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Plant secondary metabolites and their antineoplastic effects: a brief review

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Abstract

Neoplastic diseases are pathophysiological conditions that usually require surgical treatment, and the use of chemotherapy drugs that aim to eliminate cancer cells, however, the low toxic selectivity of these drugs can determine many devastating adverse effects. Empirically, many medicinal plants are used in the treatment of cancer, and reports of cures for this pathophysiological condition through the use of these plants have been observed in popular medicine. The present work sought to identify whether there is scientific evidence for the use of fruits and medicinal plants as a therapeutic aid in the treatment of different neoplasms, through a descriptive and exploratory review of the literature that was based both on the popular practice of using some fruits and plants medicinal products and in the scientific literature of sites such as: SciElo, Science Direct, Web of Science, PubMed and BVS (Brazilian Virtual Library). The different edible plants and vegetables presented in the present study can be considered important sources of active compounds with antineoplastic action, as they negatively modulate the progression of the development of cancer cells observed in different types of tumors.

Key words: Cancer, Neoplasms, Medicinal plants, Biological activities, Antitumor activity

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1. Introduction

According to the document World cancer report 2014 by the International Agency for Research on Cancer (Iarc), of the World Health Organization (WHO), cancer should be considered a public health problem, especially among developing countries, in view of that in the coming decades, the impact of this disease on the population will correspond to 80% of the more than 20 million new cases estimated for 2025 in the world population [1].The literature reports that, currently, the types of cancer with the highest incidence in the world are breast, lung, intestine, stomach, uterus, and prostate. In men, the most frequent cancers are lung (16.7%), prostate (15.0%), intestine (10.0%), stomach (8.5%), and liver (7.5%). On the other hand, in women, cancers of the breast (25.2%), intestine (9.2%), lung (8.7%), cervix (7.9%), and stomach (4.8%) are the most frequent [2]. There are different strategies used in treating different types of cancer. Among these strategies are surgical procedures, the use of conventional chemotherapy drugs [3], as well as the empirical use of medicinal plants [4]. However, the use of medicinal plants is not always related to cancer itself, but also to symptoms correlated to this pathophysiological condition, such as pain and inflammation, nausea, vomiting or even increased oxidative stress [5]. In this way, cancer treatment is very complex because it is a multifactorial disease that requires multiple interventions, whether medical, nutritional, or related to changes in lifestyle. In addition, its association with mental, emotional, social, and spiritual problems is attributed. The therapeutic modalities currently available for treating malignant neoplasms are surgery, radiotherapy, chemotherapy, and hormone therapy. Furthermore, the use of medicinal plants or their constituents are considered auxiliary agents during cancer treatment [6]. The use of medicinal plants (phytotherapy) is an ancient practice and emerged in China around 3000 years ago, where the properties of camphor and ginseng for therapeutic purposes were described [7]. Initially, phytotherapy was closely related to rituals and prayers and was considered the only traditional means of preventing or treating pathologies and injuries of individuals from traditional communities [8]. Knowledge about herbal medicine was passed from generation to generation and from then on, through ethnobotany, ethnopharmacology, and other branches of science, new herbal medicines were developed and used in the treatment of human diseases [9]. The literature reports a growing use of complementary or integrative therapies in the treatment of cancer, which are described as a set of prevention, diagnosis, and treatment practices, apart from the dominant medical model, where there is a predominance of allopathy [10] and in Brazil, it is estimated that more than 60% of all cancer patients use complementary methods of treatment in the course of their illness [11]. In addition, there is a lack of uniformity in cancer treatment, and the need to reduce patients' anxiety, and for them to regain control of their health. These factors are pointed out as possible reasons for cancer patients to seek non-conventional medicine based solely on allopathy [12]. In this way, knowledge of the therapeutic potential of certain fruits, medicinal plants, and/or their chemical constituents in the

pathophysiology of cancer can be very useful in the treatment of cancer patients, since, in general, these vegetables and their chemical constituents cause few adverse effects. When compared to allopathic medicines [6]. One of the main factors that limit the use of medicinal plants for therapeutic purposes in clinical treatments is the scarcity of studies that prove their effectiveness and/or possible unwanted toxic adverse effects or interactions with conventional medications in use. In this sense, many specific studies are needed on the mechanisms of action, bioavailability, and phytochemistry, in addition to other scientific aspects that justify or not the use of these substances of natural origin, during the treatment of cancer patients [9].

