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REVIEW ARTICLE

Phytotherapeutics of Polyphenolic-loaded Drug Delivery Systems: A Review

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ABSTRACT

Phytopharmaceuticals stand out as recent promising candidates for the treatment of chronic diseases. Nanotechnology has become an important part of pharmaceutical industry, since it involves the development of novel drug delivery systems (nanomedicines) for the benefit of human health. The usefulness of nanotechnology has also been extended to natural products where, number of efforts is made for improvisation of bioavailability and therapeutic potential of polyphenolic compounds. A variety of novel drug delivery systems have been developed for polyphenolic compounds to enhance the relative bioavailability. The developed formulations have also shown sustain or prolonged release properties and also target delivery as evidenced by *in-vitro* and *in-vivo* studies. The novel formulations of Quercetin, Green tea catechins, epigallocatechin gallate, Genistein, Resveratrol, Breviscapine and Scutellarin etc. have been prepared by novel techniques and found to increase the therapeutic efficacy against various diseases. The present review focuses on various novel formulations developed for polyphenolic compounds including their therapeutic applications.

Key words: Polyphenolic compounds, quercetin, rutin, resveratrol, nanotechnology, novel formulations,

INTRODUCTION

An extremely diverse and important class of natural products are secondary metabolites from plants which have industrial and biomedical applications and also useful candidates for drug design.[1] Further, cosmetic formulations incorporating phytochemicals are also gaining popularity to protect the skin against exogenous and endogenous harmful agents.[2] Naturally occurring polyphenolic metabolites such as flavonoids are mainly present in higher concentration in fruits, grains, tea leaves, and many traditional herbs.[3] Polyphenolic substances/compounds and biotechnological products are receiving constant recognition from the viewpoint of antioxidation and have shown to be effective antioxidants in biological systems.[4] The term polyphenolic is often used for phenolic compounds such as flavonoids, tannins, and phenolic acids containing various phenolic rings with multiple hydroxyl groups. A revised definition of a polyphenolic compound proposed by Quideau *et al.* explains their biosynthetic origin: The term "polyphenol" should be used to define "phytochemicals containing phenolic rings without nitrogen group in their basic structure and should be biosynthesized via shikimic acid and/or polyketide pathway(s)."[5] Inadequate aqueous solubility of active pharmaceutical ingredients (APIs) is a major concern in the formulation and development of novel delivery systems since it directly affects the bioavailability.[6] Several approaches are developed to improve the solubility of such APIs. Salt formation,[7] crystal engineering,[8] nanosizing,[9] lipid formulation,[10] cyclodextrin complexation,[11] and prodrug strategies[12] are the most widely used novel techniques in developing novel formulations. At present, these techniques are also utilized to improve the bioavailability of several polyphenolic compounds.

Phytopharmaceuticals protrude as recent favorable drugs to treat persistent disorders. Minimum side effects and large abundance of phytochemicals from medicinal plants open new opportunities to alleviate human disorders and highlight the era of "back to nature."[13] Quercetin (QT), rutin (RT), luteolin, diosmin, and curcumin are potential flavonoidal drugs that possess strong antioxidant activity,[14] with other potential activities such as anti-inflammatory,[15] anticancer, and antiulcer.[16] Nanotechnology has become an important part of pharmaceutical industry since it involves the development of novel formulations (nanomedicines) for the welfare of human well-being. Development of novel dosages and formulations of such compounds has magnetized an increasing surveillance in the pharmaceutical field in modern years.[17] The use of nanotechnology in various sectors of therapeutics has revolutionized the field of medicine. Micro and nano-particulate systems have of paramount advantages over unit dosage forms.[18] Novel drug delivery systems such as microspheres, microcapsules, nanoemulsions, inclusion complexes, solid-lipid nanoparticles (SLNs), phytosomes, and niosomal formulations have been developed to increase the therapeutic efficacy of many drugs for various diseases. The usefulness of nanotechnology has also been extended to natural products where the numbers of efforts are made for improvisation of bioavailability and therapeutic potential of polyphenolic compounds. Hence, the present review discusses various novel drug delivery systems

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developed for polyphenolic compounds and their potential therapeutic applications. The comprehensive data of novel approaches utilized for the development of drug delivery systems for polyphenolic compounds are depicted in Table 1.

NOVEL DRUG DELIVERY SYSTEMS FOR POLYPHENOLIC COMPOUNDS

Quercetin- and kaempferol-loaded drug delivery systems

Quercetin (3,3',4',5,7-pentahydroxyflavone; QT), an abundantly distributed polyphenolic compound, is present in many medicinal plants and functional foods. QT is used as antidiabetic and anticancer, used in the treatment of cardiac disorders and long-term prostate infections, and also used to improve the physical endurance.[80,81] QT is considered as a potential chemopreventive agent due to its involvement in the suppression of oxidative stress, proliferation, and metastasis. Oral administration of a quick-dissolving QT formulation enhances the patient convenience with immediate onset of action. A demand for the development of such systems is need of the hour since QT has poor solubility and high melting point. In spite of this, several nanodrug delivery systems have been developed by many workers to improve the stability and therapeutic efficacy of QT. Several attempts have been made to develop, characterize, and investigate the improved therapeutic efficacy of QT-loaded drug delivery systems.

Considering the successful applications of nanosuspension technology for poorly soluble drugs, Gao *et al*. used evaporative precipitation-to-aqueous solution (EPAS) and high pressure homogenization (HPH) process to prepare and characterize QT-loaded nanosuspensions and to check their feasibility. Differences in the results of differential scanning calorimeter and X-ray measures were observed between the two processes. The crystalline-to-amorphous phase transition was shown in the profile of EPAS dried powder. However, in HPH process, the initial crystalline state of drug was also maintained. Dissolution test results indicated that the EPAS process showed a higher improvement in the drug solubility and dissolution rate than the HPH process.[19] A novel fast-dissolving composite microparticles of QT [Figure 1] was developed using coaxial electrospraying technique by Li *et al*. Solutions of QT and polymer were encapsulated along with polyvinyl pyrrolidone. A rapid release of QT was observed for microparticles in dissolution studies within 1 min. It was also supported by rate permeation studies of QT through sublingual mucosa.[20] In view of the potential therapeutic activity of QT for topical application, Gloria *et al*. prepared, characterized, and stabilized QT in mesoporous silica (MCM-41). Different complexes have been prepared by a kneading method, varying the QT/silica weight ratios. The hydrophilic/lipophilic character of MCM-41 was also modulated by functionalizing the silica surface with octyl chains. Infrared (IR) spectroscopy showed the formation of hydrogen-bonded adducts with silica Si-OH groups in both matrices, irrespective of surface fictionalization. However, detailed spectral analysis suggests that in octanol matrix, Q molecules are more dispersed and form stronger hydrogen-bonded adducts with residual Si-OH. When exposed to ultraviolet (UV) irradiation, mesoporous silica significantly improved QT stability over time, indicating a certain capacity in preserving the efficacy against skin damage. The most stable complex was prepared at pH 5.0 that fits perfectly the skin pH value, suggesting the advantageous applicability of MCM-41 as carrier in the topical field. Hence, it was concluded that MCM-41 can be considered as a novel antioxidant carrier for dermal drug delivery.[21] In another study by Simona *et al*., mesoporous silica nanoparticles functionalized with aminopropyl (NH2-MSN) for QT delivery were evaluated for

