QUERCETIN LOADED NANOFORMULATIONS
FOR THERAPEUTIC PURPOSES: A REVIEW[1]

NANOFORMULAÇÕES CARREADAS COM QUERCETINA
PARA FINS TERAPÊUTICOS: UMA REVISÃO

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ABSTRACT

Quercetin (Q) is a natural polyphenolic flavonoid compound present in a variety of food plants such as onions, tomatoes, apples, green vegetables, beans and other dietary sources. It is known that quercetin has numerous nutraceutical properties. However, its oral delivery continues to be a barrier due to its low bioavailability. Thus, the incorporation of quercetin in a drug delivery system has been considered a promising alternative for oral administration of this compound. This review includes articles from the National Library of Medicine (*MedLine*), *Scopus* and *Web of Science* databases, using descriptors and search strategy, "nanoformulation" OR "nanoparticles" AND "quercetin" AND "effects". Taken together, the results of these studies have provided an understanding of the biological action of quercetin and of its functional effects such as antioxidant, anti-cancer, and anti-toxic. The present review allows an analysis of the benefits of quercetin in health, and whether these could be further improved if quercetin was incorporated into a nanostructure, solving problems related to its bioavailability.

Keywords: antioxidant, flavonoid, nanoparticle, nanotechnology, nutraceutical.

RESUMO

Quercetina (Q) é um flavonóide naturalmente presente em uma variedade ampla de alimentos, como cebola, tomate, maçã, vegetais verdes, feijão e outras fontes dietéticas. Sabe-se que a quercetina possui numerosas propriedades nutracêuticas. No entanto, a sua utilização por via oral continua sendo uma barreira devido à sua baixa biodisponibilidade. Assim, a incorporação da quercetina em sistemas de liberação de fármacos, é considerada uma alternativa promissora para administração deste composto por via oral. Esta revisão inclui artigos dos bancos de dados da Biblioteca Nacional de Medicina (MedLine), Scopus e Web of Science, usando os seguintes descritores e estratégia de busca, "nanoformulações" ou "nanopartículas" e "quercetina" e "efeitos". Em conjunto, os resultados desses estudos proporcionaram uma compreensão da ação biológica da quercetina, dos seus efeitos funcionais, como antioxidantes, anti-câncer e antitóxicos. Esta revisão permite uma análise dos benefícios da quercetina na saúde e se estes podem ser potencializados se a quercetina for incorporada em nanoestruturas, no sentido de minimizar problemas relacionados à sua biodisponibilidade.

Palavras-chave*: antioxidante, flavonóide, nanopartícula, nanotecnologia, nutracêutico.*

INTRODUCTION

Nutraceuticals have recently been an issue of considerable interest because of their excellent functional properties in health promotion and disease prevention. Especially those lipophilic, whose health benefits have been associated with their antioxidant, anti-inflammatory, and anti-tumor properties. However, there are some limitations when using them in food and especially in the administration of these compounds orally, due to their low solubility in water, low oral absorption, and low bioavailability. These restrictions limit the application of these lipophilic substances in biological research studies, so that they need to be overcome (D'ANDREA, 2015; EZHILARASI et al., 2013).

Among the several known nutraceuticals, quercetin (Q), 2- (3,4-dihydroxyphenyl) -3,5,7-trihydroxy-4H-1-benzopyran-4-one (Figure 1A) flavonoid is outstanding. The quercetin represents about 95% of total flavonoids ingested in the human diet (MOMIC, 2007), and its main sources are onion (284-486 mg/kg), apple (21-72 mg/kg), and broccoli (30 mg/kg), mainly in the form of glycoside (Figure 1B).

