer progression varies from slow-growing tumors to aggressive malignancy, although the majority of cases progress slowly [2, 4]. The risk of developing prostate cancer increases with advancing age, and the disease is predominantly diagnosed in elderly men [5]. Prostate cancer contributes significantly to the increasing global mortality rate among men [6]. According to the Global Cancer Observatory (GLOBOCAN) 2022, prostate cancer ranks fourth in cancer incidence worldwide, with 1,466,680 new cases, and ranks eighth in cancer-related mortality, with 396,792 deaths. In comparison with other continents, the incidence and mortality of prostate cancer in Asia are the lowest, especially in East Asia and South-Central Asia [7]. In 2022, the reported incidence and mortality were 13,130 new cases and 4,860 deaths [8]. These epidemiological trends emphasize the growing burden of prostate cancer and highlight the need for effective and accessible therapeutic strategies, particularly in regions where treatment-related toxicity and resistance remain major clinical challenges.

The therapy strategies for prostate cancer require consideration of tumor characteristics, prostate-specific antigen (PSA) levels, tumor grade, tumor stage, and the risk of recurrence [6]. Although conventional treatments such as radiotherapy, chemotherapy, and surgery remain the mainstay of management, these treatments are often associated with potential drug resistance and adverse effects that may lead to additional health complications [9, 10]. These limitations indicate the urgent need for alternative treatment strategies with enhanced efficacy, reduced toxicity, and the ability to overcome drug resistance [11]. In this context, the utilization of natural products has gained considerable importance in anticancer drug discovery due to their diverse therapeutic possibilities and relatively minimal side effects [12, 13].

Numerous natural products rich in bioactive compounds have been reported to exhibit anti-inflammatory, antioxidant, and anticancer activities [14–16]. Furthermore, natural products have demonstrated significant anticancer activity by modulating various cellular processes, including angiogenesis, proliferation, differentiation, invasion, migration, and metastasis [17]. Among natural products, medicinal fungi have emerged as an important source of bioactive compounds with diverse therapeutic effects, including anticancer activity [18]. Within this group, *Cordyceps militaris* has attracted considerable attention as a potential anticancer agent due to its reported biological activities, including immunomodulatory, anti-inflammatory, antimicrobial, and antitumor effects [19]. *C. militaris* is a parasitic fungus that grows on the larvae and pupae of Lepidoptera, characterized by yellow to orange fruiting bodies [20, 21]. This fungus is considered rare in nature and occurs naturally in tropical and subtropical regions of Asia [20, 22]. It consists of two main components, the fruiting body and the supporting mycelium [23]. *C. militaris* has long been traditionally used as a medicinal fungus in several Asian countries, such as Korea and China; it contains several compounds, such as cordycepin, cordycepic acid, sterols (ergosterol), nucleosides, and polysaccharides that have been widely investigated for their roles in various biological activities that are beneficial to health [19, 24].

Cordycepin, recognized as the primary compound of *C. militaris*, has been reported to exhibit anticancer activity by inhibiting cell proliferation, inducing apoptosis, suppressing platelet aggregation, regulating steroidogenesis, and reducing inflammation [19]. A study on rat glioma cell lines demonstrated that cordycepin induces apoptosis by upregulating TP53 protein expression [25]. Other than that, polysaccharides extracted from *C. militaris* can inhibit cancer cell proliferation by upregulating cellular ROS levels and activating the endogenous apoptosis pathway [26]. *In vivo* studies using xenograft mice demonstrated that nucleoside-enriched ethanol extracts of C. *militaris* inhibit the growth of human colorectal cancer cell lines by inducing cell cycle arrest and mitochondria-mediated apoptosis [22]. Despite these findings, variability in experimental models, dosages, and cancer types restricts the generalizability of existing results, highlighting the need for integrative approaches to better contextualize compound–target relationships [19, 22, 25, 26].

In the context of prostate cancer, the anticancer activity of *C. militaris* has also been investigated in both *in vitro* and *in vivo* studies; however, the clinical relevance of *C. militaris* in prostate cancer remains unclear, particularly with respect to how its diverse bioactive compounds interact with prostate cancer-associated molecular targets and therapy resistance pathways [27–29]. This limitation underscores the need for an integrative, systems-level approach, such as network pharmacology, to systematically elucidate the complex compound-target-pathway interactions that underlie its anticancer effects [30]. Pharmacology network has also been applied to several previous studies on *C. militaris*, particularly in lung, breast, and colorectal cancers [19, 24, 31, 32]. However, these findings cannot be directly extrapolated

to prostate cancer due to its distinct disease biology, therapeutic landscape, and resistance mechanisms. Specifically, the present study provides disease-specific insights by focusing on prostate cancer, which is driven by unique regulatory pathways and key signaling proteins that underlie its progression and therapy resistance. Therefore, this study aimed to: (1) identify bioactive compounds of *C. militaris* with potential relevance to prostate cancer; (2) predict and analyze compound-target interactions within a prostate cancer-specific molecular network; (3) identify key hub proteins and enriched signaling pathways associated with disease progression and therapy resistance.

2. Materials and Methods

2.1. Analytical Tools in Silico Prediction

This study used multiple online resources, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), PubChem (https://pubchem.ncbi.nlm.nih.gov/), WAY2DRUG PASS (https://www.way2drug.com/passonline/), SwissTarget Prediction (http://www.swisstargetprediction.ch/), Similarity Ensemble Approach (SEA) (https://sea.bkslab.org/), GeneCards (https://www.genecards.org/), Gene Expression Profiling Interactive Analysis 2 (GEPIA2) (http://gepia2.cancer-pku.cn/#index), Online Mendelian Inheritance in Man (OMIM) (https://www.omim.org/), Draw Venn Diagram (https://bioinformatics.psb.ugent.be/webtools/Venn/), ShinyGO 0.85 (http://bioinformatics.sdstate.edu/go/), Kyoto Encyclopedia of Genes and Genomes (KEGG) (https://www.genome.jp/kegg/), Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) version 12.0 (https://string-db.org/), Cytoscape 3.10.3, ADMETLab 3.0 (https://admetlab3.scbdd.com/), ProTox 3.0 (https://tox.charite.de/protox3/).

2.2. Analytical Methods in Silico Prediction for Interactions of C. militaris Bioactive Compounds and Prostate Cancer

2.2.1 Identification and Structure Profiling of C. militaris Compounds

The compounds of *C. militaris* were collected from relevant scientific studies that performed metabolite profiling of *C. militaris* fruit bodies extracts. A systematic literature search was performed using the keywords '*Cordyceps militaris*', 'bioactive compounds', and 'GC-MS' or 'LC-MS'. Eligible studies were those that performed metabolite profiling of *C. militaris* fruiting-body extracts using GC-MS or LC-MS, were published between 2015 and 2025, and were available in full-text English. Studies that did not perform GC-MS or LC-MS analysis, were published before 2015, were available only as abstracts, and lacked primary data were excluded. The bioactive compounds of *C. militaris* collected from relevant scientific studies were confirmed and profiled using the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) to obtain Simplified Molecular-Input Line-Entry System (SMILES) data. PubChem provides access to a wide range of compounds via multiple identifiers, including compound names and molecular formulas, and enables retrieval of 2D and 3D structural representations [33].

2.2.2. Biological Activity Prediction of C. militaris Bioactive Compounds

C. militaris bioactive compounds' potential as prostate cancer agents was evaluated using WAY2DRUG PASS (https://www.way2drug.com/passonline/) through the Structure-Activity Relationship (SAR) analysis, which compares the structures of *C. militaris* compounds with known active compounds exhibiting specific biological activities [33]. The biological activity analysis used the Probability active (Pa) value, which indicates the potential bioactivity of a tested compound. Pa values are divided into three categories, including Pa ≥ 0.7, Pa 0.3-0.7, and Pa ≤ 0.3. A Pa value ≥ 0.7 indicates a high likelihood of activity, both computationally and in laboratory testing. A Pa value of 0.3-0.7 indicates that the compound shows potential activity in computational predictions but has not yet been confirmed or shows low potential in laboratory assays. Pa ≤ 0.3 indicates that the compound is unlikely to exhibit the tested activity, meaning it has low potential both computationally and in laboratory assays [34].

