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REVIEW ARTICLE

Lipid nanoparticles: An advanced delivery system for quercetin

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ABSTRACT

Quercetin is a flavonoid with strong antioxidant activity considered as a potential drug candidate for number of chronic diseases; crude quercetin suffers from poor water solubility and consequently topical inactivity. Therefore, quercetin formulation within a suitable system that overcomes its solubility limitation is a matter of investigation. Many approaches were tested to improve quercetin delivery to skin. One effective approach is lipid nanocapsules. These nanoformulations are ideal in terms of average particle size and homogeneity (PDI). Hence, lipid nanoparticles are an attractive candidate for the encapsulation of quercetin for potent and effective drug delivery.

KEY WORDS: Antioxidant, Liposomes, Nanotechnology, Quercetin, Solid lipid nanoparticles

INTRODUCTION

Flavonoids are one of the most prevalent groups of substances in nature, and studies have linked their anti-oxidant and anti-carcinogenic properties to a number of favorable biological benefits. Although their potential for the prevention or treatment of several chronic illnesses has been investigated, a significant limitation still exists due to the limited bioavailability of these compounds and, in certain cases, their instability toward pH, temperature, and light. To get beyond these restrictions, nanotechnology has become a viable solution.

Quercetin is a polyphenolic compound present in onions, apples, red wine, and green tea as shown Table 1. Besides its anticancer, anti-inflammatory activities and both pro-oxidant and antioxidant activities depending on the redox of cells state and concentration of flavonoids other significant properties are shown such as antioxidant, neuroprotective, antidiabetic, anti-allergic, and antimicrobial activity, as shown in Figure 1. Quercetin inhibits asthma if inhaled; it is also widely used to prevent and treat SARS-CoV-2 and as an antiviral, quercetin prevents the replication of rhinoviruses both *in vitro* and *in vivo*. Any composition that might help an organism absorb quercetin more effectively may be significant in this situation. Furthermore, because quercetin rapidly degrades in alkaline settings, it is impractical to increase its content in processed food items because doing so will shorten their shelf lives.

Finding ways to transmit quercetin more effectively to the areas where it could be useful is required in this situation. Since nanocarriers may be loaded with quercetin, they can extend their duration in circulation, pass through biological barriers, and evade the immune system and renal clearance, boosting the bioavailability of this chemical. Nanotechnology may be an ideal technique for achieving this aim. Nanoparticles are distinct carriers for brain distribution, because they may be functionalized with certain ligands to target particular cells or respond to stimuli in the targeted site.

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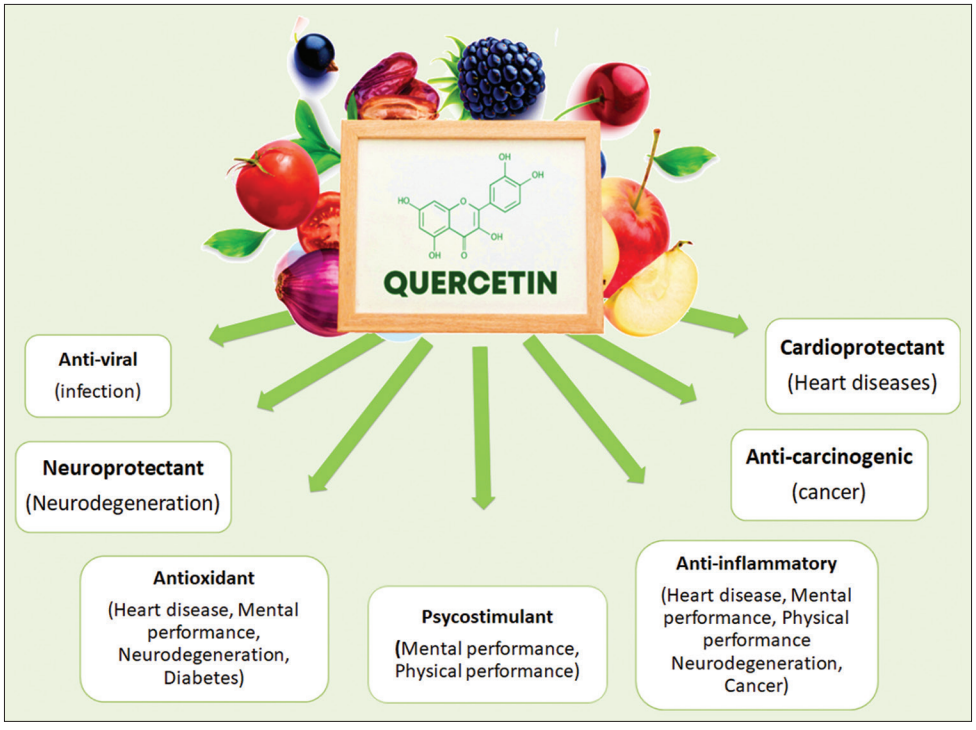

Figure 1: Pharmacological activities of quercetin.