Figure 1 - Chemical structure of quercetin (A) and quercetin 4'-bD-Glucoside (B) (Author source).
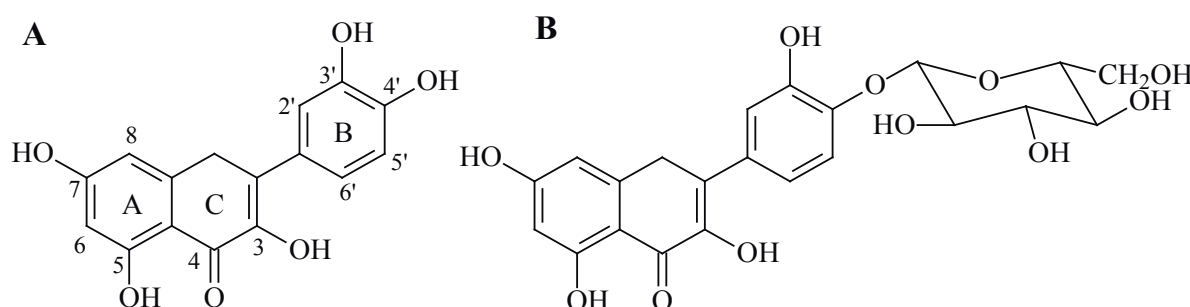
The chemical and biological properties of quercetin have aroused great interest among researchers, which makes it one of the most studied flavonoids. The most commonly reported effects of quercetin are anti-inflammatory, antioxidant, lipid lowering, psychostimulant activity, as well as the ability to promote mitochondrial biogenesis in humans. Mitochondrial biogenesis is the increase in mitochondrial density and volume that generates an improvement in mitochondrial functionality (DAVIS; MURPHY; CARMICHAEL, 2013). Quercetin presents as a yellow-orange powder with the molecular formula $C_{15}H_{10}O_7$ and a molar mass of 302.24 g/mol for the anhydrous form and 338.27 g/mol for the dihydrate form (BORGHETTI, 2006). It is practically insoluble in water (0.17-7.7 mg/mL) and has a very low oral bioavailability (16.2%). This way, its clinical application is limited (GAO et al., 2009). Quercetin undergoes autoxidation in organic solutions or the aqueous medium at pH above 8.0. Autoxidation is dependent on the pH and buffer solution, as well as in the presence of oxidants and is related to the dissociation of the OH groups of the molecule, which occurs with the increase

of pH in the solution. In addition, this compound, like other flavonoids, is photosensitive (ADER; WESSMANN; WOLFFRAM, 2000; MOMIĆ et al., 2007).

Molecules that exhibit low aqueous solubility and low permeability through plasma membranes have deficient bioavailability after oral administration, which may lead to fluctuations in plasma concentration or to food dependence for absorption to occur. Thus, many efforts have been expanded to develop carriers of functional lipophilic foods that can bypass these problems (AUGUSTIN; HEMAR, 2009; OEHLKE et al., 2014).

For this, some characteristics are required, such as the absence of acute and chronic toxicity, sufficient encapsulation capacity, possibility of release control, targeting of the compound to the specific target, storage stability and large-scale production facility (BARRATT, 2000; COUVREUR et al., 1995; MEHNERT; MÄDER, 2001).

Accordingly, numerous technologies have been developed to improve aqueous solubility, to protect degradation and oxidation, and to increase oral bioavailability (FATHI; MOZAFARI; MOHEBBI, 2012).

Among the various strategies, nano-carrier systems have recently been developed for the efficient delivery of lipophilic nutraceuticals. Because of their extremely small size, nano-transporters have demonstrated many advantages, such as improved solubility in water, increased gastrointestinal tract (GIT) time, improved physicochemical stability in GIT, increased intestinal permeation, controlled delivery in TGI, intracellular and transcellular delivery (OEHLKE et al., 2014; PARK; SHIN, 2015). When nano-carriers are used in the feed system or oral delivery system, they should be considered stable in food formulations, non-toxic, biodegradable, and compatible with various forms of food processing (MCCLEMENTS et al., 2009).

Nano-sized particles have novel physiochemical properties, which have been developed for plentiful applications in a variety of fields, especially in pharmaceutical. New nanoformulations have been developed for lipophilic compounds. Nanoformulations can be classified into three categories according to the types of wall and material; lipid and surfactant based delivery systems (nanoliposome, nanoemulsion, solid lipid nanoparticles, nanostructured lipid carriers), nano-carriers based on polysaccharides (polymer nanoparticle, polymeric micelles, and inclusion complex) and protein-based nano-transporters (protein complex and casein micelles) (OEHLKE et al., 2014; PRADHAN et al., 2013).

