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EVALUATE APIGENIN BASED NANO FORMULATION FOR THE TREATMENT OF SKIN CANCER

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Abstract

Many intrinsic and extrinsic processes work together to cause cancer. Recent years have seen increased focus on discovering and perfecting safe and effective cancer treatments based on natural extracts. Research into the efficacy of various compounds synthesized from natural sources as cancer treatments continues. Apigenin is a favonoid found in high concentrations in many plant foods. The pharmacological and biological effects of apigenin have been mapped out through many years of study. Although studies on the anticancer effects of api genin have been conducted in a number of different cancer types, a more universal scientific understanding of how api genin affects things like apoptosis, cell signaling, and the oncogenic protein network has yet to be established. So, the goal of this research was to zero in on how apigenin affects oncogenic pathways in many different malignancies.

Keywords: Apigenin, MicroRNAs, Cell signaling, Nano-formulations, Therapeutic benefts

INTRODUCTION

Plants produce flavonoids, which are natural chemicals with numerous phenolic units. Flavonoids can lower cancer risk, therefore it's important to consume enough of them. Flavonoids regulate immune cell development and activity in a direct manner. In addition, it inhibits T-effector cell development and stimulates T-regulatory cells through decreasing mTOR activity. Chemically speaking, apiginin (AN) is a trihydroxy flavone and occurs naturally as a crystalline solid (3-OH group). Chamomile, artichoke, parsley, and vine-spinach are only few of the natural sources that contain it. Several therapeutic effects, including those against cancer, free radicals, diabetes, inflammation, stress, and bacteria, have been described. Multiple in vitro and in vivo studies have characterized AN as an anticancer agent, showing that it kills cancer cells by triggering cell cycle arrest, immune response activation, cell apoptosis, and autophagy. AN is a BCS-II medication, meaning that it is poorly soluble in water and has low bioavailability. Scientists have been working on an unique nano-drug delivery technology to boost the medication's therapeutic potential, circulation time, drug release, and cellular absorption.

Cancers of the skin may be divided into two major categories: (a) those that begin in the melanocytes and (b) those that begin in the epidermis. They account for the vast majority (95%) of skin cancers, with the remaining 5-7% being made up of uncommon and very dangerous forms of the disease. Historically, basal cell carcinomas (BCCs) have made up the vast majority of skin malignancies, with cSCCs making up just 20%. Yet, in the Medicare fee-for-service group, a recent research indicated that the incidence ratio of BCC to SCC was 1:1. In addition, during the years 1976-1984 and the years 2000-2010, the incidence rates for cSCC rose by a whopping 263%. The aging of the population and advancements in diagnosis [8] are to blame for this increase.

In this article, we examine the skin's protective qualities against nanoparticle invasion. We describe the standard of care for treating skin malignancies in the clinic today, with a focus on alternatives to surgery. The variety of nanoparticles used for topical distribution is also summarized, with an emphasis on those used to treat skin malignancies. Multiple in vitro and in vivo studies have characterized AN as

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an anticancer agent, showing that it kills cancer cells by triggering cell cycle arrest, immune response activation, cell apoptosis, and autophagy.

Formulation of Apigenin Nanoparticles

Figure 1 shows the molecular self-assembled process used to create AN-LC-CS-TPGS-NPs, with a few tweaks. Table 1 details what went into the making of AN-LC-CS-TPGS-NPs. The AN-LC-CS-TPGS-NPs were suitable for usage after being centrifuged for 30 minutes at 18,000 rpm. Lyophilization followed by a wash with Mili Q water yielded the final product.

Table 1. Formulation composition of Apigenin-loaded hybrid nanoparticles

Code	Formulation Variables			Responses					
				Particle Size (nm)		Encapsulation Efficiency (%)		Drug Release (%)	
	Lecithin (A) (mg)	Chitosan (B) (mg)	TPGS (C) (%)	Actual Value	Predicted Value	Actual Value	Predicted Value	Actual Value	Predicted Value
F1	80	20	0.75	101.28	103.13	52.65	53.80	36.47	37.61
F2	180	20	0.75	171.32	170.53	63.12	62.61	60.40	63.41
F3	80	60	0.75	190.04	189.83	68.23	70.14	56.60	58.59
F4	180	60	0.75	227.24	225.39	79.54	77.95	53.53	55.39
F5	80	40	0.5	162.29	160.88	60.4	63.39	52.75	54.46
F6	180	40	0.5	201.21	204.43	71.04	70.19	62.51	60.35
F7	80	40	1	175.21	174.99	64.54	63.56	56.50	55.66
F8	180	40	1	245.00	244.40	71.34	73.36	67.11	65.39
F9	130	20	0.5	131.58	133.14	56.32	57.12	54.78	53.13
F10	130	60	0.5	204.75	203.37	74.12	73.46	58.63	56.93
F11	130	20	1	159.25	156.63	61.56	60.29	57.38	55.07
F12	130	60	1	230.52	231.96	77.13	76.63	66.19	64.04
F13 *	130	40	0.75	184.05	185.75	67.78	66.88	59.32	58.60
F14 *	130	40	0.75	187.43	185.75	67.23	66.88	58.45	58.60
F15 *	130	40	0.75	185.76	185.75	68.13	66.88	58.04	58.60

