NANOENCAPSULATED QUERCETIN FOR THE TREATMENT OF LIVER CANCER: A LITERATURE REVIEW[1]

QUERCETINA NANOENCAPSULADA NO TRATAMENTO DO CÂNCER DE FÍGADO: UMA REVISÃO DE LITERATURA

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ABSTRACT

Quercetin, a natural flavonoid found in many kinds of food such as fruit and vegetables, is one of the most prominent dietary antioxidants known for its anticarcinogenic potential. In the last decade, there has been an increase in studies involving this flavonoid. The aim of this review is to evaluate the association between nanoparticles with quercetin and hepatocarcinoma or liver cancer. A review of papers published in the last 10 years in PubMed, Web of Science and Scopus databases was performed using quercetin and nanoparticles as descriptors. Papers containing the descriptors quercetin, nanoparticles, liver cancer (hepatocarcinoma) were classified. The increase in studies related to nanoencapsulated quercetin indicates its therapeutic potential, which could be powerful in cancer prevention. In vivo and in vitro studies suggest that quercetin has anticancer effects that inhibit tumor growth, discontinuing cell cycle and inducing apoptosis. The need for further studies about the potential therapeutic effects of quercetin nanoparticles is highlighted.

Keywords: flavonoid, hepatocarcinoma, nanoparticles.

RESUMO

A quercetina, um flavonóide natural, presente em uma infinidade de alimentos como, frutas e vegetais, é considerada um dos antioxidantes dietéticos mais proeminentes e é bem conhecida pelo seu potencial anticarcinogênico. Na última década, observou-se um aumento em estudos que envolvam esse flavonóide. O objetivo desta revisão foi avaliar a associação entre nanopartículas com quercetina e o hepatocarcinona ou câncer de fígado. Os dados para esta revisão foram obtidos através de buscas nas bases de dados Pubmed, Web of Science e Scopus de artigos publicados nos últimos 10 anos usando os descritores quercetina, nanopartículas. Foram classificados os artigos que contém os descritores quercetina, nanopartículas e câncer e os artigos que contém os descritores quercetina, nanopartículas, câncer de fígado (hepatocarcinoma). Este aumento nos estudos relacionados ao uso da quercetina nanoencapsulada comprova o seu potencial terapêutico potente na prevenção do câncer. Estudos in vivo e in vitro sugerem que a quercetina exerce efeitos anticancerígenos através da inibição do crescimento tumoral, interrompendo o ciclo celular e induzindo a apoptose. Destaca-se a necessidade de mais estudos para um potencial uso terapêutico das nanopartículas com quercetina.

Palavras-chave: *flavonóide, hepatocarcinoma, nanopartículas.*

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INTRODUCTION

During the last decade, there has been an increase in scientific studies about non-nutritional components of the diet. These components are present in diet and could protect the body from harmful effects of degenerative diseases, cancer, and cardiovascular diseases. Two distinct groups of phytochemicals, carotenoids, and flavonoids represent valuable food constituents (SURH, 2003). An important point, which draws researcher's attentions to these natural compounds, is the presence of numerous phytochemicals in plant-derived foods. A large number of biological activities of these compounds are still unknown (KRIS-ETHERTON et al., 2004). However, it is known that these plant-derived phytochemicals activate several cells signaling pathways important in the prevention of physiological disorders, which are primarily responsible for the development of cancer, and neurodegenerative and cardiovascular diseases (LEE et al., 2011). Several scientific studies of experimental animal models evaluated the mechanism of action of phytochemicals and describe how food supplements with a large number of phytochemicals could prevent degenerative diseases (CROWE et al., 2011).

