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REVIEW ARTICLE

COMBINATION OF NATURAL DRUGS: AN EMERGING TREND IN CANCER CHEMOTHERAPY

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ABSTRACT:
Cancer is major health burden in developed countries as well as developing countries around the globe. Breast cancer, lung cancer, prostate cancer and colon cancer are responsible for more than 50 percent of total deaths due to cancer . Chemotherapy is most popular and convenient form of treatment against almost all types of cancer. Products of natural origin are employed in chemotherapy for long time in the form of chemopreventive, chemosensitizing and chemotherapeutic agents. Combination drugs chemotherapy is considered to be more effective and safer way of treatment. This short review is an attempt to cover the combination of drugs from plant origin that are effective in most common cancers and their clinical status.
Keywords: Chemotherapy, Carcinoma, Melanoma, Cytotoxicity, Clinical trial

INTRODUCTION:

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. Cancer is caused by both external factors (tobacco, infectious organisms, chemicals, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism). Ten or more years often pass between exposure to external factors and detectable cancer. Cancer is treated with surgery, radiation, chemotherapy, hormone therapy, biological therapy, and targeted therapy. The American Cancer Society estimates that in 2012 about 173,200 cancer deaths will be caused by tobacco use. Many of the more than 2 million skin cancers that are diagnosed annually. Cancer researchers use the word "risk" in different ways, most commonly expressing risk as lifetime risk or relative risk[1].

The National Cancer Institute estimates about 1,638,910 new cancer cases are expected to be diagnosed in 2012. In 2012, about 577,190 Americans are expected to die of cancer, more than 1,500 people a day. Cancer is the second most common cause of death in the US. By 2030, the global burden is expected to grow to 21.4 million new cancer cases and 13.2 million cancer deaths simply due to the growth and aging of the population, as well as reductions in childhood mortality and deaths from infectious diseases in developing countries[2].

Table 1: Cancer facts and figures according to National cancer Institute (NCI)

Estimated New Cancer Cases and Deaths by Sex, US, 2012						
	Estimated New Cases			Estimated Deaths		
	Both Sexes	Male	Female	Both Sexes	Male	Female
Breast	229,060	2,190	226,870	39,920	410	39,510
Prostate	241,740	241,740	-	28,170	28,170	-
Lung & bronchus	226,160	116,470	109,690	160,340	87,750	72,590
Colon	103,170	49,920	53,250	51,690	26,470	25,220
Ovary	22,280	-	22,280	15,500	-	15,500
Liver & intrahepatic bile duct	28,720	21,370	7,350	20,550	13,980	6,570
Small intestine	8,070	4,380	3,690	1,150	610	540
Brain & other nervous system	22,910	12,630	10,280	13,700	7,720	5,980
Skin (excluding basal & squamous)	81,240	46,890	34,350	12,190	8,210	3,980
Melanoma-skin	76,250	44,250	32,000	9,180	6,060	3,120
Pancreas	43,920	22,090	21,830	37,390	18,850	18,540
Urinary bladder	73,510	55,600	17,910	14,880	10,510	4,370
Kidney & renal pelvis	64,770	40,250	24,520	13,570	8,650	4,920
Genital system	340,650	251,900	88,750	58,360	28,840	29,520
Lymphoma	79,190	43,120	36,070	20,130	10,990	9,140
Myeloma	21,700	12,190	9,510	10,710	6,020	4,690

The primary modalities of cancer treatment are surgery, chemotherapy, and radiotherapy; these may be used alone or in combination. Surgical treatment[3,4] depends on the stage of cancer, the organ affected and the patient condition. In surgically treated patients, pain relief can often be achieved and long term neurological stabilization tends to persist more often that it does with conservatively treated patients. Surgical intervention may be appropriate for patients with advanced disease for avoiding urgent life-threatening symptoms or serious functional disorders that annoys patients daily life, but surgical treatment for elderly cancer patients should be carefully considered after weighing the risk of post operative mortality, morbidity, functional deterioration due to the surgery and speculated life surgery. Common surgical techniques are Laser surgery[5], Cryosurgery[6], Electrosurgery, Mohs surgery, Laparoscopic surgery, and Thorascopic surgery. Most often an adjuvant chemotherapy along with the surgical treatment of cancer is recommended. Surgical procedures for treatment of cancer is limited by Bleeding, Damage to internal organs and blood vessels, Reactions to drugs used (anesthesia) or other medicines, Problems with other organs, such as the lungs, heart, or kidneys, Infection at the site of the wound is another possible problem etc[7,8].