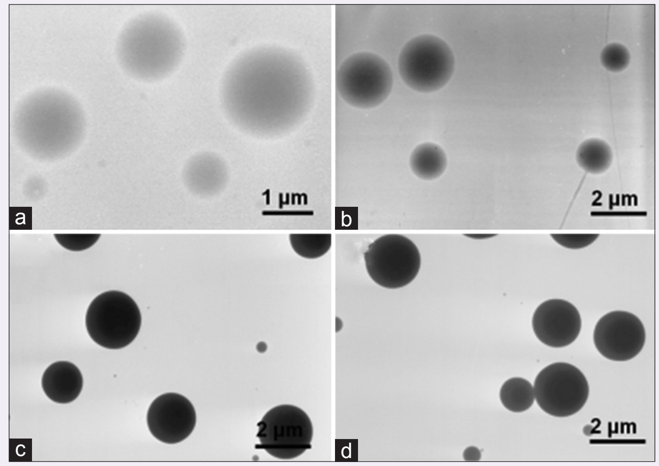

Figure 1: Transmission electron microscopic images of fast-dissolving core-shell composite microparticles of quercetin fabricated using single PVC-spinneret (a) and coaxial electrospray processes (b-d) (Courtesy - PLoS One 2014 18;9 (3):e92106)

transdermal permeation. Organic–inorganic molecular interaction parameters were studied in detail followed by photostability of after UV irradiation. The penetration of QT was found to be increased for inclusion complex with inorganic nanoparticles after 24 h of postapplication. A 50% inhibition of JR8 human melanoma cells was observed for QT with NH2-MSN complex at concentration of 60 µM.[22] Nanoparticles of polylactic acid (PLA) embedded with QT (PLA-QT) was developed by Pandey *et al*., by novel precipitation technique. The dimension range of 32 ± 8–152 ± 9 nm with an entrapment efficiency of 62% ±3% (w/w) was found for nanoparticles. During cytotoxicity studies, it was shown that 50% cancer cells of the breast were killed by at a PLA-QT at the concentration of 100 µg/ml within 2 days.[23] In a comparative study of resveratrol (R) and QT-eluting stent with bare metal stent (BMS) in the treatment of neointimal hyperplasia and reendothelialization arterial angioplasty, stenting was carried out *in-vivo*. Morphometric and histological finding were studied for the prepared delivery systems. Results showed that R and QT were released in a controlled manner dose dependently and reduced in-stent stenosis by stimulating reendothelialization of injured carotid of the rat. Stents coated with arborescent polyisobutylene-polystyrene (arbIBS) polymer films loaded with a synergistic combination of R and QT showed better activity.[24] Zheng *et al*. prepared a nanoliposomal QT (nLQT) for anticancer activity. Results showed a significant downregulation of NF κBp65, histone deacetylase 1 (HDAC1) and cyclin D1followed by upregulation of caspase 3 after exposure of E cancer cells to nLQT. Attenuation of HDAC1and promotion of expression of E cadherin was also demonstrated by immune cytochemistry. In particular, enhanced E-cadherin expression reflected the reversed epithelial–mesenchymal transition capacity of nLQT, acting as cancer-attenuator/preventive agent. Further, apoptotic effects of liposomal QT combined with CD133 antiserum were also detected and it was concluded that combination of LQ with CD133 has greater anticancer activity.[25] QT-loaded self-nanoemulsifying drug delivery system (QT-SNEDDS) composed of Capmul MCM, Tween 20, and ethanol was prepared, characterized, and screened for antioxidant activity to measure the anticancer efficacy. The developed formulation was found to be cytotoxic against MCF-7 cell lines. QT-SNEDDS revealed significant anticancer activity against 7,12-Dimethylbenz[a]anthracene (DMBA)-induced breast tumors at a dose of 50 mg/kg and may be attributed to its antioxidant

Table 1: Novel drug delivery systems for various polyphenolic compounds and their therapeutic efficacy

Name of the polyphenolic compound	Novel drug delivery system	Method of preparation	Route of administration	Biological/pharmacological activity reported	Reference
Quercetin	Nanosuspension	Evaporative precipitation and high homogenization press process	Oral	-	[19]
	Fast-dissolving core-shell composite microparticles	Coaxial electro-spraying method	Topical	Permeation rates across the sublingual mucosa	[20]
	Mesoporous silica (MCM-41) complex	Kneading method	Transdermal	-	[21]
	Mesoporous silica nanoparticles (NH2-MSN)	-	*In-vitro*	*In-vitro* anticancer	[23]
	PLA nanoparticles	Precipitation technique	*In-vivo*	Cytotoxicity against breast cancer cell lines (100 µg/ml)	[23]
	(QT)-eluting stent	-	Oral Oral	Neointimal hyperplasia and reendothelialization in a rat model of arterial angioplasty and stenting Anticancer	[24]
	Nanoliposomes	-		Cytotoxic against MCF-7 cell lines and antitumor against DMBA-induced breast tumors	[25]
	Self-nanoemulsifying drug delivery systems	-	Oral	*In-vivo* antioxidant potential with special reference to drug-induced cardiotoxicity and nephrotoxicity	[26]
	Novel quercetin (QR), loaded nanoparticles	-	Oral *In-vitro*	Anticancer Anticancer	[27] [27]
	Sterol-containing SLNs	Solvent evaporation method	Oral	Tissue distribution studies *in-vivo*	[28]
	Cationic nanostructured lipid carriers	-	*In-vitro*	Anticancer	[29]
	Nanostructured lipid carriers	Phase inversion-based method	*In-vitro*		[30]
	A multilamellar niosomal vesicle	Lipidic film method	-	Antioxidant effect	[31]
	Nanocrystals	High-pressure homogenization and bead mill method		-	[32]
Rutin	Nanocrystals	Lyophilization method	-	-	[33]
	Multiple emulsions	Spinning disc reactor	-	-	[34]
	Phytosome	Precipitation method	Oral	Antidiabetic	[35]
Green tea catechins, epigallocatechin gallate	A nanogold (PNG) nanoparticle	-	Oral	Anticancer and antioxidant activity	[17]
	Catechin-loaded and gelatin-conjugated CNTs	-	*In-vitro*	Anticancer	[36]
	A liposomal co-delivery system	-	*In-vitro*	Anticancer	[37]
	EGCG, conjugated with nanoparticles	-	*In-vitro*	Anticancer	[38]
	EGCG in chitosan nanoparticles	-	Oral	Anti-proliferative	[39]
	(+)-catechin- and EGCG-loaded niosomes	-	*In-vitro*	Enhanced drug absorption on human intestinal Caco-2 cell monolayer	[40]
Genistein	Microspheres	-		-	[41]
	Nanoparticles	-	*In-vivo*	The relative bioavailability	[42]
	NLCs	-	*In-vitro*	Anticancer	[43]
	Genistein loaded-PLA nanocapsules (gel)	Nanoprecipitation method	Transdermal	Showed good skin permeation	[44]
	A NLC	Melt emulsification method	*In-vitro*	*In-vitro* growth inhibition on human lens epithelial cells.	[45]
	Genistein-loaded NPs	Modified nanoprecipitation method	Oral	Anticancer	[46]

Contd...

Table 1: Contd...

