Phytochemical nanocarrier: a green approach towards cancer therapy

Abstract
Phytochemicals serve as a promising and effective research area with a bright future. Researchers have faced a serious challenge in designing and developing an alternative, eco-friendly, biocompatible, and cost-effective strategy in a greener way due to the rising incidence of cancer, expensive treatment, various limitations in conventional therapy, and high toxicity of current anticancer drugs. Using a Novel drug delivery system for phytomolecules is expected to overcome the drawback of cancer treatment. The present review article is directed to supply an overview of Current cancer therapy via phytochemicals.

Keywords: Phytochemicals, nanoformulation, NDDS, cancer

Introduction

According to WHO, Cancer is the second leading cause of death globally. Lung, prostate, colorectal, stomach, and liver cancer are the most common types of cancer in men, whereas breast, colorectal, lung, cervical, and thyroid cancer are the most common in women. Present anticancer therapy has lots of side effects and the disease has continued throughout the life until the medicines continuously going on. Several cancerous are there which are not completely cured by synthetic medicines. In this regard, complete curable treatment is urgently needed. There is a need to look for more efficacious agents with lesser side effects hence, medicinal plants are increasingly gaining acceptance globally and various phytoconstituents have been reported to be effective in the treatment of cancer.

Over the past few years, the interest in research work toward the nano-sized phytoformulation has grown as a consequence of the pharmacological action of various phytoconstituents, thus putting more demands on the use of phytoconstituents. “Thus, the nano-sized NDDSs of herbal drugs have a number of advantages for herbal drugs, including enhancement of solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improving tissue macrophage distribution, sustained delivery, and protection from physical and chemical degradation” [1,2]. Phytochemicals that have or seem to possess significant effect on human health are grouped as: carotenoids, phenolic compounds (flavonoids, phytoestrogens,

and phenolic acids), phytosterols and phytostanols, tocotrienols.

Table 1. Cancer Rates by Country 2021 as per Global Cancer Data by Country

Country	Cancer Rate	Male Cancer Rate	Female Cancer Rate
Australia	468	579.9	363.1
New Zealand	438.1	526	358
United States	352.2	393.2	321.2
Belgium	345.8	371.1	329.9
France	344.1	405.6	292.9
Denmark	340.4	360.4	325.5
Netherlands	334.1	355.1	318.9
Canada	334	343.3	329.7
United Kingdom	319.2	344.7	299.8
South Korea	313.5	332.1	310.6
Germany	313.1	345.9	289.4
Switzerland	311	343.6	285
Sweden	294.7	313.4	279.8
Italy	290.6	318.8	270.8
Spain	272.3	328.6	227.1
Poland	253.8	292.5	229.2
Singapore	248.9	280.2	223.2
Japan	248	285.9	220.5
India	96.4	94.8	98.7

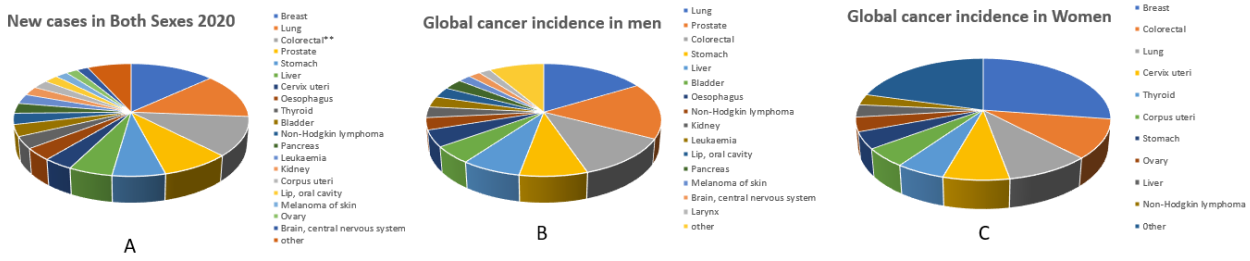

Figure 1: Distribution of Cases for the Most Common Cancers in 2020 for (A) Both Sexes, (B) Men, and (C) Women. For each category, area of the pie chart represents the proportion of the total number of cases. Source: GLOBOCAN 2020.

