

# Recent Developments in Formulation Design of a Multifunctional Phytochemical Quercetin: A Review

Rashmi Mallya\*, Kunal Patil

## ABSTRACT

Quercetin is a polyphenolic flavonoid, found naturally and widely distributed in many plants. Quercetin has a plethora of activities and due to its diverse activity profile and multifunctionality on various targets, it has become an upcoming area of interest for several researchers. Evidences suggest that researchers have put up a way forward and explored the novel approach of quercetin lipid-based formulations. Recent literature studies indicate that lipid-particulate, emulsion and vesicular systems were found to be successful in comparison to the conventional formulations. These formulations comprise of a suitable combination of natural lipids with surfactants, cosurfactants and cosolvents. Customizing lipid nanoparticles with quercetin to a particular target may also be a revolutionary method in order to optimize the therapeutic activity of drugs and mitigate toxicity. There is an increasing need to develop these novel formulations as they enhance the solubility profile, improves stability and has an expanded biological profile. Regardless of its enormous potential linked with the delivery of several lipophilic drugs with improved bioavailability using novel lipid-based nano-formulations, these lipid formulations have certain drawbacks, which limits its commercialization and market potential. This review updates and increases knowledge about quercetin-lipid based formulations having anticancer, anti-inflammatory, antioxidant, dermatological and CNS activity as well as those useful in treating several bone disorders. This review also compiles recent advances in methods, formulation composition, targets, experimental models and route of administration for quercetin containing lipid-based formulations.

**Key words:** Anticancer, Antioxidant, Lipid-based drug delivery, Quercetin, Vesicular systems.

Rashmi Mallya\*, Kunal Patil

Department of Pharmacognosy & Quality Assurance, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Mumbai, Maharashtra, INDIA.

## Correspondence

Dr. Rashmi Mallya

Professor, Dept of Pharmacognosy & Quality Assurance, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, P.O. Box-400056, Mumbai, Maharashtra, INDIA.

Phone no : 91-9819720372

E-mail: rashmi.mallya@bncp.ac.in

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## INTRODUCTION

Quercetin (QUE; 3,5,7,30,40-pentahydroxyflavone) is one of the well-known flavonoids which comes under the subclass flavanol.<sup>[1]</sup> The German nutrition expert Prof. Stephan C. Bischoff quoted that, "Quercetin is a most promising compound for disease prevention and therapy".<sup>[2]</sup> The average daily intake of QUE is about 25 mg in humans, according to the US Department of Health and Human Services.<sup>[1,3]</sup>

Quercetin has shown good potential health benefits in humans and it can be used as a nutritional supplement in pharmaceutical and food industries.<sup>[4]</sup> Quercetin acts as a nutraceutical through functional foods with a concentration range of about 10–125 mg per serving.<sup>[5]</sup> Quercetin is a versatile molecule that have been investigated extensively for their pharmacological properties including antioxidant,<sup>[4,6]</sup> anti-obesity,<sup>[4,7]</sup> anti-carcinogenic,<sup>[4,8]</sup> antibacterial and anti-inflammatory activity.<sup>[4,9]</sup> It was reported with substantial evidence that quercetin exhibits chemo-protective activity against certain types of cancers (including stomach, prostate, bladder and esophagus), as free radicals are considered to be one of the major factors of cancer formation.<sup>[10,11]</sup> A large body of evidence also shows it has a beneficial effect

on diabetes and allergic conditions. Quercetin also helps in inhibiting the enzyme that leads to nerve, eye and kidney damage in diabetic patients.<sup>[12]</sup>

Quercetin has major limitations like low bioavailability and poor absorption like other flavonoids but quercetin derivatives seem to increase the rate of absorption in the stomach and small intestine.<sup>[4,12]</sup> Due to extensive metabolism, the bioavailability of quercetin is found to be very low. The delivery systems are hence designed to protect the components from chemical degradation. By encapsulating a substantial quantity of functional components so that the nutraceuticals incorporated can be released at a controlled rate and to a specific site of action or within a particular gastrointestinal tract (GIT) region.<sup>[4]</sup> To overcome the limitations of bioavailability and absorption, novel drug delivery systems were developed.

Novel drug delivery systems are developed with an intention to overcome the disadvantages associated with conventional drug delivery systems. Novel drug delivery systems not only minimize repetitive administration to address non-compliance, but also help to improve therapeutic efficacy by reducing

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toxicity and increasing bioavailability.<sup>[13]</sup> Novel formulations are reported to have considerable advantages over traditional formulations of plant active ingredients and extracts, which includes improved solubility, bioavailability, protection from toxicity, improved pharmacological function, stability enhancement, increased distribution of tissue macrophages, sustained delivery and protection against physical and chemical degradation. Conventional dosage forms are unable to meet the requirements of prolonged release dosage form.<sup>[14]</sup>

Lipid-based delivery systems (vesicular carriers and lipid particulate systems) have been reported as the most effective delivery system as depicted in Figure 1.<sup>[15]</sup> Lipid based delivery systems are made up of biodegradable and biocompatible lipids for controlled release, targeted delivery and drug protection.<sup>[15]</sup> Lipid-based delivery systems can be tailored to target various skin conditions considering various factors like the delivery system selected, formulation composition, manufacturing processes and process variables.<sup>[15,16]</sup>

## CHEMISTRY OF QUERCETIN

Quercetin consists of a flavonoid ring structure; comprising of five hydroxyl groups. The structural characteristics of flavonoids consist of 2 benzene rings (A and B) which are connected by a pyrene ring (C) as depicted in Figure 2.

Quercetin generally exists in the glycoside form, in which one or more hydroxyl groups are replaced by different types of sugar groups as seen in isoquercetin which is stated in Table 1.<sup>[4]</sup>

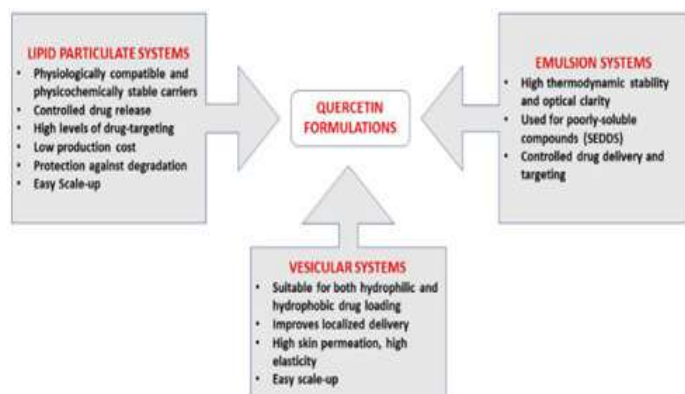


Figure 1: Types of lipid-based drug delivery systems.<sup>[15,17]</sup>

Table 1: Summary of quercetin and its derivatives.<sup>[4]</sup>

Systematic name	Source	R1	R2	R3	R4	R5	R6	R7
Quercetin	Dietary flavonoid Caper, black chokeberry, onion, tomato and lettuce	OH	OH	OH	H	OH	H	OH
Quercetin 3-O-Glucoside (isoquercetin)	Beans, salvia and buckwheat	O-Glucose	OH	OH	H	OH	H	OH
Quercetin 7-methylether (rhamnetin)	Cloves	OH	OH	OH	H	OH	H	O-Methyl
Quercetin 6-C-glucoside	Isolated from <i>Ulmus wallichiana</i> plant	OH	OH	OH	H	OH	Glucose	OH
Quercetin 4'-methylether (tamaraxetin)	Minor product in o-methylation of quercetin	OH	OH	O-Methyl	H	OH	H	OH

## NEED FOR LIPID-BASED DRUG DELIVERY SYSTEMS

Lipid-based drug delivery system<sup>[15]</sup> is a promising approach to enhance the water solubility of lipophilic drugs such as quercetin by incorporating them into lipid-based nanocarriers which comprise of liquid and solid lipids.<sup>[15,18]</sup> From the previous decades, the emerging applications of lipids as carriers for poorly water-soluble drugs have taken new horizons in oral medicines.<sup>[19,20]</sup> Lipid-based systems overcome the drawbacks of conventional colloidal systems hence due to the growing need towards lipid-based drug delivery systems, the American Association of Pharmaceutical Scientists has formed a "Lipid-Based Drug Delivery Systems Focus Group".<sup>[19]</sup>

Lipid-based drug delivery systems have several advantages over conventional systems as depicted in Figure 3.