2. Methodology

The present work used a descriptive and exploratory study, based both on the popular practice of using some fruits and medicinal plants and on the scientific literature of sites such as SciElo, Science Direct, Web of Science, PubMed, and BVS (Virtual Library of Brazil). The following terms were used as keywords: Cancer, Neoplasms, Medicinal plants, Biological activities, antitumor activity. As exclusion criteria, articles describing plants or fruits with non-medicinal purposes were eliminated from the search, and, as inclusion criteria, only published works describing plants with medicinal purposes and popular applicability were selected.

3. Results and Discussion

3.1. The importance of using medicinal plants in the treatment of cancer

The range of conventional antineoplastic drugs has low selective toxicity, as it causes the death of both cancer cells and normal cells, and the consequences of using these drugs are the most diverse adverse effects. Thus, the search for new compounds that present greater selective toxicity becomes clinically useful, which validates the search for new pharmacological targets from natural products, mainly directed to plants used in folk medicine [13]. The search for antineoplastic drugs has increased, with the aim of expanding the possibilities of treatments, making them more effective and selective, or aiming to discover new strategies that prevent the advancement of cancer. In this sense, many medicinal plants have been usually used in folk medicine with the aim of reducing the symptoms and signs presented in cancer patients [14].

3.2. Scientific evidence of the biological activity and antitumor effect of different plants

3.2.1 Morinda citrifolia (Noni)

For over 2,000 years the fruit *Morinda citrifolia* L. (Rubiaceae), known as Noni or Noni Tahiti, has been used in Polynesia, China, India and elsewhere to treat ailments such as burns, wounds, tumors, indigestion and menstrual irregularities [15]. In America, Noni fruit is prepared for the purpose of nutritional supplementation. It is also used as an aid in the treatment of any type of cancer and to promote good general health, as it acts as a stimulant of the immune system [12]. Noni is a small tree of the Rubiaceae family, originating in southwest Asia and was spread by man across India and the Pacific Ocean to the islands of French Polynesia. The traditional use of *Morinda citrifolia* by Polynesians was attributed to effects related to antibacterial, antiviral, antifungal, antitumor, anthelmintic, analgesic, anti-inflammatory, hypotensive and immunostimulant activity [16]. Noni has common applicability in popular use as an antineoplastic and currently, it is known that the benefits of the fruit go beyond what the Polynesians knew, being used as an auxiliary therapy in the treatment of cancers such as those of the abdominal cavity, liver, lung, skin, among others. In Brazil, Noni is consumed in the form of tea or juice mixed with other fruits to mask its flavor. Among its benefits are: stimulating the production of macrophages and T lymphocytes of the immune system, acting on the body's defenses and helping in the treatment of pathologies caused by bacteria, viruses, fungi and even those related to neoplastic processes [17-18]. The literature also reports that xeronine, the main compound found in Noni fruit, has an analgesic effect and the ability to inhibit the growth of malignant tumors. In addition, squalamine, another substance present in Noni fruit, is capable of inhibiting the formation of new blood vessels responsible for the blood supply of tumors, which determines a reduction in the development of tumor cells [19]. In this way, Noni pulp is rich in anthocyanins (pigments belonging to the flavonoid group), in addition to being rich in tetraterpenes and ascorbic acid [20]. Tetraterpenes and vitamins are the most widely studied compounds as agents used in the prevention of diseases, as they act as antioxidant agents, and in this way, sequester singlet oxygen, remove peroxide radicals, negatively modulate carcinogenic metabolism, inhibit cell proliferation, stimulate communication between cells (gap junctions) and increasing the immune response [20]. With regard to flavonoids, they also constitute an important class of polyphenols, present in relative abundance in the pulp of the Noni fruit. These compounds have diverse biological activities, including anticarcinogenic properties [20]. The literature also reports that the content of yellow flavonoids found in the pulp of Noni is higher than that found, for example, in the pulp of several other fruits [21], and that although Noni has high concentrations of vitamin C, the amount of this vitamin in the fruit decreases with ripening [22]. More information on the biological effects of *Morinda citrifolia* is summarized in Table 1.

