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Role of antioxidants in the treatment of hepatocellular carcinoma: Integrative review

Papel dos antioxodantes no tratamento do carcinoma hepatocelular: Revisão integrativa

Papel de los antioxidantes en el tratamiento del carcinoma hepatocelular: Revisión integrativa

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Abstract
Theorical framework: Hepatocellular carcinoma is a unique cancer that typically arises in the setting of chronic liver disease at a rate dependent upon the complex interplay between the host, disease, and environmental factors. Unfortunately, with contemporary management, patients with advanced hepatocellular carcinoma have few treatment options, and the prognosis is poor. Objective: Evaluate the role of antioxidants in the treatment of hepatocellular carcinoma. Methodology: It is an integrative review, with a qualitative approach. Based on research on ScienceDirect and PubMed databases, 12 articles were selected that were consistent with the theme and the inclusion and exclusion criteria, through the association of descriptors and keywords. Results: Studies *in vivo* demonstrated a positive correlation of antioxidants in the treatment of hepatocellular carcinoma. The antioxidants were able to promote inhibition of development tumor through promotes decrease of proinflammatory cytokines IL-1 and IL-6 and changes the ratios of Bax/Bcl2 that supports apoptosis. In oxidative stress, may be able to direct free radical scavenging activity. Among the main antioxidants with advanced preclinical evidence in the treatment of hepatocellular carcinoma is curcumin with tests in humans, and gallic acid, quercetin and resveratrol with several tests *in vitro* and in vivo. Conclusion: This study highlights that antioxidants can be a promising therapy in the treatment of hepatocellular carcinoma.
Keywords: Carcinoma hepatocellular; Antioxidant; Oxidative stress.

Resumo
Marco teórico: o carcinoma hepatocelular é um câncer único que geralmente surge no contexto de doença hepática crônica dependente da interação entre hospedeiro, fatores ambientais e a capacidade de desenvolvimento da doença. Infelizmente, com o manejo contemporâneo, os pacientes com carcinoma hepatocelular avançado tem poucas opções de tratamento, e o prognóstico é ruim. Objetivo: avaliar o papel dos antioxidants no tratamento do carcinoma hepatocelular. Metodologia: trata-se de uma revisão integrativa, com abordagem qualitativa. Com base em pesquisas nas bases de dados ScienceDirect e PubMed, foram selecionados 12 artigos que foram consistentes com o tema e os critérios de inclusão e exclusão, por meio da associação de descritores e palavras-chave. Resultados: Estudos realizados *in vivo* demonstraram uma correlação positiva no uso de antioxidantes no tratamento do carcinoma hepatocelular. Os antioxidantes foram capazes de promover a inibição do desenvolvimento tumoral diminuíndo as citocinas pró-inflamatórias IL-1 e IL-6 e alterando a relação entre Bax/Bcl2 que suportam a apoptose, além de direcionar a eliminação de espécies reativas. Entre os principais antioxidantes com evidências pré-clínicas avançadas no tratamento do carcinoma hepatocelular está a curcumina com testes em humanos, o ácido gálico, quercetina e resveratrol com vários testes *in vitro* e *in vivo*. Conclusão: Este estudo destaca que os antioxidantes podem ser uma terapia promissora no tratamento do carcinoma hepatocelular.
Palavras-chave: Carcinoma hepatocelular; Antioxidante; Estresse oxidativo.

Resumen
Marco teórico: el carcinoma hepatocelular es un cáncer singular que suele surgir en el context de una enfermedad hepatica crónica dependiente de la interacción entre el huésped, los factores ambientales y la capacidad de desarrolar la enfermedad. Desafortunadamente, con el tratamiento actual, los pacientes con carcinoma hepatocelular Avanzado

tienen pocas opciones de tratamiento y el pronóstico es malo. Objetivo: evaluar el papel de los antioxidantes en el tratamiento del carcinoma hepatocelular. Metodología: se trata de una revision integradora, con enfoque cualitativo. A partir de búsquedas en las bases de datos ScienceDirect y PubMed, se seleccionaron 12 artículos que fueron consistentes con la temática y los criterios de inclusion y exclusion, mediante la asociación de descriptors y palabras clave. Resultados: Los estudios realizados *in vivo* han demonstrado una correlación positiva en el uso de antioxidantes en el tratamiento del carcinoma hepatocelular. Los antioxidantes fueron capaces de promover la inhibición del desarrollo tumoral al disminuir las citocinas proinflamatorias IL-1 e IL-6 y alterar la relación entre Bax/Bcl2 que apoyan la apoptosis, además de dirigir la eliminación de especies reactivas. Entre los principals antioxidantes con evidencia preclínica avanzada en el tratamiento del carcinoma hepatocelular se encuentra la curcumina con pruebas en humanos, ácido gálico, quercetina y resveratrol con varias pruebas *in vitro* e *in vivo*. Conclusión: Este studio destaca que los antioxidantes pueden ser una terapia prometedora en el tratamiento del carcinoma hepatocelular.
Palabras clave: Carcinoma hepatocelular; Antioxidante; Estrés oxidativo.

1. Introduction

Hepatocellular carcinoma (HCC) is the primary cancer of the liver, that is, cancer derived from the main liver cells the hepatocytes and is associated with a high rate of morbidity and mortality. HCC represents the fifth most common type of cancer in the world and the third leading cause of cancer-related mortality, with more than 800,000 deaths per year (Zhang et al., 2016). In the last two decades, it has become the most "emerging" liver disease worldwide; despite the reduction in cases of viral hepatitis, changes in lifestyle led to the development of HCC (Masarone et al., 2018).

HCC is a biological complex and heterogeneous disease starting from etiologic factors. In addition to viral hepatitis are race, heavy alcohol use, cigarette smoking, obesity (particularly central/abdominal obesity), Diabetes Mellitus, aflatoxin B1, dietary habits, and iron accumulation (Wang et al., 2016; Bartolini et al., 2018). These risk factors for HCC usually induce an increase in the production of reactive species in the liver leading to oxidative stress; this fact has attracted the attention of many researchers investigating the relationship between oxidative stress and the development of HCC and the possibility of using antioxidants for treatment (Wang et al., 2016; Masarone et al., 2018; Uchida et al., 2020).