NEW DRUG DELIVERY APPROACHES

Various novel drug delivery systems and drug targeting systems are currently under development to reduce the drug degradation and loss, prevent or minimize harmful side effects, and enhance drug bioavailability and the amount of the drug accumulated in the required zone. Among drug carriers one can use soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, niosomes, transferosome, nanoparticles, and micelles.

“There are two major mechanisms for drug action and release: (i) passive and (ii) active targeting. Controlled drug release and subsequent biodegradation are important for developing successful formulations” [3]. “Sustained drug release involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer. The pulsatile release is often the preferred method of drug delivery, as there is the rapid and transient release of a particular amount of drug within a short time period. It is achieved by using drug-carrying polymers that respond to specific stimuli” [4].

“Presently novel drug delivery systems have been widely utilized only for chemical drugs, but they have their own limitations hence, turning to safe, effective, and time-tested Ayurvedic herbal drug formulation would be a preferable option” [5].

POTENTIAL OF NOVEL DRUG DELIVERY FOR HERBAL DRUGS

“India has a vast knowledge base of Ayurveda whose potential is only being realized in recent years. This ayurvedic drug delivery system used for administering the medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. Many times, herbal extracts will be destroyed in the highly acidic pH of the stomach. Other components might be metabolized by the liver before reaching the blood” [6]. “It results in less amount of drug reaches to blood circulation and not being able to achieve ‘minimum effective level’, which leads to no therapeutic effect. Phytopharmaceuticals are pharmaceuticals using traditional compounds derived from plant origin. Natural compounds are more easily and more readily metabolized by the body. Therefore, they produce fewer (if any) side effects and provide increased absorption in the bloodstream resulting in more thorough and effective treatments” [6].

“Lipid-based drug delivery systems have been investigated in various studies and have shown their potential in controlled and targeted drug delivery” [7]. “Phytochemical nanocarrier forms a bridge between the conventional delivery system and the novel delivery system” [8].

“If purified phytochemicals are incorporated in novel drug delivery systems, we can get the benefits of both. Thus, it is important to incorporate the novel drug delivery system in Indian Ayurvedic medicines to combat serious diseases” [7].

DIFFERENT STRATEGIES FOR THE DEVELOPMENT OF ANTICANCER PHYTOCHEMICALS:

“The power of medicinal plants as therapeutic agents depends upon the quality and quantity of active phytochemicals present in them. These natural phytochemicals can also be used in anticancer therapy, but they still need further research. The purification of active phytomolecules may involve various strategies such as combinatorial chemistry, isolation assays, and bioassay-guided fractionation. Then, a suitable source is used for the fractionation of active extracts, tested for bioactivity and various analytical must be used for the separation of active fractions. There are so many dyeing agents used for the detection of natural compounds in medicinal plants” [9]. “These procedures could be changed, however, purity, quality, and quantity of the bioactive

compounds should be high as possible and this can be achieved by using high-quality solvents, matrices, and careful handling. After purification of these phytomolecules, they must be examined for in-vitro or in-vivo anticancer effects. If a better anticancer property is achieved by the molecule, then other aspects like pharmacokinetics, pharmacodynamics, immunogenicity, metabolic fate, biosafety and side effects, drug interactions, dose concentration, etc. must be researched for future drug designing. A detailed scheme of bioactive compound synthesis, optimization, characterization, testing, and potential application as a cancer therapeutic agent is shown in Figure 2". [9]