The parameter chosen for its relevance to prostate cancer to evaluate the potential of C. militaris bioactive compounds as a prostate anticancer agent is Tumor Protein 53 (TP53). TP53 functions as a critical transcription factor that plays an essential role in maintaining cellular homeostasis by regulating multiple genes and cellular processes [35]. Cellular stressors such as DNA damage, hypoxia, or oncogene activation trigger TP53 to act as a tumor suppressor. This protein subsequently inhibits the transcription of various oncogenes, thereby preventing the proliferation of cells with malignant potential [36]. TP53 dysregulation has also been associated with prostate cancer progression toward a more aggressive and therapy-resistant phenotype [35]. TP53 expression enhancer activity was used as an initial screening parameter to prioritize *C. militaris* bioactive compounds with predicted tumor-suppressive and pro-apoptotic relevance. This selection was not intended to represent the sole biological driver of prostate cancer, but rather as a biologically grounded filter to identify compounds with potential relevance to cancer-related regulatory mechanisms. An androgen receptor (AR) expression inhibitor was also included as an

additional parameter due to the androgen-dependent progression of prostate cancer, as decreasing androgen receptor expression can interfere with proliferation pathways, reduce cell survival, and induce tumor regression [37, 38].

2.2.3. Target Proteins Identification and Pathway Annotation

Target proteins of *C. militaris* bioactive compounds were identified and analyzed using SwissTargetPrediction (http://www.swisstargetprediction.ch/) and SEA (https://sea.bkslab.org/), with retrieved SMILES data of each compound as input. In SwissTargetPrediction, predicted targets were retrieved using the default settings and were restricted to *Homo sapiens* by selecting the corresponding organism option on the platform. For SEA, target predictions were also obtained using the platform's default similarity parameters, and all predicted targets meeting the platform-defined statistical significance criteria were collected. Redundant targets resulting from overlap between the two platforms were removed to ensure a non-redundant target set. Prostate cancer-associated genes data were obtained from GEPIA2 (http://gepia2.cancer-pku.cn/#index), GeneCards (https://www.genecards.org/), and OMIM (https://www.omim.org/). In GEPIA2, genes were identified by differential expression analysis between prostate adenocarcinoma (PRAD) and normal prostate tissues, using default parameters with $|\log2FC| > 1$ and a statistical significance threshold of $p < 0.01$. GeneCards was queried using the keyword "prostate cancer," without applying a relevance score cutoff. OMIM entries were retrieved using the same disease keyword, and genes were included if annotated as directly associated with prostate cancer-related phenotypes. Duplicates across databases were then removed before downstream analysis. The dataset obtained from both C. *militaris* and prostate cancer proteins was further mapped using the Draw Venn Diagram (https://bioinformatics.psb.ugent.be/webtools/Venn) to identify overlapping proteins. The overlapping proteins were subsequently analyzed using ShinyGO version 0.85 (http://bioinformatics.sdstate.edu/go/), focusing on biological process and pathway analyses based on KEGG (https://www.genome.jp/kegg/) [39].

2.2.4. Pharmacology Network Analysis

The interactions between targets of *C. militaris* compounds and prostate cancer-related proteins were analyzed using STRING version 12.0 (https://string-db.org/) to identify potential interacting proteins and conducting KEGG pathway enrichment analysis [39]. The analysis began with inputting the identified target proteins into the 'multiple proteins' section, and the organism was set to Homo sapiens. Furthermore, the interaction confidence score was adjusted to the highest threshold (0.900) in the advanced setting to ensure the reliability and accuracy of the interaction results [40]. In addition, the analysis represented protein-protein interactions (PPI) as nodes and edges, with nodes representing proteins and edges indicating interactions between them via linking lines. The protein interactions derived from STRING were further analyzed using CytoScape version 3.10.3 to visualize the biological network [40]. The number of nodes could affect the analysis, as performing a comprehensive analysis for each protein would require a longer, more complex process. CytoScape facilitates the identification of key proteins that play essential roles within biological networks using the CytoHubba plugin, which evaluates nodes based on classical network metrics, including degree, closeness centrality, and betweenness centrality [39, 40]. Degree reflects the number of proteins interacting with a specific node. Closeness centrality predicts the speed at which information flows through a node, as well as the length of the shortest paths from that node to all other nodes in the network. Betweenness centrality emphasizes the communication flow, whereby nodes with high betweenness centrality are considered significant for controlling information flow within the network [39]. Thus, the analysis can be conducted more efficiently by identifying the top 10 target proteins based on classical metrics, such as the highest degree scores, which represent the number of interactions a protein has with other proteins in the network [40].

2.2.5. Pharmacokinetic and Toxicity Analysis

The analysis was conducted using ADMETLab version 3.0 (https://admetlab3.scbdd.com/) and ProTox version 3.0 (https://tox.charite.de/protox3/), with SMILES data as input. ADMETLab was used to evaluate Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) parameters to assess the drug development potential of the investigated compounds and their compliance with Lipinski's Rule of Five (Ro5). The assessed parameters included P-glycoprotein (P-gp) inhibitor and substrate potential, predicted oral bioavailability (F20% and F30%), blood-brain barrier (BBB) permeability, human hepatotoxicity (H-HT), drug-induced liver injury (DILI), and FDA maximum recommended daily dose (FDAMDD). Compounds were considered to exhibit favorable or acceptable ADMET profiles when they showed predicted oral bioavailability, manageable P-gp interaction profiles, and low or moderate toxicity risk (including H-HT and DILI). Their compliance with Lipinski's Rule of Five (Ro5) was also considered in predicting the likelihood of success or failure of a compound in drug development by

estimating its drug-likeness based on similarity to known drugs. Compliance with Lipinski's Rule of Five (Ro5) requires at least two of the five criteria, including a molecular weight below 500 Dalton, high lipophilicity indicated by LogP value 2-3, fewer than 10 hydrogen bond acceptors, fewer than 5 hydrogen bond donors, and a molar refractivity ranging from 40 to 130. These criteria serve as a fundamental basis for the classification and selection of potential drug candidates [39]. ProTox was utilized to predict compound toxicity, including the lethal dose 50 (LD_{50}) values [39].

3. Results and Discussion

3.1. C. militaris Compounds Identification and Structure Profiling

A total of 50 compounds in *C. militaris* were identified through a scientific literature review that performed metabolite profiling of *C. militaris* fruit bodies extracts using GC-MS analysis, as shown in Table 1 [41, 42]. Furthermore, PubChem was used to obtain the canonical SMILES notations of the 50 compounds, which served as input data for further analysis using prediction tools.

3.2. Target Proteins of C. militaris Bioactive Compounds

Target proteins for the 19 selected compounds were identified and analyzed using SwissTargetPrediction and SEA, with each compound's SMILES data as input. In contrast, prostate-cancer-associated proteins were retrieved from GEPIA2, OMIM, and GeneCards. A Venn Diagram was then used to identify the proteins that intersect, and the results are shown in Figure 1. A total of 499 proteins were found to overlap between *C. militaris* bioactive compounds and prostate cancer-associated proteins. In addition, the results revealed that C. *militaris* compounds targeted 61 proteins but were not associated with prostate cancer, whereas 14,501 proteins were associated with prostate cancer but were not targeted by *C. militaris* compounds. Although the predicted C. militaris compounds did not target most prostate cancer-associated proteins, this finding highlights the selective rather than exhaustive nature of natural product-based multitarget modulation. The 499 overlapping targets include several key regulatory proteins and signaling nodes known to play central roles in prostate cancer progression and therapy resistance. Therefore, the therapeutic relevance of *C. militaris* may lie not in broad target coverage but in modulating high-value hub proteins and cancer-relevant pathways. The overlapping proteins were further analyzed using ShinyGO to identify relevant biological pathways, revealing that *C. militaris* compound targets are involved in multiple pathways (Figure 2), including Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor resistance, Prostate cancer, HIF-1 signaling pathway, Proteoglycans in cancer, cyclic Adenosine Monophosphate (cAMP) signaling pathway, Rap1 signaling pathway, Pathways in cancer and PI3K-Akt signaling pathway.

3.3. Biological Activity of C. militaris Bioactive Compounds

Table 2 shows the Pa values of 50 compounds for the TP53 expression enhancer and AR expression inhibitor parameters. A Pa value ≥ 0.7 was set as the cutoff to enable more accurate predictions, indicating strong potential for biological activity in both computational analysis and experimental assays. Based on this threshold, 19 out of 50 compounds were predicted to have significant TP53 expression enhancer activity and were selected for further analysis. Furthermore, the results indicated that compound C21 (Adenosine) was predicted to have the highest potential for TP53 expression-enhancer activity among all compounds, including those with Pa values ≥ 0.7. In addition, a SAR-based visualization of the predicted scores for the 19 selected compounds, ranked by their TP53 expression enhancer scores, is shown in Figure 3.

3.4. Pharmacology Network Analysis

The results from STRING analysis using a score confidence of 0.900 revealed proteins involved in the eight pathways predicted to be associated with prostate cancer as the disease target, as detailed in Table 3. Furthermore, the analysis showed a total of 346 target proteins (nodes) and 937 interactions (edges).