Evidence strongly indicates that oxidative stress could be sufficient to induce liver cancer. The mechanism of hepatocarcinogenesis-related oxidative stress involves modification of nuclear factor-erythroid 2 (Nrf2), regulation of antioxidant, phase II enzyme gene expression, DNA damage, lipid peroxidation, increased proinflammatory cytokines, depletion of DNA repair enzymes, p53 gene mutation, and mitochondrial dysfunction (Masarone et al., 2018; Raghunath et al., 2018; Uchida et al., 2020). Therefore, oxidative stress emerges as a villain in the development and progression of cirrhosis and promotes cancer cell dedifferentiation and the progression of different forms of cancer, including HCC (Bartolini et al., 2018).

In view of the evidence showing the involvement of oxidative stress in the development of hepatocellular carcinoma, researchers have turned their attention to the treatment of hepatocellular carcinoma with the use of antioxidants. This article seeks to conduct an integrative literature review to assess the role of antioxidants in the treatment of hepatocellular carcinoma.

2. Methodology

This work is based on the type of exploratory research with qualitative approach. The integrative review of the literature aims to detail the studies listed, their main results, for future repetitions by other researchers (Pereira et al., 2018). The work was carried out following the formulation of the guiding question, the research strategy, the selection of criteria and data extraction (Whittemore & Knafl, 2005).

The review was carried out using five main steps: planning; the database searching; literature selection, data mining, comprehensive literature analysis; and, finally, the strategies identification (Garcia et al., 2016). The review planning is described in Table 1.

Table 1. Planning for the review of use antioxidants in treatment of Hepatocellular carcinoma, studies *in vivo* and *in vitro*.

Issue	Description
Questions	What is reported in literature about use antioxidants in treatment of Hepatocellular carcinoma between 2010 and 2020 in study preclinical?
Keywords	"Antioxidant treatment AND Hepatocellular carcinoma AND *in vivo* induced by diethylnitrosamine"
Data Base	PuBMed and ScienceDirect
Type of documents	Scientific publications
Framework timeline	10 years (2010 to 2020)

Source: Authors.

The Table 1 summarizes the research planning to better conduct the research, reports the questions that guided the research, the descriptors used, the databases consulted, the research period as well as the types of documents used in the presentation of the results.

The search in the databases resulted in 130 articles from PubMed and 155 articles from ScienceDirect. The elimination parameters were to select the equals from one place and separate what is different in both, among them, those who had the title of the *in vivo* work and made with antioxidant compounds were selected. Since *in vitro* studies were discarded. In addition, another established criterion was to select the articles in which hepatocellular carcinoma was induced with diethylnitrosamine. After reading the abstracts, 30 articles were selected that fit the pre-established criteria. After reading the full 30 articles 18 were discarded for not having a dose of diethylnitrosamine or the dose of antioxidant administered and treatment time. Thus, in the end, 12 articles were used in this review.

3. Results and Discussion

3.1 Involvement of oxidative stress in the development of hepatocellular carcinoma

Oxidative stress is defined as a state of imbalance between the production of reactive oxygen species (ROS) and endogenous antioxidant capacity. Such imbalance is associated with the development of chronic diseases, including damage to essential organs such as the liver, in addition to being associated with the emergence of neurodegenerative diseases and cancer (Wang et al., 2016).

The most common ROS are the superoxide radicals ($O^{\cdot -2}$), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$), which have an oxidation capacity superior to molecular oxygen in its fundamental state. These compounds are formed during the metabolic reactions of organisms, inevitable for the metabolism of aerobic organisms (El-Sayed et al., 2015).

The process leads to the oxidation of biomolecules and the consequent loss of their biological functions, the manifestation of which is the oxidative damage against cells and tissues, leading to the development of an etiological process of numerous chronic diseases (Wang et al., 2016).

Exposure to oxidizing agents can lead to the activation of an important gene, p53, which has the function of repairing damage caused to cells. The activation and stabilization of p53 inhibits the progression of damaged cells (Sahu & Jena, 2011).

Research over the years has shown that a mutation in the p53 protein is associated with a wide variety of neoplastic diseases (Zhou, Hao & Lu, 2019). Mutations in the p53 protein may also be related to greater ease of development of metastasis, as well as to the poorer prognosis of the patient (Matsushita et al., 2012; Zhou, Hao & Lu, 2019).

The p53 protein and NF-κB act in several cell signaling pathways and are activated in response to numerous stimuli (Matsushita et al., 2012; Long et al., 2019). NF-κB was initially identified as a transcription factor involved in the inflammatory response; however, experimental evidence suggests that it regulates cell growth, survival, and apoptosis (Huang et al., 2016). The activated p53 protein induces the expression of several genes related to apoptosis and DNA repair (Long et al., 2019).

Constitutive activation of NF-κB, as well as mutations in the p53 protein, are frequently seen in several types of cancer. These changes are associated with greater survival of tumor cells, in addition to the development of metastasis, angiogenesis, and resistance to chemotherapy (Huang et al., 2016; Long et al., 2019).

The tumor suppressor protein p53 is a positive regulator of the proapoptotic proteins Bax, Bad and Bak, in addition to preventing the activation of the anti-apoptotic protein Bcl-2. Studies show that p53 promotes the transcription of Bax and Bak by activating the release of cytochrome c from mitochondria, resulting in cell apoptosis (Chiu et al., 2003). In addition, studies comparing knockout animals for hepatic p53 with normal animals show that hepatic p53 expression is a limiting factor between tumor regeneration and development. P53 knockout animals, when exposed to hepatotoxic agents, show a progression in tumor development, while animals with normal p53 expression show an increase in mitosis and liver regeneration (Huang et al., 2016; Long et al., 2019).

Although the liver is an organ with a high capacity for regeneration and has high levels of endogenous antioxidants capable of preventing damage caused by the excess of ROS, repeated exposures to oxidizing agents such as N-nitrous compounds can result in mutation in p53, leading to DNA damage and tumor progression (Khan et al., 2012).

Other stress response systems include the redox-sensitive transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2). This transcriptional element controls the expression of wide groups of genes included in detoxification and antioxidant defense. The oxidative stress promotes a high expression of Nrf2 and thus regulates proliferation, survival, and invasion processes in the tumor cells; this is observed in HCC with cellular proliferation and metastasis through the diminution of the apoptotic signaling pathway (Zhang et al., 2016; Raghunath et al., 2018).

Nrf2 is the primary governor of the antioxidant response pathway. During normal physiological conditions, KEAP1 acts as a negative regulator of Nrf2 and maintains a basal level of Nrf2. When activated, Nrf2 translocates to the nucleus, binding to specific AREs in the DNA, triggering the transcription of target genes (Zhang et al., 2019).

