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Herbal and Synthetic Drug Combinations in Cancer Therapy- A Review

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ABSTRACT

Cancer is one of the leading and most serious diseases in the current decade, every year millions of people die because of various kinds of cancers. Many aspects relate to the cause of disease besides heredity, food habits, smoking, nutritional behaviors, radiation etc. Cancer is a high mortality disease and the therapeutics for cancer, especially for cancer metastasis is still imperfect. The successful cancer treatment till now has been under study, only chemotherapy and radiation treatments are at times successful. Alternative and less toxic medication is very much in need towards the disease, the use of concepts of herbal medicine with synthetic drug could present better drug leads towards the inhibitory treatment of Cancer. Nature shows plethora of medicinal plants with anticancer and antioxidant activities which may suppress the disease completely. By applying combination therapy instead of monotherapy can lead to improved efficacy and reduced toxicity of the conventional method of treatments of cancer.

KEYWORDS: *ABC transport system, Anticancer, Curcumin, Acetazolamide, Flavanoids , Histone deacetylase*

1. INTRODUCTION

In spite of good advances in diagnosis and treatment cancer is still a big treat that involves transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis. Cancers is the second most common disease in India cause more than 70.3 million deaths per year.

It is estimated that the number of new cancer persons will reach 15 million every year by 2020 worldwide[1] and among them about 70% may be in developing countries.

Combination chemotherapy simply means the use of more than one chemotherapy agent at a time to treat cancer. In the past years, cancer can often treated with a single drug, but current treatments method involves combination of one or more drugs simultaneously. Since chemotherapy drugs affect cancer cells at different points in the cell cycle, using a combination of drugs increases the chance that all of the cancer cells will be destroyed. At the same time, using more than one drug has the disadvantage of increasing the risk of drug interactions, and if there is a problem, it may be hard to know which drug was at fault. Recently, chemotherapy has also been used with a type of immunotherapy known as checkpoint inhibition, and may increase the chance that the immunotherapy drugs will be effective.

The anticancer properties of plants have been recognized for centuries. Isolation of podophyllotoxin and several other compounds (known as lignans) from the common mayapple (*Podophyllum peltatum*) ultimately led to the development of drugs used to treat testicular and small cell lung cancer. The National Cancer Institute (NCI) has screened approximately 35,000 plant species for potential anticancer activities. Among them, about 3,000 plant species have demonstrated reproducible anticancer activity.

The use of combination chemotherapy to treat cancer was inspired in the 1960s when scientists wondered whether the approach to treating tuberculosis using a combination of antibiotics to reduce the risk of resistance—would work for the treatment of cancer as well. Using this approach, cancers that had previously been almost universally fatal such as acute lymphocytic leukemia and Hodgkin's lymphoma became largely curable. Since that time, combination chemotherapy has been adopted for the treatment of many other cancers as well[2].

In the 1970's, combination chemotherapy was found to be more effective than single drugs for people with lung cancer, and more effective than "sequential chemotherapy" or using chemotherapy drugs one at a time in sequence, rather than at the same time.

It's only in the last decade that chemotherapy has been added to a new type of immunotherapy called checkpoint inhibition. In some situations, adding chemotherapy drugs appears to make the immunotherapy drugs more effective.

At the current time, combination chemotherapy may be more appropriate in some situations and with some cancers, while single-drug chemotherapy may better in others.

APPROACHES FOR COMBINING CANCER DRUGS

One of the combination treatment approaches is to co-administer drugs that work by different molecular

mechanisms and thereby increasing tumor cell killing while reducing the likelihood of drug resistance and minimizing overlapping toxicity[3].

Another approach is to treat patients with drugs that block the particular mechanism of resistance their tumors have developed, and then treat them again with the drug to which they grew resistant. The idea is that this combination approach may "re-sensitize" the patients to the original treatment.

