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# EXPLORATION OF ANTICANCER POTENTIAL OF PHYTOCONSTITUENTS AND ITS NANO APPROACHES

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## Abstract

From the beginning of civilization medicinal plants have been used, and it is most evident from the historical document and conventional herbal medicine formula. However, the lack of details on plant-based therapeutic medicine is essential for attracting interest of investigators to investigating of natural products as a suspected drug for dangerous diseases, like cancer. Now cancer is a major problem in worldwide. In consideration of many accessible treatments, a huge majority of patients die every year from cancer diseases. Bioactive phytoconstituents are preferred because they only suggested distinctly on cancer cells, without modifying normal cells. Most of studies has demonstrate the anticarcinogenic impacts of phytoconstituents that can attenuate the molecular mechanisms which involves migration, cell proliferation, invasion and apoptosis. Nanocarriers are helps to increase the stability and solubility properties of phytoconstituents which can extend their half-life in the blood, and even accomplish site-targeting delivery. This review deals with the different phytoconstituents used in cancer treatment and anticancer potential of nano based phytroconstituents.
***Keywords***: Phytoconstituents, Nanocarriers, Anticancer potential.

## Introduction

Cancer, most common widely spreded dangereous diseases in the world can cause high morbidity rate as wellas mortality rate. Traditional treatments are include surgery, chemotherapy, and radiation. These trigger toxicity complications to the patient due to non-specific to the cancer cells. (Vyas *et al.,* 2020; Aljabali *et al.,* 2020; Chaurasiya and Mishra, 2018a; Jain *et al.,* 2018). The role of the plant as a medication has been overlooked due to the absence of specific pharmacological and biochemical mechanisms. Interestingly, plants are subjected to toxic metals, environmental toxins and carcinogens constantly and widely as opposed to human beings. (Ashraf, 2020; Nandi *et al.,* 2020; Ashraf *et al.,* 2019a; Ashraf *et al.,* 2019b; Kirti and Prabhakar, 2016).

Phytoconstituents, a family of biologically active compounds which can be derived from grains, herbs, vegetables, and other plant parts have been shown to be potential candidates for such treatment (Kumar *et al.,* 2019; Vyas *et al.,* 2017). Numbers of experiments have shown that such chemopreventive phytoconstituents can control the molecular and cellular events, like DNA repair, apoptosis, metastasis, and cell cycle. (Wei *et al.,* 2019; Baena *et al.,* 2016; Kaur *et al.,* 2016a; Kaur *et al.,* 2016b; Lall *et al.,* 2015). In addition, most of these natural substances are usually less toxic and well accepted in normal cells. Natural products are acceptable in healthy cells even at higher doses as opposed to chemotherapeutic drugs (Attri *et al.,* 2019).

Nanotechnology correlated to pharmaceutical technologies offers the ability for safe and efficient drug delivery (Mishra *et al.,* 2019a Mishra *et al.,* 2018b; Mishra *et al*., 2018c; Mishra *et al*., 2018d; Mishra *et al*., 2017; Devi *et al.,* 2014; Prabhakar *et al*., 2011a). Nanoparticles (NPs) show controlled drug delivery by evasion of the reticuloendothelial system (RES), enhanced permeability, manipulation of retention effect, and site-specific targeting. Nanotechnology is the most beneficial and fastest method to counter life threatening diseases, such as cancer, in pharmaceutical research (Kaur *et al.,* 2020; Patil *et al.,* 2019 Mishra *et al.,* 2019b).

Drug delivery systems using nanotechnology for the delivery of natural compounds indicated that this technology could have significant benefits compared to traditional cancer treatments. The benefit of this nanotechnology is that NPs encapsulated drugs can be shielded against the harmful effects of external exposure (Navya *et al.,* 2019). The half-life of the drug can therefore be prolonged in systemic circulation. Moreover the delivery of water-insoluble drugs can be enhanced through nano-particles, chemotherapeutic agents are increasing their transfer through biological membranes (Duan & Li, 2013), can only supply drugs to cancer cells (Alexies *et al.,* 2008), enhance the distribution of drugs, provide sustain drug releases and assist in the delivery of two or more drugs contrasted with non-encapsulated free drugs for combin therapy. Different nanocarrier based phytoconstituents in cancer treatment and their effectiveness are described in Table 1.

