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DRUG REPURPOSING: A NEW ERA OF CANCER THERAPY USING TRADITIONAL DRUGS

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ABSTRACT
Drug repositioning has gained popularity as a strategy for finding new uses for available, commercially available, or unapproved medications to treat a targeted ailment. Due to the original drug's easily available efficacy and safety profile and regulatory bodies' approval, drug repositioning lowers overall development costs and risk assessment. One of these fields is drug repurposing, which is used in cancer. Cancer is a disease of altered signaling and metabolism, causing uncontrolled division and survival of transformed cells. One of the traditional drugs is disulfiram, which is usually used as an alcoholic-aversive agent. Recent cancer research showed that it can be used in non-small-cell lung cancer by oxidative stress by yielding reactive oxygen species. Another example is gemcitabine, which is used as an antiviral now, and by drug repurposing, it can be used as an antipancreatic cancer drug. Other drugs such as glipizide, interferon, nelfinavir, niclosamide, warfarin, thalidomide, auranofin, ferroquine, celecoxib, sildenafil, digoxin, valproic acid, statins, itraconazole, and retinoic acid will be mentioned later.

KEYWORDS: Drug repurposing, cancer, Warfarin, Gipizide, Thalidomide.

INTRODUCTION
Drug repurposing (DR) is a strategy for identifying novel therapeutic uses for existing drugs that significantly differ from their intended use and applications. As a result, DR aims to find novel applications for existing (well-known) drugs. Because it begins with compounds—often FDA-approved medications with well-characterized pharmacology and safety profiles—the area of DR is expanding quickly.

In the 1920s, an unintentional discovery led to the first instance of pharmacological repositioning. Further methods for accelerating the process of drug repositioning were developed after almost a century of development. Sildenafil, minoxidil, aspirin, valproic acid, methotrexate, and other well-known medications developed using the DR technique are some of the most effective and well-known. For example, sildenafil was developed for the treatment of hypertension and angina pectoris and is used for erectile dysfunction (Mithun, 2020).

Table: 1Drugs

Drugs	Original use	Repurposing use	References
Disulfiram	Alcohol-aversive agent	Non-small-cell lung cancer	J. Mutschler (2016), but in 2019, Elmira Ekinci Chen Lu (2021) Ying Xu (2021)
Glipizide	Oral hypoglycemic agent	Prostatic cancer	R. N. Borden (1979) Cuiling Q. (2016)
Interferon	Antiviral	Anticancer	David Goldstein (1988) Kartaie (2020) M. RaZa (2011)
Nelfinavir	Antiviral	Anticancer	Anne (2000) David (2017) (Mahbuba,2020)
Niclosamide	To treat tapeworm	Anticancer	Wei Chen (2018)

	infestations		
Propranolol	Antihypertensive	Infantile hemangioma	Abdulrahman (2017) Sabrina (2020) Ana I. (2021) Joanne (2021) James (2021)
Warfarin	Anticoagulant	Anticancer	J. D. Horton (1999) Anna (2019) Rita (2021)
Gemcitabine	Antiviral	Pancreatic cancer	Kyungjin Lee (2017) T. Namba (2015) Bishal (2017)
Thalidomide	Sedative hypnotic	Multiple myeloma	G. Gasprini (2001) Ramon (2006) T.M. Moehler (2006)
Auranofin	Rheumatoid arthritis	Anticancer	C. Fan (2014) Xin (2014) Christine (2015) C. K. Mirabelli (1985) Christine (2007) Warren (2014)
Ferroquine	Antimalarial	Anticancer	Christophe (2006) Waseem (2015) Avelino (2015)
Celecoxib	Anti-inflammatory	Breast cancer	Paul (2012) Emanuela (2011) Johanna (2010) Bin (2020) D. Lu (2012)
Digoxin	Heart failure	Lung cancer	Marie (2021) Sheng-Yi Lin (2015) Yingying Wang (2020)
Valproic acid	Anticonvulsant	Inhibits histone deacetylases (anticancer)	Mohamed (2019) Masum (2020) J. Hrebackova (2010)
Statins	Antihypercholesterolemia	Anticancer	Michael (2004) Kelvin (2003) Nirmala (2021) David (2002)
Itraconazole	Antifungal	Ovarian cancer	G. E. Piérard (2000) Rachel (2017)
Retinoic acid	Acne	Breast cancer	Mei-Chih Chen (2014) Hua S. (2009)

Disulfiram (DSF) holds a unique place in the pharmacological relapse prevention of alcohol dependency as an alcohol-aversive drug. Contrary to anticraving medications, disulfiram functions by inducing an unpleasant reaction when paired with alcohol instead of altering the neurological ways of addiction (Mutschler, J, 2016).

Yet in 2019, Elmira Ekinci showed that disulfiram had been linked to several anticancer processes, including producing reactive oxygen species, activating the mitogen-activated protein kinase pathway, and suppressing the ubiquitin-proteasome system, and induction of oxidative stress. Disulfiram also inhibits the P-glycoprotein multidrug efflux pump and the activation of NF-kB, both of which are critical in the development of drug resistance, which helps reverse the resistance to chemotherapy medicines. Disulfiram's metal chelating abilities and capacity to inactivate Cu/Zn superoxide dismutase and matrix metalloproteinases have also been reported to inhibit angiogenesis. The DNA repair protein O6-methylguanine DNA methyltransferase is widely expressed in brain tumors, and the proteasomes, DNA topoisomerases, DNA methyltransferase, and glutathione S-transferase P1 have all been shown to be inhibited by disulfiram. DSF has the ability to target tumors, according to Chen Lu (2021). It has a successful breakthrough in treating non-small-cell lung cancer (NSCLC) and glioblastoma. Its antitumor effect has been reported in many preclinical studies and recently on seven types of cancer in humans: NSCLC, liver cancer,

breast cancer, prostate cancer, pancreatic cancer, glioblastoma (GBM), and melanoma (GBM).

Glipizide is a second-generation oral hypoglycemic drug with the same potency as glibenclamide. It is entirely absorbed after oral administration and acts quickly (R.N. Brogden, 1979) and has been shown to inhibit the growth and spread of prostate cancer (PC). Angiogenesis is closely linked to the emergence of several types of human cancer. Intriguingly, the MTT assay and flow cytometry analysis show that glipizide dramatically decreases microvessel density in PC tumor tissues but does not prevent prostate cancer cell proliferation. Moreover, via controlling the HMGIY/angiopoietin-1 signaling pathway, glipizide prevents human umbilical vein endothelial cells from forming tubular structures. Together, these findings show that glipizide can be repurposed as a robust therapy by focusing on tumor-induced angiogenesis to treat PC.