The analysis conducted in CytoScape identified 10 proteins predicted to play significant roles in the biological network associated with prostate cancer based on the applied metrics (Table 4), and the interactions among the top 10 proteins, as determined by the highest degree scores, were visualized in Figure 4. It can be seen that SRC has the darkest green color and the largest size, followed by Estrogen Receptor 1 (ESR1) and Mitogen-Activated Protein Kinase 1 (MAPK1). These three main proteins are the most promising candidates for further analysis.

SRC is a non-receptor tyrosine kinase that plays a key role in modulating several signaling pathways [43]. SRC is critically involved in regulating various biologically active signaling pathways, including essential processes such as gene transcription, immune response, cell adhesion, cell cycle progression, apoptosis, migration, and transformation [44]. Elevated SRC activity has been reported to enhance cancer cell motility and facilitate metastasis [45].

Table 1. SMILES profiles of *C. militaris* compounds.

Code	Molecular Formula	Compounds Name	SMILES
C1	C6H13NO2	Isoleucine	CC[C@H](C)[C@@H](C(=O)O)N
C2	C5H9NO2	Proline	C1C[C@H](NC1)C(=O)O
C3	C2H5NO2	Glycine	C(C(=O)O)N
C4	C3H7NO3	Serine	C([C@@H](C(=O)O)N)O
C5	C4H9NO3	Threonine	C[C@H]([C@@H](C(=O)O)N)O
C6	C4H8N2O3	Asparagine	C([C@@H](C(=O)O)N)C(=O)N
C7	C6H11NO4	α-Aminoadipic acid	C(CC(C(=O)O)N)CC(=O)O
C8	C9H11NO3	Tyrosine	C1=CC(=CC=C1C[C@@H](C(=O)O)N)O
C9	C7H19N3	Spermidine	C(CCNCCCN)CN
C10	C4H9NO2	γ-Aminobutyric acid (GABA)	C(CC(=O)O)CN
C11	C3H7NO2	Alanine	C[C@@H](C(=O)O)N
C12	C4H7NO4	Aspartic acid	C([C@@H](C(=O)O)N)C(=O)O
C13	C5H9NO4	Glutamic acid	C(CC(=O)O)[C@@H](C(=O)O)N
C14	C9H11NO2	Phenylalanine	C1=CC=C(C=C1)C[C@@H](C(=O)O)N
C15	C6H14N2O2	Lysine	C(CCN)C[C@@H](C(=O)O)N
C16	C4H12N2	Putrescine	C(CCN)CN
C17	C5H12N2O2	Ornithine	C(C[C@@H](C(=O)O)N)CN
C18	C5H10N2O3	Glutamine	C(CC(=O)N)[C@@H](C(=O)O)N
C19	C6H9N3O2	Histidine	C1=C(NC=N1)C[C@@H](C(=O)O)N
C20	C11H12N2O2	Tryptophan	C1=CC=C2C(=C1)C(=CN2)C[C@@H](C(=O)O)N
C21	C10H13N5O4	Adenosine	C1=NC(=C2C(=N1)N(C=N2)[C@H]3[C@@H]([C@@H]([C@H](O3)CO)O)O)N
C22	C10H13N5O3	Cordycepin	C1[C@H](O[C@H]([C@@H]1O)N2C=NC3=C(N=CN=C32)N)CO
C23	C9H12N2O6	Uridine	C1=CN(C(=O)NC1=O)[C@H]2[C@@H]([C@@H]([C@H](O2)CO)O)O
C24	C4H4O4	Fumaric acid	C(=C/C(=O)O)\C(=O)O
C25	C6H8O7	Isocitric acid	C(C(C(C(=O)O)O)C(=O)O)C(=O)O
C26	C4H6O4	Succinic acid	C(CC(=O)O)C(=O)O
C27	C4H6O5	Malic acid	C(C(C(=O)O)O)C(=O)O
C28	C6H12O7	Gluconic acid	C([C@H]([C@H]([C@@H]([C@H](C(=O)O)O)O)O)O)O
C29	C6H13O9P	Myo-inositol 1-phosphate	[C@H]1([C@H](C([C@@H]([C@@H](C1O)O)O)OP(=O)(O)O)O)O
C30	C5H10O6	Xylonic acid	C([C@H]([C@@H]([C@H](C(=O)O)O)O)O)O
C31	C6H14O6	Mannitol	C([C@H]([C@H]([C@@H]([C@@H](CO)O)O)O)O)O
C32	-	Inositol	-
C33	C6H16O18P4	Myo-inositol	[C@H]1([C@@H]([C@@H]([C@H]([C@@H]([C@H]1OP(=O)(O)O)OP(=O)(O)O)OP(=O)(O)O)OP(=O)(O)O)O)O
C34	C6H6O2	Catechol	C1=CC=C(C(=C1)O)O
C35	C16H32O2	Palmitic acid	CCCCCCCCCCCCCCCC(=O)O
C36	C15H30O2	Pentadecanoic acid	CCCCCCCCCCCCCCC(=O)O
C37	C18H32	Octadecatriene	CCCCCCCCCCC/C=C/C=C/C=C
C38	C18H32O2	9,12-Octadecadienoic acid	CCCCCC=CCC=CCCCCCCC(=O)O
C39	C20H38O2	9-Octadecenoic acid, ethyl ester	CCCCCCCC/C=C/CCCCCCCC(=O)OCC
C40	C18H32O2	Linoleic acid	CCCCC/C=C\C/C=C\CCCCCCCC(=O)O
C41	C35H48O3S	Dehydroergosterol tosylate	CC1=CC=C(C=C1)S(=O)(=O)O[C@H]2CC[C@]3(C(=CC=C4C3=CC[C@]5([C@H]4CC[C@@H]5[C@H](C)/C=C/[C@H](C)C(C)C)C)C2)C
C42	C28H44O	Ergosterol	C[C@H](/C=C/[C@H](C)C(C)C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3C2=CC=C4[C@@]3(CC[C@@H](C4)O)C)C
C43	-	1,4-Bis[(trimethylsilyl)methyl]benzene	-
C44	C17H32	3-methylidenehexadec-1-ene	CCCCCCCCCCCCCC(=C)C=C
C45	C18H34	Octadecyne	CCCCCCCCCCCCCCCCCC#C
C46	C16H30O2	Palmitelaidic acid	CCCCCC/C=C/CCCCCCCC(=O)O
C47	C8H14O	9-Oxabicyclo[4.2.1]nonane	C1CCC2CCC(C1)O2
C48	C21H36O2	Isopropyl linolenate	CC/C=C\C/C=C\C/C=C\CCCCCCCC(=O)OC(C)C
C49	C28H44O	Ergosta-4,6,22-triene-3beta-ol	C[C@H](/C=C/[C@H](C)C(C)C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2C=CC4=C[C@H](CC[C@]34C)O)C
C50	-	Hexadecanoic acid trimethylsilyl ester	-

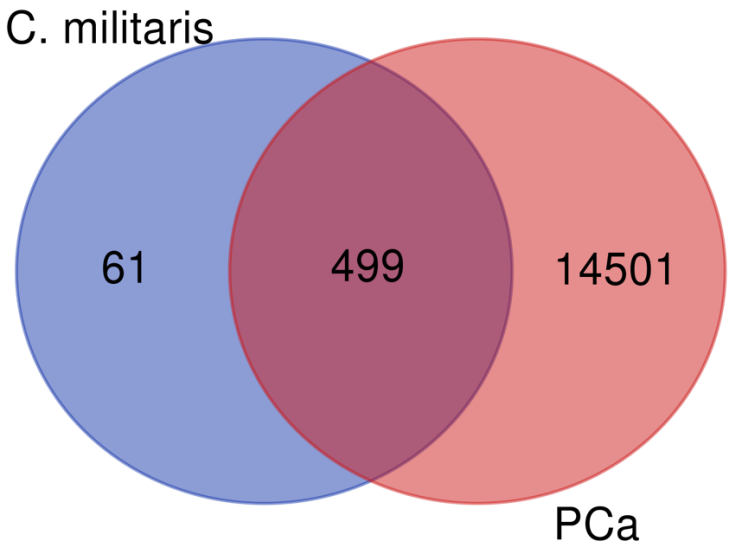

Figure 1. Shared proteins between *C. militaris* compounds and prostate cancer-associated proteins.