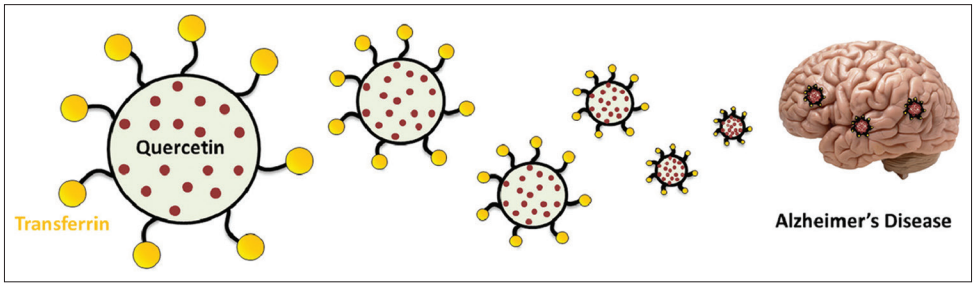

Figure 2: Transferrin functionalizes liposomes for brain targeting.

In this case, it is necessary to find methods to get quercetin more efficiently to the regions where it may be helpful. The bioavailability of this substance can be increased by loading nanocarriers with quercetin, which can extend their time in circulation, cross biological barriers, dodge the immune system, and avoid renal clearance. The use of nanotechnology could be the best method to accomplish this goal. Because they may be functionalized with specific ligands to target specific cells or respond to stimuli in the target site, nanoparticles are unique carriers for brain distribution.

Table 1: Quercetin content in selected foods

Source	Content of Quercetin (mg/100 g)
Apples	4.45
Broccolis	3.24
Onions	13.29
Spinaches	4.29
Black tea leaves	205.62
Green tea leaves	255.55
Red wines	0.84

LIPOSOMES

Liposomes are spherical vesicles which are composed of a double layer of phospholipids that are same to cell membrane in the body; they can be made of natural non-toxic phospholipids and cholesterol in the form of one or multiple concentric bilayers capable to encapsulate hydrophobic and hydrophilic drugs. Size of liposomes depends on the preparation method and their composition with diameters ranging from 50 nm to more than around 1 lm. They are the most commonly used systems for drug delivery as both hydrophobic and hydrophilic drugs can be encapsulated in the lipid membrane as well as internal core. Traditional liposomes are not preferred to be used in drug delivery due to their week resistance to enzymatic degradation, gastric acidity, and poor stability during storage, easy phospholipids oxidation, short duration of release, and minimal encapsulation efficiency. These

limitations lead to quick leakage of loaded drugs and can be overcome by surface modifying with polymeric coating. Several polymers can be utilized for liposomes coating such as pectins, chitosan, hydroxypropylmethyl cellulose, carbopol, and hydroxyethyl cellulose. Several studies used methacrylic acid and Eudragit S100 (1:1) which is a polyanionic copolymer of methyl methacrylate that does not dissolve at gastric pH and soluble above pH 7 for the coating of quercetin loaded cationic liposomes, thus providing two advantages: Protecting the liposomes from acidic degradation, and allowing the release of the payload in the region of the intestinal tract with near-neutral pH, that is, the large colon or intestine, where proteolytic enzymes and bile salt are concentration is low they have achieved the formulation of quercetin in a pH-sensitive nanocarrier system by a simple, fast, and easily scalable sonication method, without the use of organic solvents. Therefore, the proposed formulation was capable to regulate oxidative and inflammatory conditions that can cause cell modifications and damage of DNA.[1] Application of liposomes in functional foods is limited due to the same mentioned limitations, a study by Huang *et al*., 2020, created liposome-containing chitosan hydrogel beads with quercetin and linseed oil added. A combination of liposomes and chitosan hydrochloride solution was injected into a sodium tripolyphosphate solution to create the hydrogel beads. The created spheres displayed a clear three-dimensional network structure, which demonstrated that the chitosan hydrogel beads had been successfully manufactured. The physical stability of the liposomes in the gastrointestinal system was enhanced, the release of functional quercetin in the liposomes was postponed, and finally, the oral bioavailability was raised thanks to the binding effectiveness of the chitosan hydrogel beads. In the meanwhile, the encapsulation of chitosan hydrogel beads increased the chemical stability of the bioactives by isolating the interface between oxygen in the air and quercetin in liposomes.[2]