The antiviral agent interferon (IFN) was found during research on the interference of viruses. Inducible cytokines are members of the multigene IFN family. They have antiviral properties. Rita recently discovered in 2021 that it can be utilized in cases of melanoma, multiple myeloma, hairy cell leukemia, carcinoid tumors, and follicular lymphoma. Patients with certain types of cancer receive extensive treatment with interferons (IFNs) and pleiotropic cytokines of type I IFNs, as well as those with viral illness. IFN-alpha may influence tumor cell activities in a variety of ways. These cytokines can also encourage host immune cells to differentiate and become more active. Early research using mouse tumor models demonstrated the significance of host immune pathways in developing a persistent anticancer response following IFN-alpha/beta treatment of the mice. IFN-alpha has since been shown to have additional immunomodulatory effects, including actions on T-cells and dendritic cells, which may result in IFN-induced antitumor immunity, as various studies have noted (Maria, 2007). The most effective treatment for symptomatic nodular lymphoma and hairy cell leukemia is probably interferon. Papillomas and condylomas can be successfully treated with interferon, and its usage as a local agent is likely to grow. For the following few years, it is unlikely that the list of responsive tumors to alpha interferon or other subtypes as a single drug would significantly grow. Nonetheless, there are notable responses in both renal carcinoma and melanoma. It is crucial to be aware of the potential for both a delayed and an intensifying response with treatment duration; consequently, treatment with interferon may necessitate longer treatment times than with conventional chemotherapy. Interferon should also be used as a second-line treatment because prior chemotherapy failure does not predict response to interferon. The "fourth arm" of cancer therapy, however, definitely involves using such biological agents in combination with other medicines. With the interferons, there appears to be a simple option. They can be administered at pharmacological levels. Their antiproliferative impact is probably caused by stimulating certain enzymes that have a cytostatic effect in a small but therapeutically significant subset of malignancies. Alternatively, treatment with interferon may necessitate longer treatment times than with conventional chemotherapy. Interferons can also be utilized at physiological levels, which are more likely to have immunological and cell membrane effects, such as stimulating NK cells and Fc-receptor and tumor-antigen expression. Due to this, cytotoxic medicines may require high doses, but other biological agents, such as monoclonal antibodies or LAK cells, may be combined at much lower levels and still produce the desired results. It will be crucial to determine the best biological dosages of interferons over the coming years so that we can optimize their therapeutic value and prevent the misconception that they are only cytotoxic (David Goldstein, 1988). Dormancy, a stage in which cancer cells persist before overt lesion formation, is responsible for the latency associated with bone metastases emergence in castrate-resistant PC. We have revealed the crucial involvement of tumor-intrinsic immune signaling in maintaining cancer cell dormancy using single-cell transcriptomics and ex vivo profiling. It has been shown that growing PC cells in the bone experience a decrease in tumor-intrinsic type I IFN. In order to accelerate the spread of cancer, this loss reduces the tumor's immunogenicity, treatment response, and bone cell activation. Histone deacetylase HDAC inhibition improved long-term antitumor immunity and inhibited cancer growth in bone via restoring tumor-intrinsic IFN signaling. Important findings, such as lack of tumor-intrinsic IFN signaling and immunogenicity, were validated in patients. bone metastases compared to primary tumors (Kartaie, 2020). Other studies indicate that IFN has been used clinically to treat a variety of malignancies, albeit with mixed results and side effects that can be severe. Despite ample evidence implicating a role for IFN-γ in tumor immune surveillance, a steady flow of reports has suggested that it may also have protumorigenic effects under certain circumstances. The authors propose that IFN-γ treatment is a double-edged sword whose anti- and protumorigenic activities depend on the cellular, microenvironmental, and/or molecular context. As such, inhibition of the IFN-γ/IFN-γ receptor pathway may be a viable new therapeutic target for a subset of malignancies (M Raza, 2011) in comparison to primary tumors and bone metastases (Kartaie, 2020). IFN has been clinically used to treat a variety of malignancies, according to other studies, though with varying degrees of success and potentially harmful side effects. IFN- is implicated in tumor immune surveillance by a large body of evidence, but a steady stream of papers suggests that it may also have protumorigenic effects in some situations. IFN therapy is a double-edged sword whose anti- and protumorigenic effects depend on the cellular, microenvironmental, and/or molecular context. Hence, blocking the IFN-/IFN-receptor pathway could become a

promising new therapeutic target for a certain type of cancer (M Raza, 2011).

Nelfinavir is one of the numerous protease inhibitors currently on the market and is used to reduce viral replication and enhance immune function in HIV-infected people. It is given along with other antiretroviral medications. Nelfinavir has been studied as an adjunctive antiretroviral medication for patients receiving nucleoside reverse transcriptase inhibitors (NRTIs) or as first-line therapy for patients who have not received antiretroviral therapy (Anne, 2000). In 2017, David claimed that nelfinavir has powerful anticancer activities against a variety of tumors. The control of various physiological processes, including the unfolded protein response, cell cycle, apoptosis, autophagy, the proteasome pathway, oxidative stress, the tumor microenvironment, and multidrug efflux pumps, is a component of nelfinavir's anticancer strategy. Many clinical studies found that nelfinavir treatment for patients with cancer resulted in moderate and reversible toxicities, either due to radiation therapy or chemotherapy alone or in combination. Exploiting nelfinavir's anticancer off-target effects will make it possible to quickly integrate this more recent option into the current library of cancer chemotherapeutics since it has been a safe medicine of choice for both adult and pediatric HIV-infected patients for more than 20 years (Mahbuba, 2020).

In 1953, niclosamide was found at the chemotherapeutic research labs of Bayer. In 1959, it was sold under the name Bayluscide and was intended to be used as a molluscicide to eradicate snails, which serve as an intermediate host for schistosomiasis. It was shown to be effective against human tapeworm (Cestoda) infection in 1960 by Bayer scientists, and it was released as Yomesan for human usage in 1962. In 1982, the US FDA approved niclosamide for use in treating tapeworm infection in humans. It is also listed on the World Health Organization's list of essential medications or in the study by Wei Chen (2018). The function of niclosamide in PC was discovered in 2018. The oral antihelminthic medication niclosamide, a salicylamide derivative, is used to treat tapeworm infections. Moreover, it has been utilized as an anti-infective agent in the future. It is has been proven to have anticancer properties in several malignancies, including breast cancer, ovarian cancer, colorectal cancer, and acute myeloid leukemia (AML). Several signaling pathways, including NF-kB, Wnt/b-catenin, Notch, and mTORC1, that are involved in oncogenesis and oncoprogression are targeted by niclosamide. According to in vitro studies, niclosamide is a potent molecule as a Wnt/b-catenin signaling and anticancer agent for human prostate and breast cancer. It targets the Wnt coreceptor LRP6 on the cell surface.

