

Dual Targeting of EGFR and DRD2 by Plant Agents: As a Potential Anti-Cancer Effect

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ABSTRACT: Cancer remains one of the leading causes of death worldwide. Genetic mutations promote uncontrolled cell proliferation and survival, leading to tumor development. The epidermal growth factor receptor (EGFR) and the dopamine D2 receptor (DRD2) are two receptors that are critical for tumor growth and metastasis. This study aimed to evaluate the potential of three naturally derived compounds, corosolic acid, artemisinin, and taxifolin, as alternative agents to inhibit EGFR and DRD2 signaling pathways and potentially exhibit anticancer effects. Molecular docking analysis was conducted using PyRx and AlphaFold to determine binding affinities between the compounds. Docking results revealed relatively strong receptor–ligand interactions between all combinations of chemicals and receptors. Additionally, MTT assays were used to assess cell viability in the COLO320, U937, HTB-11, and SK-MEL-28 cancer cell lines. MTT assay results showed that all three compounds significantly reduced cell viability in a time-dependent manner, with greater reductions after 84 hours compared to 24 hours. Overall, the findings suggest that corosolic acid, artemisinin, and taxifolin exhibit promising anticancer potential through the dual targeting of EGFR and DRD2. These results provide a foundation for future research to improve current cancer treatments and discover drug therapies for different types of cancer.

KEYWORDS: Medical and Health Sciences, Oncology, EGFR and DRD2, Corosolic Acid, Artemisinin, and Taxifolin, Molecular docking and MTT assay.

■ Introduction

General Cancer:

In 2022, there were 9.7 million cancer-related deaths and 20 million new cases worldwide, making cancer one of the leading causes of death.^{1,2} It is anticipated that there will be 35 million new cases of cancer by 2050.¹ Of the hundreds of forms of cancer, in adults, the most commonly diagnosed types include breast cancer, colorectal cancer, and lung cancer.^{1,2} Some other common forms include melanoma and leukemia.¹ In terms of childhood cancers, leukemia is most common in children, and neuroblastoma is most common in babies.^{1,2} There is a heightened risk of cancer development associated with factors such as advanced age, detrimental behaviors including smoking and excessive alcohol intake, physical inactivity, and additional variables. This underscores the importance of sustaining healthy habits and a lifestyle to mitigate cancer risk.³

Cancer cells arise when normal, healthy cells fail to respond to cellular signals that regulate cell-cycle homeostasis, leading to uncontrolled proliferation. Cancer cells can also develop from genetic mutations in DNA sequences that affect gene expression and protein production.^{3,4}

Roles of EGFR and DRD2 in Cancer:

EGFR:

Epidermal growth factor receptors (EGFRs) are transmembrane glycoproteins that are a subclass of receptor tyrosine kinase (RTK). They bind to transmembrane epidermal growth factors (EGFs) and related growth factors, thereby regulating cell growth, division, survival, migration, and metabolism.

When an EGFR ligand binds to the receptor, it initiates phosphorylation, a signaling pathway in which the kinase enzyme moves phosphate groups from ATP to other molecules.⁵ The result of phosphorylation can either activate or deactivate molecules, impacting cell proliferation, signaling, and growth.⁵⁻⁷

However, mutations in the EGFR gene often lead to EGFR overexpression and the development of cancer cells. EGFR signaling pathways regulate cell growth and proliferation, and overexpression of the receptor in these pathways leads to uncontrolled cell division.^{6,8} In non-small-cell lung cancer (NSCLC), which makes up 80–85% of lung cancer diagnoses, 43–89% of the cases result from EGFR mutations.^{9,10} EGFR overexpression is also commonly observed in several other cancer types. For instance, 60–80% of colorectal cancer tumors exhibit EGFR overexpression.⁶ In neuroblastoma, heightened EGFR levels promote tumorigenesis and aggressive tumor behavior.⁸ In leukemia, elevated EGFR expression is associated with poor prognosis, and in melanoma, increased EGFR expression is linked to the progression of melanocytic cells.⁶ These various forms of cancer will serve as the center of focus of this paper.

