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**THERAPEUTIC POTENTIAL OF QUERCETIN BASED ON NANOTECHNOLOGY:
A REVIEW**

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Artigo

Therapeutic Potential of Quercetin Based on Nanotechnology: A Review

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Potenciais Terapêuticos da Quercetina Baseados na Nanotecnologia: Uma Revisão

Resumo: A quercetina, um flavonoide natural, ganhou considerável interesse por apresentar inúmeros benefícios para saúde, porém, algumas limitações quando administrada por via oral restringem seu uso. Nesse contexto, para melhorar sua biodisponibilidade, pesquisadores estão trabalhando na aplicação da nanotecnologia, através do uso de nanocarreadores, para direcionar a quercetina aos locais de ação específicos. Os estudos indicam que o câncer é a doença mais investigada devido à alta mortalidade e mau prognóstico em todo o mundo, sendo relatado os efeitos antiproliferativos e apoptóticos em diferentes tipos de neoplasia, incluindo câncer de mama. O maior interesse também tem sido focado em doenças inflamatórias e cardiovasculares. Assim, esta revisão apontou os cenários de desenvolvimento mais relevantes, destacando os estudos que utilizam os sistemas de administração de ativos, mostrando que as pesquisas apresentam resultados promissores.

Palavras-chave: Flavonóides; quercetina; nanotecnologia; sistema de entrega de medicamentos; nanoterapêutica.

Abstract

Quercetin, a natural flavonoid, has attracted considerable interest in its numerous health benefits; nevertheless, some limitations restrict its oral use. Therefore, to improve its bioavailability, investigators are applying nanotechnology, specifically nanocarriers, to direct quercetin to specific sites of action. Studies indicate that cancer is the most investigated disease due to high mortality and poor prognosis around the world, and the antiproliferative and apoptotic effects in different types of neoplasia, including breast cancer, have been reported. The greatest interest has also been focused on inflammatory and cardiovascular diseases. Thus, this review outlines the most relevant development scenarios, highlighting studies using the delivery mechanisms, showing that the studies present promising results.

Keywords: Flavonoids; quercetin; nanotechnology; drug delivery system; nanotherapeutics.

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Therapeutic Potential of Quercetin Based on Nanotechnology: A Review

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1. Introduction

Over the last 25 years, flavonoids have gained substantial attention from researchers, and the number of articles regarding these molecules has grown exponentially.⁴¹ This is because this group of natural polyphenols, synthesized by plants, are commonly used in human diets and are thought to improve bodily functions.⁴³⁻⁴⁶

The polyphenol quercetin is a natural flavonoid found in abundance in medicinal plants, fruits, leaves and vegetables.¹⁶ It is therefore considered beneficial to human health.⁴⁸ Thus, a diet rich in quercetin is recommended.¹² Some sources recommend that daily intake should be approximately 15 mg.³ Quercetin may also be given as a dietary supplement.²⁸

The literature highlights quercetin's high solubility in organic solvents, including ethanol, methanol, dimethylformamide (DMF) and acetone.⁹ The structure of

quercetin places it in the flavone group, its characterized by the presence of 5 hydroxyl groups at the 3, 3', 4', 5 and 7 positions (Figure 1), and the so-called pentahydroxyflavone.

Moreover, its biological activity is influenced by the association of metallic ions with hydroxyl and carbonyl groups, through the formation of complexes.⁴

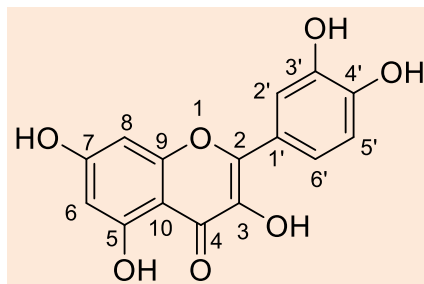


Figure 1. Structure of quercetin

Particularly, bioavailability of quercetin is very low due to its poor aqueous solubility and instability, difficuting its application in the pharma sector.⁵ To overcome these barriers and improve efficacy, research in the field of nanotechnology is a tool that has been extensively investigated.² In this purview, success in the therapeutic field has focused several approaches in the development, characterization and application of systems designed to improve the efficacy and safety of conventional treatments.³⁹

Thus, this review aims to describe current research efforts involving nanotechnology associated with quercetin in order to demonstrate its therapeutic potential.