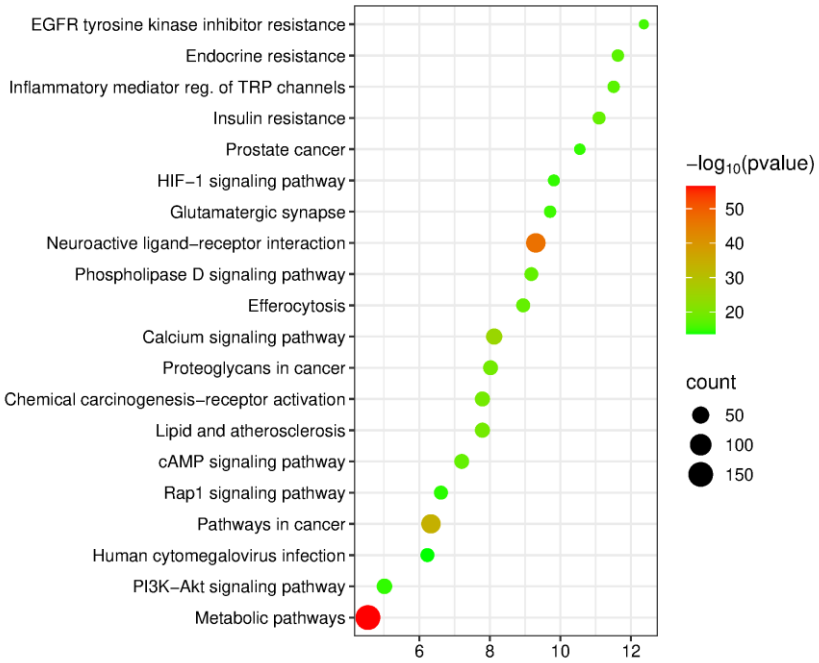

Figure 2. Annotation of the top 20 biological pathways targeted by *C. militaris* compounds through KEGG pathway analysis.

ESR1 is the gene encoding the estrogen receptor alpha (ERα) protein [46]. Recent studies indicate that ESR1 has potential as a prognostic marker in prostate cancer. This finding suggests that ESR1 plays a critical role in cancer initiation and progression, with high ESR1 expression levels and variations being associated with an increased risk of prostate cancer [44].

MAPK1, also known as extracellular signal-regulated kinase 2 (ERK2), is a key member of the MAP kinase family that has been extensively studied. MAPK1 plays a crucial role in various cellular signaling cascades regulating diverse biological processes, including immune response, proliferation, differentiation, and cell development [47].

The top 10 proteins were subsequently submitted to the ShinyGO platform for KEGG pathway analysis. The EGFR tyrosine kinase inhibitor resistance pathway (Figure 5) was selected as the focus of this study on prostate cancer. This pathway represents a major therapeutic target in various types of cancer, where EGFR is often mutated or overexpressed [48].

The proto-oncogene SRC is involved in this pathway, maintaining the survival of prostate cancer cells. A

Table 2. Predicted biological activity of *C. militaris* bioactive compounds.

Code	Compounds Name	TP53 expression enhancer	AR expression inhibitor
C1	Isoleucine	0.588	0.230
C2	Proline	0.294	0.231
C3	Glycine	-	-
C4	Serine	0.704	0.205
C5	Threonine	0.682	0.198
C6	Asparagine	0.614	0.205
C7	α-Aminoadipic acid	0.708	0.218
C8	Tyrosine	0.640	0.298
C9	Spermidine	0.340	0.202
C10	γ-Aminobutyric acid (GABA)	0.602	0.236
C11	Alanine	0.655	0.250
C12	Aspartic acid	0.688	0.229
C13	Glutamic acid	0.703	0.212
C14	Phenylalanine	0.578	0.227
C15	Lysine	0.571	-
C16	Putrescine	0.523	0.296
C17	Ornithine	0.566	-
C18	Glutamine	0.605	0.213
C19	Histidine	0.387	-
C20	Tryptophan	0.371	-
C21	Adenosine	0.934	-
C22	Cordycepin	0.806	-
C23	Uridine	0.923	-
C24	Fumaric acid	0.720	0.467
C25	Isocitric acid	0.617	0.259
C26	Succinic acid	0.723	0.437
C27	Malic acid	0.699	0.293
C28	Gluconic acid	0.821	0.220
C29	Myo-inositol 1-phosphate	0.561	0.480
C30	Xylonic acid	0.821	0.220
C31	Mannitol	0.817	0.285
C33	Myo-inositol	0.561	0.480
C34	Catechol	0.731	0.625
C35	Palmitic acid	0.740	0.374
C36	Pentadecanoic acid	0.740	0.374
C37	Octadecatriene	0.775	0.512
C38	9,12-Octadecadienoic acid	0.764	0.359
C39	9-Octadecenoic acid, ethyl ester	0.773	0.277
C40	Linoleic acid	0.764	0.359
C41	Dehydroergosterol tosylate	-	0.206
C42	Ergosterol	0.577	0.421
C44	3-methylidenehexadec-1-ene	0.589	0.457
C45	Octadecyne	0.413	0.447
C46	Palmitelaidic acid	0.791	0.399
C47	9-Oxabicyclo[4.2.1]nonane	0.618	0.443
C48	Isopropyl linolenate	0.655	0.264
C49	Ergosta-4,6,22-triene-3beta-ol	0.278	0.521

reduction in growth signals from the androgen receptor (AR) leads to SRC phosphorylation by EGFR in prostate cancer cells. SRC phosphorylates MAPK kinase (MEK) with or without mediation by paxillin (PXN), followed by activation of MAPK1 to enhance pro-survival factors such as BCL2-like 1 (Bcl-xL). Mitogen-Activated Protein Kinase Kinase (MEK/MAPK2) then phosphorylates the Y-box binding protein 1 (YB-1), which interacts synergistically with ribosomal S6 kinase (RSK) and Raf-1 to maintain sustained gene expression [49]. SRC activation mediates resistance to EGFR tyrosine kinase inhibitors through bypass mechanisms and ligand-independent activation. At the same time, downstream pathways such as PI3K-Akt remain active despite EGFR inhibition, thereby promoting therapy resistance and potential metastasis in cancer [43].

MAPK1 can be activated by growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and nerve growth factor (NGF), as well as by

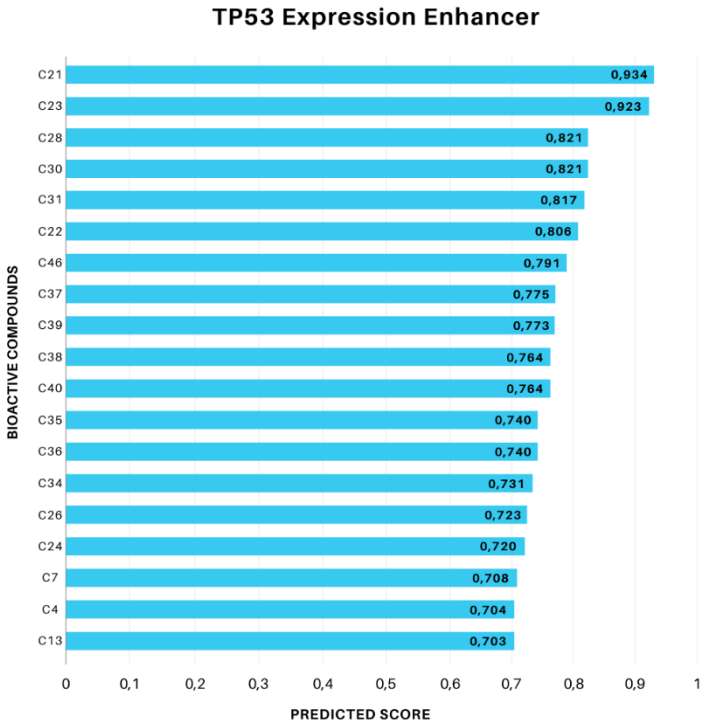

Figure 3. SAR-based analysis visualization of TP53 expression enhancer activity for 19 selected compounds ranked by highest Pa scores (PA ≥ 0.7).

Table 3. Proteins involved in prostate cancer pathways identified through KEGG pathway analysis.