**Phytoconstituents in cancer treatment**

Since ancient times plants and their formulations have been used for medicinal purpose. Traditional medicine professionals use different herbal medicines with different philosophies and cultural backgrounds to treat disease forms (Bawa *et al.,* 2019; Prabhakar and Doble, 2011b; Prabhakar and Doble, 2009). Natural products derived from plants are non-toxic to human cells, and are also better tolerated, thereby drawing attention from current drug discovery. A phytoconstituents (Mishra *et al.,* 2019c; Mishra *et al.,* 2019d; Mishra *et al.,* 2018e) may suppress a malignant preneoplastic cell transformation or block the metabolic conversion of the procarcinogen. Cellular and signaling events involved in the development, invasion and metastases of cancer cells can also be modulated (Neupane *et al.,* 2017; Singh *et al.,* 2016).

***Curcumin***

Curcumin, a hydrophobe polyphenol extracted from the turmeric spice over the past decades, is one successful nutraceutical ingredient and the scientist's curiosity has been attired by curcumin, because of its high therapeutic potential for cancer. Curcumin prevents carcinogenesis has been found (Shehzad and Lee, 2013).

Dendrimers has appeared as a distinctive polymeric globular nanoparticulate drug delivery system that could be used sensibly to tackle the most deadly cancer of diseases. The inimitable molecular topography of this delivery system may allow the provision of a different nature, such as lipophilic or hydrophilic drugs and macromolecules as proteins or the RNA, of bioactive anticancer bioactive substances (Saluja *et al.,* 2019).

Ghaffari *et al*, 2020 enhanced the solubility and bioavailability of curcumin by entrapment in a polyamidoamine (PAMAM) dendrimer, and a polyplex was formed by grafting Bcl-2 siRNA onto the surface amine groups to produce PAMAM-Cur/Bcl-2 siRNA nanoparticles (NPs). The PAMAM-Cur/Bcl-2 siRNA NPs showed more effective cellular uptake, and higher inhibition of tumor cell proliferation compared to PAMAM-Cur nanoformulation and free Cur, due to the combined effect of co-delivery of Cur and Bcl-2 siRNA. The newly described PAMAM-Cur/Bcl-2 siRNA polyplex NPs could be a promising co-delivery nanovehicle (Ghaffari *et al.,* 2020).

Liposomes effectively encapsulate turcumin in a polymer form, resulting in an improved water solubility and bioavailability of the aforementioned hydrophobic agents (Sheikhpour *et al.,* 2020). In 2020, Vetha *et al*. reported use of small photodynamic therapy (BLED-PDT)-induced CUR molecules, encapsulated in liposome nanocarriers (LIP-CUR). In A549 in vitro cancer cells, BLED-PDT initiated and $^1O_2$ induced LIP-CUR coupled with BLED, ultimately leading to apoptotic cell death by Caspase-3 triggered. A new strategy on the treatment of cancer could be developed as a result of the interaction of a non cytototoxic dose of the small CUR molecule co-treated with BLED to cause BLED-PDT (Vetha *et al.,* 2020).

***Withania somnifera***

It is a root extract from the Solanaceae family and is a popular and widely-used herb in the traditional Indian medicine system. Modern medicine has become increasingly attractive in its medicinal features, primarily because of the anti-microbial, anti-oxidant, anti-diabetic, anti-carcinogenic and antinineuro-degenerative properties (Dar *et al.,* 2016; Palliyaguru *et al.,* 2016; Sangwan *et al.,* 2004). In vivo, the activity of an alcoholic *withania somnifera* root extract in a murine sarcoma model was initially reported (Devi *et al.,* 1992).

