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Review Article

Apigenin And Its Anticancer Activity By Using Molecular Docking

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ABSTRACT

The number of humans suffering from different types of cancers is increasing annually and ultimately demanding research and development of therapies. Compounds available in nature are being studied for their chemotherapeutic activities. Apigenin is one of the most efficient natural compounds. As a natural flavone, apigenin is abundantly present in vegetables, chamomile, fruits, kumquats, tea, and wheat sprouts. Chemo-preventive aspects of apigenin have come to light in recent years. Several studies have highlighted the activity of apigenin on significant cancers through mechanisms like inhibition of cell proliferation, induction of autophagy, angiogenesis, hindrance of cell cycle progression, and so on. This review elaborates on the mechanisms through which apigenin attempts to cure different types of cancers such as breast cancer, cervical cancer, lung cancer, pancreatic cancer, and prostate cancer.

INTRODUCTION

Cancer, the second most common cause of human death worldwide, requires meticulous medical care. This disease results from abnormal proliferation and differentiation of cells as tumorigenic factors govern it. The most efficacious therapeutic method to treat cancer is still chemotherapy. In-depth understanding has proven the side effects and attained drug resistance of synthetic small molecular compounds to have attracted great concern [1]

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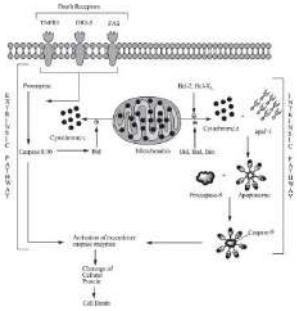

Figure 1. Intrinsic and extrinsic pathways of cellular apoptosis from Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry p. 357 [2]

Flavones, natural as well as edible small molecules, are in great demand in anti-cancer agent development since they possess remarkable physiological effects, low toxicity, and non-mutagenic properties in the human body [1]. In several in vitro and in vivo experimental models, the significant biological actions of flavonoids, the naturally occurring polyphenols, are associated with decreased risk of cancers such as prostate and colon cancers [3,4]. Flavopiridol, quercetin, and epigallocatechin gallate are some of the flavonoids that have recently become apparent as potent anticancer drug candidates. The others have progressed into the stage of clinical trials. The biological activities being reported for flavonoids are anti-inflammatory, antioxidant, anti-allergenic, antitumor, and hepatoprotective effects [4]. Apigenin is one of the most abundant flavonoids in the plant kingdom. It is found in fruits like oranges, herbs like chamomile and thyme, vegetables like parsley and celery, and in tea, beer, and wine. These are known chemically as 40,5,7-trihydroxy flavones. On different organs such as the heart, brain, liver, and lung, the effects are seen to have the potential to express themselves as therapeutic in diseased conditions, including hypertension, hyperlipidemia, osteoporosis, hyperglycemia, and immune regulation [3]. Chinese medicinal herbs include apigenin as an active ingredient. Naturally, apigenin is conjugated to a glycoside in vivo. Apigenin is responsible for decreasing cancer cell motility. Cancer cell migration and invasion are inhibited as well. During the process of stimulation of an immune response, multiple signaling pathways and protein kinases such as MAPK/ERK, PI3K/AKT, JAK/STAT, NF-κB, and Wnt/β-catenin are modulated by apigenin [1]. Apigenin occurs in nature with its glycosides; apigenin 7-O-glucoside is their base compound. Another natural apigenin derivative used in medicine is vitexin (apigenin 8-C-glucoside), which belongs to the C-glycosyl-flavonoid subclass [5]. Chinese cabbage, bell pepper, garlic, bilimbi fruit, guava, wolfberry leaves, and local celery are rich in apigenin [6]. In the treatment and prevention of several types of cancer, natural substances have often been given great attention [4]. A new direction to chemotherapy is introduced by the consolidation of conventional chemo drugs with flavonoids. This is because chemotherapeutic agents can be made vulnerable to tumor cells by apigenin [7]. Apigenin is classified as a class II molecule in the Biopharmaceutical Classification System (BCS) due to its high membrane permeability and low solubility. BCS plays a role in indicating the absorption, solubility, and intestinal permeability of oral drugs and is therefore considered useful for drug discovery, development, and regulatory issues. In the present study, we encompass the advantageous effects of apigenin, with an emphasis on breast cancer, cervical cancer, lung cancer, pancreatic cancer, and prostate cancer [3].