Another approaching is making the cancer cell to keep inside the cell for more time. one mechanism by which cancer cells resist treatment is by expelling cancer drugs. For example, healthy cells have proteins known as transporters that pump out toxic agents. One such group of proteins, called ATP-binding cassette (ABC) transporters, is able to expel some chemotherapy drugs, including doxorubicin, and some targeted therapies, like imatinib. When giving with other drug which will inhibit the cell transport system (ABC transport system) make the drug to accumulate within the cell and there by increased activity can be obtained.

The next approche to increase the treatment effect is to Erasing Reversible Modifications. Drug resistance can also emerge as a result of alterations in cancer cells' epigenetic codes . One type of epigenetic alteration, called DNA methylation, occurs when enzymes attach chemical tags named methyl groups to DNA. Another type, termed histone modification, occurs when enzymes attach chemical tags to histones, proteins that are involved in "packaging" DNA into compact structures[4]. Both DNA methylation and histone modifications can turn nearby genes on or off.

the researchers showed that treating mice bearing cisplatin(platinol) -resistant ovarian tumors with decitabine (Dacogen) —a drug that inhibits DNA methylation—reversed *hMLH1* methylation and re-sensitized the tumors to cisplatin. Furthermore, a recent study comparing DNA methylation across the genome of several cisplatin-sensitive and -resistant ovarian cancer cell lines confirmed that methylation of *hMLH1*, among other genes, may cause cisplatin resistance.

The next aopproch to increase the activity and efficacy of cancer drug is to altering the tumor microenvironment. For that combining immunotherapic drugs with usual cancer drug can be utilized. Immunotherapies—therapies that enable the immune system to fight cancer—have generated robust and durable responses in patients with different types of cancer. For example a drug combination that can overcome a form of resistance to immune checkpoint inhibitors in mice which results from the myeloid cells in the tumor cells. Immune checkpoint inhibitors enable T cells to recognize and kill cancer cells; myeloid cells neutralize their effect by inactivating T cells.

PERSONALIZING COMBO THERAPIES

Despite the challenges, the cancer research community continues to see drug combinations as the future of therapy. Most researchers agree that successfully reining in a cancer's growth and spread and extending patient survival will involve a barrage of multiple compounds. And this approach is spreading into the growing field of precision oncology, where researchers are looking in patients' genomes for clues to which therapies are most likely to be effective. Several years ago, frustrated by the lack of FDA-approved treatments that offer lasting benefit and by an inability to find an appropriate clinical trial for many of her patients, oncologist Razelle Kurzrock, director of the Center for Personalized Cancer Therapy at the University of California, San Diego (UCSD), decided to start her own customized therapy trial. In her team's I-PREDICT (Investigation of Profile Related Evidence to Determine Individualized Cancer Therapy) study[5], patients often receive a custom two- or three-drug combination therapy—either FDA-approved drugs or experimental drugs from clinical trials—to target the specific mutations identified in thei r tumors. According to Shumei Kato, a UCSD medical oncologist and a co investigator on the I-PREDICT trial, several thousand patients have been through genomic screening, and hundreds are receiving a customized combination of cancer drugs through the I-PREDICT or similar UCSD-led trials. And for some patients, it appears to be working.On Mother's Day, 2017, Lisa Darner had muscle spasms and lost consciousness. At her local hospital in San Diego, physicians told her that she had suffered a grand mal seizure—and that she had cancer in several major organs, including the brain, which caused the seizure. She quickly received brain radiation therapy followed by standard chemotherapy for lung cancer, which her oncologists considered to be the most likely primary tumor. While receiving nonspecific chemotherapy, Lisa opted to also have her tumor biopsy analyzed using a comprehensive genetic panel—not always part of routine cancer care—that homed in on two actionable mutations: an epidermal growth factor receptor (EGFR) gene amplification and an alteration in a cell cycle gene called CDKN2A. Kurzrock and her colleagues at UCSD's Moores Cancer Center came up with a triple drug combination including palbociclib (Ibrance), a cell cycle kinase inhibitor; a small molecule inhibitor of EGFR, erlotinib (Tarceva); and an antibody that also targeted EGFR, cetuximab (Erbitux). In August 2017, confined to a wheelchair because of her progressing disease, Darner started the custom combo as part of the I-PREDICT trial.Aside from a rash (a side effect of the drugs), she responded well and is still on the treatment. "My tumors were still growing in August, but by October, scans showed everything was receding or has stabilized," she says. "There are places where you can't see a tumor anymore."Unfortunately, not all patients are as lucky[6]. "The patient has high expectations from their cancer treatment, but the reality is that it is not always that great," says Kato. "We're not saying this is for sure a better approach. It's a work in progress. But I think that continuing to do the standard-of-care approach, when it's known not to be beneficial, will not change outcomes for cancer patients. We need to try something different to see a different, better result."