There is an increasing need to develop novel delivery vehicles that indirectly enhance the and low oral bioavailability it affects its application as a therapeutic agent.<sup>[25]</sup> However, it was reported by a few researches that there is a significant improvement in the biodistribution through oral delivery by lipid-based quercetin formulation.<sup>[25,26]</sup> Lipid-based drug delivery systems contains various nanocarriers including microemulsions,<sup>[25,27]</sup> nanosuspensions,<sup>[25,28,29]</sup> phospholipids complexes,<sup>[25,30]</sup> liposomes,<sup>[25,26,31]</sup> nanoparticles<sup>[8,25,32]</sup> and nanostructured lipid carriers;<sup>[25,33]</sup> these were prepared to induce topical delivery,<sup>[25,34]</sup> such as skin,<sup>[8,25,33,35,36]</sup> brain,<sup>[32]</sup> lung<sup>[25,37]</sup> and colon delivery.<sup>[25,38]</sup> The biodistribution of quercetin was found to change with different formulations and it showed a diverse range of activity profiles as shown in Figure 6.<sup>[25]</sup> Hence in this review, we have explored all quercetin lipid-based formulations till date having multifunctional activities.

## QUERCETIN LIPID-BASED FORMULATIONS

Quercetin is one of the important bioflavonoids which is obtained naturally from plants and there is mounting evidence that it can act as a multifunctional drug due to its diverse activity profile as depicted in Figure 4.

Quercetin lipid-based formulations have been classified into various types as shown in Figure 5. Several formulations have been developed by researchers till date. Table 2, 3a, 3b, 4a and 4b summarizes promising effects of 28 quercetin lipid-based formulations having multifunctional activities which include anti-cancer, anti-inflammatory, antioxidant and dermatological activity, formulations which cross the BBB treating various CNS ailments as well as formulations used for the treatment of bone-related disorders.

Quercetin has been formulated into various novel formulations like solid-lipid microparticles, solid-lipid nanoparticles (SLN), Nanostructured-lipid carriers (NLC), nanoemulsions, microemulsions, Self-emulsifying drug delivery systems (SEDDS), liposomes, niosomes, phytosomes, transferosomes as stated in Table 2 and it was found that these formulations have better efficacy, stability and diverse therapeutic actions as compared to conventional quercetin formulations. This review surmised the expanded activity profile, formulation composition and method of preparation of various quercetin lipid-based formulations in detail which have been reported till date.

### Quercetin lipid-based formulations with anticancer activity

There is growing proof which suggests that quercetin has possible anticancer effects and it tends to interfere synergistically when used in conjunction with approved anticancer drugs like irinotecan and cisplatin.<sup>[39]</sup> Studies indicate that quercetin seems to reduce cisplatin-induced cytotoxicity against ovarian cancer in various murine models of cancer.<sup>[39,40]</sup>

### Lipid particulate system containing quercetin formulation

#### *Solid Lipid Nanoparticle (SLN) containing formulation<sup>[41]</sup>*

SLNs are the first-generation lipid nanocarriers. These are developed to formulate drug in solid lipids preferably by cold or hot homogenization technique, depending upon thermal stability of the drug.<sup>[42]</sup>

Researchers developed SLN formulation of quercetin containing cholesterol or phytosterol to enhance the cellular penetration of quercetin for targeting hepatocellular carcinoma cells. Quercetin-SLN's cytotoxicity was evaluated by MIT assay on HepG2 cells. The authors emphasized on advantages of SLN compared to other conventional colloidal drug delivery systems in terms of solubility, toxicity, biocompatibility, efficiency and protection of active compounds from chemical degradation.<sup>[14]</sup> Twenty- three different formulations of SLN loaded with quercetin was prepared by using the emulsification solvent evaporation method. This study demonstrated that since quercetin is a highly lipophilic drug molecule it could be conveniently mixed with SLN structure and it was reported that the entrapment efficiency was 100% for all formulations. This research identifies that the IC<sub>50</sub> value of quercetin

**Table 2: Summary of formulations containing lipid-particulate drug delivery systems.**

Sr no	Type of lipid-based drug delivery system	Formulation composition	Method of preparation	Experimental model	Route	Therapeutic activity	Ref
1.	<b>Solid-lipid microparticles</b>	Quercetin Phosphatidyl choline	Hot Emulsion technique	No <i>in-vivo</i> studies conducted	Topical	Enhances stability, Penetration of skin-care products	[96]
2.	<b>Nanostructured lipid carriers</b>	Quercetin Soy lecithin Glyceryl tridecanoate Glyceryl tripalmitate Vitamin E acetate	Phase-inversion method	MCF-7 and MDA-MB-231 breast cancer cells	-	Breast cancer	[43]
		Quercetin Natural lipids (Illipe butter and Calendula oils)	Emulsion and sonication method	Pig ear skin RBL-2H3 (Rat basophilic leukemia) HaCaT cell lines H3D-PT	Topical	Prevents skin damage caused by UV-B radiations	[101]
		Quercetin Tocopherol acetate Phospholipid	Emulsification technique	Caco-2 cells Male Wistar rat models	-	Improves brain delivery of quercetin	[116]
3.	<b>Solid-lipid nanoparticles</b>	Quercetin Cholesterol/ Phytosterol Lecithin Cetyl alcohol	Solvent evaporation method	HepG2 cells	-	Anticancer activity on hepatocellular carcinoma cells	[41]
		Quercetin Palmitic acid Tween 80	Homogenization and Ultra-sonification method	Pig ear skin Franz cells	Transdermal	Antioxidant Enhances skin permeability	[105]
		Quercetin Glyceryl monostearate Hydrogenated Soya	Emulsion solvent preparation followed by cold homogenization	Sprague Dawley Rat models	Oral	Treatment of post-menopausal osteoporosis	[117]

in cholesterol SLNs was roughly about six times less than free quercetin and induces aggregation of quercetin in HepG2 cells. Phytosterol loaded SLN were found to be cell toxic. Thus, it was concluded that cellular penetration of quercetin was enhanced by sterol containing solid lipid nanoparticle for targeting hepatocellular carcinoma cells.

#### Nanostructured lipid carriers (NLC) containing formulation<sup>[43]</sup>

NLCs were developed by replacing a fraction of solid lipids with liquid lipids to form drug incorporated matrix.<sup>[42]</sup> NLCs belong to the class of second-generation lipid carriers which were developed to overcome the drawbacks of first-generation lipid nanocarriers like SLN which includes drug escape through matrix during storage and lower drug loading efficiency. Currently, NLCs are considered as potential drug carriers due to their biocompatibility and superior formulation properties over SLNs.<sup>[42]</sup>

Studies report that biocompatible and biodegradable quercetin-nanostructured lipid carriers (Q-NLC) were synthesized using a novel phase inversion-based process method. As quercetin application in cancer is limited due to its poor water solubility, poor cellular bioavailability and high instability and to overcome this problem, the researchers used a strategy to encapsulate quercetin into biodegradable and biocompatible nanoparticles.<sup>[43,44]</sup> Nanoparticle drug delivery system has gained considerable interest in cancer research because nanocarriers can enhance absorption, improve intracellular penetration, protect the drug against degradation, prolongs drug circulation time and lower toxicity.<sup>[43,45]</sup> It was reported that the physical stability of Quercetin-NLC

formulation was good as compared to native quercetin. The authors conducted an *in-vitro* release study which depicted that the stability of quercetin was considerably increased by nanoencapsulation to about 95%.<sup>[43]</sup> Quercetin-NLC significantly increased cytotoxicity in a dose-dependent manner and induced apoptosis in MCF-7 and MDA-MB-231 breast cancer cells.<sup>[43,46]</sup> This novel formulation of quercetin with nanostructured lipid carriers has over 3 times the dose benefit of indigenous quercetin to decrease the viability of breast cancer cells.<sup>[43]</sup> The study reported that quercetin induces growth inhibition in MCF-7 cells by inducing cell cycle arrest and apoptosis. Thereby it was concluded that Quercetin-NLC formulation can be a potential breakthrough for the treatment of breast cancer with minimal side-effects.