STRUCTURE OF APIGENIN

Figure 2 Structure of Apigenin

ACTIVITIES OF APIGENIN OF DIFFERENT CANCERS

Carcinogenesis is a multistep process involving genetic and epigenetic changes that lead to the initiation, progression, and development of cancer. The strategy to treat cancer is to destroy cancer cells by triggering apoptosis or inhibit cancer cell proliferation by triggering cell cycle arrest, thus making cancer a long disease, and affecting the patient's life [1]. Current strategies include promoting apoptosis or autophagy, controlling the cell cycle, preventing tumor cell migration and invasion, and stimulating the immune system in patients [8]. Apigenin has demonstrated a wide range of anti-tumor activities in vitro and in vivo [1].

Breast cancer

Breast cancer (BC) is a cancer occurring in women especially of the Western world [9] and is the second leading cause of cancer in women after lung cancer. The search for new prospective compounds that could inhibit the development of breast cancer and the analysis of their impact on tumor cells is one of the priorities in oncology [10]. Gene amplification and/or overexpression of some oncogenes have been implicated in breast cancers [9] A research study by Blokhin N. N. Russian Cancer Research Center was carried out to measure the phytoestrogen activity against breast cancer cells of ER expression and to elucidate the molecular pathways regulated by the leader compound [10]. In the study, it was found that apigenin blocks the main proliferative stimulus for the tumor line of MCF-7 cells. Also, high doses of apigenin were found to reduce the expression of one of the major tyrosine kinases supporting the growth of HER2-positive cells and simultaneously initiate apoptotic processes [10]

In another study, it was concluded apigenin dissociated the complex of HER2/neu and GRP94 that preceded the depletion of HER2/neu. Apigenin-induced degradation of mature HER2/neu involves polyubiquitination of HER2/neu and subsequent hydrolysis by the proteasome. The inhibition of the HER2/HER3 heterodimer function provided an especially effective strategy for blocking the HER2/neu-mediated transformation of breast cancer cells [9].

Cervical cancer

Cervical cancer is one of the most common cancers among women worldwide. Approximately 500,000 women are diagnosed with breast cancer each year, accounting for approximately 9% of all new breast cancer diagnoses. Flavonoids such as epigallocatechin gallate and quercetin have emerged as effective anti-inflammatory agents, and some of these have entered clinical trials. This research aims to examine the anti-cancer effects of apigenin against HeLa cancer cells [4]. Apigenin has a cytotoxic effect on cells and inhibits cell growth (reduces cell viability) depending on the dose. After 24 hours of treatment, 50 µM apigenin inhibited the growth of HeLa and C33A cells by -61.6% and 46.1-58.6%, respectively. [11]

Lung cancer

One of the most common cancers in the world is lung cancer. Lung cancer has a high mortality rate due to poor detection and resistance to some treatments. There is currently no effective chemotherapy in the treatment of lung cancer. Studies show that AKT is a target for cancer treatment. [12]

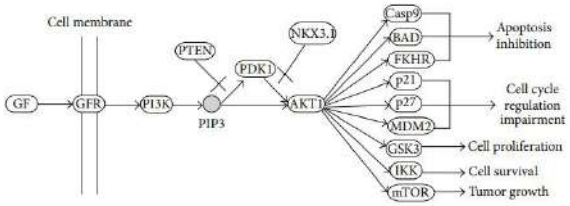

Figure 3 Regulation of AKT signaling activation [13

The discovery of new drugs that target angiogenesis and tumorigenesis, such as vascular endothelial growth factor (VEGF), is a promising treatment for human lung adenocarcinoma. VEGF is thought to be the most important factor in the development of lung adenocarcinoma. Angiogenesis VEGF provides nutrients necessary for vascular permeability of the surrounding tumour. Through a study, it was hypothesized that apigenin inhibits VEGF expression, tumour growth and angiogenesis. To test this hypothesis, we want to determine whether apigenin inhibits A549 cell proliferation, inhibits VEGF expression, inhibits VEGF expression at the transcriptional level of HIF-1 expression, or affects tumour growth and angiogenesis.