SYNTHETIC DRUG COMBINATIONS

1. **Pharmaceutical agents targeting antioxidant response pathways used in combination**

Nrf2 have a role in tumour prevention and progression, there are some pharmaceutical agents which bring the up regulation of Nrf2 expression. Curcumin, the pharmaceutical agent has the principal component curcuminoid which is derived from Curcuma longa which belongs to the ginger family Zingiberaceae. Curcumin has the capacity to suppresses the carcinogens in a Nrf2-dependen[7].

Curcuminoids are linear diarylheptanoids that upregulate Nrf2 expression and induce Nrf2 translocation to the nucleus to elicit its antioxidant effects by stabilizing protein levels of Nrf2. In addition, curcuminoids upregulate glutathione levels which have been shown to reduce ROS levels and remove carcinogens, aiding in chemoprevention. In a phase II double-blind randomized study, curcuminoids in combination with chemotherapy have displayed enhanced efficacy with regards to reduced adverse side effects and improved quality of life in patients with solid tumors, such as colorectal, gastric, and breast cancer. Curcuminoids in combination with chemotherapy have demonstrated an overall positive outcome, and have also shown to increase the survival rate in some patients

Activation of Nrf2 and GSH expression are also shown by the plant derivatives like Resveratrol, a phytoalexin by that mechanism they produce antioxidative and chemopreventive action . A phase I trial has shown that micronized resveratrol is a good agent for metastatic interruption. They shown that upregulation [8]of caspase-3, an apoptotic marker, occurred in 39% of patients with hepatic malignancies; this demonstrates the effectiveness of resveratrol in preventing malignancies in other organs. squalene, a natural isoprenoid, has also show chemopreventive actions. Various studies shown that antioxidant compound has cytoprotective properties against the side effects of chemotherapy. Squalene reduces ROS levels and upregulates glutathione levels between other detoxifying enzymes, with no effect on tumor cells as in neuroblastoma, small cell carcinoma and medulloblastoma xenografts. Squalene appears to protect against chemotherapy toxicity and might be a potent adjunct to anti-cancer treatments