Each nanoformulation has its distinct characteristics, such as encapsulation efficiency, particle stability, aqueous solubility, oral absorption, and bioavailability. In this sense, it is necessary to understand the characteristics of the core compound and nanoformulations to design and develop the best lipophilic nutraceuticals delivery (PARK; SHIN, 2015).

This review aims to describe the main potential and therapeutic effects of quercetin as well as its limitations and its relation to nanoformulations, including their advantages, disadvantages, and applications, in increasing the solubility and bioavailability of this bioactive compound.

MATERIAL AND METHODS

The study is a review of scientific papers, which included in their samples, articles on nano-encapsulation of flavonoid quercetin. The research for scientific articles was done in the *National Library of Medicine* (*MedLine*), *Scopus* and *Web of Science* databases from October to December 2016 for all studies published until the research period (December 2016). The bibliographic research was performed by a reviewer through the English language of the only intersection of the descriptors and search strategy, "nanoformulation" OR "nanoparticles" AND "quercetin" AND "effects." To compute the total number of studies identified, the duplication was verified between the databases, with each article being counted only once. Among the identified studies, those that seemed to meet the criteria for inclusion were selected, considering the title and the abstract.

The chosen studies were evaluated taking into account the reading and analysis of the full text. After this, the studies were classified as excluded or included considering the criteria established for these purposes. As the inclusion criteria: empirical studies published in scientific journals in English language, and as the exclusion criteria: books, conferences, abstracts in congresses and theses. The articles classified as included were characterized according to the type of nanoformulation, the objective of the study, preparation techniques, particle size, author and year of publication.

RESULTS AND DISCUSSION

POTENTIAL USES OF QUERCETIN

Using the selection criteria defined in the methodology of this article and after verifying the duplication of the articles among the three databases searched, a total of 103 articles were verified. After reading the abstract, 23 papers describing nanoformulations with quercetin were selected. Quercetin has a promising biological action, in the literature several pharmacological actions are described, in which nanotechnology can potentiate the biological effects of quercetin and minimize its low bioavailability. Some effects of quercetin will be described in the course of this article.

ANTIOXIDANT EFFECT

The antioxidant activity of the quercetin is greater than other well-known antioxidant molecules, such as ascorbic acid and vitamin E. The number and position of quercetin free hydroxyl groups justify this higher antioxidant activity (NUENGCHAMNONG et al., 2004). Flavonoid glycosides are widely hydrolyzed in the small intestine or by bacterial activity in the colon, producing the aglycones. Flavonoids that are not glycosylated can be absorbed more easily by epithelial cells of the large intes-

tine because of their lipophilic characteristic, which facilitates the passage through the phospholipid layer of the cell membrane. Thus, these compounds enter the circulation and are subjected to glucuronidation and/or sulfation in the liver (KAWAI et al., 2008).

Anjaneyulu and Chopra (2004) found that the antioxidant activity of quercetin is well recognized for having a suitable structure for the elimination of free radicals and chelation ions (JOSHI et al., 2011). Kalender et al. (2012) observed that the catechin associated with quercetin in groups of treated rats resulted in increased antioxidant activity. This potentiation of the antioxidant effects is due to the association of catechin with quercetin according to the authors. Boots, Haenen and Bast (2008), investigated the possible anti-inflammatory effects of quercetin at physiological concentrations and found an increase *in vivo* antioxidant capacity and anti-inflammatory effects *in vitro*. Hollman et al. (1997) evaluated the protective effect of quercetin on induced oxidative neuronal injury in rat cortical cells in primary culture and its antioxidant activities using three different free bioassay cells. These results showed that quercetin in the form of dihydroquercetin and 3-methyl-quercetin ether has antioxidant activities. Also, 3-methyl-quercetin ether showed to be a more potent neuroprotective agent among the evaluated flavonoids.

ANTI-CANCER EFFECT

The quercetin anticancer mechanisms have been associated with the removal of free radicals, inhibition of cancer cell activating enzymes, modifications of signal transduction pathways, interactions with estrogen receptors, and transcription factors (CHEN et al., 2005; CHOI et al., 2001; MURAKAMI et al., 2008).