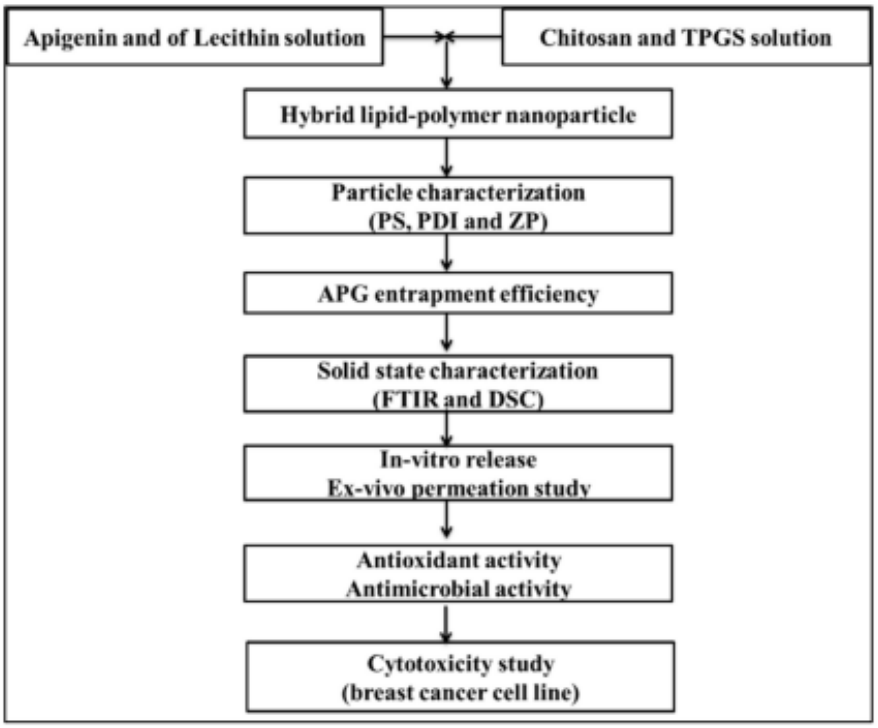

Figure 1: Flow chart of experimental design

LITERATURE REVIEW

Lalan, M., Shah, P., Barve, K. et al. (2019), Topical medication administration has emerged as an ideal method for localized self-application with limited systemic ingress for the therapy of skin malignancies, but the search for a silver bullet continues. The development of nanocarriers and other cutting-edge technologies. In addition to their enhanced specificity for their intended targets, developed nanovectors now offer the flexibility to try out a wide range of drug carriers with strikingly different characteristics. Biological approaches, like those based on nucleic acids or skin-penetrating peptide vectors, have showed promise in the treatment of skin cancer. This article provides a comprehensive overview of skin cancer, including its causes, current treatments, and potential future advances in medication delivery. Nonetheless, getting these promising new treatment approaches from the lab to the patient's bedside remains a significant challenge.

Manmohan S. Jangdey (2017) The major goal of this research was to create a unique nanoemulsion gel formulation of carbopol containing apigenin utilizing tamarind gum as an emulsifier, with the smallest droplet size, greatest drug concentration, and strongest physical stability feasible for Transdermal administration. High-speed homogenization was used to create apigenin-loaded nanoemulsion, which was then examined with regard to its shape, zeta potential, differential scanning calorimeter analysis, and penetration examinations. TEM showed spherical droplets, while FTIR checked for chemical compatibility inside the nanoemulsions. Nanocarriers treatment resulted in consistent fluorescence intensity throughout the skin's depth using CLSM, suggesting good penetration of the nanoemulsion gel through goatskin. Melanoma (A341) cells were more sensitive to the nanoemulsion gel's toxicity at concentrations between 0.4 and 2.0 mg/ml, whereas HaCaT cells were less sensitive. The carbopol-based nanoemulsion gel formulation of apigenin may be more effective in penetrating goatskin than the currently marketed version. This research concludes that apigenin's innovative nanoemulsion gel may be useful in the future for the treatment of skin cancer.

