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CURCUMIN AND CAPSAICIN: FROM SPICES TO CANCER-SUPPRESSING AGENTS

CURCUMINA E CAPSAICINA: DE ESPECIARIAS A AGENTES SUPRESSORES DE CÂNCER

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ABSTRACT
It is currently accepted that the inflammatory cascade plays a fundamental role in the tumor cell development stages, being the inflammation process linked to tumor progression and dissemination. In this context, natural products (NPs) represent potential anticancer drugs due to their ability to interact with several immunological mediators and, therefore, ability to produce an immunomodulatory response. To elucidate the potential roles of curcumin and capsaicin as cancer-suppressing agents, presenting the recently published laboratorial and clinical researches. In this review it will be addressed the effects of both these NPs in relation to pancreatic, gastric, breast, lung and prostate cancer. A bibliographic review was performed on the Pubmed (Medline) and Scientific Electronic Library Online (Scielo). The inclusion criteria consisted of articles written in English and published between the years of 2000 and 2020. Curcumin and capsaicin demonstrated to be able to modulate multiple important molecular targets that are responsible for cancer development. *In vivo* and *in vitro* studies elucidated that the NPs acted in many signaling pathways on the different types of cancer, causing antiproliferative, antisurvival, and antimigratory effects on a variety of cancer cell lines. This review concluded that both curcumin and capsaicin are effective compounds on preventing and treating the neoplasms studied. However, the applications of this phytochemicals on humans are still limited and in need for more studies.

KEYWORDS: Capsaicin. Curcumin. Plant extracts. Antitumor agents. Cancer.

RESUMO
Atualmente aceita-se que a cascata de inflamação tem um papel fundamental nos estágios de desenvolvimento da célula tumoral, sendo a inflamação um processo ligado a progressão e disseminação do tumor. Nesse contexto, compostos naturais representam drogas potenciais contra o câncer por sua habilidade de interagir com diferentes mediadores inflamatórios e, assim, capacidade de produzir uma resposta imunomoduladora. Esse estudo buscou elucidar o potencial da curcumina e da capsaicina como agentes supressores tumorais apresentando estudos laboratoriais e clínicos recentemente publicados. Assim, nessa revisão foi levantado os efeitos de ambos os compostos mencionados em relação aos cânceres de pâncreas, de estômago, de mama, de pulmão e de próstata. Trata-se de uma revisão bibliográfica realizada nas bases de dados do PubMed (Medline) e *Scientific Electronic Library Online* (Scielo). Os critérios de inclusão consistiram em artigos escritos

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em inglês e português publicados entre os anos de 2000 e 2020. Curcumina e capsaicina demonstraram ser capazes de modular múltiplos alvos moleculares importantes que são responsáveis pelo desenvolvimento de cânceres. Estudos *in vivo* e *in vitro* elucidaram que estes compostos naturais agiram em diversas vias de sinalização nos diferentes tipos de cânceres, causando efeitos antiproliferativos, antisobrevivência e antimigração em uma variedade de linhagens celulares cancerígenos. Com base na revisão deste artigo, concluiu que tanto a curcumina quanto a capsaicina são compostos efetivos na prevenção e tratamento das neoplasias estudadas. Entretanto, as aplicações destes fitoquímicos em humanos ainda são limitadas, havendo a necessidade de mais estudos.

PALAVRAS-CHAVE: Capsaicina. Curcumina. Extratos vegetais. Antineoplásicos. Câncer.

