Narrative review

Role of polyphenols in the prevention and treatment of non-metastatic breast cancer

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Abstract
Breast cancer is one of the most frequently diagnosed neoplasms in women worldwide and represents the second leading cause of death in this population group. Primary prevention is essential for the early detection of breast cancer with emphasis on annual screening to provide timely treatment, based on a multidisciplinary management that includes the areas of surgery, oncology, pathology and nutrition. A literature search was performed using the Medline, HINARI, ARDI, and SciELO databases to study the anticarcinogenic role of polyphenols in non-metastatic breast cancer. Original articles in English and Spanish from primary and secondary sources were selected, reviewed and analyzed. Polyphenols are dietary compounds that have gained importance in recent years for their anticarcinogenic role in the prevention and treatment of non-metastatic breast cancer. They include curcumin, resveratrol, quercetin, epigallocatechin gallate and luteolin. Polyphenols possess anti-inflammatory, antioxidant and anticarcinogenic properties. Their introduction as a preventive measure could reduce the incidence of breast cancer and, in those cases with a confirmed diagnosis, improve the effect of chemotherapeutic treatment.

Keywords
Polyphenols, Flavonoids, Breast Neoplasms, Diet..

Resumen
El cáncer de mama es una de las neoplasias diagnosticadas con mayor frecuencia en las mujeres a nivel mundial y representa la segunda causa de muerte en este grupo poblacional. La prevención primaria es esencial para la detección temprana del cáncer de mama con énfasis en el tamizaje anual para brindar un tratamiento oportuno, basado en un manejo multidisciplinario que incluye las áreas de cirugía, oncología, patología y nutrición. Con el objetivo de estudiar el rol anticarcinogénico de los polifenoles en el cáncer de mama no metastásico, se realizó una búsqueda bibliográfica utilizando las bases de datos Medline, HINARI, ARDI y SciELO. Se seleccionaron, revisaron y analizaron artículos originales en idioma inglés y español de fuentes de tipo primaria y secundaria. Los polifenoles son compuestos provenientes de la dieta que han adquirido importancia en los últimos años por su rol anticarcinogénico en la prevención y tratamiento de cáncer de mama no metastásico. Entre ellos se encuentran la curcumina, el resveratrol, la quercetina, el galato de epigalocatequina y la luteolina. Los polifenoles poseen propiedades antiinflamatorias, antioxidantes y anticarcinogénicas. Su introducción como medida de prevención podría disminuir la incidencia del cáncer de mama y, en aquellos casos con diagnóstico confirmado, mejorar el efecto del tratamiento quimioterapéutico.

Palabras clave
Polifenoles, Flavonoides, Cáncer de Mama, Dieta.

Introduction

Breast cancer is one of the most commonly diagnosed neoplasms in women worldwide; nearly two million cases were diagnosed in 2020, and this number will continue to increase.[i] Treatment is a multidisciplinary and comprehensive approach that includes surgery, chemotherapy, radiotherapy, and nutrition. However, there have been limitations in treatment, such as high drug resistance, poor therapeutic response, severe side effects, and low adherence to treatment, among others.[ii] In recent years, a large number of natural compounds have been studied which, due to their wide range of health effects, could have a signifi-

cant impact on the prevention and treatment of this pathology.

Polyphenols are molecules found in foods that can provide anti-inflammatory, antioxidant, and anticarcinogenic effects.[iii] These compounds are commonly present in fruits, vegetables, and seeds, which are available and consumed in the regular diet. However, more prospective studies are required to determine their anticarcinogenic properties.[iv]

Primary prevention of breast cancer includes annual mammography screening starting at age 40, which is considered the gold standard. Additionally, a diet rich in polyphenols is suggested due to their anti-inflammatory, antioxidant, and anticarcinogenic properties.

A literature review was conducted using critical analysis and specific selection parameters, such as compliance with quality and scientific accuracy, relevance, and the validity of the title, authors, abstract, and accurate results. The search was made in electronic databases such as Medline through the PubMed platform, HINARI, ARDI, and SciELO.

The analysis focused on original articles and literature reviews in Spanish and English. Keywords such as "Polyphenols," "Breast Cancer," and "Diet" using the Boolean operators "AND" and "OR" were applied in the search strategy. This review aims to study the anticarcinogenic role of polyphenols in non-metastatic breast cancer.