## Emulsion systems containing quercetin formulations

#### Nanoemulsion containing quercetin formulation<sup>[47]</sup>

The authors developed a nanoemulsion containing quercetin formulation in aerosol form using low and high energy homogenizers. This study focuses on developing aerosol nanoemulsions using palm oil esters. The aerosol technique is preferred over others because it facilitates the uniform distribution of the drug and this leads to a greater penetration into the peripheral or the alveolar region of the lung. Various studies reported that quercetin could inhibit the proliferation of multiple cancer cells which includes lung cancer, prostate carcinoma, colon cancer and pancreatic cancer. It was reported that using a combination of emulsifiers and lipids leads to significant enhancement in the absorption of quercetin.<sup>[48]</sup> The nanoemulsion delivery system enhances the bioavailability of poorly soluble drugs and decreases the degradation and metabolism of drugs. Nanoemulsions have the potential to deliver proteins as well as other traditional drug compounds to the lung because of its high solubilizing power and drug protective action. The nanoemulsions showed advantages as that of a solution like physicochemical properties and it is hypothesized that nanoemulsions perform as a solution when nebulized and will result in improved aerosolization performance. Oil, lecithin, tween 80 and the aqueous phase was used to developed optimal quercetin nanoemulsion formulation. Laser diffraction size analysis of the aerosol and its excellent distribution and penetration capacity generated from quercetin nanoemulsions shows its suitability for efficient pulmonary delivery for lung cancer treatment.

#### Microemulsion containing quercetin formulation<sup>[49]</sup>

Savare *et al.* developed a formulation of microemulsion loaded with quercetin for the treatment of brain tumours via the intranasal pathway. It was reported that intranasal drug delivery was found to be a promising approach for direct delivery of a neurotherapeutic agent to the nose and further to the brain bypassing the BBB and trigeminal nerve pathways. Quercetin shows a promising ability to inhibit angiogenesis and it stops the new blood cell formation in blood vessels that are responsible for tumour growth. Quercetin microemulsions were prepared by spontaneous emulsification technique by slowly pouring oil, surfactant and co-surfactant mixture. Thereby, it was concluded that drug-loaded quercetin microemulsion for intranasal administration can be a very promising and effective approach for delivering an anticancer agent for the treatment of a brain tumour.

## Vesicular systems containing quercetin formulations

#### Liposomes containing formulation<sup>[39]</sup>

Studies report that quercetin-copper based liposomal formulations were synthesized by researchers and they explored the therapeutic potential of quercetin which describes that there is a need to improve the solubility of quercetin and different strategies have been employed to generate more water-soluble pro-quercetin compounds that biologically convert

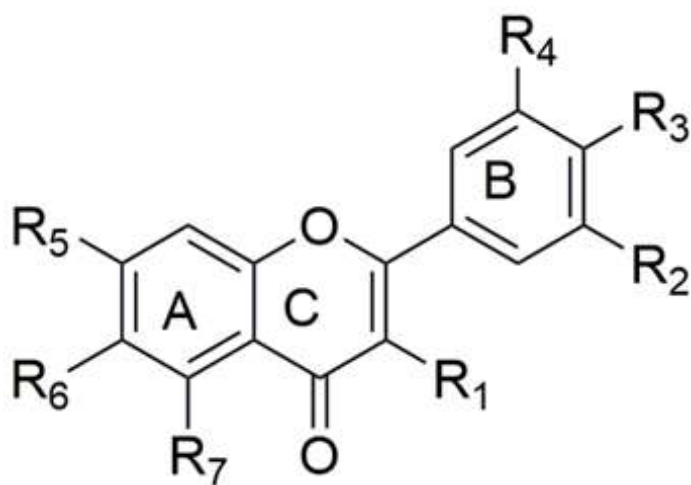


Figure 2: Chemical structure of quercetin and its main derivatives.

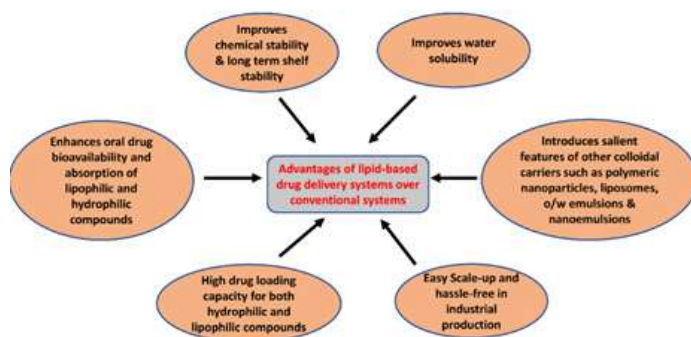


Figure 3: Advantages of Lipid based drug delivery systems over conventional systems.<sup>[19,21-24]</sup>

to quercetin<sup>[50]</sup> as well as various formulation strategies involving the use of liposomes,<sup>[51]</sup> polymers<sup>[52]</sup> or milling to produce nanocrystals.<sup>[53]</sup> This research shows that a copper-quercetin liposomal formulation is suitable for intravenous use and at least 100 times the apparent solubility of quercetin is improved by the resulting formulation. The authors

highlighted that the novel liposome technology with encapsulated copper in quercetin was found to be extremely efficient and when compared to indigenous quercetin the liposomal quercetin formulations often show increased blood circulation and decreased rates of elimination from the plasma compartment.<sup>[54]</sup> The novel copper-based liposomal formulations

**Table 3a: Summary of formulations containing emulsion drug delivery systems.**

Sr no.	Type of lipid-based drug delivery system	Formulation composition	Method of Preparation	Experimental model	Route	Therapeutic activity	Ref
1.	Nanoemulsions	Quercetin Palm-based esters Soyabean Lecithin	Homogenization method	-	Pulmonary	Lung Cancer	[47]
		Quercetin Oleth-20 Oleth-30	Sub-Phase inversion temperature method	CDC 641 T cell	Topical	Cosmetic formulations	[109]
		Quercetin <i>A. saturoioides</i> extract Egg lecithin Octyldodecanol	Spontaneous emulsification method	Franz diffusion cells	Topical	Antioxidant	[83]
		Quercetin Oleic acid Oils Tween-20 PEG-400 Propylene glycol Transcutol P	Spontaneous emulsification method	Synoviocyte HIG-82 cell lines CFA-induces wistar rat arthritis models	Topical	Rheumatoid arthritis	[125]
		Quercetin Lipid-based nanocarrier	Phase-inversion temperature method	Carrageenan-induced hind paw edema rat models	Oral	Anti-oedematous activity Antioxidant	[68]
		Quercetin Oleic acid PEG 400 Tween 80	Titration method	Wistar rat models	Intranasal	Treatment of cerebral ischaemia	[117]
		2.	Self-emulsifying drug delivery system (SEDDS)	Quercetin Surfactants and co-surfactants	Spontaneous self-emulsification method	Caco-2 cells	Oral

**Table 3b: Summary of formulations containing emulsion drug delivery systems.**

Sr no.	Type of lipid-based drug delivery systems	Formulation composition	Method of preparation	Experimental model	Route	Therapeutic activity	Ref
3.	Microemulsions	Quercetin Oils Tween-80 Polyethylene glycol	Spontaneous emulsification method	Sheep nasal mucosa	Intranasal	Brain cancer	[49]
		Quercetin Castor oil Lecithin	Solvent diffusion method	Globet cells OVA-immunized and challenged mice models	Oral	Allergic asthma Anti-inflammatory	[72]
		Quercetin Propylene glycol Span-80 Tween-80	Emulsion preparation method	Hairless mice IL-1700 mice models L929 mice fibroblasts	Topical	Photo-chemoprotective agent	[106]

led to more stable and consistent formulations of quercetin which have an added advantage in willingness of liposomes to improve the longevity of an associated anticancer drug. There have been ongoing attempts to investigate and determine the importance of quercetin as a component in cancer therapy combinations.