In the process of liver carcinogenesis, a chronic activation of Nrf2 is observed via interaction with the inhibitory protein of Nrf2 KEAP1; the integrity of this protein is essential to guarantee liver functionality. The processes that lead to an increase or decrease in the levels of the Nrf2 protein can sensitize or protect the cells against cell death induced by oxidative stress. On the other hand, mutations in the Nrf2 protein may be associated with loss of antioxidant detoxification capacity, as well as its chronic stimulation may favor its cytotoxic role, impairing the antioxidant balance. Thus, Nrf2 has been considered both as a tumor suppressor and oncogene (Hayes et al., 2010; Menegon, Columbano & Giordano, 2016).

Mutations in the constitutive activation of Nrf2 increase oncogenic potential and contribute to drug resistance. This fact shows how important it is to protect Nrf2 or its regulators such as KEAP1 from genotoxic damage to prevent the tumor process (Ngo et al., 2017).

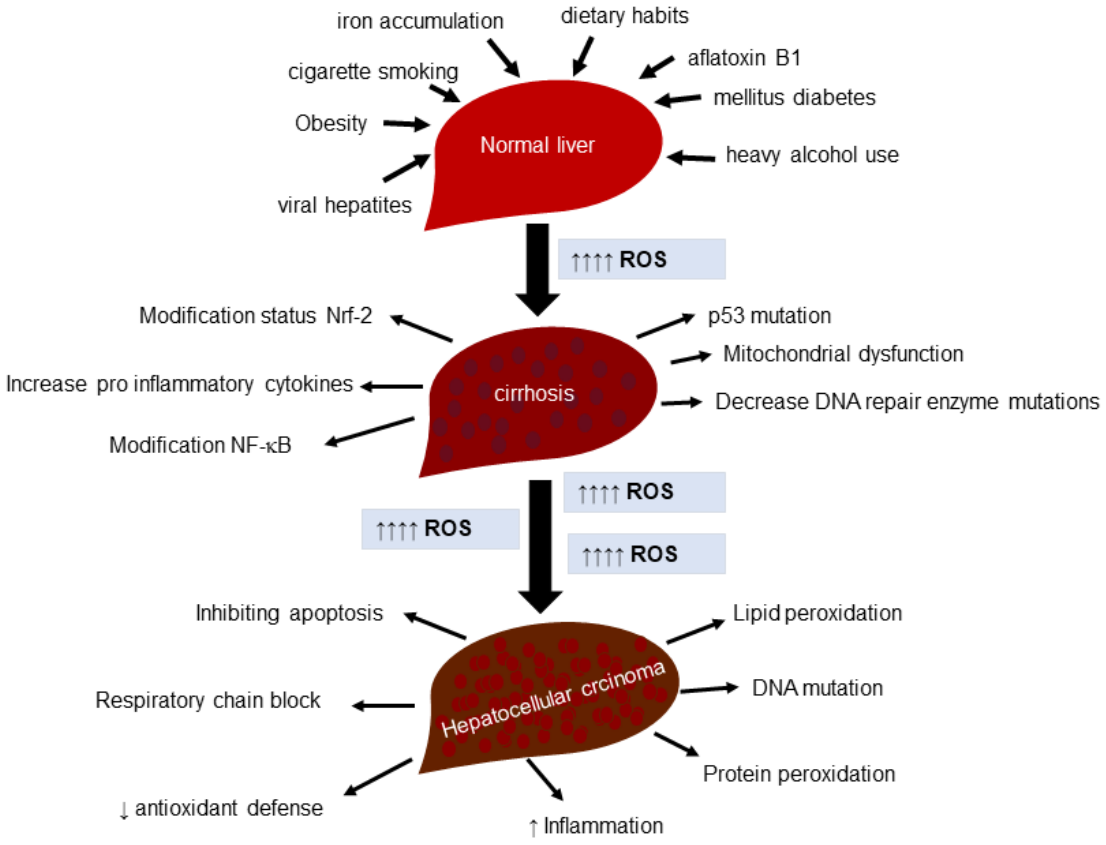
Chronic inflammation in the liver is an important factor in the development of HCC because it induces oxidative stress and results in production of proinflammatory cytokines interleukin (IL)-1β, IL-6, CXCL-8 and necrosis factor (TNF)-α.

This production increases atypical cytokines and the resulting ROS, leading to DNA damage and promotes hepatocarcinogenesis (Wang et al., 2016).

Research shows that mitochondrial dysfunction may be involved in oxidative damage of liver diseases. This dysfunction may be induced through mtDNA mutation by ROS and highly reactive aldehydes, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE), through lipid peroxidation following the interaction between ROS and polyunsaturated fatty acids. The inhibition of cytochrome C oxidase by MDA leading to mitochondrial uncoupling, which results in apoptosis or mutation that leads to cancer (Wang et al., 2016; Masarone et al., 2018).

Accumulating evidence has indicated that oxidative stress is associated with the development of hepatocellular carcinoma, but the mechanisms are not yet fully understood. Figure 1 show some damage-induction mechanisms via oxidative stress that can trigger HCC. Understanding the mechanisms of oxidative stress involved in the development of HCC is important because they would assist in the search for new therapeutic alternatives related to the administration of antioxidant substances.

Figure 1. Mechanisms of oxidative stress in the development of hepatocellular carcinoma. There are several risk factors for the development of hepatocellular carcinoma associated with an increase in the production of reactive oxygen species (ROS). First, there are changes that favor the development of cirrhosis that progresses to hepatocellular carcinoma. Nrf-2 (nuclear factor [erythroid-derived 2]-like 2), NF-κB (nuclear factor kappa B), DNA (deoxyribonucleic acid).



Source: Authors.

Figure 1 shows the oxidative mechanisms involved in the development of hepatocellular carcinoma, such as the involvement of Nfr-2, NF-κB and p53, in addition to the associated inflammatory process and the reduction in cellular antioxidant status. Therefore, based on scientific evidence, the use of antioxidants in the treatment of hepatocellular carcinoma ca be an interesting alternative, as discussed in the section antioxidants with potential therapeutic activity in hepatocellular carcinoma, which show clinical evidence.

3.2 Antioxidants with potential therapeutic activity in hepatocellular carcinoma

Recent studies show that the treatment of hepatocellular carcinoma (HCC) lies with antioxidant substances and results in the activation of apoptosis-related signaling pathways. Thus, some antioxidants may be potential candidates for the treatment of HCC since the main treatment includes surgical removal and liver transplantation. Surgical removal is of little hope for restoration to health, due to the poor prognosis and serious side effects (Zhang et al., 2012; Zhang et al., 2016).