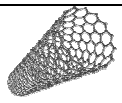
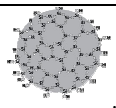
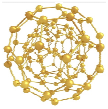
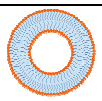
Kim *et al*., 2020 examined the impact on fatty acid synthesis with the LNCaP and 22Rv1 human prostate cancer cells of ethanol extract of *Withania somnifera* root (WRE) standardized for one of its components (withaferin A). Intracellular levels of acetylCoA, complete free fatty acids and neutral lipid droplets have decreased significantly in LNCaP and 22Rv1 cells in the course of WRE therapy. WRE had greater potential than cerulenine and etomoxir for inhibition of fatty acid inhibition at an equimolar concentration. Downregulation of cMyc and p-Akt (S473) proteins on both cell lines results from exposure to WRE. However, only c-Myc overexpression conferred clonogenic survival defense and WRE lipogenesis inhibition. To conclude, these findings show that WRE prevents the synthesis of fatty acids in human prostate cells (Kim *et al.,* 2020).

Dar *et al*., analyze 2019, as part of its cytotoxicity of various human cancer cell lines, a novel protein fraction, here called WSPF, isolated from Withania somnifera. The WSPF demonstrated apoptotic activity with an IC50-value of 92µg/mL against human breast cells, for each line of cancer cells tested. MDA -MB-231 cells induced WSPF-mediazed with mitochondrial apoptosis via extensive generation of reactive oxygen species, Bax / Bcl-2, mitochondrial membrane potential loss and caspase-3 activation. The latest findings indicate that proteins in this group are potential therapeutic agents for three-fold negative treatment of breast cancer (Dar *et al.,* 2019).

***Allium sativum (Garlic)***

The intake of garlic is strongly linked to lower cancer risk, particularly for gastric or intestinal cancer (Zhang *et al.,* 2020). Current statistics from the laboratory suggest that garlic has successful cancer cell kill components. Several international organizations, comprising the World Health Organization (WHO), National Cancer Institute (NCI), and the American Institute of Cancer Research (AICR), advised that a daily dietary intake of garlic should be related to the reduced risk of cancer (Chakarborty *et al.,* 2014; Surh *et al.,* 2003).

**Table.1 :** Nanocarrier based phytoconstituents in cancer treatment.

| Nano carriers | Phytoconstituents | Cancer type | Advantages | References |
|---|---|---|---|---|
|  Single walled carbon nanotubes |  Curcumin | Lung adenocarcinoma | Enhanced aqueous solubility; A reasonable and optimal drug delivery system has increased the impact of anticancer | Singh *et al*., 2018 |
|  Silica nanoparticles | | Liver cancer, Cervical cancer | Boost bioavailability of curcumin to prevent and treat cancer; For molecular imaging, act as auto-fluorescence probe | Elbialy *et al*., 2020 |
|  Gold nanoparticles |  Resveratrol | Hepatoma | Tumor growth inhibition; triggered tumor apoptosis | Zhang *et al*., 2019 |
|  Niosomes |  Gingerol | Breast cancer | Improved bioavailability | Behroozeh *et al*., 2018 |
|  Liposome |  Quercetin | Bladder carcinoma | Improved permeation and retention effect; targeted targeting; increased efficacy of the antitumors; reduced toxicity | Hu *et al*., 2017 |

The effects of Z-ajoene on Glimediated transcription and pancreatic cancer cells are determined by Lee *et al*. Authors found that the Z-ajoene in Sonic Hedgehog (Shh) stimulated C3H10T1/2 mesenchymal stem cells that inhibit Gli transcriptional activity. In addition, Z-Ajoene reduced FoxM1, one of the Gli-target protéins, and subsequently reduced the cell cycle-related protein expressions. In addition, Z-ajoen reduced proliferation of cells and improved the PANC-1 process G2/M. Such results suggest that Z-ajoene can prevent the proliferation of pancreatic cancer cells. Therefore, Z-ajoen may be a leading compound in anti-pancreas development (Lee *et al.,* 2019).

Kaowinn *et al*., synthesized the reductive amination process for N-benzyl-N-methyl-dodecan-1-amin (BMDA) and assessed the possible action of BMDA against A549 lung cancer cells with cancer-like stem cell phenotypes attributable to cancer-upregulated gene (CUG2) over-expression. The BMDA therapy also decreased the growth of the tumor in xenographic nude mice. However, inA549-CUG2 cells, which includes TGF-β signaling, BMDA blocked cell proliferation, invasion and spherical shape. Such findings suggest that BMDA is a successful anti-CUG2 anti-cancer weapon (Kaowinn *et al.,* 2018).