*Niosomes containing quercetin formulation*<sup>[55]</sup>

Studies suggest that a novel formulation of cationic PEGylated niosome was developed which is an encapsulated form of quercetin, doxorubicin and siRNA and can be used for treatment of cancer by using the approach of combination therapy. The researchers developed

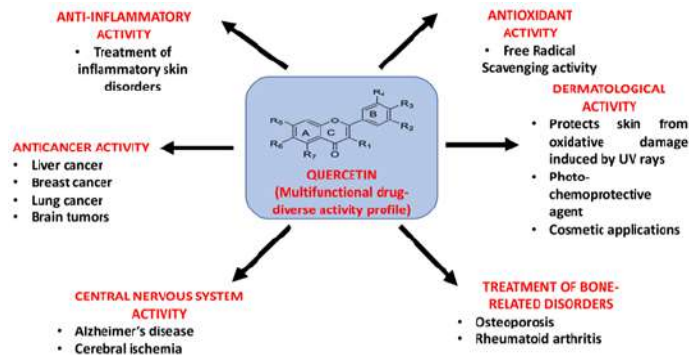


Figure 4: Multifunctional activities of Quercetin.

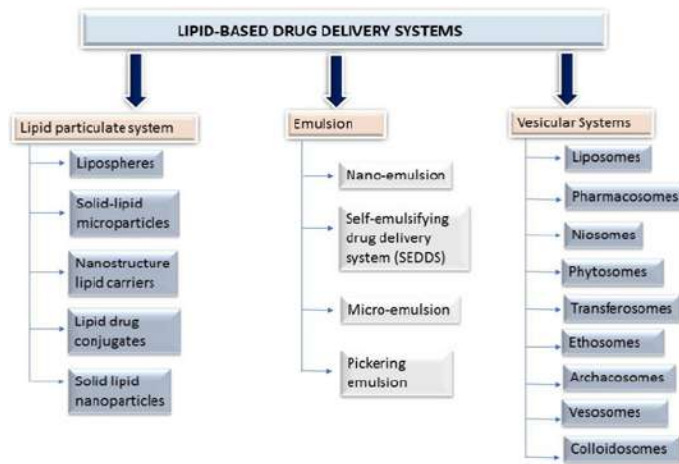


Figure 5: Classification of lipid-based drug delivery systems.

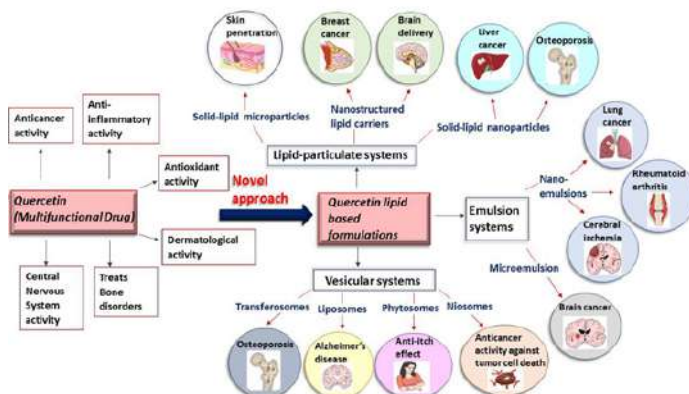


Figure 6: Schematic representation of multifunctional activities of quercetin and its transition to novel lipid-based formulations for targeted delivery.

vesicles of doxorubicin using quercetin (chemosensitizer) and Tween 60 (surfactant). Quercetin as herbal medicine and chemo-sensitizer possesses antioxidant and anti-proliferative activity against any cancer cells.<sup>[56]</sup> Quercetin is capable of averting the tumor proliferation by activating the intrinsic pathway of apoptosis.<sup>[57]</sup> Quercetin attenuates doxorubicin-induced cardiotoxicity in mice.<sup>[58]</sup> In this study, researchers sought to develop this novel formulation in order to overcome multidrug resistance and achieve synergistic anti-tumor effects. Doxorubicin and quercetin loaded nano-niosomes were prepared by thin-film technique and it was found that this formulation at a lower dose shows higher toxicity against cancer cells. Triple combination therapy (doxorubicin, quercetin and siRNA) can reduce several cancer cell pathways and increase prospects of survival in cancer patients. It was found that a low concentration of quercetin decreases the intracellular level of ROS, thus exhibiting the anti-neoplastic properties of the drug in cancer cells and quercetin can reduce the doxorubicin-induced oxidative stress results. Thus, it was concluded that co-delivery of Nio-siRNA-DOX with co-administration of a high dose of Nio-quercetin (triple combination therapy) decreased cell survival and shows superior therapeutic efficacy and anticancer activity.

Quercetin lipid-based formulations were explored for its anticancer activity and it was concluded that the above stated formulations were found to be effective in various types of cancers which includes increasing cellular penetration in hepatocellular carcinoma cells, treatment of breast cancer, lung cancer, brain tumors. These novel formulations showed superior therapeutic efficacy and anticancer activity in comparison to the conventional quercetin formulations.

*Quercetin lipid-based formulations with anti-inflammatory activity*

Quercetin is reported to be a long-lasting anti-inflammatory substance since it expresses high anti-inflammatory potentials in different cell types including human and animal models.<sup>[59-65]</sup> It is known to possess mast cell stabilizing and it also plays an important role in modulating biphasic and regulatory action on inflammation and immunity.<sup>[65,66]</sup> Apart from this quercetin also has an immunosuppressive effect on dendritic cells functions.<sup>[67]</sup>

**Emulsion systems containing quercetin formulation**

*Nanoemulsion containing quercetin formulation*<sup>[68]</sup>

Quercetin was encapsulated in a nanosized emulsion to develop a formulation that is able to demonstrate its anti-oedematous effect. Several studies reveal the multiple biological activities of quercetin in which one of the principle activities of quercetin is to block inflammatory mediators.<sup>[69]</sup> Quercetin reduces inflammation by scavenging free radicals that activate transcription factors for generation of pro-inflammatory cytokines.<sup>[70]</sup> Quercetin loaded into a lipid-based nanocarrier is a strategy to improve the water solubility, bioavailability and to protect the drug against degradation. Nanoemulsion delivery systems possess an advantage over other systems in terms of solubility and degradation. Quercetin-nanoemulsion depicts a protective role against neuro- and hepatotoxicity induced by oxaliplatin.<sup>[71]</sup> This study describes that quercetin loaded with nanoemulsion shows enhancement in anti-inflammatory effect as compared to native quercetin. The researchers reported that Quercetin-nanoemulsion exhibits pronounced anti-oedematous property when evaluated in the carrageenan hind paw edema model in rats and reduces the activation of NF-κB pathway. Carrageenan is the phlogistic agent of choice for testing anti-inflammatory drugs as it is known to be antigenic. Quercetin -nanoemulsion exhibits good oral anti-oedematous property as compared to native quercetin which was administered with the same treatment protocol. Thus, it was concluded

that quercetin loaded nanoemulsions exhibited good anti-inflammatory activity in animal models.