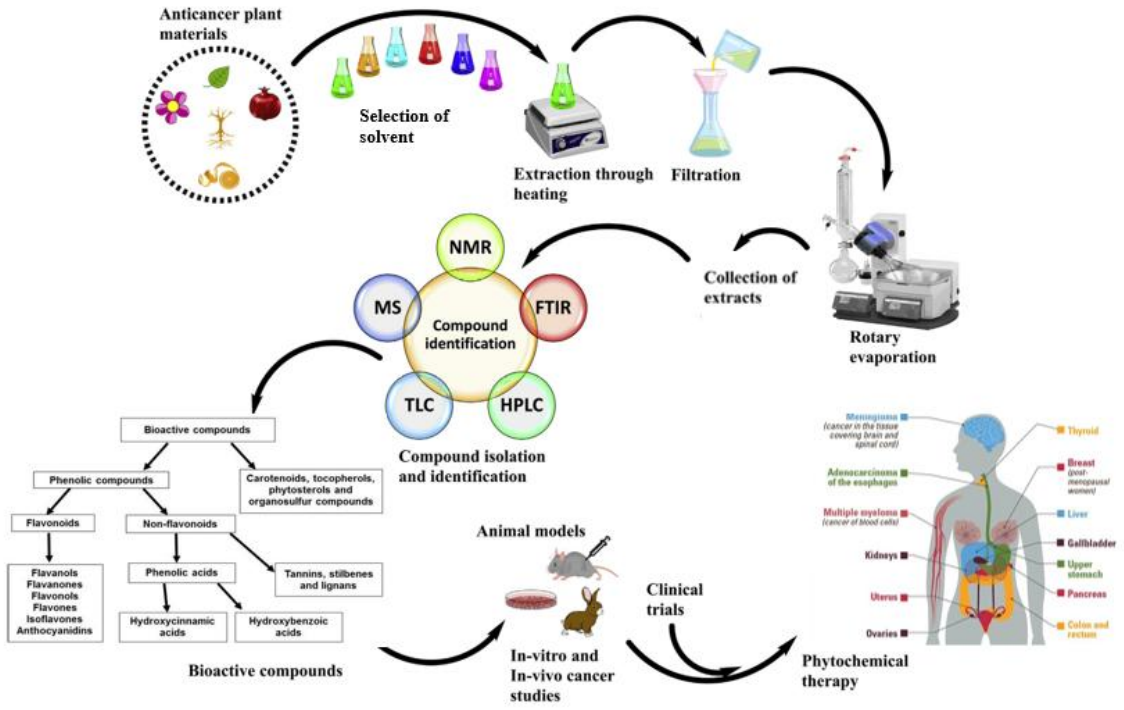

Figure 2: Detailed scheme of anticancer phytochemical synthesis, optimization, characterization, and prospective use as cancer therapeutic agent

PHYTOCHEMICALS NANOFORMULATION FOR CANCER THERAPY:

Ferulic Acids: It is found in *Angelica sinensis, Cimicifuga heracleifolia and Ligusticum chuangxiong.* It is a phenolic phytochemical present in seeds and leaves. FA exhibits a wide variety of biological activities [10]. The poor water solubility of FA increases by encapsulating it

in Nanosponge in the proportion of 1:4 (FA: NS). The cytotoxicity assay indicated that FA treatment reduced viability and enhanced apoptosis of cancer cells [11]. A combination of free FA and Aspirin, as well as chitosan-coated solid lipid nanoparticles, gives a chemopreventive effect [12]. "FA, was successfully encapsulated in the blend of PLGA/PEO nanofibers using the electrospinning technique to improve both stability and efficiency of FA while reducing chemotherapeutic side effects and can be useful in providing a high local drug concentration to destroy the tumor cells" [13].

Ellagic Acid

"Obtained from fruit of Punica granatum belonging to family Lythraceae. Pomegranate peel ellagic acid forms an inclusion complex with β-CD was formed. Prepared β-CD-ellagic acid microspheres show an inhibitory effect on tumor cell proliferation and have the potential for clinical use in oncotherapy" [14]. "EA-loaded nanoparticles are a promising route for promoting EA bioavailability and solubility while improving its antibabesial efficacy *in vitro* and *in vivo"* [15]. "EA Nanoparticles were able to sustain the diffusion release of EA and enhance the cytotoxicity of EA (6.9-fold) against the colon adenocarcinoma. Nano-encapsulation of EA into the PCL would be an encouraging route to promote EA bioavailability and to improve its anticancer efficacy" [16].

Eugenol

"Eugenol is a photogenic bioactive component frequently found in diversified herbal plants possessing well-defined functional attributes. Prominent sources of eugenol are clove, cinnamon, tulsi, and pepper. Prominent sources of eugenol are clove, cinnamon, tulsi and pepper. The clove bud nanoscale emulsion system, produced using varying surfactant concentrations, gives cytotoxicity on thyroid cancer cell line (HTh-7)" [17]. "Dacarbazine- and eugenol-loaded liposomes were successfully developed for a combinatorial approach against melanoma. Combining eugenol with dacarbazine resulted in a much higher anti-melanoma activity of the

formulation. This resulted in significantly higher cytotoxicity, increased apoptosis, and much decreased migration and proliferation of the cancer cells" [18].