EGFR Inhibitors:

Current EGFR inhibitors include two groups of drugs: tyrosine kinase inhibitors (TKIs), which are small molecules that competitively bind to the intracellular catalytic site of EGFR, and monoclonal antibodies (mAbs), which block receptor dimerization and phosphorylation.^{5,11} In the past, FDA-approved TKIs such as erlotinib and gefitinib, which are taken

orally, have been used in advanced treatments for NSCLC.^{10,11} Erlotinib has shown increased effectiveness and promising results in certain individuals with a history of adenocarcinoma of Asian ethnicity, female gender, and never-smokers; however, due to drug resistance, it has been proven ineffective for other individuals. Furthermore, erlotinib has shown harmful side effects such as diarrhea and skin toxicity. It has also been revealed that taking erlotinib during chemotherapeutic processes does not show an increase in survival and that it can be difficult to afford.¹² Similarly, gefitinib at low nanomolar concentrations has demonstrated tumor regression and symptom alleviation in some individuals; it has several drawbacks and side effects similar to those of erlotinib.^{11,12}

DRD2:

The dopamine D2 receptor (DRD2), located in the brain, is a G protein-coupled receptor that is part of the neural circuit overseeing the brain's control, behavior, reward, and motivation systems. Involving the neurotransmitter dopamine, DRD2 contributes to the transmission of information from dopaminergic neurons via pathways that connect the brain to various parts of the body. Because dopamine influences bodily functions beyond the brain, its receptors are often expressed in intracellular pathways throughout the body. In fact, DRD2 overexpression has been linked to tumorigenesis and the development of cancers such as colorectal and lung cancer. Studies have shown that upregulation of DRD2 expression in colorectal cancer cells is associated with poor survival, whereas depletion of DRD2 expression is associated with reduced cancer-like characteristics of high, uncontrolled levels of proliferation, migration, and invasion.^{13,14}

Plant-derived DRD2 Antagonists:

In efforts to identify effective treatments for DRD2-overexpressing cancer cells, the use of plant-derived compounds has gained popularity. Specifically, compounds that act as D2 receptor antagonists have been studied in prior clinical trials to evaluate anticancer effects.^{13,15,16} One naturally occurring compound, Berberine (BBR), is an alkaloid extracted from various plants and has demonstrated anti-tumor effects. BBR regulates the cell cycle to promote controlled cell proliferation and prevent abnormal cell cycle patterns that lead to the formation of cancer cells. In fact, BBR has been shown to promote and regulate apoptosis through the modulation of caspases. BBR elevates caspase expression while reducing Bcl-2 expression, thereby activating a signaling cascade that culminates in the mitochondria, the organelle that regulates apoptosis. Additionally, BBR inhibits metastasis by targeting multiple tumor-related signaling pathways and regulatory proteins, thereby preventing cell invasion.^{16,17} Another plant-derived compound is Stepholidine, derived from the Chinese herb *Stephania intermedia*, which acts as an antagonist at D1 and D2 receptors and exhibits anti-tumorigenesis effects.¹⁵

Limitations of Available Research:

While research has been conducted on the effectiveness of certain drugs on lung cancer, promising results were only re-

flected in groups of individuals of certain backgrounds, gender, ethnicity, etc. In fact, although drugs like erlotinib and gefitinib showed initial improvements, over time, they developed resistance to these drugs, thereby limiting their efficacy.¹⁰⁻¹² Moreover, no research has yet been conducted on potentially effective drugs that can universally improve the conditions of all patients, not only certain individuals.

Hypothesis and Aim of This Study:

The chemicals corosolic acid, artemisinin, and taxifolin present anticancer characteristics by interfering with EGFR signaling pathways and DRD2 mechanisms. These drugs may serve as potential treatments for different forms of cancer that include EGFR or DRD2 overexpression. This paper investigates the effectiveness of the chemical drugs corosolic acid, artemisinin, and taxifolin on the following cancer cell lines: COLO320 (colorectal adenocarcinoma), U937 (pro-monocytic), HTB-11 (neuroblastoma), and SK-MEL-28 (melanoma).¹⁸ In these cancer cells, receptors such as EGFR and DRD2 are overexpressed, resulting in potential carcinogenesis and tumorigenesis.^{6,8,13} Although research on anticancer substances such as taxifolin, corosolic acid, and artemisinin is limited, available studies indicate that these compounds may be effective against certain cancers.¹⁸ Past studies of taxifolin in cancer cells have revealed that taxifolin suppresses abnormal cell proliferation by inducing cell cycle arrest, apoptosis, and limiting migration, specifically in breast, lung, prostate, and melanoma cancer cell lines.¹⁹ Additionally, corosolic acid has been shown to limit cell proliferation by inducing apoptosis and reducing cell invasion across various cell lines, including glioma, lung, cervical, and prostate cancer cell lines.²⁰ Lastly, artemisinin has reduced cell proliferation by inducing G1 cell cycle arrest and inhibiting signaling pathways, and has shown effectiveness against leukemia, colon, breast, and prostate cancers.²¹