Chitosan is biocompatible, non-toxic, and biodegradable natural polysaccharides that are regarded as safe by food and drug administration. It is very suitable to be applied in oral and nasal routs due to its mucoadhesivity properties, bacteriostaticity, and its ability to improve transport through biological membranes. Chitosan hydrogels have mostly been investigated for pharmaceutical drug delivery applications such as oral delivery of drugs, artificial cartilage engineering, wound-healing, as well as transdermal application. The skin's barrier function prevents quercetin from entering the body to utilize its anti-aging and antioxidant activities. Therefore, numbers of studies on transdermal liposome drug delivery systems have been performed to achieve efficient penetration through skin barrier. One of these studies was conducted by Seong *et al*., 2018, based on layer-by-layer technology to enhance liposome stability, involving coating of liposome surface with multiplied layers using chitosan and its derivatives based on the opposite charge attraction between polymer electrolytes. To explore the pH-sensitive drug release of the formulation under skin pH circumstances, N-succinyl-chitosan (NSC), a well-known pH-sensitive polymer electrolyte, was utilized as a coating over liposomes to increase the solubility of chitosan in water. Chitosan's amine group is converted into NSC by adding a succinyl group. By regulating the level of succinylation, NSC a substance that is biocompatible and safe for the human body – can be made available to a polymer that is sensitive to pH. Skin penetration and drug release were comparatively greater in the normal skin pH when multilayered quercetin loaded liposomes were created, and findings showed an increase in stability against surfactants compared to liposomes without coating.[3] A similar study conducted by Jeon *et al*., 2015, to investigate chitosan-hyaluronate complex using electro static attractions based on layer-by-layer method. They improved the liposome stability by fabrication of multilayered liposome using layer by layer deposition of poly electrolytes. They also looked at the possibilities and functions of alternately depositing chitosan and hyaluronate on liposomes as drug delivery vehicles for transdermal use. The lipid membranes of the liposomes had quercetin put on them. According to the findings, appropriately coated multilayered liposomes with polyelectrolytes of hyaluronate and chitosan through electrostatic contact have better stability and may serve as a viable drug delivery method for the transdermal distribution of the lipophilic antioxidant quercetin.[4]

Since quercetin has a well-proved role in reducing different human tumors, numbers of studies are conducted every year to optimize its anticancer activity and disintegrate the toxicity of traditional chemotherapy. Nanotechnology has recently sparked interest in possible applications for the treatment of cancer. Liposome drug-delivery systems are among the most often employed nanocarriers for pancreatic cancer medication administration since they are the most developed and have received regulatory clearance for a number of liposomal formulations. Traditional chemotherapeutic medications can be liposomally encapsulated to provide passive tumor targeting with fewer adverse effects. Passive targeting has given way to active targeting as a result of recent advancements.[5] Riaz *et al*., in 2019, formulated various types of quercetin loaded liposomes with different peptide densities, that is, 0.5%, 1.0%, and 2.0% and non-targeted liposomes with the aim to target lung cancer sites by quercetin-loaded liposomes to. In addition, they revealed that T7 targeted liposomes containing QR were used for the first time to treat lung cancer in BALB/c nude mice harboring orthotopic lung tumor implantation through pulmonary administration and bioluminescent imaging. The lipid bilayer of the liposomes contained quercetin. DSPE-PEG (2000)-MAL was initially conjugated to the distal end of T7 peptide to provide liposomes the targeting capability. T7 surface functionalized liposomes are a potential nanocarrier for lung cancer treatment through receptor-mediated targeting

at the tumor site, according to *in vivo* and *in vitro* data.[6] To fill the gap of quercetin low bioavailability, Patel *et al*., in 2020, developed a combination of quercetin and low concentration of mycophenolic acid (which is also reported as an anticancer agent to synergistic effects of quercetin for breast cancer treatment) encapsulated in liposome nanoparticles. Findings showed that mycophenolic acid has inhibited cytochrome P450 enzymes and, further, increased quercetin bioavailability hence improved its therapeutic efficacy. Results from *in vivo* and *in vitro* studies showed that combination treatment (MPALNP + QC-LNP) had greater anticancer effects than separate formulations or free medications.[7] In a related study, Jiang *et al*., in 2019, examined the combined anticancer effects of IGF-1R siRNA liposome-based codelivery and 7-O-geranylquercetin on human NSCLC NCI-H460 and A549 cells *in vitro* and *in vivo*. 7-O-geranylquercetin is an O-alkylated derivative of quercetin with stronger anti-tumor activity against various cancer cells. The study served as a guide for the beneficial interactions between chemotherapeutic drugs and siRNAs in the treatment of lung cancer.[8]