Discussion

Overview of polyphenols and their mechanism of action

Polyphenols are natural compounds synthesized exclusively by plants, responsible for their nutritional qualities, astringency, color, and aroma.[v] They are found in a wide variety of food groups, including quercetin in fruits, vegetables, and cereals, flavanones in citrus fruits, and isoflavones in soy. Among the most commonly consumed foods are tea, coffee, cocoa, and red wine, rich in flavonoids, mainly in the form of catechins, epicatechins, and procyanidins.[vi,vii]

Polyphenols are a heterogeneous group of secondary metabolites synthesized by the pentose phosphate, shikimate, and phenylpropanoid pathways. They belong to a broad group of chemicals characterized by having one or more aromatic rings with two or more hydroxyl groups. These compounds can occur free, conjugated with sugars, acids, and other biomolecules, both soluble and insoluble.[viii]

The mechanism of action rests on the antioxidant properties. According to Cory, *et al.*, the *'biochemical scavenger theory'* suggests that polyphenols scavenge free radicals, forming stable chemical compounds. In addition, there is evidence that they may protect against oxidative stress by producing hydrogen peroxide.[ix]

Polyphenols have been studied for their positive effects on cardiovascular, neurodegenerative, metabolic, and neoplastic diseases.[x,xi] The possible anticarcinogenic benefit of polyphenols may be linked to a reduction of rapid cell proliferation, which has been explored as an adjuvant treatment in non-metastatic breast cancer.[xii]

The chemical structure of polyphenols differs, and most are found in the form of esters, polymers, or glycosides, which determines their bioavailability, i.e., the amount of circulating active metabolites in plasma and target organs. In addition, the concentration of polyphenols in different foods is variable.[xii]

The bioavailability of natural polyphenols in food depends on the type of antioxidant metabolite and microorganism metabolization in the colon prior to absorption. Polyphenols offer health benefits such as antioxidant effects at the signaling pathways, modulation of oxidative pathways, and epigenetic modifications.[xiii]

Polyphenols with beneficial properties include curcumin, resveratrol, quercetin, luteolin, and epigallocatechin gallate.[xv] Curcumin is a polyphenol derived from turmeric that has demonstrated antibacterial, antiviral, anti-inflammatory, and anticarcinogenic properties. Anticarcinogenic activity is achieved by apoptosis of tumor cells, inhibiting tumor growth and reducing cell viability.[xiv]

Resveratrol belongs to the stilbenes group and is present in grapes, wine, red fruits, peanuts, cocoa, and dark chocolate. It has anti-inflammatory properties, estrogenic and anti-estrogenic activity, neuroprotective, and cardioprotective benefits, antioxidant, antimicrobial, and anticarcinogenic effects. Its antiproliferative activity is associated with the inhibition of ribonucleotide reductase, an enzyme essential for synthesizing DNA precursors, which interferes with cell multiplication. At high concentrations, resveratrol leads to inhibition of cell growth and induces autophagy and apoptosis via mitogen-activated protein kinase (MAPK), which links extracellular signals to the intracellular process that controls growth, proliferation, migration, and apoptosis.[xv,xvi]

Quercetin, present in onions, red apples, grapes, spinach, capers, watercress, and cherries, has demonstrated antioxidant, anti-

inflammatory, antimicrobial, and anticarcinogenic properties. The anticarcinogenic activity is based on the inhibition of free radical-mediated carcinogenesis through the positive regulation of the enzymatic and non-enzymatic system, eliminating free radicals and reducing DNA damage by stopping cell division in the G2/M phase in tumor cells.[xvii,xviii]

Luteolin is found in numerous fruits, vegetables, and other edible plants and has proven anti-allergic, anti-inflammatory, antidiabetic, neuroprotective, and anticarcinogenic properties.[xix,xx] The anticarcinogenic activity is based on the inhibition of proliferation, metastasis, tumor cell invasion, and angiogenesis through the suppression of kinases, promotion of apoptosis, and reduction of transcription factors.[xx]