Some of the effects of quercetin administration in prostate cancer cells include the inhibition of cell proliferation, induction of apoptosis mechanisms, inhibition of fatty acid synthase (FAS), reduced expression of metalloproteinase 2 (MMP-2) and metalloproteinase 9 (MMP-9). These suggest that the suppression of carcinogenesis is due to the antioxidant activity of quercetin and the reduction of the CYP450 enzyme, which plays a key role in the activation of some suspected carcinogens in humans. In addition, the quercetin showed inhibitory activity on breast and prostate cancer cells with 50.3% and 24.9% cell survival, respectively (BRUSSELMANS et al., 2005; DAKER et al., 2012; VIJAYABABU et al., 2006).

Quercetin may have a promoter effect on the p 161NK4a gene, whose hypermethylation is present in human colon cancer cells (TAN et al., 2008). Quercetin also activates the reduction of the histone deacetylases activity, thereby reducing the acetylation of histone H3, which may be responsible for subsequent sensitization induction to apoptosis. Tanigawa et al. (2008) evaluated the role of tumor suppressor protein, p53, in the HepG2 cells because it can regulate cell cycle arrest, apoptosis, and DNA repair. Its degradation and consequent loss of activity are present in many cancers.

Quercetin stimulated cellular processes that stabilize p53 mRNA and the respective protein. Thus, it induced p53-mediated cell cycle arrest and apoptosis in HepG2 cells.

To assess any potential cytotoxic effects of quercetin on prostate cancer cell lines, Nair et al. (2004) analyzed the viability of quercetin-cultured PC-3 cells for 8 days. It was verified that non-toxic cell viability in PC cells -3 cells cultured with this flavonol, as well as this did not affect the constitutive expression of the β-actin maintenance gene. In this same work, it was found that at similar concentrations (25-50 μM) even non-toxic quercetin showed antitumor activity in prostate cancer cell lines.

Increased expression of oncogenes may contribute to the development of many types of cancer. Quercetin inhibits expression of the cell cycle genes, regulates the expression of tumor suppressor genes, and negatively it regulates the expression of oncogenesis in a prostate cancer cell line. The androgen receptor (AR) is involved in the progression of prostate cancer, and its expression has been reduced by quercetin, which has also reduced tumor markers such as PSA and hK2 (SONG et al., 2008; XING et al., 2001).

Multiple drug resistance (RDM) is a leading cause of cancer treatment failure, as it involves the increased activity of ATP-binding cassette transporters (ABCs). Quercetin may inhibit the function of expression of the ABCB1 gene in many cell lines (LIMTRAKUL et al., 2005; BORSKA et al., 2010). Quercetin has been investigated in some animal models and human cancer cell lines and has been found to have anti-proliferative effects on numerous cell types, including breast, leukemia, colon, endometrial, gastric, and lung cancer. Quercetin also has an immunosuppressive effect on the functioning of dendritic cells. Thus, quercetin according to several studies plays a significant role in the treatment of cancer (HUANG et al., 2010).

ANTITOXIC ACTIVITY AND EFFECT

In addition to several therapeutic functions of quercetin, it is also involved in the elimination of toxic metabolites. Mi et al. (2005) concluded that quercetin inhibited oxidative damages in spermatogonial cells exposed to 3-methylphenol and 4-nitrophenol, toxins found in the exhaust of diesel engines. The intracellular antioxidant parameters were analyzed in embryonic hen cells after exposure to toxin 3-methylphenol and 4-nitrophenol. The toxic induced a decrease in testicular cell viability, the number of spermatogonial cells and induced lipid peroxidation. However, quercetin supplementation improved these parameters and showed anti-toxic effects.

Quercetin has been shown to have a renal protective effect against nephrotoxicity caused by the antibiotic Gentamicin, which limits its clinical use. Researchers theorize that Gentamicin acts in the formation of free radicals and quercetin, as an antioxidant, protects cells against the effects of these radicals. They found that the administration of quercetin in rats treated with Gentamicin, improved histopathological and biochemical parameters related renal function in these rats (ABDEL-RAHEEM et al., 2009).

