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ANTIOXIDANT AND ANTICANCER EFFECT OF QUERCETIN IN THE PREVENTION AND REPAIR OF CANCEL CELLS

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Abstract: Quercetin is the main flavonoid in the human diet and has been studied for a few decades. Found in fruits, vegetables and beverages, it is a very effective compound in protecting cells and other molecules mainly through the capture of reactive oxygen species (ROS). It is a molecule with antioxidant, anti-inflammatory and anticancer functions, its action is not only in the protection of healthy cells, but also in the repair or destruction of tumor cells through several mechanisms and different pathways, such as: apoptosis, blocking anti-apoptotic proteins and releasing pro-apoptotic proteins, Necroptosis can also be regulated in a controlled manner through defined signal transduction pathways causing severe damage to tumor cells and destroying them by necrosis, it also promotes an increase in autophagy stimulating a greater cycling of nutrients in the cell, blocking tumor cell multiplication and inhibiting tumor cell angiogenesis, blocking the channel for the advancement of metastasis. Studying and researching the action of quercetin on various cancer cell lines and their metabolic pathways of action in the numerous functions performed by this molecule is fundamental in research for anticancer treatment.
Keywords: Quercetin, Cancer, Apoptosis, Autophagy, Antioxidant, Anticancer, Cancer Cells, Necroptosis.

INTRODUCTION

Cancer is considered a public health problem. In Brazil, the highest prevalence is the breast for women, while for men the prostate is the most common. The World Health Organization (WHO) estimates that by 2030, there will be 27 million new cases of cancer worldwide and 17 million deaths from the disease. Developing countries will be the most affected, including Brazil (BRASIL, 2021).

It is a disease influenced by multifactorial factors, being external or internal to the organism, being interrelated. External causes refer to the environment and the habits/ customs of a society, including in the latter, the population's eating habits. Internal causes are most often genetically predetermined and are associated with the body's ability to defend itself against external causes. With the increasing number of cancer cases in the world, the population has been concerned about changing their lifestyle and eating habits.

In the last decades the number of cancer patients has grown exponentially worldwide, according to the INCA (Cancer Institute) in 2018 there were about 18 million new cases worldwide and 9.6 million deaths from cancer. illness. In Brazil in 2020, 626,030 new cases and 232,000 deaths were recorded, neoplasia has been a great challenge for science, in search of new treatments and more efficient ways to confirm the diagnosis (INCA BRASIL, 2020).

With the emergence of new studies and research carried out in vitro and in vivo with the help of technology, several factors were found, which induce the emergence of tumors as well as their proliferation and mass gain. The increase in processed foods, as well as the incorrect handling of chemicals, excessive exposure to radioactive materials, among others, has contributed to this extraordinary increase in cancer cases.

After a lot of research and experiments, some types of effective treatments were developed, but many of them are extremely aggressive to the human body, such as in cases of chemotherapy and radiotherapy sessions. However, several molecules with antioxidant actions that inhibit or correct point cell mutations were also found, which could be one of the great advances of science in relation to cancer. One of them is quercetin, a flavonoid that has antioxidant, anti-inflammatory and anticancer action. Which is present in various foods at different levels of concentration.

The chapter will address the action of quercetin in the different mechanisms of repair and inhibition of mutant cells causing tumors with high mass concentration.

FLAVONOIDS

Flavonoids are important compounds in the daily human diet, even though they are considered without nutritional value. Its structure consists of a flavanic nucleus formed by 2 benzene rings linked by a heterocyclic pyran ring. They are consumed daily and are present in fruits, vegetables, beverages and grains. Its daily consumption is between 50 and 500 mg distributed in different types: Aurones, chalcones, dihydrochalcones, flavones (apegenin, lutedin, dosmetin) flavonols (quercetin, miracetin, kaempfero). (BEHLING et al., 2020)

They play an important role, not only in the human diet, but also play important roles in: leaves, flowers and fruits, which can be protection against sunlight or defense against fungi (BEHLING et al., 2020).

Among anticancer and cancer preventive drugs, flavonoids are the most studied. They are compounds that can control several functions in specific steps of the carcinogenic process, such as the inhibition of cell proliferation and induction of apoptosis in several cancer cell lines. They also demonstrate substantial antioxidant activity, not only by inhibiting the generation and uptake of reactive oxygen species (ROS), but also by affecting the activity of several detoxifying enzymes, such as cyclooxygenases, lipoxygenases and inducible nitric oxide synthase. This antioxidant capacity of flavonoids may be responsible for their anticancer potency. Flavonoids can also influence epigenetic changes by chromatin remodeling (HASHEMZAEL et al., 2017).