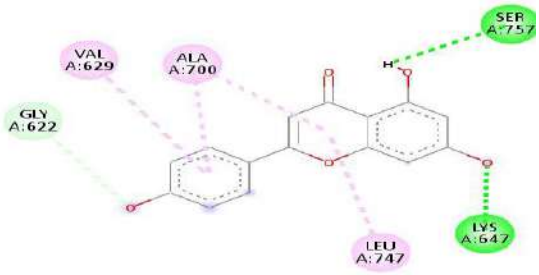

Figure 4 Apigenin inhibits VEGF expression

This protein is called Ephrin type-B receptor 4. Alanine and valine are found to be attached to the same aromatic ring and leucine and alanine is attached to another ring. Glycine and Lysine are found to be bounded to two different oxygen molecules. Apigenin treatment inhibits VEGF transcriptional activation at the transcriptional level of HIF-1 expression. per dose. Apigenin treatment inhibits the activity of the pMAP11wt VEGF reporter gene at one dose. However, apigenin treatment did not inhibit the activity of the mutant VEGF reporter gene pMAP11mut. These results indicate that apigenin inhibits VEGF transcriptional activation through the HIF-1 DNA binding site in the VEGF promoter region and that mutation of the HIF-1 binding site abolishes the inhibitory effect of apigenin. - Mutagenic flavonoids that act as inhibitors of signalling pathways.

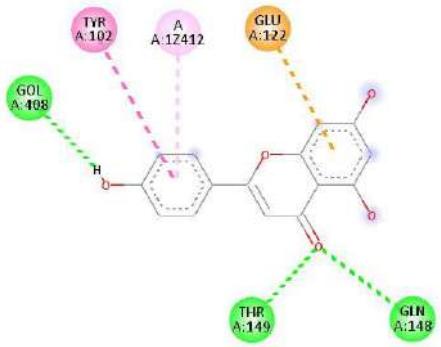

Figure 5 HIF-1 binding

This protein is HIF-1 alpha inhibitor working in lung cancer. Threonine and glutamine are seen to be attached to the same carbonyl group. Tyrosine, alanine, and glutamic acid are found to be bonded to the aromatic rings. Apigenin is an anti-inflammatory drug that inhibits protein kinases by competing with ATP. In a study, it was found that apigenin inhibited lung cancer cell proliferation and VEGF expression. Overexpression of VEGF is associated with tumour growth and angiogenesis and is inversely associated with drug resistance in non-small cell lung cancer. Apigenin specifically inhibits HIF-1β expression in cancer cells, but does not inhibit HIF-1β expression. [12]

Pancreatic cancer

Pancreatic cancer is the deadliest cancer of the digestive system. In pancreatic cancer cells, apigenin sensitizes cells to chemotherapy and affects molecular pathways such as hypoxia-inducible factor (HIF), vascular endothelial growth factor (VEGF), and glucose transporter-1 (GLUT -1).

