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APPROACHES AND ADVANCEMENTS IN THE IMPROVEMENT OF QUERCETIN BIOAVAILABILITY

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ABSTRACT

Quercetin is a plant derived aglycone form of flavonoid glycosides. It has nutritional value and well known for its diverse biological activities such as anticancer, antiulcer, antihypertensive, anti-allergy, anti-infective, immunomodulatory, anti-diabetic, anti-obesity, anti-hypercholesterolemic anti-atherosclerotic anti-inflammatory and vasodilator activities. Despite the quercetin has several health benefits, its crystallinity nature, poor solubility and extensive phase II and III metabolism exist as a major issue in its usage in clinical practice. Loading the quercetin in a suitable drug delivery system is a possible approach to overcome this issue. Several synthetic and technological approaches including different drug delivery systems have been developed in this regard. This review aimed to discuss the different approaches and advancements in the refinement of quercetin bioavailability.

Keywords: Quercetin, Bioavailability, Drug delivery systems

INTRODUCTION

Quercetin (3,3′,4′,5,7-pentahydroxyflavone), one of the significant bioflavonoids (Figure. 1) belongs to the group known as flavonols commonly found in fruits (predominantly citrus), green leafy vegetables, seeds, nuts, flowers, barks, dark cherries, berries such as blueberries and cranberries, apple, onion, green tea, red grapes, broccoli, olive oil etc., The term “Quercetin” comes from “Quercetum” a Latin word which means Oak Forest. It is a yellow coloured agent, soluble in alcohol and lipids, poorly soluble in hot water and insoluble in cold water.

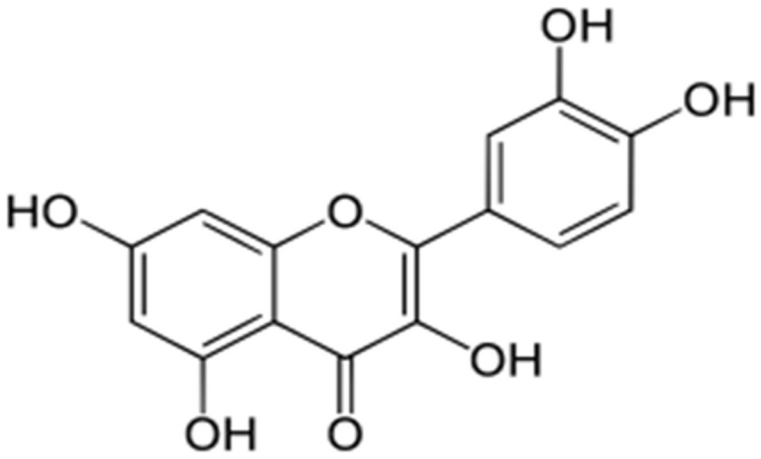

Figure. 1: Chemical structure of quercetin

Chemically, quercetin is a plant derived aglycone form of flavonoid glycosides. It has nutritional value and well known for its diverse biological activities such as anticancer, antiulcer, antihypertensive, anti-allergy, anti-infective, immunomodulatory, anti-diabetic, anti-obesity, anti-hypercholesterolemic anti-atherosclerotic anti-inflammatory and vasodilator activities. Quercetin afford protection from free radicals formed due to smoking. Cigarette tar, a source of free radicals has the ability to damage the erythrocyte membrane. It was found that the quercetin and its metabolites could defend the erythrocytes from membranous damage due to smoking [1-5].

Even though the quercetin has numerous health benefits, its bioavailability is relatively poor and highly variable. Primarily, the quercetin in foods is bonded to a sugar molecule which is known as glycoside. The isoquercetin (quercetin-3-glucoside) found in onion is formed by conjugation with glucose. In apple and tea, it forms rutin by attachment with rutinose. Variations in quercetin-conjugated glycosides influences its bioavailability, particularly, the size and polarities of these compounds may cause difficulty in crossing the gut membranes. Quercetin is a lipophilic molecule with low water solubility. Quercetin's poor solubility and its crystalline form at body temperature limits its bio-accessibility and its bioavailability. The quercetin bioavailability is related with its bio-accessibility and solubility in the vehicle used for its administration. In short, quercetin has several health benefits but unfortunately, its bioavailability is poor. Various factors such as Vitamin-C status, glucose moieties, food matrix, solubility and human factor affect the bioavailability of quercetin [6-10]. This review aimed to discuss the different approaches and advancements in the refinement of quercetin bioavailability.