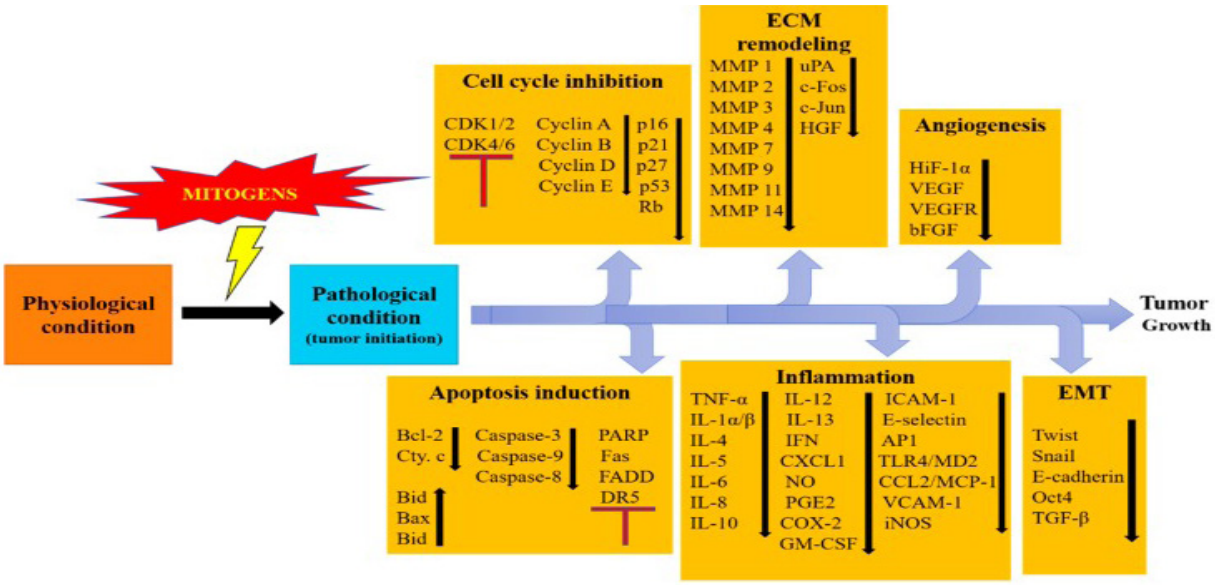

Figure 1. Effects of flavonoids linked to cancer.

Source: KASHYAP ***et al***., 2019. Fisetin and Quercetin: Promising flavonoids with chemopreventive potential. Available from: Fisetin and Quercetin: Promising Flavonoids with Chemopreventive Potential (nih.gov).

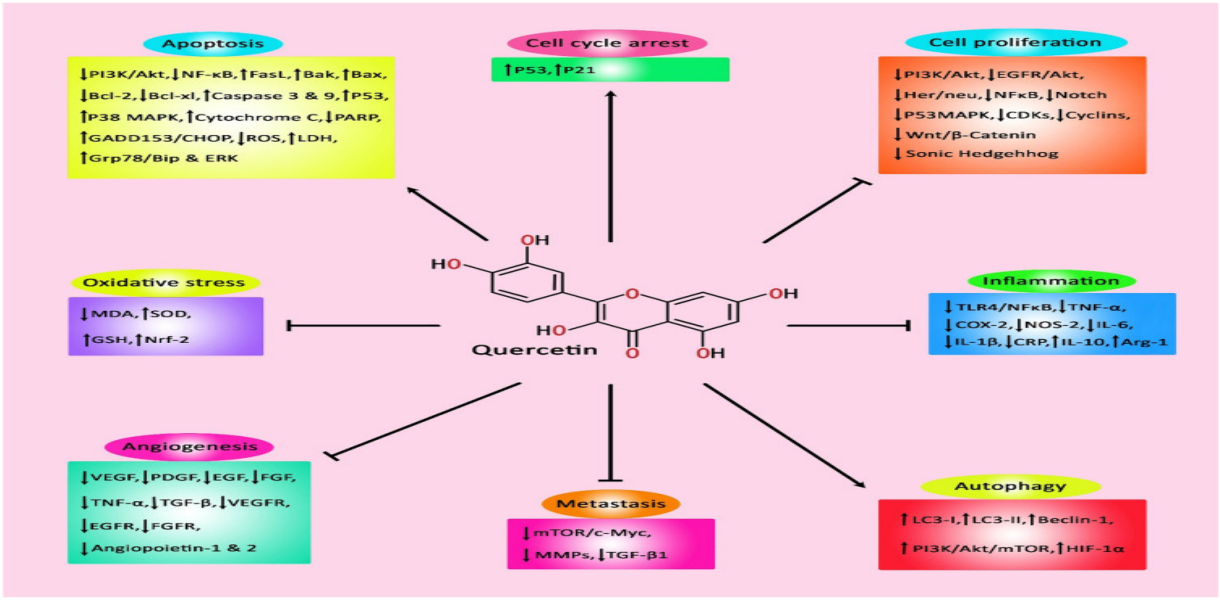

Figure 2. Functions of Quercetin in Metabolism.