1 INTRODUCTION

According to the World Health Organization (2018), cancer is the second leading cause of death around the globe, being held accountable for an estimated value of 9.6 million deaths in 2018. Still, new evidence suggests that approximately one third to half of cancers could be prevented by a healthier lifestyle, by reducing alcohol consumption, eliminating tobacco use, practicing physical activities, maintaining a body mass index (BMI) between acceptable limits, keeping a healthy diet, among others (AREM & LOFTFIELD, 2017). Furthermore, the better understanding of cancer development and progression improved screening and treatment over time, which lead to greater survival rates (AREM & LOFTFIELD, 2017). Nevertheless, despite the innumerous efforts around the world into finding an effective method of treatment for different cancer types, the available therapeutic alternatives, such as chemotherapy, keeps facing challenges regarding its efficiency on inhibiting or delaying tumor progression and reducing the amount of side effects (YOUNG & SIMMONS, 2014; BALDO & PHAM, 2013). Hence, the search for new anticancer drugs has never been so necessary and natural compounds widely used in culinary and folk medicine became an interesting option to overcome those challenges.

Diverse and complex natural products have yielded effective compounds for the discovery of new drugs. Natural products that are well tolerated and have less toxicity will help patients to achieve better treatment outcomes and improve their quality of life. Many natural products have exhibited excellent biological activities against inflammation, viruses, bacteria, tumors, etc (OLIVEIRA et al., 2017; MIYATA, 2007; SINGH et al., 2008; MAO et al., 2017; SHARMA et al., 2018).

It is already well established that there is a connection between inflammation and the progression of cancer (BALKWILL & MANTOVANI, 2001). Currently, it is accepted that the inflammatory cascade plays a fundamental role in the different stages of tumor cell development (HAMARSHEH & ZEISER, 2020). In addition, cancer cells produce numerous agents and factors that are responsible for attracting other inflammatory cells such as neutrophils, dendritic cells, macrophages, eosinophils, mast cells and lymphocytes to the site in question (COUSSENS & WERB,

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2002). And, due to the capacity that these cells have to produce cytokines, interleukins, interferons, tumor necrosis factor (TNF)-α, cytotoxic mediators (such as reactive oxygen species), matrix metalloproteinases (MMPs); there is a strong trend of tumor progression and dissemination (COUSSENS & WERB, 2002). In this context, natural products (NPs) form the basis for many widely used drugs. NPs represent potential anticancer drugs due to their immunomodulatory capabilities, which interact with several immunological mediators (WANG et al., 2018; KHALID et al., 2016; TEWARY, GUNATILAKA, SAYERS, 2017; DUTTA et al., 2019).

This review aims to elucidate the potential roles two NPs, curcumin and capsaicin, as cancer-suppressing agents, presenting the recently published laboratorial and clinical research.

2 METHODOLOGY

The information compiled was based on a survey at MedLine (Pubmed) and Scielo platforms. Only publications in English were included, and the time interval adopted was from 2000 to 2020. The following keywords combinations were applied: curcumin and capsaicin, capsaicin cancer suppressing, curcumin cancer suppressing, curcumin and cancer, curcumin and inflammation, inflammation progression cancer, pancreatic cancer and curcumin, pancreatic cancer and capsaicin, gastric cancer and curcumin, gastric cancer and capsaicin, curcumin and prostate cancer, capsaicin and prostate cancer, curcumin and lung cancer, capsaicin and lung cancer, curcumin and breast cancer, capsaicin and breast cancer. A total of 96 articles were gathered and analyzed.

3 DEVELOPMENT

3.1 Natural Products: Curcumin and Capsaicin

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), first isolated by Vogel and Pelletier in 1815, is a secondary metabolite isolated from the rhizomes of Turmeric (Curcuma longa) (PRASAD et al., 2014; KOTHA & LUTHRIA, 2019). Turmeric is a common spice used in the preparation of curries in Asian culinary, and, historically, it has been used as an insect repellent and an antimicrobial agent (MOGHADAMTOUSI et al., 2014). In folk medicine, it is also used to treat several pathologies including wound healing, respiratory problems, liver, and dermatological disorders (GOEL, KUNNUMAKKARA, AGGARWAL, 2008; ARAÚJO & LEON, 2001).