PHARMACOKINETIC AND BIOAVAILABILITY LIMITATIONS OF QUERCETIN

Generally, poor absorption, lesser intrinsic activity, rapid metabolism, inactivity of metabolites and/or rapid elimination and clearance from the body are the crucial factor for the poor bioavailability of any one of the biological active substances. Despite the quercetin has a good efficacy, intrinsic activity and therapeutic potential, some pharmacokinetic limitations and poor bioavailability continue as a major issue of its use in clinical practice. Several studies has revealed issues in the quercetin's poor absorption and rapid metabolism [11, 12]. Crystallinity and poor solubility of quercetin in the range of 2.15-7.7g/ml at 25°C in the secretion of gut, luminal efflux caused

by epithelial cells of gut, extensive phase II and III metabolism are few crucial factors behind this limitation. Improving the solubility enhances the bioavailability by increasing the amount of drug for absorption and saturates metabolic enzymes of Phase-II and III effect results in improved net influx in circulation [13]. The solubility of poorly water-soluble drugs can be improved by minimising the crystallinity or incorporation in complexes using compounds such as cyclodextrines [12]. Loading the quercetin in suitable drug delivery system is a possible approach to overcome this issue. Several synthetic and technological approaches including different drug delivery systems have been developed in this regard [14, 15].

SOME STRATEGIES TO IMPROVE THE PHARMACOKINETICS OF QUERCETIN

Several methodologies such as complexation, solid dispersions, self-emulsifying drug delivery systems, liposomes, micelles, micro and nanoparticles, nanoemulsion, polymeric nanocapsules, microparticulates, nanosponge, phytosomes, phospholipids, proniosomes and niosomes etc., have been developed for improving the quercetin's pharmacokinetics [12, 13]. Nanoformulations for the improved delivery of quercetin, uses variety of nanocarriers (Figure 2) [16-18].

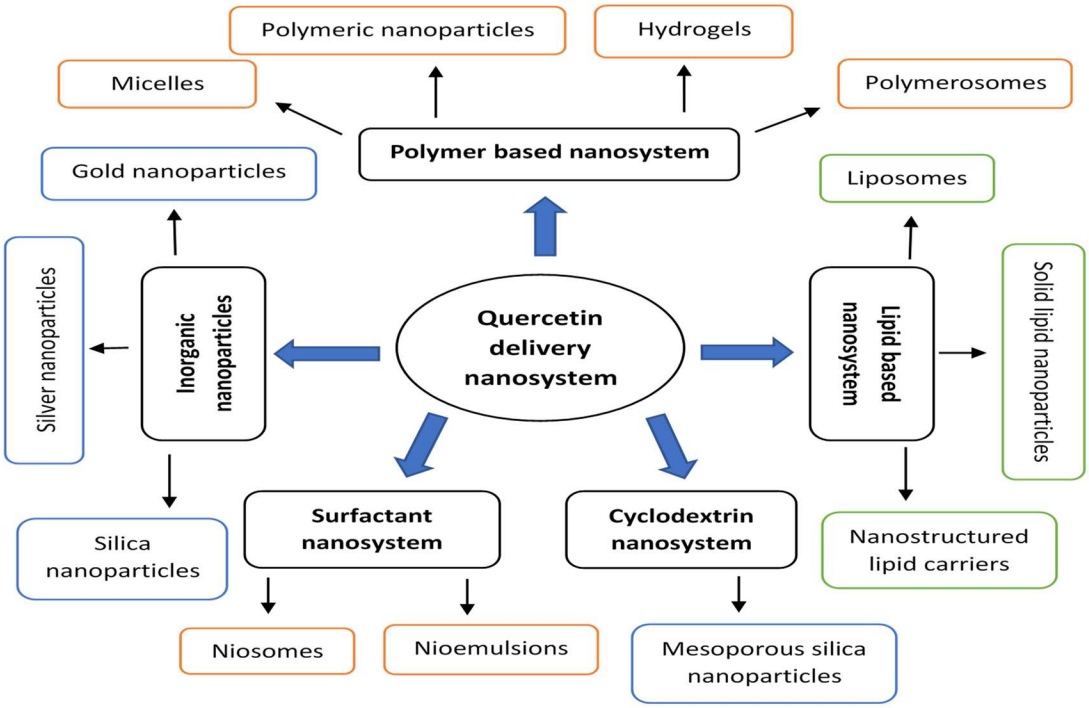

Figure. 2: Some nanocarriers used in the quercetin nanoformulations development

Nanosystems based on polymers

Polymers are one of the interesting tools for the pharmaceutical industry. Polymers are made up of high molecular weight monomers in a large chain structure. A large number of different configurations of polymer-based systems such as micelles, polymeric nanoparticles, hydrogels polymersomes, etc., have been extensively documented in the literature.