Source: *FARD et All 2021*. ***Emerging impact of quercetin in the treatment of prostate cancer***. *Available from: Emerging impact of quercetin in the treatment of prostate cancer - ScienceDirect.*

QUERCETIN

Quercetin (3, 5, 7, 3', 4' pentahydroxy flavone) is a molecule with potent antioxidant, antiviral, anti-cancer and psychostimulant anti-inflammatory action, belongs to the flavonoid class and performs numerous and important molecular actions with different functions that will be addressed in this study. The name has been used since 1857, and is derived from quercetum (oak forest), named after Quercus. In plants it is a naturally occurring polar auxin transport inhibitor (LI et al., 2016).

It has 5 hydroxyl groups attached at positions 3, 5, 7, 3', and 4' and also a catechol ring that can undergo oxidative metabolism even without demethylation, which makes it a molecule with great ability to capture electrons and high power of interaction with other molecules and cells (LI et al., 2016).

It is the main flavonoid consumed in the daily human diet, it is found mainly in its glycosylated form in various types of foods such as onion (284-486mg/kg), cabbage (100mg/kg), green beans (32-45mg/kg), broccoli (30mg/kg), tomato (14mg/kg), is also found in beverages such as: Beer, coffee, wines and chocolate drinks, with a lower content of 1mg/l, with the exception of black tea which, despite being classified as a beverage, had the highest concentration between them with approximately 10-25mg/l (BEHLING et al., 2020).

The nature of glycosylation is known to influence the efficiency of its absorption as Quercetin ($C_{15}H_{10}O_7$) is an aglycone, without a sugar attached. It is a bright citron yellow needle crystal and totally insoluble in cold water, poorly soluble in hot water, but quite soluble in alcohol and lipids (LI et al., 2016).

Quercetin is a unique compound due to its high potential to fight several cancer strains in a multi-targeted manner. Quercetin, at different concentrations and induction time, has been reported to suppress the growth of tumors of various cancer cell lines, including breast, colorectal, stomach, head and neck, lung, ovarian, bladder, melanoma, and leukemia cancers. It also inhibits P-glycoprotein release in the MCF-7 cell line and increases the in vitro anticancer activity of adriamycin in the breast cancer cell line (HASHEMZAEL et al., 2017).

It was found that its main route of action is through the mechanism of the cell death domain on the cell surface, which leads to the induction of apoptosis of several cancer cell lines, thus stopping their growth and proliferation, involving antioxidant effects and the suppression of the p53 gene. and BCL-2 protein suppressing gene transcription, which reduces the inhibitory effects of BAD protein on mitochondria, considered the intrinsic initiator of apoptosis. When p53 is inhibited, cells become more susceptible to quercetin-induced cytotoxicity. In addition, quercetin activates the domain that leads to the activation of FAS and FADD, inducing cell death in several cancer cell lines through caspase 8 activation. A significant increase in survival rate and a significant reduction in tissue volume were observed. tumor in animals treated with quercetin (HASHEMZAEL et al., 2017).

METABOLIC ACTIONS AND FORMS FOUND

After several studies conducted around the world, several unique cellular functions for quercetin have been found, which can improve mental/physical performance and reduce the risk of infection. These properties form the basis for potential benefits for general health and disease resistance, including anticancer, anti-inflammatory, antiviral, antioxidant and psychostimulant activities, as well as the ability to inhibit lipid peroxidation, platelet