OTHER THERAPEUTIC EFFECTS OF QUERCETIN

The immunomodulatory activity of quercetin has been investigated in NK (*Natural Killer*) cells, macrophages, mast cells, neutrophils and T cells. Dendritic cells (DCs) play a vital role in the link between innate and adaptive immunity (KIM et al., 2005; YU et al., 2008; YU et al., 2010). Quercetin had an efficient effect by repressing the dendritic cell-induced activation lipopolysaccharide (LPS) by reducing the production of proinflammatory cytokines and MHC class II expression and further revoking the ability of LPS-stimulated DCs to induce activation of Specific T cells both *in vitro* and *in vivo*. These results showed that quercetin might be a potent immunosuppressive agent useful in the prevention of chronic inflammation, autoimmunity, and transplantation (HUANG et al., 2010).

Huang et al. (2010) reported first that quercetin is an immune suppressor of DCs by inhibition of endocytosis, but also quercetin may be an endowed agent for the prevention and treatment of inflammatory and autoimmune diseases. Muthian and Bright (2004) found that quercetin-induced improvement in experimental allergic encephalomyelitis, blocking IL-12 and Th1 signaling. This effect may play a major role as anti-atherogenic and antihypertensive agents (VIZCAINO et al., 2006).

THE CHALLENGES OF THE EFFECTIVE USE OF QUERCETIN

Many nutraceuticals tend to lose their inherent functional characteristics due to oxidation, degradation, and reaction with other materials during processing and storage. To protect their features from the harsh external environment or to deliver them to the destination on time, they must be encapsulated using various technologies.

Based on the Biopharmaceutical Classification System (BCS), most functional food can be classified into four different systems, depending on their solubility and permeability. Most lipophilic components belong to class II or class IV in which low solubility is the main problem (VELIKOV; PELAN, 2008). Low solubility and low adsorption of bioactive compounds are also closely related to low oral bioavailability due to the lower stability of these compounds and inefficient hepatic metabolism (PATEL; VELIKOV, 2011; OEHLKE et al., 2014).

Therefore, proper nanoformulation of these functional lipophilic components is a key issue in improving its solubility, stability, effective encapsulation, permeation and bioavailability. Figure 2 shows the list of scientific articles/year of the last ten years (2006-2016) on the subject "quercetin and nanoformulations", in this search of the publications timeline, the descriptors, and strategy of the current and growing scientific interest in the subject.

Figure 2 - Timeline of the publications of the last ten years involving quercetin and nanoformulations.
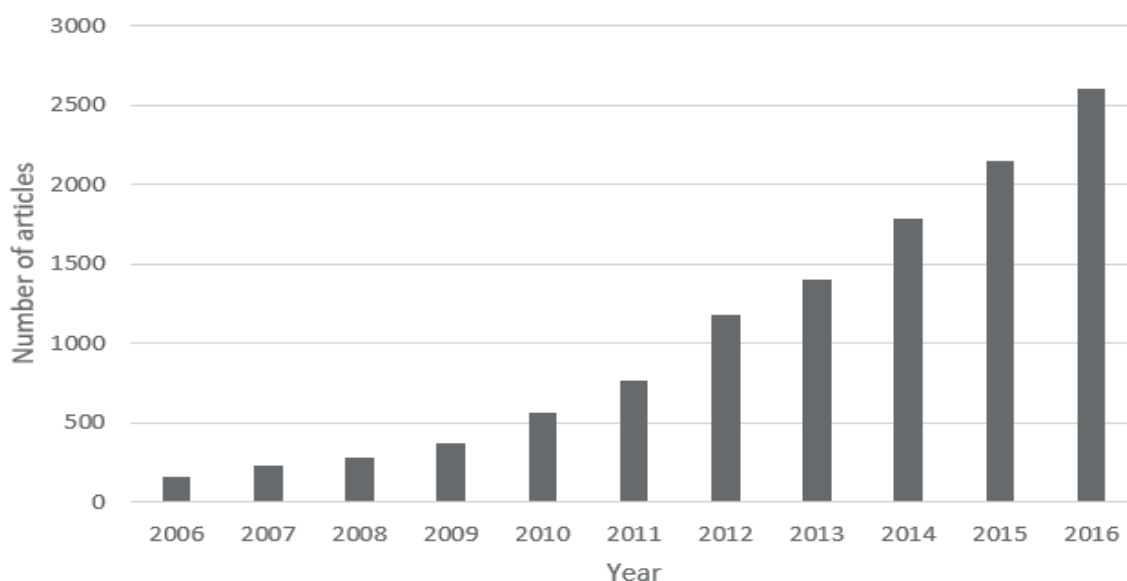
However, nanoencapsulation of a bioactive compound in the human diet should take into account important aspects such as that the component must be compatible with other components of the food matrix, preferably without changing significantly the original food characteristics such as appearance, texture, stability, and flavor (MCCLEMENTS et al., 2009). The carrier materials must maintain the stability and bioactivity of the core during processing, storage, and use because many components are chemically unstable and can be readily oxidized or degraded by light, oxygen, temperature, and pH. Finally, they protect the core physiological environment, such as harsh acidic conditions of the stomach and high activity of the digestive enzymes of the gastrointestinal tract (EZHILARASI et al., 2013; MCCLEMENTS et al., 2009)