Liver transplantation is considered to be the most effective treatment for patients with hepatocellular carcinoma. However, the low availability of organs limits the offer of this option to all candidates, and the high risk of recurrence after transplantation compromises its efficiency (Zhang et al., 2012).

Although several other studies demonstrate the importance of antioxidants associated or isolated in standard treatment or as adjuvants in HCC, there is still no drug on the market for antioxidants for the chemotherapeutic treatment of this type of cancer. Table 2 summarizes some *in vivo* studies with antioxidant compounds in HCC treatment induced for diethylnitrosamine (DEN).

Table 2. Preclinical trials of antioxidants in hepatocellular carcinoma. AT - Aristolochia tagala; CC - Curcuma caesia; DEN- diethylnitrosamine; HBVX - Hepatitis B Virus X Protein; 1,3-BPMU - Mannich Base (1,3-bis- ((3-Hydroxynaphthalen-2-yl) phenylmethyl)urea; PTE – Pterostilbene; ADE - Ajwa dates (Phoenix dactylifera L.); AAF - 2-Acetylaminofluorene.

Animals	HCC induced	Treatment	Conclusion	Reference
Female Sprague-Dawley rats weighing 65 to 85 g	Single i.p. injection of DEN (200 mg/kg), followed by promotion with phenobarbital (0.05% w/v) in drinking water, which started two weeks following DEN injection.	Food supplemented with resveratrol equivalent to 50, 100, or 300 mg/kg body weight/d. Resveratrol treatment was started four weeks before the initiation and continued for 20 weeks.	Resveratrol combats oxidative stress and suppresses inflammatory cascade in a dose-responsive fashion during DEN-induced rat liver carcinogenesis. This response could be mediated through transcriptional and translational regulation of Nrf2 signaling.	Bishayee et al., 2010
12-month-old HBx transgenic male mice	Hepatitis B virus (HBV)-associated hepatocellular carcinoma using HBVX protein (HBx) transgenic mice	Resveratrol (Sigma R5010; 30 mg/kg/d) was dissolved in H_2O and delivered to the mice by oral administration using a feeding needle once a day for 4 months.	Notably, in the HBx transgenic mice, there was a significant delay in liver carcinogenesis and a remarkable decrease in HCC incidence after receiving resveratrol for four months. Specifically, no grossly identifiable nodules could be detected in 15% of the precancerous HBx transgenic mice, whereas 55% the mice contained only small, 0.5 to 2.5 mm, hyperplastic nodules, and 15% of the mice contained 3 to 6 mm hyperplastic nodules that were later pathologically confirmed to be benign tumors.	Lin et al., 2012
Male and female B6C3 mice (21–25 days)	Single dose of DEN (1 mg/kg body weight) dissolved in sterile olive oil) at three weeks	Silibinin diet was introduced at 15 or 39 weeks, continuing for 9 weeks with or without ethanol drinking-water initiation at 16 or 40 weeks.	The effects of dietary silibinin, did not effectively inhibit hepatic tumor progression. Silibinin exerted marginal hepatoprotective effects in early stages of hepatocarcinogenesis, but when co-administered with ethanol, exacerbated the promotional effects of ethanol in HCC-bearing mice, but only in males.	Brandon-Warner, et al., 2012
Albino BALB/c mice, aged 6–8	DEN was administered by intravenous route at weekly intervals from week 10	AT 50 mg/Kg and CC 100 mg/Kg methanol extract. The exposures (to the AT or CC) were initiated from	This study suggested that CC and AT have anti-inflammation, anti-proliferative and anti-cancer properties, and that the active components of AT and	Hadem, Sharan & Kma, 2015

weeks	until the end of the experiment.	week 10 until the end of the experiment (weeks 16 or 28) by thrice weekly intraperitoneal injections.	CC may exert anticancer effects through the TNF-α-mediated NF-κB signaling.	
Male 150–170 g Wister albino rats (Rattus norvegicus)	A single-dose intraperitoneal (ip) injection of DEN (200 mg/kg/bw). Further, rats were administered phenobarbital (250 mg/kg/bw/day/orally for two weeks) as a cancer-promoting agent.	1,3-BPMU (50 mg/kg/bw/day/orally) up to the end of the experiment periods	Study showed that 1,3-BPMU maintained the architecture of the liver in DEN-induced rats and stimulates apoptosis via upregulation of caspase-3 and caspase-9, with downregulation of Bcl-2 and Bcl-XL gene expression. This investigation suggested that 1,3-BPMU might be considered a potent antitumor compound in the future. Further experiments are still needed to validate the molecular mechanism of action of 1,3-BPMU.	Vedarethinam, et al., 2016
C57 mice	Mice were injected with DEN plus CCl_4 to construct the HCC model, intraperitonially injected with DEN (200 mg/kg, BW) once, and two weeks later, mice were given a CCl_4 (3 ml/kg) injection three times a week for six consecutive weeks.	PTE 100 or 200 mg/kg for 20 weeks	The results showed that PTE inhibited tumor growth in vivo. PTE increased p53 expression, decreased SOD2 expression, and resulted in an increase in the ROS level and activation of the mitochondrial apoptotic pathway, leading to inhibition of tumor growth. Collectively, these data demonstrate that the p53/SOD2/ROS pathway is critical for PTE-inhibited tumor growth and HCC cell proliferation.	Guo et al., 2016
Swiss albino mice	100 mg/L of DEN in drinking water for eight weeks	Silybin 30 mg/kg body weight and nanoformulation of silybin equivalent to silybin dose were administered orally.	Silybin NP showed anticancer activity due to apoptotic-inducing property and cell cycle delay, thereby enhancing the survival of the tumor-bearing mice. The results of the present study seem quite promising and should be followed by the identification of the molecular mechanism regulated by the silybin NP to combat other cancers.	Zhang, Wang & Liu, 2016
Wistar rats weighing 250 ±	Administration of 0.01% DEN in	M. alba extract at a concentration of	The histological and biochemical findings demonstrated that treatment with mulberry extract	Kujawska et

