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Review Article

LIPOSOMES CONTAINING PHYTOCHEMICALS FOR CANCER TREATMENT-AN UPDATE

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ABSTRACT

Many phytochemicals exhibit promising effects in treatment and prevention of various cancers, but due to their poor water solubility, stability, bio-availability and target specificity make administering them at therapeutic doses impractical. This is especially true for curcumin, quercetin, resveratrol and berberine. There is rising activity in developing nano drug delivery systems for these phytochemicals. These nano drug delivery systems mainly include liposomes, micelles, solid lipid nanoparticles, nanoemulsions, which are biocompatible and biodegradable nanoparticles. These nanoparticles can increase the stability and aqueous solubility of phytochemicals. They can also be used as sustained drug delivery systems. Much work has also proven that they enhance the absorption and bioavailability of the phytochemicals, protect them from premature enzymatic degradation or metabolism, hence prolonging their circulation time. Besides these parameters, in this review, we have also mentioned the improved target specificity of phytochemicals to cancer cells or tumours via passive or targeted delivery. Hence, nanotechnology cleared the way for developing phytochemical-loaded nanoparticles for prevention and treatment of cancer.

Keywords: Liposomes, Phytochemicals, Phytoconstituents, Curcumin, Quercetin, Resveratrol, Berberine, Cancer

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INTRODUCTION

Cancer is one of the leading causes of human sickness or diseases, and deaths around the globe, computing for 7.6 million deaths per year [1]. There are several types of cancer, and they vary depending on cancer location, size and various other parameters [2]. Phytochemicals are biologically active compounds found in vegetables, fruits, spices, grains, and other plant foods [3]. Many phytochemicals from classical medicines have been used for the maintenance of health and prevention of diseases, especially cancer [4, 5]. Over the past few decades, research data from cell culture and some animal studies has backed that many phytochemicals have anti-cancer activities, but erratic results are found in some human clinical trials [6, 7]. The erratic results may be due to the infeasibility of high doses of phytochemicals for human studies, their low aqueous solubility, stability, bioavailability and target specificity to cancer cells and tumors, and the high degradation and metabolism by enzymes in the gastrointestinal tract, the liver and other tissues and thus short circulation time and low circulation concentrations [6, 7].

Nano-delivery systems have been developed to treat several diseases like cancer, diabetes, allergy, infections, asthma and neurological disorders [8, 9]. Indeed, a Nano sized carriers have the ability to improve biopharmaceutical parameters, pharmacokinetic properties and the therapeutic efficacy of the entrapped drugs [10]. A wide range of materials has been utilised to fabricate the Nanocarriers, including lipids [11-13]. It has been widely proposed to combine the natural phytochemicals with liposomes, because they may potentiate the phytochemical activity while reducing the dose and side effects. Liposomes can deliver the active drug to desired site of action at a satisfactory concentration [14].

Liposomes

The word liposome has been originated from two Greek words: lipo (fat) and some (body). Basically, they are synthetic microscopic vesicles spherical in shape, compromising membrane-like lipid bilayers, made up of cholesterol and natural, nontoxic phospholipids surrounding aqueous compartments.

Liposomes were first demonstrated by British haematologist Alec D Bangham in 1961 (published in 1964), at the Babraham Institute, in Cambridge [15-17].

Classification of liposomes [14]

The liposomes vary in size ranging from 20 nm to 30 µm vesicles. Moreover, liposomes can single layered or bilayered. The vesicle size is an acute parameter for calculating the circulation half-life of liposomes. Besides, size, as well as number of bilayers, affects the amount of drug entrapped in the liposomes. On the basis of their size and number of bilayers, liposomes can also be classified into one of three categories:

(1) Unilamellar Vesicles,
- (a) Small Unilamellar Vesicles (SUV),
- (b) Medium Unilamellar Vesicles (MUV),
- (c) Large Unilamellar Vesicles (LUV),
- (d) Giant Unilamellar Vesicles (GUV),

(2) Multilamellar Vesicles (MLV)

(3) Multi Vesicles liposomes (MVL).

In unilamellar liposomes, the aqueous solution is encapsulated in the single phospholipid bilayer. Whereas, in multilamellar liposomes, vesicles possess onion-like structure. Typically, several unilamellar vesicles will form on the inside of the other with smaller size, forming a multilamellar structure of concentric phospholipid spheres separated by layers of water.