Kazmi, I.; et al. (2018), In this research, phospholipid was mixed with an edge activator, and the

resulting nanosized vesicles (LT-NVs) were filled with luteolin (LT).-hydration strategy. We found the best possible set of three criteria using a Box-Behnken layout with three tiers of optimization. Phospholipid (A), edge activator (B), and sonication duration were the three factors used to tailor the formulated LT-NVs (C). Vesicle size (Y1) and encapsulation effectiveness were measured as a function of the factors employed in the study (Y2). Point prediction was used as the basis for the software's optimal composition selection (LT-NVopt). Carbopol 934 gel (1% w/v) was developed from the LT-NVopt formulation to improve skin retention. The antioxidant, antibacterial, and cytotoxicity of LT-NVoptG, as well as its viscosity, spreadability, drug content, drug release, and penetration, were also evaluated. The testing results showed that the drug's concentration, pH level, viscosity, and spreading ability were all excellent. Permeation of LT (128.21 3.56 g/cm2/h) and LT release (60.81 2.87%) were both increased in comparison to pure LT. The findings of the antioxidant and antibacterial studies showed that they were substantially (p 0.05) more effective than the controls. In the end, a skin cancer cell line was used to conduct a cytotoxicity evaluation, and the findings showed a statistically significant difference in viability percent at the concentrations examined. The IC50 value for LT-NVoptG was much lower than that of pure LT. The results of the research show that the prepared LT-NVoptG is a viable replacement for both the synthetic medication and the traditional delivery methods.

Samir Mitragotri and Vinu Krishnan (2017), Nanoparticles provide exciting new possibilities for dermatological skin disease therapy. Even when the barrier is compromised due to injury or inflammation, nanoparticles have a hard time penetrating the skin and reaching the underlying tissue. This may make it easier for nanoparticles to enter their target. Although much work has gone into creating nanoparticles for topical application, not much has been done to get them into the clinic for the treatment of skin malignancies. We provide a brief overview of the various skin malignancies and the methods currently used in therapeutic therapy. This study discusses the barriers that have been identified in the research, development, and eventual clinical use of nanoparticle technology for the topical treatment of skin cancers. In addition to critiquing the methods used to examine nanoparticle interactions inside tissue, This overview seeks to provide insight on the mechanisms that regulate nanoparticle skin penetration.

Alquraini, A., Ghoneim, M. M., Alshehri, S., Alquraini, A., Alsaidan, O. A., Ahmed, M. M., Yasir, M., Warsi, M. H., Zafar, A., Alruwaili, N. K., Imam, S. S., Alsaidan, O. A. (2015), After skin cancer, breast cancer is the most frequent cancer among women. Less hazardous than synthetic medications, natural substances are a viable option for treating breast cancer. The purpose of this research was to create and characterize Apigenin (AN) nanoparticles (NPs) that could be taken orally (AN-NPs). The self-assembly approach was used to create the hybrid AN-NPs from lecithin, chitosan, and TPGS. In addition, Box-Behnken optimization was used to further improve the NPs (3-factor, 3-level). Drug release, zeta potential, entrapment efficiency, and particle size were all examined in relation to the hybrid NPs. When compared to the formulation (ON2), we found that pure AN had a much lower IC50. When tested against pure AN, It was more effective than other methods in killing Salmonella typhimurium and Bacillus subtilis. These results demonstrate the use of a hybrid AN polymeric nanoparticle as a carrier for the treatment of breast cancer.

Interactions of apigenin with diferent molecular pathways

The fast development of treatment resistance in cancer cells is a critical challenge for molecular biologists and pharmacologists. Because of this, researchers have been able to create medicines with low cytotoxicity and great specificity. The next section briefly describes and illustrates in Fig. 2 how apigenin interacts with several molecular pathways.