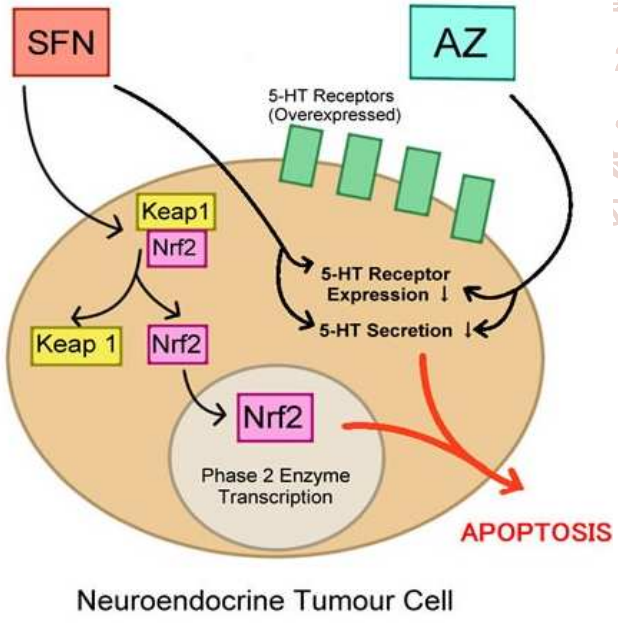

Figure 1: Regulation of Nrf2

2. Carbonic anhydrase inhibitors with anticancer agents

There are non isoform and isoform spefic CAIs. The selection of activiyy wether to use specific or non specific may depend on the nature of therapy needed. Acetazolamide is a pan-CAI that is currently in the development for the treatment of cancers, although its former FDA-approved use is primarily for glaucoma and epilepsy treatment. Acetazolamide has shown hopeful results in anti-cancer treatment whenit is given as a single drug. In the treatment of bronchial carcinoid[9] and bladder cancer AZ is combined with SFN which shown additive efficacy compared to the monotherapy of each agents.the enhanced efficacy was attributed to increased inhibitory effects on clonogenic and invasive ability in vitro, and increased tumor growth inhibitory effects in vivo SFN has also shown to play a significant role in sensitizing ovarian carcinoma cell line derivatives, adriamycin-resistant A2780/ADR and cisplatin-resistant A2780/CP. Hypoxic conditions provide optimal conditions for tumour growth and SFN modulates the pathways involved in cell proliferation and survival. Specifically, SFN activates various anti-cancer responses such as p53, ARE, IRF-1, Pax-6 and XRE while suppressing proteins involved in tumorigenesis and progression, such as HIF1α, AP-1 and CA IX. SFN has thus shown to reduce chemoresistance and may be a potential agent to be used in conjunction with chemotherapeutics. Recently, benzenesulfonamide derivatives have been synthesized to possess CAI activity for CA I, II and IX while displaying cytotoxic effects on breast cancer cell line MCF-7, with varying IC50s[10]. Another CAIX inhibitor, sulfamate (S4), was tested on a laryngeal tumor model in a study done by Meijer et al., but did not display significant anti-tumour and anti-proliferative effects to be used as a single agent [85]. However, in another study, it was postulated that in combination with the proton pump inhibitor lansoprazole it potentiated the effects of melanoma Me30966 cells treated with CAIX specific inhibitor FC9-399A or S4 treatment. This combination resulted in an enhanced dose-dependent tumor inhibitory response and cytotoxicity. Moreover, combination therapy involving CAIs continues to present promising results of enhanced efficacy, such as those shown in a study done by Gieling et al., where CAI, AZ, enhanced the efficacy and toxicity of basic toxic agent, doxorubicin (DOX) in human colon carcinoma cell line HT29 by enhancing the cellular uptake of DOX. In addition, CA9/18 cells that have upregulated CAIX expression showed the highest AZ+DOX combinatorial efficacy[11].

3. Histone deacetylase inhibitors with anticancer agents

Research on creating novel therapeutic treatments utilizes the knowledge of common epigenetic modifier mutations in specific cancers and uses them as therapeutic targets. For example, studies have introduced epigenetic modifier gene mutations into mouse hematopoietic stem cells. Results show that the epigenetic mutation increased cancer stem cell properties such as self-renewal capability[12]. Furthermore, therapeutic treatments, such as HDACi targeting epigenetic modifiers, are emerging primarily because of the plasticity of the epigenome and its reversibility. HDACs are common targets for cancer therapy as their dysregulation is associated with many forms of cancers; HDACi is therefore frequently tested in clinical trials. Trichostatin A was the first HDACi tested in clinical trials while vorinostat, a potent inhibitor of HDAC1, HDAC2, HDAC3 and HDAC6, was the first FDA-approved HDACi for the treatment of persistent, progressive or recurrent cutaneous T-cell lymphoma. Due to the successful results of vorinostat, many other HDACi has been applied in the treatment of cancers, such as romidepsin for cutaneous T-cell lymphoma[13], and Panobinostat for the treatment of multiple myeloma Repurposed HDACi have also been tailored for the treatment of diverse cancers, such as valproic acid (VPA) originally used for the treatment of epilepsy, and romidepsin originally FDA-approved for