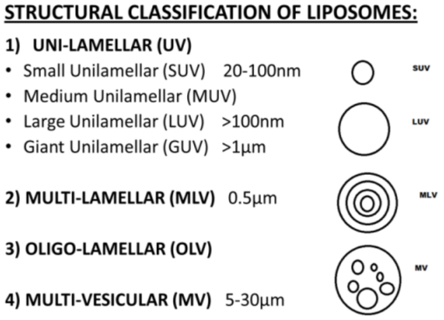

Fig. 1: Structural classification of liposomes [20]

Table 1: Benefits of liposomes containing drugs

Benefits of liposomes containing drugs	Examples
Improved solubility of lipophilic and amphiphilic drugs.	Amphotericin B, minoxidil, some peptides and anthracyclines, doxorubicin, acyclovir.
Passive targeting to the cells of immune system, especially cells of the mononuclear phagocytic system.	Antimonial, vaccines, immune-modulators, amphotericin B.
Sustain release system of systemically or locally administered liposomes.	Doxorubicin, cytosine arabinoside, cortisones, vasopressin.
Site-avoidance mechanism.	Doxorubicin amphotericin B.
Site-specific targeting.	Anti-inflammatory drugs, anti-cancer, anti-infection.
Improved transfer of hydrophilic charged.	Antibiotics, chelators, plasmids and genes.
Improved penetration into tissues.	Corticosteroids, anaesthetics and insulin.

Liposome formation

Phospholipids are amphipathic in nature. They possess an affinity for aqueous as well as polar moieties molecules since they have a hydrophobic tail and a hydrophilic head. The hydrophobic tail is compromising of two fatty acid chain containing 10-24 carbon atom and 0-6 double bonds in each chain. The macroscopic structures most often formed include lamellar, hexagonal or cubic phases dispersed as colloidal Nanoconstructs (artificial membranes) referred to as liposomes, hexasomes or cubosomes. The most common natural polar phospholipids are phosphatidylcholine. These are amphipathic molecules with a glycerol bridge linked to a pair of hydrophobic acyl hydrocarbon chains with a hydrophilic polar head group called phosphocholine. The amphipathic nature of phospholipids, as well as their analogues, provides them with the ability to form closed concentric bilayers in the presence of water. Liposomes are formed when very thin lipid films or lipid cakes are hydrated, and bundles of lipid crystalline bilayers become fluid and swell. The hydrated lipid sheets detach during agitation and self-close to form large, multilamellar vesicles prevent interaction of water with the hydrocarbon core of the bilayer at the edges [14].

Phytochemicals encapsulated in liposomes

In recent years, relative attention has been given on the development of various novel drug delivery systems (NDDS) for herbal drugs. These novel carriers should optimally accomplish two prerequisites. On the one hand, it should deliver the drug at a rate aimed by the requirements of the body, over the period of treatment or therapy. On the other hand, it should carry the active compound of the herbal drug to the site of action [21].

Liposomes have been used as novel carriers for numerous phytochemicals. Besides the properties like biocompatibility, biodegradability andquite low toxicity, liposomes have a good tendency to trap both hydrophilic and lipophilic drugs [22] and facilitate site-specific drug delivery to tumor tissues [23]. This has led liposomes as an investigational system as well commercially as a drug delivery system. Many studies have been conducted on liposomes with the goal of decreasing drug toxicity and/or targeting specific cells [24-26].

In this review, we focus on some commonly adopted phytochemicals, including curcumin, quercetin, resveratrol and berberine. So, here we investigate whether Nanoencapsulation of these phytochemicals in liposomes can enhance their characteristics and anti-cancer activities.

Curcumin

The curcumin is the active ingredient in the herbal remedy and dietary spice turmeric. Curcumin has several beneficial properties. These activities have been demonstrated both in cultured cells and in animal models and have paved the way for on-going human clinical trials. Curcumin has been found to possess anti-tumor properties and thus has a potential against chronic illness like cancer.

Lan li *et al.* incorporated curcumin in liposome for intravenous administration. The study of the *in vitro* and *in vivo* effects of this compound on proliferation, apoptosis, signalling, and the formation and development of blood vessels using human pancreatic carcinoma cells was carried out. NF-kappa B was constitutively active in all human pancreatic carcinoma cell lines evaluated and liposomal curcumin consistently suppressed its binding (electro-phoretic mobility gel shift assay) and decreased the expression of this protein complex-regulated gene products, including cyclooxygenase-2 which is immunoblots and interleukin-8 which is enzyme-linked immunoassay, both of which have been implicated in tumor growth/invasiveness. These *in vitro* changes were associated with concentration and time-dependent anti-proliferative activity and pro-apoptotic effects [27].