Flavonoids are mostly found in nature in the form of benzopyrone derivatives, which are present in a variety of plants, vegetables, and flowers. A large part of the activity of citrus flavonoids affect blood and microvascular endothelial cells; furthermore, not surprisingly, inflammation and cancer are the two major areas of research on their biological actions. Epidemiological and animal studies indicate a possible protective effect of this phytochemical against cardiovascular diseases and some types of cancer. Flavonoids can act at different stages of malignant tumor development, protecting DNA against oxidative damage, inactivating carcinogens, inhibiting expression of mutagenic genes and enzymes responsible for activation of procarcinogen substances, and activating the systems responsible for xenobiotic detoxification. In the last decade, studies about flavonoids have associated its action to enzymatic inhibition and antiproliferative activity (BENAVANTE-GARCIA; CASTILLO, 2008).

Quercetin, which is a medicinal member of flavonoid family, is present in various foods, such as fruit, vegetables, tea, wine and other dietary supplements; also, it is considered one of the most prominent dietary antioxidants. Quercetin has innumerous pharmacological effects of protection against several diseases, such as osteoporosis, some malignant tumors and pulmonary and cardiovascular diseases. Quercetin has the special ability to eliminate highly reactive species such as hydrogen peroxide, superoxide anion and hydroxyl radicals. Quercetin is well known for its anticarcinogenic potential because it has several mechanisms of cell signaling and it could inhibit enzymes responsible for activating carcinogens. In addition, it exerts an anticancer effect by binding to cellular receptors and proteins (KHAN et al., 2016). Recently a growing number of studies have shown that quercetin has multiple effects on cancer cells, including lung cancer cells, colon cancer cells, prostate carcinoma cells and pancreatic tumor cells, which can induce the apoptosis of these cells (GUO et al., 2009).

Cell death induced by quercetin and the reduction in cancer cell proliferation have been associated primarily with apoptotic mechanisms in various cancer cells, including human liver cancer cells (HepG2 Cells) (MAURYA; VINAYAK, 2015). Quercetin is the most important naturally occurring cancer-preventing agent among polyphenols; however, the clinical application of quercetin has many challenges due to its poor water solubility, low absorption, low bioavailability and chemical instability (BI; WEHRUNG; OYEWUMI, 2013). Absorption after ingestion and the ability to deliver into various body tissues are essential for quercetin to act *in vivo*. However, clinical application of quercetin is very restricted because of its low aqueous solubility, its minimal absorption in the gastrointestinal tract and its oral bioavailability of less than 17% in rats, and up to 1% in men. Thus, solid lipid nanoparticles (SLNs), a type of drug delivery system of nanoparticles, are considered as an alternative transport system to the traditional colloidal system, such as emulsions, liposomes, polymer microparticles and nanoparticles (LI et al., 2009).

The preventive and therapeutic effects of quercetin on cancer have been demonstrated through experimental results *in vitro* and *in vivo* (PATIL et al., 2003). Anticancer activity of quercetin in ovary cells was studied *in vitro*. Treatment with quercetin induced apoptosis of A2780S cells associated with activation of caspase-3 and caspase-9. Low regulation of *MCL-1* and *Bcl-2* and positive regulation of Bax and the alteration of mitochondrial transmembrane potential have been observed, suggesting quercetin can induce apoptosis of *A2780S* cells via the mitochondrial apoptotic pathway. Intravenous administration of QU/MPEG-PCL ratslles significantly suppressed the growth of ovarian tumors of *A2780S* xenograft causing the apoptosis of cancer cells and the inhibition of angiogenesis *in vivo* (GAO et al., 2012).

The study by Zhao et al. (2016) about prostate cancer *in vivo* with nanoencapsulated quercetin (DSPE-PEG2000) demonstrates a superior antitumor efficacy and a reduced tumor proliferation rate by 52.03% in comparison to the control group in a *PC-3* xenograft model in rats. Lou et al. (2016) evaluated, *in vitro*, nanoencapsulated quercetin in human neuroglioma cells, the authors found out that quercetin induced cell death in a dose and time-dependent manner. Flow cytometry results showed that the ratio of apoptosis cells increase after treatment in comparison with the untreated group. These results indicated the quercetin nanoparticle could induce autophagy and apoptosis in human neuroglioma cells. Another study conducted in *C6* Glioma cells by Wang et al (2016) shows that nanoencapsulated quercetin induced programmed cell death (necrotic) depending on the dose and time.