Polymeric micelles are colloidal nanoparticles (≤100nm) with a core-shell structure, composed of a hydrophobic core surrounded by a hydrophilic outer part. The shape of the micelles permits them to accommodate in the inner

core of diverse molecules. They can be employed as delivery platforms for the transport of active pharmaceutical ingredients and genetic material in hydrophobic nature, while the hydrophilic outer part contributes to the stabilization of the colloidal structure in a liquid medium.

Polymeric nanoparticles are conspicuous from other particles due to their size (ranging from 10nm to 10μm) and distinctive physicochemical properties. They can accommodate in the inner part or in the exterior surface of several bioactive compounds such as proteins, active pharmaceutical ingredients, genetic material etc. Polymeric nanoparticles achieve the sustained molecule release and also transfer them to the targeted site of action. The controlled release can be achieved by modifying the external stimuli such as pH, temperature, irradiation, etc.

Another one category of polymeric formulations known as hydrogels can be used as delivery systems in the case of quercetin. Based on their origin, the hydrogel can be grouped into natural, synthetic and hybrids. The cross-linking of polymers leads to 3D configuration which has capability to absorb high amounts of aqueous solutions into their polymeric network. These multifunctional systems are suitable platforms for the sustained release of the encapsulated bioactive molecules due to their high physicochemical stability, loading efficiency and absorbency, response to external stimuli, biocompatibility and biodegradability [18-23].

Polymersome, another one polymer based nanosystem has complex composition with a characteristic "pseudo-spherical" shell formed by the self-assembly behaviour of amphiphilic block co-polymers. The construction of polymersome is critically affected by a factor viz., the hydrophilic/hydrophobic ratio of a block co-polymer. The structure of polymersome permits them to accommodate the hydrophilic compounds into their aqueous interior as well as to interact with the lipophilic molecules on their exterior membranes [18, 20].

Lipid-based nanoparticles

Lipid-based nanoparticles received a great attention and become widely used in several routes of drug administration due to their cell membrane-like structure and the simplicity of surface modification. In particular, their applicability has been demonstrated in the delivery of low molecular weight active pharmaceutical ingredients as well as in the field of gene transfer. Liposomes and liposome-based nanoparticles, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLC) are few good examples for this Lipid-based nanosystem.

Liposomes and liposome based nanoparticles are vesicular systems mainly composed by phospholipids. The structural modification of lipid bilayer of these systems improve their physical properties and increase the release profile of the encapsulated active pharmaceutical ingredients. Modification of liposome surfaces using other biomaterials such as polysaccharides can develop different structural characteristics and biological behaviour including a variable release profile of the encapsulated active pharmaceutical ingredients. Already quercetin liposomes have been evaluated for their efficacy in solid tumours in murine models and their protective effect against radiation-induced acute pneumonitis and late fibrosis by controlling the oxidative damage [18, 24-26].

Solid lipid nanoparticles (SLNs) and Nanostructured lipid carriers (NLC) are another type of lipid-based nanosystems composed mainly by biocompatible and biodegradable of solid lipids. High-pressure homogenization is the most popular method for their fabrication due to its speed and reproducibility even several methods are available. SLN and NLC are used for the encapsulation of hydrophobic active pharmaceutical ingredients particularly for topical and oral administration [18, 27-29].

Surfactant-based nanoparticles

Niosomes and nanoemulsions are the good examples for surfactant-based nanoparticles. Among these, niosomes are microscopic vesicles composed of non-ionic surfactants of the alkyl or dialkyl polyglycerol and lipid compounds such as cholesterol or L-α-soya phosphatidyl-choline. Based on their size and the number of bilayers in their structure, niosomes are classified in to five types viz., multilamellar vesicles (MLV, 0.5-10μm diameter), large unilamellar vesicles (LUV, 100-3000nm diameter), small unilamellar vesicles (SUV, 10-100nm diameter), bola-niosomes, and proniosomes. There are three established preparation methods for niosomes, they are slurry, the slow spray coating and the coacervation phase separation method.

Nanoemulsions are colloidal systems consisting of two immiscible phases (dispersed and continuous) with nanosized droplets dispersed in the continuous phase. Mini emulsions, fine-dispersed emulsions, submicron emulsions are the other names of nanoemulsion. Nanoemulsion delivery systems have been developed for several routes of administration, either for topical or systemic administration [18, 30-33].