Name of the polyphenolic compound	Novel drug delivery system	Method of preparation	Route of administration	Biological/pharmacological activity reported	Reference
Silybin, Silymarin	SLB-PC-BS-MM	Coprecipitation method	Parenteral	-	[47]
	A novel silymarin-loaded SLN	Solvent evaporation method	Oral	Hepatotoprotective	[48]
	Phytoliposome for the silybin	Extrusion method	*In-vitro*	Confirmed the internalization of phytoliposome formulation in human hepatoma cells	[49]
	Silymarin-loaded sterile lyophilized wafers	-	Topical application	Dermal microvascular cell migration was studied	[50]
	A novel silymarin-loaded solid nanoparticle system	Membrane emulsification and a spray-drying technique	Oral	Hepatotoprotective	[51]
Baicalin	Liposomes	Effervescent dispersion technique	Oral	Pharmacokinetic and biodistribution studies	[52]
	Baicalin-loaded nanoemulsions	-	Oral	Bioavailability studies were carried out	[53]
	Baicalin-phospholipid complex	-	-	-	[54]
Chrysin	Nanoformulation	-	*In-vitro*	Increased cytotoxicity of breast cancer cells	[55]
	Nanoparticles of PEG-chrysin conjugates	-	*In-vitro*	Anticancer	[56]
Luteolin	Luteolin-phospholipid complex	-	Oral	Anti-inflammatory	[57]
	Polymer-encapsulated nanoluteolin		*In-vitro*	Anticancer	[58]
Apigenin	Solid dispersions of apigenin with carbon nanopowder.	-	*In-vivo*	Pharmacokinetic parameters were improved	[59]
	Apigenin-loaded ethosome formulation	-	Topical application	Anti-inflammatory	[60]
Breviscapine and Scutellarin	Breviscapine-loaded liposomes	-	*In-vivo*	Pharmacokinetic parameters were improved	[61]
	Bre-NLC ionic complex	-	i.v.	Pharmacokinetic parameters were improved	[61]
	Self-emulsifying drug delivery system loaded with scutellarin-phospholipid complex	-	Oral	Improved the intestinal absorption	[62]
	A novel scutellarin-polyrotaxane	-	*In-vitro*	Cytotoxicity against colon cancer cell lines	[63]
Diosmin	Phytosomes	Lyophilization	*In-vivo*	Intestinal permeability was improved	[64]
	Novel polymer-stabilized diosmin nanosuspensions	-	*Ex-vivo*	*Ex-vivo* permeation studies in rats were performed	[65]
Daidzin	PLGA nanoparticles loaded with daidzein	-	*In-vivo*	Pharmacokinetic parameters were improved	[66]
	Daidzein encapsulated in TPGS 1000 (TPGS) emulsified zein nanoparticles	-	Oral	Pharmacokinetic parameters were improved	[67]
Ginkgo biloba extract	Niosomes	Film dispersion-homogenization method	Oral	*In-vivo* distribution was found to be improved	[68]
	Proliposomes using oleic acid	-	Oral	The oral bioavailability was improved	[69]
	Proliposomes using bile salts	-	Oral	Enhanced the absorption in the gastrointestinal tract	[70]
	A self-emulsifying drug delivery systems	-	Oral	The relative bioavailability was found to be improved	[71]

Contd...

Table 1: Contd...

Name of the polyphenolic compound	Novel drug delivery system	Method of preparation	Route of administration	Biological/pharmacological activity reported	Reference
Resveratrol	SLNs and NLCs	-	*In-vitro*	Simulation of gastrointestinal transit was studied	[72]
	Nanochannel delivery membrane systems	-	Oral	Cardioprotective	[73]
	Lipid-core nanocapsules	-	Oral	Antiglioma effect in brain tumors	[74]
	Polymeric nanoparticles	-	Oral	Antiproliferative activity	[75]
Naringenin	Naringenin-loaded nanoparticles system	-	Oral	Hepatoprotective activity	[76]
	Submicron emulsion system	-	Topical application	Drug permeability through skin was improved	[77]
Methoxy flavonones	Nanoemulsion and nanoparticles	-	Topical application	Anti-inflammatory activity	[78]
	Self-microemulsifying drug delivery systems	Lyophilization	Oral	The oral bioavailability was enhanced	[79]

PLA=Poly (lactic acid), EGCG=Epigallocatechin gallate, NLCs=Nanostructured lipid carriers, Bre-NLC=Breviscapine nanostructured lipid carrier, PLGA=Poly (lactic-co-glycolic) acid, SLB-PC-BS-MM: Silibin-loaded phosphatidylcholine-bile salts mixed micelle system, i.v.: Intravenous

property. This appreciation was further supported by normalized levels of matrix metalloproteinase-2 (MMP-2), MMP-9, tumor necrosis factor-α (TNF-α), and interleukin-6. A higher antioxidant activity was observed at 100 mg/kg of QT-SNEDDS with 65% decrease in tumor growth as compared to QT (20%).[82] In another study, QT-SEDDS was developed, characterized, and studied for improved *in-vivo* antioxidant potential with special reference to drug-induced toxicity on heart and kidney. A fluorescent dye-loaded SEDDS formulation when incubated with Caco-2 cells showed fast internalization as evident by confocal laser scanning microscopy. A 23.75-fold increase in cellular uptake was observed for QT-SEDDS with Caco-2 cells as compared to free QT. The oral bioavailability of SEDDS was also enhanced by 5-fold as compared to free QT suspension. Finally, QT-SEDDS showed a significantly higher *in-vivo* antioxidant potential compared to free QT when evaluated as a function of ability to combat doxorubicin- and cyclosporin A-induced cardiotoxicity and nephrotoxicity, respectively.[26] Novel QT-loaded nanoparticles (QTR) using lipid nanocarriers GeluPearl (GP) comprising Precirol ATO 5 were fabricated to improve the anticancer activity of orally administered QT. QT-loaded GP nanoparticles (GPNLCs) were optimized to yield adequate colloidal stability, mean particle size in the range of 350–380 nm, and entrapment efficiency of >90%. GPNLCs were characterized by cryo-transmission electron microscopy (TEM), surface charge, fluorescence studies, and DSC analysis. Further, the *in-vitro* release studies demonstrated sustained drug release potential of QR-loaded GP. *In-vitro* lipolysis studies confirmed that lipidic nanocarriers can improve QT solubilization. QT-loaded GPNLC significantly ($P < 0.05$) reduced flank tumor volumes in C57BL/6 mice over a 22-day study period compared to QT suspension. GPSLN significantly reduced lung colonization and enhanced antimetastatic activity ($P < 0.05$) of drug against B16F10 melanoma cells in C57BL/6 mice as compared to QT suspension.[27] Varshosaz *et al*. formulated SLNs containing different phytosterols (cholesterol, stigmasterol, and stigmastanol) to improve the penetration of QT for the treatment of carcinoma of the liver. The content of sterols in QT-SLNs was studied by solvent evaporation method. Toxicity of QT-SLNs against HepG-2 cell lines was studied considering cellular uptake method. The QT-SLNs prepared with cholesterol and QT (2:1) have particle size of 78.00 ± 7.00 nm, drug loading efficiency of 99.9% ±0.5%, zeta potential of −22.7 ± 1.3 mV, and 24-h release efficiency of 56.3 ± 3.4. A more concentration of QT was found for QT-SLNs in HepG2 cells as compared to free QT and phytosterol SLNs, respectively, with minimum IC_{50} value.[28] A QT-loaded cationic nanostructured lipid carrier formulation (QT-CNLC) was prepared by Liu *et al*. and was studied after oral administration for its biodistribution pattern in tissues. QT-CNLC was prepared following standard method, and its characteristics including physical index, release profile *in-vitro*, and tissue distribution *in-vivo* were investigated. In physicochemical studies, it was observed that QT-CNLC has an average particle size of 126.6 nm, entrapment efficiency of 89.3%, and zeta potential of 40.5 mV. During *in-vitro* studies, QT-CNLC showed controlled release than free QT. A higher tissue concentration (C_{max}) of QT was observed in QT-CNLC-treated group in the lung, liver, and kidney as compared to control group. A relative intake rate (re) was found to be 1.57 for lung, 1.51 for liver, and 1.68 for kidney, thus confirming the significant deposition of QT in these tissues in the form of QT-CNLC.[29] A biocompatible and biodegradable QT nanostructured lipid carriers (QT-NLC) were synthesized using a novel phase inversion-based process method by Sun *et al*. for anticancer activity *in-vitro*. QT-NLC showed average size of 32 nm with good chemical, physical stability and also had a sustained release pattern. The encapsulation efficiency and loading capacity of QT-NLC were 95% and 11%, respectively. The aqueous solubility of QT was improved by 1000 folds. QT-NLC dramatically increased cytotoxicity in a dose-dependent manner (1–50 μM) and influenced the death at 20 μM in MCF-7 and MDA-MB-231 breast cancer cells as compared to QT.[30] A multilamellar niosomal vesicle was prepared for QT and other antioxidants by the hydration of lipidic film method using Tween-80 as surfactant. All the niosomal formulations were characterized in terms of dimensions, polydispersity index, bioactive molecule (BM) encapsulation percentage, release profiles, and antioxidant properties. Results suggest the possibility of co-encapsulation of two different BMs (one lipid soluble and the other water soluble) in the same niosomes formulation, to encapsulate one or more antioxidants, the possibility to regulate and promote the BMs release rate compared to that of vesicles containing only single BM. Such strategy may improve the solubility pattern of curcumin and QT which otherwise are poorly absorbed from gastrointestinal (GI) tract after oral administration. Improved free radical scavenging activity was achieved by synergic action of by combination gallic acid/curcumin and ascorbic acid/QT. Therefore, hydrophilic/hydrophobic niosome complexes were found to be superior than vesicles containing single BM providing enhanced antioxidant effect.[31] QT nanocrystals were prepared by Mitali *et al*., by cavi-precepitation, bead milling, and HPH techniques. Based on the physicochemical analysis of QT-nanocrystals, it was observed that HPH and bead mill techniques were efficient methods for the fabrication of QT nanosuspensions. The particle size of nanocrystals prepared by all the three methods was in the range of 276–787 nm. However, the smallest nanocrystals were produced by bead milling method with particle size of