Radiation therapy is used to kill the cancer cells. It can also affect normal cells near the tumor. Radiation is a local treatment. Two types of radiation therapy are being used: External beam radiation therapy and internal radiation therapy. Radiotherapy in particular is often used for pain relief without curative intent[9-11].

Fatigue (feeling very tired), Skin changes, Loss of appetite, hair loss, Nausea, vomiting, diarrhea, not wanting to eat, or trouble swallowing, new rash, new bruises, or bleeding, Weight loss can be common side effects of radiotherapy.

Chemotherapy is a kind of treatment that uses drugs to attack cancer cells. Chemo may be used to: Keep the cancer from spreading, Slow the cancer's growth, Kill cancer cells that may have spread to other parts of the body, Relieve symptoms such as pain or blockages caused by cancer, Cure cancer. At present more than 50 anticancer drugs have been discovered. They are used in several ways: Monotherapy or only one drug, combined modality or chemotherapy along with other treatment such as surgery and radiotherapy, Combination chemotherapy or a group of drugs which work together. Major Side effects of chemotherapy are Nausea and vomiting, Hair loss, Bone marrow changes(Red blood cells, White blood cells, Platelets), Mouth and skin changes, Fertility problems, Memory changes, Emotional changes[12,13].

NATURAL DRUGS USED IN CANCER THERAPY:

Drugs obtained from natural origin contribute a major part in cancer treatment. An analysis of the number of chemotherapeutic agents and their sources indicates that over 60% of approved drugs are derived from natural compounds[14]. Some recent developments in cancer chemotherapy from natural origin are summarized in table II.

Table2: Summary of Drugs of Plant origin in different types of cancer

Drugs	Type of cancer	Mechanism of action	Ref
Camptothecin	Metastatic colon and rectal cancer	topoisomerase I	15-23
combretastatin A-4	Lung carcinoma and breast cancer	tubulin binding	24-29
Epipodophyllotoxin	small cell lung cancer, testicular carcinoma, lymphoma	topoisomerase I and II	30
Homoharrington	Lung carcinoma, colon adinocarcinoma	Protein synthesis inhibition	31-34
Ingenol	Skin cancer	protein kinase C activation	35-39
Daidzein	Breast and prostate cancer	NADH oxidase (tNOX) inhibition	40-43
Paclitaxel	Breast, ovarian, lung, bladder, prostate, melanoma	tubulin stabilization	44-52
Protopanaxadiol	stomach, lung, liver, pancreas, ovaries, & colon	caspase 3, 8 and 9 stimulant	53-55
Triptolide	Prostate cancer	T-cell proliferation suppression, IL-2 expression and NFj-B activation	56-62
Vinblastine	Hodgkin's lymphoma, non-small cell lung cancer, breast, head and neck, & testicular cancer	tubulin binding	63,64
Quercetin/Resveratrol	Colorectal cancer	induction of expression of caspase 3/8, causing DNA fragmentation, and arresting cells in G1 phase of the cell cycle	65
7,12-dimethylbenz(a) anthracene	Breast cancer	induced mammary carcinogenesis, and suppressed proliferation and lipogenesis in MCF-7 breast cancers	66,67
docosahexaenoic acid (DHA)	Prostate cancer	increased lipid peroxidation and enhanced efficacy of anticancer drugs	68
glycyrrhizic acid and oleanolic acid	Skin cancer, Colon cancer and breast	Activate proapoptotic signaling cascades and suppression or nuclear translocation of various transcription factors including nuclear factor kappa B (NF-κB).	69
Berberine hydrochloride	Lung cancer	Bind specifically to oligonucleotides and to stabilize DNA triplexes or G-quadruplexes via telomerase and topoisomerase inhibition.	70
Curcumin	advanced pancreatic cancer	suppresses nuclear factor-nB (NF-nB) activation	71