15 g (12 weeks old)	drinking water for 13 weeks	10 g/kg feed for 13 weeks	partially suppressed DEN-initiated hepatocarcinogenesis and the appearance of pre-neoplastic lesions. Since the extract tested has been reported to possess strong free radical scavenging properties in vitro and we showed its ability to prevent oxidative damage of macromolecules in rats, it could be suggested that a direct antioxidant mechanism contributes to its anticarcinogenic activity. However, further research should be undertaken to examine whether the anti-inflammatory mechanism is also responsible for the chemopreventive effect.	al., 2016
Adult male rats (Wistar strain) weighing 170–200 g	Orally administered DEN (dissolved in 0.9% normal saline) with a dosage of 20 mg/kg body weight five times weekly for six weeks	Orally treated with a dosage of 50 mg gallic acid/kg body weight10 five times weekly for five weeks	Data in this study indicated a significant downregulation in the HSPgp96 gene expression level in the hepatic tissue in rats treated with gallic acid. Gallic acid offers a multitalented therapeutic approach in retracting the aggressiveness of HCC in rat model. The regulation of STAT3 signaling pathway via the outstanding bioactivities of gallic acid including antioxidant potential, anti-inflammatory effect, apoptotic action, and antitumor impact may be the probable mechanism by which it can offer its therapeutic action against HCC.	Agla et al., 2017
Male Wistar rats	DEN was dissolved in corn oil and two doses (180 mg/kg body weight (bw); at 15 days interval) were administered orally.	ADE 0.5 g/kg bw and 1.0 g/kg bw, daily for 10 weeks	Treatment decrease in liver enzymes ALT, AST and ALP, increase in antioxidant enzymes SOD, GR, GPx and CAT, and increased anti-tumoral cytokines (IL-2, IL-12) and decreased pro-inflammatory cytokines (IL-α, IL1β, GM-CSF). The anti-inflammatory, hepatoprotective and anticancer properties observed could be due to the presence of flavonoids such as luteolin, apigenin, quercetin, and proanthocyanidins	Khan et al., 2017

			in dates, which are rich in polyphenolic compounds.	
Male albino rats weighting 130–150g	Intraperitoneal injection of (200 mg/kg body weight) with N-diethylnitrosamine once weekly for eight weeks	Orally administered with isolated ursolic acid (500 mg/kg) after eight weeks given DEN	Ursolic acid plays a role in accelerating liver proliferation, recovering liver function, and protecting the integrity of hepatocytes against liver damage. Ursolic acid treatment revealed that it had antitumor activity, evidenced by the absence of cellular necrosis and inflammatory infiltrates in the liver section of rats. Ursolic acid is able to restore the biochemical and histological changes caused by the development of hepatocellular carcinoma.	Ali et al., 2019
Male Wistar rats, aged 4–5 weeks and weighing 140–160 g	The rats were fed with 0.03% AAF in daily diet.	The animals with HCC were treated containing 0.5%, 1% and 2% of NLE (w/w) for six months	NLE supplementation significantly alleviated AAF-induced hepatic injury and early hepatocarcinogenesis, which may result from decreasing AAF-induced inflammatory mediators and enhancing antioxidant enzyme expression.	Yang et al., 2019

Source: Authors.

Table 2 shows 12 preclinical studies conducted between 2010 and 2019 with the induction of hepatocellular carcinoma in rats through the administration of diethylnitrosamine and treatment with antioxidants. The antioxidants used in the studies were resveratrol, silibinin, silybin, gallic acid and plant extracts. The results of the studies show that the use of antioxidants modulates the hepatic oxidative status occurs mainly by altering the antioxidant enzymes SOD, GR, GPx and CAT, modifying the expression of the protein p53 and Nrf-2 and stimulates apoptosis via upregulation of caspase-3 and caspase-9, with downregulation of Bcl-2 and Bcl-XL gene expression. The inflammatory response is altered by the promotion of increseade anti-tumor cytokines (IL-2, IL-12) and decreased pro-inflammatory cytokines (IL-α, LI 1β, GM-CSF).

Therefore, the use of chemopreventive substances is emerging as a recent approach in the control of liver cancer. Chemoprevention measures are defined as the use of natural or synthetic substances capable of preventing, delaying, or reversing tumor development (Jayakumar et al., 2012). Recent studies with antioxidant substances show that, both *in vivo* and *in vitro*, these substances are able to activate the cell signaling pathways related to apoptosis in tumor cells without significantly affecting the survival of normal cells (Zhang et al., 2016). Among the main substances with chemopreventive potential are silymarin, resveratrol, quercetin, gallic acid, plant extract, and curcumin.

3.2.1 Silymarin

Silymarin is a mixture of polyphenols derived from the seeds of the Thistle plant (Silybum marianum). Popularly used for centuries as a hepatoprotective, it has been described as a hepatic elixir. Commercial preparations based on silymarin contain several flavonoids such as silybin (silybin A and B), isosilibinine (isosilibine A and B), silicristine, and silidianine; however, its main bioactive component is silybinin (Ahmad et al., 2018).

The great number of actions carried out by silymarin explains the reason why a lot of scientific studies have sought to understand how it acts in cases of tumors. The studies have shown in different oncological diseases, including hepatocellular carcinoma (HCC), that silymarin reduces cell vitality and runaway cell replication (Colturato et al., 2012; Federico, Dallio & Loguercio, 2017). It has already been used as an antidote in liver poisoning caused by acetaminophen with good results (Das, Roy & Auddy, 2011).

In different diseases, silymarin has been shown to be able to inhibit transcription factor NF-KB, which promotes decrease of proinflammatory cytokines IL-1 and IL-6 and changes the ratios of Bax/Bcl2 that supports apoptosis. In oxidative stress, silymarin may be able to direct free radical scavenging activity. Administration for four weeks, in Wistar rats, at doses conventionally used for therapeutic purposes in hypertransaminasemia would be able, in a model of CCl4-induced liver fibrosis, to reduce hepatocyte damage, oxidative stress markers, fibrosis score and tissue hyaluronic acid, and the activation of both HSC and Kupffer cells (Ramasamy & Agarwal, 2008; Das, Roy & Auddy, 2011; Clichici et al., 2015).

In an *in vivo* study, treatment with silybin-vitamin E-phospholipids complex for 12 weeks was able to reduce liver fibrosis in 35 patients who underwent liver biopsies (Loguercio et al., 2012). In an N-nitrosodiethylamine (NDEA)-induced rat model of HCC, studies show that the treatment with silymarin was able to efficaciously modulate different molecular patterns in an anticarcinogenic sense and reduce mitochondrial membrane potential probably associated with cytochrome c release in cytoplasm (Gopalakrishnan et al., 2013).

