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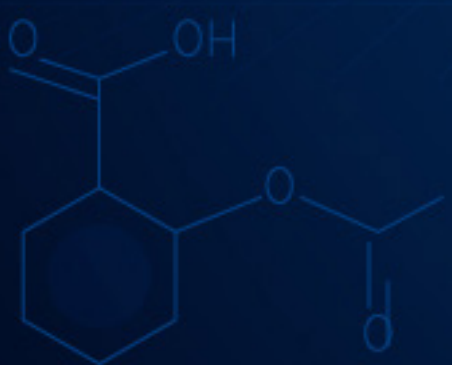

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Advances in the Use of Natural Compounds for Cancer Therapy: A Transition from Traditional Approaches to Modern Drug Guidance

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ABSTRACT

Cancer is one of the most serious and leading causes of death worldwide. Many individuals incorporate natural and nutritious foods into their diets which can help prevent cancer and reduce other health risks. Although synthetic drugs are commonly used in cancer treatment and their effectiveness is often limited by drug resistance and adverse side effects. So, physicians and researchers are increasingly focusing on natural products to enhance efficacy of conventional cancer therapies and to minimize associated toxicities. A comprehensive literature search was conducted primarily in google scholar and was supplemented by searches in PubMed, Scopus and Science Direct using relevant keywords. We found that same natural product can inhibit multiple types of cancer and may also be used in combination with pharmaceutical drugs. Important fact is that many people are unaware of anticancer activities of natural products and their potential benefits. It is equally important to highlight limitations of conventional pharmaceutical treatments. So affordable yet valuable natural products should be recognized and further investigated for their therapeutic potential in cancer prevention and treatment. This study aims to discuss different types of cancer and their relationship with natural products as well as anticancer drugs. The main objective is to investigate activity of natural products against various cancer cell types and to compare their effectiveness with that of synthetic drugs used alone. This approach may help bridge traditional and modern treatments and contributing to advancement of cancer therapy in general.

INTRODUCTION

Cancer is still the nation's second leading cause of mortality with roughly 2041910 new diagnoses and 618120 cancer death forecast for 2025. Globally, burden is also immense in 2022 number of new cases reached about 20 million with roughly 9.7 million deaths. Projections suggest that by 2050 annual incidence could rise to 30.5 million cases and approximately 18.6 million deaths. (Jaman, M. S., *et al.,* 2018) The discovery and isolation of morphine from opium in early 19th century began a new chapter in harnessing natural compounds for medicine. In spite of many decades since the introduction of major natural products that derive anticancer agents like anthracyclines, vinca alkaloids, lignan derivatives, camptothecin-based drugs, and taxanes continue to be widely used and remain essential in cancer treatment in 2025. (Jaman, M. S., et 2023) Recent scientific advances have greatly improved out understanding of natural products. By 2025, several dietary constituents and plant derived bioactive molecules have been documented to possess anticancer activity in both laboratory and animal models. (Bhuiyan, R. H., *et al.,* 2022) Even with notable progress converting natural bioactive compounds into approved drugs remains challenging because large scale production, mechanistic insights and pharmaceutical development are often difficult. This has led many global pharmaceutical companies to reduce or discontinue natural product research and focusing instead on synthetic molecules and biologic drugs. Today rapid developments in cancer therapy and technological innovation are helping address these barriers by improving drug discovery workflows enabling direct target identification and clarifying complex pharmacological activities of natural compounds. (Maniruzzaman, M., *et al.,* 2025) Natural products display diverse anticancer mechanisms depending on their chemical nature. Such as dietary molecule curcumin, sulforaphane, soy isoflavones and resveratrol can regulate pathways controlling cancer stem cell self-renewal. Research also suggests that various plant derived metabolites can induce apoptosis, consistent with known ability of most chemotherapeutic drugs to activate extrinsic and intrinsic cell death pathway. Studies across different tumor models indicate that these compounds could contribute to future therapeutic approaches. (Bhuiyan, R. H., *et al.,* 2022) It is recommended to consult a healthcare professional before adding new supplements or natural products to your regimen and particularly if you are taking medications or have existing health conditions. Examples mentioned here represent only a small fraction of vast diversity of natural products and their chemical constituents while many of these compounds occur naturally and some can also be synthesized or chemically modified in laboratory to create more purified or potent forms. Although synthetic drugs often face challenges

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such as resistance and complexity, natural products have the potential to enhance therapeutic outcomes and help overcome limitations of conventional synthetic medicines. (Jaman, M. S., *et al.,* 2017) The main purpose of this special review is to deliver a comprehensive tool for scientists that inspires innovative research and application of knowledge to global health and environmental concerns.

MATERIALS AND METHODS

We perform an extensive literature search in Google Scholar, PubMed, Scopus with keywords including natural product, Breast, Prostatic, hepatocellular, ovarian, lung Cancer, pharmaceutical Product, and Natural product like Curcumin, Baicalin, Capsiasin, Apigenin, Ginsenoside Rk1, QS-21, Ursolic Acid, cancer treatment with pharmaceutical drug like Tamoxifen, Paclitaxel, everolimus, Pembrolizumab exemestane, fulvestran, cell signaling with cancer treatment. About 1015 paper found and many papers has been rejected due to duplicate study, non-English, only abstract and study not relevant our journal aim of study. After reviewing the title and abstract, we excluded studies that were irrelevant or for which full texts were unavailable, and 96 studies satisfied our inclusion criteria and whose findings are described in this review.

Importance of natural product

Chemoprevention was first introduced in 1920s by Berenblum and after a period of limited attention and regained prominence in cancer research during 1970s through the work of sporn. Because of their high toxicity and poor biodistribution, natural retinoids were progressively substituted with safer and more effective synthetic analogs. Early clinical investigations of vitamin A derivative 13-cis-retinoic acid, followed by phase III trials in leukemia patients and assessment of high-dose regimen, succeeded by either low-dose 13-cRA or carotene. Their study demonstrated that low dose 13-cRA was more effective than carotene as a maintenance therapy. (Bhuiyan, R. H., *et al.,* 2023) a subsequent phase III trial employing high dose 13-cis-retinoic acid with interferon and tocopherol showed considerable efficacy in delaying SPT development and promoting initiation of phase III trial comparing this combination to no treatment. (Jaman, M. S., *et al.,* 2023) However due to challenges with patient accrual trial is currently delayed. Identification of key biomarkers associated with disease progression such as EGFR, COX-2, Ras along with development of targeted inhibitors against these molecules has created new avenues for chemoprevention. Several targeted inhibitors against these molecules have created new avenues for chemoprevention. Several targeted agents have since been developed including COX-2 inhibitors, EGFR inhibitors and farnesyltransferase inhibitors. Nevertheless, lack of long-term safety evidence in individuals without active malignancy has led to discontinuation of proposed clinical trials evaluating gefitinib and tipifarnib for reversal of premalignant lung lesions. Safety remains a paramount concern in studies involving human participants particularly those without overt malignancy. Ideally chemo preventive agent should be safe, effective at low doses, cost-efficient and readily accessible. (Jaman, M. S., *et al.,* 2017) Necessary for chemo prevention trials is often challenging and partly due to toxicity associated with pharmaceutical agents under investigation. Natural dietary compounds have increasingly drawn widespread attention from researcher as well as public because of their potential to suppress cancer and reduce cancer risk. Evidence from numerous epidemiological studies and animal models indicates that consumption of fruit and vegetable rich diets has been linked to a reduced risk of several types of cancer. Clinicians have increasingly focused on diet derived chemo preventive agents and reflecting patients growing interest in over counter nutritional preventive properties of wide range of nutritional compounds especially those present in green and yellow vegetable, citrus fruit and various spices. (Jaman, M. S., *et al.,* 2024) Because FPTs and SPTs share common host factors such as genetic alterations, immune function and hormonal imbalances along with environmental and occupational exposures, lifestyle influences and gene environment interactions, chemoprotective agents targeting initial tumor may also be effective in preventing SPTs. However, clinical investigations into these compounds have only recently begun (Table 2). The chemo preventive properties and molecular targets of selected promising natural compounds are discussed in detail below and summarized in Table 1. (Jaman, M. S., *et al.,* 2018)

RESULTS AND DISCUSSIONS

Natural product and pharmaceutical applications in Breast Cancer cell

BC is one of the most difficult cancers to treat, and it accounts for a significant portion of cancer-related fatalities. Natural substances can reduce aggressiveness of BC and stop growth of malignant cells and alter pathways linked to cancer. This is shown in Figure 1 and Table 1. (Mitra, S., *et al.,* 2018) According to Hu S *et al.,* 2018 curcumin has been demonstrated in vitro and in vivo studies to exert anticancer effects by altering numerous signaling cellular pathways. Its strong anticancer action was demonstrated by considerable inhibition of growth of several BC cell lines including T447D, MCF7, MDA-MB-231 and 468. Cu increase p21 expression while decreasing CDC25, CDC2 protein expression and causing cell cycle arrest at G2/M phase. It reduces BCL2, Akt, mTOR, BAX and caspase 3 cleavage. (Hu, S., *et al.,* 2018) However, Ly ZD *et al.* 2014 Bax/Bcl-2 ratio rose as a result of decrease in Bcl-2 expression and increase Bax expression. When Cu was administered to mice with MDA-MB-231 xenograft tumors and tumor weight and volume significantly decrease in comparison to control. (Lv, Z. D., *et al.,* 2014) Therefore, many chemotherapeutic drugs produce ROS and activate JNK