Amygdalin

"Amygdalin is a naturally occurring disaccharide, a source of HCN, highly concentrated in fruit kernels from *Rosaceae* species, for example, in bitter almonds, apricot, and peach. Magnetically responsive nanoparticles (MNPs) of amygdalin show inhibition of tumor growth" [19]. "Amygdalin extracted from the seeds of almonds and apricots showed cytotoxic effect on human oral cancer cell lines" [20].

Garcinol

"Garcinol is primarily present in the family Clusiaceae and genus Garcinia. Garcinol (GAR) is a naturally occurring polyisoprenylated phenolic compound. It has been recently investigated for its biological activities such as antioxidant, anti-inflammatory, anti-ulcer, and antiproliferative effect on a wide range of human cancer cell lines" [21]. "Formulation of GAR entrapped PLGA nanoparticles by nanoprecipitation shows a high amount of cytotoxicity in B16F10, HepG2, and KB cells. A considerable amount of cell apoptosis was observed in B16f10 and KB cell lines. *In vitro* cellular uptake studies and biological evaluation confirm the efficacy of the formulation for cancer treatment" [21].

Piperine

"It is an alkaloid obtained from the plant Piper nigrum and Piper longum belonging to the family Piperaceae. PE-loaded SNEDDS was prepared and optimized by Box Behnken design. The optimized PE-SNEDDS showed a better effect against hypertension than pure PE. The formulation also exhibited pronounced antibacterial activity as well as in-vitro anti-oxidant activity" [22]. "The curcumin and piperine were loaded into the gold nanogels to enhance their biodistribution and cytotoxic potential against the glioblastoma multiforme cancer cells" [23]. "Cu-Pi nanoparticles coated with PEG-containing copolymer appear to be promising to overcome oral bioavailability and cancer cell targeting limitations in the treatment of cancer" [24]. Piperine-

loaded and chitosan-coated liposomes are promising delivery systems for piperine and can increase the therapeutic efficacy against the breast cancer cell line [25].

Berberine

It is found in plants, such as *Berberis vulgaris* belonging to a family Ranunculales. TPGS-mixed phospholipid micelles show effective antitumor activity [26]. The novel self-nano emulsifying system of Berberine shows promising therapy for acute myeloid leukemia [27]. The BBR-loaded liposomes show pH-dependent extended drug release behavior in vivo and antitumor activity [28].

Diosgenin

It is present in many plants including Dioscorea nipponica, Dioscorea zingiberensis belonging to family Dioscoreaceae. "Diosgenin as an efficient anticancer agent was loaded into niosomes, MTT assay proved that free diosgenin has no significant cytotoxicity, whereas diosgenin niosome has a notable anticancer effect in HepG2 cancer cell line" [29]. Polymer nanoparticles of Diosgenin effectively kill and inhibite the proliferation of cancer cells in a dose-dependent manner and induces apoptotic cell death in cancer cells [30]. Diosgenin loaded nanoparticles have a significant anticancer potential when compared to free drug in cancer cells [31]. Diosgenin phytosomes were prepared and it shows promising anticancer activity for non-small-cell lung cancer [32].

Quercetin

"Quercetin is a flavonoid with notable pharmacological effects and promising therapeutic potential. It is widely distributed among plants and found commonly in daily diets predominantly in fruits and vegetables. Targeted nanoquercetin demonstrated a significant hepatoprotective effect compared to bulk quercetin against CP-induced hepatotoxicity" [33]. "Quercetine nanoparticles further yielded a synergistic antitumor effect with cisplatin nanoparticles in a stroma-rich bladder carcinoma model. Quercetin phosphate nanoparticles is a safe and effective way to improve therapeutic treatment for desmoplastic tumors" [34]. Quercetine nanoparticles shows effective chemotherapeutic activity [35].

TABLE 2: MECHANISMS OF ACTION OF SOME PHYTOCHEMICALS IN VARIOUS CANCER.