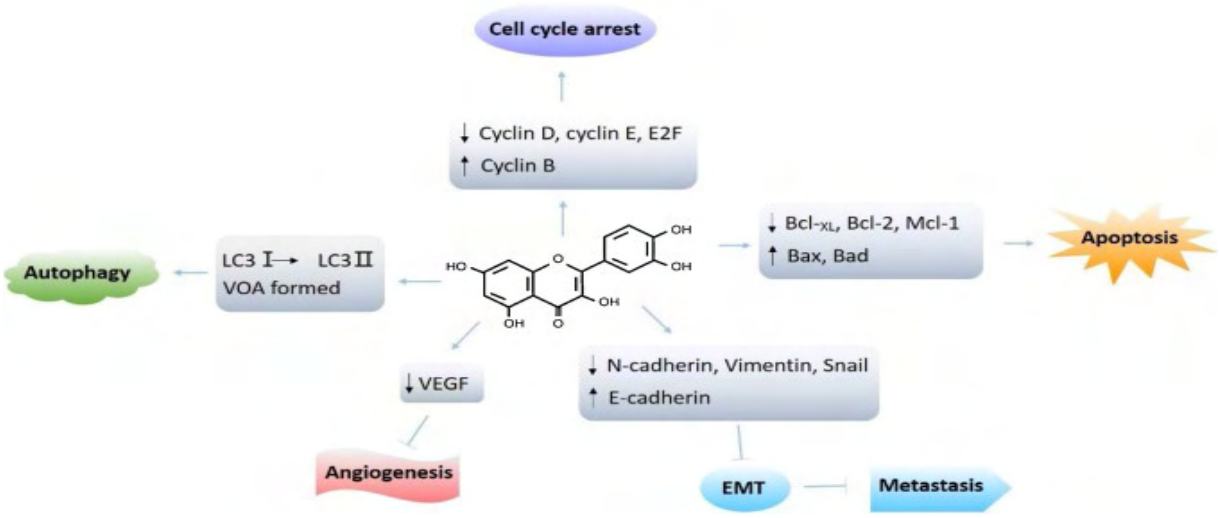

Figure 3. Quercetin anticancer effect.

TANG *et al*., 2020. Available on the website: **Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects** – ScienceDirect.

aggregation and capillary permeability, and stimulate mitochondrial biogenesis (LI et al., 2016).

As an excellent in vitro antioxidant, its activity is mainly manifested by affecting glutathione, enzymatic activity, reactive oxygen species (ROS) and regulating signal transduction pathways such as NRFB, MAPK and AMPK (FARIAS, 2019).

Quercetin can also activate apoptosis through a mitochondrial pathway involving activation of caspase-3 and caspase-9 and by the release of cytochrome c and PAR PP neckline in acute lymphoblastic leukemia (HPB-ALL and HL-60) and prostate cancer cells. (DU-145 and PC-3). Furthermore, a range of studies have shown anti-apoptotic protein modulation (Bcl-xL and Bcl-2) and pro-apoptotic protein modulation (Bax) by quercetin in human colon, adenocarcinoma and leukemia cells (POZO, 2019).

It is a very important compound in the protection of cells or other molecules such as proteins. Quercetin's anticancer effects include its ability to promote loss of cell viability, autophagy through modulation of PI3K/Akt/mTOR, Wnt/β-catenin and MAPK/ERK1/2 pathways (POZO, 2019).

It also acts as an effective ROS scavenger, and exerts antioxidant effects by free radical scavenging activity, reducing ROS level and inhibiting lipid peroxidation. There is no doubt that quercetin can also play strong anti-inflammatory effects and reduce the inflammation process (TANG et al., 2020).

It is usually found in foods in the glycosylated form, sometimes as -lycosidase. The nature of glycosylation is known to influence the efficiency of its absorption. Although quercetin-3-rutinoside is an important form of quercetin found in foods, its bioavailability is only 20% of that of quercetin-4'-glycoside (BEHNING et al., 2020),

A quercetin glycoside is formed by attaching a glycosyl group (a sugar such as the glucose, rhamnose or rutinose) as a substitute for one of the OH groups The attached glycosyl group can alter solubility, absorption and in vivo effects (LI et al., 2016).

When quercetin is absorbed from the gastrointestinal tract, it is metabolized by phase II enzymes that are in the epithelial cells of the stomach and intestines. Metabolites appear to accumulate in tissues after consumption of quercetin-rich vegetables (RAUF et al., 2018).

This shows us the way in which quercetin and its derivatives are likely to be absorbed by the body. Among quercetin derivatives, the conjugated forms of their glycosides are better absorbed than quercetin. Purified quercetin glucosides are able to interact with sodium-dependent glucose transport receptors in the mucosal epithelium and therefore can be absorbed from the small intestine in vivo (LI et al., 2016).

After absorption, quercetin becomes metabolized in various organs, including the small intestine, colon, liver, and kidney. Metabolites formed in the small intestine and liver by biotransformation enzymes include the methylated, sulfo-substituted and glucuronide-substituted forms (HOLLMAN, 2009).

CANCER CELLS

These are cells that contain and accumulate some serious error that could not be repaired by the cellular machinery, thus deregulating their replication and growth, and may affect other cells, whether close or in more distant locations. Deregulation of cell proliferation is a prerequisite for carcinogenesis. A single genetically altered cell causes abnormal proliferation, which leads to the growth of a population of clonally derived tumor cells. Cancer cells can continue to grow and divide even if they do not receive the chemical signals to do so. Normal cells only carry out the process of growth and division if they receive chemical signaling from specific receptors (POZO, 2019).