This research paper aims to evaluate the efficacy of drugs in treating certain cancers, including colorectal cancer, neuroblastoma, melanoma, and leukemia. It is hoped that the research findings from this paper can inform the development of comprehensive treatments for the cancer types listed above. It is also anticipated that these results will provide a foundation for future explorations of cancer treatment across other cancer types and stages, using small-molecule drugs targeting overexpressed proteins and receptors.¹⁸

■ Methods

Cancer Cell Models and Culturing:

Four cancer cell lines were tested in all experiments: HTB-11, a neuroblastoma cell line; COLO 320, a human colorectal adenocarcinoma cell line; U937, a pro-monocytic model cell line; and SK-MEL-28, a melanoma cell line. COLO320 cells were derived from the human colorectal adenocarcinoma cell line from ATCC. The cells were then cultured in RPMI-1640 medium (Gibco), added with 10% fetal bovine serum (FBS), 100 U/ml penicillin, and 100 µg/mL streptomycin. Cells were incubated at 37°C in a humidified environment with 5% CO₂. U937 cells from the human histiocytic lymphoma monocyte-like cell line were obtained from ATCC.

They were cultured in RPMI-1640 medium added with 10% heat-inactivated FBS, 100 U/ml penicillin, and 100 µg/mL streptomycin. Cells were kept in an incubator at 37°C with 5% CO₂. HTB-11 cells (SK-N-SH) from the human neuroblastoma cell line were obtained from ATCC. They were cultured in Eagle's Minimum Essential Medium (EMEM) added with 10% heat-inactivated FBS, 100 U/ml penicillin, and 100 µg/mL streptomycin. Cells were maintained at 37°C in an incubator with a humidified 5% CO₂ atmosphere. SK-MEL-28 cells were obtained from ATCC. They were cultured in Dulbecco's Modified Eagle Medium (DMEM) with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. Cultures were maintained at 37°C in a humidified incubator with 5% CO₂.

Molecular Docking:

Using PubChem, the 3D conformer structures of corosolic acid, artemisinin, and taxifolin were determined. AlphaFold was used to predict the structures of the EGFR and DRD2 receptors. The structures of each drug were then uploaded to the Open Babel control in the virtual screening software PyRx. Using a maximal-binding structure, the binding affinity between the specific receptor and the drug was evaluated. To visualize the molecular structure and binding site between the receptor and drug, the BIOVIA Discovery Studio Visualizer software was used. This multi-step process was performed six times, once for each drug-receptor combination.

MTT Cell Proliferation Assay:

Serial Dilution:

Serial dilutions were used to prepare 4 different solutions of corosolic acid. 10 µL of corosolic acid was dissolved in 1 mL of DMSO (Dimethyl Sulfoxide) to prepare the stock solution. Then, 900 µL of cell incubation medium was added to each tube labeled for 0.1, 0.01, and 0.001 of the stock concentration. Using a pipette, 100.0 µL of the stock solution was transferred to the tube labeled for 0.1 of the concentration. Subsequently, the solution was vortexed to ensure thorough mixing. 100.0 µL of the solution from the 0.1 concentration tube was then transferred to the next tube labeled 0.01 in the stock concentration series and vortexed. The same procedure was followed for the transfer between the 0.01 and 0.001 concentration tubes, leaving 4 tubes containing solutions of corosolic acid with varying concentrations. This process was repeated for artemisinin and taxifolin, yielding a total of 12 tubes of varying chemical solutions.