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Resveratrol (Pterostilbene)	Breast cancer	Inhibit both apoptosis and cell cycle arrest	72
ginsenoside 25-OH-PPD	prostate cancer	reduced expression of MDM2, E2F1, Bcl2, cdk2/4/6, and cyclin D1, which correlated with the cell cycle arrest in G1 and the decrease in proliferation	73
Thymoquinone	colon, prostate, pancreatic and lung cancer	anti-proliferation, apoptosis induction, cell cycle arrest and anti-metastasis/anti-angiogenesis	74
Docetaxel	Breast cancer	Bind to the β-tubulin subunits of microtubules, which prevents their depolymerization and blocks cell growth in the G_2-M phase	75

COMBINATION CANCER THERAPY:

Chemotherapy drugs are most effective when given in combination (combination chemotherapy). The rationale for combination chemotherapy is to use drugs that work by different mechanisms of action, thereby decreasing the likelihood that resistant cancer cells will develop. When drugs with different effects are combined, each drug can be used at its optimal dose, without intolerable side effects.

Combinations used in breast Cancer:

Breast cancer (malignant breast neoplasm) is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk[76]. Worldwide, breast cancer comprises 22.9% of all cancers (excluding non-melanoma skin cancers) in women[77]. In 2008, breast cancer caused 458,503 deaths worldwide (13.7% of cancer deaths in women)[77]. Breast cancer is more than 100 times more common in women than breast cancer in men, although males tend to have poorer outcomes due to delays in diagnosis[77-79]. An estimated 226,870 new cases of invasive breast cancer are expected to occur among women in the US during 2012; about 2,190 new cases are expected in men.

Nabholtz JM suggested that the taxanes and anthracyclines have emerged as the most active agents for treating women with advanced breast cancer[80,81]. Phase II trials of the docetaxel combinations with either doxorubicin or epirubicin showed high activity, with acceptable tolerability in patients with metastatic breast cancer. Consequently, three randomized trials have compared docetaxel-anthracycline-based regimens with standard anthracycline-based polychemotherapies as first-line therapy for women with advanced breast cancer. Therefore, docetaxel-anthracycline combinations represent a validated option in first-line treatment for women with advanced breast cancer, and are further evaluated as adjuvant treatment for early stage breast cancer. Joensuu H et al showed that adjuvant treatment with docetaxel, as compared with vinorelbine, improves recurrence-free survival in women with early breast cancer, when docetaxel compared with vinorelbine for the adjuvant treatment of early breast cancer[82-88], a short course of trastuzumab administered concomitantly with docetaxel or vinorelbine is effective in women with breast cancer who have an amplified HER2/neu gene. Pretreatment with dexamethasone increases antitumor activity of carboplatin and gemcitabine[89]. To our knowledge, this is the first report that DEX significantly enhances the antitumor activity of carboplatin and gemcitabine and increases their accumulation in tumors. These results provide a basis for further evaluation of DEX as a chemosensitizer in patients. Eichhorn PJ et al identified the tumor suppressor PTEN as a modulator of lapatinib sensitivity in vitro and in vivo[90]. Their data show that deregulation of the PI3K pathway, either through loss-of-function mutations in PTEN or dominant activating mutations in PIK3CA, leads to lapatinib resistance, which can be effectively reversed by NVP-BEZ235. A recent phase III trial demonstrated that the combination of capecitabine (Xeloda) and docetaxel (Taxotere) significantly improved objective tumor response rate, time to disease progression, and overall survival compared with single-agent docetaxel in anthracycline-pretreated patients with advanced breast cancer[91]. Green tea polyphenol EGCG synergistically sensitized breast cancer cells to paclitaxel in vitro and in vivo[92]. EGCG in combination with paclitaxel significantly induced 4T1 cells apoptosis compared with each single treatment. EGCG may be used as a sensitizer to enhance the cytotoxicity of paclitaxel.