Warfarin is the oral anticoagulant most frequently used to regulate and prevent thromboembolic diseases (Horton, J. D., 1999). Anna's research in 2019 demonstrated that epidemiologic and animal studies indicate that using warfarin may lower the risk of cancer. Several experimental cancer models show that warfarin has anticancer potential. In particular, investigations in mouse cancer models have demonstrated that warfarin inhibits a vitamin K-dependent protein called GAS6 via blocking AXL receptor tyrosine kinase, which may prevent the spread of cancer cells. Inhibiting GAS6-AXL signaling, a side effect of the anticoagulant warfarin, boosts antitumor immunity and prevents tumor formation independently of anticoagulation. As a result, the observed link between warfarin use and reduced cancer incidence is probably caused by an improved antitumor response and early cancer immune surveillance. According to the large observational study, a decrease in cancer incidence was also seen among habitual warfarin users. The results of the study suggest that warfarin may offer some cancer prevention. Notwithstanding numerous limitations, the findings of this study provide additional evidence in favor of the theory that warfarin use lowers the risk of developing cancer, which justifies future research. This discovery may significantly affect drug selection for patients requiring anticoagulant therapy. Low-dose warfarin inhibits tumor cell growth, migration, invasiveness, angiogenesis, and metastasis while increasing apoptotic marker expression without causing coagulation issues, according to Rita (2021). Gas6 is a vitamin K-dependent ligand of the receptor tyrosine kinase AXL. Interestingly, the same study team also showed that low-dose warfarin could make people more sensitiv, as seen in PDAC tumor cells in a KIC (p48Cre; LSL-KrasG12D; Cdkn2af/f) mouse model to gemcitabine and nab-paclitaxel therapy.

Various viruses are susceptible to gemicitabine's antiviral effects, and we have previously described how it works in combination with ribavirin to combat enteroviruses (Kyungjin Lee, 2017). Since chemotherapy resistance develops quickly in pancreatic cancer, it is one of the most challenging cancers to treat. The first-line treatment for pancreatic cancer, gemcitabine, extends patient longevity by several months. In-clinic combinations of gemcitabine and other anticancer medications do not appear to have appreciable effects on overall survival (Namba, T., 2015). One of the deadliest cancers, pancreatic cancer ranks as the fourth highest cause of cancer-related fatalities in the US. Gemcitabine, a nucleoside analogue, continued to be a primary chemotherapeutic agent for treating pancreatic cancer among the several anticancer drugs investigated. Unfortunately, due to the pancreatic tumors' cellular resistance to this treatment, gemcitabine has a low response rate and short progression-free survival in patients (Bishal, 2017).

Thalidomide is a synthetic glutamic acid derivative with a sedative-hypnotic activity that, in the 1960s, had terrible teratogenic effects (G. Gasparini, 2001). The bone marrow malignancy known as multiple myeloma is incurable and notoriously difficult to treat. Only minor

advancements have been made using intricate polychemotherapeutic regimens, transplant techniques, and supportive care. Thalidomide was released in 1999 and opened an entirely new line of treatment options for the disease at a time when new myeloma medications were desperately required. Thalidomide has shown success in patients with refractory, relapsed myeloma, even in cases in the late stages of the disease, despite the exact mechanism of action being still not fully understood (Ramon, 2006). Thalidomide (Thal) has immunomodulatory and antiangiogenic effects. Clinical studies have demonstrated that thalidomide is one of the most effective medications for a monoclonal protein reduction of at least 50% in 30% of individuals with relapsed or resistant multiple myeloma. Thal substantially boosts the total response rate in combination regimens (dexamethasone [Dex] and or chemotherapy) for relapsed and newly diagnosed patients, according to randomized trials based on a substantial body of evidence from phase II trials. Furthermore, Thal shortens the time to react in combination therapy regimens (T. M. Moehler, 2006).

Auranofin, authorized for treating rheumatoid arthritis in 1985, is one medication that is drawing more attention because of its potential to be put to other uses. Rheumatoid arthritis is characterized by ongoing joint swelling and inflammation that impairs function. As a disease-modifying antirheumatic medication (DMARD) used to treat rheumatoid arthritis, auranofin could halt the condition's course by reducing inflammation and promoting cell-mediated immunity. Moreover, auranofin blocks the release of lysosomal enzymes and antibodies involved in cytotoxicity responses and macrophage phagocytosis. Auranofin was shown to be less successful than other DMARDs, such as methotrexate, despite being regarded as safer than its injectable gold counterparts (myochrysine, anochrysine, allochrysine, and solganol), which resulted in a reduction in the clinical use of auranofin.

There may be novel uses for auranofin beyond treating rheumatoid arthritis, including the therapy of some malignancies, parasite infections, bacterial infections, HIV, and even neurological diseases like Parkinson's and Alzheimer's.

The toxicity profile of auranofin [2,3,4,6-tetra-o-acetyl-l-thio-d-glycopyranp-sato-S-(triethyl-phosphine)-gold] is well documented, and it is regarded as safe for usage in humans. It is a linearly arranged gold(I) molecule containing phosphine and thiol ligands. Following oral administration, 15%–25% of the medication can be found in the plasma, which primarily binds to albumin. After the first 20 minutes, the majority of this is absorbed through the digestive system, and after 1-2 hours, a peak plasma concentration of 6–9 g/100 mL is reached. The plasma half-life is 15 to 25 days; by 55 to 80 days, nearly the entire body has been eliminated. About 15% of auranofin is eliminated in the urine, with 85% in feces. The concentration of the injected dose in the kidneys is only 0.4%.

Auranofin has two modes of action that make it efficient against cancer cells. First, mammalian TrxR (mTrxR), a crucial regulator of redox equilibrium in the cytosol and the mitochondria, is inhibited. Because mTrxR contains selenium as selenocysteine, auranofin is a strong inhibitor of mTrxR (C. Fan, 2014). The second method involves targeting DUBs involved in cell cycle regulation, protein degradation, gene expression, and DNA repair, and inhibiting the ubiquitin-proteasome system (UPS) system (Xin, 2014). Both of these methods of action induce apoptosis.