during process of inducing apoptosis and we thought that Cu might counteract their antitumor efficacy. This agent also inhibits production of ROS and JNK pathway. Cu demonstrated antioxidant qualities in a concentration dependent manner and reduce both JNK activation and mitochondrial cytochrome c release. (Somasundaram, S., *et al.,* 2002) Accordingly, Bhat smitha S *et al.* 2021 said that isoflavonoid is abundant in soybeans is genistein. Its tumoricidal effects which include inducing cell proliferation and suppressing tyrosine kinases and regulating hedgehog Glil signaling and modulating epigenetic activities and seizing cell cycle and activating Akt and MEWK signaling pathways are being thoroughly investigated. (Bhat, S. S., *et al.,* 2021) Consequently, NF-kB and Akt signaling pathways which are known to preserve a homeostatic balance between cell survival and apoptosis are inhibited by genistein. It has been demonstrated that genistein is a strong inhibitor of angiogenesis and metastasis and possesses antioxidant qualities. Isoflavones is a promising agent for cancer chemoprevention and its effects on reversing radio resistance and chemoresistance raise cancer therapy. (Banerjee, S., *et al.,* 2008) However, Accordingly Chen D *et al.* 2007 *et al.* Apigenin can cause apoptosis in cultured leukemia Jurkat T cells and block proteosome activity and highly metastasis MDA-MB-231 cells exhibit proteasome inhibitory activity. Levels of proteasomal chymotrypsin like activity, ubiquitinated protein and buildup of proteasome target proteins in extracts of treated cells or tumors were used to measure proteasome inhibition. Caspase-3/7 activation, poly ADP-ribose polymerase cleavage and immunohistochemistry for terminal nucleotide transferase mediated nick end labeling positivity were used to quantify apoptotic cell death. (Chen, D., *et al.,* 2007) whereas, it is believed that Apigenin ability to cause oxidative damage to lipids and was genotoxic to chosen cancer cells. Apigenin's lower toxicity to healthy cells and demonstrated cytogenotoxic and pro cell death properties suggest that this may find application as an anticancer treatment. (Vrhovac Madunić, I., *et al.,* 2018) However, according to the Seo HS *et al.,* 2012 Apigenin did not cause apoptosis through intrinsic mitochondrial apoptosis pathway because it did not lower mitochondrial membrane potential and preserving red fluorescence or alter levels of BCL2 associated X protein. Extrinsic apoptosis pathway caused by apigenin increased levels of cleaved caspase-8 and induced cleavage of poly ADP-ribose polymerase. Apigenin increased levels of p53, p-p53 and p21 in MCF-7 vec and MCF-7 HER2 cells while decreasing HER2 in MCF-7 HER2 cells. (Seo, H. S., *et al.,* 2012) On the other hand, Extensive studies have been established to determine whether tamoxifen lowers risk of BC in women in good health. All of these patients' treatment details were collected as were those of 285 controls who were matched to cases in terms of age and the year BC was diagnosed and length of time in patients survived with their uterus intact. 20% of control and 24% of patients with future endometrial cancer had used tamoxifen. This is shown in Table 2 (van Leeuwen, F. E., *et al.,* 1994) Additionally, according to the Chang M *et al.,* 2012 that tamoxifen is a key aspect of therapy of BC that ER positive. It is currently accessible as a chemo preventive medication for women at high risk for BC and has been utilized in clinical settings for past 30 years. The most difficult problem with using tamoxifen is when a Breast tumor that was originally receptive develops resistance. (Chang M. 2012) Consequently, odds ratio for disease free survival was 1.27 for patients getting weekly paclitaxel and 1.23 for those receiving docetaxel in every three weeks and 1.09 for those receiving weekly docetaxel when compared to those receiving conventional therapy which involves paclitaxel every three weeks. Women with BC who get weekly paclitaxel following standard adjuvant chemotherapy with doxorubicin and cyclophosphamide have better overall and disease-free survival rates. (Sparano, J. A., *et al.,* 2008)

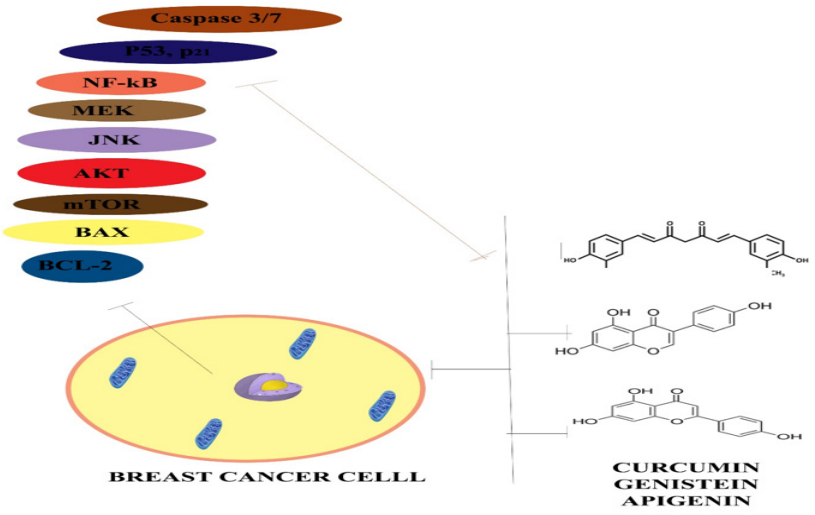


Figure 1: Natural product application and associated protein in cell signaling in breast cancer.

Table1: Natural product application in different cancer cell as potential application.

Name of Compound	Biological source	Model & Cancer type	Result	Reference
Curcumin		In vivo and in vitro Breast Csancer	Induce tumor regression, apoptosis, angiogenesis	(Hu, S., *et al.,* 2018) (Lv, Z. D., *et al.,* 2014) (Somasundaram, S., *et al.,* 2002)
genistein		In vivo and in vitro Breast Cancer	Activates on AKT and MEK signaling pathway	Bhat, S. S., *et al.,* 2021) (Banerjee, S., *et al.,* 2008
Apigenin		In vivo and in vitro Breast Cancer	reduced cellular viability /proliferation, proteasome inhibition, and apoptosis induction	Chen, D., *et al.,* 2007) (Vrhovac Madunić, I., *et al.,* 2018) 20(Seo, H. S., *et al.,* 2012)
Baicalin		In vivo and in vitro Lung Cancer	Induce apoptosis and cellular pathway	(Guo, L., *et al.,* 2024) (Chen, J., *et al.,* 2021) (Sui, X., *et al.,* 2021)
Capsiasin		In vivo and in vitro Lung Cancer	Inhibition of mitochondrial respiration	(Han, T. H., *et al.,* 2022) (Lau, J. K., *et al.,* 2014) (Chen, J. C., *et al.,* 2019)
Ursolic Acid		In vivo and in vitro pancreatic Cancer	Regulation of apoptosis and autophagy related pathway	Lin, J. H., *et al.,* 2020) (Li, J., *et al.,* 2012) (Li, Z. Y., *et al.,* 2021)
Curcumin		In vivo and in vitro pancreatic Cancer	Anti-cancer agent	(Kanai M. 2014) (Sun, M., *et al.,* 2008)
Ursolic Acid		In vivo and in vitro Colorectal Cancer	Induce cell death and autophagy related pathway	(Xavier, C. P., *et al.,* 2013) (Kim, K., *et al.,* 2019) (Zhao, H., *et al.,* 2023)
celastrol		In vivo and in vitro Colorectal Cancer	Induce TGF-β1/ Smad signaling	(Jiang, Z., *et al.,* 2019) (Bufu, T., *et al.,* 2018) (Wang, S., *et al.,* 2023)
Honokoil		In vivo and in vitro ovarian Cancer	Induce apoptosis by targeting AMPK activation	(Lee, J. S., *et al.,* 2019) (Liu, F., *et al.,* 2024) (Xin, L., *et al.,* 2023)

epigalactogachine		In vivo and in vitro ovarian Cancer	Induce cell death by DNA damage	(Rao, S. D., *et al.,* 2010) (Xinqiang, S., *et al.,* 2017) (Kim, Y. W., *et al.,* 2004)
silibinin		In vivo and in vitro cervical Cancer	Induce Drp1 dependent mitochondrial fission	(You, Y., *et al.,* 2020) (Zhang, Y., *et al.,* 2012) (García-Maceira, P., *et al.*, 2009)
catechin		In vivo and in vitro cervical Cancer	Induce Drp1 dependent mitochondrial fission	(Khojaste, E., *et al.*, 2021) (Al-Hazzani, A. A., *et al.,* 2011) (Gong H., *et al.,* 2024)
Ginsenoside Rk1		In vivo and in vitro prostate Cancer	Most effective chemo preventive	(Park, J. Y., *et al.,* 2016) (Zhang, Y., *et al.,* 2024) (Jiang, M., *et al.,* 2023)
protoapigenone		In vivo and in vitro prostate Cancer	NF-kB pathway inhibitor	(Chang, H. L., *et al.*, 2008) (Chen, H. M., *et al.,* 2011) (Abbaspour Babaei, M., *et al.* , 2017)
goniothalamin		In vivo and in vitro Oral Cancer	Anti-cancer agent	(Yen, C. Y., *et al.,* 2012) (Li, L. K., *et al.,* 2016)
Polygonaceae		In vivo and in vitro Oral Cancer	Effective for cisplatin resistant oral cancer	(Wang, Y. L., *et al.,* 2019)
catechin		In vivo and in vitro Oral Cancer	Chemo preventive agent	(Azuine, M. A., *et al.,* 1994)
QS-21		In vivo and in vitro Hepatocellular Carcinoma	induces potent humoral and cellular immunity	(Wang, Z., *et al.,* 2025)
Gingerenone A		In vivo Hepatocellular Carcinoma	Induce Nrf2–Gpx4 signaling pathway.	(Chen, Y., *et al.,* 2022) (Moaddel, R., *et al.,* 2022)