Combinations used in Prostate Cancer:

Prostate cancer is the most common human visceral malignancy and the third most common cause of cancer-related deaths among men in the Westernized world[93]. Autopsy studies show that men in the fourth decade of life have a one-third risk of harboring small carcinomas[94]. Death rates from prostate cancer vary across the globe, with Westernized nations having the highest risk of incidence and death and Asian nations having the lowest[95].

Many tumors constitutively express high levels of the inducible form of proinflammatory enzyme, cyclooxygenase-2 (COX-2)[96]. Combination of Celecoxib and docetaxel inhibited COX-2 activity and associated alteration in cell death signaling, a potential clinical use of combined dosing of COX-2 inhibitors and cytotoxic drugs at lower, nontoxic dose than currently used to treat advanced prostate cancer. McCubrey JA et al isolated cell with the cancer initiating cell (CIC) phenotype from PC3 cells[97]. Low doses of genistein can increase the sensitivity of prostate CICs to drugs such as docetaxel and cyclopamine, two drugs either used or under consideration for prostate cancer therapy. The polyamine analog PG11047 potentiates the antitumor activity of cisplatin and bevacizumab in preclinical models of prostate cancer [98]. The objective of the present study was to assess the antitumor effects of PG11047 alone and in combination with approved anti-cancer agents. Another study showed that demonstrate the potential anticancer efficacy of genistein-topotecan combination in LNCaP

prostate cancer cells and the mechanism of the combination treatment[99]. Treatments involving genistein-topotecan combination may prove to be an attractive alternative phytotherapy or adjuvant therapy for prostate cancer. An exploratory analysis of phase III trial participants found a substantial survival benefit to receiving docetaxel some months after sipuleucel-T[100]. Sipuleucel-T is an active immunotherapy that triggers T-cell responses against prostate cancer. This trial highlights major unresolved questions concerning the optimum choice, dosing, and timing of chemotherapy relative to active immunotherapy. Stearns ME and Wang M have examined whether epigallocatechin-3-gallate (EGCG), and extract of green tea, in combination with taxane (i.e., paclitaxel and docetaxel), exerts a synergistic activity in blocking human prostate PC-3ML tumor cell growth in vitro and in vivo[101].

The overall chance of death from prostate cancer, even among Westernized nations that have not historically treated the disease for cure, is 3.5% to 4%[102]. Given the large discordance between histologic incidence and death, there is great potential for overdetection and overtreatment. This is even more relevant as treatment-related morbidities associated with prostate cancer treatment can impact urinary function, sexual function, and quality of life[103]. Disease prevention thus offers an attractive paradigm for addressing this important public health problem.

Combinations used in Colon Cancer:

An estimated 103,170 cases of colon and 40,290 cases of rectal cancer are expected to occur in 2012. Colon cancer, the fourth most common cancer in the world, is one of the leading causes of cancer death in both men and women in Western countries, including the USA[104,105]. An expert panel assembled by the American Institute for Cancer Research/World Cancer Research Foundation came to a scientific consensus that there is evidence for a correlation between a high intake of saturated fats (and/or animal fat) and colon cancer risk[106].