3.2.2 Beta vulgaris (Beetroot or sugar-beet)

Beta vulgaris is cultivated for its roots, which have high nutritional value and are routinely consumed after processing [23]. Beetroots are used in salads, juices, and even in the preparation of some exotic dishes. Beetroot extract has remarkable antioxidant activity thanks to a group of molecules grouped under the name of betalains [23]. Betalains (betacyanin and betaxanthin) are composed of betalamic acid, where betacyanin has red or violet color while betaxanthin has a yellow color, but betacyanin has greater antioxidant power than betaxanthin [24]. The literature reports that betacyanins are able to inhibit lipid peroxidation and the growth of several tumor cell lines, which makes this food an invaluable source of bioactive compounds with antineoplastic properties [23].

In addition to the previously described antitumor effect, betacyanins also have the ability to reduce blood pressure by inducing an increase in the production and release of endothelium-derived relaxation factors [25-26]. The literature also reports that the addition of red beet to the diet of rats is capable of determining a reduction in the metabolic alterations observed during dyslipidemia, including a reduction in the lipid profile, in the serum concentration of total cholesterol, triglycerides and glycemia, which implies a decrease lipid peroxidation and oxidative stress [28]. In addition, beet leaves and stalks are rich in iron, sodium, potassium [29], polyphenols, β-carotene, α-tocopherol and betanin [30] and, compared to roots, beet leaves have a higher

concentration of phenolic compounds, flavonoids, and increased plasma total antioxidant capacity [31]. Thus, the importance of the biological effects of beet constituents in the control of different physiopathologies, including neoplasms, is clear. More information on the biological effects of *Beta vulgaris* is summarized in Table 1.

3.2.3 Annona muricata (Soursop)

Soursop extracts play an important role in the medicinal field, as they have antiviral, antiparasitic, astringent, antirheumatic and antileishmanial effects [32] and that, the use of soursop juice or tea, both obtained from its leaves, is also used empirically by cancer patients because, according to traditional medicine, the juice and/or tea of this fruit has an antitumor effect. However, soursop has a certain degree of toxicity (due to the action of acetogenins present in soursop) and should not be consumed in excess as a preventive measure against cancer [32]. The secondary metabolism of *Annona muricata* produces groups of bioactive phytochemicals, such as alkaloids, phenolic compounds, flavonoids, terpenes, and acetogenins, all with antioxidant properties. Other constituents of soursop are citric, oxalic, caffeic, coumaric, stearic, linoleic, malic, oleic acids; anonol, campesterol, citrulline, dextrose, ethanol, phytosterols (β-sitosterol, stigmasterol), fructose, ipuranol, manganese, leucoanthocyanins, sucrose, tannins, among others [34]. However, most Annonaceae phytochemistry studies do not focus on the alkaloids, but on a class of extremely bioactive compounds that are referred to as annonaceous acetogenins. Acetogenins are known to be compounds with potent cytotoxicity. It has been shown that the mechanism of action of acetogenins is related to the reduction of nicotinamide adenine dinucleotide (NADH): ubiquinone reductase in complex I, which is the membrane-bound protein of the mitochondrial electron transport system, and ubiquinone-linked NADH oxidase in plasma of cell membranes of cancer cells [35]. In addition to acetogenins, other compounds that are present in a large percentage in soursop are alkaloids. Several alkaloids have been identified in *Annona muricata*, including anonaine, nanomedicine, anomurine, asimilobin, anomonicin, anonaine, atherospermine, atherosperminine, coclaurine, coreximine, stepharine, muricin, muricinin, nornuciferine, reticulin (major alkaloid), tyramine, tetrahydrobenzylisoquinolines [36]. Reticulin is a common alkaloid precursor of benzylisoquinoline in the morphine and papaverine biosynthetic pathway and is structurally related to papaverine, a spasmolytic agent. This alkaloid also has several other effects, including a vasodilating effect, since it inhibits the influx of calcium into vascular smooth muscle, through blocking voltage-dependent calcium channels, a relaxing effect on skeletal muscle, determined by blocking of the neuromuscular junction, bactericidal and curative effects and effects on the central nervous system [37-40]. However, the cytotoxic effect of *Annona muricata* is attributed to the action of acetogenins, as these substances inhibit NADH oxidase and prevent oxidative phosphorylation, resulting in a decrease in cellular ATP levels and delaying the development of tumor cells [41]. In addition, neoplastic cells in the S phase of the cell cycle are more vulnerable to the action of acetogenins, and annonacin induces cell cycle arrest in the G1 phase and inhibits the progression of the S phase, in addition to stimulating the action of p53 and p21, cycle checkpoint proteins [42]. From the above, the biological relevance of the secondary metabolites of soursop is clear, mainly in the development of neoplastic cells. More information on the biological effects of *Annona muricata* is summarized in Table 1.