Recent studies demonstrated that curcumin is responsible for modulating multiple signaling pathways such as the transcription factor nuclear factor kappa B (NF-kB) (GHASEMI et al., 2019), which is responsible for cell survival, cytokine production and other cellular functions. It has been previously reported that curcumin inhibits the phosphorylation and nuclear translocation of the NF-kB p65 subunit, leading to suppression of its activity (GIORDANO & TOMMONARO, 2019). Furthermore, curcumin also modulates the different stages of cancer initiation, promotion, and progression due to its antioxidant properties, such as reactive oxygen species (ROS) inhibition, and its anti-inflammatory

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action (PULIDO-MORAN et al., 2016). As a result, curcumin has been extensively studied in the last few years regarding its potential role as a cancer-suppressing agent.

Regarding to capsaicin (trans-8-methyl-N-vanylyl-6-nonenamide), it is known that is a NP, derivative of homovanillic acid, which is responsible for the particular peppery taste present on the genus Capsicum (CHAPA-OLIVER & MEJÍA-TENIENTE, 2016). Capsaicin is extensively used as a food additive in culinary and in pharmaceutical applications (CHAPA-OLIVER & MEJÍA-TENIENTE, 2016), as well as is the main ingredient of the "pepper spray", often used by security forces to control civil unrest and in some countries for self-defense (BODE & DONG, 2011). Still, although this plant and its analogs have been used medicinally and therapeutically for centuries, it was only in recent decades that its numerous analgesic, antioxidant, anti-inflammatory and anti-obesity properties have been reported through several studies (FRIAS & MERIGHI, 2016; SRINIVASAN, 2016; ZHANG et al., 2020).

In recent years, capsaicin has shown a new medicinal potential: its anticancer activity, not only against a specific type of cancer, but for a variety of them (CHAPA-OLIVER & MEJÍA-TENIENTE, 2016). Studies have provided solid grounds that capsaicin could be a potential antitumor compound for a wide range of cancers, including breast cancer, lung cancer, gastric cancer, liver cancer, bladder cancer and others (SHARMA, VIJ, SHARMA, 2013; CHAKRABORTY et al., 2014).

In this review we will address the effects of curcumin and capsaicin in relation to pancreatic, gastric, breast, lung and prostate cancer.

3.1.1 Pancreatic Cancer

Pancreatic cancer is still one of the deadliest cancers around the globe. Accordingly, to the American Cancer Society (2020), pancreatic cancer is responsible for 7% of all cancer deaths in the US. In Brazil, the statistics are not so different, with pancreatic cancer being held accountable for 4% of all cancer deaths according to the Instituto Nacional do Câncer (2020).

The current treatments for pancreatic cancer involve chemotherapy, with gemcitabine being the most commonly used agent when the cancer is locally advanced or metastatic (MIZRAHI et al., 2020). However, this treatment has several limitations, side effects, and recently pancreatic cancer cells resistant to gemcitabine have been identified on certain types of pancreatic cancer such as pancreatic ductal adenocarcinoma (YOSHIDA et al., 2017). Natural compounds like curcumin and capsaicin are becoming an interesting alternative not only as a complement to the standard treatment but also as alternative treatment.

Curcumin acts on several different cell pathways, some of them are related to the ROS, which are important to tumor proliferation, migration and invasion (NISHIKAWA et al., 2009). Recent studies demonstrated, *in vitro*, that curcumin associated with N-acetylcisteine were able to inhibit H2O2-induced reactive oxygen species production, reduced migration and invasion of human pancreatic

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cancer cells (CAO et al., 2016). Despite the promising results, the curcumin's clinical application in therapy is still very limited because of the compound's poor bioavailability in the body due to its insolubility in water and chemical structure alterations when it enters in the circulation (NAGARAJU et al, 2019).