hematological cancers such as cutaneous and peripheral T-cell lymphoma but have also shown anti-cancer effects in solid tumours. Additionally, repurposed HDACi in combination with other agents have been tested in clinical trials; however, not all displayed promising results due to the build-up of toxic side effects or insignificant effects. For instance, recently a phase II randomized study was done testing the effects of VPA and decitabine on patients with acute myelogenous leukemia and myelodysplastic syndrome. The results demonstrated that there were no significant differences between the effects of single agent treatment with decitabine and combination therapy with decitabine and VPA. Complete remissions of 31% and 37% (p=0.497) respectively were observed, although preclinical studies demonstrated a significant difference in growth inhibition and apoptosis. Similar results were obtained in a randomized phase III study of VPA in combination with an all-trans retinoid for intensive therapy in the treatment of acute myeloid leukemia in the elderly, where the combination resulted in low complete remission rates and increased VPA-related hematological toxicities. The combination of VPA (75-100 mcg/mL) and 5-azacytidine (5-AZA) (75 mg/m^2) delivered daily for 10 days in patients with advanced cancers such as colorectal, melanoma and breast cancers, were deemed safe, but did not particularly result in enhanced anti-cancer efficacy compared to 5-AZA monotherapy[14].

HERBAL DUG COMBINATIONS

1. Curcumin with anticancer agents

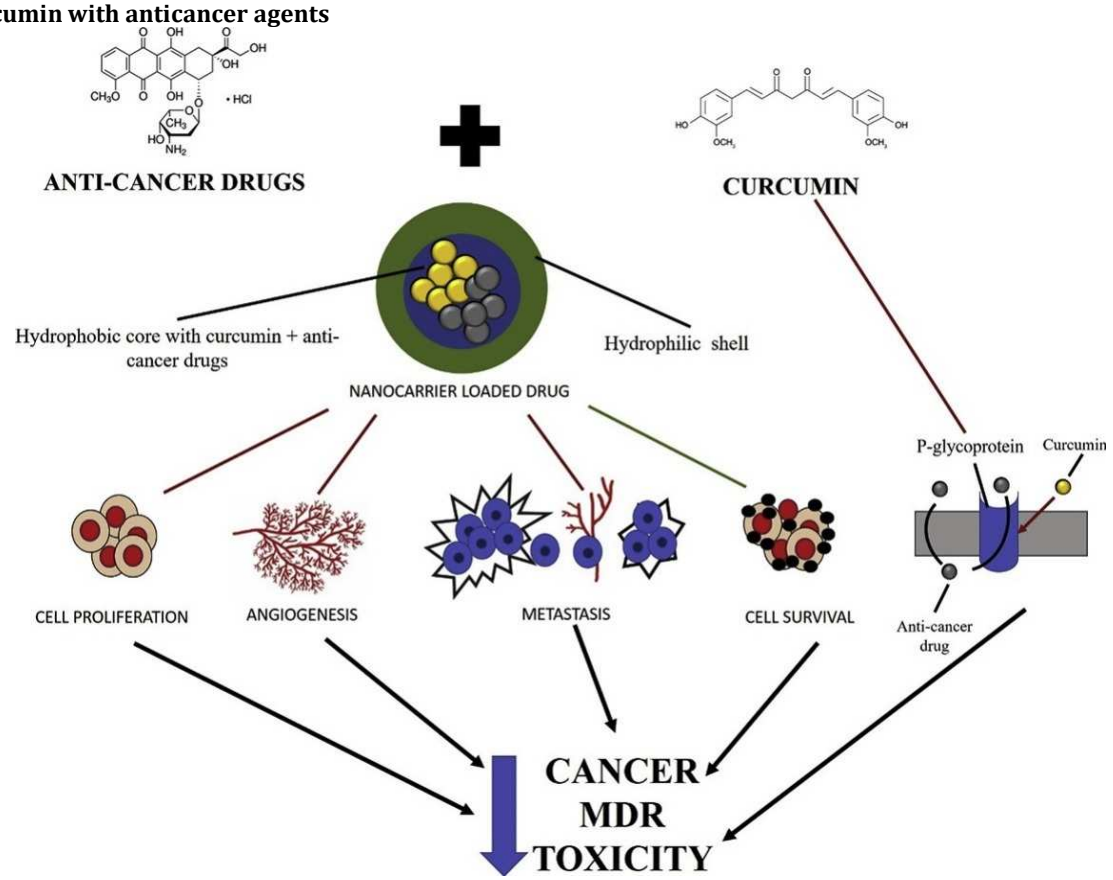

Figure 2: Combined effect of curcumin with anticancer agents

Curcumin, a yellow-colored polyphenol derived from the rhizome of turmeric (Curcuma longa), influences a wide variety of cellular processes through the reshaping of many molecular targets. One of them, nuclear factor kappa B (NF-κB), represents a strong mediator of inflammation and, in a majority of systems, supports the pro-proliferative features of cancer cells. Curcumin has shown to be successful in several types of cancer lines, mainly because of its ubiquitous action on different modulator of anti-cancer effects. Curcumin alone or in combination is nontoxic and is proposed to accentuate the therapeutic efficiency of chemotherapeutics by inhibiting ABC efflux transporter[15]. Curcumin inhibits tumor growth by arresting cell cycle progression, inducing apoptosis, inhibiting the expression of antiapoptotic proteins, inhibiting multiple cell survival signaling pathways and their cross-communication, and modulating immune responses. All these properties make curcumin a promising drug for mono or combination therapy. Hu et al. investigated the combined effect of nanoparticulate delivery of curcumin (Cur) with a kinase inhibitor, sorafenib, in the treatment of HCC. The combination will down-regulate the expression of MMP9 via NF-κB/p65 signaling pathway. Furthermore, the population of cancer-initiating cells CD133-positive significantly decreased in both MHCCLM3 cells with this combination therapy. In vivo outcomes demonstrated lung metastatic tumors to be significantly reduced compared with control treatment. Yan et al. developed glycyrrhetinic acid (GA)-modified chitosan-cystamine-poly(ϵ-caprolactone) copolymer (PCL -SS-CTS-GA) micelle for co-delivery of DOX and curcumin to HCC. GA aided in target specificity to hepatocytes due to its affinity to the liver membrane[16]. Overexpression of CD44, a single-chain glycoprotein, has been reported in a variety of colon cancer. Hyaluronic Acid (HA) is shown to have a high affinity for CD-44 receptors. So, the addition of HA provided a colon cancer-targeting