In cancer cells, metabolic reprogramming is regulated by several pathways, including phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), which promotes increased glucose uptake and glycolysis. Pi3K translates the signal through messengers that activate Akt and, then, fully active, the PI3K/Akt pathway regulates cellular angiogenesis, metabolism, growth, proliferation, survival, protein synthesis, transcription and apoptosis. They can block apoptotic pathways, thus preventing the tumor cell from being destroyed (POZO, 2019).

However, for this to be possible, the production of biomass and energy are key pieces to allow and sustain uncontrolled cell growth and expansion. As the tumor environment is very limited in nutrients, it is important that these cells have a mechanism to support the energy demand for cell proliferation and growth. Likewise, a change in glucose metabolism called the "Warbug Effect" has been described to occur in cancer cells (FARIAS 2019).

In contrast, most cancer cells produce large amounts of lactate regardless of oxygen availability, and thus their metabolism is often referred to as "aerobic glycolysis". Warburg originally hypothesized that cancer cells develop a defect in mitochondria that leads to impaired aerobic respiration and a subsequent dependence on glycolytic metabolism (Heiden et al., 2009).

Even though tumor cells produce less ATP and less efficiently, they do not stop developing and proliferating slowly. The metabolism of glucose to lactate generates only 2 ATPs per glucose molecule, while oxidative phosphorylation generates up to 32 ATPs after the complete oxidation of a glucose molecule. This raises the question of why a less efficient metabolism, at least in terms of ATP production, would be selected for cell proliferation. (HEIDEN et al., 2009).

However, aerobic glycolysis remains the preferred metabolic mechanism for

cancer cells because biomass production is prioritized over energy production. In this sense, in cancer cells, glycolysis generates high levels of carbon-rich metabolic intermediates that could be used as precursors for the new synthesis of nucleotides, lipids or amino acids (FARIAS 2019).

QUERCETIN ANTIOXIDANT EFFECT

Many compounds have been discovered by science and each of them performs numerous different and unique functions. One of these compounds was the antioxidants that play a very important role in the protection of cells and macromolecules. Quercetin, in addition to other functions, has antioxidant activity that is mainly manifested through its effect on glutathione (GSH), enzymatic activity, signal transduction pathways and reactive oxygen species (ROS) caused by environmental and toxicological factors. Quercetin shows strong antioxidant activity maintaining oxidative balance (XU et al., 2019)

It also has preventive effects against gastric, prostate, colon, bladder, lung, breast and ovarian tumors. Quercetin not only has strong antioxidant properties in scavenging free radicals, but also reduces inflammation, inhibits cell proliferation and angiogenesis (ARAUJO et al., 2015).

Thus, after several researches carried out on the subject, we have evidence that antioxidants can be a good choice in therapeutic intervention with chemotherapy for helping to reduce the size of the tumor and increase the longevity of patients (ROCHA 2018).

QUERCETIN'S EFFECTS ON PROSTATE CANCER

Prostate cancer is the second highest mortality among men, second only to lung cancer. Quercetin has demonstrated efficacy in several in vitro studies performed on prostate tumor cell lines. Quercetin treatment significantly decreased the cell viability of PCa cells (LNCaP, DU-145 and PC-3) in a time and dose dependent manner, without affecting normal prostatic epithelial cells (PrEC) (WARD et al., 2018).

Furthermore, quercetin treatment also resulted in an attenuated Bcl-xL to bcl-xS ratio and increased translocation of Bax protein to mitochondrial membrane in LNCaP human prostate cancer cells. In vitro studies with human cancer cell lines, HaCaT keratinocytes, established the anti-tumorgenic effect of quercetin through Bax overexpression and cytochrome c release and translocation of factors that induce apoptosis to the nucleus (KASHYAP, et al., 2019).

Quercetin's effect on prostate cancer cells is mainly due to the dissociation of Bax from Bcl-xL and the stimulation of caspase families causing cascades and thus unblocking pro-apoptotic pathways. Inhibition of angiogenesis is another effect of quercetin. The EGFR/PI3K/Akt/ERK1/2, NFκB, Wnt and AKT/mTOR/P70S6K pathways are influenced by quercetin in prostate cancer cells. Its antiangiogenic effects and its resulting success in releasing pro-apoptotic pathways make us believe that quercetin can be a great agent in the prevention of tumor metastases not only from the prostate but also from other cancer strains (GHAFOURI-FARD et al., 2021).