Auranofin's side effects, most of which are linked to long-term usage for chronic diseases, may be part of why its use as a rheumatoid arthritis treatment has decreased. The most frequent side effects are gastrointestinal issues, which might appear in the first few months of treatment and include loose stools, abdominal discomfort, and watery diarrhea. In about 40% of patients, loose stools emerge, although only 2%–5% of patients experience watery diarrhea. These symptoms were usually relieved by lowering or splitting the dose. These symptoms are linked to altered intestinal fluid flow, alterations in sodium, potassium, chloride, and bicarbonate secretion, and altered glucose and mannitol absorption. Additional side effects include stomatitis and mouth ulcerations, which occur in 1%–12% of patients and frequently cooccur with skin rashes, as well as skin irritations or rash, which happen in 20% of patients within the first year of treatment. Moreover, 4% of patients experience conjunctivitis, 5% develop proteinuria, and there have been a few reports of thrombocytopenia and bone marrow suppression, which are incredibly uncommon (Christine, 2015).

In 1985, Mirabelli et al. (1985) demonstrated that auranofin had high in vitro cytotoxic activity against a number of cancer cell lines, including P388 murine leukemia, which supported this usage of auranofin. Auranofin was shown to have in vivo action against P388 leukemia, with a maximum cell kill of 0.6 log at a single daily dose of 8 mg/kg administered through intraperitoneal injection. Since then, various in vitro and in vivo research have focused on auranofin's anti-tumor effectiveness.

Auranofin is more effective in reducing cell viability than cisplatin, according to Marzano et al. (Christine, 2007), who demonstrated that auranofin caused apoptosis in vitro in both cisplatin-sensitive (2008) and cisplatin-resistant (C13*) human ovarian cancer cells. Auranofin has also been shown to induce apoptosis in tumor cells in vitro by Pessetto et al. (Christine, 2015), this time in gastrointestinal stromal tumor (GIST) cells (GIST-T1), including imatinib-resistant GIST. Moreover, research was conducted on chronic lymphocytic leukemia (CLL), which is linked to high rates of relapse and treatment

resistance. According to Fiskus et al. (Warren, 2014), auranofin exhibited apoptotic efficacy against CLL cells obtained from patients and cultured cells. A phase I/II clinical trial for the treatment of CLL, small lymphocytic lymphoma (SLL), and prolymphocytic lymphoma (PLL) is now being conducted with auranofin (NCT01419691) [Christine2015]. In addition to demonstrating auranofin's in vitro and in vivo apoptotic activity against NSCLC (A549 human lung adenocarcinoma), Fan et al. (2014) also investigated how this activity might be increased by the addition of selenocysteine, a naturally occurring inhibitor of TrxR, on the theory that selenocysteine competes with thioredoxin, the substrate for TrxR.

Chen et al. showed that auranofin had a potent cytotoxic impact on chronic myelogenous leukemia (CML) expressing the fusion oncoprotein Bcr-Abl while researching its other action method against cancer cells. They also demonstrated that auranofin might overcome resistance to imatinib mesylate, the standard treatment for chronic-phase CML, a tyrosine kinase inhibitor. Point mutations in the Bcr-Abl gene lead to resistance to imatinib mesylate. While new tyrosine kinase inhibitors like nolotinib, dasatinib, and INNO-406 are effective against most of these mutations, they are ineffective against the most prevalent, a T315I missense mutation that makes up 20% of all Bcr-Abl point mutations. The Bcr-Abl expression can be inhibited by auranofin, which can also cause caspase activation, which cleaves Bcr-Abl and reduces cell proliferation. Auranofin also causes apoptosis by blocking DUBs independently of this (Xin, 2014).

Many ferrocene-based compounds were developed due to rational drug research based on the chemical structure of chloroquine. On the other hand, FQ was the most active ferrocenyl chloroquine derivative in both in vitro and in vivo studies. It was regarded as a lead compound from the beginning of its creation. FQ's capacity to circumvent the CQ-resistance issue is among its most intriguing characteristics. This characteristic prevents *P. falciparum*, the primary malarial cause, from spreading (Christophe, 2006).

The tertiary amino N(24) group and the anilino N(11) group form a potent intramolecular hydrogen bond in the molecular structure of FQ. For a while, the impact of the hydrogen bond on the antimalarial activity of FQ was up for discussion. The flip/flop hydrogen bond between the folded conformation of the uncharged FQ and the open conformation of the charged FQ should facilitate its transportation from water to hydrophobic membranes. The significance of the hydrogen bond in the molecular structure of FQ is further supported by Bio et al. (Biot C., 2010). While having nearly identical physicochemical features to FQ, it has been shown that an FQ analogue containing a methyl group in place of a hydrogen atom on the anilino N(11) showed diminished antimalarial activity against both susceptible and resistant strains of CQ.

The preferential localization of FQ at the lipid-water interface may be another factor contributing to its higher antimalarial action when compared to other medications. Another explanation for FQ's consistent effectiveness despite the strains' high resistance is that it might block the conversion of haematin into hemozoin by keeping poisonous haematin in the aqueous environment.

The stability of FQ is unaffected by this micromolar level free radical production. Moreover, the clustering of FQ near the digesting vacuole's membrane produces ROS and lipid peroxidation. Both processes kill the malarial parasites.

The mechanism of FQ as an antimalarial drug against various malarial parasite strains is still being further explored by researchers both in vitro and in vivo. Recently, Dubar et al. used a ratiometric fluorescent probe to map the subcellular processes involved in the production of HO° in P. falciparum RBCs treated with FQ. It was discovered that oxidative damage was associated with the breakdown of the digesting vacuole membrane, resulting in the parasites' death. It was established that the metallocene moiety significantly contributed to the overall mechanism of action of FQ. Moreover, FQ was predicted to be a key player in the suppression of merozoite reinvasion. The same research team has also linked FQ's capacity to produce hydroxyl radicals to rupturing the parasite's digestive vacuole membrane (Waseem, 2015).

As an anticancer agent: The results showed that FQ significantly decreased the viability of several cancer cell types, including breast, pancreatic, and PC, with IC_{50} values in the low micromolar range.