capability due to more efficient internalization of HA-functionalized NPs in cells through an HA receptor-mediated endocytosis pathway by interacting with CD44 receptors. Xia et al. capitalized this property for formulating HA-CPT/CUR-NPs. Ex vivo studies in AOM/DSS-induced colon cancer mouse model with the developed NPs showed higher permeation and accumulation of HA-functionalized NPs in colon tumor region. Anirudhan et al. designed a transdermal drug delivery system (TDDS) to encapsulate 5-fluorouracil (5-FU) and curcumin (CUR). Polymer β-Cyclodextrin and aminated nano dextran used to entrap CUR and 5-FU respectively which provides flexible kinetics for the release of drugs after treatment with specific solvents. Polysaccharides ALG and CS were used to coat the surfaces of NP's with opposite charges in the final product. In vitro studies on human carcinoma cell lines, HCT-116 depicted a reduction in cell viability from 71.1 to 48.7% at increasing concentrations, when treated with solvent dipped final formulation. Ruttala et al. designed CUR and albumin-PTX hybrid encapsulation liposomes (CL-APN) and performed in vitro cytotoxicity assay in MCF-7 and B16F10 carcinoma cell lines[17]. 1:1 M ratio of the PTX and CUR in formulation showed enhanced cytotoxicity. In cell migration assay CL-APN demonstrated the highest inhibition in both cell lines compared to control and individual drugs . To target breast cancer, Cui et al. co-delivered CUR and DOX in a pH-sensitive prodrug using transferrin Tf-PEG-CUR. Several malignant tumors overexpress Tf. This property makes it a perfect candidate for target-specific delivery to these type of cancers. Both drugs being hydrophobic were entrapped in the core of Tf-PEG-CUR/DOX NPs. Mildly acidic pH release of CUR was significantly increased from 33.6% at pH 7.4 to 72.4% at pH 5. A similar trendas observed for DOX release. In vitro cytotoxicity assay in MCF-7 cell lines showed the highest inhibition by the Tf-PEG-CUR/DOX NPs with IC50 of 2.5 μM. The concentration of DOX and CUR in tumor, lung, and liver, major target areas in breast cancer, was the highest. The preparation also presented fewer adverse effects. Its concentration in heart and kidney was lower than others in the group. This formulation showed a high inhibition rate of tumor growth (IRT) (83.5%).Using curcumin as a theranostic agent (diagnostic + therapeutic) was studied by Nguyen et al. by fabricating Cur-PLA-TPGS NPs (curcumin + paclitaxel) co-loaded with PLA-TPGS NPs (Cur + PTX)- PLA-TPGS NPs. Fluorescence of CUR in MCF7 cell and MCF7 spheroid monitored by confocal fluorescence microscopy. This concluded that the monitoring of the delivery and bio-distribution of the drug delivery system, curcumin acted as a potential fluorescent probe[18].

