

Some Natural Isolated Compounds as Anticancer Agents

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ABSTRACT

Worldwide cancer is the major cause of death. Almost 8.8 million people died due to different types of cancer such as lung cancer, liver cancer, breast cancer, stomach cancer, blood cancer etc. in 2015. Government of various countries and some private organizations are spending trillions dollars for the research in cancer. According to report of WHO treatment cost of cancer is approximately US\$ 1.16 trillion per year and this amount is increasing per year. Despite of huge work the exact cause of genesis is still unknown. Couples of therapies like chemotherapy, radiation, surgery and targeted therapy are available with some detrimental effect. Now scientists are seeking lead molecule from naturally occurring substances due to high safety margin as compared to current approaches. Natural phytochemicals are prominent strategy for prevention, treating, and curing cancer. There are many phytochemicals from herbs having potent anticancer property. Generally these phytochemicals treat cancer by different mechanisms like augmenting apoptosis, cell cycle arrest, targeting to some specific cancer inducing proteins, increasing cytotoxicity etc. This is our little attempt to gather information of phytochemicals having anticancer property such as Etoposide, Curcumin, Vincristine, etc. with postulated mechanism. Etoposide is effective in lung cancer, ovarian cancer by inhibiting type II Topoisomerase. Various research revealed that Curcumin is effective in different types of cancers by increasing apoptosis and targeting specific gene such as MDM2 oncogene is inhibited through the ETS2 transcription factor by modulation of signaling pathway PI3K/mTOR in breast cancer. Vincristine shows anticancer property by oncogenic EWS-FLI1 fusion protein inhibition which cause G2-M phase cell cycle arrest & reduce tumor. This review depicts few phytochemicals having anticancer property such as Etoposide, Curcumin, vincristine, etc. with possible mechanism.

Keywords: Vincristine; Curcumin; Etoposide; Phytochemicals; Anticancer; Type II Topoisomerase

INTRODUCTION

Globally cancer is the chief inducer of death. Cancer is a condition in which abnormal rapid cell growth due to irregularity in the genome. Mutations in tumor suppressor genes which work in cell-cycle regulation are often observed in numerous types of cancer (Bukhtoyarov et al., 2015). Almost 8.8 million people succumbed due to different types of cancer such as lung cancer, liver cancer, breast cancer, stomach cancer, blood cancer etc. (www.who.int/cancer/en/). Despite of huge work the exact cause is unknown; many therapies like chemotherapy, radiation therapy, surgery and targeted therapy are available with some toxic effect. Now scientists are focusing on naturally occurring substances from plant sources having anti-cancer properties with minimum toxic effect as compared to chemotherapy. Natural phytochemicals are prominent strategy for prevention, treating, and curing cancer. There are many phytochemicals from herbs having potent anticancer property. Generally these phytochemicals treat cancer by different mechanisms like increasing apoptosis, cell cycle arrest, targeting to some specific cancer inducing proteins, increasing cytotoxicity etc. Etoposide is effective in lung cancer, ovarian cancer by inhibiting type II Topoisomerase. Various researches show that

curcumin is effective in different types of cancer like breast cancer and lung cancer by increasing apoptosis and targeting specific gene such as MDM2 oncogene is inhibited through the ETS2 transcription factor by modulation of signaling pathway PI3K/mTOR in breast cancer. (Lazaro M, 2008) Government of various countries and some private organizations are spending trillions dollars for the research in cancer.

Sr. No	Drug	Biological Source	Chemistry	Effective organ	Side Effect	Clinical status/Marketed product www.clinicaltrials.gov	Mechanism of action
1	Etoposide (Derivative of podophylotoxin)	Dried rhizome of <i>Podophyllum peltatum</i>	<u>glycoside</u> of podophyllotoxin with a D- <u>glucose</u> derivative	Testicular Cancer, Lung Cancer Ovarian cancer	Decrease RBC count Vomiting Hair loss	Etopophos	Type II Topoisomerase Inhibitor (Wu C, et al 2011)
2	Andrographolide	Stem & Leaves Andrographis paniculata.	Diterpene lactone	Colorectal Cancer, Breast Cancer	Nausea, Diarrhea, Lymphadenopathy, emesis, Allergic reaction	Phase II	Cell cycle arrest G2/M (Sriram Rajagopal et al 2003) Down regulation of PI3Kinase Induces Cellular Apoptosis Through Caspase Independent Pathway (S. Kumar et al 2012)
3	Sulforaphane	broccoli, Brussels sprouts, cabbage,	<u>Isothiocyanate</u>	Prostate cancer, Breast Cancer, Pancreatic cancer		Avmacol	Inhibits histone deacetylase (HDAC) activity (Myzak et al 2004)
4	Pomiferin	Fruit and flower of <i>Maclura pomifera</i>	Isoflavonoid	Colon Cancer, Head & Neck cancer		Phase II	Pro-apoptotic effects; DNA fragmentation; inhibits oxidative damage of DNA; antioxidant activity; inhibits histone deacetylases; cytotoxicity of cancer cells (M. Greenwell et al 2015)