#### Microemulsion containing quercetin formulation<sup>[72]</sup>

Rogerio *et al.* developed a formulation in which quercetin is loaded in microemulsion to demonstrate its anti-inflammatory properties in a murine model of airways associated with allergic inflammation.<sup>[72]</sup> Rogerio and colleagues have performed *in-vitro* research showing that quercetin exhibits anti-inflammatory properties, which appears to be linked to its capacity to block certain inflammatory mediators.<sup>[73]</sup> Microemulsions represent pharmaceutical multifunctional formulations for various applications.<sup>[72]</sup> Microemulsions have a unique capacity for solubilizing non-polar compounds in polar media and vice-versa, which is why, they have a strong potential in pharmaceutical and

medicinal uses. Oil-in-water microemulsions enhance the bioavailability of a poorly absorbed drug.<sup>[72]</sup> Quercetin –microemulsion such as the steroidal anti-inflammatory drug dexamethasone, exhibits pronounced oral anti-inflammatory property when tested for allergic inflammation in OVA-induced airways. The *in-vivo* studies demonstrate that quercetin-microemulsion when given orally reaches enough plasma concentration and therefore they offer a consistent oral anti-inflammatory property.<sup>[72]</sup> This study indicates that when quercetin-microemulsion is given orally to mice it causes inhibition of P-selectin expression which further contributes to the anti-inflammatory action of quercetin-microemulsion.<sup>[72]</sup> The study was first conducted in an experimental model of airways allergic inflammation and was found to prevent the NF- $\kappa$ B activation in the lung of OVA-sensitized and challenged mice when this formulation

**Table 4a: Summary of formulations containing vesicular drug delivery systems.**

Sr no.	Type of lipid-based drug delivery system	Formulation composition	Method of Preparation	Experimental model	Route	Therapeutic activity	Ref
1.	Liposomes	Quercetin Cholesterol Copper	Encapsulation method	A549 lung adenocarcinoma cells and BxPC3 cells	Intravenous	Anticancer	[39]
		Quercetin Phospholipids	Colloidal dispersion method	3T3 mouse fibroblasts	Topical	Anti-inflammatory	[79]
		Quercetin Lecithin Cholesterol Tween 80	Thin-film hydration technique	No <i>in-vivo</i> studies conducted	-	Antioxidant	[90]
		Quercetin Phosphatidyl choline Cholesterol Carbopol n-hexane	Homogenization technique	Albino rats excisional wound healing models	Topical	Wound healing	[114]
		Quercetin Soybean Phosphatidyl choline Sodium cholate Cholesterol	Ethanol injection technique	Human skin keratinocyte (HaCaT)	Topical	Protects skin from UV-B radiation induced epidermal cell damage	[112]
		Quercetin dehydrate Egg Phosphatidyl choline Cholesterol	Encapsulation method	Adult male Wistar rat models	Nasal	Neuroprotective effect in Alzheimer's disease	[118]
		Quercetin dihydrate Piperine Egg L- $\alpha$ -phosphatidylcholine Cholesterol Span 60 PEG 400 Sodium alginate	Thin-film hydration, Ultrasonification and extrusion	MCF 10A cell lines	-	Anti-inflammatory	[74]

**Table 4b: Summary of formulations containing vesicular drug delivery systems**

Sr no.	Type of lipid-based drug delivery system	Formulation composition	Method of Preparation	Experimental model	Route	Therapeutic activity	Ref
2.	Niosomes	Quercetin Doxorubicin siRNA PEG	Encapsulation method	AGS, PC3, MCF7 and HFF cell lines	-	Anticancer activity against tumor cell death	[55]
		Quercetin Non-ionic surfactants	Homogenization method	No <i>in-vivo</i> studies conducted	Transdermal	Antioxidant Increases whitening capacity	[92]
3.	Phytosomes	Quercetin Phospholipids		Patch studies were done on a group of 25 healthy volunteers (Single-blind trial)	Topical	Soothing and anti-itch effect Non-sensitizing and non-photoirritant	[115]
4.	Transferosomes	Quercetin Tween 80 Phosphatidyl choline	Conventional thin-film hydration method	Glucocorticoid-induced (GIO) induced rat models	Topical	Treatment of secondary osteoporosis	[126]

was given to mouse orally.<sup>[72]</sup> Thereby, it was concluded that quercetin-microemulsion exhibits a pronounced anti-inflammatory effect.

### Vesicular system containing quercetin formulation

#### *Liposome containing quercetin formulation<sup>[74]</sup>*

In order to improve anti-inflammatory activity via the inhibition of COX-2 and NF- $\kappa$ B in TPA-induced cells in MCF-10A, quercetin was formulated in nanosized formulations.<sup>[74]</sup> Quercetin liposomes were prepared by using thin-film hydration, extrusion and ultrasonication method.<sup>[74,75]</sup> Quercetin may inhibit specific inflammatory mediators and signaling molecules like cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and transcriptional nuclear factor-B (NF- $\kappa$ B) at the molecular level; and in different cell lines at dose-dependent levels.<sup>[76,77]</sup> Inhibition of iNOS and COX2 through suppression of nuclear NF- $\kappa$ B activation is essential for anti-inflammatory expression.<sup>[74,78]</sup> The electrophoretic mobility shift for NF- $\kappa$ B DNA binding activity confirmed the anti-inflammatory activity of quercetin in the nuclei after it was delivered into the cells by this liposomal formulation. Thus, it was concluded that quercetin-nano liposomes exhibit great potential in anti-inflammatory activity.

#### *Phospholipid vesicles containing quercetin formulation<sup>[79]</sup>*

Studies state that formulations developed using phospholipid vesicles namely liposomes and PEVs (Penetration Enhancer-containing Vesicles) were loaded with quercetin to investigate their efficacy on (Tetradecanoyl phorbol-acetate) TPA-induced skin inflammation. The researchers evaluated the anti-inflammatory activity of drugs by using the most commonly used TPA-induced inflammation model in mice. *In-vivo* studies of TPA-treated mouse with two biomarkers including edema formation and myeloperoxidase (MPO) activities were evaluated for the anti-inflammatory effectiveness of quercetin nanovesicles. Empty and loaded topical phospholipid vesicles with quercetin were checked for anti-inflammatory efficacy, in comparison to drug dispersion. It was reported that quercetin decreased inflammation by reducing irritation, leukocyte accumulation and edema. *In-vivo* studies have shown that PEVs can locate the drug i.e. the dermis, inhibit leukocyte accumulation, oxidative stress and stimulate the repair of skin damage induced by TPA whereas *in vitro* studies show that quercetin-loaded PEVs could easily enter the fibroblast and diffuse in the cytoplasm, thus allowing quercetin

to exert its activity. Thereby, it was concluded that quercetin vesicular formulation may be of great potential in treating inflammatory skin disorders.

Quercetin-lipid based formulations were explored for its anti-inflammatory activity and it was concluded that these novel formulations exhibited better anti-inflammatory activity as compared to free quercetin. Besides this, it is also used for the treatment of various inflammatory skin disorders.

#### *Quercetin lipid-based formulations with antioxidant activity*

Quercetin has powerful antioxidant activity in *in-vitro* conditions and it is one of the most effective reactive species scavengers.<sup>[4,80]</sup> Quercetin prevents peroxidation which is caused by free radicals thereby exerting its antioxidant activity.<sup>[4,81]</sup> Furthermore, quercetin greatly improves the endogenous antioxidant potential of scavenging ABTS radicals by 6.2 times compared to the standard compound Trolox.<sup>[4,82]</sup>

### Emulsion systems containing quercetin formulations

#### *Nanoemulsion containing quercetin formulation<sup>[83]</sup>*

Zorzi *et al.* developed a formulation in which antioxidant activity of nanoemulsion containing extract of *Achyrocline satureioides* was compared to nanoemulsion containing quercetin. The studies carried out by Zorzi *et al.* and co-workers report that quercetin has higher antioxidant activity as compared to the other flavonoids present in *A. satureioides* extracts. Well-documented literature has shown that nano-technology based drug delivery systems have been considered to be promising drug delivery systems as compared to conventional dosage forms, due to many reasons like the reduction of side effects, increase in solubility, increase in drug stability and controlled release of an active compound.<sup>[84,85]</sup> Nanoemulsion was prepared using spontaneous emulsification by a solvent displacement method. The antioxidant activity of this formulation was evaluated by thiobarbituric acid-reactive species (TBA-RS) assay which comprises of AAPH (2,2-azobis(2-aminopropane) dihydrochloride) and egg yolk and it was reported that antioxidant effect of quercetin increased significantly.<sup>[86]</sup> It was also found that a minimal amount of quercetin in the skin was enough to produce an antioxidant effect when encapsulated in nanoemulsion form. Thus, it was concluded that the endogenous antioxidant function of the quercetin and extract could be improved with nanoemulsion.