The main disadvantages of the therapeutic use of quercetin are the poor water solubility and instability in the physiological medium, which limits the use of flavonoids for oral administration. In the last decade, there was a significant increase in the number of newly developed drug molecules that exhibit low water solubility and poor availability. A major challenge in the pharmacology is the development of drugs and bioactive compounds with good solubility and efficient oral bioavailability (ZHENG et al., 2005).

Ader, Wessmann, and Wolffram (2000) investigated the bioavailability of the flavonol quercetin after intravenous and oral application in pig by giving 0.4-5mg of quercetin in different time intervals and the blood samples were analyzed for quercetin in HPLC. The results indicate absorption of the flavonol quercetin from the small intestine mainly in the form of glucuronides. The solid dispersion of quercetin with polyvinyl pyrrolidone Kollidon[®] 25 (PVP K25) suggests an interesting way to increase quercetin solubility, antioxidant activity, and consequently, the bioavailability by various techniques, and it was possible because of the quercetin solubility increase due to the solid dispersion

formation. Hu et al. (2012) experimented that the instability of quercetin in the cell culture in which would manipulate the *in vitro* studies. They observed the transport behavior of quercetin in Neuro-2a (N2a) cells, as an exemplification to confirm conditions stability of quercetin and the structure is steadier in weak acid and less stable in DMEM (Dulbecco's Modified Eagle Medium) than H_2O at the pH of 7, which will enhance the stability of quercetin.

NANOENCAPSULATION WITH QUERCETIN: A PROMISING AND EFFECTIVE METHOD FOR THE THERAPEUTIC USE OF QUERCETIN

Encapsulation is known as a screening technique and biological organization. Encapsulation is used in product formulations to protect against oxidation, isomerization, degradation, extend the shelf life of materials, as well as for the controlled delivery of functional substances when ingested (CHIU et al., 2007).

Nanoencapsulation improves the solubility and pharmacokinetics of insoluble drugs. In many cases, drug delivery, bioavailability to tissues and target cells are significantly improved, and toxicity is reduced. It can greatly increase the delivery of drugs into tumor tissues and reduce their toxic side effects to normal cells (PARK; SHIN, 2015).

Among the main nanotechnological techniques for the incorporation of quercetin are lipid-based nanocarriers (nanoliposome, nanoemulsion, solid lipid nanoparticles and nanostructured lipid carriers). Systems based on lipid matrices are especially interesting to achieve both objectives, facilitate the incorporation into food matrices and increase the bioavailability of quercetin (LI et al., 2009).

Communication of molecular memory to a polymer network is called molecular imprinting, which is a very simple and useful method. *Molecular Imprinted Polymers* (MIP) are used in a large number of research areas, such as in chromatographic separation and solid phase extraction. Currently, researchers attempt to obtain labeled particles of the nanometric size to be used in drug delivery (CHIU et al., 2007; JAHANSHAHI et al., 2008).