Researchers found that LMP, mitochondrial dysfunction, suppression of autophagic-lysosomal function, negative regulation of Akt kinase and HIF-1, and negative control of LMP all contribute to the effective death of cancer cells brought on by FQ. Nonetheless, more research is required to comprehend how FQ performs its extralysosomal and lysosomal actions. FQ effectively induced cancer cell death independent of their p53 status and hormonal dependence. Androgen-dependent LNCaP cells harboring wild-type p53 and androgen-independent PC3 and DU-145 cells harboring nonfunctional p53—in all these cell lines FQ effectively induced cell death. Of note, FQ also reduced the viability of normal prostate epithelial cells PNT1A with $IC_{50} = 22\ \mu M$. Although this IC_{50} value is greater than that of most PC cell lines tested, we cannot conclude that FQ exhibits strong cancer cell selectivity in vitro. In actuality, identical nutritional reach normoxic circumstances were used for all viability assays on normal and malignant cell lines. A lot of solid tumors, including PCs, have harsh microenvironments with hypoxia and food deficiencies. Interestingly, FQ works best in deprived and hypoxic settings, which are common in solid tumors but unique and unnatural for healthy cells. Hence, FQ causes

roughly 60% of LNCaP cell death in serum-starved and hypoxic settings at a nontoxic concentration of 2.5 M (for normal PNT1A cells under nutrient-reach normoxic conditions). Therefore, we suppose that in vivo FQ primarily "selects" for starved and hypoxic cells. Apparently, negative regulation of prosurvival Akt kinase and HIF-1α by FQ plays an important role in FQ-induced PC cell death in serum-starved and hypoxic conditions, as both Akt and HIF-1α have been previously reported to be key survival factors for serum- or oxygen-deprived PC cells (Avelino, 2015).

The first cyclooxygenase (COX)-2 selective inhibitor (coxib) to be used in clinical settings was celecoxib. Coxibs were created to offer analgesic/anti-inflammatory activity comparable to that of nonselective NSAIDs without their upper GI toxicity, which is thought to be mostly caused by COX-1 inhibition. In the EU, celecoxib is approved for the symptomatic treatment of individuals with osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.

Celecoxib appears to have minor and comparable risks at indicated dosages for increased thrombotic cardiovascular events and renovascular, hepatic, and hypersensitivity responses. Like all coxibs and NSAIDs, celecoxib should be administered at the lowest effective dosage for the shortest amount of time possible following a careful examination of the specific gastrointestinal, cardiovascular, and renal hazards patient to reduce any risk, particularly the cardiovascular risk (Paul, 2012).

COX-2 controls angiogenesis, cell differentiation, mitosis, apoptosis, and changes in cell adhesion, in addition to controlling inflammation and the pain-stress response. Both its expression and activity are minimal in steady state. Growth factors, cytokines, tumor-promoting agents, and hormones all function as stimuli to raise COX-2 activity and expression and encourage the production of PGE2 (Emanuela, 2011). PGE2 promotes cell proliferation, angiogenesis, and metastasis while maintaining an inflammatory state, which is essential for developing tumors (Johanna, 2010). Studies have confirmed that the expression of COX-2 in cancer cells is significantly increased, which promotes the increase of prostacyclin and prostaglandin synthesis and the proliferation of tumor cells. PGE2 synthesis requires two key enzymes, microsomal prostaglandin E synthetase-1 and COX-2 (Bin, 2020). The development of tumor cells can be aided by all three chemicals. The synthesis of PGE2 and the activation of the -catenin and early growth response 1 signaling pathway were found to directly promote the proliferation of human hepatoma cells, increase the expression of -catenin and early growth response 1, and promote the proliferation, migration, and invasion of hepatoma cells (D Lu, 2012). The expression of matrix metalloproteinases 2 and 9 (MMP 2 and MMP 9) and the metastasis of ovarian cancer cells have been shown in studies to be regulated by COX-2 and its downstream gene PGE2. The extracellular matrix (ECM) and basement membrane's structural integrity will be destroyed by the overexpression of MMP, which will also encourage cancer cells' invasion and metastasis. Moreover, COX-2 activates the PGE2 signal, which is important in the control of cancer and inflammation. The imbalance of the COX-2/PGE2 signal axis results in the activation of the PI3K/Akt and mitogen-activated protein kinase pathways, which in turn promotes the growth of tumors and stimulates the expression of COX-2, creating a feedback loop. Studies have shown that celecoxib, a COX-2 inhibitor, has a therapeutic effect on neurological illnesses and can successfully lower the risk of numerous cancers (including breast, colon, and prostate) (Parkinson's disease and Alzheimer's disease). By blocking the cyclooxygenases-2/prostaglandin E2 signal axis and subsequently the phosphorylation of nuclear factor—gene binding, Akt, signal transducer and activator of transcription, and the expression of matrix metalloproteinase 2 and matrix metalloproteinase 9, celecoxib primarily controls the proliferation, migration, and invasion of tumor cells. Meanwhile, it was found that celecoxib could promote the apoptosis of tumor cells by enhancing mitochondrial oxidation, activating the mitochondrial apoptosis process, promoting the endoplasmic reticulum stress process, and autophagy. Celecoxib can also reduce the occurrence of drug resistance by increasing the sensitivity of cancer cells to chemotherapy drugs (Bin, 2020).

The foxglove plant, *Digitalis purpurea*, yields digoxin. It is a digitalis class glycoside and is cardiotonic. Digoxin has the following chemical formula: C41 H64 O14. Digoxin and other cardiac glycosides, such as digitalis, have a long history of use in clinical settings. This medication was given FDA approval in 1954 and is used to treat various heart conditions, including atrial flutter, atrial fibrillation, heart failure, and its accompanying symptoms, and to cause fetal death before an abortion. It has been supplanted by more effective treatments, including beta-blockers and calcium-channel blockers, which have fewer side effects and better safety profiles. Nowadays, it is only used as a fallback medication when first-line treatments are ineffective. Its best applications are enhancing myocardial contraction and treating mild to severe heart failure in adult patients.

Patients with systolic heart failure, sometimes referred to as heart failure with reduced ejection fraction (HFrEF) and having an ejection fraction under 40%, benefit from digoxin. Unfortunately, it does not reduce mortality in any way.

When traditional therapies cannot control the heart rate, it is utilized for atrial fibrillation or atrial flutter rate control. Digoxin should not be utilized in situations when preexcitation from accessory routes is present since it causes AV blockage and can result in ventricular tachyarrhythmias. When there is a lot of sympathetic

activity, it is useless. In these circumstances, beta-blockers are recommended.

Supraventricular tachycardias not rate-controlled by traditional therapies may benefit from digoxin.