Cyclodextrin-based nanoparticles

Cyclodextrins are a group of cyclic oligosaccharides linked with α-1,4-glycosidic bonds, forming a structure of truncated cone with a hydrophobic inner cavity and hydrophilic outer surface. They can develop a stable inclusion complexes with many organic or inorganic lipophilic molecules. Also, they can enable an adequate interaction of outer hydroxyl groups with water molecules or hydrophilic moieties. Cyclodextrins are widely applied in the pharmaceutical technology for variety of purposes such as solubility and stability improvement, taste and odour masking and reducing the toxicity. Three natural cyclodextrins known as α, β, and γ cyclodextrins are mainly employed in pharmaceutical development while the hydroxypropylated and random methylated derivatives are the most long-established chemically modified cyclodextrins. In nanotechnology, the incorporation of cyclodextrins in the nanostructured particles has been applied in many categories such as the magnetic, polymeric, lipid and solid-lipid nanoparticles as well as in the newer types like mesoporous, gold, and silver ones [18, 34-36].

Inorganic nanoparticles

Inorganic nanoparticles are a broad category of highly stable organizations composed of magnetic or other inorganic material. They are non-toxic, biocompatible systems with magnetic properties that enable their use as theranostics, combining diagnosis and treatment. Gold and silver, the oxides of iron, cooper, and the dioxides of titanium and silicon are the main nanomaterials used for their fabrication. The quercetin formulation into inorganic nanoparticles is used either for imaging or for therapeutic purposes especially in the cases of cancers, neurological or metabolic diseases [18, 37-41]. However, every delivery system has its own merits and demerits and the particular choice should rely on the moiety's nature and its characteristic features (Table 1) [18].

Table 1: Advantages and disadvantages of various drug delivery nanoformulations

Parameters	Polymer based nanosystems	Lipid based nanosystems	Surfactant based	CDBN	Inorganic NP

							nanosystems			
	PM	**PN**	**HG**	**PS**	**LS**	**SLN-NLC**	**NS**	**NE**		
Advantages										
Biocompatibility	++	++	++	++	+++	+++	++	+++	+++	+
Biodegradability	+	++	+++	++	++	++	++	++	+++	+
High Loading efficiency	++	++	+++	++	++	+++	++	+++	++	+
Chemical versatility	+++	++	+	++	+	+	+	+	+	+
Physicochemical stability	+++	++	++	++	+	++	++	++	++	+++
Controlled release Properties	++	++	++	++	++	++	++	++	++	++
Administration by different routes	++	++	+	++	++	++	++	++	++	++
Stimuli responsiveness	+++	++	+++	++	+	+	+	+	+	+++
Improve of ADME(T)profile	+++	++	+	++	++	++	++	++	++	+
Targeting	++	++	+	+	+	+	+	+	+	+++
Imaging	+	+	+	+	+	+	+	+	+	+++
Theragnostic	+	+	+	+	+	+	+	+	+	+++
Precision medicine	+	+	+	+	+++	+	+	+	+	++
Disadvantages										
Nanotoxicity	++	++	+	++	++	++	++	+	+	+++
High cost	+	+	+	++	++	++	++	+	+	+++
Limitations in scale-up	+	+	+++	++	++	++	++	+	++	+++
Immunogenicity	++	++	+	++	+	+	+	+	+	+++
Lack in regulatory framework	++	++	+++	++	++	++	+++	+	+++	++

PM- Polymeric micelles; PN- Polymeric nanoparticles; HG- Hydrogels; PS- Polymerosomes; LS- Liposomes; SLN-NLC- Solid lipid nanoparticles-Nanostructured lipid carriers; NS- Niosomes; NE- Nanoemulsions; CDBN-

Cyclodextrin based nanoparticles; NP- Nanoparticles; ADME(T)- Absorption, Distribution, Metabolism, Excretion and Toxicity; +++- High; ++- Medium; +- Low

Manca ML, *et al.,* 2020 [15] formulated nanosuspension of quercetin to evaluate its cutaneous bioavailability. In this study two different concentrations viz., three and five percentage of quercetin nanosuspension was prepared by wet media milling method by using Tween 80 and poloxamer 188 as stabilizers. In this study, nanocrystals of quercetin showed a mean diameter in the range between 326 and 474nm and polydispersity index lower than 0.30. This size reduction showed improved solubility, dissolution rate of quercetin and its accumulation in different skin layers as well as bioavailability in the *in vitro* studies.