Schröder CP, Maurer HR demonstrated in vitro, that pretreatment of human LS 174T colon cancer cells with nontoxic concentrations of tributyrin augments the sensitivity to spontaneous NK cell activity two-fold[107]. However, when NK cells have been activated with an optimized combination of IL-2 and IL-12, the immunocytotoxicity increases up to five-fold (from 14% to 70%), versus a 3.8-fold increase against untreated cancer cells. These data suggested a synergistic link between induction of tumor cell differentiation and immunological defense mechanisms that may provide a rational basis for the improvement of clinical protocols, especially for colon cancer. In vitro[108], viable cell growth was determined by trypan blue exclusion assay and cell death was investigated by flow cytometry. ALA (50 µg/ml) and HESW (E1, EFD = 0.22 mJ/mm², 1000 shots or E2, EFD = 0.88 mJ/mm², 500 shots) showed a significant reduction of cancer cell proliferation at day 3 compared to cells exposed to ALA ($p < 0.01$) or HESW ($p < 0.001$) alone. In vivo, apoptosis detection was carried out by TUNEL assay, the pro-apoptotic gene Bad and Bcl-2 mRNA expression was evaluated by quantitative SYBR Green real time RT-PCR and cleavage of poly (ADP-ribose)-polymerase (PARP) was investigated by Western Blotting. The interaction between HESW and ALA is then effective in inducing apoptosis on a syngeneic colon cancer model[108]. Antitumor activities of carboplatin and gemcitabine with or without DEX pretreatment were determined in six murine-human cancer xenograft models, including cancers of colon (LS174T)[89]. Although DEX alone showed minimal antitumor activity, DEX pretreatment significantly increased the efficacy of carboplatin, gemcitabine, or a combination of both drugs by 2-4-fold in all xenograft models tested and increased their accumulation in tumors. Majumdar AP et al described that the combination of curcumin and resveratrol was found to be more effective in inhibiting growth of p53-positive (wt) and p53-negative colon cancer HCT-116 cells in vitro and in vivo in SCID xenografts of colon cancer HCT-116 (wt) cells than either agent alone[110]. In vitro studies have further demonstrated that the combinatorial treatment caused a greater inhibition of constitutive activation of EGFR and its family members as well as IGF-1R. Their current data suggest that the combination of curcumin and resveratrol could be an effective preventive/therapeutic strategy for colon cancer. In other review Felth J et al described that some cardiac glycosides (digitoxin, digoxin, Convallatoxin) have been reported to exhibit cytotoxic activity against several different cancer types like colorectal cancer etc[111]. The combination of oxaliplatin and oxaliplatin exhibited synergism including the otherwise highly drug-resistant HT29 cell line. These findings demonstrate that such substances may exhibit significant activity against colorectal cancer cell lines.

Combinations used in lung cancer:

Lung cancer is the leading cause of cancer-related death in the world and can be broadly classified into small cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC)[112]. NSCLC accounts for approximately 85% of all lung cancers[113], and unlike SCLC, NSCLC is less sensitive to chemotherapeutic agents.

Natural compounds in combination with chemotherapy agents enhance anticancer activities of drugs and reduce their toxicity. Milczarek M et al determined an effect of isothiocyanates and 5-fluorouracil used alone or in combination (in sequential or co-administrative treatments) on normal cell lines-V79[114]. There was observed an antagonistic effect which was mainly dependent on the cell cycle distribution and their combination increased the cell number in the S phase. Another combination therapy using paclitaxel (PTX) as chemotherapeutic molecule and theophylline (TH) as differentiative agent in the prevention of metastasis in B16-F10 melanoma-bearing C57BL6/N mice. In vitro proliferation studies demonstrated that TH enhanced the antiproliferative effect of PTX. This study demonstrated that the simultaneous treatment of mice with TH and a low dose of PTX produced a similar anti-invasive effect than that caused by highly toxic PTX concentration[115]. Antitumor activities of carboplatin and gemcitabine with DEX pretreatment were determined in human cancer xenograft models, including lung (A549 and H1299) cancer[89]. DEX pretreatment significantly increased tumor

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carboplatin levels, including 200% increase in area under the curve, 100% increase in maximum concentration, and 160% decrease in clearance. DEX pretreatment similarly increased gemcitabine uptake in tumors. In other review PG11047 is a polyamine analog currently in Phase I trials for advanced cancer in combination with a number of approved anti-cancer agents[98]. The antitumor efficacy of PG11047 as a single agent, and in combination with cisplatin and bevacizumab, was tested in models of lung (A549) cancer and the result that PG11047 potentiated the antitumor effect of cisplatin. Green tea is now recognized as the most effective cancer preventive beverage[116]. The synergistic enhancement of apoptosis and GADD153 gene expression in human non-small cell lung cancer cells by the combination of EGCG and celecoxib were mediated through the activation of the MAPK signaling pathway. This article reviews the synergistic enhancement of apoptosis, gene expression, and anticancer effects using various combinations of EGCG and anticancer drugs. Saha A et al studied the enhancing effects of EC on inductions of growth inhibition and apoptosis in human lung cancer cell lines PC-9 and A549 with curcumin. The combination similarly increased both apoptosis and expression of GADD153 and GADD45 genes, associated with their enhanced protein production[117]. This report is the first report on the enhancing effects of EC on curcumin, and the data suggest that EC plays a significant role in the enhancement of the cancer-preventive activity of curcumin in the diet.