### *Self-emulsifying drug delivery system containing quercetin formulation*<sup>[87]</sup>

In order to enhance its antioxidant potential as compared with the indigenous drug, the researchers developed a formulation which formulates quercetin into a novel self-emulsifying drug delivery system. A documented literature has shown that self-emulsifying drug delivery systems (SEDDS) have a remarkable capability to have higher drug loading capacity which is an essential requirement in antioxidant therapy. SEDDS in an appropriate composition, which includes a mixture of oil, surfactant, co-surfactant and drug substance offers unique advantages like prevention of drug precipitation on intestinal dilution, increase in solubilisation capacity, protecting the drug from chemical and enzymatic degradation and enhanced membrane permeability.<sup>[88]</sup> The *in vivo* antioxidant activity of quercetin-self emulsifying drug delivery system (QT-SEDDS) was checked against Cyclophosphamide-induced nephrotoxicity and Doxorubicin-induced cardiotoxicity and it was found that QT-SEDDS shows a remarkable increase in *in-vivo* antioxidant activity as compared to native quercetin. In comparison to quercetin, this novel formulation has excellent antioxidant property since it is capable of scavenging free radicals such as DPPH.<sup>[89]</sup> The DPPH scavenging assay demonstrates comparable antioxidant activity between QT-SEDDS and free quercetin. Thereby, it was concluded that quercetin loaded into novel self-emulsifying drug delivery system exhibits greater antioxidant activity as compared to free quercetin.

### *Vesicular system containing quercetin formulation*

#### *Liposome containing quercetin formulation*<sup>[90]</sup>

A novel formulation was developed by Chen *et al.* and group in which quercetin and EGCG (Epigallocatechin -3-gallate) were co-encapsulated in the form of liposomes to show optimum antioxidant activity. Liposomes are small artificial vesicles mainly composed of phospholipid and cholesterol.<sup>[91]</sup> They can encapsulate hydrophobic and hydrophilic molecules.<sup>[92]</sup> The design of a multi-component delivery system has attracted great attention and it is believed to have a promising approach in improving the performance of bioactive ingredients. The most promising liposomal system shows desirable efficacy and it was characterized by examining the slow leakage and high stability properties. The DPPH radical assay was used by authors to evaluate the free radical scavenging activities of the active ingredients.<sup>[93]</sup> The results obtained from the studies reported that synergistic antioxidant activity of the two polyphenols was observed due to co-encapsulation. Hence it can be concluded from the above results that co-encapsulation of EGCG and quercetin enhanced the antioxidant activity.

#### *Niosome containing quercetin formulation*<sup>[94]</sup>

Studies report that researchers developed a formulation in which quercetin is loaded in niosomes to improve its antioxidant property. Niosomes are non-ionic surfactants containing the novel vesicular system. Niosomes have several advantages in transdermal drug delivery systems such as better penetration, higher skin retention and sustained drug release and are more stable as compared to other drug delivery systems. Quercetin-loaded niosomes were prepared with Span 60/RH40. A mini column centrifugation technique has been used to determine the efficiency of drug entrapment in quercetin-loaded niosomes. The antioxidant activity of formulation was studied by measuring the bleaching rate of DPPH and it was reported that quercetin loaded niosomes have shown good antioxidant potential.

Quercetin-lipid based formulations were explored for its antioxidant activity and it was concluded that these novel formulations had the potential to increase the intrinsic antioxidant activity of native quercetin. Quercetin lipid-based formulation with dermatological activity

Quercetin is a flavonoid with promising antioxidant and anti-inflammatory activities and hence it is a candidates' first choice for skin supplementation. In cellular and animal models, quercetin showed interesting actions like cell protection against UV radiation to helping skin regeneration in wound healing. Quercetin has limited skin penetrability due to its poor solubility hence researchers have developed several formulations to enhance its dermal penetration.<sup>[95]</sup>

### *Lipid particulate systems containing quercetin formulation*

#### *Solid lipid microparticles containing quercetin formulation*<sup>[96]</sup>

Studies reported that a formulation was developed in which lipid microparticle was loaded with quercetin to check its photostability and chemical stability with an aim to increase its stability in topical formulations.<sup>[96]</sup> Literature studies report that topical application of quercetin inhibits oxidative skin damage and inflammatory processes induced by the solar UV radiation.<sup>[96-98]</sup> Lipid microparticles (LMs) are composed of lipid matrix and stabilized by surfactant molecules.<sup>[96,99]</sup> Their components are biodegradable and physiologically compatible and include excipients that are approved for preparation of cosmetics and topical formulations.<sup>[99,100]</sup> LMs possess good adhesive properties for skin surface and protect active ingredients from degradation.<sup>[96]</sup> Lipid microparticles are loaded with quercetin and were developed through a hot emulsion technique. The aging study was done to check the stability of microencapsulated quercetin and it was found that incorporation of quercetin in LMs enhances the chemical stability of flavonoid in a cream vehicle. Thereby, quercetin lipid microparticles was found to be an effectively targeted strategy to improve photostability and chemical stability in dermatological products.

#### *Nanostructured lipid carriers containing quercetin formulation*<sup>[101]</sup>

Pivetta *et al.* developed a formulation in which the nanostructured lipid carriers (NLC) were loaded with quercetin to enhance its permeation and to obtain a safe topical formulation. It was documented that quercetin can block ultraviolet (UV) radiations and induced inflammation via NF- $\kappa$ B inactivation on primary keratinocytes and studies demonstrate that quercetin topical formulation prevents skin damage induced by UVB radiation.<sup>[97,102]</sup> A promising vehicle that promotes permeation and provides space for retaining the drug better than solid-lipid nanoparticles (SLNs) was found to be the nanostructured lipid carrier (NLC).<sup>[33,42]</sup> NLC is able to use medications topically since they are very well absorbed on the skin.<sup>[42,103]</sup> NLC was prepared by the sonication and emulsion method.<sup>[104]</sup> The skin permeation study was done by the researchers on pig ear skin and it was found that drug penetration into the skin enhances when quercetin is encapsulated in NLC. The *in-vitro* phototoxicity studies show that quercetin- nanostructured lipid carriers may be regarded as a promising cosmetic ingredient. Quercetin encapsulation was found to increase the penetration of quercetin into the dermis and epidermis without reaching the receptor fluid. Thus, it was concluded that quercetin loaded in nanostructured lipid carriers is a promising approach for obtaining a safe topical formulation.

#### *Solid lipid nanoparticles containing quercetin formulation*<sup>[105]</sup>

Researchers developed a formulation in which quercetin -solid lipid nanoparticles (QSLN) were prepared to enhance skin permeation and to protect the skin from ultraviolet rays. Solid lipid nanoparticles can effectively encapsulate drug molecules, increase their stability and control the drug release rate. QSLN was prepared with a certain amount of palmitic acid and by using different ratios of surfactant (tween 80). Different QSLN formulations were prepared by homogenization and ultra-sonification method. *In vitro* skin permeation study was performed by researchers to investigate the effect of QSLN and it was found that this

optimal formulation has 5.1 and 2.4 times higher quercetin permeation rate through the skin as compared to the other formulations. QSLN may therefore be beneficial for transdermal delivery because it protects the skin against ultraviolet-induced oxidative stress.