It may also potentiate the effects of other therapeutic options against prostate cancer. For example, a combination of TRAIL and quercetin has been touted as a new modality for treating prostate cancer. These types of strategies can overcome resistance to apoptosis in cancer cells by unlocking anti-apoptophic pathways. Furthermore, the combination of quercetin with paclitaxel or docetaxel exerted beneficial therapeutic effects in animal models of prostate cancer, reducing the side effects of the mentioned chemotherapeutic agents

and increasing the quality of life of patients with the disease undergoing treatment. The impact of reversing quercetin resistance to docetaxel supported the clinical application of this substance in docetaxel-resistant prostate cancer. Based on the heterogeneity of cancer promotion mechanisms, such combination therapies can be effective in cancer treatment as they can affect different mechanisms in the carcinogenic process. However, the most effective dose and duration of quercetin in humans must be identified in clinical trials, as quercetin has been shown to affect the expression of various proteins, the expression levels of these targets in each individual can affect the response to this drug in different groups. human beings (JUNG et al., 2010).

QUERCETIN'S EFFECTS ON OVARIAN CANCER

Ovarian cancer is the second most prevalent gynecological neoplasm in Brazil, second only to cervical cancer. Of the confirmed cases, 95% of all ovarian neoplasms are derived from the epithelial cells that line the ovary, the remaining 5% are from the germ cells that form the eggs and stromal cells that produce most of the female hormones (INCA BRASIL 2021).

Quercetin also induces apoptosis through intrinsic and caspase-dependent pathways. It also evoked anticulum endoplasmic stress (ER) in ovarian cancer, resulting in mitochondria-mediated apoptosis. Furthermore, quercetin was able to induce autophagy which has a protective role in ovarian cancer cells. However quercetin induced stress, apoptosis and autophagy through a p-STAT3/Bcl-2 axis (SHAFABAKGHSH, ASEMI 2019)

Another study demonstrated that quercetin decreases the viability and induced apoptosis of metastatic ovarian cancer cells, being able to decrease several anti-apoptotic molecules, including Bcl-2 and Bcl-xL and increase pro-apoptotic molecules, including caspase-3, caspase-9, Bid, Bax, Bad and cytochrome c. Furthermore, quercetin inhibits the growth of metastatic ovarian cancer cells by inducing mitochondria-mediated apoptosis. In a recent study, the anticancer effects of the nano-formulation of quercetin were examined, this form significantly inhibited the growth of ovarian cancer cells, both in vitro and in mice with xenograft ovarian cancer. After being formulated, it has been shown to induce apoptosis by activating caspase-3, caspase-9 and Bax, and reducing MCL-1 and Bcl-2 (SHAFABAKGHSH, ASEMI 2019).

QUERCETIN EFFECTS ON BREAST CANCER

Breast cancer is the most common among women, and it is also the one with the highest mortality rate among them, but even though it is less recurrent, it can also affect males. Conventional treatments have not been very effective against this lineage of cancer that affects breast cells, the main cause of the failure is related to its side effects and the evolutionary form of this type of cancer. Which leads us in search of new discoveries so that we can obtain better results (INCA BRASIL, 2020).

Quercetin was studied in MCF-7 breast cancer cell lines, and once again demonstrated great ability to react together with conventional treatments, suppressing the growth of MCF7 cells stimulating apoptosis and necroptosis through cough signaling. The role of apoptosis was determined using the pan-caspase inhibitor Z-VAD, which irreversibly binds to the catheter at the lytic site of caspases and was used to selectively inhibit the apoptosis pathway. In the presence of Z-VAD, cell viability increased significantly compared to its absence. In the presence of the necroptosis inhibitor Nec-1, cell viability increased compared to the absence of Nec-

1. Furthermore, the Nec-1 inhibitor further increased cell viability compared to Z-VAD, and was slightly more effective in protecting cancer cells (KHORSANDI et al., 2017).

Apoptosis is regulated in part by the Bcl-2 gene that enhances cell survival and the pro-apoptotic protein Bax. Inhibition of apoptosis partially depends on the balance between Bcl-2 and Bax. Quercetin-treated MCF-7 cells exhibited a large number of nuclei with condensed chromatin, which indicates cellular apoptosis (KHORSANDI et al., 2017).

Necrosis has long been considered an accidental way of cell death, but studies have recently reported that just like death by apoptosis, necroptosis can also be regulated in a controlled manner through defined signal transduction pathways (KHORSANDI et al., 2017).

Quercetin has also been tested in combination with other therapies, when administered with a variety of chemotherapeutic agents, marked potentiation of anti-cancer effects was observed, apoptosis was detected at mRNA expression levels and in addition quercetin was shown to sensitize MCF- 7 to the medically doxorubicin (Dox) which is used to treat neoplastic diseases including breast cancer (DHANARAJ et al., 2021).