276.7 nm as compared to the coarse QT (50.1 μm). Nanosuspensions of QT nanocrystals prepared by all the three methods were compared for particle size, dissolution rate, and zeta potential. It was found that overall dissolution rate of nanosuspensions was enhanced.[32] Magnetic core-shell nanoparticles for QT were prepared and studied for anticancer activity by Verma *et al*. QT-loaded poly (lactic-co-glycolic) acid (PLGA)-magnetic nanoparticles (MNPs) were administered by single round of nebulization to human lung carcinoma cell line A549. A significant reduction in the number of viable A549 cells was observed by nebulization.[83] A schematic model of QT-loaded PLGA-MNPs is shown in Figure 2.

Rutin-loaded drug delivery systems

Rutin, (2-(3,4-dihydroxyphenyl)-4,5-dihydroxy-3-[3,4,5-trihydroxy-6-[(3,4,5-trihydroxy-6 methyl-oxan-2-yl) oxymethyl] oxan-2-yl] oxy-chromen-7-one) (RT), also called as sophorin, is one of the important flavonoidal compounds found in a number of plants,[84] such as buckwheat, fruit and fruit rinds of orange, grapefruit, lemon, and lime. Several studies proved its therapeutic efficacy for antioxidant,[85,86] hepatoprotective,[87] and anti-inflammatory effects.[88] In spite of potential therapeutic uses of RT, the poor aqueous solubility and bioavailability by oral route limit its use. Therefore, it imposes yet some restraints to further pharmaceutical use, especially for oral administration.[89] Several attempts are made by many investigators to enhance the oral bioavailability RT by various techniques.

Rachmat *et al*. prepared nanocrystals of RT (RTNCs) by lyophilization method and characterized by studying their morphology, particle size analysis, redispersability, and dissolution profile. Further, tablets loaded with RTNCs were produced by direct compression and tested for dissolution. The average particle diameter of nanosuspensions of RT was found to be 727 nm (PCS). After redispersion, the average size PCS of RT was found to be 721 nm and polydispersity index was found to be 0.288. The visibility of images of RT nanosuspension and redispersed RTNCs was similar under light microscopy. It was also observed that the crystalline state of the RTNCs remained unchanged on HPH and lyophilization. RTNCs-loaded tablet showed better dissolution profile than microcrystal-loaded tablet.[33] To increase the bioavailability, an attempt has been made by Mahmood *et al*. to encapsulate RT in multiple emulsions using a spinning disc reactor as a novel processing aid. The time-dependent stability of the multiple emulsions was explored using particle size, microscopy, and visual assessment and stability index measurements. Results showed that RT was successfully encapsulated within the internal aqueous phase of oil-in-water-in-oil multiple emulsions, giving an encapsulation efficiency of 80%. Formation of multiple emulsions was confirmed by confocal laser microscopy.[34] Prasanna *et al*. prepared, characterized, and studied RT-phospholipid complex (RPC) for antidiabetic activity in streptozotocin-induced model along with bioavailability studies. Serum glucose and altered lipid parameters were decreased after oral administration of RPC at 50 and 100 mg/kg body weight. A higher serum concentration (13.20 μg/ml) of RT in RPC was observed at 1st h as compared to pure RT during bioavailability studies.[35]

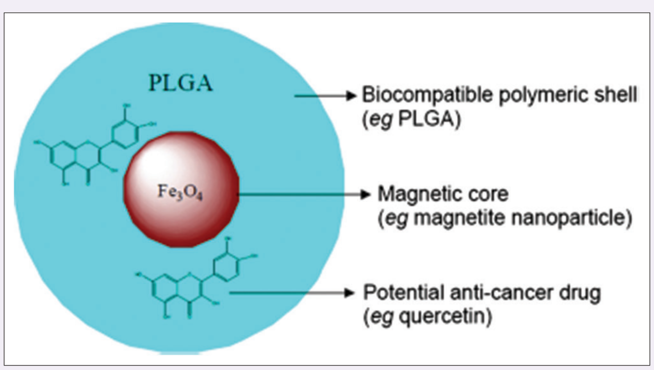

Figure 2: A schematic model of drug-loaded magnetic core-shell nanostructures for quercetin (Courtesy - Journal of Nanobiotechnology 2013;11:1-12)

Green tea catechins- and epigallocatechin gallate-loaded drug delivery systems

Catechin, an active ingredient of green tea, has been widely studied for its anticancer property as a co-adjuvant therapy. Flavonoids such as (+) catechin and (−) epigallocatechin gallate (EGCG) have shown various health-beneficial activities such as antioxidant, anticancer, and anti-inflammatory activities in *in-vitro* and *in-vivo* studies.[90-93] Hence, these natural molecules have been considered as potential candidates in pharmaceutical, cosmeceutical, and nutraceutical industries. However, poor bioavailability and stability make their choice as drugs for the development of novel drug delivery systems.[94] Enzymatic degradation and membrane permeation problems limit the oral bioavailability and absorption of (+)-catechin and EGCG. Advanced drug carrier systems for these compounds have been attempted by many researchers to protect from GI enzymes and to prevent the absorption barriers.

Hsieh *et al*. prepared a nanogold (PNG) nanoparticle conjugated with different ratios of EGCG. PNG-EGCG nanoparticles were then evaluated for physicochemical properties, antioxidant activity, *in-vitro* cytotoxicity, and *in-vivo* anticancer activity. EGCG-PNG particles at a ratio of 23:2.5 showed longer EGCG activity half-life (110 days vs. 5 h) and controlled release (2 h vs. 30 min) and were sturdy at varied PH conditions. The EGCG-PNG and EGCG-PNG (23:2.5 ppm) conjugates showed significant superoxide radical and lipid peroxyl radicals scavenging activity. EGCG-PNG particles at varied ratios increased the cytotoxicity as compared to native EGCG or PNG alone. *In-vivo* anticancer studies showed decrease in the tumor volume and angiogenesis in the rats pretreated with EGCG-PNG conjugates.[17] Catechin-loaded, gelatin-conjugated, and biocompatible CNTs (Gel-CT-CNTs) were prepared, characterized, and studied for their possible anticancer activity against prostate cancer cell lines and compared simultaneously with irradiation of X-rays. Gel-CT-CNTs significantly inhibited tumorigenic cell population as compared to free catechin *in-vitro*. Further, decrease in the protein level of stem cell-related transcription factors and Nanog, oct4, and β-catenin by increasing the radiosensitivity of cancer cells after combination of irradiation of X-rays and treatment with Gel-CT-CNTs.[36] A liposomal co-delivery system of paclitaxel (PTX) along with EGCG was developed by Ramadass *et al*. An entrapment efficiency of 77.11% ±2.30% and 59.11% ±3.51% was observed for PTX and EGCG, respectively. The *in-vitro* efficacy of the liposomes was studied by their ability to promote apoptosis and curtail cell invasion against breast cancer cells. Better results were shown after treatment with PTX/EGCG-loaded liposomes for all the parameters studied.[38] In another study by Lu *et al*., EGCG has been conjugated with nanoparticles and tested as an anticancer agent. Cellular uptake of a dextran-coated MNP was determined by flow cytometry, confocal microscopy, or potassium thiocyanate colorimetric method. Results showed that EGCG enhanced the internalization of MNPs by glioma cells than vascular endothelial cells. In addition, application of magnetic force further potentiated MNP uptake, suggesting a synergetic effect of EGCG and magnetic force.[38] An oral formulation was developed using nanotechnology by Siddiqui *et al*., to encapsulate EGCG in chitosan nanoparticles for antiproliferative and proapoptotic effects against human melanoma Mel 928 cells. Nano-EGCG-treated cells showed marked induction of apoptosis and cell cycle inhibition along with the growth of Mel 928 tumor xenograft. Inhibition of proliferation of Ki-67 and PCNA and induction of apoptosis (Bax and PARP) of tumors of treated mice was observed after treatment with nano-EGCG.[39] (+)-Catechin- and EGCG-loaded niosomes were prepared, characterized, and evaluated to study their capacity to transport and reuptake by human intestinal Caco-2 monolayer. The uptake of catechin, EGCG, and their niosomes by Caco-2 cells was found to be 1.22 ± 0.16, 0.90 ± 0.14, 3.25 ± 0.37, and 1.92 ± 0.22 μg/mg protein, respectively, in triplicate experiments. The apparent coefficient values were found to be 1.68 ± 0.16, 0.88 ± 0.09, 2.39 ± 0.31, and 1.42 ± 0.24 cm/s for catechin, EGCG, and their niosomes, respectively. The absorption pattern of niosomal formulations was also enhanced significantly as compared to pure drugs. In addition, niosomal formulations showed stronger stability and were found to be less toxic.[40]