Hepatocellular carcinoma (CHC) is the fifth most common cancer in the world being the most common type of liver cancer, accounting for 83% of all cases. Over the past 5 years, the reported survival rate is approximately 7%, and CHC causes more than 600,000 deaths annually, being the third leading cause of cancer death in the world (GHOSH et al., 2012; MANDAL et al., 2014). Several studies evaluated the use of quercetin nanoparticles in liver cancer (GUO et al., 2009; GROSH et al., 2012; MAURYA; VINAYAK, 2015; GUAN et al., 2016; WANG et al., 2016).

A study conducted by Mandal et al. (2014) expose rats to diethylnitrosamine (DEN) to induced hepatocellular carcinoma. The administration of DEN generates reactive oxygen species, regulation of *TNF-α*, *IL-6*, activation of *MMP-13*, severe oxidative damage, hyperplastic nodules with preneoplasia lesions and histopathological changes in the liver. Nanocapsules (group III), free QC (group IV) and nanoencapsulated QC (NQC, group V, 8.98 μmol/kg) were intravenously injected in rats once a week for 16 weeks. Results showed that nanoencapsulated quercetin restricted all changes in the development of DEN-mediated hepatocarcinogenesis; therefore, authors concluded that nanoencapsulated quercetin could be used as a potent therapeutic formulation in the prevention of hepatocarcinogenesis.

In the last decade, there was an increase in studies about this flavonoid. According to a survey conducted in the Web of Science database, in 2008 there were only 1 publication related to the words quercetin, nanoparticles and cancer. In the following years, from 2009 to 2012, 2, 4, 3 and 7 studies were published, respectively. In 2013, studies about this flavonoid increased considerably, 12 studies were published, while in subsequent years, from 2014 to 2016, 23, 16 and 38 articles were published, respectively. Until now, 21 studies have been published in 2017. Figure 1 shows this increase that is related to the use of nanoencapsulated quercetin which demonstrates its strong therapeutic potential in the prevention of diseases such as hepatocarcinoma.

Figure 1 - Last decade studies related to nanoencapsulated quercetin.
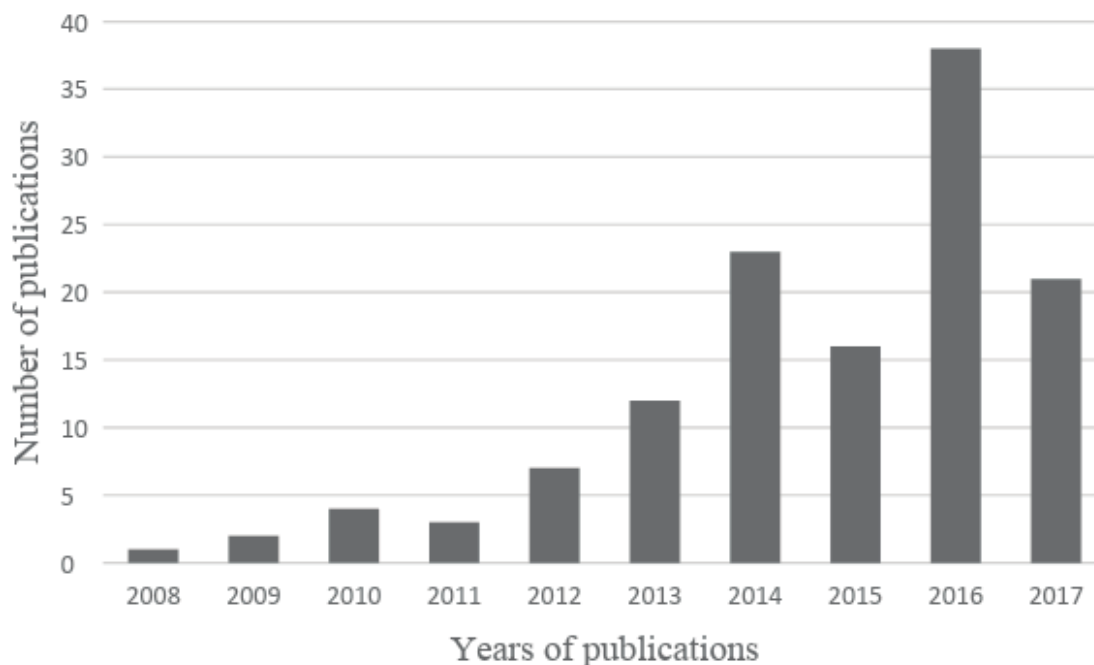
Source: Web of Science database, 2018.