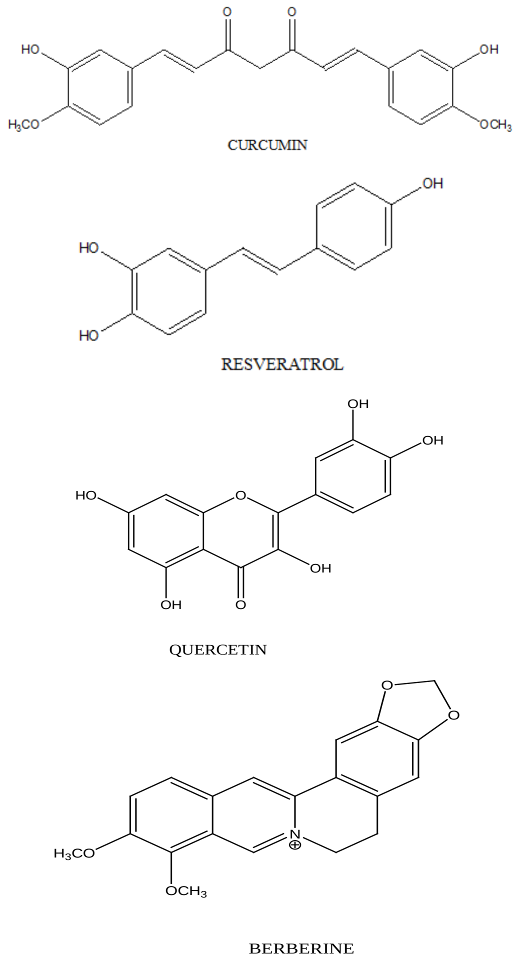

Fig. 2: Chemical structures of phytochemicals

In vitro studies of neuroblastoma cell lines NB1691, CHLA-20, and SK-N-AS were carried out by Wayne S. Orr *et al.* by treating it with various doses of liposomal curcumin. Dispersed neuroblastoma was entrenched *in vivo* by tail vein injection of NB1691-luc cells into SCID mice, which were then treated with 50 mg/kg/day of liposomal curcumin 5 d/week intraperitoneally. NF-κB activation which is suppressed by curcumin and proliferation of all neuroblastoma cell lines, *in vitro*. *In vivo*, curcumin treatment resulted in a significant decrease in disseminated tumor burden. Curcumin-treated tumors had decreased NF-κB activity and significantly lowered the tumors cell proliferation and an increase in tumor cell apoptosis, as well as a decrease in tumor vascular endothelial growth factor levels and microvessel density [28].

Curcumin is insoluble in water, therefore the researchers here has encapsulated it in cyclodextrin. Now this formulation is followed by second encapsulation in liposomes to treat osteosarcoma. Osteosarcoma is a cancer of the bone that is most common in adolescents and young adults. Treatment of this involves surgery, usually followed by chemotherapy or radiation. The potential of this formulation was evaluated against cancer models of osteosarcoma and breast cancer. It resulted in the promising anticancer activity both in vitro and in vivo against both the cancers cell line. Besides this activity, it also initiated the caspase cascade that leads to apoptotic cell death in vitro as compared to dimethyl sulfoxide (DMSO)-curcumin that induced autophagic cell death. So it was concluded that curcumin loaded cyclodextrin liposomes showed significant potential as a delivery vehicle for the treatment of cancers of different tissue origin [18].

Saengkrit *et al.* developed a cationic liposome, in which they encapsulated curcumin modified with three components of dimethyl dioctadecyl ammonium bromide (DDAB), cholesterol and a nonionic surfactant. This study was conducted to determine the role of DDAB, a cationic surfactant, in liposome containing curcumin. The response was evaluated against two types of cell lines (HeLA and SiHa). They showed that DDAB is a potent inducer of cell uptake and cell death in both cell lines. Cytotoxicity of DDAB-containing liposomes was found out to be high and needed to be optimised. They concluded that the anticancer efficiency and apoptosis effect of this formulation was higher than those of others [19].

In another study authors developed a liposome containing a combination of curcumin and resveratrol in order to increase the bioavailability of curcumin against prostate cancer. They conducted *in vitro* and *in vivo* studies in mice of 6-8 w old. HPLC analysis was performed of serum and prostate tissues obtained for investigation. The results obtained were interesting. Lipo curcumin alone showed a serum concentration of 100ng/ml after 1.5 h, whereas the combination of lipo curcumin with resveratrol showed a serum concentration of 252ng/ml, which remained stable between 238-245ng/ml for 4 h [29].

Quercetin

Quercetin is one of the most prominent dietary antioxidants. Its application in pharmaceutical industry is due to its property, but it requires a proper formulation to provide protection against degradation, to enhance its aqueous solubility and improve bioavailability.