Genistein-loaded drug delivery systems

Genistein (4′,5,7-trihydroxyisoflavone; GNT) is one of the most abundant and best-studied soy isoflavones and has received great attention for its many physiological functions. It is a natural product with potential applications for skin cancer treatment and chemoprevention. However, the clinical use of GNT was hindered by its poor water solubility and oral bioavailability. Nanotechnology-based studies have been carried out for GNT by many workers to improve its solubility and bioavailability.

In the earliest studies, Wu and Li prepared and optimized GNT-chitosan microspheres with central composite design. Results of the study showed that the theoretical drug content was 13%–15%, the concentration of organic phase was 30%–40%, and the concentration of oil phase was 68%–72%.[41] To enhance the oral bioavailability of GNT, Tang *et al*. formulated, and developed an optimized Eudragit nanoparticles containing GNT (GNTNPs). GNTNPs possessed mean particle size of 120 nm. Encapsulation efficiency and drug loading of the GNTNPs were approximately 50.61% and 5.02%, respectively. The relative bioavailability of GNT from the nanoparticles at a dose of 100 mg/kg was found to be 241.8%.[42] Nanostructured lipid carriers of GNT (GNTNLCs) were fabricated by Aditya *et al*. Entrapment efficiency of GNTNLCs was found to be >75%. Encapsulation of GNT into NLCs also increased the solubility of GNT in simulated intestinal medium up to 75% which otherwise was 20%. Further, GNTNLCs increased the cell growth inhibition of prostate cancer cells.[43] GNT-loaded-PLA nanocapsules (GNT-NC) were prepared by nanoprecipitation method, and physicochemical characterization and stability studies for 90 days were conducted. A skin permeation experiment for semisolid formulations incorporated with GNT-NC was carried out using porcine ear skin. The results showed a mean diameter of 139 ± 7.31 nm, polydispersity index of 0.128 ± 0.08, and encapsulation efficiency of 89.63 ± 2.27%, and drug loading from 0.6 to 1.4 w/w% was observed for optimized GNT-NC and was found to be stable for 90 days. Permeation experiments demonstrated that a higher amount of GNT reached deeper layers of the skin and increased penetration was achieved when GNT-NC was incorporated in a semi-solid gel formulation.[44] An NLC for drug delivery of GNT was produced with Compritol 888 ATO, Gelucire 44/14, and Miglyol 812N and stabilized by Solutol® HS15 by melt emulsification method with four independent variables. Particle size of 90.16 nm and high encapsulation efficiency (91.14%) were observed for the optimized GNT-NLC. *In-vitro* release experiments indicated a prolonged and controlled GNT release for 72 h. *In-vitro* growth inhibition assay showed an effective growth inhibition of GNT-NLCs on human lens epithelial cells (HLECs).[45] Zhang *et al*. prepared GNT-loaded NPs were prepared using TPGS-b-PCL copolymer by a modified nanoprecipitation method and characterized for particle size, surface charge, morphology, drug loading and encapsulation efficiency, *in-vitro* release, and physical state of the entrapped drug. The percentage of GNT-loaded in the PCL and TPGS-b-PCL NPs was 8.21% and 8.69%, respectively. Higher cellular uptake efficiency was observed for TPGS-b-PCL NPs (1.25-, 1.22-, 1.28-fold) than PCL NPs. A highest level of cytotoxicity (HeLa cell lines - IC_{50} values 24.3, 13.6, and 5.0 μg/mL after treatment for 24, 48, and 72 h, respectively) and tumor cell growth inhibition was achieved by TPGS-b-PCL NPs. *In-vivo* anticancer studies showed that the GNT-loaded TPGS-b-PCL NPs were more effective in inhibiting tumor growth in the subcutaneous HeLa xenograft tumor model in BALB/c nude mice.[46] Figure 3 shows SEM images of TPGS-b-PCL NPs.

Silybin- and Silymarin-loaded drug delivery systems

Silymarin (Sm), present in fruits of milk thistle, *Silybum marianum* Gaertn., contains approximately 60%–70% of silybin (SLB), a potent antioxidant. Wide arrays of biological and pharmacological effects such as antioxidant, antifibrotic, anti-inflammatory, immunomodulatory, and even liver-regenerating effects have been shown by SLB and Sm. Sm has so far been used for treating diverse liver and gallbladder disorders such as cirrhosis, hepatitis, and jaundice and for protecting the liver against poisoning from chemical and environmental toxins on account of its antihepatotoxic and antioxidative properties. In spite of such potential medicinal effects, both SLB and Sm have poor water solubility which restricts their clinical utility.[95-97]

Duan *et al*. prepared SLB-loaded phosphatidylcholine-bile salts mixed micelle system (SLB-PC-BS-MM) for parenteral administration using the coprecipitation method. Formation of the complex was confirmed by differential scanning calorimetry, and the optimized formulation was characterized by SEM, TEM, solubility studies. The formulation was found to be stable and improved the water solubility and mean retention time *in-vivo*.[47] A novel Sm-loaded SLN was prepared by Cengiz *et al*. and studied for hepatoprotective activity *in-vivo*. Improved hepatoprotective activity was observed for Sm-loaded SLN against D-GaIN/TNF-α-induced liver toxicity as compared to Sm.[48] A novel phytosome carrier-mediated vesicular system (phytoliposome) for the SLB was prepared for improving the efficacy of phospholipid molecular complexes. In this study, the marketed phytosome formulation of SLB was screened into liposomes by extrusion method by maintaining the vesicle sizes. The phytoliposome formulation satisfied all the quality parameters as evidenced by host–guest interaction studies and NMR experiments. Further, it was also confirmed the internalization of phytoliposome formulation in human hepatoma cells.[49] Sm-loaded sterile-lyophilized wafers for topical application were prepared and studied for migration of endothelial cells. Xanthan gum was used for the preparation of wafers and sterilized with 25 and 40 kGy gamma radiation. Further, xanthan gels were studied for their rheological properties which showed that with increase in the dose of gamma rays and enhanced the viscosity coefficient of Sm wafers. 89%–90% of Sm was found to be retained

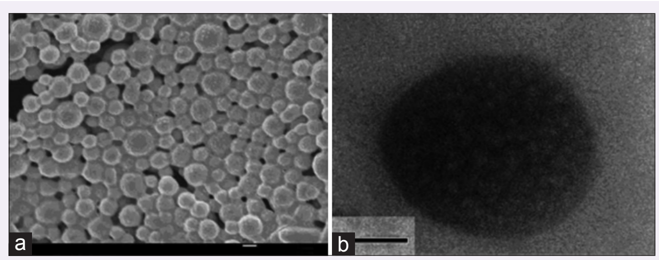

Figure 3: FESEM image (a) and transmission electron microscopy image (b) of genistein-loaded TPGS-b-PCLNPs (Courtesy - International Journal of Nanomedicine 2015;10:2461-2473)

in the wafers after irradiation as shown by high-performance liquid chromatographic (HPLC) analysis. In dermal cell migration studies, Sm wafers successfully retained its ability to overcome high glucose-induced reduction in endothelial cell migration.[50] Yang *et al*. used spray-drying and Shirasu porous glass membrane emulsification method to develop solid nanoparticle system for hepatoprotection. Results showed that, Sm-loaded nanoemulsion has globules with narrow size distribution. In the nanoparticles, Sm was found to be present in crystalline form. *In-vivo* experiments showed that Sm-loaded solid nanoparticles has improved hepatoprotective activity as compared to Sm powder and the commercial product.[51]