In malignant breast diseases, epidermal growth factor plays an important role, through the propagation of cell growth and proliferation by angiogenesis and metastasis. Nanoparticle-based quercetin caused a significant reduction in the expression of several proteins, including Vimetine, Snail, N-cadherin, Slug, MMP-2, MMP-9, Akt, and PI3K and GSK3ß attenuating or even inhibiting tumor enlargement, extending longevity. of patients and decreasing the effects of radiotherapy and chemotherapy treatments (RAUF et al., 2018).

FINAL CONSIDERATIONS

Quercetin proved to be a molecule with great metabolic potential, performing several functions in the protection of healthy cells and macromolecules, mainly through the capture of reactive oxygen species (ROS). It also demonstrated its reparative action on tumor cells, especially through apoptosis and necroptosis, delaying or destroying the tumor

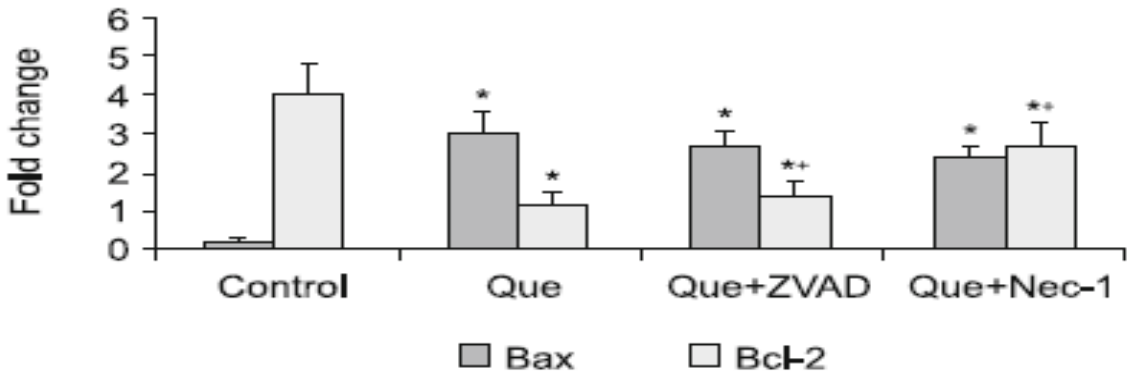

Table 1: Quercetin's effect on Bax and Bcl-2.

Source: KHORSANDI *et al.*, 2017. **Quercetin induces apoptosis and necroptosis in breast MCF - 7cancer cells.** Available from: Quercetin induces apoptosis and necroptosis in MCF-7 breast cancer cells - PubMed (nih.gov).

cell, being very active in the repair and partial elimination of several cancer cell lines such as breast, prostate, intestine, colon and ovary.

Its effectiveness as a future alternative treatment was attested, being less invasive and with gratifying results, it also proved its effectiveness in conjunction with conventional treatments, increasing its action on tumor cells and decreasing adverse reactions, improving the well-being and lifestyle of patients tested in cancer treatment.

However, its applicability depends a lot on dosage and time, even though quercetin is a molecule with a powerful antioxidant and anti-inflammatory function, it also has pro-oxidant properties, when used in high doses and for long periods it can change from a beneficial action to something harmful. cells and the human organism generating excessive oxidative stress through the inhibition of antioxidant systems. That is, in some cases it is not effective, leading to unexpected and negative results. Thus, the development of new therapeutic strategies and compounds remains a major challenge in the battle against cancer and other diseases.

REFERENCES

BRASIL. **Instituto do câncer**. Brasília 2021. Disponível em: Tipos de câncer | INCA - Instituto Nacional de Câncer acesso: 02 de setembro de2021

ARAUJO *et al*., 2015. **ANTIOXIDANTES NA PREVENÇÃO DO CÂNCER EM IDOSOS.** Disponível em: cliente=13-41ec4af 2d1b366b9c09361970b1bdecc.pdf (fiponline.edu.br) acesso: 08/05/2021.

BRASIL. Ministério da Saúde. **Portal da Saúde**. Brasília 2021. Disponível em: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/21003-inca-estina-que-havera-596-070-novos-casos-de-cancer-em-2021>Acesso em: 26 de abril de 2021.

BRASIL. **Instituto do câncer**. Brasília 2021. Disponível em: Estatísticas de câncer - INCA - Instituto Nacional de Câncer acesso em: 24 de abril de 2021

BRASIL. **Instituto do câncer**. Brasília 2021. Disponível em: Estimativa 2020 - Introdução - INCA - Instituto Nacional de Câncer acesso em: 24 de abril de 2021.

FARIAS M., POZO C. **O Efeito Anticâncer da Quercetina: Implicações Moleculares no Metabolismo do Câncer.** Disponível em: IJMS | Free Full-Text AMetabolism (mdpi.com), acesso em: 25 de abril de 2021.