2. Materials and Methods

This is a review of the literature. To study the scientific and technological progress regarding quercetin associated with diseases, including with nanocarriers, we conducted a search of scientific databases (ScienceDirect, PubMed and Scopus) or patent resources (European Patent Office (EPO), World Intellectual Property Organization (WIPO) and Patent Lens (LENS).

The descriptors used in this study were

present in the titles and or abstracts until October 2018, when the search was performed. The following descriptors were associated with quercetin using the Boolean "AND" operator: Cancer, inflammatory, cardiovascular, viral, liposomes, cyclodextrins and metal nanoparticles.

3. Results and Discussion

3.1. Therapeutic potential of quercetin

Stimulated by the importance of consuming fruits and vegetables for improving health, e.g., for prevention of hypertension,¹⁰ several studies have demonstrated the therapeutic potential of quercetin in the prevention and treatment of various diseases, including hypertension.²⁷⁻³⁸ Moreover, its antioxidant, antiangiogenic, anti-inflammatory and anti-protozoal properties²⁸⁻⁵³ have also been reported; it is also thought to be a hepatoprotective,¹⁷ gastroprotective²⁵ and antibacterial agent.⁵⁶

In particular, it is a promising chemotherapeutic agent, with in treatment of several cancers, including lung,⁸ breast,¹ cervix³² and hematological cancers.³⁰

3.2. Nanotechnology as an alternative

Nanotechnology is defined as the development, characterization and application of systems on the nanoscale.¹⁴ Nanoscale generally suggests the range of 1 to 100 nm, and nanomaterials are structured and/or sized in that range.⁴⁴

Several recent studies reported excellent optical, magnetic, catalytic and electrical properties of nanostructures that can be manipulated by changing their size, shape or atomic composition.¹³⁻⁴³

Nanotechnology in the form nanomedicine, by virtue of its compatibility with biological systems, represents an effort to overcome the limitations and disadvantages inherent in conventional medicines. This means that bioavailability increases with increasing solubility, stability, dissolution rate and surface area; in addition, there is controlled release, reduction of side effects and potentiating of pharmacological action.⁶⁻⁵²

In the case of quercetin, limitations such as low availability, low aqueous solubility (around 60 mg/L), poor intestinal permeability and physiological instability,⁵⁻⁵¹

have been targets of several studies that attempted to overcome these limitations. These goals are fundamental for achieving effective and safe responses to the analyzed formulations.

Therefore, several types of nanostructures have been developed, including mesoporous silica nanoparticles,⁴⁹ liposomes,⁵⁴ cyclodextrin,²⁵ chitosan nanoparticles,² PLGA polymer nanoparticles,²⁰ biogenic nanomaterials³⁵ and other technologies.

4. Trends in Quercetin and Nanostructure Research

The scientific community has been attracted to the therapeutic properties of quercetin. We searched for investigations of diseases treated with quercetin and nanocarriers in ScienceDirect, PubMed and Scopus, returning a total of 1356, 3781 and 10041 scientific articles, respectively (Figure 2a). We also searched the European Patent Office (EPO) (286), World Intellectual Property Organization (WIPO) (321) and Patent Lens (LENS) (389) as databases for deposited patents (Figure 2b).