Pathway Code	KEGG Pathways	Involved Proteins
hsa01521	EGFR tyrosine kinase inhibitor resistance	MAPK1, PLCG1, PDGFRB, MAPK3, KDR, FGF2, ERBB2, EGFR, AXL, MET, GSK3B, SRC, BCL2L1, GRB2, BCL2, IL6, RAF1, PRKCA, AKT1, IGF1R, AKT3
hsa05215	Prostate cancer	MAPK1, CCND1, MDM2, PDGFRB, CCNE1, MAPK3, CDK2, ERBB2, EGFR, GSK3B, HSP90AA1, HSP90AB1, MMP9, AR, GRB2, BCL2, GSTP1, FGFR1, RAF1, AKT1, SRD5A2, IGF1R, AKT3
hsa04066	HIF-1 signaling pathway	MAPK1, PLCG1, EGLN3, MAPK3, ERBB2, EGFR, HK2, NOS3, INSR, NOS2, EGLN1, TLR4, GAPDH, BCL2, IL6, PRKCA, AKT1, EGLN2, PFKFB3, HK1, IGF1R, AKT3
hsa05205	Proteoglycans in cancer	MAPK1, MMP2, CCND1, MAPK14, PLCG1, SMO, MDM2, MAPK3, KDR, FGF2, ERBB2, EGFR, PDCD4, SHH, PRKACA, CASP3, MET, ROCK2, PTK2, PPP1CC, CTSL, MMP9, SRC, TLR4, GRB2, PTPN6, FGFR1, RAF1, ESR1, PRKCA, AKT1, ITGB3, PTPN11, IGF1R, CDC42, AKT3
hsa04024	cAMP signaling pathway	MAPK1, PTGER2, MAPK3, GRIA4, ADRB2, CHRM1, PRKACA, EDNRA, ROCK2, F2R, PPP1CC, TNNI3, PDE4B, PLD1, PDE4D, PTGER3, DRD2, PDE10A, ADORA1, ADCY10, ADRB1, GABBR1, PDE4A, MAPK8, PPARA, GCG, MAPK9, CHRM2, RAF1, ADCY5, AKT1, GRIN2B, ADORA2A, AKT3
hsa04015	Rap1 signaling pathway	MAPK1, MAPK14, PLCG1, PDGFRB, ITGA2B, MAPK3, KDR, FGF2, EGFR, INSR, ADORA2B, P2RY1, MET, F2R, ITGAL, DRD2, CNR1, SRC, ITGB2, FGFR1, RAF1, PRKCA, ADCY5, AKT1, ITGB3, GRIN2B, ADORA2A, IGF1R, CDC42, AKT3
hsa05200	Pathways in cancer	MAPK1, MMP2, CCND1, GSTM2, PLCG1, PTGER2, SMO, EGLN3, RARA, CDK4, MDM2, PDGFRB, ITGA2B, CCNE1, MAPK3, EPAS1, FGF2, CDK2, ERBB2, EGFR, PPARG, PTGER1, SHH, PTGER4, F2, TERT, PRKACA, PPARD, CASP3, EDNRA, MET, ROCK2, NQO1, F2R, GSK3B, NOS2, RARB, HSP90AA1, PTK2, PLD1, ESR2, PTGER3, CASP8, RXRG, EGLN1, PTGS2, CASP7, HSP90AB1, MMP9, PIM1, HDAC1, RXRB, AR, BCL2L1, ALK, GRB2, MAPK8, BCL2, GSTP1, IL6, FGFR1, MAPK9, RAF1, ESR1, PRKCA, ADCY5, RXRA, AKT1, EGLN2, IGF1R, CDC42, AKT3
hsa04151	PI3K-Akt signaling pathway	MAPK1, CCND1, CDK4, MDM2, PDGFRB, ITGA2B, CCNE1, MAPK3, KDR, FGF2, CDK2, ERBB2, EGFR, NOS3, INSR, CHRM1, MET, F2R, GSK3B, HSP90AA1, PTK2, MCL1, PRKAA2, HSP90AB1, TLR4, BCL2L1, GRB2, BCL2, IL6, FGFR1, CHRM2, RAF1, PRKCA, RXRA, AKT1, ITGB3, IGF1R, AKT3

insulin [50]. Additionally, MAPK1 has been identified as a transcription factor that regulates chromatin structure and transcriptional processes through interactions with specific DNA sequences, ultimately controlling gene expression and contributing to cancer development. Imbalances in the expression or dysfunction of this transcription factor can trigger uncontrolled cell proliferation and promote carcinogenesis [49].

Table 4. Top 10 proteins based on degree scores.

Names	Degree	Closeness Centrality	Betweenness Centrality	Total Score	Pathways
SRC	8	0.8999999999999999	0.08194444444444443	0.98194444	EGFR tyrosine kinase inhibitor resistance, Proteoglycans in cancer
ESR1	8	0.8999999999999999	0.1375	1.0375	Proteoglycans in cancer, Pathways in cancer
MAPK1	7	0.8181818181818181	0.09027777777777776	0.9084596	EGFR tyrosine kinase inhibitor resistance, Prostate cancer, HIF-1 signaling pathway, Proteoglycans in cancer, cAMP signaling pathway, Rap1 signaling pathway, Pathways in cancer, PI3K-Akt signaling pathway
AKT1	7	0.8181818181818181	0.055555555555555546	0.87373737	EGFR tyrosine kinase inhibitor resistance, Prostate cancer, HIF-1 signaling pathway, Proteoglycans in cancer, cAMP signaling pathway, Rap1 signaling pathway, Pathways in cancer, PI3K-Akt signaling pathway
HSP90AA1	6	0.75	0.01944444444444444	0.76944444	Prostate cancer, Pathways in cancer, PI3K-Akt signaling pathway
MAPK3	5	0.6923076923076923	0.018518518518518517	0.71082621	EGFR tyrosine kinase inhibitor resistance, Prostate cancer, HIF-1 signaling pathway, Proteoglycans in cancer, cAMP signaling pathway, Rap1 signaling pathway, Pathways in cancer, PI3K-Akt signaling pathway
HSP90AB1	5	0.6923076923076923	0.005555555555555556	0.69786325	Prostate cancer, Pathways in cancer, PI3K-Akt signaling pathway
EGFR	5	0.6923076923076923	0.023148148148148143	0.71545584	EGFR tyrosine kinase inhibitor resistance, Prostate cancer, HIF-1 signaling pathway, Proteoglycans in cancer, Rap1 signaling pathway, Pathways in cancer, PI3K-Akt signaling pathway
GRB2	4	0.6428571428571428	0.012499999999999997	0.65535714	EGFR tyrosine kinase inhibitor resistance, Prostate cancer, Proteoglycans in cancer, Pathways in cancer, PI3K-Akt signaling pathway
PRKACA	3	0.6	0.0	0.6	Proteoglycans in cancer, cAMP signaling pathway, Pathways in cancer

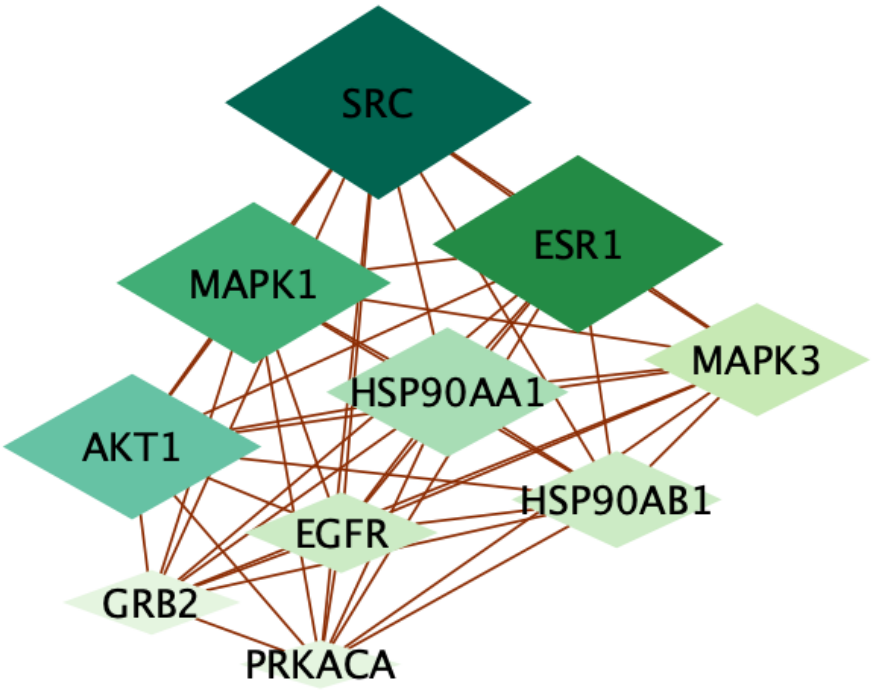

Figure 4. Analysis of interactions for the top 10 proteins based on the highest degree scores.