Indeed, silybin could interfere with the process of tumoral induction through inflammatory cascade regulation and by decreasing ROS genotoxic potential. Moreover, it could also interfere with tumor promotion by blocking most of the signaling pathways activated in HCC. Finally, silybin is able to improve the quality of life of patients who have undergone conventional treatment with Sorafenib in advanced forms of HCC (Federico, Dallio & Loguercio, 2017).

3.2.2 Resveratrol

Resveratrol (3,4′,5-trihydroxy-trans-stilbene) is a phytochemical found in several dietary sources, such as grapes, berries, peanuts, and red wine. It is best known as the compound to reduce the incidence of heart disease (Vidavalur et al., 2006), but in recent years, several studies have shown the antitumor potential of resveratrol.

Resveratrol significantly inhibited human hepatoma cell viability and induced apoptosis *in vitro* and showed efficacy *in vivo* in a xenograft model. The study of the molecule's mechanisms of action showed that it modified the MAPKs pathway and increased the p-JNK expression, which exerted pro-apoptotic functions; however, it decreased the p-ERK expression, which plays a cytoprotective role. The results suggest that resveratrol may be a potential therapeutic agent for hepatocellular

carcinoma (Xie et al., 2014). In other studies, using human HCC xenograft, data showed that resveratrol markedly reduced tumor size. Additionally, the immunohistochemical the expression level of p-c-Met and Ki-67 was evaluated, and the results showed a significant suppression of these proteins (Gao et al., 2017).

Resveratrol induced apoptosis and inhibited the proliferation, migration, and invasion of HCC cell lines (HepG2 and Hep3B). In addition, it inhibited MARCH1 and phospho-protein kinase B (p-AKT) expression but upregulated the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) dose dependently, both *in vitro* and *in vivo*. MARCH1 knockdown by small interfering RNA (siRNA) also increased PTEN expression. Meanwhile, MK2206 (an AKT inhibitor) and bisperoxovanadium (BPV; a PTEN inhibitor) combined with resveratrol decreased MARCH1 expression more than the single-treatment HCC group. These results suggested that resveratrol affects the biological characteristics of HCC via downregulation of MARCH1 expression (Dai et al., 2020).

Resveratrol was administered dietarily (50-300 mg/kg) in rats with HCC induced with DEN. The results showed elevated protein and mRNA expression of hepatic nuclear factor E2–related factor 2 (Nrf2). Also shown were attenuation of oxidative stress and suppression of inflammatory response mediated by Nrf2, which could be implicated, at least in part, in the chemopreventive effects of this dietary agent (Bishayee et al., 2010).

The regulation of activity of pro-apoptotic members of the Bcl-2 family could be a crucial for inhibition HCC. Studies showed that resveratrol inhibited Bcl-2 expression and concomitant up-regulated pro-apoptotic protein Bax, causing a significant decrease in Bcl-2/Bax ratio. The apoptosis regulators were further detected, and the precursor forms of caspase-3/7 induced by resveratrol were down-regulated in HCC cells. TUNEL assay revealed that resveratrol induced cell apoptosis by increasing HCC apoptosis rate. As a sirtuin (SIRT) 1 activator, resveratrol elevated SIRT1 protein expression and its enzyme activity and decreased expression levels of phosphorylated (p)-phosphoinositide-3-kinase (PI3K), p-AKT Serine/Threonine Kinase 1 (AKT), and its downstream target p-Forkhead Box O3a in HepG2 cells. Furthermore, inhibition of SIRT1 enzymatic activity by EX527 resulted in increased phosphorylation levels of PI3K and AKT. This demonstrated that resveratrol inhibited the PI3K/AKT pathway by SIRT1 activation (Chai et al., 2017).

Other studies showed that resveratrol inhibited the viability and mortality of HCC cells through inducing autophagy via regulating the p53 and PI3K/Akt pathways. Enhancing autophagy can augment the antitumor effects of resveratrol in HCC (Zhang, Yin & Sui, 2018).

3.2.3 Quercetin

Quercetin is a flavonoid present in vegetables, fruits, teas, and red wine, and represents one of the antioxidants of plant origin with the greatest antioxidant potential (Dajas et al., 2003). In its chemical structure, it has phenolic hydroxyl groups, which give them an antioxidant action with important therapeutic potential against many diseases including ischemic heart disease, arteriosclerosis, liver fibrosis, kidney damage, and chronic biliary obstruction. The use of flavonoids such as quercetin can prevent or slow the progression of liver fibrosis, reducing the action of free radicals, which are related to oxidative stress, responsible for liver damage (Peres et al., 2000; Tokyol et al., 2006). Therefore, other antioxidants can act in a similar way to quercetin in reducing liver damage, among which we can mention gallic acid and its ester derivatives.

Data of quercetin show that is a potent inhibitor of SHP2 catalytic activity and suppressed the expression of SHP2 in hepatocellular carcinoma cells. The upregulation of SHP2 expression has been reported in many human cancers; a decrease in SHP2 activity inhibits tumor cell growth and is a promising target for chemotherapy. Quercetin inhibited tumor progression by apoptosis, metastasis, and autophagy. The protective function of quercetin has proved to be closely related with JAK2 and STAT3 signaling (Wu et al., 2019). Quercetin enhanced the phosphorylation of signal transducer and activator of transcription

proteins 1 (STAT1), promoted endogenous IFN-α-regulated gene expression, and sensitized the antiproliferative effect of IFN-α on hepatocellular carcinoma HepG2 and Huh7 cells (Igbe et al., 2017).

3.2.4 Gallic acid

Gallic acid (3,4,5-trihydroxybenzoic acid) is one of the most putative polyphenols, it exists in pomegranate, grapes, nuts, green tea, oak bark, different berries, mango, as well as in red wines. Also, it is considered one of the major active compounds in tannins, known as galatotanin (Fernandes & Salgado, 2016).

Studies have shown that gallic acid has a variety of pharmacological actions, including antioxidant, anti-inflammatory, antimicrobial, antiviral, and antitumor activities (Locatelli et al., 2009). In animal models, gallic acid reduces oxidative stress and improves levels of glutathione (GSH), GSH peroxidase, GSH reductase, and GSH-S-transferase in liver tissue, as well as catalase (Giftson, Jayanthi & Nalini, 2010).

Gallic acid is known to induce cell death or cell cycle arrest in several tumor cell lines without affecting normal cells (Locatelli et al., 2009). A recent study showed that gallic acid and its ester derivative dodecyl gallate has important hepatoprotective activity against liver damage induced by carbon tetrachloride. Hepatoprotection is directly related to the modulation of oxidative balance and restoration in the expression of the p53 gene (Perazzoli et al., 2017).