3.2.4 Aloe vera (Aloé)

Aloe vera is a plant commonly used empirically mixed with water, juice, milk, honey or wine by cancer patients. Some phytochemical studies have demonstrated the presence of compounds of pharmacological interest, to which various activities have been attributed: antiseptic (saponin and anthraquinone); antitumor (mucopolysaccharides), anti-inflammatory (steroids and salicylic acid), antioxidant (vitamins), immunoregulatory and detoxifying (glucomannans) [6]. The literature reports that *Aloe vera* is able to potentiate the immune system response, increasing the cytotoxicity of natural killer cells on cancer cells in vitro and in vivo [43], and that flavonoids, carotenoids, aloin, aloe-emodin and acemannan, present in *Aloe vera*, seems to be directly involved in this anticancer effect [44-45]. In this sway, aloe-emodin, present in aloe vera, binds to the mammalian target of the rapamycin 2 complex (mTORC2) of cells, inhibiting its kinase activity. This leads to a suppression of prostate cancer progression, for example [46]. The literature also reports that the topical use of *Aloe vera* in gel form also determines beneficial effects during the treatment of mice with skin carcinoma, where these beneficial effects of *Aloe vera* are related to the decrease in the number of papillomas during skin cancer [47] and that among the constituents of *Aloe vera*, the polysaccharides acemannan and glucomannan, act as immunomodulators, while the anthraquinone aloe-emodin is pointed out as the main responsible for the anticancer activities[48]. The previously described information points to the relevant importance of the secondary metabolites of *Aloe vera* as possible new biological assets, useful in the treatment of cancer. More information on the biological effects of *Aloe vera* is summarized in Table 1.

3.2.5 Curcuma longa (Turmeric)

Among the various factors involved in the etiology of cancer, one of the most discussed currently has been the redox imbalance, where the production of free radicals has been greater than the amount of antioxidants presents in the body. Among free radicals, reactive oxygen species (ROS) stand out, whose presence of unpaired electrons gives them characteristics of instability, with the potential to trigger an increase in oxidative stress, which has been described as one of the main factors related to the appearance of diseases such as atherosclerosis, cataracts, neurodegenerative diseases in particular cancer. Antioxidants are molecules that have the property of blocking, inhibiting, or delaying oxidative deterioration, reducing the action of free radicals [49]. Turmeric is an example of a plant product that acts by "sequestering" reactive oxygen species in situations of cellular oxidative stress [50]. *Curcuma longa* is commonly used in cooking to season meat, rice, and salads, among other dishes [51], however, its use has been increasing and can be administered in different ways. In general, it can be used through decoction or infusion of the rhizome, micronized powder tincture, and dry extract, among other preparations [52]. The chemical composition of turmeric is quite varied, with the main classes of compounds being volatile terpenes, present in the essential oil of different parts of the plant, in addition to curcuminoids, major components of non-volatile production.

Table 1. Particularities of medicinal plants used empirically by cancer patients

Scientific name of medicinal plant	Method of preparation for consumption	Pharmacological properties	Mechanism of antitumor or antineoplastic action of related biologically active compounds	References
Morinda citrifolia	Teas and Juices	Immune system stimulant, healing, antidysmenorrheic, antibacterial, antiviral, antifungal, anthelmintic, analgesic, anti-inflammatory, hypotensive, antitumor and antineoplastic effects	Xeronine has an analgesic effect and squalamine inhibits blood supply to the tumor by inhibiting local angiogenesis Anthocyanins, carotenoids and ascorbic acid scavenge free radicals and decrease oxidative stress and metabolism of carcinogenic cells	[15-22]
Beta vulgaris	Fresh (raw), cooked or juice	Antioxidant activity	Betalains inhibit lipid peroxidation and the growth of different types of tumor cells	[23], [25], [29-31]
Annona muricata	Fresh (raw) or juice	Antiviral, antiparasitic, astringent, antirheumatic and antitumor effect	Annonacin induce tumor cell damage and death and inhibits the cell cycle of cancer cells	[32-34]
Aloe vera	Added and mixed with water, juice, milk, honey, or wine	Antiseptic, anti-inflammatory, antioxidant, immunostimulating, detoxifying, and antitumor effects	Aloeemodin binds to the mammalian target of rapamycin complex 2, inhibits protein phosphorylation and suppresses the progression of cancer cells	[44]