Natural product and pharmaceutical application in Lung Cancer cell

LC progression is influenced by inflammation in a number of way including angiogenesis, treatment resistance, apoptosis, metastasis and cell proliferation. Scutellaria baicalensis Georgi has an active ingredient called baicalin which has anticancer properties against a variety of malignancies. Baicalin suppressed progression of urethane induce lung cancer in mice in vivo and exhibited potent anti-proliferative, anti-migratory, anti-inflammatory, and pro-apoptotic effects in vitro. Baicalin restricted LC in vitro and in vivo via increasing SOCS1 expression which in turn deactivated NF-kB/ STAT3 pathway. This is shown in Figure 2. (Guo, L., *et al.,* 2024) However, according to the Chen *et al.* 2021 naturally occurring substance with anti-inflammatory, antioxidant and anti-cancer effects is baicalin. It reversed levels of EMT markers and decreased expression levels of p-PDK1, p-AKT and dose dependently inhibited migration and proliferation of NCI-H446 human NSCLC cells. (Chen, J., *et al.,* 2021) Moreover, Key factor of baicalin induced cell cycle arrest was suppression of Ak/mTOR pathway. Anticancer impact of baicalin was considerably diminished in both H1299 and H1650 cells upon transfection with Akt Agonist SC79 or AKT plasmid. (Sui, X., *et al.,* 2021) Consequently, Capsiasin is known to suppress HIF activity in LC while in H299 cells it did not alter overall HIF-1α protein expression along with that of its downstream targets including PDK1 and Glut1 and it reduced HIF-1α accumulation by inhibiting mitochondrial respiration which raised intracellular oxygen levels. (Han, T. H., *et al.,* 2022) Therefore, Capsiasin induced apoptosis in human SCLC cells was mediated through TRPV receptor family and this apoptotic effect was abolished when TRPV6 was silenced using siRNA technology. Intracellular calcium and calpain pathway mediated capsaicin proapoptotic action when untreated SCLC cell activity of calpain 1 and 2 was tripled in human SCLC cells treated with capsiasin. (Lau, J. K., *et al.,* 2014) Hence, according to the Jhy Cheng chen *et al.* 2019 capsiasin reduced expression of ERCC1 in two HLAC and transfection with constitutive active AKT vectors enhanced AKT activity which in turn raised quantity of ERCC1 protein and boosted capsiasin induced cell survival. In A549 and H1975 cells, downregulation of ERCC1 and inhibition of AKT were associated with capsiasin synergistic enhancement of erlotinib induced cytotoxicity and suppression of NSCLC cell growth. (Chen, J. C., *et al.,* 2019) Consequently, Evarolimus alone and plus 30 Gy cohort demonstrated a marked decrease of tumor growth and a decreased average tumor volume and at a time of compared to radiation and vehicle 30 nM evarolimus dramatically decreased protein levels of mTOR downstream effector p70-S6K and greatly inhibited levels of p-p70-S6K when compared to either treatment alone. (Mauceri, H. J., *et al.* , 2012) However, 7 patients received one cycle, twenty-eight patients received two or more cycles and 35 patients who were evaluated best response was 26 patients 74 % progression, 8 patients 23% stable illness and 1 patient 3% partial response. OS was correlated with high levels of p-AKT expression. (Tarhini, A., *et al.,* 2010) Therefore, alpelisib is a selective PI3Kα inhibitor has demonstrated promise compensatory survival mechanism including as autophagy and frequently hinder its effectiveness because of increased apoptosis that elevated early and late apoptotic populations and elevated levels of cleaved PARP and caspase-3, CQ further inhibited tumor cell growth, viability, migration and colony formation more efficiently than alpelisib alone. (Kim, J., *et al.,* 2025)

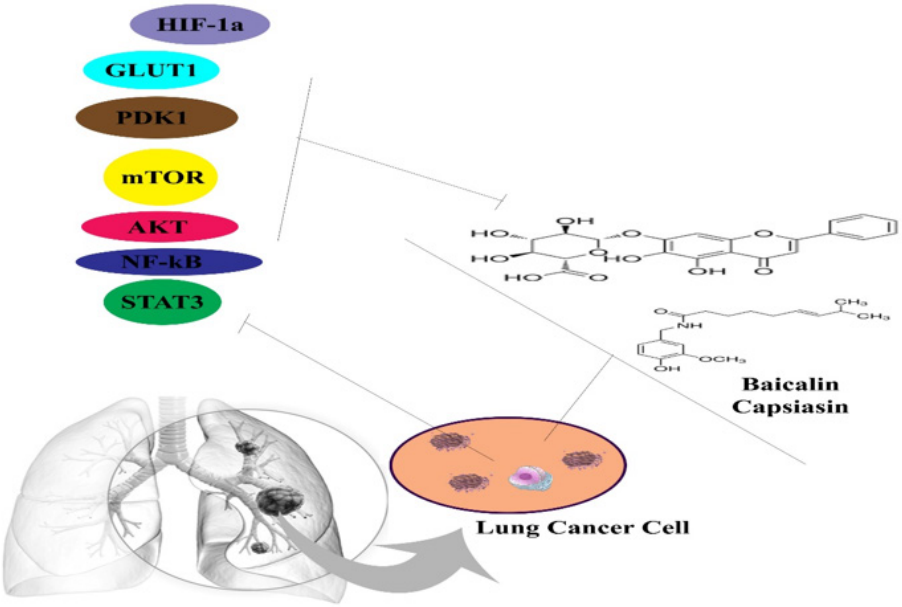
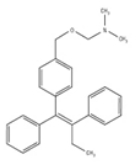
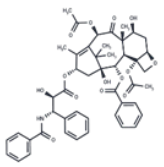
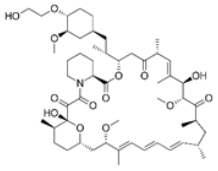
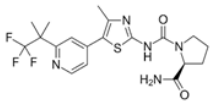
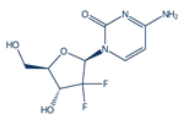
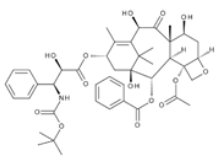
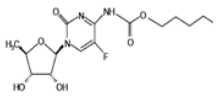
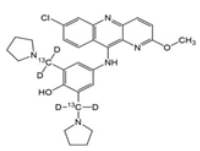
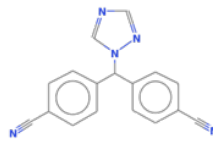
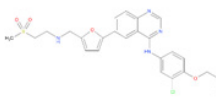
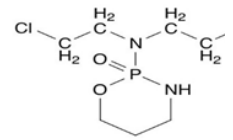
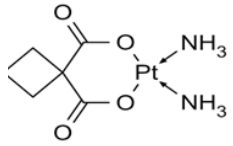
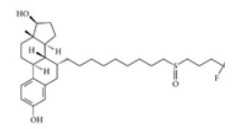
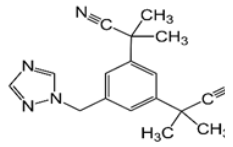
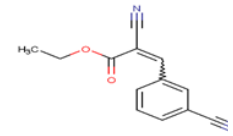
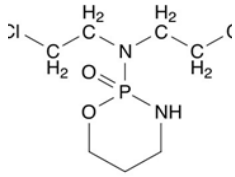


Figure 2: Natural product application and associated protein in cell signaling in Lung Cancer.

Table 2: Association of PI3K/AKT/PTEN/mTOR pathway in Lung cancer

Name of compound	Chemical structure	Model & Cancer type	Result	Reference
Tamoxifen		In vitro and Breast Cancer	Increase risk of endometrial cancer	(van Leeuwen, F. E., *et al.,* 1994) (Chang M. 2012)
Paclitaxel		In vivo & vitro and Breast Cancer	Drug improvement	(Sparano, J. A., *et al.,* 2008)
everolimus		In vitro and Lung Cancer	Increase antitumor activity of tumor	(Mauceri, H. J., *et al.,* 2012) (Tarhini, A., *et al.,* 2010)
Alpelisib		In vitro and in vivo Lung Cancer	Autophagy suppression	(Kim, J., *et al.,* 2025)
Gemcitabine		In vivo and in vitro pancreatic Cancer	Chemotherapeutic agent	(Heinemann V. *et al.* , 2000) (Amrutkar, M., *et al.,* 2017)
Docetaxel		In vivo and in vitro pancreatic Cancer	Antitumor agent	(Okada, S., *et al.,* 1999) (Liu, P., *et al.,* 2020)
capecitabine		In vivo and in vitro colorectal Cancer	Low-cost anticancer agent	(Hirsch, B. R., *et al.,* 2011) (Cassidy, J., *et al.,* 2022)
Pembrolizumab		In vivo and in vitro colorectal Cancer	Durable antitumor	(Diaz, L. A., *et al.,* 2022)
Letrozole		In vivo and in vitro ovarian Cancer	Aromatase inhibitor	(Bowman, A., *et al.,* 2002) (Heinzelmann-Schwarz, V., *et al.* , 2018)
Lapatinib		In vivo and in vitro ovarian Cancer	NRF2 inhibitor	(Kankia, I. H., *et al.,* 2017) (Liao, Q., *et al.,* 2020)