Digoxin use has shown some success in the treatment of fetal supraventricular tachyarrhythmia. The lowest effective dose should be administered to the mother as digoxin might cause uterine contractions and result in abortion (Marie, 2021).

Lung Cancer

The most common form of lung cancer, non-small cell lung cancer, has a high fatality rate globally. Recently, it has been proposed that cardiac glycoside digoxin could be a cutting-edge chemotherapy drug. Src is an oncogene that contributes significantly to cancer development, making it a possible target for cancer treatment. Here, we looked at whether digoxin could slow the spread of lung cancer by preventing Src activity. Using assays for colony formation, migration, and invasion, the effects of digoxin on the activities of lung cancer cells were examined. Src and its downstream proteins' mRNA and protein expression levels were examined using Western blotting and qPCR tests, and the cellular cytotoxicity effects were measured using a cell viability assay. Digoxin suppressed the proliferation, invasion, migration, and colony formation of A549 lung cancer cells, according to the results of the cell function experiments. Digoxin had similar effects on other lung cancer cell lines as well. Digoxin was also discovered to drastically inhibit EGFR and STAT3 activity and Src activity and protein expression in a dose- and time-dependent manner. Data suggested that digoxin is a potential anticancer agent that may suppress lung cancer progression by inhibiting Src and the activity of related proteins (Sheng-Yi Lin, 2015).

In 2020, Yingying Wang conducted research entitled "Digoxin Suppresses Tumor Malignancy through Inhibiting Multiple Src-Related Signaling Pathways in Non-Small Cell Lung Cancer" and he concluded the following.

According to epidemiological research, it might be employed as a cancer therapy sensitizer or an anticancer medication. The well-known anticancer medication adriamycin frequently induces cardiotoxicity, which restricts its use. Digoxin's anticancer properties have lately been studied, both in vitro and in vivo, in relation to human NSCLC. Digoxin decreased A549 and H1299 cells' in vitro survival, increased DNA damage by encouraging the production of ROS, and inhibited the repair of DNA double-strand breaks (DSB) and single-strand breaks (SSB). In A549 and H1299 cells, the combination with adriamycin had synergistic antiproliferative effects at the ratios of 1/2IC50DIG:IC50ADR and IC50DIG:IC50ADR. Digoxin significantly reduced A549 development in zebrafish and nude mice xenograft models when used in vivo. Adriamycin cotreatment decreased the cardiotoxicity while also improving antitumor effectiveness. Our results indicate that digoxin may be used as an anticancer medication by preventing both DNA DSB and SSB repair and using adriamycin in combination with digoxin for the treatment of human non-small cell lung cancer makes sense (Yingying Wang, 2020).

Valproic acid: The first anticonvulsants were developed in 1857 when Edward Sieveking realized that potassium bromide could treat catamenial epilepsy. On the other hand, Albert Hauptmann unintentionally discovered the antiepileptic efficacy of barbiturates in 1912 when he noticed how it affected the frequency of seizures in epileptic patients. Valproate was first produced in 1881, but Pierre Emyard first discovered its anticonvulsant qualities in 1962. Today, it is used for almost all types of seizures (Mohamed, 2019).

Valproic acid is a branched, short-chain fatty acid derivative of the naturally occurring valeric acid.

Inhibiting histone deacetylase, blocking voltage-gated ion channels, and affecting GABA (-aminobutyric acid) levels in the brain are just a few of the ways valproic acid's pharmacologic actions manifest.

A known pathophysiology of seizure genesis and propagation is impaired GABAergic inhibitory function, and antiepileptic medicines may be able to affect this pathway. The tricarboxylic acid (TCA) cycle produces GABA from -ketoglutarate, which is then converted by GABA transaminase and succinate semialdehyde dehydrogenase into succinate semialdehyde and succinate, respectively. According to earlier research, valproic acid blocks the enzymes that cause GABA to be degraded, succinate semialdehyde dehydrogenase, and GABA transaminase.

Valproic acid may also have antiepileptic effects by blocking voltage-gated sodium, potassium, and calcium channels, which lowers the frequency of high-frequency neuronal firing. Through altering GABA and/or glutamate-mediated neurotransmission, valproic acid influences nociception and the biochemical phenomena of aura. Valproic acid has been shown to decrease neurogenic inflammation in neuropathic pain through the GABA-A receptor. Histone deacetylase (HDAC) has recently been shown to be inhibited by valproic acid, specifically HDAC1 (Masum, 2020).

Combating Cancer

In various tumor models, it has recently been shown to inhibit histone deacetylases (HDAC), modify the cell cycle, cause tumor cell death, and prevent angiogenesis. Although the precise mechanisms by which VPA fights cancer are still unknown, it is known that HDAC inhibition, extracellular-regulated kinase activation,

protein kinase C inhibition, Wnt signaling activation, proteasomal degradation of HDAC, potential downregulation of telomerase activity, and DNA demethylation are all involved in this effect. The primary mechanism of VPA's anticancer activity appears to be histone hyperacetylation due to HDAC inhibition. Preclinical findings imply that using VPA in conjunction with cytostatics enhances the anticancer impact of chemotherapy. Preexposure to VPA improves the cytotoxicity of topoisomerase II inhibitors and the effects of pretreatment with HDAC inhibitors, which increases the efficiency of 5-aza-2'-deoxycytidine, VP-16, ellipticine, doxorubicin, and cisplatin. HDAC inhibitors are thought to potentiate the effects of anticancer medications in two ways that are neither mutually exclusive nor synergistic. While the second involves mechanisms other than apoptosis, the first requires apoptosis and can be either p53-dependent or independent. In resistant chronic myeloid leukemia (CML), VPA restores sensitivity to imatinib. We have demonstrated the synergistic effects of VPA and cisplatin in neuroblastoma cells. VPA can be taken orally, crosses the blood-brain barrier, and can be used for extended periods. Clinical trials in patients with malignancies are being conducted. Using VPA prior to or with anticancer drugs may thus prove to be a beneficial treatment (J. Hrebackova, 2010).