Quercetin has been investigated in a number of animal models and human cancer cell lines and has been found to have ant proliferative effects in numerous cancer cell types, including breast, leukaemia, colon, ovary, squamous cell, endometrial, gastric, and non-small-cell lung. Phase I clinical trials has demonstrated the proof of in vivo lymphocyte tyrosine kinase inhibition and antitumor activity of parenteral quercetin. More clinical oriented research needs to be done in this area to discover effective dosage ranges and protocols [30].

Li-Juan Chen et al. encapsulated quercetin in a non-aqueous interior of the PEG liposome. Then, they tested the pharmacokinetic properties and biodistribution in tumor-bearing mice. The authors also testes the anti-cancer efficacy of liposomal quercetin in vivo and in-vitro. The liposomal treatment resulted in inhibition of cell proliferation in vitro. This inhibitory effect was dose and incubation time-dependent. For example, when CT26 cells were treated for 36 h, the percentage inhibition of 1 and 10 Ag/ml quercetin liposome was 21% and 71.5%, respectively. When CT26 cells were treated by 10 Ag/ml quercetin liposome, the percentage inhibition was 42% for 24 h and 81% for 96 h. The Liposome could also inhibit CT26 cell proliferation but did not showed such time and dose-dependent effect [31].

Quercetin when combined with some other anti-cancer phytoconstituents, it has shown an effective line of treatment.

The co-encapsulation of quercetin with vincristine into liposome formulation demonstrated the most effective tumor growth inhibition in the JIMT-1 human breast tumor xenograft. Man-Yi Wong with Gigi N. C. Chiu reported that this liposome formulation showed an enhancement in cytotoxicity of vincristine when encapsulated with quercetin. Hence, quercetin reduced the efflux of vincristine from cancer cells [32].

Beside co-encapsulation, modern techniques have been employed to develop the new delivery system. Su Nam Park *et al.* developed a liposome/hydrogel system. In this, they prepared ceramide liposomes composed of biocompatible membranes and porous cellulose hydrogel.

The aim of their study was to enhance transdermal permeation of quercetin and rutin. To evaluate the effect they carried Franz Diffusion. Considering of skin permeability, the liposome/hydrogel complex system (Q 67.42%, R 59.82%) was superior to phosphate buffer (pH 7.4)(Q 2.48%, R 1.89%), the hydrogel single system (Q 31.77%, R 26.35%) or the liposome single system (Q 48.35%, R 37.41%) [33].

Resveratrol

Resveratrol is a natural polyphenolic compound found in trees, peanuts, grapevines and exhibit multi-pharmaceutical activities. Several types of research have been conducted in last two decades; that demonstrate that resveratrol possesses anti-inflammatory, anti-cancer, antiviral, anti-arthritic and anti-oxidant properties [34]. Its poor absorption, bioavailability and low selectivity have limited its clinical use. Resveratrol interferes with all three stages of carcinogenesis–initiation, promotion and progression.

An increased consumption of tobacco and alcohol has led to a steady increase in the incidence of head and neck cancers in Asia. The consequences associated with the present surgical and chemotherapeutic interventions has led to develop a safe alternative for therapy. Here, the authors have explored the synergistic therapeutic potential of a phytochemical and chemotherapeutic agent incorporated in PEGylated liposome. Resveratrol and 5-fluorouracil were co-encapsulated in a single PEGylated Nano-liposome. The thermal analysis and the nuclear magnetic resonance results showed that resveratrol was restricted near the glycerol backbone of the liposomal membrane while 5-fluorouracilrestricted closer to the phosphate moiety, which affected the release kinetics of both drugs. This Nano-formulation was evaluated *in vitro* on a head and neck cancer cell line NT8e. It was found to exhibit a GI50 similar to that of free 5-fluorouracil. Further, gene expression studies indicated that the combination of resveratrol and 5-fluoro-uracildisplayed different effects on different genes that may affect the overall antagonistic effect. *In vitro* tests showed that the co-encapsulation of resveratrol and 5-fluorouracil in a liposomal Nano-carrier decreased the cytotoxicity in comparison with the free drug combination [35].

Wenlong Wang *et al.* investigated the drug release behaviors and anti-cancer performance of polymer-RES conjugates. They prepared a PEGylated Resveratrol with and without glycine for anticancer drug delivery. The results showed an increase in drug loading capacity and drug loading efficiency of the conjugate with glycine as compared to that without glycine; it was found out to 12.5% and 84.5% respectively [36].