In HCC rat model, treatment with gallic acid offers a multitalented approach in retracting the aggressiveness of HCC. We suggest that the regulation of STAT3 signaling pathway via the outstanding bioactivities of gallic acid, including antioxidant potential, anti-inflammatory effect, apoptotic action, and antitumor impact may be the probable mechanism by which it can offer its therapeutic action against HCC (Aglan et al., 2017). Studies in vitro show that gallic acid was able to inhibit the proliferation of HepG2 cells in a time- and dose-dependent manner. The effect of gallic acid in culture cell induced caspase-3, caspase-9 and reactive oxygen species activity, elevated the expression of apoptosis regulator Bcl-2-like protein 4, and reduced the mitochondrial membrane potential. When compared with HL-7702 normal human hepatocytes, gallic acid demonstrated selective toxicity for HCC cells (Sun et al., 2016). Similar effects were observed with propyl gallate one derivative of gallic acid; besides that, propyl gallate increased the intracellular levels of superoxide and reactive oxidative stress as well as the formation of autophagosomes and lysosomes in zebrafish model (Wei, Huang & Chang, 2019).

3.2.5 Plant extracts

Medicinal plants have long been used in the treatment of liver diseases or the maintenance of a healthy liver. In recent years, studies have shown several plants extracts with anti-tumoral activity included activity of treatment of HCC induced by diethylnitrosamine (DEN).

In recent years, *Smallanthus sonchifolius* (Yacon) has emerged as a potential anticancer agent. Previous in vitro studies indicated that the crude extract of Yacon and the phytochemicals derived from the plants exerted the cytotoxicity against breast cancer, colon cancer, and cervical cancer (Siriwan, Naruse & Tamura, 2011; De Ford et al., 2015; Kitai et al., 2017). The anticancer property and hepatoprotective effects were attributed to sesquiterpene lactones (Sandhu et al., 2010; Kitai et al., 2015). Yacon extract was found to show a potent inhibitory effect on liver cancer HepG2 cell survival with IC_{50} 58.2 ± 1.9 μg/ml, inhibiting the growth and migration in addition to inducing necrosis and cell cycle arrest (Sandhu et al., 2010).

Ashwagandha (Withania somnifera) is a natural herb that has been investigated in a wide range of conditions including as an anticancer agent (Prakash, Gupta & Dinda, 2002; Sandhu et al., 2010). Recent studies demonstrated that Ashwagandha water extract (ASH-WX) showed be a powerful antioxidant that can inhibit cancer cell growth (Jayaprakasam et al., 2003). ASH-WX showed a marked effect on the cells, causing shrinkage and accumulation of dead HepG2 cells when

compared with control untreated cells; it demonstrated a significant increase in the activities on total antioxidant glutathione S-transferase and glutathione reductase. The treatment of HCC cell reported an induction of apoptosis related to increase of Bim, t-Bid, and caspase-8 in addition to promoting a significant decrease in the concentration of TNF-α, but these results should be confirmed in animal studies (Ahmed et al., 2018).

Sclerocarya birrea (A. Rich.) Hochst., known as marula, is a savannah tree belonging to the Anacardiaceae family (Gouwakinnou et al., 2011) it is an important food and medicinal source (Hamza et al., 2006). Different parts of the plant are traditionally used. The fruits are eaten or processed to make beer or jam; the kernels are eaten or used for oil extraction; the leaves are used as forage for livestock; and the stem bark, root, and leaf extracts of S. birrea are used against human ailments (Gouwakinnou et al., 2011). It was also demonstrated that methanol and water root extracts have been shown in antioxidant activity. Moreover, water and acetone extracts of S. birrea stem bark showed anticancer and pro-apoptotic activities (Tanih & Ndip, 2013).

S. birrea methanolic root extract showed a high content of polyphenols, flavonoids, and tannins, presenting potent antioxidant activity when tested with superoxide, nitric oxide, ABTS, and beta-carotene bleaching assays. The anti-tumoral effect of S. birrea methanolic root extract was evaluated on the hepatocarcinoma cell line HepG2 and was observed to have an important capacity on induced apoptosis and generated reactive oxygen species (ROS) in dose-dependent manner. Moreover, it induced mitochondrial membrane depolarization and cytochrome c release from mitochondria into the cytosol. It suggests that the apoptosis occurred in a mitochondrial-dependent pathway. S. birrea methanolic root extract was evaluated in normal human dermal fibroblasts and showed selectively, being less toxic to normal cells when compared with hepatocarcinoma cell (Armentano et al., 2015).

Mushrooms and truffles have been part of culinary culture since antiquity; they have been used in traditional Chinese medicine for dozens of centuries. Later adopted by Western medicine, mushrooms are now emerging as possible natural products for the treatment of conditions such as obesity, Type 2 Diabetes Mellitus, and liver diseases (Chaturvedi et al., 2018). Mushrooms are a rich source of bioactive compounds known for their modulatory activities on the gut microbiota and enteric absorption, their antioxidant activity and their pro-apoptotic action; they seem like interesting candidates for HCC therapeutics (Jayachandran, Xiao & Xu, 2017).

Mushroom extracts or isolated compounds have the capacity to induce apoptosis in HCC cell lines and in vivo xenograft models via the mitochondrial pathway, increase the pro-apoptotic Bax to anti-apoptotic Bcl-2/Bcl-xL ratio and facilitates the induction of MOMP and subsequent CYC, HtrA2/Omi and Smac release into the cytosol, leading to a decrease in DYm and the activation of caspases (Wang et al., 2016; Yang et al., 2018; Liu et al., 2018; Chen et al., 2019). PARP cleavage was also observed upon treatment with either isolated compounds or extracts (Wang et al., 2016; Yang et al., 2018). Further, promoting the activation of mitochondrial-related apoptosis pathway leads to cell death in the HCC cell lines and tumor size regression in *in vivo* xenograft models (Liu et al., 2018; Chen et al., 2019). Other studies also observe, in an HCC cellular model (Huh7), upon treatment with an extract rich in triterpenes and an isolated triterpene (GL22) from Ganoderma leucocontextum, upregulation of p53 (Liu et al., 2018). Modulation of pathways crucial for cell survival seem to be related to the pro-apoptotic effects observed in HCC cell lines and in *in vivo* xenograft models (Fontes et al., 2019).