As it can be observed above, quercetin has been used and tested by authors in several types of cancers, this review is justified because it focuses on the use of nanoencapsulated quercetin in the treatment of hepatocellular carcinoma, which is the third most frequent cancer in the world (GHOSH et al., 2012).

MATERIAL AND METHODS

DATA SOURCE

For this review on Web of Science, Scopus and PubMed the search focused on papers published in the last 10 years. All studies about the association of quercetin nanoparticles with hepatocarcinoma or liver cancer were included. The terms "quercetin," "nanoparticles" and "cancer" were used as descriptors.
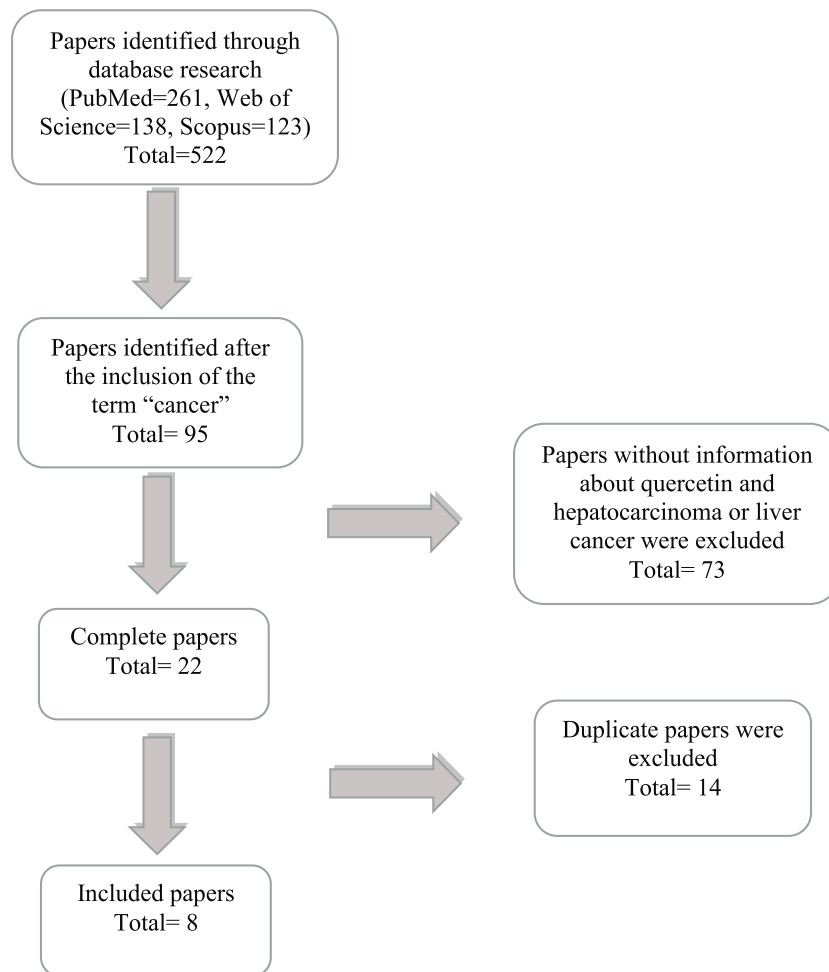
SELECTION CRITERIA

All studies about the association between quercetin and hepatocarcinoma or liver cancer and quercetin anti-proliferative effects on animals or cells were included in this literature review. The exclusion criteria were used as: (i) no information on quercetin nanoparticles, (ii) no information of cancer (iii) no information on the effect of quercetin nanoparticles associated with hepatocarcinoma or liver cancer.