Epigallocatechin gallate found in green tea exhibits various anti-inflammatory, antioxidant, anticarcinogenic, and chelating activities, as well as the ability to scavenge free radicals. The anticarcinogenic effect stems from the capacity to modulate cell signaling pathways, inhibit cell proliferation and angiogenesis, and induce apoptosis.[xxi,xxii]

Chocolate also has a high concentration of flavonoids. Procyanidins are found mainly in cocoa, almonds, and green apples. In vivo, studies have shown to increase the proapoptotic action of Bax protein and inhibit tumor cell proliferation by inducing apoptosis through caspase-3 activation via the mitochondrial pathway.[xxiii,xxiv]

Polyphenols in the prevention of nonmetastatic breast cancer

Polyphenols possess excellent anti-free radical properties and are the principal dietary antioxidants with vasoprotective, vasodilatory, antilipemic, antithrombotic, anti-inflammatory, antiapoptotic, and antiatherosclerotic actions.[xxiv,xxv] A combination of these mechanisms might contribute to the preventive character against breast cancer.

It is estimated that daily consumption of 400-600 grams of fruits and vegetables is associated with a lower incidence of breast cancer due to their high content of phytochemical substances with a predominance of polyphenols that can modulate gene expression and inhibit carcinogenesis. There should be variety in the diet, consuming foods such as apples, grapes, almonds, cocoa, carrots, strawberries, blueberries, coffee, and others.[xxvi]

A study conducted in 2019 revealed that a high intake of isoflavones (such as those in soy) at doses of approximately 10 mg/day reduces the risk of breast cancer by 3 %.[xxvii] In addition, polyphenols have been shown to act at the level of signaling pathways and protein modification to prevent breast cancer progression, acting on transcription factors such as NF-kB, Wnt/B - catenin, peroxisome proliferator-activated receptor gamma receptor (PPAR-y).[xxvii,xxviii]

A study published in November 2020 established through cell cultures that 1µM of β-carotene is sufficient to decrease the expression of the anti-apoptotic protein BLC2 and PARP and reduce the proinflammatory and survival protein NF-kB. This compound has cytotoxic effects produced by various mechanisms, such as decreased oxidative stress, reduced activity, and phosphorylation of MAPKs, in particular protein kinase B (AKT). [xxix]

The importance of including polyphenols in the diet for breast cancer prevention has been investigated. Dysregulation of cell division is one of the core features of tumors, and the anti-cancer properties of polyphenols are mainly evidenced by blocking cell cycle progression at crucial transition points, especially the suppression of phosphorylation of tumor suppressor proteins.[xxx]

Polyphenols versus conventional treatment in breast cancer management

Conventional treatment for breast cancer includes local interventions, such as surgery or radiation therapy, and systemic therapies, such as cycles of chemotherapy, hormonal therapy, and targeted therapies on a case-by-case basis.[xxxi] However, in recent years it has been established that tumor cells can be resistant to these treatments due to the cellular ability to eliminate the chemotherapeutic, increase the production of antiapoptotic proteins, and modulate signaling pathways involved in carcinogenesis.[xxxii]

Both *in vitro* and *in vivo* studies have shown that combinations of chemotherapeutics with natural polyphenols increase the efficacy of the chemical, decrease chemical resistance, and prevent the development of adverse effects.[xxxiii] A 2023 systematic review by Torić *et al.* demonstrated that the combination of olive oil polyphenols, especially hydroxytyrosol, tyrosol and its derivatives oleuropein, and lapatinib inhibits growth and proliferation by inducing the apoptotic pathway, likewise, it increases the expression of apoptosis-inducing BAX and SMAC genes while decreasing the expression of the apoptosis inhibitor BCL2 and the SURVIVIN gene.[xxxiv]

Wen *et al.* studied the insensitivity of doxorubicin (DOX) as a chemotherapeutic

in breast cancer; they concluded that its combination with curcumin increases sensitivity by decreasing the minimum inhibitory concentration of the chemical (IC50). In addition, it specifically increases sensitivity in two breast cancer cell lines: MCF-7 and MDA-MB-231, through inhibition of the ABCB4 gene without altering protein production, leading to an increased amount of doxorubicin (DOX) in the tumor cell.[xxxv,xxxvi]