In order to overcome those unfortunate chemical characteristics, the researchers started to explore curcumin analogs both natural like Bisdemethoxycurcumin and synthetic like the FLLL11 and FLLL12. The natural analog, Bisdemethoxycurcumin, when combined with gemcitabine, induced the greatest mitochondrial dysfunction and apoptosis in some pancreatic cancer cells lines (YANG et al., 2016). The synthetic analogs, FLLL11 and FLLL12, on the other hand, were proved to be more effective than the original compound in inhibiting cell viability and inducing apoptosis on pancreatic cancer cells (FRIEDMAN et al., 2009). Literature data also demonstrated that pancreatic ductal adenocarcinoma cells resistant to gemcitabine were able to be re-sensitized by the action of curcumin due to its inhibition of the PRC2-PVT1-c-Myc axis, making curcumin an attractive compound to overcome chemoresistance in pancreatic cancer (YOSHIDA et al., 2017).

Capsaicin, like curcumin, is an interesting natural compound that can work in synchrony with the chemotherapy agent gemcitabine. A study testing the possible antitumor activity of several bioactive food components, observed that capsaicin when applied together with resveratrol had a synergetic effect with gemcitabine, enhancing its apoptosis efficacy in a pancreatic adenocarcinoma cell line called CAPAN-2, a cell line that is less sensitive to gemcitabine than the BXPC-3 cell line, which was also used in the study and had a better treatment response to the combination between resveratrol, capsaicin and gemcitabine than to the treatment with gemcitabine alone (VENDRELY et al., 2017). Moreover, the combination between capsaicin and resveratrol was able to increase the radiosensitivity on pancreatic ductal adenocarcinoma cells, which lead to a significant tumor volume reduction in a xenografted mouse preclinical model, however, the same results were not observed in radioresistant tumor cells (VENDRELY et al., 2019).

Furthermore, capsaicin alone is also a promising antitumor agent because studies, *in vivo*, observed that capsaicin when given orally suppressed the growth of pancreatic tumor xenografts in athymic nude mice without any side effects with increased apoptosis that was mediated by the generation of ROS and mitochondrial death pathway (ZHANG et al., 2008). Although clinical studies are still pending, these results bring hope to new and more natural treatments of one of the deadliest cancers around the globe.

3.1.2 Gastric Cancer

Gastric cancer is one of the most common and deadly neoplasms in the world, with both its incidence and mortality being highly variable by the affected stomach region and highly dependent on diet and Helicobacter pylori infection (RAWLA & BARSOUK, 2019). Its etiology is multifactorial, although the infection by the bacteria H. pylori is considered to be the primary cause of this type of

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cancer (RAWLA & BARSOUK, 2019; CORREA, 2013). Treatment currently includes mainly surgery and chemotherapy, although recent clinical trials data on the efficacy of immunotherapy have demonstrated its potential as an alternative treatment option, especially in patients with advanced gastric cancer stages (PARK et al., 2018).

Studies demonstrate that curcumin can act in different ways to regulate tumor growth. This compound has been shown to be able to inhibit the proliferation of SGC-7901 gastric cancer line cells (LIU et al., 2016; ZHANG et al., 2020) by downregulating the c-Myc/H19 pathway, which is capable to directly inhibit the tumor suppressor gene p53 activation and therefore promote gastric cancer progression (LIU et al., 2016). Additionally, curcumin has also been shown to induce apoptotic cell death and protective autophagy in human gastric cancer cells, *in vitro* (LI et al., 2017); down-regulate phosphatidylinositol-3 kinase (PI3K), protein kinase B (p-Akt), and phosphorylated mammalian target of rapamycin (p-mTOR) pathways, all responsible for promoting cell growth and survival (FU et al., 2018); and inhibit oncogenic pathways, both *in vitro* and *in vivo*, accompanied by significant gastrin downregulation and hypoacidity in the stomach (CAI et al., 2009; ZHOU et al., 2017).

Further investigation reported curcumin enhances the anti-cancer effects of 5-fluorouracil plud cisplating (FP) therapy in human gastric cancer AGS and MGC-803 cells through cancer cells growth inhibition, resulting in a synergic drug when combined with chemotherapy (KOO et al., 2004; HE et al., 2017). Therefore, curcumin and its analogs have been reported to play an anti-cancer role in gastric tumor models through multiple antitumor mechanisms, such as suppressing multiple signaling pathways, inhibiting cancer cell proliferation, inducing apoptosis and reducing chemotherapy-resistance.