Baicalin-loaded drug delivery systems

Baicalin (BA) is an important and major metabolite of medicinal plant *Scutellaria baicalensis* Georg. Wei *et al*. prepared a liposome system loaded with BA (BA-LP) to increase its oral bioavailability. Effervescent dispersion technique was used to prepare BA-LP and characterization was done for its physical attributes and *in-vitro* release. BA-LP was administered orally to rats to assess the pharmacokinetic and biodistribution pattern using carboxymethyl cellulose suspension containing BA (BA-CMC) as control. It was observed that a threefold increase in the peak concentration BA-LP as compared to 2.82-fold that of BA-CMC. The biodistribution studies showed a 5.59-fold and 2.33-fold increase in drug concentrations for BA-LP and BA-CMC, respectively.[52] Zhao *et al*. prepared BA-loaded nanoemulsions (BAN-1 and BAN-2) by internal or external drug addiction and *in-vivo* and *in-vitro* evaluations. The results showed that the mean droplet size, polydispersity index, and drug content of BAN-1 and BAN-2 were 91.2 ± 2.36 nm and 89.7 ± 3.05 nm, 0.313 ± 0.002 and 0.265 ± 0.001, and 98.56% ±0.79% and 99.40% ±0.51%, respectively. *In-vitro* release results showed sustained-release characteristics. BAN-1 formulation was stable for at least 6 months and was more stable than BAN-2. In rats, the area under the plasma drug concentration-time curve value of BAN-1 was 1.8- and 7-fold more than those of BAN-2 and free BA suspension after oral administration at a dose of 100 mg/kg.[53] Rawat *et al*. prepared BA-phospholipid complex (BA-PLC) and evaluated for various physicochemical parameters. Results revealed that BA-PLC improved water/n-octanol solubility of BA significantly. Improved dissolution was shown by BA-PLC.[54]

Chrysin-loaded drug delivery systems

Chrysin (CRN) is a natural flavonoid which has been reported to have some significant biological effects on the processes of chemical defense, nitrogen fixation, inflammation, and oxidation. Anari *et al*. developed a nanoformulation of CRN loaded with PLGA-polyethylene glycol (PEG). The nanoformulation enhanced the solubility of CRN, drug tolerance. *In-vitro* cytotoxicity of pure and nano-CRN was studied by the MTT assay. Nano-CRN therapy developed increased cytotoxicity to breast cancer cells without damaging the normal cells.[55] In another study by Zheng *et al*., nanoparticles of PEG-CRN conjugates were used for efficient delivery of doxorubicin (DOX) loaded in the nanoparticles. The self-assembly, drug release profiles, interactions between nanoparticle and drug, cellular uptake, and *in-vitro* anticancer activity of the DOX-loaded nanoparticles were investigated. The results revealed that the mean diameters of drug-loaded nanoparticles were <200 nm. The drug release rate was closely related to the chain length of PEG, shorter PEG chain resulted faster release. The mPEG-CRN conjugate was nontoxic to both 3T3 fibroblasts and HepG2 cancer cells. A higher capability in endocytosis was showed by mPEG1000-CRN nanoparticles with IC_{50} of 4.4 μg/mL, as compared to drug-loaded m PEG2000-CRN nanoparticles.[56]

Luteolin-loaded drug delivery systems

Luteolin (3',4',5',7-tetrahydroxyflavone; LTN) a flavonoidal compound found in nature possesses anti-inflammatory, antioxidant, and neuroprotective properties. LTN successfully inhibited TNF-α and nitric oxide in an activated macrophage-like cell line.[98] Many authors demonstrated its potent anti-inflammatory activity in various models.[99,100] LTN also exerted antiamnesic[101] and anticancer activities.[102]

A novel carrier system incorporating LTN was developed, characterized, and studied for its anti-inflammatory activity. Complexation of LTN with phospholipid enhanced the dissolution and absorption profile of LTN. The prepared LTN-phospholipid complex (LTN-PC) showed drug loading of about 72.64% and average particle size was found to be 152.6 nm. The solubility of LTN as LTN-PC was increased about 2.5 times more as compared to pure LTN in water. In the diffusion study, LTN-PC showed 95.12% of drug release at the end of 2 h. Animal studies demonstrated significant differences in response of LTN-PC and LTN. Thus, LTN-PC improved bioavailability and efficacy of LTN.[57] A water-soluble polymer-encapsulated nano-LTN (LTNn) was prepared by Majumdar *et al*. and evaluated for its anticancer activity against lung cancer and head-and-neck cancer. *In-vitro* studies demonstrated that LTNn inhibited the growth of lung cancer cells (H292 cell line) and squamous cell carcinoma of head-and-neck (SCCHN) cells (Tu212 cell line). The IC_{50} values against Tu212 and H292 cells were found to be 4.13 μmol/L and 14.96 μmol/L, respectively. LTNn significantly inhibited the tumor growth of SCCHN in comparison to free LTN during *in-vivo* studies.[58]

Apigenin-loaded drug delivery systems

Apigenin (4′,5,7-trihydroxyflavone) (AP), a common bioactive flavonoid, is found in a large variety of fruits, plants, and vegetables. According to the biopharmaceutics classification system, AP has high intestinal membrane permeability and poor solubility, which can be improved by increasing the dissolution rate of the drug.[103]

An effort has been made to improve the oral bioavailability of AP using carbon nanopowder as drug carrier. AP and CNP were used to prepare a solid dispersion system and evaluated for *in-vitro* and *in-vivo* parameters. A 275% increase in dug release after 60 min for CNP-AP system was observed in dissolution studies as compared to pure AP. Pharmacokinetic studies of SD formulations showed that the AUC_{0-t} of AP was 0.83 times more for the CNP-AP system than pure AP, depicting improved bioavailability. Further, no significant difference on intestinal toxicity was observed in CNP-AP system, CNP alone, and control groups.[59] An AP-loaded ethosome (APE) topical formulation was optimized, designed, and studied for *in-vitro* and *in-vivo* anti-inflammatory activity. It was observed that, in APE formulations, as the amount of phospholipids increased the encapsulation efficiency was found to be increased. Further, with increase in the levels of phospholipids, skin deposition and transdermal flux of AP was improved. During *in-vivo* studies, all the APE formulations showed anti-inflammatory activity by inhibition of cyclooxygenase-2 levels in mouse model.[60]