Solnier J, *et al.,* 2021 [42] conducted a non-blinded crossover bioavailability study in healthy adult volunteers to evaluate the solubility and GI absorption of free quercetin and novel quercetin lipomicel delivery system. This study found a significantly enhanced oral absorption of quercetin with lipomicel delivery system compared to free quercetin. Moreover, improvements in *in vitro* gastric stability and intestinal solubility were observed with lipomicel that leads to significantly higher blood concentration and enhanced duration of a stable concentration of quercetin in the body. Importantly, eight to nine fold increases in AUC and Cmax were attained with the lipomicel delivery system and tenfold higher quercetin plasma concentrations detected at 12h after administration compared to free quercetin.

Najafabadi RE, *et al.,* 2018 [43] formulated the quercetin conjugated with superparamagnetic iron oxide nanoparticles by means of nanoprecipitation method. The prepared nanoparticles were characterized by X-ray diffraction, scanning electron microscope and FTIR analyses and its bioavailability was checked in vivo on Wistar male rats. By HPLC method bio-distribution of quercetin was evaluated in plasma and brain tissue. This research revealed a higher concentration in the plasma and brain of the rats fed with quercetin- superparamagnetic iron oxide nanoparticles in comparison to free quercetin. This study confirmed that the superparamagnetic iron oxide nanoparticles as a targeted drug delivery system enhances the bioavailability of quercetin in the brain about ten folds higher than free quercetin and could be used for the treatment of neurodegenerative disorders.

Dian L, *et al.,* 2014 [44] encapsulated the quercetin in soluplus polymeric micelles by modified film dispersion method and evaluated the oral bioavailability of quercetin *in vitro* dialysis test which showed the quercetin-loaded polymeric micelles significant sustained release property and estimated that the formulation was stable for at least six months under accelerated conditions. Moreover, *in vivo* pharmacokinetic study in beagle dogs showed that absorption of quercetin after oral administration of quercetin-loaded polymeric micelles was improved significantly with a half-life 2.19-fold longer and a relative oral bioavailability of 286% as compared to free quercetin. Thus, the quercetin-loaded polymeric micelles provide a promising carrier candidate with efficient delivery of quercetin for therapeutic treatment in near future. This study explores an interesting alternative approach for design and fabrication of novel polymeric micelles as delivery systems for bioactive compounds.

Abdulhameed HM, *et al.,* 2022 [45] reported that the concurrent ketoconazole administration with quercetin significantly improves the mean plasma concentration in healthy volunteers group comparing with the group of volunteers received quercetin only. This study proved that the bioavailability of quercetin will be increased by its administration together with ketoconazole, due to enzyme inhibiting effect of ketoconazole which delay elimination and increase the AUC of quercetin.

Riva A, *et al.,* 2019 [46] formulated quercetin phytosome, a food grade lecithin based formulation and evaluated its solubility by *in vitro* incubation in simulated gastrointestinal fluids and oral absorption by randomized

crossover pharmacokinetic study in healthy volunteers in comparison with free quercetin. In this study, the quercetin phytosome formulation revealed a significant improvements in both *in vitro* solubility and oral absorption studies comparing with unformulated quercetin. These results suggest that quercetin phytosome allows the oral administration of quercetin in a safe and bioavailable manner, thus facilitating the effective utilization of this natural compound to treat various human diseases.

Li H, *et al.,* 2021 [47] prepared the quercetin loaded nanosuspension and evaluated its stability in artificial gastric and intestinal juice. The difference in oral bioavailability of conventional nanosuspension with metabolic inhibitors (piperine or sodium oleate) added nanosuspension was evaluated *in vivo* in Sprague-Dawley rats. The results of the study revealed that the metabolic inhibitors added nanosuspension is an effective solution to enhance the oral absorption of quercetin.

Joseph A, *et al.,* 2022 [48] formulated a natural self-emulsifying reversible hybrid hydrogel system of quercetin and conducted a randomized double blinded comparative crossover study with unformulated quercetin. This study found that the quercetin hydrogel system offer significant solubility, stability, and bioavailability of quercetin upon single-dose oral administration.

CONCLUSION

Quercetin has many health benefits but unfortunately, its bioavailability is poor. Many factors such as glucose moieties, solubility, human factor, Vitamin-C status and food matrix affect the bioavailability of quercetin. The development of drug delivery strategies is crucial for its use in a clinical practice. Several methodologies such as complexation, solid dispersions, self-emulsifying drug delivery systems, liposomes, micelles, micro and nanoparticles, nanoemulsion, polymeric nanocapsules, microparticulates, nanosponge, phytosomes, phospholipids, proniosomes and niosomes etc., have been developed for improving the quercetin's pharmacokinetics which are promising and offer a good opportunity to enhance the bioavailability and clinical applications of quercetin.

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AUTHORS CONTRIBUTION

All the authors have contributed equally

CONFLICTS OF INTERESTS

Declared none

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