In reference to capsaicin, this compound has been shown to suppress proliferation and induce apoptosis *in vitro* in a dose-dependent manner, due to modulation of apoptotic proteins including the elevation of cleaved caspase-3 expression and the reduction of B-cell lymphoma 2 (Bcl-2), as well as modulate Mitogen-Activated Protein Kinase (MAPK) signaling in human gastric cancer cells, a pathway involved in cell proliferation, cell differentiation, and cell death, being an essential pathway for cell survival and growth during carcinogenesis (PARK et al., 2014).

Nevertheless, further investigation indicated that capsaicin induces apoptosis in human adenocarcinoma cells (AGS) through upregulating p53, and that the ability of capsaicin to induce the expression of proapoptotic proteins such as Bax, caspase-3 and caspase-8 was almost completely obliterated by knocking down p53, which implies the apoptotic activity of capsaicin is p53-dependent (SARKAR, BHATTACHARJEE, MANDAL, 2015).

Furthermore, latest studies have illustrated two other capsaicin anticancer mechanisms. The first one consists of capsaicin's anti-metastatic potential against gastric cancer, achieved by inhibiting the transforming growth factor beta (TGF-β) signaling pathway, a key player in the metastasis induction. The anti-metastatic mechanism unlike the apoptosis one previously mentioned is independent of p53 or p21, even though it was found to be dependent on SMAD family member 4

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(SMAD4) (SARKAR et al., 2020). Whereas the second mechanism is significantly suppressing cell growth, while altering histone acetylation. It can also restore hMOF - a major histone acetyltransferase for H4K16 with reduced activity in gastric cancer tissues - activity *in vivo* and *in vitro* (WANG et al., 2016). However, previous studies have demonstrated that capsaicin induces divergent effects on cancer growth depending on the gastric cancer cell line, such as the down-regulation of tumor-associated NADH oxidase (tNOX) mRNA and protein on SNU-1 cells or tNOX expression being hardly affected on TMC-1 cells (WANG et al., 2011), that being a relevant point to be taken in consideration since capsaicin may lead to significant cytotoxicity and apoptosis or low cytotoxicity and very little apoptosis depending on the cell line. Also, current evidence suggests capsaicin plays a part in gastric cancer carcinogenesis if combined with *Helicobacter pylori* infection. When associated, capsaicin and *H. pylori* synergistically contribute to accelerated differentiated epithelial cell types loss, leading to chronic gastritis and gastric tumorigenesis in a mouse model, reportedly caused by an unbalance between Th1 and Th2 immune responses, more specifically by interleukin 6 (IL-6) stimulation and interferon gamma (IFN-γ) inhibition (AZIZ et al., 2020).

Hence, capsaicin's role in gastric cancer carcinogenesis still remains controversial. Several evidences previously mentioned pointed out the anti-carcinogenic and anti-inflammatory effects of this compound. In contrast, capsaicin also reportedly plays a part in favor of carcinogenesis when combined with *H. pylori* infection, as well as can exhibit only modest anti-cancer effects depending on the gastric cancer cell line.

3.1.3 Breast Cancer

Breast cancer is the second most incident tumor in the world, accounting for about 2 million new cases in 2018. In addition, it is the fifth leading cause of overall cancer death, totaling approximately 626,000 deaths in the same year (GLOBOCAN, 2018). Despite being a heterogeneous disease that converges in a broad clinical morphological spectrum, there is a consensus that the development of the different subtypes of this carcinoma is based on the signaling of pathways regulated by genetic and hormonal aspects, mainly focused on the expression of the estrogen receptor (ER), the progesterone receptor (PgR), the human epidermal growth factor receptor 2 (HER2) and Ki-67 (RAKKA & GREEN, 2017).