MTT:

10.0 µL of solutions of corosolic acid, artemisinin, and taxifolin at varying concentrations were pipetted into four 96-well plates: the first seeded with HTB-11 cells, the second with COLO320 cells, the third with U937 cells, and the fourth with SK-MEL-28 cells. After incubation, depending on the treatment duration (24 hours or 84 hours) for each 96-well plate, 10.0 µL of MTT was added to all experimental groups and the control group. The 96-well plates were incubated for 30 minutes at 36.7°C, after which 70.0 µL of DMSO (Dimethyl Sulfoxide) was added to each well to dissolve the MTT for-

mazan. The MTT assay measures cell viability, proliferation, and cytotoxicity by spectrophotometrically quantifying the conversion of yellow MTT to purple formazan by metabolically active mitochondria. Following the procedure, the plates were left at room temperature for approximately 15 minutes, and then a spectrophotometer with a 595 nm wavelength was used to measure the solution's absorbance. Data were collected twice by spectrophotometry for each cell plate and then recorded.

Statistical Analysis:

From the MTT cell viability, proliferation, and toxicity assay data, the mean and percentage change for each group were calculated. Additionally, a two-tailed t-test was performed for each experimental group against the control group, with an alpha (p) value of 0.05. Error bars represent the standard deviation expressed as a percentage of the mean.

Results and Discussion

3.1. Molecular Docking of Corosolic Acid, Artemisinin, and Taxifolin with EGFR and DRD2, Respectively:

Molecular docking in PyRx revealed that corosolic acid, artemisinin, and taxifolin had favorable binding affinities with both EGFR and DRD2 (Figure 1). Corosolic acid exhibited a binding affinity of -8.6 kcal/mol with EGFR and -7.9 kcal/mol with DRD2; artemisinin exhibited a binding affinity of -7.3 kcal/mol with EGFR and -7.6 kcal/mol with DRD2; and taxifolin exhibited a binding affinity of -8.3 kcal/mol with EGFR and -8.1 kcal/mol with DRD2. The high binding affinities show that the three chemicals disrupt cell signaling pathways and induce cell apoptosis.

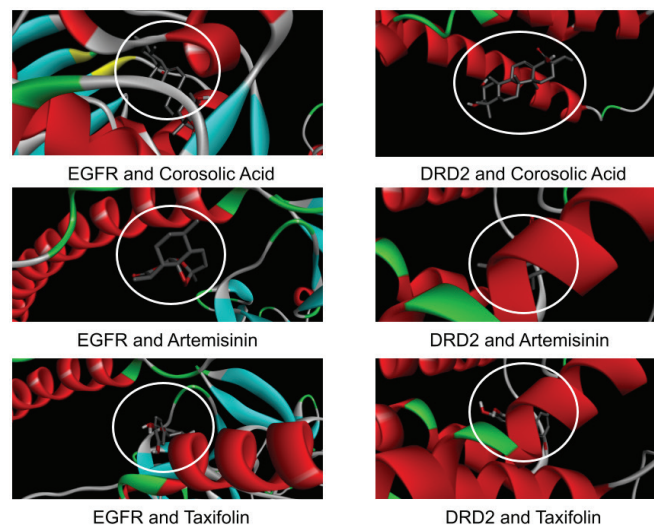


Figure 1: Molecular docking interactions between corosolic acid, artemisinin, and taxifolin with EGFR and DRD2 receptors. Left Column: interactions with EGFR. Right Column: interactions with DRD2. The top row corresponds to corosolic acid, the middle row to artemisinin, and the bottom row to taxifolin.

3.2. MTT Cell Proliferation Assay Data Reduces Cell Survival

3.2.A. HTB-11 Cells

Corosolic acid, artemisinin, and taxifolin significantly reduced cancer cell survival in HTB-11 cells in a dose-dependent

and time-dependent manner ($p < 0.05$). All chemical concentrations tested reduced HTB-11 cell absorbance and viability (Figure 2), and longer treatments produced stronger effects. After 24 hours, corosolic acid at $10\mu\text{m}$ significantly decreased cell viability by 21.20%, while after 84 hours, artemisinin at $10\mu\text{m}$ significantly decreased cell survival by 52.25%.