Compound	Source	Cancer	Proposed Anticancer Mechanism	Reference
Capsaicin	Chilli pepper (Capsicum)	Pancreatic cancer	Blocks AP1, NF-κB and STAT3 signaling, cell cycle arrest, inhibition of β-catenin signaling	[36, 37]
Lycopene	Tomatoes, papaya, pink grapefruit, pink guava, red carrot	Prostate cancer, Breast cancer, cervical cancer	Dietary Antioxidant, Affecting NF-κB signal transduction, Antiangiogenic effect, Inhibition of Wnt-TCF signaling	[38, 39]
Catechins	Green tea and other beverages	Neuroblastoma, Breast cancer, Prostate cancer	Cell cycle at G2 phase, protection against oxidative stress, Affecting STAT3-NFκB and PI3K/AKT/mTOR pathways	[40, 41]
Cucurbitacin B	Medicinal plants (Cucurbitaceae family)	Colorectal cancer, Lung cancer, Neuroblastoma, Breast cancer, Pancreatic cancer	Inhibitors of JAK-STAT3, HER2-integrin, and MAPK signaling pathways	[42, 43, 44]
Benzyl isothiocyanate (BITC)	*Alliaria petiolata*, pilu oil, papaya seeds	Leukemia, Breast cancer, Prostate cancer, Lung cancer, Pancreatic cancer, Colon cancer, Hepatocellular carcinoma	G_2/M Cell cycle arrest and apoptosis, down-regulation of MMP-2/9 through PKC and MAPK signaling pathway, inhibition of	[23, 24]
Isoflavone	Soy, lentils, beans, and chickpeas	Leukemia, Lymphoma, Gastric, Breast, Prostate, Head and Neck carcinoma, and Non-Small Cell Lung	Inhibition of c-erB-2, MMP-2, and MMP-9 signaling pathways, Affecting IGF-1R/p-Akt signaling transduction	[45, 46]

		Cancer		
Piperlongumine	Roots of long pepper	Multiple myeloma, melanoma, Pancreatic cancer, colon cancer, Oral squamous cell carcinoma, Breast and Prostate cancer	Autophagy-mediated apoptosis by inhibition of PIK3/Akt/mTOR	[47]
Anacardic acid	Cashew nuts	Cervix adenocarcinoma, Squamous cell carcinoma; Peripheral blood; Non small cell lung cancer, Prostate cancer	Inhibited both inducible and constitutive NF-κB activation; down-regulated p300 histone acetyltransferase gene; Inhibited Tip60 HAT	[48]
Caffeic acid	Coffee	Breast; Melanoma;	T-47D Inhibited DNA methylation catalyzed by DNMT	[49]
Epigallocatechin 3-gallate (EGCG)	Green tea	Colon; Prostate; Esophageal; Breast, Hepatocellular	Reversed hypermethylation of p16INK4a, RARβ Induced apoptosis and down-regulated Bcl-2 in HepG2	[50, 51]

TABLE 3: SOME MARKETED HERBAL NANOFORMULATIONS

Marketed Products	Drug Used	Type of Formulation	Target Disease	Company
vincaXome	Vincristine	Liposomes	Solid tumor	Nextar, USA
Genexol-PM	Paclitaxel	Polymeric Micelles	Breast Cancer, NSCLC	Lupin Ltd.
Vitablossom	Fisetin &	Liposomes	Dietary	Vitablossom USA

	Quercetin		Supplements	
Doxil	Doxorubicin	Liposomes	Ovarian Cancer, Multiple Myeloma	GlaxoSmithKline Manufacturing S.p.A. Parma, Italy
TIG 10	Curcuma Aromatica, BalsamOdendron Mukul, Lepidium Sativum etc.	Capsule	Breast cancer, Uterine Cancer	Shri Ram Herbal, Banglore

CONCLUSIONS AND FUTURE PROSPECTS

It has been evident from the present review that phytochemicals prove a promising and effective research area for the future. Cancer therapy has a higher cost with various limitations. The efficacy of phytochemicals is because of higher biodegradability, biocompatibility eco-friendly, and cost-effective strategy in a greener way. Under this scenario, phytomolecules are expected to reshape cancer treatment in the next decade. This comprehensive review paper provides information on phytochemicals with the potential to cure different types of cancer. Further, extensive research work should be carried out on these phytochemicals to evaluate their possible applications and toxicology against a wide range of cancer.

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