The release of reactive oxygen species (ROS) during the inflammatory process triggers cellular stress capable of altering signaling pathways, playing an important role in tumor progression. The research by Onoda and Inano (2000), showed that mammary glands of female wistar-MS rats stimulated with estrogen and progesterone in a culture with lipopolysaccharide (LPS), when treated with curcumin, showed inhibition of nitric oxide production (NO) and the inducible nitric oxide synthase (iNOS). Still, the study by Khorsandi et al. (2018), demonstrated that the Layered double hydroxide (LDH) curcumin associated with photodynamic treatment (PDT) in the human breast cancer cell line MDA-MB-231, mediated a positive increase in intracellular ROS and lactate dehydrogenase release,

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promoting the cytotoxic and antiproliferative effect, inducing apoptosis, autophagy and arrest of the G0/G1 cell cycle.

The nuclear factor kappa-B (NF-κB), regulates the activation of numerous inflammatory pathways which are excellent promoters of carcinogenesis. Evidence demonstrates that the mesenchymal epithelium transition (EMT) is an important stage in terms of tumor progression and metastasis (CREIGHTON; CHANG; ROSEN, 2010). In this sense, Huang et al. (2013) showed that when triggering EMT via LPS in MCF-7 and MDA-MB-231 breast cancer cell lines, curcumin treatment decreased the expression of the vimentin marker and increased E-caderin (marker and protein associated with cytoskeleton remodeling and responsible for the tissue invasion process), reflecting on the control of invasiveness, *in vitro*, through NF-κB-negative signaling pathway.

It is known that the binding of estradiol to the ER, can activate complex altered nuclear signaling and gene transcription pathways, leading to uncontrolled cell proliferation, alteration of cycle control and inhibition of apoptosis, progressing to tumor initiation (YAGER; DAVIDSON, 2006). Based on this pathological scenario, associated with the theoretical support of previous studies regarding the potential antitumor action of curcumin, investigations, *in vivo*, demonstrated that Female Augustus Copenhagen Irish (ACI) rats that received polymeric curcumin implants, reduced their multiplication rates and tumor volume, this decrease being attributed to the modulation of the activity of liver CPP450s enzymes, thus resulting in a greater amount of non-cancerous estradiol metabolites (BANSAL et al., 2014).

Capsaicin can also be applied to tumor control since its activity can result in the cell cycle being stopped in G0/G1 through negative regulation of tNOX (tumor-associated NADH oxidase). Islam et al. (2019) demonstrated through the cellular thermal shift assay (CETSA) that tNOX is a capsaicin binding target and when this substance is inhibited, a cascade of events occurs: the levels of NAD+ decrease, also resulting in the reduction of sirtuin desatylase-1 (SIRT1) and, subsequently in the acetylation of p53/c-MYC which suppresses the cyclins that regulate the passage of phases in the cell cycle, thus resulting in the cycle stop and control of cell proliferation (RAHMAN & ISLAM, 2011).

In addition, studies suggest a potential that can be used in the treatment of breast cancer, since capsaicin demonstrated, *in vitro*, mitochondrial dysfunction through activation of the intrinsic pathway of apoptosis, with activation of caspase-7 and cleavage of Poly [ADP-ribose] polymerase 1 (PARP-1) (CHANG et al., 2011) and ability to modulate mainly the EGFR/HER-2 pathways, resulting in the stopping of the cell cycle in G0/G1 and apoptosis (THOENNISSEN et al., 2009).

3.1.4 Lung Cancer

Lung cancer is a malignant disease, thus, is considered a worldwide health problem. Since the mid-1980s it has been the leader in mortality, accounting for approximately 13% of all new cases of cancer per annum (BRASIL, 2020). Considering that smoking is the main risk factor, lung cancer is one of the main causes of preventable death (GELATTI & LORANDI, 2020). Although it is considered

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one of the most common malignant neoplasia in the world, the treatment is still strictly related to the prognosis of each patient, since it is the determining factor for the choice of effective therapy, ranging between: surgery, radiotherapy or systemic therapy. It is essential to analyze that, although chemotherapy agents are extremely important, studies show that Curcumin and Capsaicin, can be beneficial and also significantly assist when used as an adjunct to standard chemotherapy agents (MEHTA, PATEL, SADIKOT, 2014).