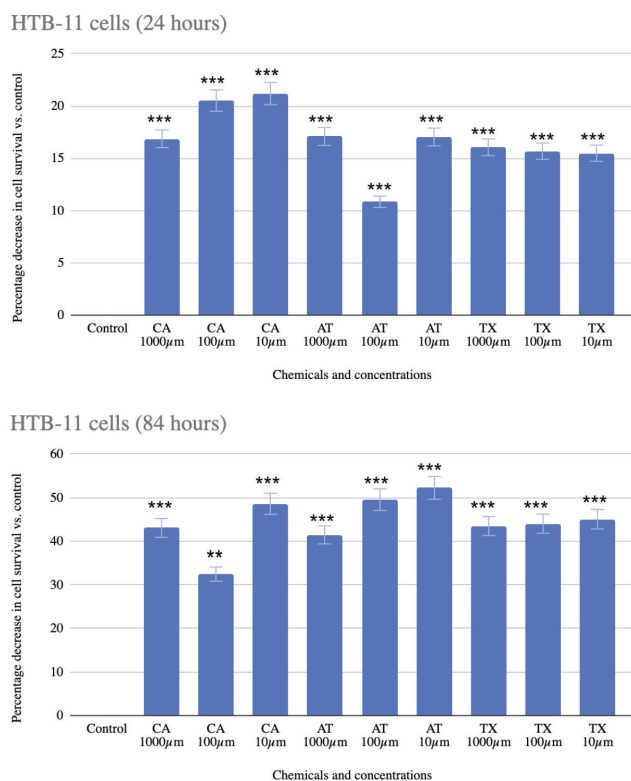


Figure 2: Corosolic acid at $10\mu\text{m}$ significantly reduced cell survival at 24 hours; artemisinin at $10\mu\text{m}$ significantly reduced cell survival of HTB-11 cells at 84 hours; * = $p < 0.05$ compared to control; ** = $p < 0.01$ compared to control; *** = $p < 0.001$ compared to control.

3.2.B. COLO320 Cells:

Corosolic acid, artemisinin, and taxifolin significantly reduced cancer cell survival in COLO320 cells (Figure 3) in a dose-dependent and time-dependent manner ($p < 0.05$). All chemical concentrations tested reduced COLO320 cell absorbance and viability, and longer treatments produced stronger effects. After 24 hours, artemisinin at $1000\mu\text{m}$ significantly decreased cell survival by 23.88%, while after 84 hours, corosolic acid at $100\mu\text{m}$ significantly decreased cell survival by 37.84%.

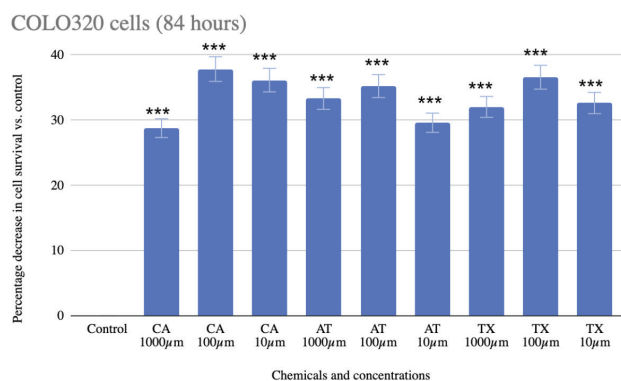
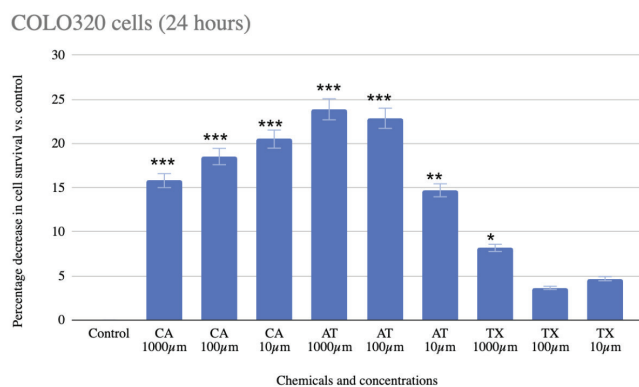


Figure 3: Artemisinin at $1000\mu\text{m}$ significantly reduced cell survival at 24 hours; corosolic acid at $100\mu\text{m}$ significantly reduced cell survival of COLO320 cells at 84 hours; * = $p < 0.05$ compared to control; ** = $p < 0.01$ compared to control; *** = $p < 0.001$ compared to control.