Cyclophosphamide		In vivo and in vitro cervical Cancer	Induce immunosuppress and oxidative stress	(Cui H., *et al.,* 2016) (Isono-Taniguchi, R., *et al.,* 2022)
carboplatin		In vivo and in vitro cervical Cancer	Anti-cancer drug than cisplatin	(Lorusso, D., *et al.,* 2014) (Nam, E. J., *et al.,* 2013) (Pectasides, D., *et al.* , 2009)
fulvestrant		In vivo and in vitro prostate Cancer	AR receptor inhibitor	(Bhattacharyya, R. S., *et al.,* 2006) (Dahut, M., *et al.* , 2023)
Anastrozole		In vivo and in vitro prostate Cancer	Aromatase inhibitor	(Boccardo, F., *et al.*, 2005) (Santen, R. J., *et al.,* 2001)
Atezolizumab		In vivo and in vitro Hepatocellular Carcinoma	Potent for liver transplantation	(Yao, R. R., *et al.,* 2025) (Ventura, I., *et al.,* 2024)
cyclophosphamide		In vivo and in vitro Hepatocellular Carcinoma	induced hepatotoxicity via modulating oxidative stress, apoptotic signals, and cytokine pathway	(Chen, L., *et al.,* 1996) (Sharata, E. E., *et al.,* 20250

Natural product and pharmaceutical application in pancreatic Cancer cell

According to the Lin J-H, *et al.* 2020 Gemcitabine has been shown that reception for advanced glycation end products resistance in PC. Apple peels, rosemary and thyme are natural sources of UA and a pentacyclic triterpenoid that has been shown to have anticancer properties. UA decrease cell viability, cell cycle arrest and ER stress in PC cell line which in turn caused dose dependent apoptosis and autophagy. This is shown in Figure 3. (Lin, J. H., *et al.,* 2020) Moreover, UA is known as anti-inflammatory and immunosuppressive drug that is derived from Chinese herbs and edible vegetables. It was discovered that apoptotic cascade involved both intrinsic and extrinsic mechanisms. Possible signaling pathways focus on c-JUN, PI3K/AKT/NF-kB pathway inactivation. Caspase 9 activation brought on by UA was partially reversed by JNK inhibitor. Akt inhibitor reduced viability of MIA-PaCa-2 cells but did not replicate effect of UA on caspase 8-9. (Li, J., *et al.,* 2012) However, In vitro findings demonstrated that GEM resistant PC cells had significantly higher levels of NF-kB/p65, RAGE, MDR1 than MIA-PaCa-2 cells. UA treatment downregulate RAGE, pP65 and MDR1 and these levels more decrease in combination of UA and GEM. (Li, Z. Y., *et al.,* 2021) Consequently, according to the Kanai M. *et al.* 2014 says that several molecular targets in preclinical model and 30 molecular targets have been found. NF-kB is believed to be one of the main targets of curcumin activity among these several molecules. Patients' plasma curcumin levels stay low even after consuming gram level dosage curcumin which is insufficient to produce anticancer effects of curcumin. (Kanai M. 2014) Additionally, In PC cells, curcumin modulate miRNA expression by upregulating miRNA-22 and downregulating miRNA -199a. Suppression of miRNA-22 either through curcumin treatment or transfection with miRNA-22 mimics in PxBC-3 cells and led to reduce expression of its target genes SP1 and ESR1. (Sun, M., *et al.,* 2008) Hence, 20-30% patients

gemcitabine treatment provided therapeutic benefits and alleviate symptoms were compared to 2% patients treated with 5-FU and single agent gemcitabine increased 1 year survival to 18%. Gemcitabine treatment is predicted to improved efficacy and combination treatment in 1 year survival rate increased 28%. (Heinemann V. *et al.,* 2000) Besides, although gemcitabine shows suboptimal clinical efficacy largely due to molecular mechanisms that restrict its cellular uptake, activation and overall effectiveness as well as rapid onset of chemoresistance within weeks of treatment and it remains a cornerstone therapy for PDAC across all stage of disease. (Amrutkar, M., *et al.,* 2017) Whereas, docetaxel exhibits encouraging anti-tumor action in PC and it was administered to 21 eligible patients. All patients MST of 118 days. Patients primary grade 3-4 toxicities were neutropenia, leukocytopenia, anemia, thrombocytopenia, nausea, anorexia. (Okada, S., *et al.,* 1999) Therefore, curcumin combined effects with gemcitabine or docetaxel on PC cell invasion, migration, apoptosis and proliferation were examined. It may cause apoptosis on PCs through PARP/caspase-3 signaling pathway and enhance pro-apoptotic effects of gemcitabine or docetaxel. (Liu, P., *et al.,* 2020)

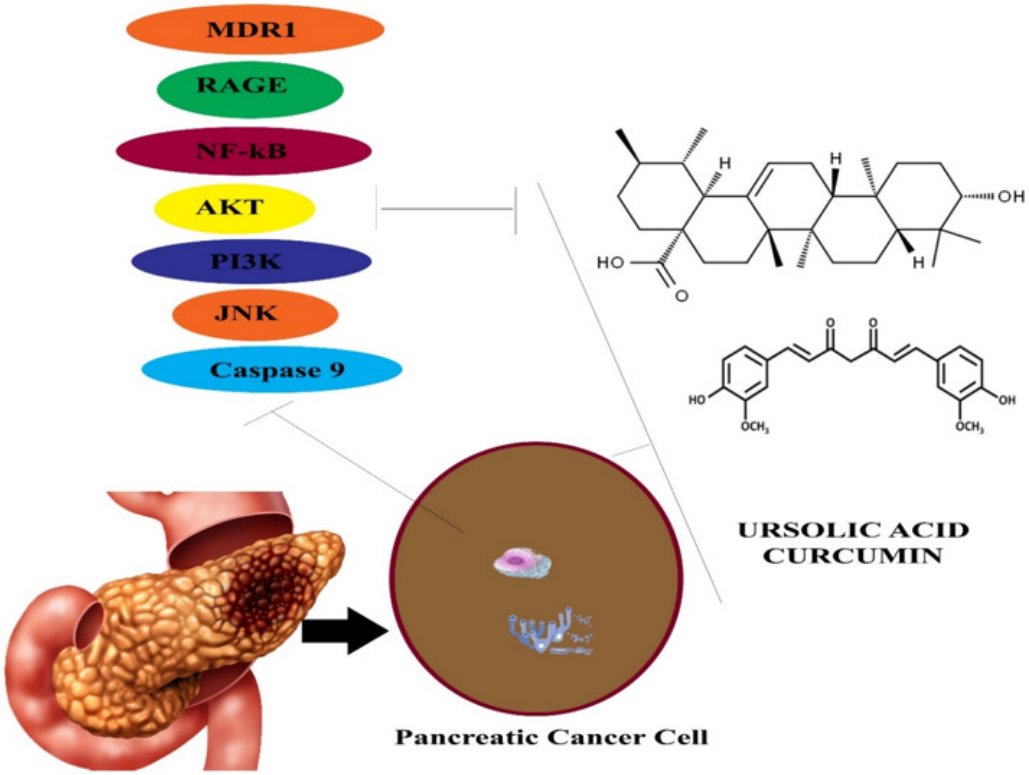


Figure3: Natural product application and associated protein in cell signaling in pancreatic cancer.

Natural product and pharmaceutical application in Colorectal Cancer cell

According to the Cristina P.R Xavier *et al.* 2013 says that colorectal carcinomas with P53 mutations are resistant to 5-FU and most often used chemotherapeutic medication for treatment of colorectal cancer. UA causes apoptosis without aid of caspase and amplifies effects of 5-FU linked to c-JUN. By causing LC3 and p62 levels with participation of JNK pathway and UA also influenced autophagy. This is shown in Figure 4, (Xavier, C. P., *et al.* , 2013) Moreover, UA in apoptotic mechanism in HCT116 and HT29 cells was clarified in relation to STAT3. UA caused a large amount of cytotoxicity and rise in TUNEL positive cells and sub G1 apoptotic part and cleavage of caspase 3 and PARP. UA inhibited STAT3 and reduced JAK2 and STAT3. (Kim, K., *et al.,* 2019) However, impact of UA in colorectal cells was evaluated with respect to proliferation, migration, clonogenicity, apoptosis, cell cycle regulation and Wnt/β-catenin signaling. In vivo UA models evaluation included tumor formation, apoptosis, cell cycle progression and activation of Wnt/β-catenin pathway. (Zhao, H., *et al.,* 2023) Therefore, according to the Jiang Z *et al.,* 2019, celastrol a key ingredient in root extract of traditional Chinese herb has been demonstrated to suppress TGF-β1/Smad signaling and preventing growth and metastasis of colorectal cancer cells. It can lower expression of TGFβ1, TGFβRI and TGFβRII. (Jiang, Z., *et al.,* 2019) Whereas, Celastrol inhibited migration and proliferation of CRC cells and PI3K/AKT pathway expression of MMP3 and MMP7 were likewise reduced by its therapy through Akt suppression than mTOR and induced AKT silencing. (Bufu, T., *et al.,* 2018) Wang S., *et al.,* 2023 says that celastrol has been proposed as a novel HDAC inhibitor and characterized as an epigenetic modulation of immune system with potential therapeutic applications in inflammatory and cancerous diseases. It may also reprogram macrophage polarization from M2 to M1 phenotype by altering colorectal tumor

microenvironment in both in vitro and in vivo models. (Wang, S., *et al.,* 2023) Additionally, US FDA authorized capecitabine for use in adjuvant settings in 2005 and use of oral version of drug has growing in popularity. It has been used for a variety of off-label purpose and neoadjuvant therapy of rectal cancer or metastatic colorectal cancer. (Hirsch, B. R., *et al.,* 2011) Besides, Capicitabin was associated with reduced incidences of diarrhea, stomatitis, nausea, alopecia and grade 3-4 neutropenia and demonstrating safer profile compared to 5-FU/leucovorin. Its treatment decreases number of cases of neutropenic fever/sepsis and hospitalizations. Its dose modification strategy decreased recurrence of important toxicities without sacrificing effectiveness. (Cassidy, J., *et al.,* 2022) Therefore, pembrolizumab has demonstrated a better progression free survival than chemotherapy and it exhibits mismatch repair deficiencies or microsatellite instability. It responsible for 2% common grade 3 or worse adverse events which included increased colitis, diarrhea and fatigue. (Diaz, L. A., *et al.,* 2022)