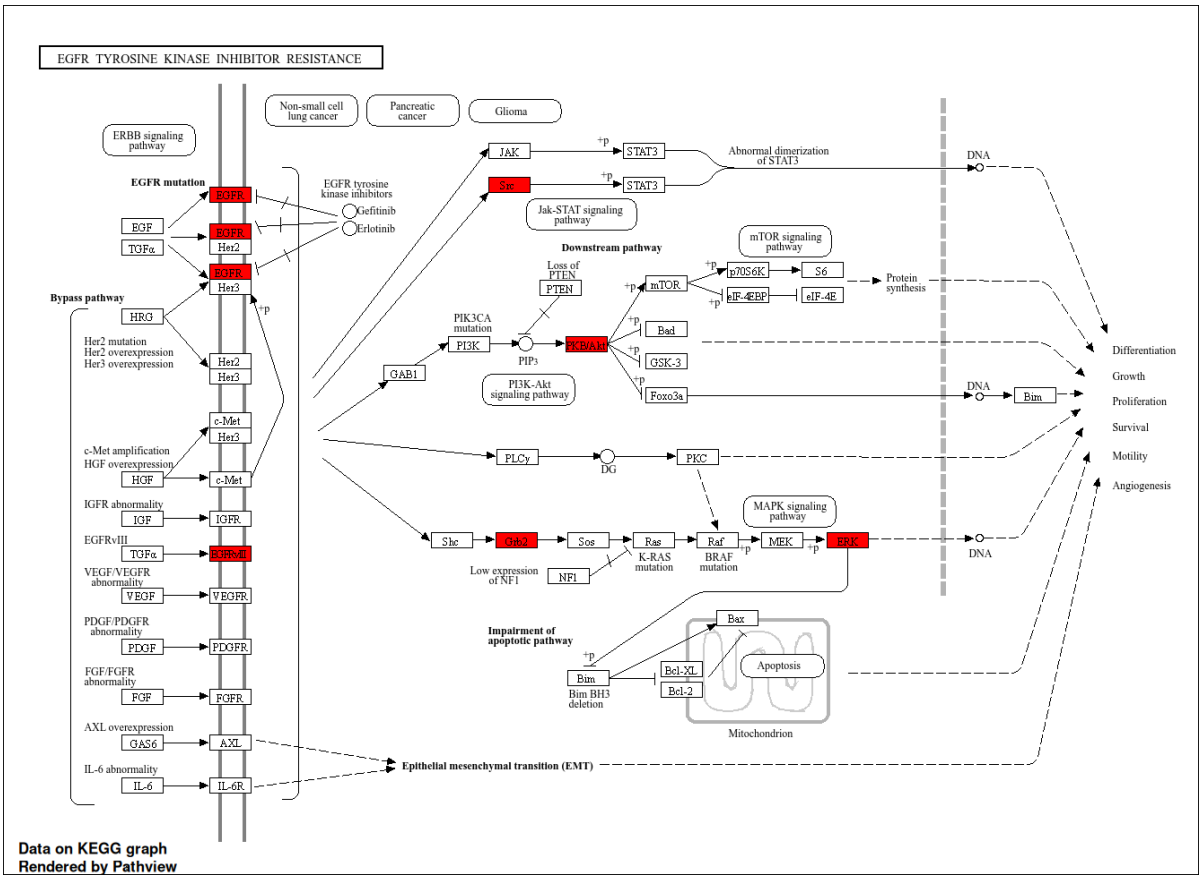

Figure 5. EGFR tyrosine kinase inhibitor resistance pathway.

Downregulation of MAPK1 effectively inhibits tumorigenicity and metastasis of prostate cancer cells, whereas overexpression of MAPK1 enhances tumorigenicity and metastatic potential [44].

Current cancer therapies are increasingly moving toward targeting relevant proteins, including SRC, ESR1, and MAPK1 (ERK2). SRC Family Kinase (SFK) inhibitors are small molecules with oral bioavailability and are generally classified into two categories based on their inhibitory mechanisms against SRC family proteins. These include ATP-competitive inhibitors that directly suppress tyrosine kinase activity and inhibitors that disrupt protein-protein interactions, targeting domains such as Src Homology 2 (SH2) or Src Homology 3 (SH3) or substrate-binding sites. These inhibitors have also been investigated in prostate cancer, and preclinical data show that their inhibitory effects not only target prostate cancer epithelial cells but also various stromal cell components, including osteoclasts, osteoblasts, and endothelial cells within the tumor immune microenvironment (TIM). One of the most clinically studied SFK inhibitors in prostate cancer is dasatinib. Dasatinib is an orally bioavailable tyrosine kinase inhibitor that acts competitively at the ATP-binding site and has been approved by the FDA for the treatment of patients with chronic myeloid leukemia or Philadelphia chromosome–positive acute lymphoblastic leukemia who have failed first-line therapy with imatinib [51]. Preclinical evidence demonstrates that dasatinib significantly inhibits prostate tumor growth and metastasis processes in both *in vitro* and *in vivo* models; however, clinical trials to date have not shown satisfactory outcomes, either as monotherapy or in combination [51, 52]. Future clinical success will require the development of inhibitors with greater specificity and improved tumor cell penetration, along with efforts to minimize side effects, overcome drug resistance mechanisms, and identify predictive biomarkers to select patients most likely to respond to therapy [52].

Various ERK inhibitors are also being increasingly investigated in preclinical and clinical studies; however, no ERK inhibitor has yet been approved clinically [52]. Direct inhibition of ERK1/ERK2 (MAPK1) within the MAPK pathway is increasingly considered a promising therapeutic strategy. Several small-molecule inhibitors targeting ERK1/ERK2 have been identified in recent years, including ulixertinib (BVD-523) and temuterkib (LY3214996), which have shown significant therapeutic potential in overcoming acquired resistance to therapy and suppressing downstream ERK signaling. Ulixertinib (BVD-523) is an orally bioavailable pyridine-pyrrole small molecule and the first ERK1/ERK2 kinase inhibitor to reach clinical trials. Ulixertinib functions as a potent,

selective, and reversible ATP-competitive inhibitor of ERK1/ERK2. This inhibitor has demonstrated the ability to suppress the proliferation of tumor cell lines harboring activating mutations in the MAPK pathway in *in vivo* studies and significantly inhibit tumor growth in models with Kirsten Rat Sarcoma (KRAS) and B-Raf (BRAF) mutations. Ulixertinib is currently under Phase I/II clinical trials for patients with advanced solid tumors and is being investigated clinically for the treatment of non-Hodgkin lymphoma, acute myeloid leukemia (AML), advanced solid tumors, and pancreatic cancer. Although the development of ERK1/ERK2 inhibitors has made significant progress, no ERK-targeted therapy has yet received FDA approval. Further optimization is still required to advance the development of more effective drugs [53].

Subsequently, recent studies have shown that ESR1 has potential as a prognostic marker in prostate cancer [46]. Common treatments for prostate cancer include docetaxel, prednisone, cabazitaxel, abiraterone acetate (AA), and sipuleucel-T. All of these drugs specifically target the androgen receptor (AR); however, the combination of docetaxel and prednisone with ADT was found to be active against the estrogen receptor (ER). This combination resulted in low ESR1 and high ESR2 expression, with no correlation between ESR levels and clinical factors. It was independently associated with improved outcomes and longer duration of castration-resistant prostate cancer (CRPC) [54]. There are also antiestrogen drugs that selectively target estrogen and its receptors, including selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) specific for estrogen receptor alpha (ERα) [46]. SERMs exhibit tissue-specific agonist or antagonist activity in estrogen receptor-expressing tissues such as the breast, bone, prostate, and testes, whereas SERDs act as ER antagonists. SERMs bind the ER and inhibit ER signaling, while SERDs also bind the ER and block its signaling, but their mechanism also involves inducing estrogen receptor degradation [54].

Tamoxifen, a SERM, was initially developed for contraceptive purposes before becoming widely used as an anticancer agent for ERα-positive tumors of the breast and uterus. Tamoxifen exhibits mixed pharmacologic activity, acting as either an antagonist or agonist depending on ER expression levels. Its use has been proposed and investigated for prostate cancer treatment. Several preclinical studies report that tamoxifen can inhibit prostate cancer cell growth and may provide clinical benefit when used in combination with immunotherapy, transforming growth factor beta (TGFβ) inhibitors, or Wingless and Int-1 (Wnt) pathway antagonists. Furthermore, high-dose tamoxifen administration has been reported to be well tolerated in patients with castration-resistant prostate cancer who have undergone multiple lines of therapy, demonstrating antiproliferative effects mediated via inhibition of the phosphatidylinositol-4-phosphate 5-kinase-α/AKT signaling pathway, as well as decreased expression of matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF) [46].

Fulvestrant, a SERM, acts as an ERα antagonist and can increase receptor turnover, thereby limiting the number available for further activation. Its efficacy exceeds that of tamoxifen, with a higher binding affinity for ERα than estradiol. Additionally, fulvestrant and other antiestrogens have demonstrated potential antitumor activity in prostate cancer through mechanisms dependent on estrogen receptor beta (ERβ). These findings indicate that both SERMs and SERDs could be optimized within a personalized therapeutic framework for prostate cancer. However, their use as monotherapy has not resulted in complete tumor regression. Clinical application of SERMs must still be considered carefully, as most available evidence remains from *in vitro* studies. This caution extends to the use of fulvestrant, which has produced contradictory results in clinical studies of men with castration-resistant prostate cancer, necessitating further evaluation [46].

