IJHS

Editorial

Liposome as nanocarriers for the delivery of phytomedicines: implication in the treatment of cancer

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WEBSITE: ijhs.org.sa
ISSN: 1658-3639
PUBLISHER: Qassim University

The researchers have been facing several challenges in the designing of the treatment strategies to fight against the cancer. Since ancient times, the addition of natural foods in the diet has been reported for the prevention of several diseases including cancer.[1] The recent advancements have shown immense attention in the discovery of drug utilizing the herbal products with minimal toxicity.[2] Several studies support the claim that more than 30% cancer related death could be avoided by including high amount of natural foods in the diet.[3] Noticeably, almost half of the drugs that have been made available in the market in the last three decades are either directly from the plants or altered chemically.[4] Numerous studies demonstrated the use of plant materials in different ways as the crude extracts, bioactive secondary metabolites, *etc*. as phytomedicine.[5] The phytomedicines, also known as nutraceuticals, are exploited individually or in combination with chemotherapeutic agents in the chemoprevention as well treatment of different types of cancers.[6,7]

However, the major downsides of most of the phytomedicines are the variability in the acidic pH, insolubility, and low bioavailability, that can lead to minimal therapeutic index.[8] Keeping these challenges into considerations, the researchers have made immense attention to design the effective strategies to utilize their maximum potential without any adverse effects. In the last two decades, the researchers have proposed different types of delivery systems as niosomes, phytosomes, nanoparticles, microspheres, emulsions, liposomes, *etc*. These carriers have opened the new vistas for the delivery of phytomedicines to augment their therapeutic potential. Among them, the liposomal formulations have several advantages in the efficacy of phytoconstituents due to enhanced stability of the carriers and bioavailability of the payloads with minimal toxicity as reviewed by Cheng *et al*. 2022.[9] The liposomes are the colloidal vesicles with varying range from 15 nm to 5 μm in diameter that are formed spontaneously following the hydration of various lipids in the aqueous solution. The liposomes can encapsulate the hydrophobic payloads in the phospholipid bilayer, hydrophilic in the aqueous core and amphiphilic in the bilayer surface according to the lipophilicity of the drugs. They can have single or multiple concentric membranes represented as unilamellar (ULV) or multilamellar vesicles (MLV), respectively. However, the ULVs can also be categorized into two sub classes as larger unilamellar (LUV) and small unilamellar vesicles (SUV).

So far, the herbal extracts or phytoconstituents encapsulated many liposomal formulations have been characterized and evaluated against different types of cancer models *in vitro* as well as *in vivo*. Among them, several liposomal formulations of phytomedicine have been exhibited to augment the solubility, bioavailability, prolonged release, and site-specific delivery of payloads as well. Therefore, these carriers of herbal drugs are categorized into four generations according to their characteristics and functions, as conventional, stimuli responsive, sterically stabilized, and actively targeted and theranostic liposomes.[10-12]

At present, the use of conventional liposomes has been limited in the preparation of herbal drug formulations due to their rapid clearance from the bloodstream, degradation, aggregation, and coalescence. However, the selection of lipids, their molar concentration with phase-transition temperature (Tc), surface charge, size, and the methods of preparation define the characteristics of liposomes. Several studies suggested the inclusion of cholesterol in the suitable amount enhance the stability of conventional liposomes.[13-15] The stealth or sterically stabilized liposomes are commonly used in the clinical trials, increase the stability in circulation, and reduce their uptake by reticuloendithelial system (RES). These liposomes are also called PEGylated liposomes as the polyethylene glycol (PEG), a hydrophilic polymer is coated on the surface of conventional liposomes.[16] Recently, my research group prepared and characterized the PEGylated liposomal formulations of diallyl disulfide (DADS) and demonstrated the use of DADS to enhance the activity of oxaliplatin in colorectal cancer (CRC) model *in vitro*.[17] Subsequently, we also exhibited the chemopreventive effect of diallyl trisulfide (DATS) encapsulated PEGylated liposomes in azoxymethane-induced CRC model *in vivo*.[18] Besides, we have developed the

stealth liposomes of thymoquinone and reported the stability, increased sensitivity to lung cancer cells *in vitro* and safety level of doses *in vivo*.[19]

The stimulus responsive liposomes are prepared by modifying the conventional liposomes with the addition of different phospholipids and other chemical constituents to trigger the structure that are capable of releasing the high concentration of herbal drugs at tumor sites. Several strategies have been proposed by the researchers in the activation of this class of liposomes using internal as well as external stimuli. According to the form of triggering approaches, they denoted as thermosensitive, ultrasound responsive, enzyme responsive, and pH-sensitive liposomes to name a few.[20] Recently, we developed the novel PEGylated pH-responsive liposomal formulation of thymoquinone considering low solubility of the compound and pulmonary delivery challenges. We reported the inhibition of cancer promotion and progression in the lungs and protection of liver metastasis as well in chemically induced small cell lung carcinoma model *in vivo*.[21] The engraftment of targeted ligand or antibody on the surface of liposomes, to specific receptors specifically expressed on the cancer cells, is the third-generation strategy of the liposomal formulation for site-specific delivery of herbal drugs.[22] The fourth generation theranostic liposomes have the competence of site-directed delivery of phytomedicine with controlled release responsive to the triggering mechanism and imaging efficiency with diagnostic agents.[23] Certainly, the various classes of liposomes as carriers of herbal drugs have shown great potential and will significantly promote the drug designing approaches. Therefore, it is concluded that different strategies should be applied according to the characteristics of the molecule/s for the development of novel delivery system of phytomedicines.