The effects of curcumin may be relevant for various lung diseases that are characterized by abnormal inflammatory responses, such as asthma or chronic obstructive pulmonary disease (AGGARWAL et al., 2007), and may also play an important role in the treatment of lung cancer (LELLI et al., 2017).

Studies have reported the use of curcumin with antitumor potential, as its act in downregulating NF-kB has been demonstrated, with inhibition of IκBα kinase and AKT, (AGGARWAL et al., 2005) and protein-1 (AP-1), which is responsible for proliferation and mutation to tumor cells (LELLI et al., 2017). Furthermore, curcumin also has properties that allow a control of the P53 gene, in this way, there is control of the cellular cycle and apoptosis of metastatic tissue cells (PARK et al., 2002). It is important to emphasize, that not only in cases of lung cancer, but in all neoplasia, the P53 gene is undoubtedly one of the most important for a constant tumor evolution, after all, it provides a constant apoptosis to an uncontrolled replication of cells (DUFFY, SYNNOTT, CROWN, 2017).

MiRNAs are small RNAs that regulate genetic expression at a transcriptional level, which perform a great importance in growth, proliferation, differentiation, and apoptosis (TAJUDDIN et al., 2019). In the pathology of lung cancer, the expression of MiRNAs and their precursors, exhibit different mutations in their sequence, and thus are responsible for the rise and prognosis of lung cancer, as well as, greater resistance to drugs used in the treatment of this disease (YAO et al., 2015). Nevertheless, it has been shown that Curcumin has pharmacological properties that are able to mediate the modulation of precursor MiRNAs (LELLI et al., 2017). Therefore, Curcumin is extremely beneficial and able to inhibit the growth of cancerous cells through the modulation of MiRNAs and their precursors.

In relation to capsaicin, it is known that has been used medicinally for centuries, however, recently its effects have been discovered for anti-cancer, anti-inflammatory and pro-apoptotic activity (HUANG et al., 2013). Capsaicin is also responsible for inhibiting the vascular endothelial growth factor (VEGF), essential for pro-angiogenic activities, which has a mitogenic and anti-apoptotic effect, allowing for increased vascular permeability and cell migration. In this way, VEGF is considered one of the main mediators of angiogenesis, therefore, it is an important approach for the development of potential anticancer therapy for lung cancer regression (CHAKRABORTY et al., 2014). The development of therapies specifically aimed at the treatment of lung cancer may use anti-VEGF strategies, thus, it would be possible a combinatorial mechanism with immunological checkpoint inhibitors or agents that inhibit signaling of activated proangiogenic pathways and factors in response

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to VEGF blockade (FREZZETTI et al., 2017). According to Min et al. (2004), capsaicin directly inhibited VEGF, proliferation, DNA synthesis and chemotactic motility. Thus, together, these studies suggest the potential of NPs with antitumor activity.

3.1.5 Prostate Cancer

Prostate cancer (PC) is a relevant cause of disease worldwide, being the most commonly diagnosed cancer in men and the fifth most common cause of cancer death globally (PERNAR et al., 2018). According to Malinowski et al. (2019), the development of PC is affected by several risk factors not yet fully understood such as older age and genetic predisposition. As for the treatment methods it includes hormonotherapy, pharmacological blockage of androgen production or blockage of testosterone from reaching cancer cells. However, studies have demonstrated new treatment solutions with NPs. Curcumin and capsaicin are a well-known cancer suppressing agent due to their antiproliferative and proapoptotic properties. *In vitro* and *in vivo* studies illustrated the mechanisms of these compounds on prostate cancer, due to their ability to influence on many keys signaling pathways and molecular targets.