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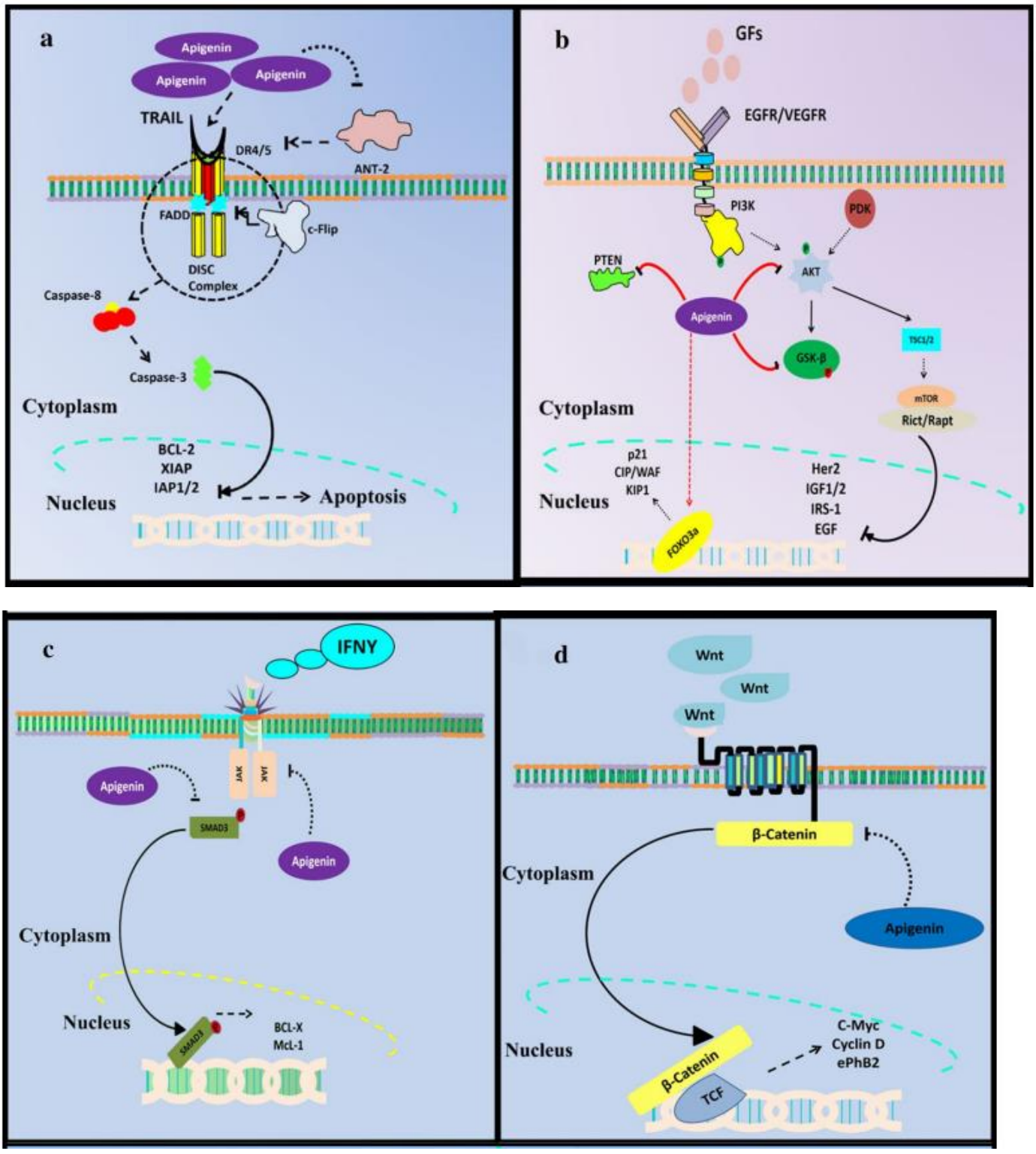