2. FLAVONOIDS AND ISOFLAVNOIDS WITH ANTICANCER AGENTS

Polyphenols may selectively enhance the activity of some cytostatics against tumor cells, and at the same time, exert a cytoprotective effect on normal tissues. The most often described mechanism of flavonoid anticancer activity is their ability to inhibit proliferation and induce programmed cell death in cancer cells. At the molecular level, this activity is related to inhibition of intramolec-ular signal transduction pathways necessary for cell sur-vival such as the Ras/Raf/MEK/ERK, PI3K/Akt/mTOR, Ras/Ras protein, Raf/Raf kinase, MEK/mitogen activated protein kinase, ERK/extracellular signal regulated kinase, PI3K/phosphoinositide 3-kinase, Akt/PKB/protein kinase B, and mTOR/mammalian target of rapamycin kinase[19]. Paclitaxel, known also as Taxol, isolated from the bark of the Pacific yew (Taxus brevifolia) is widely used in treatment of breast, ovarian and lung cancers. Moreover, the combination of paclitaxel and cisplatin is an effective second-line therapy for patients with metastatic breast cancer. Paclitaxel analogues, such as docetaxel and caba-zitaxel, are also used as anticancer drugs (for treatment of aggressive breast and prostate cancers). A recent study confirmed that prenylated compounds derived from hop (Humulus lupulus L.), such as isoxanthohumol, enhance in vivo activity of paclitaxel.28 According to the literature, naringenin also enhances the sensitivities of cancer cells to doxorubicin both in vitro and in vivo. In another study, central nervous system cancer cells were used as an experimental model. This group of cancers is difficult to treat. The complex anatomical and histological structure of the central nervous system is the reason why complete removal of the cancer-af-fected tissue is often impossible. These types of cancer are also highly resistant to pharmacotherapy. Additional difficulty in the therapy is the necessity to protect neu-rons from damage. It is a known fact that nerve cells are very sensitive to oxidative stress. Having high anti-oxidant activity, flavonoids may play an important role in preventing neuronal death during anticancer ther-apy. Therefore, the study on employment of flavonoids in combination therapy of the central nervous system cancers was preceded by the assessment of their impact on normal nerve cell survival[20]. Another promising example of using quercetin in combination chemotherapy was a study carried out with MOGGCCM astrocytoma cells. Preincubation of the glio-blastoma cell line with this flavonoid increased sensitiv-ity of the cells to induction of programmed cell death by means of Temodal. Interestingly, the type of programmed cell death induced by these two compounds was depen-dent on quercetin concentration. Incubation of the astro-cytoma cells with Temodal and this flavonoid at the con-centration of 1-5 μM effectively inhibited autophagy, whereas higher concentrations of the natural compound induced apoptosis. E combination of chrysin with cytostatics is more effective in induction of programmed cell death than using single chemotherapeutics. For the majority of tested cancer cells, changes in the mechanisms regulat-ing cell cycle progression were observed. Mutual action of anticancer drugs and other flavonoids, such as com-bination of temozolomide and quercetin, significantly increased apoptosis of human glioblastoma cells induced by temozolomide, the anticancer drug used in treatment of brain cancers. Moreover, quercetin administered at the proper concentration considerably increased the che-mosensitivity of breast and liver cancer cells to doxoru-bicin, and therefore enhanced the response of tumors to chemotherapy.