Notably, while these developed drugs exert their therapeutic effects through highly specific inhibition of individual oncogenic targets or hormone receptors, the predicted *C. militaris* bioactive compounds appear to modulate multiple signaling proteins simultaneously, including SRC, MAPK1/3, AKT1, and ESR1. Rather than directly replicating the mechanisms of these established drugs, *C. militaris* compounds may complement existing therapies by providing broader pathway-level modulation, potentially reducing compensatory signaling and resistance development. Comparison with these developed drugs provides a biological basis for evaluating *C. militaris* as an alternative or adjuvant therapeutic candidate in the management of prostate cancer, with the potential to modulate clinically relevant molecular mechanisms. Following this, as shown in Figure 6, this finding suggests that the 19 compounds may potentially modulate the biological activity of the associated target proteins. The predictions revealed interactions between several compounds from C. *militaris* and the top 10 target proteins, except for HSP90AB1, which was not targeted by any compounds. None of the selected *C. militaris* compounds were predicted to directly target HSP90AB1, which may reflect the chemical nature of the identified compounds, which are predominantly

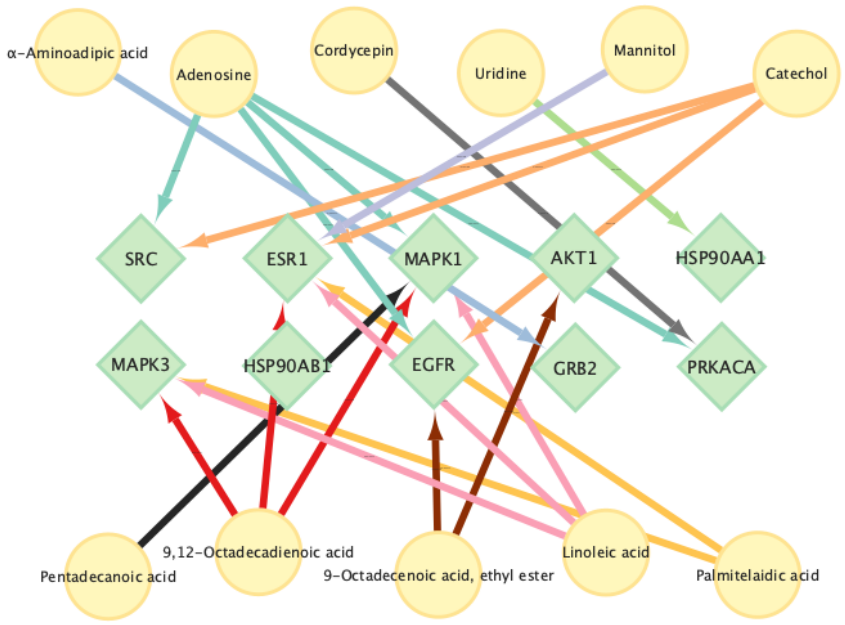

Figure 6. The compound-target interactions of *C. militaris* compounds targeting the top 10 proteins.

small polar molecules and metabolites that may lack structural features required for effective interaction with molecular chaperones such as HSP90AB1.

The compound-target interaction network reveals distinct and heterogeneous interaction patterns among the selected bioactive compounds. Adenosine exhibited the broadest predicted interaction profile, targeting SRC, EGFR, MAPK1, and PRKACA, suggesting its potential involvement in multiple signaling components relevant to prostate cancer progression. Catechol was predicted to interact with SRC, ESR1, and EGFR, suggesting a possible association with receptor- and signaling-adaptor–related regulatory processes. In contrast, cordycepin, one of the most extensively studied bioactive compounds of *C. militaris*, the present network pharmacology analysis predicted a relatively selective interaction profile, with PRKACA emerging as its primary associated target. This selective pattern contrasts with the broader interaction profiles observed for several other compounds. It may reflect context-dependent or indirect biological effects that are not fully captured by target prediction-based network models. This selectivity distinguishes cordycepin from other compounds in the network and suggests a more specific regulatory role rather than broad engagement of targets. Other metabolites, such as uridine and mannitol, displayed limited interaction profiles, primarily involving HSP90AA1 and ESR1, indicating more constrained molecular associations within the network. Several lipid-associated compounds, including linoleic acid, palmitelaidic acid, 9,12-octadecadienoic acid, and 9-octadecenoic acid ethyl ester, were predicted to interact with multiple proteins, including MAPK3, MAPK1, EGFR, ESR1, and AKT1, reflecting their broader association with proteins involved in signal transduction and cellular regulation. Collectively, these findings demonstrate that the selected compounds do not act as a homogeneous group but instead exhibit variable degrees of target engagement across key prostate cancer-associated proteins. Certain compounds exhibited broader or more relevant interaction profiles with major hub proteins.

3.5. Pharmacokinetic and Toxicity Evaluation

The results revealed that all 19 compounds met Lipinski's Ro5 (Table 5). Although all selected compounds met Lipinski's Ro5, a closer examination of ADMET predictions revealed several parameters that may limit the drug-development potential of specific compounds. Notably, adenosine and cordycepin exhibited high predicted drug-induced liver injury (DILI) scores (>0.95), suggesting a potential risk of hepatotoxicity upon systemic exposure. These findings indicate that, despite their biological relevance and predicted target interactions, such compounds may require careful dose optimization, structural modification, or targeted delivery strategies in future development. In contrast, other compounds displayed more favorable safety profiles, highlighting their potential prioritization for subsequent experimental validation. Importantly, these ADMET predictions are computational estimates and should be interpreted as hypothesis-generating rather than definitive indicators of clinical safety.

Compound toxicity levels can be classified into six categories based on their oral lethal dose (LD_{50}) values.

Table 5. ADMET and drug-likeness profiles of *C. militaris* bioactive compounds.

Code	Compounds Name	Pgp-inhibitor	Pgp-substrate	F20%	F30%	Blood-Brain Barrier	H-HT	DILI	FDAMDD	Lipinski's Ro5
C4	Serine	1.0634307727741543e-06	0.44203352928161612	0.00056821107864379 88	9.78708267211914e-05	0.67495256662 36877	0.28867900371551514	0.01393667422235012	0.004426766186952591	Accepted
C7	α-Aminoadipic acid	5.523165924614659e-09	5.523165924614659e-09	0.00035488605499267 58	0.00020521879196166992	0.00020521879196166992	0.22089646756649017	0.02545567788183689	0.069206401705741 88	Accepted
C13	Glutamic acid	1.938251159572246 3e-07	0.005722408648580313	0.00129151344299316 4	0.00212347507476806 64	0.07901848852 63443	0.16197699308395386	0.01154851168394088 7	0.017782980576157 57	Accepted
C21	Adenosine	5.763367516919970 5e-05	0.390754491090774 54	0.28070217370 98694	0.97941984608 76942	0.65252113342 28516	0.80967593193 0542	0.95090097188 94958	0.142202496528625 5	Accepted
C22	Cordycepin	0.000844653230160 4748	0.654272198677063	0.13404500484 466553	0.77098357677 45972	0.38102540373 802185	0.81087893247 60437	0.97657960653 30505	0.394512861967086 8	Accepted
C23	Uridine	0.000102634119684 80796	0.086563460528850 56	0.07297587394 714355	0.75355477631 09207	0.43784064054 489136	0.67394614219 66553	0.92317909002 30408	0.018252637237310 41	Accepted
C24	Fumaric acid	1.379927709876938e-07	0.010456398129463 196	0.50874871015 54871	0.27703279256 82068	8.97047448233 9341e-06	0.82023805379 86755	0.97480553388 59558	0.053286347538232 8	Accepted
C26	Succinic acid	1.575293936184607 4e-05	0.000952813425101 3398	0.01079857349 395752	0.09864383935 928345	0.24346069991 588593	0.36320614814 7583	0.28961560130 119324	0.067204222083091 74	Accepted
C28	Gluconic acid	9.027544045636 66e-09	0.148138478398323 06	0.10613930225 372314	0.48126065731 048584	0.03176151961 088180 5	0.56483179330 82581	0.08189443498 849869	0.018688101321458 817	Accepted
C30	Xylonic acid	1.497971737762782 1e-07	0.093098476529121 4	0.11319750547 409058	0.56938859820 36591	0.04905254766 345024	0.52701163291 93115	0.09963728487 491608	0.017594940960407 257	Accepted
C31	Mannitol	7.320770123442344e-07	0.285435527563095 1	0.12454956769 943237	0.14169418811 798096	0.03263729810 714722	0.37386938929 5578	0.00348317902 535200 1	0.002553861122578 3825	Accepted
C34	Catechol	0.017333006486296 654	0.074695311486721 04	0.82773905992 50793	0.87778768688 44032	0.55548322200 77515	0.34347510337 82959	0.18484042584 896088	0.572100400924682 6	Accepted
C35	Palmitic acid	2.055681761703454e-05	0.014421335421502 59	0.73822057247 16187	0.92565549910 06851	0.02099774777 889251 7	0.42295941710 472107	0.18754458427 4292	0.178302556276321 4	Accepted
C36	Pentadecanoic acid	2.714468246267642 8e-05	0.016545804217457 77	0.67480319738 38806	0.88913670182 22809	0.02751692198 216915	0.41999721527 09961	0.19277247786 521912	0.173313885927200 32	Accepted
C37	Octadecatriene	0.025814065709710 12	0.189394205808639 53	0.89664227515 45906	0.99240070348 60551	9.52211166804 7728e-07	0.50110971927 64282	0.20064054429 531097	0.387918472290039 06	Accepted
C38	9,12-Octadecadienoic acid	0.000600019178818 9113	0.006922835484147 072	0.14869517087 9364	0.67135792970 65735	0.07261374592 781067	0.10924310982 227325	0.00403947010 636329 65	0.063248604536056 52	Accepted