6	Gambogenic acid	Garcinia hanburyi tree.	Xanthonoid	Breast cancer Lung cancer			By suppressing MDA-MB-231 breast cancer cell growth by Imparting apoptosis through mitochondrial pathways & death receptor (Zhou et al 2013)
7	Lycopene	Tomato Watermelon Carrot	tetraterpene carotene	Breast cancer	diarrhea, nausea, stomach pain, allergic reaction	Phase II	Inhibit proliferation decrease cyclic dependent kinase activity arrest G1 Phase (<i>Bhuvanewari and Nagini 2005</i>)
8	vincristine	<u>Catharanthus roseus</u>	Alkaloid	Lymphoma	Constipation Hairloss Change in sensation Difficulty in walking Headache	I.V. <u>Alcrist</u> <u>Vincristine Sulphate</u> <u>Oncocristin -AQ</u>	oncogenic fusion protein EWS-FLI1 is Inhibited which causes G2-M phase cell cycle arrest (<i>Zöllner S et al 2017</i>)
9	Docetaxel	bark of the rare Pacific yew tree <i>Taxus brevifolia</i>	<u>diterpenes.</u> Taxanes (Pengxiang and Didier 2012)	Breast cancer Head & neck Stomach cancer Prostate & lunge cancer	Low blood count Vomiting Hairloss Muscle pain Liver problem	Slow I.V. taxotere	Inhibits angiogenesis promote apoptosis (<i>Herbst & Khuri 2003</i>)
10	paclitaxel	Pacific yew <i>Taxus brevifolia</i> , (<i>Priyadarshini and Keerthi 2012</i>)	diterpene with taxan ring	Breast Lung Cervical Pancreatic cancer <u>Kaposi's sarcoma</u> Ovarian	Bone marrow suppression Heart problem Lung inflammation	I.V. oraxol	CLIP-170 Microtubule-binding protein increase the potential of paclitaxel to block the advancement of cell cycle at mitosis and to generate apoptosis in breast cancer cells (<i>Sun et al 2012</i>)
12	Squalamine	<i>Squalus acanthias</i> (shark)	Aminosteroid	Ovarian Prostate CNS Tumor	Liver toxicity. Nausea.	Phase II	Squalamine blocked VEGF-induced activation of MAP

				Lung cancer	Fatigue. Anorexia. Muscle weakness		kinase and cell proliferation in human vascular endothelial cells. Block angiogenesis with or without HER2 gene overexpression (Williams J. & Dan Li et al 2002)
14	Indirubin	Danggui Longhui Wan,		Breast Lung Prostate	mild abdominal pain, diarrhea, and nausea	Phase IV	Cyclin-dependent kinases is inhibited due to which G1 G2/M phase cell cycle arrest(Lee J. Moon M et al 2005)(Hoessel et al 1999)
15	Epigallocatechin gallate	leaves of <u>green tea</u> <u>black tea</u> <u>white tea</u> onion	<u>polyphenol</u> catechin	Colon Breast Prostate	Stomach upset Constipation	Phase I	By increasing pro-oxidation which leads to DNA cleavage and increase apoptosis (S. Azam et al 2004) Inhibit cell proliferation
16	Curcumin	Curcuma longa Family <u>Zingiberaceae</u> <u>e. (Kuttan R. et al 1985)</u>	phenol Curcuminoids <u>diarylheptanoid</u>	lung cancer	Increased risk of bleeding Increased menstrual flow. Hypotension Nausea. Diarrhea.	Phase II	(Animal model) curcumin Inhibit NF-kappaB in cancer cells inhibition of MDM2 oncogen through the ETS2 transcription factor by PI3K/mTOR signaling pathway modulation. Inhibition of spleen tyrosine kinase (Syk) leads to inhibition of Akt and its target Bad in B lymphoma Increase Apoptosis Inhibit angiogenesis (Lazaro M 2008)
17	Podophyllotoxin	roots and rhizomes of <u>Podophyllum</u> species.	Glycosides	Burning, Redness, Pain, Itching, Swelling, CNS	burning, redness, pain, itching, swelling. <u>CNS</u>	Phase II	Tubulin polymerization is inhibited due to which cell cycle arrest in the metaphase