Another study conducted in 2021 by Özdemir *et al.* demonstrated that a high dose of resveratrol (185 μM) inhibits tumor growth, invasion, and migration in the MDA-MB-231 cell line, concluding that the combination of cisplatin with resveratrol increases the percentage of apoptosis allowing the use of less of the toxic chemical while avoiding its adverse effects.[xxxvii,xxxviii]

In addition, the 2021 study by Jin *et al.* concluded that the combination of resveratrol with DOX inhibits cell proliferation, suppresses tumor cell growth, and increases the influx of chemotoxicant into the tumor cell without affecting mammary epithelial cells.[xxxix]

The effectiveness of quercetin added to chemotherapeutic drugs against breast cancer has been demonstrated. Safi *et al.* established that quercetin added to docetaxel (DOCE) treatment produces a synergism that increases apoptosis through a mechanism that increases the expression of p53-associated X protein and BCL2. [xl] Moreover, Roshanazadeh *et al.* observed that in the MDA-MB-231 cell line treated with 5-fluorouracil and quercetin, it was possible not only to decrease cell viability but also to inhibit cell migration. [xli]

Several studies have found that luteolin induces apoptosis in the MDA-MB-231 cell line, inactivating the caspases and poly-ADP-ribose polymerase (PARP) cascade. [xlii] In addition, it generates a regulation on the expression of four genes (AP2B1, APP, GPNMB, and DLST), which are associated with drug resistance, macrophages, apoptosis, and inhibition of histone deacetylases (HDAC), expressed in breast cancer.[xliii]

The effects of epigallocatechin gallate have been shown to activate caspases, which generate a proapoptotic action;[xxi] in combination with DOCE and paclitaxel, it activates caspase-3 and p53 and increases the expression of the p53 tumor suppressor gene. This flavonoid inhibits telomerase activity, causing cell cycle arrest and inducing senescence in cancer cells. EGCG and cisplatin combined enhance apoptosis by positively regulating Nrf2/HO-1 expression. The combination of doxorubicin with this polyphenol improves treatment efficacy by inhibiting tumor growth and angiogenesis and enhances apoptosis and necrosis in breast cancer cells.[xxi,xliv]

Procyanidin (ProB2) has a high antitumor effect without having toxic results on healthy breast cells. Its use has been studied in combination with the chemotherapeutic DOCE, which works on the microtubules of cancer cells, stopping the cell cycle and inducing apoptosis. However, its use has been limited by cumulative toxicity and cellular resistance. The combination of procyanidin B2 and DOCE was investigated in the MCF-7 cell line demonstrating antiproliferative effects and increased sensitivity to chemotoxicity.[xlv,xlvi]

Conclusion

Polyphenols have excellent vasoprotective, vasodilatory, antilipemic, antithrombotic, anti-inflammatory, antiapoptotic, and antisclerotic properties. The anticarcinogenic role of dietary polyphenols in the prevention and treatment of non-metastatic breast cancer lies mainly in their antioxidant properties, which nullify free radicals, promote a proapoptotic state, and form stable chemical compounds.

It is worth considering the variable and inexact concentration of polyphenols in each food, and it is difficult to determine the number of fruits, vegetables, and seeds needed to reach the optimal daily amount, which is also unknown. Currently, the consumption of 400-600 grams of foods rich in polyphenols is associated with a lower incidence of non-metastatic breast cancer; however, the minimum amount of each polyphenol needed to generate relevant effects in prevention is unknown.

The ability of polyphenols to be included in the diet of breast cancer patients has been demonstrated to improve sensitivity to chemotherapeutics, such as the combination of curcumin and lapatinib, curcumin and resveratrol with doxorubicin, resveratrol with cisplatin, quercetin with DOCE and 5-fluorouracil, epigallocatechin gallate with DOCE, paclitaxel, and doxorubicin, as well as procyanidin with DOCE. These combinations increase drug uptake and the apoptotic process, prevent drug resistance, and decrease the adverse effects of the chemotherapeutic.

Conventional treatment for breast cancer is based on surgery, chemotherapy, and radiotherapy, depending on individual cases. However, ideally, the treatment should be integral, including the nutritional aspect, since it is crucial during the preventive and treatment phases. Consumption

of natural polyphenols in the diet increases the efficacy of the chemical, decreases resistance to chemotherapeutics, and helps prevent adverse effects.

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