DISCUSSION

Multiple therapeutic designs have been developed to target various cancer pathways. Combination therapy has provided the most effective results with regards to anti-cancer effects. Its superiority stems from the ability to target multiple pathways, which essentially minimizes drug resistance because cancer cells are frequently incapable of adapting to the simultaneous toxic effects of two therapeutic agents. Moreover, various pathways are dysregulated in cancer cells and have disrupted homeostatic environments that generally contribute to the rapid proliferation rate. For instance, studies have shown that various cancers have mutations in tumour suppressor genes, such as p53, that normally function to activate cell cycle arrest when DNA is damaged. However, if tumour suppressor genes are mutated, accumulation of damaged DNA and inhibition of cell cycle

arrest contribute to increasingly rapid proliferation rates and a more aggressive cancer. Additionally, in cancer cells, upregulated production of autocrine growth factors or an upregulated autocrine loop can further contribute to the growth of tumour cells. If the tumour size has increased substantially, neoadjuvant chemotherapy might be indicated prior to surgical resection of the tumour; here, combination chemotherapy may potentially aid in survival. With regards to autocrine growth factors, if VEGF is upregulated, metastasis can also occur, which may worsen the prognosis and survival rate. Therefore, targeting various pathways via multiple drug combinations can increase the chance of disease control and decrease the chance of cancer cells becoming increasingly malignant and incurable. Also, in some cases, the dose requirement of each agent in combination therapy can be reduced, which reduces the side-effects compared to monotherapy, albeit some combination therapies have been shown to increase toxicity. An additional advantage of combination therapy is that multiple drugs can target the heterogeneous nature of tumours, correspondingly increasing the chance of killing all cancer cells, including the cancer stem cell population that is known to contribute to drug resistance and cancer recurrence after remission in later years. It should be noted, however, that studies have also revealed some disadvantages of combination therapy use in cancer. Firstly, the combination of multiple agents can synergistically or additively create therapeutic benefits, but can equally produce unwanted side-effects. This can make it difficult to identify the responsible agent and as a result, it would be difficult to assess which agent's dose should be lowered. If the therapeutic agents act similarly, where their side-effect profiles are similar, the accumulation of side-effects can create more severe clinical symptoms and grade 3/4 toxicities that can severely impact and alter the patient's life expectancy. As an example, in a phase I/II study performed by Berdeja et al, the combination of panobinostat and carfilzomib resulted in treatment-related heart failure while treatment-related death rose in patients with relapsed/refractory multiple myeloma. Obviously, complications from combination therapies can create further problems for patients in terms of financial and general well-being. Drug interaction should be thoroughly considered when creating a combination therapy regimen for cancer. For instance, one drug may inhibit the metabolic activity of the secondary or tertiary agent, formally leading to the buildup of toxicity which consequently has a detrimental effect on the patient's health.

CONCLUSION

Generally speaking, use of drug combination has better therapeutic outcomes than use of single anticancer drug. But at the same time it is less economic than single drug. Apart from the Cost-effective consideration drug combinations is one of the safest and efficient treatment options for cancer. Increasing experimental data and clinical evidence suggest it might be a good way to use drug combination in controlling tumor growth and metastasis. The toxicities developing during conventional monotherapy can be reduced by using combinations of drugs also there is a chance for increased toxicity due to increased number of drugs. Drug sensitivity tests, cancer biomarker detecting and pharmacokinetics are designed to select effective drugs and to discard ineffective drugs. They can make a good balance between drug activity and toxicity.

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