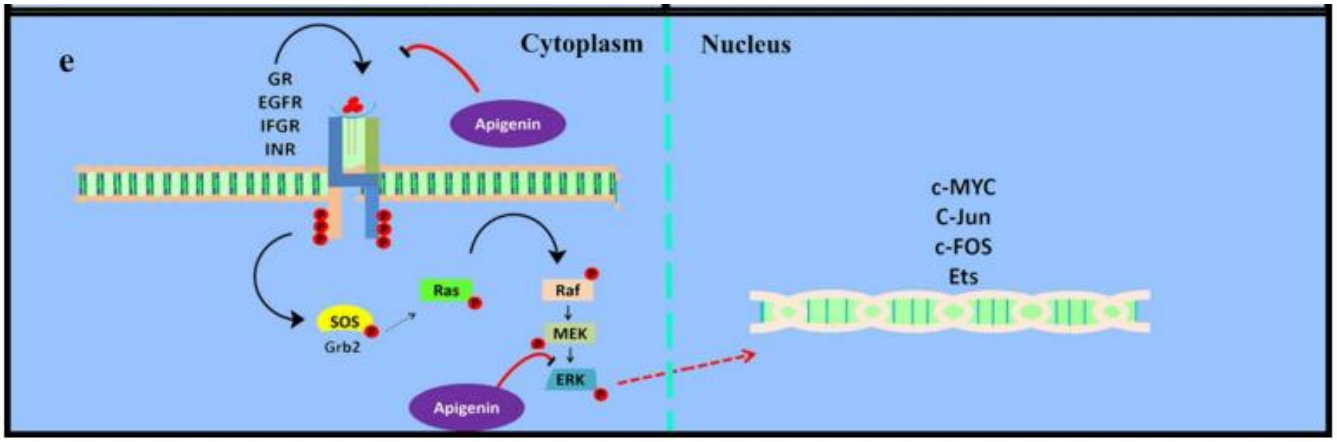

Fig. 2: Modulation of various signaling cascades by Apigenin.

By inhibiting JAK and SMAD3 phosphorylation, apiginin activates the JAK-STAT cell death pathway. Apigenin acts as a mediator of Wnt/-catenin regulation by blocking nuclear translocation and inhibiting -catenin. When -catenin is inhibited, its target genes that regulate cell proliferation and growth are silenced. Apigenin inhibits mitogen-activated protein kinase (MAPK) signaling by reducing ERK expression and promoting upstream growth factor binding. SOS and Grb2 are phosphorylated in response to MAPK signaling activation, which then increases Raf/Ras phosphorylation. Apigenin blocks proto-oncogenes like c-Myc, c-Jun, and c-FOS by interfering at the ERK level and suppressing its expression.

Apigenin and miRNA interplay: a potential new avenue for cancer treatment

MicroRNAs (miRNAs) are tiny molecules that regulate gene transcription and translation in a variety of ways. Their roles in these processes have attracted a lot of interest recently. Here, we'll discuss apigenin and how it influences the expression of microRNAs (miRNAs) in cancer, including oncogenic and tumor suppressor miRNAs. Together with tailored miRNA mimics and miRNA inhibitors, apiginin was recently shown to help stop the growth and kill off certain cancer cells.

Cancer cells may be made more susceptible to the chemotherapy drug doxorubicin by apiginin. Apigenin's ability to inhibit doxorubicin-induced chemoresistance in BEL-7402 cells through regulation of miR-101 expression is a relatively new finding. Apiginin stimulates the production of miR-101 in BEL-7402 cells. BEL-7402 cells are resistant to doxorubicin because their expression of miR-101 was downregulated and their expression of nuclear factor erythroid related factor 2 (NRF2) was raised. When apigenin is present, miR-101 directly targets NRF2 and reduces its expression, making BEL-7402 cells more sensitive to doxorubicin. It is hypothesized that chemotherapy-resistant cancers have altered crucial metabolic pathways. Glutamine metabolism is altered by oncogenic KRAS via a mechanism that is not well understood, and this has deleterious effects on prognosis and chemoresistance in patients with pancreatic cancer. Nevertheless, using a glutaminase inhibitor prior to gemcitabine therapy has been found to sensitize pancreatic cancer cells to the drug. These findings support further investigation into the potential use of glutaminase inhibitors in the secondary treatment of pancreatic cancer in patients with KRAS mutations. In hepatocellular carcinoma, apigenin and miR-520b mimics have been demonstrated to increase doxorubicin sensitivity in BEL-7402/ADM cells. Mice given miR-520b mimics had much less aggressive tumors, whereas mice given miR-520b mimics with apigenin had significantly reduced tumor growth. However, researchers have just recently started to untangle the intricate web of connections between apigenin and miRNAs in cancer regulation, despite these discoveries. Although apigenin's tumor-inhibiting mechanisms have been shown, they are still poorly understood. Therefore, future research should focus on discovering miRNAs that are a direct target of

apigenin and understanding how to transfer these tactics into innovative therapeutic regimens for diverse cancers.