3.2.C. U937 Cells:

Corosolic acid, artemisinin, and taxifolin significantly reduced cancer cell survival in U937 cells in a dose-dependent and time-dependent manner ($p < 0.05$). All chemical concentrations tested reduced U937 cell absorbance and viability only in longer treatments (Figure 4). After 84 hours, taxifolin at $10\mu\text{m}$ markedly reduced cell survival by 28.45%.

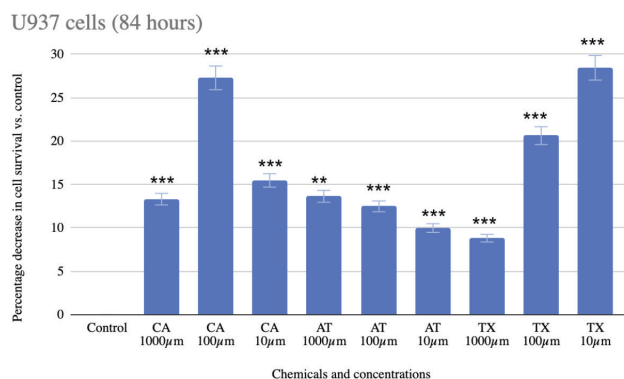


Figure 4: Taxifolin at $10\mu\text{m}$ significantly reduced cell survival of U937 cells at 84 hours; * = $p < 0.05$ compared to control; ** = $p < 0.01$ compared to control; *** = $p < 0.001$ compared to control.

3.2.D. SK-MEL-28 Cells:

Corosolic acid, artemisinin, and taxifolin significantly reduced cancer cell survival in SK-MEL-28 cells (Figure 5) in a dose-dependent and time-dependent manner ($p < 0.05$). All chemical concentrations tested reduced SK-MEL-28 cell absorbance and viability, and longer treatments produced stronger effects. After 24 hours, taxifolin at $100\mu\text{m}$ significantly decreased cell survival by 19.01%, while after 84 hours, artemisinin at $100\mu\text{m}$ significantly decreased cell survival by 40.26%.

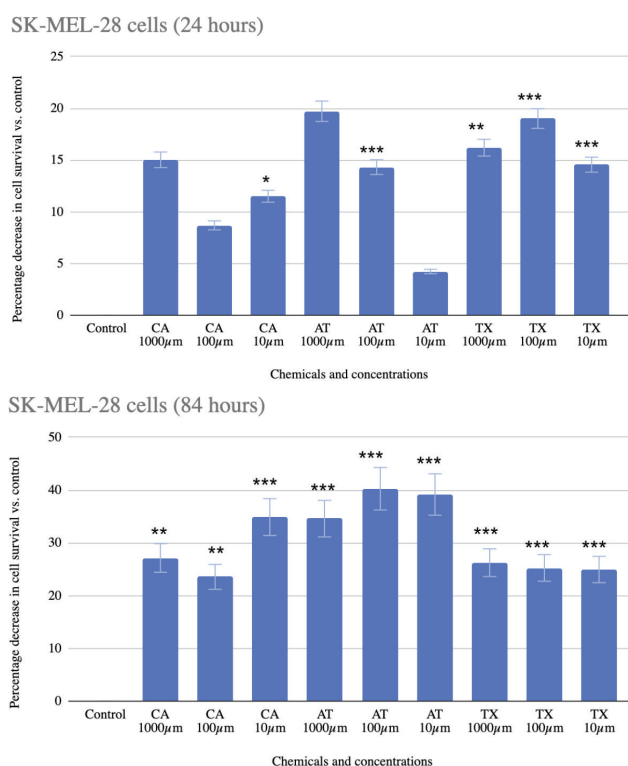


Figure 5: Taxifolin at 100µm significantly reduced cell survival at 24 hours; artemisinin at 100µm significantly reduced cell survival of the SK-MEL-28 cells at 84 hours; * = $p < 0.05$ compared to control; ** = $p < 0.01$ compared to control; *** = $p < 0.001$ compared to control.

Discussion:

As shown in the MTT assay, all three chemicals reduced cell viability (Figure 2-5). In HTB-11, COLO320, U937, and SK-MEL-28 cells, 84-hour treatments resulted in a greater decrease in cell survival than 24-hour treatments. This suggests that long-term treatments are more effective at inducing cell apoptosis and may reveal anticancer effects. In particular, although the short-term treatment of U937 cells showed no effect after 24 hours (Figure 4), it showed statistically significant results after 84 hours of incubation. This demonstrates that long-term treatment can mitigate delayed apoptosis and other effects and may be more effective than short-term treatment. Thus, apoptosis in colorectal, skin, and neuronal cancer cells can be induced by corosolic acid, artemisinin, and taxifolin.