Recent studies showed that curcumin modulates MicroRNAs (miRNAs), which are non-coding small RNA that regulates genes related to cancer resistance by repressing translation. The upregulation of miR-143 caused the downregulation of the oncogene Phosphoglycerate Kinase-1 (PGK1), reducing prostate cancer cell proliferation and migration (CAO et al., 2017). The miR-34a is another type of microRNA, known to be an important tumor suppressor. It has been reported that this miRNA is upregulated by curcumin, inhibiting cell proliferation in human prostate cancer cells PC-3 and DU145 (ZHU et al., 2019). Not only that, but the phytochemical is able to decrease the expression of an important protein on Notch pathway called Notch 1. The Notch gene influences on cell cycle regulation, thus controlling proliferation and apoptosis (SHA et al., 2016). In addition, research by Katta et al (2019), proved the significant gene networking alterations induced by curcumin in both androgen-dependent non-metastatic prostate cancer LNCaP line cells and androgen-independent metastatic prostate cancer C4-2B line cells, been able to inhibit tumor signaling pathways, such as MYC Proto-Oncogene, basic helix-loop-helix (bHLH) Transcription Factor (MYC) and Transforming growth factor beta (TGF-β).

Capsaicin has also demonstrated to influence on microRNAs. The research by Zheng et al. (2015) illustrated that in the case of castration resistant prostate cancer (CRPC), the androgen receptor (AR) has an essential role, becoming more sensitive and leading to the development of castration-resistant prostate cancer (PCa). Other studies showed that capsaicin could induce autophagy blockage, promoting cytotoxicity and contributing to antiproliferation on androgen-sensitive and androgen-independent prostate cancer cells (RAMOS-TORRES et al., 2015). Besides that, the phytochemical can suppress the activity of prostate cancer stem cells (CSCs) by regulating the Wnt/β-catenin pathway, which has proven to be an important pathway to regulate the activity of cancer stem

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cells (ZHU et al., 2019). Additionally, long-term oral administration of capsaicin on a Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP) model could effectively reduce malignant transformation and metastasis on prostate cancer cells (VENIER et al., 2015).

Furthermore, combinations with capsaicin have been studied. Data from literature demonstrated that brassinin, an organic compound previously identified as a constituent of cabbage, combined with capsaicin, could enhance cytotoxicity and apoptosis, causing the suppression of cell proliferation on PC-3 cells (KIM et al., 2015). Docetaxel, main chemotherapy drug for CRPC treatment, has also been studied in combination with capsaicin. The synergistic effect reduced the tumor growth of PC3 cells both *in vivo* and *in vitro* by activation of AMPK, which is an enzyme that, beyond other functions, induces apoptosis and blocks cell cycle (SÁNCHEZ et al., 2019).

FINAL CONSIDERATIONS

Cancer is a disease characterized by disordered cell growth, which invades tissues and organs and can spread to different regions of the body. Currently, it is considered the second leading cause of death worldwide, and despite the countless efforts of science combined with technology, it has not yet been possible to identify an effective, universal and complete, with minimum collateral effects, treatment for cancer. However, it was recently observed that in addition to all the traditional therapies available such as chemotherapy and radiotherapy, there is growing strong evidence of a new alternative/ complementary medicine capable of contributing to this process of fighting cancer, known as “medicinal power of plants”.

Upon that, the present work compiled a wide range of scientific studies regarding the potential antitumor outcome of the compounds curcumin and capsaicin in the following neoplasms: gastric, pancreatic, mammary, pulmonary and prostatic. In general, the data showed that these medicinal plants seem to act in a unique way in the multiple stages of carcinogenesis and may significantly modify tumor progression. Therefore, in view of the above, it is extremely important to emphasize the need of further supporting studies to elucidate the effect of these substances on the human body, aiming at making them therapeutic tools complementary to those already well-established.

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