## Emulsion systems containing quercetin formulation

### *Microemulsion containing quercetin formulation*<sup>[106]</sup>

Vicentini *et al.* and co-workers developed a formulation to evaluate the *in vivo* photoprotective effect of w/o microemulsion containing quercetin against dermal damage induced by UV-B irradiation. Quercetin is known to modulate NF- $\kappa$ B activation triggered by various inducers in different cell types.<sup>[73,107,108]</sup> It was reported that the incorporation of quercetin in w/o microemulsion optimizes the effect of the formulation.<sup>[35]</sup> *In vivo* studies show that microemulsion-quercetin (MEQ) topical treatment probably inhibits the activity of UV-B exposed skin matrix metalloproteinases (MMPs) via MMP inhibition. Studies were conducted by researchers on hairless mice with MEQ and it was reported that topical treatment of the formulation reduces glutathione (GSH) levels, which demonstrates that the formulation significantly prevented UV-B irradiation-induced GSH depletion.<sup>[35]</sup> The study indicates that MEQ formulation has been able to mitigate the impact of histological skin alterations arising from UV radiation, in particular harming the connective tissue. Thereby, it was concluded that w/o microemulsion incorporating quercetin could act as a photo-chemoprotective agent on human skin.

### *Nanoemulsion containing quercetin formulation*<sup>[109]</sup>

Literature studies report that a formulation of quercetin loaded cationic nanoemulsion was developed by using the sub-Phase Inversion Temperature (PIT) method. Nanoemulsion has several benefits over other conventional methods such as high optical clarity, increased bioavailability and good sedimentation stability.<sup>[109,110]</sup> Nanoemulsion can be used as an approach for the incorporation of cosmetically active substances.<sup>[109]</sup> The PIT method offers many advantages over other methods because the scale up is easy and the typical costs are compatible with industry requirements.<sup>[111]</sup> The best formulation was achieved using surfactant mixture HLB equivalent to 12.5.<sup>[109]</sup> The bioactive nanodroplets show adherence to the hydrophobic substrate, which shows an interesting application as a hair conditioner.<sup>[109]</sup> Thus, it was concluded that nanoemulsion loaded quercetin formulation exhibits excellent characteristics for its potential application in cosmetics.

## Vesicular system containing quercetin formulation

### *Liposomes containing quercetin formulation having cosmetic applications*<sup>[112]</sup>

Researchers report that quercetin was loaded in deformable liposomes form to check their efficacy against UV-B rays induced skin damages in *in-vitro* and *in-vivo* conditions. The documented literature studies show that quercetin provides cellular protection against UV radiation and for this same reason deformable liposome formulation of quercetin was formulated to improve its' anti-UVB effect. Deformable liposomes can penetrate the skin *in-vivo*, more efficiently than conventional liposomes by transferring therapeutic amounts of drugs.<sup>[113]</sup> Quercetin was incorporated into deformable liposomes by the ethanol injection technique. A series of 7 formulations including liposomes quercetin using different amounts of surfactants were prepared and it was found that the composition of soyabean phosphatidylcholine (PC), cholesterol (Chol) and Tween 80 show higher encapsulation efficiency as compared to other formulations. *In vitro* and *in vivo* studies indicate that quercetin-deformable liposomes have significant advantage over quercetin suspension in protecting the skin against UVB radiation damage. Histopathological studies also report the same. Thereby it was concluded

that quercetin loaded deformable liposomes have a great potential to enhance the anti-UVB effects of quercetin in both *in vivo* and *in vitro* conditions.

### *Liposomes containing quercetin formulation having medicinal applications*<sup>[114]</sup>

Jangde *et al.* and group developed a formulation in which quercetin is loaded in liposomes to study the wound healing activity in albino rats.<sup>[114]</sup> A two-stage delivery mechanism consisting of a quercetin-liposome composed of biocompatible membranes containing porous Carbopol hydrogel was developed to improve the bioavailability of quercetin.<sup>[114]</sup> The effect of interactions between two delivery systems was studied by using Franz diffusion cell. Quercetin-liposomes-hydrogel film novel formulation was developed to check the wound healing activity in albino rats. *In vivo* hydrogel performance was histologically assessed by using excision wound models.<sup>[114]</sup> *In-vitro* drug release studies report that drug-loaded liposomes show high burst release as compared to hydrogel containing liposomes which report delayed burst release. Thereby it was concluded by the results of *in vivo* and *in vitro* studies that quercetin-liposome-hydrogel film (QLH) report good activity for the treatment of connective tissue disorders and wound healing.<sup>[114]</sup>

### *Phytosomes containing quercetin formulation*<sup>[115]</sup>

Togni *et al.* evaluated photo irritant and sensitizing effect of quercetin and 2% phospholipid formulation on healthy volunteers. The phototoxicity assay was done and the skin area was carefully examined and there were no skin reactions observed on UV exposure. Similarly, the formulation was examined on healthy volunteers and the results show no allergic reactions on healthy volunteers. It was found that 2% quercetin-phospholipid formulation lacks photo irritancy and no adverse effects were reported. Thus, it was concluded that quercetin -2% phospholipid found to be neither sensitizing nor photo irritant and therefore it is considered as a safe topical formulation.

Quercetin lipid-based formulations were explored for its skin-related or dermatological activity and it was concluded that the above stated formulations were found to enhance the photostability and chemical stability in various dermatological products, protects the skin from oxidative stress induced by ultraviolet rays,<sup>[105]</sup> acts as a photo-chemoprotective agent on human skin, has potential applications in cosmetics and also used in wound healing.

## Quercetin lipid-based formulations with CNS activity

Quercetin is a ubiquitous flavonoid; common in plants and it is known as a cognitive enhancer in traditional and oriental medicine. Researchers have shown the protective effects of quercetin in *in-vitro* and *in-vivo* studies for neurodegenerative and cerebrovascular diseases. Several studies report that quercetin destabilizes and increases the clearance of abnormal proteins such as hyperphosphorylated tau and beta-amyloid peptides, which are key pathological marks of Alzheimer's. The ability of quercetin to reverse cognitive impairment and to improve its memory during aging were also well reported.<sup>[7]</sup>

## Lipid particulate system containing quercetin formulation

### *Nanostructured lipid carriers (NLCs) containing quercetin formulation*<sup>[116]</sup>

Researchers developed a formulation in which quercetin was loaded in nanostructured lipid carriers (NLCs) employing biocompatible components like tocopherol acetate and phospholipids for enhanced brain delivery. Nanocarriers possess properties to enhance permeation, bioavailability, efficacy and, reduce the side effects. The pharmacokinetic studies report that NLCs have enhanced the relative bioavailability,

retarded drug clearance and the biological residence time is 2.5 times higher than other delivery systems. This study shows that when quercetin is loaded in NLCs it exhibits substantial neuroprotective potential and easily passes through the BBB. The *in vitro* and *in vivo* studies show that nano lipid carriers (NLCs) loaded with quercetin show better brain delivery of neuroprotective agents for various neurological disorders and therefore it was concluded that NLCs can offer a better platform for brain delivery of quercetin.

### Emulsion system containing quercetin formulation

#### *Nanoemulsion system containing quercetin formulation*<sup>[117]</sup>

Studies have proven that formulations in which quercetin is loaded in nanoemulsion form and administered via a non-invasive nasal route is useful for cerebral ischemia treatment. The process of ionic gelation was used to manufacture quercetin mucoadhesive nanoemulsion (QMNE). Based on different Tween 20: PEG 400 and labrasol ratios; over 71 nanoemulsions were prepared by researchers. QMNE may circumvent BBB quickly and reach the brain, minimizing unnecessary side effects and thus seems as a promising cerebral ischemic management approach. QMNE was evaluated in middle cerebral artery occlusion (MCAO)-induced cerebral ischemia rat's model for grip strength, histopathological examination and locomotor activity studies were carried out by researchers and, significant results were observed. Thus, it was concluded that QMNE is a novel, non-invasive, effective and, safe brain targeted delivery system for the treatment of cerebral ischemia.