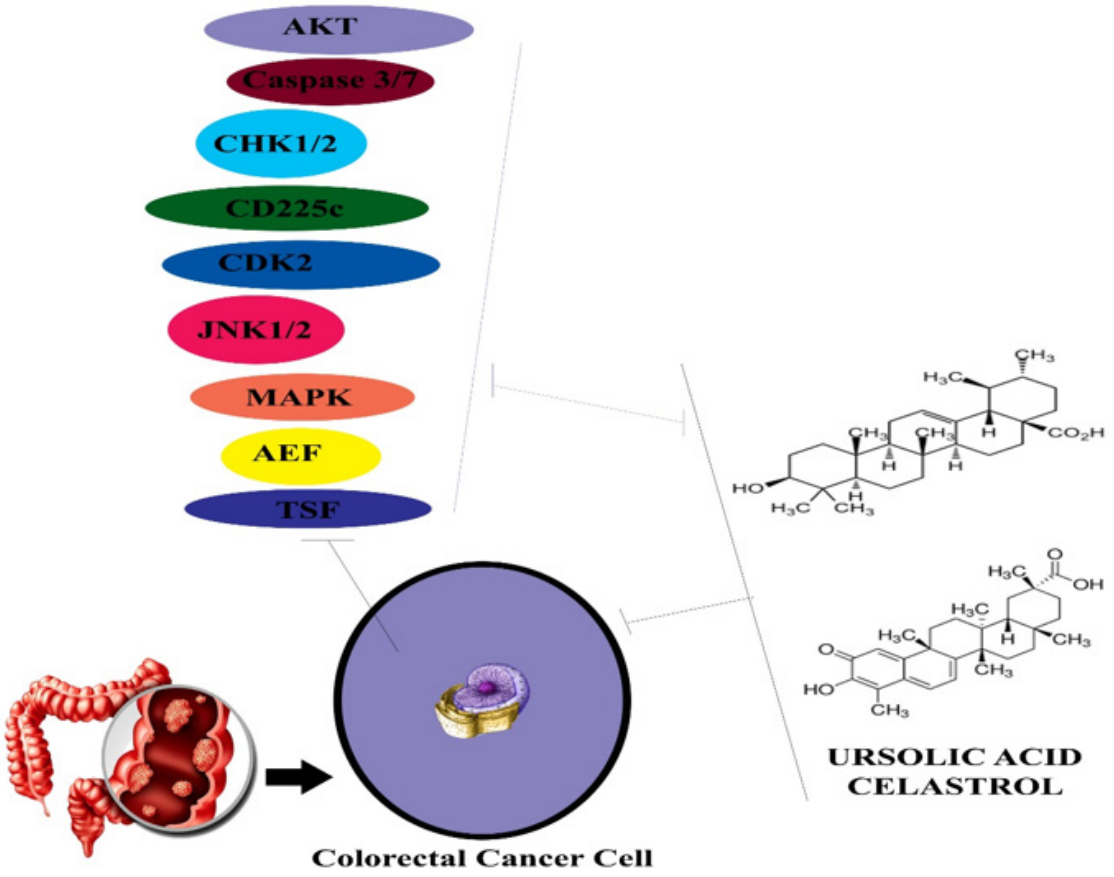


Figure4: Natural product application and associated protein in cell signaling in colorectal cancer.

Natural product and pharmaceutical application in Ovarian Cancer cell

According to the Lee J.S *et al.,* 2019, Honokoil has comparatively minimal toxicity and works against several cancer types and half maximal inhibitory concentration values of 48.71 μM for SKOV3 cells. It reduced viability through caspase 3,7,9 and cleavage of ADP polymerase and induce AMPK/rapamycin signaling pathway was necessary for apoptosis to occur. This is shown in Figure 5. (Lee, J. S., *et al.,* 2019) Additionally, Honokoil inhibited OVCA cell's ability to proliferate and survive, triggered apoptosis and reduced cell propensity to migrate and invade and downregulated YAP/TAZ pathway. YAP agonist stimulation reduced effects of Honokoil on OVCA cell biology to a certain extent. (Liu, F., *et al.,* 2024) Therefore, Honokoil preserved reproductive parameters in animals including fertility, GSI, PCNA, circulating E2 and AMH levels as well as number of primordial and preantral follicle. Its administration was associated with apoptosis, involving Pho-p5, Bax, cytochrome c, cleaved caspase3 and PARP with pyroptosis mediated by Pho-NF-kB, p65, NLRP3, caspase-1, IL-1β and IL-18 (Xin, L., *et al.,* 2023) Consequently, Green tea contains EGCG which treated on SKOV-3 cells and reduced cell viability and proliferation, apoptosis, DNA fragmentation. (Rao, S. D., *et al.,* 2010) However, EGCG were found in PubChem as potential human gene targets. JUN, FADD, NFKB1, Bcl-2, HIF1α and MMP proteins associated in ovarian cancer

cell treatment associated with DNA replication, cell cycle and cellular assembly signaling proteins. (Xinqiang, S., *et al.,* 2017) Accordingly, EGCG inhibited ovarian cancer cells development and caused apoptosis. EGCG stopped cell cycle SKOV-3 at G1 phase and associated with Bax, p21, Rb, cyclin D1, CDK4 and Bcl-XL. (Kim, Y. W., *et al.,* 2004) Whereas, 4 patients had a partial marker response while 14 more individual had a stable marker. ER and PR receptor levels were considerably greater in tumors from UICC stable group than in progressive disease group and stable disease was closely correlated with both of these. (Bowman, A., *et al.,* 2002) Furthermore, Original and matched recurrent HGSOC showed significant ER expression by IHC in platinum resistant subgroup. A noticeably longer recurrence free survival when taking letrozole versus was linked to future usage of letrozole as maintenance medication. (Heinzelmann-Schwarz, V., *et al.,* 2018) Moreover, Basal and inducible production of HER1 is regulated by NRF2 treated with activator tBHO produce HER1. tBHO cytotoxic effects of lapatinib or erlotinib were diminished and levels of p-NRF2, HER1 and Akt rose. (Kankia, I. H., *et al.,* 2017) Additionally, in vivo model EGFR receptor influences ovarian reserve and reproductive potential. Lapatinib high dose application proved that modest drop in body weight than lower dose. (Liao, Q., *et al.,* 2020)

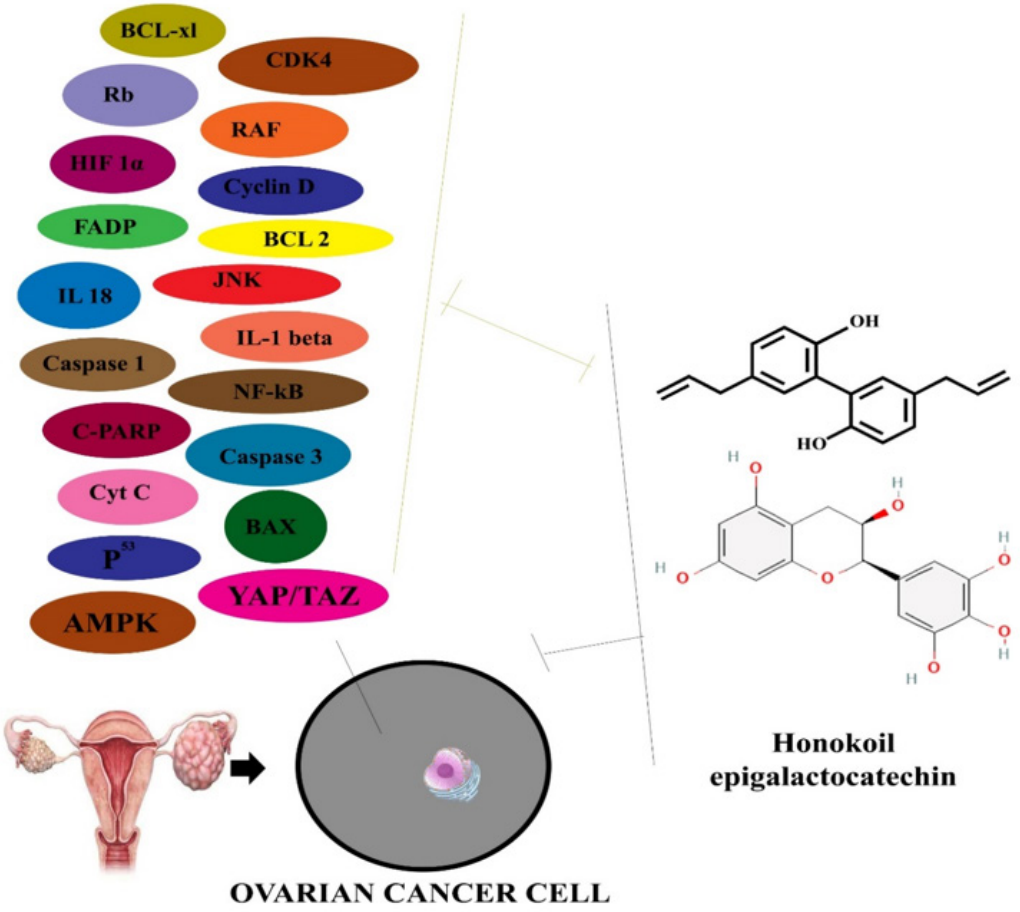


Figure5: Natural product application and associated protein in cell signaling in Ovarian cancer