				Depression	<u>depressio</u> <u>n</u>		(Gordaliza M et al 2000).
18	Ellagic acid	<u>Myriophyllum spicatum</u>	Polyphenolic	Prostate cancer Breast Cancer. Colorectal cancer		Phase II	Decrease Angiogenesis by Down regulation of Heme Oxygenase (HO) and By lowering epoxyeicosatrienoic acid synthesis or increasing its degradation (EETs) Antiproliferative effect is due to inhibition of DNA methyltransferase I (DNMT I)) (Vanella L et al 2013)
19	ginsenosides	Root of panax ginseng (Shihonget al 2014)	Steroid glycoside & Titerpene saponin	Lung cancer	Restlessne ss, insomnia, anxiousne ss	Phase II	Inhibit capillary genesis Inhibit TNF-a release Down regulate nucleophosmin (Chen S et al 2014)
20	Resveratrol	roots of Polygonum cuspidatum. (AluyenJ. et al 2012)	Phenol	Colon cancer Bladder cancer Liver cancer	Sometime s slow blood clotting	Phase I	Apoptosis is induced due to lower expression of HSP-70 and HSP-27 Active form of NF-κB is inhibited which influences apoptosis through down regulation of the genes VGEF Bcl-2, Bcl-xL, XIAP, and c-IAP. Resveratrol inhibit COX by activation of macrophage-inhibitory-cytokine-1 which decrease proliferation.) (Hu Wang et al 2014)
21	Camptothecin	bark of <i>Camptotheca acuminata</i> (Chinese happy tree)	Alkaloids	cervical cancer gastric cancer	myelosup pression, vomiting, diarrhoea	Phase I	Act as DNA topoisomerase I poision and induce apoptosis (Martino E. et al 2017)

22	Rosmarinic acid	(<i>Rosmarinus officinalis</i> Fam: <u>Blechnaceae</u> <u>Ocimum basilicum</u> <u>Ocimum tenuiflorum</u>	polyphenolic diterpenes,	Lung Liver Prosted Myeloid leukemia Breast Pterygium	Uterine bleeding, Allergic reactions & skin redness, Kidney irritation ----- -----	-----	suppression of NF-κB signaling in H22 tumor-bearing mice (Cao W et al 2016)
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DISCUSSION

Cancer is becoming a high profile disease in developed and developing worlds. In 2007 the WHO published that in 2005, 7.6 million people died from cancer related diseases with the majority of these people living in low-income countries. In the United States cancer is the cause of 1 in 4 deaths and in 2010 it was estimated there were over 1.5 million new cases of cancer (Jemal et al 2010). Cancer Research UK said in 2012 14.1 million adults were diagnosed with cancer and 8.2 million people were killed by cancer globally (www.cancerresearchuk.org) Therefore, the demand for a cure and the prevention of cancer is extremely high.

Chemically-derived drugs have been developed and other cancer treatments pre-exist. (Seidel et al 2012). However, current methods such as chemotherapy have their limitations due to their toxic effects on non-targeted tissues furthering human health problems (Ochwang'I et al 2014). Therefore, there is a demand for alternative treatments with naturally-derived anticancer agents with plants being the desired source.

Increasing demand for plant-derived drugs is putting pressure on high-value medicinal plants and risking their biodiversity (Zschocke et al 2000). Increasing

populations, urbanization and deforestation are contributing to species endangerment in developing countries. To aid conservation of these species germplasm conservation, cryopreservation, tissue cultures and plant part substitution strategies need to be in place (Kasagana et al 2011). Mass cultivation of medicinal plant species and utilizing raw by-products in industries may also help with conservation. (Phillipson et al 1997) (Sahpazidou et al 2014)

Plant-derived anticancer agents are effective inhibitors of cancer cells lines, making them in high demand. Exploitation of these agents needs to be managed to keep up with demands and be sustainable.

CONCLUSION

This review article explains potential anticancer active ingredients from natural source. They would be least toxic and more effective than rest synthetic molecules. Till the date, no significant and systematic studies been carried out. Thus it is desirable to pursue research endeavor on these compounds and they would be brought to market in coming days. Hence millions of patients will be benefitted.

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