### Vesicular system containing quercetin formulation

#### *Liposomes containing quercetin formulation*<sup>[118]</sup>

Researchers developed a quercetin-liposome based formulation in the form of nasal delivery and evaluated its effect by studying neurodegeneration in animal models for Alzheimer's disease. Liposomes have long been utilized as a method of drug distribution in the brain since particles can entrap the compounds thereby inhibiting rapid elimination or degradation as well as promoting penetration through the BBB.<sup>[119]</sup> Compared to the oral route, the nasal route offers greater bioavailability due to shorter distance to the cerebral target and easier brain penetration.<sup>[120]</sup> It is shown that quercetin encapsulated liposomes nasally administered is a novel strategic approach to protect hippocampal against neurodegeneration and provides beneficial effects in very low doses. Quercetin liposomes also penetrate easily into the cerebrospinal fluid. Thus, it was concluded that the nasal administration of quercetin-liposome may be a novel therapeutic strategy against Alzheimer's disease. Quercetin-lipid based formulations which cross the BBB were explored and it was concluded that these formulations has better brain delivery as compared to conventional quercetin formulations. Besides this, it improves cognition in neurodegenerative disease like Alzheimer's as well as it is also used in the treatment of cerebral ischemia.

### Quercetin lipid-based formulations to treat bone-related disorders

Quercetin is an important common element in fruits and vegetables and it is shown that bone formation in bone cells is increased and bone defects healing is improved.<sup>[121]</sup> It is possible that quercetin also stimulates osteoblasts and increases bone formation locally.<sup>[122]</sup> Quercetin lipid-based formulations can be considered as a safe and effective agent for stimulation of bone structure activation and reconstruction of bone defects.<sup>[121]</sup>

### Lipid particulate systems containing quercetin formulations

#### *Solid-lipid nanoparticles containing quercetin formulation*

Studies reported that a formulation in which quercetin is loaded in solid lipid nanoparticles (SLNs) form was evaluated for its effect on bone health in comparison to free quercetin which was further studied for osteoprotective activity in ovariectomized (OVx) rats. Solid lipid nanoparticles (a colloidal submicron particulate delivery system) have gained increasing attention for the oral delivery system as compared to conventional emulsions.<sup>[123]</sup> The advantage of this system includes high bioavailability, high compatibility and, controlled release.<sup>[123]</sup> Researchers used the emulsion solvent evaporation process combined with the cold homogenisation system to prepare quercetin solid lipid nanoparticles. Quercetin recently has shown an ability to reduce bone loss in ovariectomized (OVx) mice.<sup>[124]</sup> The biomechanical strength studies report that QSLNs prevent loss of bone biomechanical strength of femur and L-5 vertebrae and maintain bone quality under estrogen deficiency.<sup>[117]</sup> The results also show that QSLNs was found more potent than quercetin in inhibiting osteoclast genesis from bone marrow cells. *In vitro* release studies show better release profile of QSLNs than quercetin. *In vivo* study reported positive results in the estrogen deficiency-induced bone loss model of osteoporosis. Thereby, it was concluded that QSLNs based system was found to recover the bone loss in comparison to the free quercetin treatment group and this system inhibits bone loss without any hyperplastic impact on the uteri of OVx rats.<sup>[117]</sup>

### Emulsion systems containing quercetin formulations

#### *Nanoemulsion containing quercetin formulation*<sup>[125]</sup>

The researchers have worked out a formula for effective rheumatoid arthritis management that evaluates quercetin in a nanoemulsion based gel on CFA-induced Wistar rat arthritis model.<sup>[125]</sup> Literature studies report that nanoemulsions have high drug loading capacity, protect active ingredients of the drug, controlled or sustained release of drugs and, excellent drug permeation.<sup>[125]</sup> Quercetin-Nanoemulsion was developed using the spontaneous emulsification technique using the Box- Behnken experimental design. *In vitro* studies demonstrate that quercetin-nanoemulsion not only improved the solubility of quercetin but also the diffusion rate due to its lipoidal nature. The cytotoxicity study results show that quercetin-nanoemulsion has no toxic effect on synoviocytes and has a strong inhibitory effect on lipopolysaccharide (LPS). Thereby it was established that the effective treatment of rheumatoid arthritis by a topical route is a promising approach.

### Vesicular systems containing quercetin formulation

#### *Transferosomes containing quercetin formulation*<sup>[126]</sup>

Pandit *et al.* and group developed a formulation in which quercetin was loaded in transferosomes to treat osteoporosis and further loaded in chitosan film. Transferosomes are specially designed vesicular particles consisting of an inner aqueous compartment enclosed by lipid vesicles. The conventional thin-film hydration method used a rotary evaporator to prepare the transferosomes. Researchers performed *ex-vivo* permeation studies on Wistar rat skin and the results demonstrate that transferosomes enhanced the permeation of quercetin as compared to free quercetin. Quercetin loaded transferosomes show decline in the osteoclast genesis and osteoblast apoptosis, which further results in an increase in femur thickness, length, density, weight and, mineralization of bones. Hence the above-mentioned reasons conclude that quercetin-

loaded transferosomes were found to be a good alternative in oral administration of quercetin to treat osteoporosis.

Quercetin-lipid based formulations were found to treat various bone-related disorders and it was concluded that these novel formulations were effective in the treatment of rheumatoid arthritis as well as in osteoporosis.

## CONCLUSION

Majority of natural plants including citrus fruits, leafy vegetables, berries contain the multifunctional flavonoid quercetin and possesses various activities like anticancer, anti-inflammatory, antioxidant, dermatological, ability to cross the BBB (CNS activity) and treats bone related disorders. From the studies described herein, the potential of quercetin is evident and therefore quercetin is considered as a promising molecule in combating various disorders.

Quercetin has been repurposed by several researchers and made into novel lipid-based formulation since it possesses high bioactivity, low cost, easy scale-up and better therapeutic profile. Approaches such as microparticles, nanostructured lipid carriers, nanoparticles, nanoemulsions, microemulsions, liposomes, phytosomes, niosomes and transferosomes, promise significant success which help to overcome the oral-bioavailability related issues of quercetin. This review mainly focuses on applications of quercetin containing lipid novel formulations in targeting its destinations and have highlighted its effective treatment potential mainly in skin-related disorders, treating various cancers including breast, brain, liver and lung, bone-related disorders like rheumatoid arthritis and osteoporosis and neurodegenerative diseases like Alzheimer's.

All these possible targets and applications of quercetin require a successful targeted delivery to various organs which could be achieved using these novel formulations. In this review we have also compiled variation of formulations in terms of excipients used, method and their therapeutic activity profile. Multiple insights have been drawn from these studies that give a focussed direction and the need to develop research towards the successful positioning of quercetin lipid-based formulations as biosafe and to achieve efficient applications.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**ABTS:** 2,2-azinobis(3-ethylbenzothiazoline-6-sulfonic acid); **BBB:** blood brain barrier; **COX-2:** cyclooxygenase-2; **CFA:** complete Freund's adjuvant; **chol:** cholesterol; **CNS:** Central nervous system; **DPPH:** 2,2-diphenyl-1-picrylhydrazyl; **EGCG:** Epigallocatechin-3-gallate; **GSH:** Glutathione; **HepG2 cells:** liver hepatocellular carcinoma; **HLB:** Hydrophilic-lipophilic balance; **iNOS:** inducible nitric oxide synthase; **LMs:** lipid microparticles; **LPS:** lipopolysaccharide; **MCAO:** middle cerebral artery occlusion; **MCF-7:** Michigan Cancer Foundation-7; **MEQ:** Microemulsion-quercetin; **MMPs:** matrix metalloproteinases; **MPO:** Myeloperoxidase; **MTT:** 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; **NF-KB:** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **NLC:** Nanostructured lipid carriers; **OVx:** Ovariectomized; **PC:** phosphatidylcholine; **PEVs:** Penetration enhancer containing vesicles; **PIT:** Phase inversion Temperature; **QLH:** Quercetin-liposome-hydrogel film; **QMNE:** Quercetin mucoadhesive nanoemulsion; **Q-NLC:** Quercetin-nanostructured lipid carriers; **Quer:** Quercetin; **ROS:** Reactive oxygen species; **SEDDS:** Self-emulsifying drug delivery system; **SLN:** Solid lipid Nanoparticles; **TBA-RS:** Thiobarbituric acid -reactive species; **TPA:** Tetradecanoyl phorbol acetate.

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