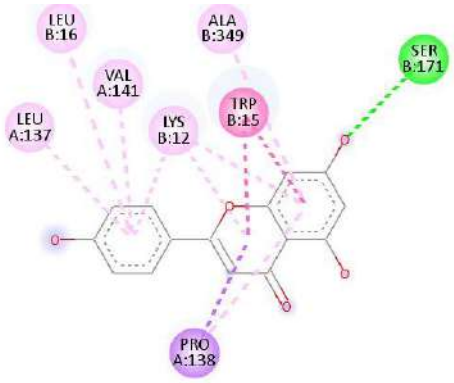

Figure 6 Apigenin interaction with HIF, VEGF, GLUT 1

This protein is equilibrative nucleoside transporter 1. Lysine is found to be attached to all three aromatic rings. Leucine and valine is attached to the same ring. Serine is seen to be bonded to an oxygen molecule. The natural flavonoid apigenin is a potential molecule to overcome anti-inflammatory drugs in pancreatic cancer. The serine/threonine kinase glycogen synthase kinase 3β (GSK-3β) functions as a target of flavonoids and is responsible for the main upstream regulator of NF-κB transcriptional activity. NF-κB enters the nucleus of pancreatic cancer cells. Conventional chemotherapy inhibits apoptosis by stimulating the NF-κB pathway. GSK-3β activity is inhibited by apigenin. Additionally, this flavonoid plays an important role in inhibiting the growth of cancer cells in vitro. Apigenin (0, 10, 25, and 50μM) activates the apoptosis of pancreatic cancer cells by inhibiting the GSK-3β/NF-κB pathway. [8] In this study, treatment of human pancreatic cancer cells with apigenin inhibited DNA synthesis and cell proliferation through G2/M cell cycle arrest. Downregulation of cyclin A, cyclin B, cdc25A, and cdc25C occurred. [14]

Prostate cancer

The most common non-skin cancer in men is prostate cancer which is the leading cause of cancer-related death. In a research study on how apigenin impedes cell cycle progression at G2 phase in the prostate cancer cell, it has been documented that apigenin inhibits the formation of tumors in a variety of animal models. Further studies revealed that apigenin's anti-inflammatory effects were linked to the breakdown of cancer cell G2/M phase arrest. Because each action can have a different impact on cancer cells, it is unclear if this effect affects the G2 phase or the M phase. The foundation of the battle against cancer still revolves around paclitaxel/taxol, which targets cancer cell mitosis. The combination of apigenin with mitosis-targeting drugs is worth thinking about if apigenin influences the transition from G2 to the M phase since it may affect the cycling of cancer cells in G2 and M phases. The study's objective was to learn more about apigenin's G2/M arrest effect. This study demonstrates that apigenin influences prostate cancer cells in the G2 phase as opposed to the M phase. Downregulation of transcriptional regulators that cause the G2-M transition, such as CDK1, CyclinB1, Polo-like Kinase 1 (PLK1), and Aurora A, has been reported to have an effect. As compared to benign prostatic hyperplasia, the mRNA levels of Cyclin B1, CDK1, PLK1, and Aurora A are much higher in primary localized prostate cancer. [15]

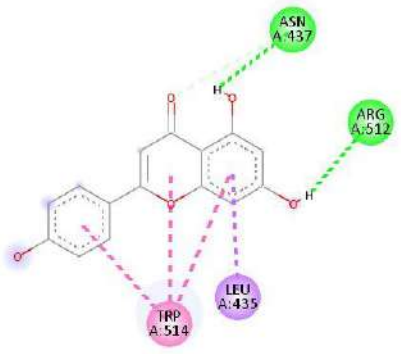

Figure 7 Apigenin with Cyclin B1, CDK1, PLK1, and Aurora A

This protein is Serine/threonine-protein kinase PLK1. Asparagine and L-arginine are found to be attached to the hydrogen groups. Trytophan is seen to be bonded to the three aromatic rings.

CONCLUSION

Cancer is the most common and main cause of death worldwide. Current treatment can cause side effects such as loss of appetite, constipation, bleeding, diarrhoea, oedema, fatigue, and hair loss, and can kill the elderly. Apigenin is a powerful drug since it has fewer side effects and appears to reduce the risk of cancer. This flavonoid appears to regulate many cellular processes, including angiogenesis, apoptosis, cell cycle, and many other genetic processes. [16] There still is some scope for other therapeutic activities of apigenin to emerge into the mainstream treatments which might get covered in the near future.

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