Breviscapine- and scutellarin-loaded drug delivery systems

Breviscapine (BVN) is the total flavonoid constituents (the content of scutellarin [SCU] ≥85%) extracted from the dried whole plant of *Erigeron breviscapus* (VANT.) Hand, Mazz popularly used in China to cure paralysis. Several studies proved its efficacy in the treatment of cerebral infarction, coronary heart disease, and angina pectoris. Pharmacokinetic studies on BVN or SCU have been much investigated in rats[104] and other higher animals after oral administration, and it was observed that the oral absolute bioavailability was quite poor in dogs. SCU (4'5,6-trihydroxyflavone-7-glucuronide) is used clinically to treat paralysis induced by cerebrovascular diseases and acute cerebral infarction.[105,106] In recent years, it has been reported that SCU can induce cell death in the human colon cancer cell line.[61] SCU can also inhibit tumor proliferation and migration and regulate cell adhesion in oral squamous cell carcinoma.[107] However, decreased bioavailability and low stability demands novel drug delivery for BVN and SCU to improve the clinical efficacy. Zhou *et al*. prepared a BVN-loaded pluronic P85-coated liposomes using cholesterol and l-α-phosphatidylcholine. The particle sizes, zeta potential, and encapsulation efficiency of the formulations were studied. *In-vitro* drug release and permeability of Caco-2 cells were investigated along with characteristics and pharmacokinetics of the liposomes was evaluated in rats. Results of the study suggested that the diameter of liposomes was 118.8 ± 4.9 nm with and a zeta potential of −35.4 ± 1.5 mV. A significant increase in the absorption of BVN in Caco-2 cells was observed with 5.6-fold enhancement in its oral bioavailability in rats.[108] Li *et al*. developed BVN-nanostructured lipid carrier (BVN-NLC) ionic complex to improve the pharmacokinetic profiles of BVN. BVN-NLC developed was analyzed by TEM, mean particle size, polydispersity index, zeta-potential analysis, and entrapment efficiency. *In-vitro* stability was studied in fresh plasma and liver slurry of rats. *In-vivo* pharmacokinetics was analyzed after intravenous injection at a dose equivalent to BVN (10 mg/kg). Results revealed that the mean particle size of BVN-NLCs was found to be ~170 nm with entrapment efficiency of ~89%. After intravenous administration in rats, the BVN-NLCs showed a 32 times increase in the AUC_{0-t} and a 12 times increase in $T_{1/2}$ as compared to the commercially available BVN solution.[109] A SCU-PC-loaded supersaturated self-emulsifying drug delivery system (Super-SEDDS) was developed, characterized, and studied for its *in-vitro* and *in-vivo* efficacy. Super-SEEDS enhanced the progressive dissolution from 70% to 100% and also increased the intestinal absorption of from 0.04 to 0.12 μg/cm as compared to SCU powder. Furthermore, in *in-vivo* studies, Super-SEEDS achieved AUC_{0-t} of SCU up to approximate 1.7-fold increase as compared to SCU powder. The activity of Super-SEEDS was found to be superior as compared to SCU-PC and SEDDS.[62] A novel SCU-polyrotaxane (SCU-PR) was synthesized, characterized, and studied for cytotoxicity against colon cancer cell lines (HCT116 and LOVO) by Jiang *et al*. Results showed that the IC_{50} values of SCU-PR were found to be 1.03×10^{-6} and 1.01×10^{-6} mol/L, respectively, and significantly lower as compared to free SCU.[63]

Diosmin-loaded drug delivery systems

Diosmin (DSN), a venotonic flavonoid, is widely used in the treatment of carcinoma of the liver and colon. To improve the intestinal permeability and drug dissolution, Freag *et al.* developed a phytosome formulation of DSN. Phytosome formulation was prepared using SPC and solvent mixture of dimethyl sufoxide: T-butyl alcohol in 1:2 ratio following lyophilization technique. IR and DSC studies confirmed the complex formation. The lowest particle size was found to be 316 nm for lyophilized phytosomal nanocarriers (LPNs) with adequate zeta potential and good *in-vitro* stability. About 80% of DSN was found to be permeated through oxygenated rat intestine as compared to the suspension of DSN.[64] Novel polymer-stabilized DSN nanosuspensions were developed using bottom-up nanoprecipitation technique. Noneverted sac and HPLC techniques were used for the characterization of DSN-nanosuspensions *ex-vivo*. Results revealed that DSN nanosuspension (DSN: hydroxypropylmethyl cellulose 2:1) was found to optimized formulation. The lowest particle size was 336 nm with 99.9% drug loading and improved the reconstitution properties with mannitol incorporation and dissolution profile. About 89% of DSN was permeated from the nanosuspension after 120 min as compared to conventional drug suspension.[65]

Daidzin-loaded drug delivery systems

Daidzein (4′,7-dihydroxylisoflavone, DZN) is a water-insoluble isoflavone,[110] isolated mainly from leguminous plants, used in treating hypertension, coronary heart disease, cerebral thrombosis, and menopause syndrome. Recently, studies demonstrated that DZN inhibition the growth of cancer cells by activating a cell death pathway and prevent the outset of diabetes.[111-113] However, the lower bioavailability of DZN limits its usage as medicine. Animal experiments showed that the absolute bioavailability of DZN suspension after oral administration to rats was only 6.1%. 6.[114] Many concrete efforts are made to improve the bioavailability of this isoflavone by converting it into a microparticulate system.

PLGA nanoparticles loaded with DZN, viz., DZN-loaded PCs PLGA nanoparticles (DZN-PC-PLGANs) and DZN-loaded cyclodextrin inclusion complexes PLGA nanoparticles (DZN-CD-PLGANs) were prepared by Ma *et al*. to improve the oral bioavailability of DZN. The average efficiency of drug entrapment, size of particle, and zeta potential of DZN-PC-PLGANs and DZN-CD-PLGANs were 81.9% ±5%, 309.2 ± 14.0 nm, −32.14 ± 2.53 mV and 83.2% ±7.2%, 323.2 ± 4.8 nm, −18.73 ± 1.68 mV, respectively. In pharmacokinetic studies, relative bioavailability of DZN-PC-PLGANs and DZN-CD-PLGANs was found to be enhanced about 5.57- and 8.85-fold, respectively, compared to DZN suspension as control.[66] In another study, DZN was encapsulated in TPGS 1000 (TPGS) emulsified zein nanoparticles (TZN). Adding TPGS as an emulsifier increased the encapsulation efficiency of DZN in ZN from 53% to 63%. DZN-loaded TZN had a slower DZN release compared with DZN-loaded ZN in both simulated digestive fluids and a pH 7.4 buffer. Cellular uptake and transport studies revealed that DZN in TZN were taken up more efficiently into Caco-2 cells and transported more quickly through Caco-2 monolayer than DZN solution. A pharmacokinetic study demonstrated that the C_{max} of DZN in mice after oral administration of DZN loaded TZN was 5.66 ± 0.16 μM, which was improved by 2.64-fold compared with that of DZN solution (2.14 ± 0.04 μM).[67]

Ginkgo biloba extract-loaded drug delivery systems

Ginkgo biloba extract (GbE) has been used medicinally since centuries in China to treat asthma, bronchitis, and for the management of cardiovascular diseases.[115] A number of pharmacological investigations have been carried out by many researchers for its antioxidant, antitumor, and protective effects on central nervous system and therapeutic effects for cerebral and peripheral vascular diseases.[116-119] These therapeutic effects are presumed to be due to the presence flavonoids and terpenoid lactones. However, the oral bioavailabilities of these flavonoids are found to be relatively low due to their poor solubility.[120] Considering this, many drug delivery systems have been attempted to enhance the bioavailability of GbE.

Jin *et al*. developed a favorable GbE incorporated niosomal drug delivery system (GbEns) with improved oral bioavailability using film dispersion-homogenization method. Characterization of GbEns was carried out for their physical attributes. Drug release studies *in-vitro* and distribution studies *in-vivo* were studied for GbEns. Further, GbEns showed minimum particle size of 141 nm, and in stability studies, no significant change in drug entrapment efficiency was observed for the GbE niosomes at 4°C and 25°C. The *in-vitro* studies suggested that GbE niosomes can extend the release of flavonoidal glycosides in phosphate-buffered solution (pH 6.8) till 48 h. *In-vivo* distribution studies suggested that the flavonoid glycoside content in the heart, lung, kidney, brain, and blood of rats treated with the GbEns was found to be considered than in the rats treated with the oral GbE tablet.[68] To improve the oral bioavailability of GbE, Zheng *et al*. prepared proliposomes using oleic acid derivative of branched polyethylenimine (bPEI-OA). A significant increase in absorption constant (Ka) and apparent permeability coefficient (Papp) from bPEI-OA-functionalized proliposomes was observed. The oral bioavailability of bPEI-OA-organized proliposomes was remarkably increased in comparison with control and conventional proliposomes.[69] Similarly, GbE-loaded proliposomes (P-GbE) using bile salts were prepared and optimized for various physical attributes. *In-vitro* studies showed delayed release and enhanced dissolution of Ginkgo flavonoids and terpene lactones from GbE proliposomes. Proliposomes significantly enhanced GbE absorption in the GI tract and decreased its elimination. The bioavailabilities of QT, kaempferol, isorhamnetin, ginkgolide A, ginkgolide B, and ginkgolide C from proliposomes relative to the control were 245%, 211%, 264%, 203%, 333%, and 294%, respectively.[70] SEDDS of GbE was prepared, optimized, and tested for its oral bioavailability by Tang *et al*. Optimized SEDDS showed droplet size distribution of about 100 nm. A faster rate of dissolution was observed for the active components of GbE-SEDDS as compared to GbE tablets. The relative bioavailability of SEDDS for bilobalide and ginkgolide A and B after single-dose administration (800 mg) was found to be 162.1, 154.6, and 155.8%, respectively, as compared to GbE tablets.[71]