Natural product and pharmaceutical application in Cervical Cancer cell

According to the Yanting *et al.* 2020 silibinin is the main natural flavonoid that has been used in cancer medicine and its application is linked to cell cycle arrest and induction of apoptosis in surviving cancer cells. SB reduced ROS levels, mtDNA copy number, mitochondrial membrane potential and ATP production. This is shown in Figure 6. (You, Y., *et al.,* 2020) However, it has been found that SB is a potent anti-cancer drug and it inhibit proliferation through mitogenic signaling pathways. HeLa cells treated with SB experienced a G2 arrest and a reduction of CDK that implicated in both G1 and G2 advancement. (Zhang, Y., *et al.,* 2012) Therefore, SB control HIF-1α suppression associated with dp-mTOR and its effector P70S6K, 4E-BP1. SB activated Akt and decrease VEGF in HeLa and Hep3B cells. (García-Maceira, P., *et al.,* 2009) Consequently, Curcumin and catechin metabolites lower VEGF expression and miR-210 and miR-21 down-regulation whereas miR-126 up-regulated. These metabolites generated by intestinal microbiota may offer a promising treatment option

for cervical cancer. (Khojaste, E., *et al.,* 2021) Whereas, CH component of green tea is widely used herbal remedies in the world and caused increase caspase 3,8,9 in multiple time and triggered apoptosis. (Al-Hazzani, A. A., *et al.,* 2011) Additionally, NPS can cause cancer cells to undergo apoptosis and increase production of ROS and alter potential of mitochondrial membrane. It can function as a carrier free drug delivery method that exhibits synergistic pharmaceutical effect and improves drug stability. (Gong H., *et al.,* 2024) Besides, CTX reduce oxidative stress and immunosuppression while DBLP alone inhibit development of tumor and CTX repressed tumor growth. Combination therapy inhibition was 9% than alone. (Cui H., *et al.,* 2016) Furthermore, 1 individual experienced platinum allergy and 4 patients experienced a recurrence within 6 months of platinum dosage and 6 patients experienced progressing disease after previous platinum-based chemotherapy. 1 with grade 2 and 1 with grade 3 both 2 or more non hematological toxicities and grade 3 or more. (Isono-Taniguchi, R., *et al.,* 2022) However, cddp based chemotherapy included 7 qualifying studies with total of 1181 subjects and objective RR was 49.3% while CBDCA was 48.5%. Median PFS for therapies based on CDDP and CBDCA was 5.9 months and 6.9 months. (Lorusso, D., *et al.,* 2014) Therefore, Eun Jin Nam *et al.,* 2013 proved that no statistically significance differences between carboplatin and historical cisplatin group in terms of survival was seen and both treatments got an average of 7.5 and 6.0 cycles. (Nam, E. J., *et al.,* 2013) Hence, comparison with lower performance status 0 or 1 has a higher RR except for myelotoxicity. 6% patients had febrile neutropenia while 44% of patients had neutropenia grade ¾. Drug application improved anemia 22% while thrombocytopenia affected 14% in grade 3 sensory neuropathy developed in 3 patients 6%. (Pectasides, D., *et al.,* 2009)

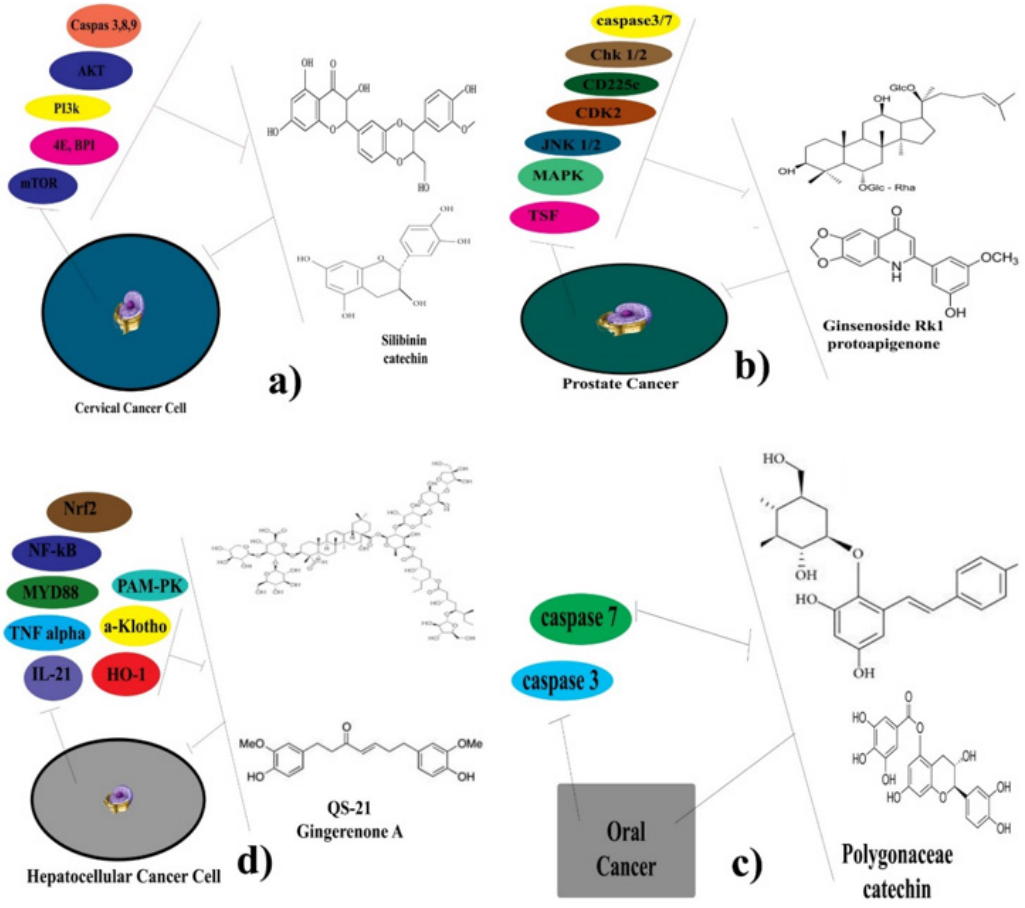


Figure 6: Natural product application and associated protein in cell signaling in a) Cervical Cancer, b) Prostate Cancer, c) Oral Cancer, d) Hepatocellular Cancer.

Natural product and pharmaceutical application in Prostate Cancer cell

According to the Park JY *et al.,* 2016 PC-3 cells treated with MG exhibited activity with a half maximal inhibitory concentration of 48 μg/ml. They proved that Ginseng is an herbal medicine and reduce proliferation of prostate cancer cells. This is shown in Figure 6. (Park, J. Y., *et al.,* 2016) However, BG is a novel form of processed ginseng have several anti-cancer properties. They separate in several molecular weight that were form 95% AEF, TSF and 8 chromatographic peaks significantly aided in black ginseng ability to prevent prostate cancer. (Zhang,

Y., *et al.,* 2024) Therefore, AR signaling inhibitor inhibit formation of tumor transcriptionally and expression of AR in athymic nude mice. GCK reduced expression levels of cell cycle regulators and hindered proliferation of PCs while E-cadherin elevated GCK-stimulated LNCaP and 22Rv1 cells and down-regulated MMP9 and vimentin. (Jiang, M., *et al.,* 2023) Hence, Protoapigenone stopping cancer cells at S and G2/M phases and triggering apoptosis, cell growth and activation of p38, MAPK and JAK1/2 acted as key mediators in protoapigenone induce cell death. Suppression of protein expression through use of inhibitors or siRNA reversed protoapigenone induce apoptosis through reducing quantity of cleaved caspase-3 by altering Cdk2 and p-Cdc25C, p38, MAPK. (Chang, H. L., *et al.,* 2008) Additionally, WYC02-9 may use ROS to cause DNA damage and apoptotic cell death. 3 PCs had cell proliferation suppressed by WYC02-9 and raised intracellular ROS production, DNA damage induction, treatment with WYC02-9 activated ATM-p53-H2AX pathway and checkpoint signal Chk1/2 while also increasing proportion of cells in S and G2/M phase of cell cycle. (Chen, H. M., *et al.,* 2011) However, In PC3 cells treated with biseugenol B and mitochondrial membrane potential was modulated through Bcl-2 downregulation and Bax upregulation which subsequently triggered cytochrome c from mitochondria into cytoplasm. Apoptosis was altered as a result of cyt C release activating caspase-9 which turn activated caspase 3/7 with cleaved p-ADP ribose indicated engagement of intrinsic apoptosis pathway and increase caspase-8 indicated involvement of extrinsic apoptosis mechanism. (Abbaspour Babaei, M., *et al.,* 2017) Consequently, PC treatment approach particularly HR or AR independent PC would be to target down regulation of AR when AR promoter luciferease reporter plasmid was introduce into LNCaP cells via transfection. ICI reduced its activity indicating that AR gene was directly suppressed. (Bhattacharyya, R. S., *et al.,* 2006) Therefore, Dahut M *et al.,* 2023 try to say that PC could have treated enzalutamide and its treatment could inhibit carcinoma cells develop mesenchymal traits with or without loss of traditional epithelial characteristics is one of the processes underlying tumor resistance to different treatments. (Dahut, M., *et al.,* 2023) Besides, 73% of patients bicalutamide group and 10% bicalutamide-tamoxifen and 51% bicalutamide-anastrozole group development of gynecomastia. According to this treatment PSA level dropped 97% and 86% and 37%, 35% and 69% of patients experienced adverse events. (Boccardo, F., *et al.,* 2005) Although, Estrogens may have effect on PC and its application experienced lower PSA levels and only 2 patients reported it's an analgesic medicine that slight relief their bone pain. (Santen, R. J., *et al.,* 2001)