Curcio et al. (2012) investigated the possibility of employing these monodisperse printed nanoparticles as devices for sustained binding/release of controlled quercetin. Printed polymers for use in administering medications should possess a certain degree of flexibility to minimize the potential for irritation to the surrounding tissues and to achieve a rapid equilibrium between release and reabsorption of the template into the cavity, forming the cavities printed in the absence of the mold, to preserve their selectivity properties. Flavin and Resmini, (2009), reported that *in vitro* release studies *in* plasma-simulating fluids and cytotoxicity tests indicated the suitability of these materials as devices for the controlled/sustained administration of quercetin in biological fluids and quercetin anti-proliferative activity after the IPM assessment.

Kumari et al. (2010), studied the encapsulation of quercetin with poly (L-lactic acid) (PLA) nanoparticles by solvent evaporation. The efficiency of nanoencapsulation and the antioxidant effect of quercetin evaluated by HPLC proved to be efficient in 96.7%. PLA is extensively used for the encapsulation of various therapeutic agents, due to their high hydrophobicity, biodegradability, biocompatibility, low toxicity, strong mechanical resistance and slow release of the drug. Priprem et al. (2008) report the successful encapsulation of quercetin in chitosan liposomes and nanoparticles. The nanoparticles loaded with quercetin with PLA were characterized by scanning electron microscopy, atomic force microscopy, and UV-Vis. The effect of the PLA-loaded quercetin nanoparticles on the fluorescence quenching of the BSA protein was also evaluated. Quantification of encapsulation efficacy, antioxidant activity and an *in vitro* release were performed to improve its function in the pharmaceutical domain. The molecule with PLA encapsulated with quercetin presented greater solubility in water and constant release (KUMARI et al., 2010; PRIPREM, 2008).

Quercetin and resveratrol (RES) stimulate a synergistic inhibition of adipogenesis and increase apoptosis in adipocytes, and sodium deoxycholate (SDC) has necrotic effects. The nanoencapsulation of quercetin and RES on liposomes with SDC had an encapsulation efficiency of approximately 97%. According to the authors, this method may be a new advance for subcutaneous lipogenesis (CADENA et al., 2013).

Tan et al. (2011) investigated chitosan lecithin nanoparticles as a topical quercetin release system. The quercetin-loaded nanoparticles showed greater permeability, and increased significantly the accumulation of quercetin in the skin, especially in the epidermis. The interaction between the nanoparticles and the skin surface altered the morphology of the stratum corneum and broke the close conjugation of the corneocyte layers due to the high permeability of quercetin in the skin. According to the authors, the nanoparticle formulations obtained with chitosan lecithin as the delivery vehicle may be promising for the topical supply of quercetin. Song et al. (2008) investigated that antioxidant activity of quercetin and β-carotene by co-encapsulation in a nanoparticle. They observed that nanoparticles holding quercetin, had a faster rate of reaction when compared to β-carotene encapsulated nanoparticles. Kouassi et al. (2012), studied linoleic acid (LA) that was encapsulated in the presence or absence of quercetin in a dual polymer system of whey protein and kappa-carrageenan using ultrasound. The antioxidant activity of quercetin and the encapsulation stability with LA were 83% with efficient encapsulation.

Gao et al. (2012) found that quercetin exhibited anti-cancer activity in A2780S ovarian cancer cells. The encapsulation of quercetin in MPEG-PCL micelles suppressed the growth of A2780S ovary tumors and induced apoptosis of cancer cells and inhibition of angiogenesis *in vivo*. Thus, the encapsulation of quercetin using polymers may enhance the therapeutic effects of quercetin.

Frenzel et al. (2015) the studied liposomes were formed from highly unsaturated soybean phospholipids and incorporated flavonoid quercetin as an encapsulating model. They verified the

physical-chemical properties as well as the sensory properties after coating with Whey Protein Isolate (WPI) in a functional beverage by Spray Drying.

Among the results, both physical stability and *in* vitro stability under gastric digestion condition were significantly improved. The bitter taste of quercetin was also masked after coating with WPI. WPI-coated liposomes have been shown to be a suitable delivery system for water with insoluble bioactive compounds because of excellent system stability and non-toxicity for use as a feed additive.