Resveratrol-loaded drug delivery systems

Resveratrol (3,5,4'trihydroxy stilbene) (RES), a nonflavonoid polyphenolic compound, has been found to be a prominent and potential phytopharmaceutical used in the treatment of cancer, neurodegenerative and metabolic disorders, and cardiovascular diseases. It is commonly found in foods with maximum concentration in grapes, peanuts, berries, and red wine. There are several references which support that RES attenuates many age-related chronic diseases and improves overall health status in mammals, including humans.[121] In plants, RES is synthesized in response to various environmental stress factors and considered as a phytoalexin.[122,123] RES exists in *cis*- and *trans*- configurations, of which *trans*-RES is the principal biologically active form. Despite several therapeutic activities of RES, the clinical applications are commonly limited due to poor solubility and stability. Some investigators have succeeded to improve the solubility of RES by formulating polymeric nanoparticles and liposomes.

RES-loaded SLNs and NLCs were prepared by Neves *et al*. These lipid nanoparticle systems were characterized and evaluated for their quality. Results showed spherical and uniform nanoparticles with a smooth surface. Entrapment efficiency of ~70% was obtained for both SLNs and NLCs. Both the formulations were found to be stable for 2 months. The *in-vitro* release studies showed that in both the nanosystems, a negligible release of RES was observed. RES was found to be remained associated with lipid nanoparticles after incubation with digestive fluids in simulation studies.[72] A sustain release formulation to study the long-term release of atorvastatin (ATS) and *trans*-RES (t-RES) was prepared and characterized by Sih *et al*. and evaluated for management of atherogenic dyslipidemia and promoting cardioprotection. Acetone diffusion, gas flow analysis, SEM, and TEM characteristics were studied for the nanomembranes followed by surface charge analysis of nanochannels. One-month *in-vitro* sustained release data was established for ATS and t-RES. Human microvascular endothelial cells were used to establish the influence of the membranes on cell viability using MTT assay.[73] Figueiro *et al.* prepared and evaluated t-RES-loaded lipid-core nanocapsules (RES-LNC) for antiglioma effect in brain tumors. A significant decrease in the viability of c6 glioma cells was observed for RES-LNC as compared to solution of RES. Interestingly, RES-LNC was found to be more selective for cancer cells and nontoxic to healthy neural cells. It was concluded that the induction of apoptotic cell death by RES-LNC may be due early arrest in the S and G1 phases of the cell cycle. *In-vivo* studies suggested that, RES-LNC (5 mg/kg/day) markedly decreased the size of brain-implanted c6 tumors and reduced the incidence of malignant tumor-associated characteristics as compared to RES solution.[74] In another study by Sanna *et al*., polymeric nanoparticles (NPs) encapsulating *trans*-resveratrol (RES-NPs) were designed, characterized, and evaluated for antiproliferative activity using human PCa cells. Encapsulation efficiencies of RES-NPs were ranged from 74% to 98%.[75] Using a dual carrier approach, Soo *et al*. coencapsulated pristine RES alongside of inclusion complex of cyclodextrin-RES in hydrophilic and lipophilic compartments of liposomes. The novel formulations were found to be stable and enhanced the cytotoxic profile of RES as compared to conventional liposome formulations.[124]

Naringenin-loaded drug delivery systems

Naringenin (4,5,7-trihydroxy flavanone, NGN) is among the highly utilized flavonoids by humans and is easily detected in the human serum after its intake due to its good bioavailability.[125] As a flavonoid, NGN has antioxidant and anti-inflammatory activities and low toxicity so has potential to be used as a therapeutic tool.[126,127] Yen *et al*. developed a novel NGN-loaded nanoparticles system (NGNPs) to improve the physicochemical properties and hepatoprotective activity which was compared with NGN alone. Results exhibited that NGNPs had a significantly higher rate of release than NGN, thus enhancing its solubility. As compared to NGN, liver protection was more by NGNPs with considerable reduction in liver function index and lipid peroxidation, in conjunction to a substantial increase in the levels of the antioxidant enzymes ($P < 0.05$).[76] In another study by Tsai *et al*., a submicron emulsion system for NGN was prepared and studied for stability, drug permeability through skin, and skin irritation. The results showed that submicron emulsion formulations of NGN enhanced the transdermal amount and deposition amount in the skin as compared to aqueous solution of NGN. Stability studies of the submicron emulsions revealed that the level of drug was more than 98% after 3 months of storage at 25°C and 40°C. Further, it was also observed that NGN-loaded submicron emulsion had less skin irritation.[77]

Methoxyflavonone-loaded drug delivery systems

Domínguez-Villegas *et al*. isolated four flavonones from *Eysenhardtia platycarpa* leaves to prepare novel formulations for inflammatory disorders. Two topical novel formulations in the form of nanoemulsion and nanoparticles were prepared following established methods. Nanoemulsion system showed droplet size <70 nm and polymeric nanoparticles with a size of 156–202 nm possessing zeta potential values >25 mV that provided good stability and obtained high entrapment efficiency (78%–90%). All formulations revealed profiles of steady-state release over time and steady increase of flavanones in the skin permeation test. Vehiculized nanosized systems of prenylated flavanones significantly improved the anti-inflammatory activity in mice. 5-hydroxy-7-methoxy-6-prenylflavanone-loaded formulations showed better anti-inflammatory activity.[78] Oral absorption of methoxyflavones was improved by (SMEDDS) and cyclodextrin (CD) complex formulations. KP-SMEDDS was formed by combination of polyoxyethylene castor oil (53.3%), propylene glycol (26.7%), and triglyceride of coconut oil. Lyophilization method was applied to prepare a complex of 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD) and KP. The results showed that KP-SMEDDS and KP-2-HP-β-CD complex improved the dissolution rate of methoxyflavones in both 0.1 N HCl and 0.2 M PBS pH 6.8 compared to KP dissolved in a solution of propylene glycol, PEG 400, ethanol, and water. KP-SMEDDS and KP-2-HP-β-CD formulations showed about 10- and 3.5-fold greater Pap *P* values of methoxyflavones in Caco-2 cells. The values of oral bioavailability for KP-SMEDDS formulations were higher than that of KP (25.38-, 42.00-, and 26.01-fold for PMF, TMF, and DMF respectively). For the KP-2-HP-β-CD complex, oral bioavailability values were 21.63-, 34.20-, and 22.90-fold greater than those of KP, respectively.[79]

CONCLUSION

Polyphenolic compounds such as flavonoids, tannins, and phenolic acids are paying much attention due their pharmaceutical, nutraceutical and therapeutic properties. The micro and nanotechnological concepts of pharmaceutical industries have been utilized to develop novel phytopharmaceutical preparations for such compounds with improved pharmacokinetic profile. A variety of novel drug delivery systems have been developed for polyphenolic compounds to enhance the relative bioavailability. The developed formulations have also shown sustain or prolonged release properties and also target delivery as evidenced by in-vitro and in-vivo studies. The novel formulations of Quercetin, Green tea catechins, epigallocatechin gallate, Genistein, Resveratrol, Breviscapine and Scutellarin have been prepared by novel techniques and found to increase the therapeutic efficacy against various diseases. Detailed clinical studies of such formulations along with safety data will be helpful to bring them in the market which in turn will help to improve the human health.

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Conflicts of interest

There are no conflicts of interest.

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