Natural product and pharmaceutical application in Oral Cancer cell

According to the Yen CY *et al.,* 2012 they published that GTN is a bioactive styryl lactone have strong tumorigenesis properties. Ca9-22 OSCC cells treatment reduced cell proliferation in both concentration and time dependent way. They observed that GTN treatment caused a marked and concentration dependent increase in Sub G1 cell population and Annexin V positive cells and indicating cell cycle arrest and induction of apoptosis in Ca9-22 cells. (Yen, C. Y., *et al.,* 2012) However, apoptosis mechanisms of GTN was assayed by mitochondrial potential assay and cyt C ELISA. Release of mitochondrial cyt c into cytosol was made easier by depolarization of transmembrane potential of mitochondria and they analyzed initiator caspase 9 and executioner caspase-3/7 by caspase tests. (Li, L. K., *et al.,* 2016) Therefore, according to Chinese medicine, polygonum cuspidatum exhibits diverse bioactivities including anti-inflammatory, anti-cancer, anti-angiogenic, anti-HIV, anti-HBsAg, anti-microbial and neuroprotective effects. AO, MDC, LysoTracker Red labeling in CAR cells and it was discovered that PCE induced autophagy. (Wang, Y. L., *et al.,* 2019) Moreover, In vivo analysis catechin and turmeric induce tumor and suppressed gross tumor yield and burden more successfully than when using either substance alone. (Azuine, M. A., *et al.*, 1994) Consequently, placebo treated patients compared to 22 out of 75 with erlotinib treated patients. 66 patients without prior OC and HR for OCFS was 0.6 and 1.9 in 84 patients with prior OC and 1.2 in ITT sample. (William, W. N., *et al.,* 2014) whereas, 3-year CSF rate was 74% in patients receiving placebo and compared to 70.5% in those treated with erlotinib. LOH positive had substantially lower 3-year CFS than LOH negative groups. Higher EGFR gene copy number was associated with decreased CFS and LOH positive status. This result of synthetic application proved that natural products have more authentic and combination therapy could improve these strategies.

Natural product and pharmaceutical application in Hepatocellular Carcinoma

According to the Wang Z *et al.* 2025, Use of CpG 1018S with QS-21 raised number of HBV specific CD4+ and CD8+ T cells lowered TIM-3 and TIGIT levels and improved dendritic cell activation, maturation and antigen presenting function. In vivo treatment enhanced secretion of IL-21 and TNF-α and restored T cell polyfunctionality. (Wang, Z., *et al.,* 2025) However, Yonger chen *et al.* found that mice treated 4% DSS and effect of GA examined in liver tissues. LPS was used to generate HepG2 cells in order to observe how GA affected ferroptosis. They determined Fe2+, MDA, SOD, AST and ALT and GA increased expression of Gpx4 in DSS induced animal and reduced ferroptosis in DSS induced liver damage. (Chen, Y., *et al.,* 2022) Therefore, Gingeron A and 6-shogaol both killed senescent cells but proliferating cells were unaffected. Gingeron A is the main component of giger extract and it was strongly proved that senescent cells were strongly destroyed by this natural element. (Moaddel, R., *et al.,* 2022) Hence, atezolizumab therapy associated with 8 LT recipients with recurrent PLC and 2 ICC and

6 HC. They observed 3 therapy cycles and showed that Liver rejection was linked to LT and recurrence. (Yao, R. R., *et al.,* 2025) Consequently, Patients with advanced hepatocellular carcinoma responded well to combination therapy consisting of bevacizumab and atezolizumab plus sorafenib. Its treatment helps to identify important markers AFP, TGF-β. (Ventura, I., *et al.,* 2024) Moreover, CPA and IFA were extremely cytotoxic to MCF-7 transfectant that expressed β galactosidase. CYP2B1 inhibitor metyrapone could reduce this cytotoxicity and stopped G2-M phase. (Chen, L., *et al.,* 1996) Additionally, ROS functions as damage associated molecular patterns and quickly activate TLR4/MYD88/NF-kB and NLRP3 inflammasome signaling cascades are produced in response to CPA. CPA application reduces oxidative stress in liver dysfunction and also associated with Nrf2/HO-1, α-klotho and P-AMPK. (Sharata, E. E., *et al.,* 2025)

Discussion

Multiple biological processes involved in carcinogenesis. Bioactive compounds derived from plants, microorganisms, and marine sources can exert antioxidant, anti-inflammatory, and immunomodulatory effects that help reduce cancer risk. Several natural products, including curcumin, resveratrol, epigallocatechin gallate (EGCG), sulforaphane, lycopene, genistein, and quercetin, have demonstrated promising anticancer activities in preclinical and clinical studies. These compounds can regulate key signaling pathways associated with cell proliferation, apoptosis, angiogenesis, and metastasis while also protecting cells from oxidative stress and DNA damage. Furthermore, emerging evidence suggests that natural products may influence the expression of non-coding RNAs, including miRNAs and lncRNAs, thereby contributing to the regulation of cancer-related genes and metabolic pathways. Although the preventive potential of natural products is promising, further studies are required to establish their efficacy, optimal dosage, bioavailability, and long-term safety before they can be fully integrated into cancer prevention strategies. Pharmaceutical drugs exert anticancer effects through diverse mechanisms that target key processes involved in tumor initiation, progression, and metastasis. Conventional chemotherapeutic agents, such as alkylating agents, antimetabolites, and microtubule inhibitors, primarily act by disrupting DNA replication, cell division, and cellular metabolism, leading to cancer cell death. In contrast, targeted therapies are designed to inhibit specific molecular abnormalities that drive tumor growth, including dysregulated signaling pathways, growth factor receptors, and oncogenic proteins. For example, tyrosine kinase inhibitors and monoclonal antibodies selectively block aberrant signaling networks involved in cell proliferation, survival, angiogenesis, and metastasis. Immunotherapeutic agents enhance the body's immune response against cancer cells by targeting immune checkpoints or stimulating immune effector mechanisms. The effectiveness of these drugs varies among different cancer types due to differences in genetic mutations, molecular characteristics, tumor microenvironment, and drug resistance mechanisms. Advances in precision medicine have further enabled the development of personalized therapeutic strategies based on the molecular profile of individual tumors, thereby improving treatment efficacy and patient outcomes. Natural products have gained significant interest in cancer prevention and treatment due to several potential advantages over conventional pharmaceutical drugs. Many natural compounds exhibit multitargeted mechanisms of action, enabling them to simultaneously modulate multiple signaling pathways involved in cancer development, including inflammation, oxidative stress, apoptosis, angiogenesis, and metastasis. In contrast, many targeted pharmaceutical agents are designed to act on specific molecular targets, which may contribute to the development of drug resistance over time. Natural products are also often associated with lower toxicity and fewer adverse effects when consumed at appropriate doses, potentially improving patient tolerance and quality of life. Furthermore, numerous clinically approved anticancer drugs, such as paclitaxel, vincristine, and camptothecin derivatives, were originally derived from natural sources, highlighting the importance of natural compounds in drug discovery. However, natural products also face challenges, including poor bioavailability, variable composition, limited potency, and insufficient clinical validation. Therefore, rather than replacing pharmaceutical drugs, natural products are increasingly being investigated as complementary or adjunctive therapies that may enhance therapeutic efficacy, reduce side effects, and help overcome drug resistance in different types of cancer. Natural products have emerged as promising adjuncts to conventional cancer therapies due to their ability to modulate multiple molecular pathways involved in tumor progression, metastasis, and drug resistance. Compounds such as curcumin, genistein, apigenin, baicalin, capsaicin, ursolic acid, celastrol, honokiol, epigallocatechin gallate (EGCG), silibinin, catechins, ginsenoside Rk1, protoapigenone, goniothalamin, QS-21, and gingerenone A have demonstrated anticancer activities in breast, lung, pancreatic, colorectal, ovarian, and prostate cancers. These natural agents exert their effects through the regulation of key signaling pathways, including PI3K/Akt/mTOR, MAPK/ERK, Wnt/β-catenin, NF-ϰB, JAK/STAT, TGF-β, and EGFR, leading to inhibition of cell proliferation, induction of apoptosis, suppression of angiogenesis, and reduction of metastatic potential. In breast cancer, curcumin, genistein, and honokiol have been shown to enhance sensitivity to chemotherapeutic agents such as doxorubicin, paclitaxel, and tamoxifen by suppressing survival pathways and reversing drug resistance. In lung cancer, EGCG, baicalin, celastrol, and silibinin may improve the efficacy of cisplatin, gefitinib, and erlotinib through inhibition of EGFR signaling and oxidative stress. In pancreatic cancer, curcumin, ursolic acid, and capsaicin have demonstrated synergistic effects with gemcitabine by targeting NF-ϰB and PI3K/Akt-

mediated resistance mechanisms. In colorectal cancer, curcumin, apigenin, catechins, and goniothalamin have been reported to enhance the antitumor activity of 5-fluorouracil, oxaliplatin, and irinotecan while modulating Wnt/β-catenin signaling and cancer stem cell populations. In ovarian cancer, celastrol, honokiol, baicalin, and EGCG may potentiate the effects of platinum-based chemotherapy and paclitaxel by promoting apoptosis and reducing chemoresistance. In prostate cancer, genistein, silibinin, ursolic acid, and ginsenosides have shown synergistic interactions with docetaxel, enzalutamide, and androgen-deprivation therapies through modulation of androgen receptor signaling, inflammation, and cell-cycle regulation. Furthermore, accumulating evidence suggests that these natural compounds can influence the expression of non-coding RNAs, including miRNAs and lncRNAs, thereby regulating oncogenic and tumor-suppressive pathways involved in cancer progression and therapeutic response. Their ability to target multiple hallmarks of cancer while potentially reducing toxicity makes them attractive candidates for combination therapy. Nevertheless, challenges related to bioavailability, pharmacokinetics, optimal dosing, and clinical validation remain significant barriers to their widespread clinical application. Future studies and well-designed clinical trials are needed to establish the safety, efficacy, and therapeutic value of combining natural products with conventional pharmaceutical drugs across different cancer types.