Molecular docking (Figure 1) shows that all three chemicals exhibited strong binding affinities for both EGFR and DRD2, suggesting that each compound may serve as an agent targeting signaling pathways. Because EGFR is often overexpressed and harbors mutations that can drive cancer, particularly colorectal and lung cancers, the strong binding and interactions between the chemicals and their receptors suggest potential regulation of cell proliferation, division, and growth.^{5,6,8} Additionally, inhibition of the DRD2 signaling pathway can reduce metastasis and increase DRD2 receptor expression. The chemicals' ability to regulate signaling pathways across different parts of the body may provide a therapeutic strategy for treating various forms of cancer.

Inhibition of these signaling pathways correlates with MTT assay results. The effects of cell regulation and limited gene expression are evidenced by significantly lower MTT absorbance values and reduced cell viability. The combination of *in vitro* cell viability data and *in silico* docking analysis indicates that corosolic acid, artemisinin, and taxifolin can act as dual agents that inhibit EGFR and DRD2 signaling pathways in colorectal, skin, blood, and neuronal cancer cells. Their ability to regulate cellular pathways via naturally derived compounds highlights their advantage over existing drugs, such as erlotinib and gefitinib, which have harmful side effects.^{11,12} Rather than developing resistance or showing effectiveness only for certain groups of people, these three chemicals exert anticancer effects by targeting overexpression and signaling pathways.

To further interpret these results at a mechanistic level, it is plausible that corosolic acid suppresses EGFR autophosphorylation and downstream PI3K/AKT signaling, thereby reducing cancer cell survival, while taxifolin may block DRD2-mediated MAPK and STAT3 pathways linked to tumor progression.^{13,18} The results suggest potential dual targeting of both neuroregulatory and proliferative signaling pathways involved in cancer, supporting a systems-level therapeutic approach.¹⁸ Additionally, the fact that these compounds come from plants may provide pharmacological advantages such as lower toxicity, improved bioavailability, and potential synergistic effects with existing chemotherapeutics.^{16,17} However, these mechanistic interpretations remain predictive, as neither receptor activity nor downstream signaling was directly measured in this study.

Further work should incorporate mechanistic validation using assays such as Western blotting for phosphorylated EGFR, AKT, ERK, and STAT3, as well as analyses of DRD2 and EGFR expression to confirm pathway involvement. Functional assays, including Annexin V/propidium iodide (PI) staining, lactate dehydrogenase (LDH) release, and caspase activation assays, would further clarify whether the observed reduction in viability is due to apoptosis, necrosis, or other forms of cell death. *In vivo* studies would also be necessary to evaluate therapeutic relevance under physiological conditions and to confirm pathway-specific inhibition.¹⁸ These findings suggest that corosolic acid, artemisinin, and taxifolin may serve as promising multitarget agents with potential activity against EGFR- and DRD2-associated signaling in cancer, warranting further experimental validation.¹⁶⁻¹⁸

Conclusion

This study explores potential treatments for cancers associated with the overexpression of EGFR and DRD2 receptors. Although current EGFR and DRD2 receptor inhibitors exist as current treatments, they have their own limitations of drug resistance and harmful side effects. Thus, naturally derived compounds corosolic acid, artemisinin, and taxifolin were researched to determine if their anticancer properties could inhibit receptor pathways.

Together, the experimental and computational results indicate that corosolic acid, artemisinin, and taxifolin exert anticancer effects by reducing cancer cell survival and targeting receptor pathways. This study suggests that prolonged

treatment may yield greater therapeutic benefits, indicating that these drugs may act as dual agents targeting signaling pathways implicated in carcinogenesis. Specifically, all drugs' efficacy increased within 84 hours, suggesting that incorporating long-term treatments in the future may be beneficial. This anticancer discovery can inform future *in vivo* and mechanistic studies that may advance drug treatments for its various types. Overall, this work serves as an initial screening study that highlights corosolic acid, artemisinin, and taxifolin as promising candidates for further mechanistic validation.

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