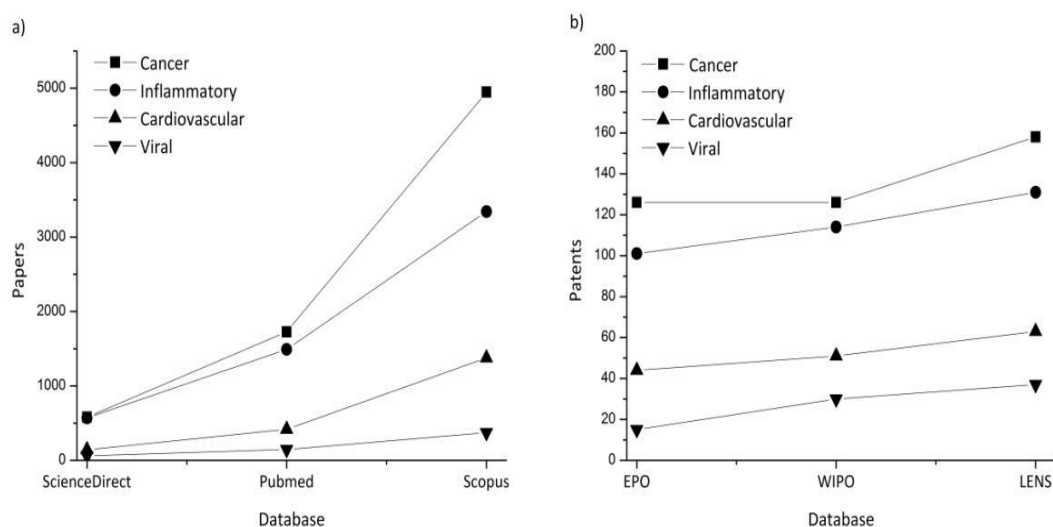


Figure 2. Trends in research involving the therapeutic potential of quercetin. a) Search for articles published, by disease; b) Search of patents filed, by disease

These numbers accurately reflect the current setting in the study of this polyphenol. Cancer was the main disease investigated (7256), with the highest number of patents (410), followed by inflammatory diseases (5404; 346) and cardiovascular diseases (1936; 158). Among the cancers, breast cancer was the most-studied, with 1503 published articles and 23 patent registries, highlighting the severity of this frequently-diagnosed malignant neoplasm, one of the major causes of death in women worldwide.³¹⁻³³

Figure 3 presents findings involving the use of nanotechnology and quercetin. The relevance of nanostructures in biomedical applications is undeniable, but, given the limitations of quercetin in this area, its use is intriguing. In absolute numbers, the Scopus database yielded 844 studies, followed by ScienceDirect (229) and PubMed (198) (Figure 3a). Investigations using liposomes accounted for the largest number of articles (498), followed by articles focused on micelles (349).

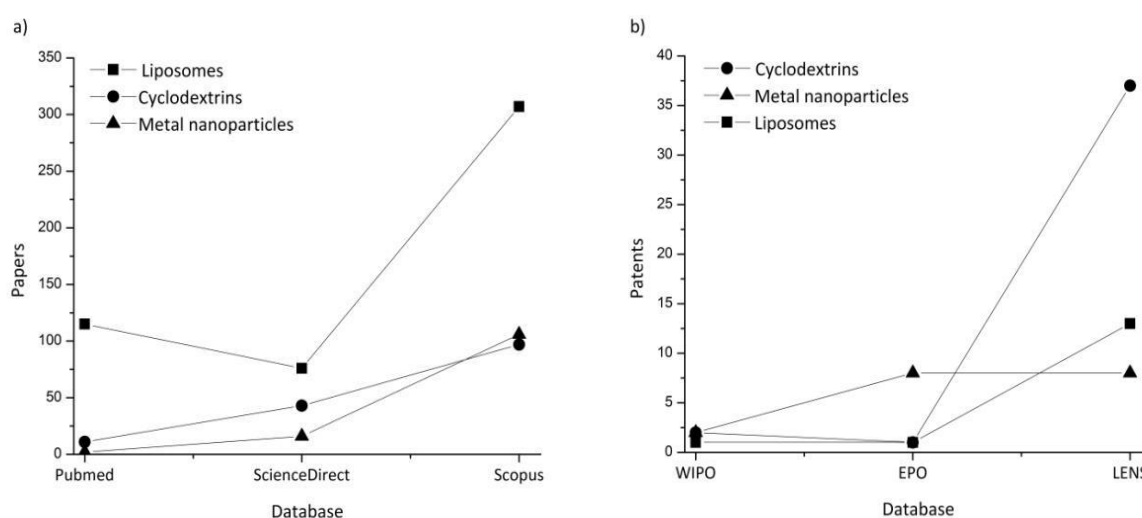


Figure 3. Distribution of studies involving nanocarriers associated with quercetin. a) Search for published articles; b) Search for deposited patents

Patent research deserves special consideration in view of the fact that, although publications are related to liposomes and micelles, the largest number of patent applications are linked to cyclodextrins (40) (Figure 3b).