Liu et al. (2014) developed a new cationic charged quercetin NLC (QR-CNLC) and studied its biodistribution *in vivo* after oral administration. They observed that QR- CNLC delivers a slower release compared to a quercetin solution *in vitro,* and quercetin can be significantly accumulated in the lung, kidney, and liver after oral administration. Therefore, the nanostructured cationic lipid carriers may be an attractive nanocarrier system for oral delivery of hydrophobic bioactive components.

Karadag et al. (2013) and Karadag et al. (2014) prepared quercetin as dispersion nanosuspension using the *Tween* 80 surfactant using the High-Pressure Homogenization (HPH) technique to improve its solubility in water. Maltodextrin was used to encapsulate quercetin and dried by *Spray Drying*. The nanosuspension of quercetin by *Spray Drying* presented higher antioxidant activity than the untreated samples. The authors suggest that the combination of HPH treatment with *Spray Drying* may be an excellent method for the preparation of quercetin-based functional food products.

Table 1 summarizes the scientific papers selected by this review of the last 5 years on the therapeutic effects of nanoencapsulated quercetin. The table shows the type of nanoformulation, preparation material, preparation technique, study objective, particle size, and references.

Table 1 - Physicochemical characteristics nanoencapsulated quercetin of the main articles of the last five years.

Nanoformulations	Materials	Preparation techniques	Results found	Particle size	References
Nanoliposomes	Phospholipid, whey protein isolate	Thim film hydration method	Test the physical-chemical and sensory properties in a beverage	Diverse sizes depending on production step	Frenzel et al. (2015).
Protein Complex	Sodium caseinate	Spontaneous precipitation	Chemical stability and antioxidant activity	130-161nm	Patel et al. (2012)
Nanosuspension	Pluronic F68, lecithin	Precipitation by evaporation in Aqueous solution (EPAS), High pressure homogenization (HPH)	Compare EPAS and HPH method e To assess its viability to form a chemically stable quercetin nanosuspension	EPAS 251.6nm- -282.6nm HPH 192.5nm- 213.6 nm	Gao et al. (2011)
	Tween 80	High pressure homogenization	Form a quercetin nano-suspension to improve its solubility in water by the HPH method	400nm	Karadag et al. (2014)

| Nanoemulsions | Tween 80, Span 20 | High speed homogenization | To prepare the quercetin-loaded nanoemulsion, particle size and stability. | Diverse sizes depending on production step | Karadag et al. (2013) |
| Nanostructured lipids carriers (NLCs) | Gycerol monostearate, médium chain triglycerides, soy lecithin | Emulsifying at high temperature and solidification | Formulate the cationic-quercetin conjugate and evaluate its biodistribution in vivo after oral administration | 127 nm | Liu et al. (2014) |

FINAL CONSIDERATIONS

Flavonoids have received much attention in recent years due to the various beneficial effects observed. Because of the antioxidant effect, they have become important dietary compounds with promising therapeutic potential. Epidemiological reports and evidence suggest that diets rich in flavonoids, such as quercetin, have effects on the prevention and treatment of cardiovascular disease, cancer, and renal and hepatic impairment. However, little is known about the bioavailability, absorption, and metabolism of polyphenols in humans. In this work, some studies on the biological, physical and chemical properties of quercetin were discussed, as well as the role of quercetin in the biosynthesis of nanoparticles against diseases such as cancer.

The main methods of nanotechnology were discussed with the aim to nanoencapsulate quercetin. These methods are promising in the improvement of the low aqueous solubility and consequently the low bioavailability of this compound when used by oral. This low bioavailability of quercetin leads to a poor biological effect, as well as possible fluctuations in the plasma concentration of this bioactive compound when used orally. Colloidal carriers with quercetin have been of great interest because they are promising systems that can meet the requirements described above. Thus, the use of these systems enables bioactive compounds to be delivered and so, to provide maximum therapeutic activity, to prevent degradation or inactivation during displacement to the target site, and to protect the body from adverse reactions due to inappropriate distribution. Through this review, the current and growing interest of the scientific community regarding the nanoencapsulated bioactive compounds, in particular, quercetin, is verified. There is also a vast field still unexplored by science regarding bioactive compounds, their therapeutic effects, and nanoformulations.

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