Code	Compounds Name	Pgp-inhibitor	Pgp-substrate	F20%	F30%	Blood-Brain Barrier	H-HT	DILI	FDAMDD	Lipinski's Ro5
C39	9-Octadecenoic acid, ethyl ester	0.5665455460548401	0.0019722343422472477	0.82889315485 95428	0.96672854572 53456	1.27225548567 36679e-05	0.53441119194 03076	0.03266021981 835365	0.1520933 06183815	Accepted
C40	Linoleic acid	0.004632151219993 83	0.0003302 26379446 6853	0.14780837297 439575	0.38828730583 19092	0.01227513700 723648	0.13774743676 185608	0.00042830928 578041 494	0.0348837 11487054 825	Accepted
C46	Palmitelaidic acid	0.0027174 61669817 567	0.0021396 75896614 79	0.53563031554 22211	0.92868352681 39839	0.00014001446 834299 713	0.68760269880 2948	0.04177798330 783844	0.2090938 83633613 6	Accepted

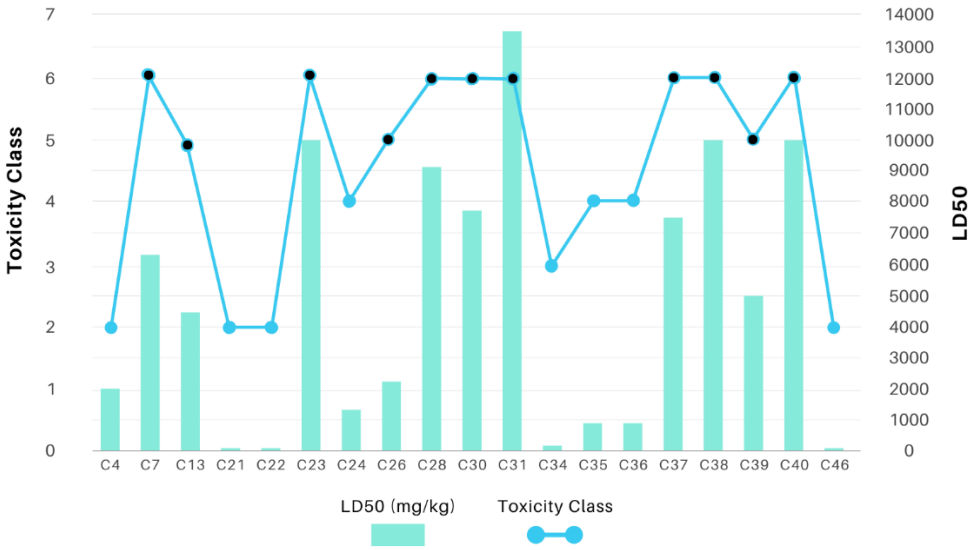

Figure 7. Toxicity prediction of *C. militaris* compounds.

Class I includes compounds with LD_{50} ≤ 5 mg/kg, which are fatal if ingested. Class II comprises compounds with LD_{50} values ranging from 5 to 50 mg/kg and are also considered fatal upon ingestion. Class III consists of compounds with LD_{50} values between 50 and 300 mg/kg, categorized as toxic if ingested. Class IV includes compounds with LD_{50} values ranging from 300 to 2,000 mg/kg and are classified as harmful if ingested. Class V comprises compounds with LD_{50} values between 2,000 and 5,000 mg/kg, which may be harmful if ingested. Class VI includes compounds with LD_{50} values greater than 5,000 mg/kg and is categorized as non-toxic [39]. Toxicity evaluation of the 19 selected compounds was conducted using ProTox, and the results are shown in Figure 7. There are 11 compounds classified in classes V and VI that were considered relatively safer for further drug development and are marked with black dots. Moreover, compound C31 (Mannitol) was identified as the safest candidate for further analysis based on the ProTox predictions. Yet, additional evaluation is still required to fully verify the toxicity safety of all compounds.

4. Conclusions

This study provides a disease-specific, system-level perspective on the potential relevance of *C. militaris* bioactive compounds in prostate cancer using a network pharmacology-based in silico approach. Nineteen compounds, selected based on predicted TP53 expression enhancer activity and drug-likeness criteria, were predicted to interact with several prostate cancer-associated molecular targets, including SRC, ESR1, MAPK1, AKT1, HSP90AA1, MAPK3, EGFR, GRB2, and PRKACA. Network topology analysis further identified SRC as a central hub protein, suggesting its potential role as a key mediator of the multitarget effects of C. *militaris* compounds. In addition, HSP90AB1 emerged as an important hub protein within the interaction network, although the selected compounds did not directly target it. Pathway enrichment analysis indicated that these

targets are predominantly involved in cancer-related signaling pathways, particularly those associated with EGFR tyrosine kinase inhibitor resistance, highlighting a potential mechanistic link to therapy resistance in prostate cancer.

Despite these insights, several limitations inherent to computational approaches should be acknowledged. The predicted compound-target interactions were based on in silico models and have not yet been experimentally validated. Moreover, compound selection relied on predefined Pa thresholds, which may have excluded potentially relevant metabolites. The inclusion of ubiquitous metabolites also represents an inherent limitation of metabolite-driven network pharmacology approaches and should be interpreted cautiously when inferring therapeutic relevance. The Pa ≥ 0.7 threshold was selected to prioritize compounds with higher confidence in predicted biological activity, thereby reducing false-positive associations in downstream network analyses. While using a lower Pa cutoff may increase the number of included compounds, it would likely yield less specific predictions and greater network noise. Conversely, a more stringent threshold could further reduce compound numbers but risk excluding potentially relevant bioactive molecules. Therefore, the chosen cutoff represents a balance between prediction confidence and compound diversity. Future studies may benefit from sensitivity analyses using alternative Pa thresholds to further assess the robustness of compound selection.

In addition, TP53 primarily functions as an upstream tumor suppressor that regulates multiple downstream signaling pathways, including MAPK, PI3K–AKT, and SRC-related signaling cascades, rather than acting as a highly connected interaction hub. Consequently, compounds predicted to enhance TP53 activity may exert their effects by modulating downstream or functionally associated hub proteins, such as SRC, ESR1, and MAPK1, which play central roles in signal transduction and therapy resistance in prostate cancer. Nevertheless, we acknowledge that selecting compounds based on a single upstream parameter may bias network topology and represents a limitation of the current screening strategy. Molecular docking analyses were also not performed to confirm binding affinities, and pharmacokinetic predictions did not account for actual in vivo bioavailability or tissue-specific concentrations. Accordingly, the findings of this study should be interpreted as hypothesis-generating rather than confirmatory.

Based on the identified network characteristics, future studies should prioritize experimental validation of compounds predicted to interact with central hub proteins, particularly SRC and key components of the EGFR-related resistance pathways. Molecular docking may serve as an initial validation step to assess binding affinity, followed by in vitro evaluation using androgen-sensitive and castration-resistant prostate cancer cell lines. Subsequent in vivo studies using appropriate prostate cancer models will be required to evaluate therapeutic efficacy, toxicity, and pharmacokinetics. Overall, this study offers prostate cancer–specific insights into the system-level mechanisms of action of C. *militaris* bioactive compounds and provides a rational framework to guide future experimental and translational investigations.

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