Future Perspectives

Overall past paradigms have evolved to highlight a renewed and expanding role for natural products in pharmaceutical industry. Several complex challenges remain to be addressed in order to accelerate and improve success of natural product-based drug discovery. First, how can optimal experimental model be selected to thoroughly characterized anticancer activity of natural products? Given the diverse character of cancer, it is widely recognized that a compound showing no activity in one model may still be effective in others. Furthermore, anticancer effects of natural products may arise not only from direct tumor cell targeting but also from modulation of tumor microenvironment or systemic effects within host. (Sobuj, D. R., *et al.,* 202 & Jaman. M. S., *et al.,* 2025) This complexity underscores challenges of choosing suitable models to accurately capture therapeutic potential of candidate compounds. Seconds, how can direct targets and mechanisms of action of natural compounds be efficiently identified? Effective and targeted cancer therapies require a comprehensive grasp of mechanisms by which this compounds act. Current methodologies, however, remain technically challenging and often demonstrate low efficiency. Additionally, since natural products frequently act through multiple, interconnected mechanisms, strategies are needed to capture a complete and integrated view of their modes of action. Third, how can development of promising natural compounds into marketable drugs be accelerated? A major challenge for many bioactive natural products lies in large scale production to meet manufacturing demands which often limits their translation from promising candidates to clinical application. (Sobuj. D. R., *et al.,* 2025) Continued advancements in cancer therapy concepts coupled with adoption of innovative technologies will be essential to address these challenges and streamline drug development process and enhance likelihood of clinical success.

CONCLUSION

Main finding of this review underscore valuable contribution of natural products sourced from medicinal plants, marine organisms and micro-organisms to discovery of novel anticancer compounds. These agents may provide effective strategies to address growing challenge of multidrug resistance in cancer therapy. Even so, world's vast natural diversity continues to offer untapped potential. As technology progresses, improved screening methods will help identify new prototypes of bioactive compounds more rapidly and enhancing efficient exploration of natural sources. By modulating essential pathways like cell growth, differentiation, apoptosis, new vessel formation, metastatic dissemination and they shape cancer initiation and progression. Moreover, these natural compounds tend to affect cancer cells and tumors more strongly than normal cells. In addition, reports of natural compounds administered in conjunction with synthetic chemotherapeutic agents reveal an appealing prospect for developing combination treatment strategies. The application of natural products in modulating cancer cell responses often demonstrates advantages over conventional synthetic drugs, highlighting their unique mechanisms, multi-target effects and generally lower toxicity. This underscores critical importance of understanding natural products and their biological sources, as such knowledge can inform development of more effective, safer and innovative anticancer therapies. By exploring rich chemical diversity of nature and researchers can identify novel compounds that not only complement existing treatments but also provide solutions to challenges such as drug resistance and paving the way for more personalized and sustainable cancer management strategies.

Data Availability

Not Applicable

Abbreviations

LC, Lung Cancer; BC, Breast Cancer; PC, Prostate Cancer; TNBC, Tripple Negative Breast Cancer; ER, Estrogen Receptor; PR, Progesterone Receptor; IHC, Immunohistochemistry; OS, Overall Survival; CTC, Circulating tumor Cell; ctDNA, Circulating tumor DNA; CIN, Chromosomal Instability; CCND1, Cyclin D1; CK18, Cytokeratin 18; BLT, Basal to luminal transition; PDA, Poorly Differentiated Adenocarcinoma; TGFβ, Transforming Growth Factor beta; TIL, Tumor Infiltrating Lymphocytes; IntClus, Integrative Clustering;

DWI, Diffusion weighted imaging; MRI, Magnetic Resonance Imaging; Invasive Ductal Carcinoma; CGH, Comparative Genomic Hybridization; FISH, Fluorescence in situ Hybridization; TC, Tubular Carcinoma; RB, retinoblastoma; NST, Non special type Carcinomas; CVN, Copy Number Variations; ROS, Reactive oxygen species; SSBs, Single stranded DNA breaks; DSBs, Double stranded DNA breaks; RNS, Reactive nitrogen species; GM-CSF, granulocyte macrophage colony stimulating factor; ATM, Ataxia Telangiectasia Mutated; ATR, Ataxia Telangiectasia and Rad3 related; DNA PK, DNA activated protein kinase; Chk, Checkpoint kinase; Cdk1, Cyclin-dependent kinase; CDC, cell division control protein; mTOR, mammalian target of rapamycin; PI3K, Phosphoinisitide 3-kinases; Apaf-1, apoptotic protease activating factor 1; AIF, apoptosis inducing factor 1; NBS1, Nijmegen breakage syndrome 1; NHEJ, non-homologues end joining repair; HR, homologous recombination; DDR, DNA Damage response; GSTA1, glutathione S-transferase A1; HER2/3, human telomerase reverse transcriptase; JNK, jun N-terminal kinase; APE1, apurinic endonuclease 1; EGFR, Epidermal growth Factor receptor; RTKs, receptor tyrosine kinases; COX-2, cyclooxygenase-2; CYP19/1A1/1A2, cytochrome P45019/1A1/1A2; DNMT1/3a, DNA(cytosine-5)-methyltransferase 1/3a; EGFR, epidermal growth factor; FoxM1, forkhead box M1; AKT, protein kinase B; PTEN, phosphatase and tensin homolog; IL, interleukin; LC3, microtubule-associated protein light chain 3; MMP-2, matrix metalloproteinase-2; CCR6, C-C chemoattractant cytokine Receptor 6; ATF2, Activating transcription Factor2; PIP2/3, Phosphatidylinositol 4,5-bosphophate 2/3; VGFA, Vascular Endothelial Growth FactorA; HIF1, Hypoxia Inducible Factor-1; LNM, Lymph Node Metastasis; CDH1, Cadherin Protein-1; RSU1, Ras suppressor-1; PINCH1, protein containing Five LIM Domains; UTR, 3-Untranslated region; MDM2, Mouse Double Minute 2 Homolog; NAC, N-acetyl cysteine; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2 associated X; Bad, Bcl-2 associated agonist of cell death; CDK4, cyclin dependent kinase 4; CDC2, cell division cycle2; KLF16, kruppel Like Factor-16; PARP, poly ADP ribose polymerase; 4EBP1, Eukaryotic translation Initiation Factor 4E-binding Protein 1 Phosphorylated; PIK3CA, Phosphatidylinositol-4-5, Bisphosphate 3-kinase Catalytic subunit Alpha; PINK1, PTEN Induced kinase-1; CXCR4, C-X-C chemokine receptor type 4; SOD2, Superoxide Dismutase 2 mitochondrial; HUVEC, Human Umbilical vein Endothelial cells; STX3, Shiga Toxin 3; MFN2, Mitofusin-2; VGFR-2 Vascular endothelial growth factor-2; STAT3, signal transducer and activator of transcription 3; TrxR1, thioredoxin reductase 1; DNA, Deoxyribose nucleic acid; MAPK, mitogen-activated protein kinases; NQO1, NADPH quinone dehydrogenase 1; RNA, Ribo nucleic acid; Human lymphocyte; LDH, Lactate Dehydrogenase; GSH, non-enzymatic antioxidant, SOD, enzymatic antioxidants; Mcl-1, Myeloid cell leukemia; FLIP, c-FLICE inhibitory protein; Forkhead box O3, transcription factor FOXO3a; EMT, epithelial mesenchymal transition; Glut1, glucose transpoter 1; GSK3, glycogen synthase kinase 3; CSCs, Cancer stem cells; TEAD, Transcriptional Enhanced Associate Domain; EBV, Epstein Barr Virus; NSCLC, non-small cell lung cancer; NF-kB, Nuclear Factor-kB; LCIS, ceRNA, endogenous RNA; MBC, Medullary carcinoma; ERK, Extra cellular single regulated protein kinase; HDACi, DNA methylation inhibitor; HPV, Human papillomas Virus; P-MVs, platelet-secreted microvesicles; SLFN5, Human Schlafen 5; mPTP, hirsutine-mediated mitochondrial permeability transition pore; p-PDK1, phosphor-3-phosphoinositide dependent protein kinase 1; p-AKT, Phosphor-serine/threonine-protein kinase; ISL, Isoliquiritigenin; ACY1, Aminoacylase 1; Pec, Pectolinarigenin; STMN1, Stathmin; HGF, hepatocyte growth factor, Apigenin, APG; CAP, Capsaicin, 8-methyl-N-geranyl-6-nonamide; IL-1β, Interleukin-1β; TNF-α, Tumor necrosis factor-α; HMGB1, high-mobility group protein B1; UA, Ursolic acid. Cu, Curcumin.

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