5. Recent Advances in Therapeutic Applications in Nanotechnology

The solubility of bioactive molecules is influenced by the size and shape of the particles; therefore, smaller size with higher surface area results in increased dissolution rates.³⁴⁻³⁷ Aghapour *et al.*¹ synthesized

quercetin-conjugated silica nanoparticles using an ultrasound-assisted wet impregnation method. Their aim was to evaluate the effect on growth inhibition and induction of apoptosis in MCF-7 cells, a breast cancer cell line. They found that their nanoparticles were spherical with an average size of 84 nm with 45 % quercetin quantified in the system. Regarding biological assays, they demonstrated that 10 μ M quercetin nanoparticles and 100 μ M quercetin were effective against breast cancer cells. The system inhibited cell proliferation by inducing apoptosis at lower concentrations than those achieved by the isolated substance.

Baksi *et al.*² used an ionic gelling method for encapsulating quercetin chitosan

nanoparticles in order to evaluate its effectiveness in cancer therapy. They also performed a controlled-release study and found that the system was very effective in increasing the bioavailability of poorly-soluble substances. The potential of free substance and nanoparticles were explored using *in vitro* and *in vivo* studies. They found that the release of flavonoids occurred over a period of 12 h at pH 7.4 (67.28 %), and *in vitro* cytotoxicity assays showed that the IC₅₀ of nanoparticles was significantly lower than that of quercetin alone ($p < 0.05$). Moreover, treatment of mice with A549 and MDA MB 468 cells produced significant reductions in tumor volume.

Sarkar *et al.*⁴⁹ studied the effect of folic acid-labeled mesoporous silica quercetin-nanoparticles on two human breast cancer cell lines (MDA-MB 231 and MCF 7). They found that, without causing any toxicity to normal cells, the nanoparticles induced apoptosis and decreased cell proliferation. The authors concluded that the reported effects were due to the delivery of quercetin with better bioavailability to the specific site of action.

Wong *et al.*⁵⁴ aiming at synergism between vincristine and quercetin, prepared liposomal formulations with effects against xenografts of breast cancer JIMT-1, a cancer subtype that currently does not have effective treatment options. The authors found that the best synergistic ratio for the drugs was 2:1 (IC: 0.0900), with good antitumor activity at two-thirds of the maximum tolerated dose of vincristine in SCID mice. There was no significant weight loss in the animals. This result suggested low toxicity and increased exposure to drugs in the tumor as a result of increased persistence of the drugs in the circulation.

Other studies related to cancer therapy are summarized in Table 1.

5.2. Inflammatory diseases

One of the first studies to demonstrate the effects of free quercetin against sepsis (a systemic inflammatory response), both prophylactically and therapeutically *in vivo*, was reported by Liao and Lin.²⁹ They found that the bioactive substance reduced proinflammatory cytokine levels while increasing levels of the anti-inflammatory cytokine IL-10 in a lipopolysaccharide-induced inflammation model in mice.

Penalva *et al.*⁴⁰ orally administered zein nanoparticles combined with 2-hydroxypropyl- β -cyclodextrin and quercetin in a mouse sepsis model. Their strategy was to potentiate the bioactive anti-inflammatory effect using cyclodextrin and zein nanoparticles, known to promote improvements in the oral bioavailability of various molecules. The authors demonstrated that animals treated with the nanoparticles had significantly lower levels of TNF- α (pro-inflammatory cytokine) than did control animals; as a result, less severe endotoxemia symptoms were observed.

Castangia *et al.*⁷ demonstrated that chitosan/nutriose-coated polyethylene glycol nanovesicles protected quercetin during its course through the upper gastrointestinal tract and prevented its early release. Because of its specific delivery to the colon, quercetin was able to exert its anti-inflammatory action locally.

Guazelli *et al.*²² demonstrated that quercetin did not lead to beneficial effects in experimental animal colitis models; however, oral administration of bioactive encapsulated microcapsules decreased neutrophil recruitment, reduced IL-1 β and IL-33 production and prevented the reduction of IL-10 compared to the effects of free quercetin.