Due to their efficacy and safety records that have been established, statins are the preferred medication for the management of hypercholesterolemia. Patients with generally normal plasma cholesterol levels also play a growing role in managing cardiovascular risk. Although all statins have the same mechanism of action, they vary in chemical makeup, pharmacokinetic characteristics, and ability to reduce cholesterol. Statins' water solubility is controlled by their chemical composition, affecting how well they are absorbed, distributed, metabolized, and excreted. With elimination half-lives of 1–3 hours, lovastatin, pravastatin, and simvastatin are generated from fungal metabolites. Lipophilic statins are more sensitive to this process except for pitavastatin, which has a limited amount of cytochrome P450 system metabolism. All statins are selective for action in the liver, chiefly due to effective first-pass uptake: hydrophilic drugs are taken up by active carrier-mediated mechanisms, whereas lipophilic medicines are primarily taken up by passive diffusion via hepatocyte cell membranes. According to clinical trials, rosuvastatin, atorvastatin, simvastatin, and pravastatin are the most efficient medications for lowering low-density lipoprotein cholesterol. Statins are often well tolerated, and major side effects such as muscle toxicity resulting from rhabdomyolysis are uncommon.

Consideration of the differences between the statins helps provide a rational basis for their use in clinical practice (Michael, 2004).

Statins as anticancer agents: 3-Hydroxy-3-methylgutaryl CoA reductase inhibitors, also known as statins, are effective in treating and preventing cardiovascular disorders. Based on preclinical evidence of their antiproliferative, proapoptotic, anti-invasive, and radiosensitizing capabilities, there is growing interest in their use as anticancer medicines. Mevalonate and its downstream products are less abundant due to statins' inhibition of 3-hydroxy-3-methylgutaryl CoA reductase, which disrupts the rate-limiting step of the mevalonate pathway. These downstream products are crucial for maintaining membrane integrity, cell signaling, protein synthesis, and cell cycle progression. Statins may therefore affect tumor genesis, development, and metastasis by altering these pathways in cancerous cells. In animal preclinical tumor models and cancer cell lines, statins have been shown to suppress growth. The predominant dose-limiting toxicity of statins in human phase I trials was myotoxicity and phase II trials in other tumor types are currently being conducted to assess their efficacy. Combinations with chemotherapeutic or other molecularly targeted drugs, radiation, maintenance therapy in minimum disease status, and chemopreventive therapy are some potential future paths in developing statins as anticancer medicines (Kelvin, 2003).

Statins Used in Cancer Treatment

Breast cancer is more likely to grow and return if a person is overweight or obese. Tumor cells have a strong affinity for cholesterol, and accumulating intracellular cholesterol promotes cancer growth, proliferation, and metastasis. Moreover, it has been demonstrated that blocking the mevalonate pathway, a metabolic route involved in cholesterol synthesis, or reducing cholesterol, can stop the spread of cancer. It has become popular to utilize statin, a medication that blocks the HMG-CoA reductase enzyme, as a treatment for mycobacterial infection, insulin resistance, and cancer. Statin inhibits the rate-limiting step in the mevalonate pathway. In addition, inhibiting the cholesterol biosynthetic pathway has shown a promising effect in reducing the formation of mammospheres enriched with cancer stem cells, indicating that the cholesterol biosynthetic pathway is a potential therapeutic target for statin treatment in breast cancers.

Other statins like simvastatin, atorvastatin, and rosuvastatin inhibit the growth of ovarian cancer cells by inhibiting the geranylgeranylation and expression of transforming growth factors (TGF-1) and vascular endothelial growth factor (VEGF), as well as the tumor-promoting cytokines and mediators IL-6, IL-8, and TNF-. Statins have been employed as a sole agent to stop the growth of several cancer cells and trigger their apoptosis. Also, they have been used in conjunction with other chemotherapeutic medications to enhance the effectiveness of the medications and the patient's condition. According to clinical data, using statins and trastuzumab together reduces the cardiotoxicity of trastuzumab-based therapy in HER2-positive breast

tumors. Radiation resistance in head and neck malignancies is inhibited by statins (pitavastatin, simvastatin, lovastatin, atorvastatin, pravastatin, and rosuvastatin) inhibition of the mevalonate pathway, demonstrating the importance of this route as a target for combating the emergence of resistance. In addition, statins combined with metformin have been demonstrated to reduce all-cause mortality in high-risk PC patients, particularly in postdiagnosis circumstances.

The effect of statin on cancer cells, including medulloblastoma brain tumor, colorectal cancer, lung cancer, oral squamous cell carcinoma, anaplastic thyroid cancer, and hepatic cancer, was examined in vitro. Lovastatin increases sensitivity by activating the tumor-suppressive protein bone morphogenetic protein (BMP) and decreasing the cancer stemness of colorectal cancer cells. Inhibiting the activity of DNA methyltransferases (DNMTs) causes demethylation and activates BMP signaling, which causes a change in the stem-like state to a differentiated form of cancer cells and the induction of p21 cip, leading to cell-cycle arrest. These events are also responsible for the anticancer effects of statins. In contrast, it causes cell-cycle arrest and apoptosis to stop the development of breast cancer cells. Simvastatin has been demonstrated to concurrently influence both intrinsic and extrinsic apoptosis in PC cells. Caspase 9/3 cleavage and phosphorylated Bad are increased, but Bcl-2 and Bcl-xL, intrinsic apoptotic indicators, are decreased. It enhances TNF, Fas-L, Traf, and caspase 8 cleavage while causing extrinsic apoptosis. Moreover, it causes the death of cholangiocarcinoma cancer cells by preventing Rac1 from functioning normally, reducing Rac1 activity, and preventing the production of ATP-binding cassettes (ABCA1 and ABCG1). Simvastatin's ability to fight cancer is further strengthened in salivary adenoid cystic carcinoma (SACC) by its ability to suppress microRNA-21, which is abundantly expressed in tumors and encourages the growth of tumors. According to a clinical trial done on a cohort of 15,264 hyperlipidemic PC patients in Taiwan's National Health Insurance Research Database (NHIRD), those taking simvastatin or lovastatin had a lower mortality rate. Simvastatin also increases the radiosensitivity of esophageal tumors by upregulating the tumor suppressor protein PTEN and blocking the PI3K/Akt pathway, which reduces cell growth, invasion, and migration, and induces apoptosis (Nirmala, 2021).