Ginkgo biloba extract (EGb) is an herbal supplement obtained from the leaves of the Ginkgo tree. Ginkgo has been extensively administered over centuries in traditional Chinese medicine. Studies show that Ginkgo biloba extract contains flavone glycosides (primarily quercetin, kaempferol, and isorhamnetin) and terpene lactones (Bonassi et al., 2018).

Recently, it has been reported that antioxidant properties of Ginkgo biloba induce hepatoprotective effects in non-malignant liver injuries (Yuan et al., 2007; Zhang et al., 2015) as well as preventive effects against liver tumor initiation (Wang et al., 2020). Due to its antioxidant and cytoprotective properties, it is administered for the prevention and treatment of

a variety of diseases such as cognitive function disorders, peripheral blood flow insufficiency, tinnitus, and vertigo (Li et al., 2018; Thancharoen et al., 2019). The active constituents of EGb seem to exert its effects through interaction with multiple molecular mechanisms and signaling pathways. ERK1/2-signaling and cell cycle control gene-dependent regulation has been proposed in gastric cancer (Liu et al., 2015), steroidogenesis pathways and aromatase activity in breast cancer cells (Zhou et al., 2020), the mitochondrial pathway of apoptosis in melanoma (Cao et al., 2019), or STAT3-activity in prostate cancer cells (Jeon et al., 2015) has been described.

Czauderna et al., 2018 observed that hepatoma cell lines, primary human HCC cells and immortalized human hepatocytes exposed to various concentrations (0–1000 μg/ml) of EGb promotion have anti-proliferative and pro-apoptotic effects, mainly in hepatoma cells. Consistently, EGb treatment caused a significant reduction in colony- and sphere-forming ability in hepatoma cells and no mentionable changes in immortalized human hepatocytes. Transcriptomic changes involved oxidative stress response as well as key oncogenic pathways resembling Nrf2- and mTOR signaling pathway. The treatment confers protective effects in non-malignant cells; EGb significantly impairs tumorigenic properties in cancer cells by affecting key oncogenic pathways. Results provide the rationale for clinical testing of EGb in preventive and therapeutic strategies in human liver diseases.

EGb exerts an anticancer effect on HepG2 cells by activating p53 and inhibiting nuclear factor NF-κB signaling pathways. This study confirms that EGb inhibits proliferation and triggers apoptosis of HCC cells through the NF-κB/p53 signaling pathway (Wang et al., 2020).

Troxerutin (TXER), a natural compound extracted from horse chestnut or wild chestnut, has the ability to restore enzymatic activities and the architecture of liver cells. TXER significantly reduced DNA damage induced by DEN, cell proliferation, inflammation, fibrosis, and liver hyperplasia (Subastri et al., 2018).

3.2.6 Curcumin

Curcumin (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione) is a yellow-colored polyphenol obtained from turmeric (Curcuma longa) that has been known for thousands of years for its pharmacological activities (Matzorou et al., 2018) and has been demonstrated to exert effective antiangiogenic, anti-inflammatory, antioxidant and antitumoral effects (Abrahams et al., 2019). In model of xenograft tumor, the curcumin was administered in animals at a dose of 50, 100 mg/kg daily for two weeks. The results demonstrated that curcumin inhibited HCC proliferation in vivo by inhibiting VEGF expression and the phosphoinositide 3-kinase (PI3K)/AKT serine/threonine kinase 1 (AKT) signaling pathway (Pan et al., 2018).

In vitro studies with curcumin encapsulated in nanoparticles of chitosan or silica showed that encapsulation of curcumin was able to improve the stability of curcumin, in addition to increasing cytotoxicity in hepatocellular carcinoma (Hep G2) cells and could be considered a new drug for treatment of hepatocellular carcinoma (Kong et al., 2019).

Other studies have shown that curcuma oil shows promising properties for hepatoprotection in Con A-induced injury and for a chemotherapeutic effect against inoculated hepatoma in mice. It retains anti-inflammation, anti-oxidation, and antitumor properties while adding potential advantages: multiple target effects and fewer side effects. Furthermore, it may be useful for hepatoprotection, HCC chemoprevention, and for cancer patients as a long-term maintenance drug to prevent tumor recurrence (Li et al., 2014).

In a pilot study, patients with HCC were administered a dose of 4 g curcumin associated with 40 mg piperine and 500 mg taurine daily for three successive treatment cycles, each was 30 days. Patients were followed-up for a period of 24 months, and the study found a significant decrease in the levels of serum IL-10 and miR-21, while it resulted in a non-significant upregulation of serum miR-141 expression level. At the end of the follow-up period, the median overall survival (OS) rate was

found to be 17.00 months with a worse OS in patients with high baseline levels of circulating IL-10 and miR-21 compared to those with low levels. In contrast, a low baseline level of circulating miR-141 was associated with poor prognosis (Hatab et al., 2019).

4. Conclusion

Several *in vitro* studies show the important antitumor effect of several antioxidants in the treatment of hepatocarcinoma. In recent years, animal studies have demonstrated the antitumor effects of some antioxidants in the treatment of chemically induced cellular hepatocarcinoma; however, clinical trials are still deficient.

Despite the large number of preclinical studies dealing with different aspects of the biological effects of resveratrol, its translation to clinics for cancer therapies is far from reality due to a variety of challenges.

Studies with gallic acid also show its antitumor potential in the treatment of cellular hepatocarcinoma; however, clinical trials have not yet been conducted to demonstrate its effectiveness in humans.

Numerous studies with plant extract rich in phenolic compounds including quercetin, resveratrol, and gallic acid have also shown, in preclinical trials, the antitumor effect in the treatment of cellular hepatocarcinoma. However, the treatment of cellular hepatocarcinoma with antioxidants still seems to be a great challenge.

Future studies could be conducted to evaluate the efficacy in the clinical treatment of hepatocellular carcinoma, especially with three antioxidants that are already on the market as drugs and have shown promise in preclinical studies, silymarin, curcumin and resveratrol. Silymarin is used in the treatment of liver disease and is safe, however, as a chemotherapeutic agent it has only been tested in preclinical trials. Curcumin is a phytotherapic used clinically in the treatment of osteoarthritis and inflammatory diseases, proving to be safe, however there are no clinical trials that prove its effects in the treatment of hepatocellular carcinoma. Resveratrol is a medicine used clinically in the prevention of cardiovascular diseases and which has an important antioxidant action, without clinical trials showing its action in the treatment of hepatocellular carcinoma.

Conflict of Interest:

The authors declare no conflict of interest.

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