SELECTION OF PAPERS

Upon Using "quercetin" and "nanoparticles" as descriptors, 522 papers were found. Adding "cancer" as a descriptor, the number of papers decreased to 95. Titles and abstracts were analyzed to examine the use of quercetin nanoparticles with hepatocarcinoma or liver cancer. After the full texts were selected, 73 studies were excluded because there was no mention about the effect of quercetin nanoparticles on hepatocarcinoma or liver cancer. From the remaining papers, 14 were duplicates, leaving a total of 8 papers that were included in this literature review. Figure 2 illustrates the study selection processes.

Figure 2 - Flowchart of the selection of study.

Papers identified through
database research
(PubMed=261, Web of
Science=138, Scopus=123)
Total=522

↓

Papers identified after
the inclusion of the
term "cancer"
Total= 95

→ Papers without information
about quercetin and
hepatocarcinoma or liver
cancer were excluded
Total= 73

↓

Complete papers
Total= 22

→ Duplicate papers were
excluded
Total= 14

↓

Included papers
Total= 8

DATA EXTRACTION

The data extracted from papers were: (i) type of nanoparticle, (ii) nanoparticle diameter, (iii) treatment dose, (iv) duration of exposure, (v) *in vitro* or *in vivo*, (vi) results and (vii) author and year of publication. Table 1 presents these data, which will be addressed in detail in the Results and Discussion section.

RESULTS AND DISCUSSION

Table 1 shows information about the papers reviewed, such as the nanoparticle type, nanoparticle diameter, treatment dose, exposure time, *in vitro* or *in vivo* methods, results and authors and year of publication. The papers are presented in descending order.

Table 1 - Data from the reviewed papers.

Nanoparticles	Nanoparticle diameter (nm)	Treatment dose	Exposure Time	Method: In Vitro In Vivo	Results	Author, Year
Gold Nanoparticle with quercetin	100	10 - 60 µg/mL 30, 40 and 50 µg/mL	24 h 0, 7, 14, 21, 28 and 35 days	*In Vitro* *MHCC97H, Hep3B, HCCLM3* and *Bel7402* Cells In Vivo Rats	Inhibited proliferation, cell migration and colony formation, both methods increased apoptosis	Ren et al. (2017)
Modified lipid coated nanoparticles SRF + QT	93.9	5 and 10 µM	72 h 0, 7, 14 and 21 days	*In Vitro* *HepG2* Cells In Vivo Rats	Both methods inhibited tumor growth	Wang et al. (2016)
Quercetin nanoparticles	100-200	10 mg/kg	10 days	*In Vitro* *HepG2* Cells *In Vivo* Rats	Both methods suppressed tumor growth	Guan et al. (2016)
Gold nanoparticle with quercetin	100	12 and 24 µg/mL	0, 6, 12, 18 and 24 h	*In Vitro* *HepG2* Cells	Apoptosis induction, cell proliferation inhibition	Bishayee; Khuda-Bukhsh and Huh (2015)
Lipid nanoparticle with quercetin	78	1, 5, 10, 20, 50, 75 and 100 µM	1, 4 e 24 h	*In Vitro* *HepG2* Cells	Accumulation of quercetin in *HepG2* cells	Varshosaz et al. (2014)
Quercetin nanoparticles	100	200 mg/kg 8.98 µM/L	16 weeks	*In Vivo* Swiss albino rats	Restricted changes in hepatocar-cinomas development	Mandal et al. (2014)
Quercetin nanoparticles	270	200 mg/kg 8.98 µM/L	18 weeks	*In Vivo* Swiss albino rats	Reduced liver cancer induction	Ghosh et al. (2012)
Nickel nanoparticles with quercetin	30	25 µM/mL 50 µM/mL 2 µg/mL	72 h	*In Vitro* *SMMC-7721* Cells	Cell proliferation inhibition	Guo et al. (2009)

The increase in studies about the use of quercetin nanoparticles associated with liver cancer or hepatocarcinoma reinforces the therapeutic potential of quercetin in the prevention and treatment of liver cancer.