Ultra deformable liposomes are able to increase the skin penetration of the drugs. In this study, resveratrol and 5-fluorouracil were encapsulated in ultra-deformable liposomes. This formulation was evaluated to treat non-malanomic skin cancer. The *in vitro* studies were performed against cancer activity on human skin cancer cells. Furthermore, percutaneous permeation of this formulation was tested using human stratum corneum and viable epidermis. It showed improvement in anti-cancer activity on skin cancer cells when compared to both, free drug form and single entrapped agents. The authors concluded that resveratrol and 5-fluorouracil co-loaded ultra-deformable liposomes could be a new Nanomedicine for the treatment of squamous cell carcinoma, Bowen’s disease and keratoacanthoma [37].

Gliomas are the most common form of primary brain tumors. They usually cause due to abnormal proliferation of glial cells which provide support and protection to neurons. Glioma is accounts for 29% of all primary brain tumors and 80% of malignant tumors [38].

A study was conducted, in which the authors opted to enhance the circulation time, biological half-life and passive brain targeting of resveratrol. Hence, they formulated a liposome incorporating resveratrol. They coated the liposome with D-α-tocopheryl polyethene glycol 1000 succinate (TPGS) (RSV-TPGS-Lipo). RSV-TPGS-Lipo showed significantly higher cytotoxicity than RSV-Lipo (uncoated liposomes) and free RSV. In both cases, uncoated and TPGS coated liposomes, the cellular uptake was increased. RSV, RSV Lipo and RSV-TPGS-Lipo were found to be hemocompatible and safe after i. v. administration. Area under the curve (AUC) and plasma half-life (t1/2) after i. v. administration of RSV-TPGS-Lipo was found to be approximately 5.73 and 6.72 times higher than that of RSV-Lipo as well as 29.94 and 29.66 times higher than that of RSV, respectively. Thus, the outcome indicates that RSV-TPGS-Lipo is a promising carrier for glioma treatment with improved pharmacokinetic parameters. Moreover, brain accumulation of RSV-Lipo and RSV-TPGS-Lipo 2 was found to be significantly higher than that of RSV ($P<0.05$) Results are suggested that both RSV-Lipo and RSV-TPGS-Lipo are the promising tools of RSV for the treatment of brain cancer [39].

Berberine

Berberine is considered as one of the most conventional components of Chinese medicine system. It possesses a vast variety of pharmacological activities [40]. However, because of its lipophilicity, its application was limited. But, now in recent years due to the emergence of novel nanoparticulate drug delivery system, its application has been explored, especially against cancer cells.

Wen Tan *et al.* carried out studies on various approaches to prepare liposomes. These approaches included active loading method, thin film evaporation method, and a combination of active loading methods and the thin film evaporation. They concluded that the average encapsulation efficiency of the optimised liposome was 78.51%±2.45%, with a size range of 2.2–3.5 µm [41].

Girish Sailor et. al, prepared berberine loaded liposome using thin film hydration method. They compared the release of berberine from liposomes and suspension. The suspension showed the full release of berberine within 10 h while liposomes showed 70% release in 24 h. So it was concluded that liposomes can be used as controlled drug delivery system [42].

Lin et al. formulated liposomal berberine with different lipid compositions. The liposomes which were produced by a thin-film hydration/extrusion method, containing 5 mol% PEG exhibited the highest encapsulation efficiency (14%) and a size of 121.6 nm. In vitro cell inhibition studies showed that the IC50 of berberine solution toward HepG2 cells was 4.23 g/ml while that of liposomal berberine was only 1.67 g/ml. This indicated that the cytotoxicity of berberine to HepG2 cells is higher in liposomal berberine by about 2.5 times. The pharmacokinetic studies were conducted in rats and the in vivo studies revealed that berberine was not detected more than 3 h after injection of berberine solution, but berberine was detectable until the 72nd hour after the injection of liposomal berberine. The liposomes effectively extended the circulation time in vivo. Delayed elimination of liposomal berberine was also observed in plasma and tissue [43].

CONCLUSION

In conclusion, liposomes, as nanoparticles are commonly used biocompatible and biodegradable nanoparticles. They are used as phytochemical carriers. Nanotechnology has an enormous ability for improving solubility, stability, bioavailability and anticancer activities of curcumin, quercetin, resveratrol and berberine. However, more studies are needed to optimise formulations of nanoparticles for enhancing their anti-cancer activity as well as efficacy. Besides, their tumor-targeting specificity, and lowering other parameters like their cost, side-effects and toxicity, are also required.

CONFLICT OF INTERESTS

Declared none

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