HASHEMZAEL *et al*., 2017. **Efeitos indutores de anticancerígenos e apoptose de quercetina *in vitro* e *in vivo.***

HEIDEN M.G, CANTLEY L.C., THOMPSON C.B. **Entendendo o Efeito Warburg:** Os Requisitos Metabólicos da Proliferação Celular.

Hollman, P.C.; Katan, M.B. **Absorção, metabolismo e biodisponibilidade de flavonoides. Em *Flavonoides em Saúde e Doenças;* Rice-Evans, C.A., Packer, L., Eds. Marcel Dekker Inc.: Nova Iorque, NY, EUA, 1998; pp. 483-522.Acesso dia 06/05/2021.**

KASHYAP *et al*., 2019**. Fisetin e Quercetin: Flavonoides promissores com potencial quimiopreventivo**. Disponível em: Biomolecules | Free Full-Text | Fisetin and Quercetin: Promising Flavonoids with Chemopreventive Potential | HTML (mdpi.com) acesso em: 11/05/2021.

LI, *et al*., **Quercetina, Inflamação e ImUnit.** Disponível em: Nutrients | Free Full-Text | Quercetin, Inflammation and Immunity | HTML (mdpi.com). Acesso 05/05/2021.

ROCHA, SOUZA, 2018. **SÍNTESE, CARACTERIZAÇÃO E ESTUDO DAS PROPRIEDADES ANTIOXIDANTES DE COMPLEXOS CONTENDO QUERCETINA E ÍONS COBRE.**

TANG, *et al*., 2020. Disponível em: **Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects** – ScienceDirect. Acesso em: 06/05/2021.

WARD *et al*., 2018. **Quercetina inibe o câncer de próstata atenuando a sobrevivência celular e inibindo vias anti-apoptóticas.** Disponível em: Quercetin inhibits prostate cancer by attenuating cell survival and inhibiting anti-apoptotic pathways | World Journal of Surgical Oncology | Full Text (biomedcentral.com). Acesso em: 11/05/2021.

GHAFOURI-FARD *et al*., 2021. **Impacto emergente da quercetina no tratamento do câncer de próstata.** Disponível em: https://www.sciencedirect.com/science/article/pii/S0753332221003334 acesso em 11/09/2021.

JUNG *et al*., 2010. Quercetin aumenta apoptose induzida por TRAIL em células cancerosas da próstata através do aumento da estabilidade proteica do receptor de morte 5. Disponível em: **Quercetin aumenta apoptose induzida por TRAIL em células cancerosas da próstata através do aumento da estabilidade proteica do receptor de morte 5 (nih.gov)** acesso em: 04/10/2021.

KHORSANDI *et al*., 2017 **A quercetina induz apoptose e necroptose na mama MCF** - 7células cancerosas, disponível em: Quercetin induz apoptose e necroptose em células cancerígenas de mama MCF-7 - PubMed (nih.gov) acesso: 8/09/2021.

HEIDEN, CANTLEY, THOMPSON 2009. **Entendendo o Efeito Warburg: Os Requisitos Metabólicos da Proliferação Celular.** Disponível em: Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation (nih.gov). Acesso em: 06/05/2021.

BRUNA PAOLA, MURINO RAFACHO 2020. **Minieditorial: Quercetina Melhora o Perfil Lipídico e Apolipoproteico em Ratos Tratados com Glicocorticoides em Altas Doses.** Disponivel em: https://www.scielo.br/j/abc/a/T96SMKYvPC5BsLdMpmHvVVh/?lang=en&format=pdf. Acesso em: 02/09/2021.

FARD *et al*., 2021. **Impacto emergente da quercetina no tratamento do câncer de próstata.** Disponível em: Impacto emergente da quercetina no tratamento do câncer de próstata - ScienceDirect acesso em: 06/10/2021.

OZKAN, BAKAR 2020. **Potenciação do efeito da lonidamina por quercetina na mama humana MCF-7 células cancerosas por meio de regulação negativade expressão de mRNA de MMP-2/9** Disponível em: SciELO - Brasil - Potentiation of the Effect of Lonidamine by Quercetin in MCF-7 human breast cancer cells through downregulation of MMP-2/9 mRNA Expression acesso em: 06/10/2021.

RAUF *et al*., 2018. **Potencial anticâncer da quercetina: uma revisão abrangente** Disponível em: Potencial anticâncer de quercetina: Uma revisão abrangente - PubMed (nih.gov). Acesso em: 06/10/2021.

SHAFABAKGHSH, ASEMI 2019. Quercetina: um composto natural para tratamento de câncer de ovário. Disponível em: **Quercetina: um composto natural para tratamento de câncer de ovário (nih.gov)**. Acesso em: 06/10/2021.