Emerging clinical data demonstrates the effective anti-inflammatory and cardioprotective effects. It is now widely recognized that blood monocyte migration to the artery wall is significant in mediating atherogenesis, which is predominantly an inflammatory process. High-sensitivity C-reactive protein (hsCRP) and soluble CD40 ligand levels are two inflammatory indicators that statin therapy has been proven to reduce in patients significantly. In addition, it has just been revealed that statin therapy for patients is linked to a notable decrease in mortality soon after percutaneous coronary procedures. The suppression of inflammatory processes could possibly cause these immediate effects of statin therapy. Also, the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study's findings supported the notion that stopping statin therapy dramatically raises the incidence of events in people with acute coronary syndromes. Interestingly, the increased event rate occurred during the first week after the onset of symptoms and was independent of cholesterol levels. [David 2002]

In summary, statins are now recognized as powerful anti-inflammatory agents that exert beneficial effects beyond low-density lipoprotein cholesterol reduction. Upregulation of endothelial function (i.e., eNOS enzyme activity) is thought to be a primary mechanism responsible for these anti-inflammatory properties. Pruefer et al. provided additional evidence that statin therapy attenuates inflammation and further extends our understanding of this very exciting class of cardiovascular agents.

A triazole antifungal with a broad spectrum of activity is itraconazole. Itraconazole has been effective in treating various superficial fungal infections during the past 20 years, including hard-to-treat dermatophytoses and onychomycoses. Itraconazole has less extensive clinical expertise in the management of deep mycoses. Nonetheless, the outcomes for aspergillosis, blastomycosis, paracoccidioidomycosis, systemic candidosis, and sporotrichosis are all quite positive. Itraconazole is less effective in the treatment of chromomycosis and coccidioidomycosis. Itraconazole has been well tolerated with doses of up to 400 mg/day, generally free of serious adverse effects. However, a potential for drug interactions exists, mediated through the cytochrome P450 enzyme 3A4 system, which should be considered when itraconazole is used as part of a multidrug regimen (G. E. Piérard, 2000).

A broad-spectrum antifungal drug is itraconazole. An expanding body of in vivo, in vitro, and clinical evidence has also proven its antineoplastic properties. When coupled with other chemotherapeutic drugs, it also has a synergistic effect. To decrease tumor growth, it inhibits the Hedgehog pathway, stops angiogenesis, slows endothelial cell proliferation, arrests the cell cycle, and stimulates autophagocytosis. They enable itraconazole to boost medication efficacy and overcome drug resistance, either alone or in combination with other cytotoxic medicines.

At presentation, ovarian cancer is at an advanced stage in 70–75% of patients and has a 5-year survival rate of ~40%. Although the initial response rates to first-line chemotherapy are high, resistance is common, as reflected by poor survival. Itraconazole has been utilized in refractory diseases to try and reverse such chemoresistance. In total, 55 patients were treated in a retrospective study with either chemotherapy

administered alone (regimes of pegylated liposomal doxorubicin, gemcitabine, docetaxel, irinotecan, or paclitaxel) or chemotherapy administered alone (docetaxel-based chemotherapy, in 79%) in combination with itraconazole. Moreover, 19 female patients received the combination medication twice weekly, which included 400–600 mg of itraconazole daily for four or five days. Both the overall survival time (642 days, compared with 139 days in those who did not receive itraconazole; P=0.0006) and the median progression-free survival time (103 days, compared with 53 days in those who did not receive itraconazole; P=0.014) were significantly longer for those receiving itraconazole. The overall response rate following treatment was 18%, with a greater proportion of the itraconazole group exhibiting a response (32% in the itraconazole group, 11% in the control group). The continued use of itraconazole likely explains the improved survival rates.

In a different study, itraconazole was added to the treatment plan for nine patients with recurrent clear-cell ovarian cancer to enhance chemotherapy efficacy. Every two weeks, itraconazole 400 mg per day was given for four days. In comparison to median overall survival times previously reported in other studies, which ranged between 7 and 10 months, a response rate of 44% was achieved.

Few individuals with refractory disease—particularly a few female patients—are eligible for such research since treatment is often stopped after resistance. Another drawback is that patients' cytotoxic regimens vary, doses are regularly changed, and individuals are not randomized (Rachel, 2017).

When topical use of vitamin A (retinol) failed to treat dyskeratotic diseases, the narrative of vitamin A acid began.

The application of retinoic acid in breast cancer treatment was first mentioned in the 1970s (Lotan, 1979). A retinoic acid-binding protein is believed to be an important factor in breast cancer progression. The latest report indicates that other treatments, such as curcumin, may restore retinoic acid sensitivity in triple-negative breast cancer cell lines. Different retinoic acid signaling is how aldehyde dehydrogenase 1A3 (ALDH1A3) promotes breast cancer progression. In addition to the aforementioned, it was discovered that a distinct protein, kinase C, is also involved in stimulating the retinoic acid pathway in breast cancer. Importantly, early altered breast epithelial cells may undergo redifferentiation in response to retinoic acid, highlighting the preventive role retinoic acid plays with regard to breast cancer. Using proteomic analysis, Kamal et al. highlighted the impact of retinoic acid on breast cancer cell lines. The advancement of breast cancer was discovered to be correlated with retinoic acid sensitivity and retinoic acid receptor (RAR) amplification. Retinoic acid interferes with the activation of LSD1 via protein kinase A, which in turn impairs estrogen signaling in breast cancer cells. Breast cancer growth and lung metastases were also found to be decreased by retinoic acid. Retinoic acid has been shown to control breast cancer cells' procoagulant activity. It's interesting to note that retinoic acid was shown to activate microRNA-21 in breast cancer, suggesting a biological relationship and potential molecular targets. Moreover, the activation and production of the aromatase enzyme may be inhibited by retinoic acid, suggesting that the amount of estrogen present in breast cancer cells is insufficient to support cancer cell proliferation. In addition to growth inhibition, retinoic acid can downregulate MMP-9 by modulating its regulatory molecules, impacting breast cancer cells' invasion ability. Additionally, retinoic acid may inhibit telomerase activation by inducing histone deacetylation in estrogen receptor-negative breast cancer cells (Mei-Chih Chen, 2014). Importantly, Hau et al. elucidated the genomic antagonism between retinoic acid and estrogen signaling in breast cancer and published their findings in the journal, Cell (Hua S., 2009). Their study demonstrates the important and sound reasoning behind the use of retinoic acid in treating breast cancer. Since HOXA5 is involved in the death of breast cancer cells, it has been suggested that retinoic acid controls HOXA5 through RAR-. RAR signaling in breast cancer cells is thought to directly target the cell cycle control gene Btg2. Moreover, retinoic acid may increase sensitivity to taxol in breast cancer cells by downregulating survivin and promoting abnormal mitotic progression that results in death. Retinoic acid is successful in treating breast cancer in numerous studies, it has also been proposed and is presently used in combination therapies with other powerful drugs (such as tamoxifen, taxol, and interferon) (Mei-Chih Chen, 2014).

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