Guo et al. (2009) studied the effect of nanoencapsulated quercetin on positively charged functionalized nickel (Ni) nanoparticles on cell absorption in hepatocellular carcinoma cells (*SMMC-7721*). For this study, the authors used electron microscopy, electrochemical characterization and MTT assay. Ni nanoparticles could improve permeability of cancer cells and accumulation of quercetin in *SMMC-7721* cells, indicating that Ni nanoparticles with quercetin could inhibit cancer cell proliferation.

Gosh and colleagues published in 2012 a study on the use of nanoencapsulated quercetin as a therapeutic procedure against diethylnitrosamine-induced hepatocarcinogenesis (DEN) in rats. DEN is a carcinogenic substance, which induces hepatic carcinoma. Authors observed that nanoencapsulated

quercetin significantly reduced the induction of liver cancer by DEN. In this same line Mandal et al. (2014) also published a study on the control and efficacy of nanoencapsulated quercetin in MMP-13 cells in DEN induced hepatocarcinogenesis in albino rats. These rats exhibited an increased expression of TNF-α, IL-6, activation of MMP-13, severe oxidative damage, hyperplastic nodules with pre-neoplastic lesions and histopathological changes in the liver. The treatment was administered with empty nanocapsules (group III), free QC (group IV) and nanocapsulated QC (NQC; group V; 8.98 µmol / kg) injected intravenously to the rats once a week for 16 weeks. The results showed that nanoencapsulated quercetin restricted all changes in the development of DEN-mediated hepatocarcinogenesis. The authors conclude that nanocapsulated quercetin can be accepted as a potent therapeutic formulation in the prevention of DEN mediated hepatocarcinogenesis.

Varshosaz et al. (2014) conducted a study to improve cellular penetration of quercetin by sterol, since it has low solubility which limits its clinical use. Authors used solid lipid nanoparticles (SLNs) with quercetin prepared by a solvent emulsification-evaporation method. The morphology of QT-SLNs was obtained by scanning electron microscopy. Cytotoxicity was analyzed by MTT method in *HepG2* cells in hepatocarcinoma and cellular absorption by fluorescence microscopy. QT-SLNs caused accumulation of quercetin in *HepG2* cells.

Bishayee, Khuda-Bukhsh and Huh (2015) conducted a study to test the biological activity of gold nanoparticles with quercetin (QT-AuNPs) also in *HepG2* cells in hepatocarcinoma. The authors' aim was to obtain a controlled release of the drug. Mitochondrial membrane potential (*MMP*), reactive oxygen species (ROS), cell cycle, apoptosis, DNA damage and caspase-3 activity were analyzed by flow cytometry; also, expression profiles of different pro-apoptotic and epigenetic signals were studied using immunoblotting. A cytotoxicity test indicated that QT-AuNPs destroyed more cancer cells than normal cells. Also, it was observed that QT-AuNPs induced apoptosis in *HepG2* cells by activating *p53*-ROS, inhibiting the proliferation of hepatocarcinoma by stopping cell cycle.

Guan et al. (2016) reported a limited use of quercetin due to its instability and low solubility. To overcome these disadvantages quercetin nanoparticles were produced to study its properties and therapeutic efficacy for liver cancer. Cellular absorption was analyzed using *HepG2* cells and the effects on apoptosis were studied with flow cytometry. Results were obtained using the transmission of electron microscopy, scanning electron microscopy and the size analysis indicated a stability of quercetin nanoparticles with encapsulation at an efficiency of 93.74%. *In vitro* results indicated that quercetin nanoparticles induced apoptosis in *HepG2* cells and the *in vivo* rat model diminished hepatic tumor growth by 59.07%. Therefore, quercetin nanoparticles could be used as a possible intravenous treatment for liver cancer, since the pharmacological effects of these nanoparticles were satisfactory.