References

1. Zhang L, Song J, Kong L, Yuan T, Li W, Zhang W, *et al*. The strategies and techniques of drug discovery from natural products. Pharmacol Ther 2020;216:107686.
2. Chopra B, Dhingra AK. Natural products: A lead for drug discovery and development. Phytother Res 2021;35:4660-702.
3. Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. J Nat Prod 2020;83:770-803.
4. Ma L, Zhang M, Zhao R, Wang D, Ma Y, Li A. Plant natural products: Promising resources for cancer chemoprevention. Molecules 2021;26:933.
5. Chopra AS, Lordan R, Horbańczuk OK, Atanasov AG, Chopra I, Horbańczuk JO, *et al*. The current use and evolving landscape of nutraceuticals. Pharmacol Res 2022;175:106001.
6. Caesar LK, Cech NB. Synergy and antagonism in natural product extracts: When 1+1 does not equal 2. Nat Prod Rep 2019;36:869-88.
7. Castañeda AM, Meléndez CM, Uribe D, Pedroza-Díaz J. Synergistic effects of natural compounds and conventional chemotherapeutic agents: Recent insights for the development of cancer treatment strategies. Heliyon 2022;8:e09519.
8. Mahomoodally MF, Sadeer N, Edoo M, Venugopala KN. The potential application of novel drug delivery systems for phytopharmaceuticals and natural extracts-current status and future perspectives. Mini Rev Med Chem 2021;21:2731-46.
9. Cheng X, Yan H, Pang S, Ya M, Qiu F, Qin P, *et al*. Liposomes as multifunctional nano-carriers for medicinal natural products. Front Chem 2022;10:963004.
10. Coimbra M, Isacchi B, van Bloois L, Torano JS, Ket A, Wu X, *et al*. Improving solubility and chemical stability of natural compounds for medicinal use by incorporation into liposomes. Int J Pharm 2011;416:433-42.
11. Kumari S, Goyal A, Gürer ES, Yapar EA, Garg M, Sood M, *et al*. Bioactive loaded novel nano-formulations for targeted drug delivery and their therapeutic potential. Pharmaceutics 2022;14:1091.
12. Sogut O, Sezer UA, Sezer S. Liposomal delivery systems for herbal extracts. J Drug Deliv Sci Technol 2021;61:102147.
13. Ahmed KS, Hussein SA, Ali AH, Korma SA, Lipeng Q, Jinghua C. Liposome: Composition, characterisation, preparation, and recent innovation in clinical applications. J Drug Target 2019;27:742-61.
14. Anderson M, Omri A. The effect of different lipid components on the *in vitro* stability and release kinetics of liposome formulations. Drug Deliv 2004;11:33-9.
15. Briuglia ML, Rotella C, McFarlane A, Lamprou DA. Influence of cholesterol on liposome stability and on *in vitro* drug release. Drug Deliv Transl Res 2015;5:231-42.
16. Cattel L, Ceruti M, Dosio F. From conventional to stealth liposomes: A new Frontier in cancer chemotherapy. J Chemother 2004;16 Suppl 4:94-7.
17. Alrumaihi F, Khan MA, Babiker AY, Alsaweed M, Azam F, Allemailem KS, *et al*. The effect of liposomal diallyl disulfide and oxaliplatin on proliferation of colorectal cancer cells: *In vitro* and *in silico* analysis. Pharmaceutics 2022;14:236.
18. Alrumaihi F, Khan MA, Babiker AY, Alsaweed M, Azam F, Allemailem KS, *et al*. Lipid-based nanoparticle formulation of diallyl trisulfide chemosensitizes the growth inhibitory activity of doxorubicin in colorectal cancer model: A novel *in vitro*, *in vivo* and *in silico* analysis. Molecules 2022;27:2192.
19. Khan A, Alsahli MA, Aljasir MA, Maswadeh H, Mobark MA, Azam F, *et al*. Safety, stability, and therapeutic efficacy of long-circulating TQ-incorporated liposomes: Implication in the treatment of lung cancer. Pharmaceutics 2022;14:153.
20. Jain A, Jain SK. Stimuli-responsive smart liposomes in cancer targeting. Curr Drug Targets 2018;19:259-70.
21. Khan A, Alsahli MA, Aljasir MA, Maswadeh H, Mobark MA, Azam F, *et al*. Experimental and theoretical insights on chemopreventive effect of the liposomal thymoquinone against benzo[a]pyrene-induced lung cancer in Swiss Albino mice. J Inflamm Res 2022;15:2263-80.
22. Giri TK. Breaking the barrier of cancer through liposome loaded with phytochemicals. Curr Drug Deliv 2019;16:3-17.
23. Kundu P, Singh D, Singh A, Sahoo SK. Cancer nanotheranostics: A nanomedicinal approach for cancer therapy and diagnosis. Anticancer Agents Med Chem 2020;20:1288-99.