CONCLUSION:

Numerous experimental, clinical, and epidemiologic studies indicate that combination of drugs particularly natural drug combination show promise as anticancer drugs chemotherapy. The clinical application of these combination drugs is still limited by the lack of randomized evidence of their efficacy and safety. The combination therapy is definitely a promising area in chemotherapy to reduce the dose of anticancer drugs henceforth the adverse effects as well but more clinical studies are required.

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Table3: Summary of combinations of drugs of herbal origin in different types of cancer

Drugs	Mechanism of Action	Clinical Status	Type of Cancer	Ref
Isothiocyanates and 5-fluorouracil	Increased the cell number in the S phase		Lung cancer	114
paclitaxel (PTX) and theophylline (TH)	TH enhanced the antiproliferative effect of PTX		Lung metastasis	115
Docetaxel and doxorubicin	Showed high activity, with acceptable tolerability	II	Metastatic breast cancer	80,81
Trastuzumab and docetaxel/vinorelbine	Specific for HER-2-overexpressing tumor cells	II	Breast cancer	82-88
Glucocorticoid and irinotecan	Decreased incidence and duration of diarrhea		Advanced colorectal cancer	118
Celecoxib and docetaxel	Inhibit COX-2 activity and associated alteration in cell death signaling		Advanced prostate cancer	96
Dexamethasone and carboplatin/ gemcitabine	Enhanced the antitumor activity and increased their accumulation in tumors		Colon, Lung, and Breast cancers	89
Budesonide and loperamide	Decreased incidence and duration of diarrhea		Advanced Colorectal cancer	118
Cisplatin and HemoHIM	Enhanced the antitumor efficacy and decreased the tumor size and weight		Melanoma	119
genistein and cyclopamine	BC cells are usually more rapidly proliferating than the CICs		Prostate cancer	97
Lapatinib and trastuzumab	Inhibited growth of HER2þ tumors resistant to anti-HER2 therapy	III	Advanced and metastatic breast cancer	90
capecitabine (Xeloda) and docetaxel (Taxotere)	Improved tumor response rate, time to disease progression, and overall survival	III	Advanced breast cancer	91
PG11047 and cisplatin and bevacizumab	Inhibit polyamine biosynthetic enzymes, induce the polyamine catabolic enzymes spermidine/spermine N(1)-acetyltransferase (SSAT) and spermine oxidase (SMO)	I	Lung and Prostate cancer	98
genistein-topotecan			Prostate cancer	99
Sipuleucel-T and docetaxel	Triggers T-cell responses	III	Advanced prostate cancer	100
EGCG and paclitaxel/ sulindac/ celecoxib/ doxorubicin	Inhibits TNF-α-induced promoter activity of the chemokine IL-8 by an interference with the IκB/NFκB pathway/ activation of the MAPK signaling pathway/ inhibited P-glycoprotein (P-gp) efflux pump activity/ blocking human prostate PC-3ML tumor cell growth in vitro and in vivo.		Breast carcinoma / lung cancer/ liver cancer/ Prostate cancer	92,101, 116,120, 121
Curcumin with (-)-epicatechin (EC)	Increased both apoptosis and expression of GADD153 and GADD45 genes		Lung cancer	117
Gemcitabine and Guggulsterone	Enhanced antitumor efficacy through apoptosis induction by suppressing Akt and nuclear factor κB activity		Pancreatic Cancer	29
Curcumin and resveratrol	Inhibiting growth of p53-positive (wt) and p53-negative colon cancer HCT-116 cells in vitro and in vivo in SCID xenografts of colon cancer HCT-116 (wt) cells		Colorectal cancer	110
Convallatoxin and oxaliplatin	Exhibited synergism including the otherwise highly drug-resistant HT29 cell line		Colon cancer	111

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