The therapeutic potential of Apigenin in cancer treatment

Researchers are becoming more committed to extracting apigenin's medicinal potential after hearing reports of its enormous therapeutic and health benefits. Many patents have been filed thus far showing that apigenin has anticancer properties. In this article, we surveyed the research behind some of the currently-issued and recently-issued patents on apigenin. The combination of apigenin, curcumin, and honokiol is patented as a medicinal formulation. It has been shown that this medication combination is effective in treating lung cancer. Direct induction of apoptosis in lung cancer cells by the pharmacological composition inhibits tumor development and promotes chemoprevention. In a nutshell, it slowed glycolysis and ATP generation, inhibited PD-L1, and downregulated ANT2. Apigenin has also been shown to regulate the transition from epithelial to mesenchymal cells (EMT). Apigenin can prevent EMT and reverse it, according to a patent that was recently abandoned. Indeed, in a dose-dependent fashion, apigenin-treated cells show reduced expression of mesenchymal marker and epithelial marker. A second patent showed that irradiation apigenin is more effective than untreated apigenin in killing lung cancer cells. Radiation-activated apigenin has many notable effects, one of the most notable being the induction of ROS production, which in turn induces death in lung cancer cell lines.

In addition, a pharmaceutical composition including both chyrophanol and apigenin suppressed choriocarcinoma cells. This chemical sped up apoptosis and slowed down cell migration in a dose-dependent manner. Combining the proprietary pharmaceutical formulation with selective inhibitors of PI3k/Akt/mTOR and ERK signaling increased the formulation's potency significantly. The mixture also included cisplatin and paclitaxel, which dramatically increased the effectiveness of chemotherapeutic drugs. Apigenin's potential as an anticancer drug has resulted in the registration of many patents. Despite these efforts, further research is needed to get apigenin from the laboratory to the clinic.

Apigenin nano-formulations for sustainable delivery

The wealth of knowledge gained in the field of nanotechnology over the last decades has allowed researchers to build more targeted, efficient, and cost-effective nano-formulations capable of eradicating a wide spectrum of ailments. Researchers all around the globe are increasingly using nano-based medication delivery devices due to their specific targeting and low cytotoxicity.

Because of their powerful anti-oxidant, anti-proliferative, antifungal, antibacterial, and antipesticidal capabilities, natural chemicals have received a great deal of attention in recent years. As a result of their appealing properties, several medications based on natural substances are undergoing testing for the treatment of various ailments. Apigenin administration through nanoparticles has been shown to be effective and has great promise as a cancer therapy. Nanoparticles containing apigenin, for instance, have been shown to inhibit the development of hepatocellular carcinoma in mice. Anticancer activity of apiginin-linked gold nanoparticles (ap-AuNPs) in epidermoid squamous carcinoma cells A431 has been observed. Apigenin served as a stabilizer and reduced cytotoxicity in tethered nanoparticles. Using a chick chorioallantoic membrane (CAM) assay, we found that ap-AuNPs inhibited angiogenic processes in A431 cells. In addition, ap-AuNPs induced apoptosis, suggesting they have potential as a treatment for skin cancer. Chemotherapy resistance in non-small-cell lung cancer is mediated by nuclear factor E2-related factor 2 (Nrf2). Docetaxel (DTX) is currently the gold standard treatment for NSCLC. However, the existence of Nrf2 renders the chemotherapeutic approaches useless. According to the research, apigenin has the potential to reduce Nrf2 activity. Treatment of A549 NSCLC cells with a nano-formulation based on hyaluronic acid nano-structured lipid carriers (NLCs) containing apigenin resulted in decreased production of Nrf2. It was discovered that apoptosis may be induced along with

proliferation suppression using DTX and HaApG-NLCs. A549 cells treated with Ha-ApG-NLCs displayed lower levels of expression of Nrf2, MRP2, HO-1, and Bcl-2 as determined by real time-protein chain reaction (RT-PCR). Based on these results, Ha-ApG-NLCs are a promising drug delivery platform with the potential to lessen treatment resistance in lung cancer.

CONCLUSION

Apigenin has significant anticancer activity in cell culture and in animal models. This biofavonoid is found in nature, and its minimal cytotoxicity gives it targeted and specific anticancer effects. Apigenin, among other things, regulates important signaling molecules that help set off metastasis, proliferation, and invasion in cancer cells. Nevertheless, it is not yet known how apigenin exerts cell growth inhibition through signaling cascades and molecular cross-talks, therefore much more study is needed to reveal these intricate relationships. Although its enormous anti-proliferative potential, apigenin's limited solubility in water and other organic solvents has significantly impeded the development of apigenin medication formulation. While apigenin's inherent instability makes it more challenging to create long-lasting pharmaceuticals, the compound may be rendered more soluble by being converted into glycosidic or acylated forms [82]. These properties allow for the development of novel apigenin formulations that disperse readily in the circulation and are quickly eliminated in the urine.

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