Still in 2016, Wang and his colleagues reported that the combination of therapies could provide a potential solution for tumor treatment and drug resistance. A targeted delivery of sorafenib (SRF)

and quercetin (QT) was studied using nanoparticles coated with modified lipids to co-deliver these hydrophobic drugs in treatment of hepatocellular carcinoma. Physical-chemical characteristics and release profiles were evaluated *in vitro* and *in vivo* tests. The combination of SRF and QT was more effective than other treatments which used only the drug, obtaining an inhibitory effect of tumor growth both *in vitro* and *in vivo* tests. Results indicated that these nanoparticles could provide a promising platform for the delivery of multiple anticancer drugs in combined therapy with the possibility to increase therapeutic efficacy in hepatocellular carcinoma.

Ren et al. (2017) studied gold nanoparticles with quercetin to explore possible mechanisms in the regulation of antitumor activity in liver cancer cells. *In vitro* tests with liver cancer cells and *in vivo* tests with rats demonstrated an inhibition of liver cancer cell proliferation, cell migration and colony formation; therefore, the progression of liver cancer was reduced. Also, these nanoparticles increased the apoptosis of cancerous cells, accelerated the cleavage of caspase-9 and caspase-3 and induced the release of cytochrome c (Cyto-c) thus contributing to the apoptosis in liver cancer cells. In addition, the gold nanoparticles with quercetin have provided new mechanisms for further investigation of possible therapeutic strategies and inhibition of liver cancer.

It is interesting to observe that the articles present several formulations of nanoparticles with several other substances associated with quercetin with the function of protecting it, since it has low solubility and high instability according to (GUAN et al., 2016). Of the various formulations that the articles bring on nanoparticles, Bishayee, Khuda-Bukhsh and Huh (2015) and Ren et al. (2017) bring gold associated with quercetin, it is observed that there is not yet a standardization of formulations even because the field is very vast. As for the size of the nanoparticles, the largest were from the study of Ghosh et al., 2012, which presented 270nm, all other studies showed sizes below 100nm, but with large variations. Two variables that show large variations between studies are dose and exposure time, the highest doses and time of exposure to treatment are observed in the studies of Mandal et al. (2014) (200 mg / kg and 16 weeks) and Ghosh et al. (2012) (200 mg / kg and 18 weeks). As for the in vivo and in vitro method, five articles were made in vivo, six articles in vitro, three in vivo and in vitro.

Although the reviewed articles present a wide range of formulations, sizes, dose, time of exposure, and method used, all articles show that nanoencapsulated quercetin associated with other substances presented great potential for the treatment of liver cancer. There is agreement of the results presented regarding inhibition of cell proliferation, inhibition of tumor growth, induction of apoptosis accumulation of quercetin in HepG2 cells and reduction of liver cancer induction. These results provided new mechanisms for investigating possible therapeutic strategies perhaps by proposing a standardized protocol for the treatment of liver cancer with quercetin-based nanocapsules.

CONCLUSION

Quercetin is a powerful therapeutic agent against cancer and a dietary antioxidant in fruits and vegetables. Quercetin prevents tumor proliferation, induces cell cycle arrest and it is a therapeutic agent for hepatocarcinoma. Recent studies have demonstrated a good efficacy and reduction of side effects of the nanoparticle delivery of drugs. Therefore, as discussed in the results, a significant association between quercetin and its anticancer effects was established. The *in vivo* and *in vitro* studies indicate that quercetin inhibits tumor growth, disrupted cell cycle and induces apoptosis. The need for further studies of the possible therapeutic use of nanoparticles with quercetin is emphasized.

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