***Glycyrrhiza glabra***

It is generally called Licorice, a perpetual legume, which originates in various regions such as the Middle East, Southern Europe and India. Glycyrrhizin, glycyrrhizinic acid, globrin A&B, glycyrhetol, glabrolide, isoglabrolide, isoflavones, coumarins, and triterpene sterols are the key phytoconstituents. Licorice and its derivatives can protect it from the damage caused by cancerous DNA and may also be suppressive agents. Lipoxygenase and cyclooxygenase is an inhibitor of glycyrrhizic acid, which inhibited protein kinase C and reduced epidermal receptor production. Licorice polyphenols cause cancer cell apoptosis (Wang and Nixon, 2001).

Cai *et al*., assessed and examined its targets by proteomic and biological study, the impact of Glycyrrhizic Acid (GA) on hepatocellular carcinoma stemming. Results showed that GA can in vitro repress stemming and differentiate HCC. The GEO analysis shows that after GA regulation, cell distinction and pluripotence of stem cells is upregulated and down-regulated, respectively. Experimental evidence has further shown that c-Jun N-Kinase 1 (JNK1) prevents stemming and causes HCC differentiation. The results showed that GA would inhibit tumor growth by targeting JNK1 by differentiation and repression of stem (Cai *et al.,* 2020).

***Podophyllotoxin***

In addition to the congeners and derivatives, Podophyllotoxin (PPT) has strong biological consequences, in particular antineoplasty. A highly inhibitory effect in the production of tumor cell growth has led to the development of three of the most used antibody drugs in the world: etoposide, teniposide and etoposide phosphate water-soluble medication. Their clinical performance and fascinating action mechanism sparked great interest in additional modulation of PPT to boost the antitumor activity (Liu *et al.,* 2015).

Kim *et al.*, looked into the possibility of radiosensitizing β-apopicropodophyllin (APP) in non-small cell lung (NSCLC) cells. The findings of a clonogenic test showed that APP and IR combinations suppress cell growth and enhance cell death in NSCLC cells. The results of this study are focused on the predictive data. APP / IR therapy postponed care for NCI-H460 or NCI-H1299 cell xenographer mice by 22.38 and 16.83 respectively, relative to controls, to reach 1, 53 and 1, 38, respectively (Kim *et al.,* 2019).

***Eugenol***

This stops the progression of cancer by altering the function of several genes involved in cell growth, angiogenesis and apoptosis. It also avoids the production of the disorder by means of a receptor of the tumor and the disease (Al-Sharif *et al.,* 2013). In fact, eugenol was found to induce apoptosis and to suppress invasion and angiogenesis in a rat model for gastric carcinogenesis (Abdullah *et al.,* 2018).

Cui *et al*. explored and explained the fundamental molecular mechanism, the potential beneficial consequences of eugenol in vivo. Real-time polymerase chain reaction quantified relatively high levels of TRIM59 and p65 at NSCLC. TRIM59-deficient H1975 cells were developed for Xenograft tumor models, and progression of tumors was controlled. Eugenol therapy greatly impaired the growth of xenograft tumor and increased tumor-bearing mice's overall survival. Mechanistically, eugenol inhibited p65, thereby reducing the tone of TRIM59. The TRIM 59 has completely recapitulated the eugenol-emitted anti-tumor phenotype (Cui *et al.*, 209).

## Conclusion

Due to its low prices and effectiveness over the side effects of conventional drugs, the world is moving towards natural products. Researchers are stepping up efforts to develop phytopharmaceuticals for serious metabolic syndromes such as cancer. Bioactive plants and their phytochemicals have been tested for this reason but very a few have entered the therapeutic level. Bioactive phytochemical materials are a promising lead for the production of effective anti-cancer drugs. As a therapeutic tool, phytochemicals have been very successful. Nanoparticular characteristics may help to successfully resolve normal phytochemic obstacles.

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