SOLID LIPOID NANOPARTICLES

As poorly soluble medications have been developed over time, appropriate nanocarriers based on polysaccharide complexes and hydrogels have been created to enable their administration in aqueous environments and *in situ* while preventing potential undesirable side effects. SLNs outperform hydrogel in terms of lipophilic drug delivery, biocompatibility, and toxicity.[9] In addition, SLNs have a good cost-effective ratio and are more physically stable than liposomes. SLNs are one of the most promising nanocarriers for both hydrophilic and lipophilic drugs due to their high encapsulation efficiency, low toxicity, and capacity to control the kinetics of drug release. They typically consist of an aqueous environment and a stabilizing environment that increases physical stability during storage and lowers the energy barrier between the lipidic core and aqueous environments.[10] Quercetin was encapsulated in lipid nanoparticles by Pinheiro *et al*. in 2020 to benefit from its neuroprotective qualities in Alzheimer's disease. To enable passage of the blood-brain barrier through the transferrin receptors overexpressed in brain endothelial cells, SLNs were functionalized with transferrin as shown Figure 2. Due to quercetin's significant neuroprotective effect, the study developed and optimized SLNs that were loaded with quercetin and functionalized with transferrin with the purpose of improving the bioavailability and site-specific transport of quercetin into the brain. Due to their greater ability for site-specific transport of quercetin into the brain, the created nanocarrier system functionalized with transferrin and loaded with quercetin appears to be promising for the treatment of neurological illnesses, specifically nanostructured lipid carriers (NLC) and Alzheimer's disease.[11]

The fundamental benefit of SLNs is their ability to maintain a solid form even at physiological body temperature for humans. They can improve the benefits of polymeric nanoparticles and liposomes while reducing the need for organic solvents during production. In addition, the bioactives trapped in the SLN can be regulated in their release. SLNs are also capable of overcoming the problems with P-glycoprotein-mediated efflux and low solubility, poor permeability, and oral delivery of quercetin. SLN may have many benefits, but if it is digested in the intestinal environment, it is ineffective. Hence, it makes sense to alter the surface of SLN to better shield the lipid core from the hostile environment of the gut. SLNs were coated with chitosan in several of the methods to promote regulated and sustained vesicle absorption through lung administration. Numerous investigations covered the fabrication of plain and SLNs with chitosan surface modifications for quercetin encapsulation. Caco-2 cells were used to examine the impact of surface coating on cellular absorption of quercetin. When compared to untreated SLNs, the surface-coated SLNs demonstrated significantly increased quercetin absorption into Caco-2 cells and were stable for up to 3 months of storage at temperatures up to 40°C.[12]

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NLCS

NLCs feature more lipid matrix flaws than SLNs, which can be exploited to encapsulate lipophilic medicines to boost their physical stability and drug loading capability. By a process termed as high-pressure homogenization, which is simple for large-scale synthesis and hence has economic potential, NLC is made utilizing generally regarded as safe lipids, such as triglycerides, monoglycerides, fatty acids, and wax. NLCs are a potentially effective medication delivery method for both lipophilic and hydrophilic drugs. Through two basic strategies – polymer-coated lipid nanoparticles and lipid nanoparticles-hydrogel – many natural polymers,

including polysaccharides and proteins – have been used to improve the performance of lipid nanoparticles. Polymer-coated NLC has received a lot of attention in recent years due to their potential to improve NLC's physical stability and gastrointestinal tract behavior. Based on the electrostatic interaction, polymers may be introduced to the solution before or after the synthesis of NLC to create polymer-coated NLC. This coating method may alter the features of NLC, including size and structure, because to the complicated interaction between NLC and the coating layer.

CONCLUSION

On the basis of its antioxidant, anti-cancer, and anti-inflammatory effects, quercetin is the topic of extensive research. Quercetin and other flavonoids have frequently demonstrated *in vitro* that they possess the structural capacity to function as potent antioxidants. Being a significant flavonoid intake component, quercetin may be essential in the battle against a number of chronic degenerative disorders. Liposomes are spherical carriers composed of a double layer of phospholipids that are same to cell membrane in the body. They may be produced from cholesterol and natural, harmless phospholipids in the form of one or more concentric bilayers that can encapsulate both hydrophobic and hydrophilic medications. Liposome sizes can range from around 50 nm to more than 1 lm17, depending on their composition and manner of manufacture. Since both hydrophilic and hydrophobic medicines may be encapsulated in the internal core and lipid membrane, they are the most widely utilized methods for drug delivery. SLNs are one of the most promising nanocarriers for both hydrophilic and lipophilic drugs due to their high encapsulation efficiency, low toxicity, and capacity to control the kinetics of drug release. When compared to SLNs, NLCs feature more lipid matrix flaws that can be exploited to encapsulate lipophilic medicines.

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