Table 1. Studies using quercetin in nanocarriers for the treatment of cancer

Nanocarrier	Type	Results	References
Monomethoxy poly(ethylene glycol)–poly(ϵ -caprolactone) nanomicelles	Colorectal	Induction of cellular apoptosis, inhibition of tumor angiogenesis and restriction of cell proliferation	Xu <i>et al.</i> (2015)
Poly(lactic acid)-based polymeric nanoparticles	Lung	Particle size with excellent distribution index and increased cytotoxic effect of quercetin on cancer cells	Nie <i>et al.</i> (2017)
Poly (lactic-co-glycolic acid)-D- α -tocopheryl polyethylene glycol 1000 succinate nanoparticles	Liver	More effective encapsulation of quercetin and correct system targeting for malignant neoplastic cells	Guan <i>et al.</i> (2016)
Nanomicelles	Prostate	Increased tumor permeability and reduced tumor proliferation	Zhao <i>et al.</i> (2016)
Amphiphilic chitosan nanoparticles	Breast	Higher flavonoid release at acidic pH, proving to be a promising system	Pedro <i>et al.</i> (2018)

One of the more recent studies to report the *in vivo* effects of phytosome nanoparticles on quercetin was reported by the El-Fattah *et al.* (2017). The study addressed the long-term limitations of hormone replacement therapy, used to relieve menopausal symptoms. In this respect, the use of quercetin as a phytoestrogen is promising. Quercetin nanoparticles were created using the thin film hydration method. The authors studied anti-inflammatory effects, as well as the estrogenic activity of quercetin in a model of ovariectomized rats. They found that, because of the better bioavailability, quercetin carried in nanoparticles (10 mg/kg) showed almost identical effects in terms of improvement as did free quercetin at high dose (50 mg/kg).

5.3. Cardiovascular diseases

Giannoulia *et al.*²⁰ showed that polymeric nanoparticles of poly lactic-co-glycolic acid with quercetin, prepared using the electrohydrodynamic atomization process, had great potential for prevention of atherosclerosis. They found that quercetin was released from the nanoparticles in two phases, the first one at 24 hours, followed by a sustained release for 59 days.

Specific and controlled delivery of antioxidants at the site of action have also been subjects of research because of the benefits that these molecules present with respect to the preventive and therapeutic treatment of various cardiovascular diseases.²³

Farrag *et al.*¹⁹ prepared starch nanoparticles with quercetin using nanoprecipitation. The authors sought to obtain biodegradable antioxidant nanoparticles in view of the use of natural, biocompatible and biodegradable starches. They found that the kinetics of release and antioxidant activity of quercetin depended on the origin of the starch, such that after 4 h, potato starch nanoparticles released 59.9 % of quercetin, pea starch particles released 57.5 % and corn starch particles released 41.7 %.

Soloviev *et al.*⁵⁰ in a comparative study of the arrhythmogenic effects of peroxyxynitrite, a compound that acts on the oxidative stress of cardiac tissues, and the cardioprotective profile of phosphatidylcholine liposomes loaded with quercetin, found that the system provided protection against myocardial lesions induced by peroxyxynitrite. Changes such as arrhythmias, contractile diffusion and changes in action potentials were stimulated. Nanoparticles restored normal cardiac contractility, demonstrating cardioprotective efficacy in cardiac ischemia and a decomposing effect on peroxyxynitrite compounds.

Cote *et al.*¹¹ performed a study with resveratrol and quercetin carried by polymeric micelles seeking a cardioprotective action from co-administration with doxorubicin, an antibiotic used in the treatment of cancer that has high cardiotoxicity. The compounds were administered to Swiss Webster ND4 mice at a ratio of 10:10:1. This reduced cardiotoxic levels relative to levels found in mice treated with the drug alone, demonstrating that the combination was a viable and effective strategy for decreasing the cardiotoxicity of doxorubicin.

6. Conclusion

This review highlighted the most relevant developments in therapeutic strategies that have been developed to improve the oral bioavailability of quercetin in order to

maximize its potential. When the bioactive compound is encapsulated in nanocarriers, the formulations facilitated increased targeted delivery of quercetin along with improved stability, resulting in efficient therapeutic responses to the molecule. Therefore, these new nano-scale distribution systems may evolve as an effective strategy for the treatment of various diseases.

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