To be continued

Table 1. Particularities of medicinal plants used empirically by cancer patients

Continuation

Scientific name of medicinal plant	Method of preparation for consumption	Pharmacological properties	Mechanism of antitumor or antineoplastic action of related biologically active compounds	References
Curcuma longa	Micronized powder, decoction, infusion, dry extract	Anti-inflammatory and analgesic	Curcumin inhibits the production of cyclooxygenases and TNF-α and the synthesis of other inflammatory mediators and antagonizes the effects of NF-κB, and the structural organization of tubulin and microtubule formation of cancer cells	[52], [57-58], [74]
Euterpe oleracea	Fresh (raw) or juice	Pro-apoptotic and anti-proliferative effects on cancer cells	Polyphenols modulate different stages of the apoptotic process and/or the expression of regulatory proteins, including downregulation of NF-kB, caspase-3 cleavage, downregulation of anti-apoptotic Bcl-2 and Bcl-XL expression, and increased expression of the proapoptotic Bax and decrease oxidative stress. Cyanidin-3-glucoside is a potent cell antiproliferative agent.	[59-61], [65]
Anacardium occidentale	Fresh (raw), juices and ice cream	Gastroprotective, antimicrobial and antitumor effect.	Anacardic acid inhibits histone acetyltransferase p300 and the DNA transcription and repair system of cancer cells, blocks the effects of NF-κβ and tumor cell survival and expansion	[69-72], [75]

These occur in greater proportion in the rhizomes of the plant, with emphasis on curcumin (CUR) 77%, demethoxycurcumin (DMC) 17% and bisdemethoxycurcumin (BDMC) 3%, in addition to minor curcuminoids [53].Due to the structural profile of curcumin, related to its phenolic nature and the existing conjugation extension, several works have explored its action as an antioxidant agent in different models. This activity can be attributed to two related subunits: methylene α to carbonyls and phenolic hydroxyls. In both cases, the antioxidant activity is related to the donation of radical hydrogen, which reacts with reactive oxygen species (ROS) and neutralizes possible cell damage resulting from the presence of these intermediates [53]. An important biochemical target of curcumin is through inhibition of the Nuclear Factor Kappa B (NF-κB) pathway. NF-κB participates in inflammatory responses, tumor processes, and some parasitic infections [54]. Initially, the extracellular stimuli that activate the NF-κB formation cascade depend on the presence of reactive oxygen species, which result from injuries, inflammatory processes, and oxidative stress. The presence of phenolic hydroxyls and the 1,3-dyketenic subunit of curcumin manage to capture the radicals of these reactive species, minimizing the activation of the pathway [55]. The literature reports that the curcumin also inhibits nitric oxide synthase and DNA binding of the c-jun/AP-1 transcription factor, which are downstream points in the NF-κB pathway [54]. In addition to NF-κB, another important nuclear factor for cell activation, known as AP-1, can be simultaneously inhibited by curcumin [53]. The inhibitory action of curcumin on transcription factors results in the decrease of a wide variety of cytokines and chemokines involved in the inflammatory response, such as tumor necrosis factor-alpha (TNF-α), interleukins 1, 5, 6, 8, 12, and 18 and interferon-gamma (INF-γ) [56]. Curcumin and its more active benzylidene derivative also act by inhibiting the structural organization of tubulin and, consequently, the formation of microtubules, culminating in cell death by apoptosis, an important process in the containment of certain types of cancer, such as epithelial cancer lung [53]. The literature also reports that turmeric also has a potent anti-inflammatory action by inhibiting inflammation factors such as phospholipase A, LOX – lipoxygenases, COX-2 – cyclooxygenases, leukotrienes, thromboxanes, prostaglandins, TNF-α, MCP-1[56] nitric oxide, collagenase, elastase and hyaluronidase [57]. In addition, curcumin associated with cyclosporine in combined chemotherapy potentiates the blocking effect of NF-κB and T cell proliferation [58]. From the above, it is evident that the constituents of turmeric have different biological activities that can be explored in more detail in order to establish the real value of these substances in the treatment of neoplasms. More information on the biological effects of *Curcuma longa* is summarized in Table 1.

3.2.6 Euterpe oleracea (Açaí)

Açaí is a fruit originating in the Amazon and widely consumed in the northern region of Brazil, being rich in several polyphenols, with anthocyanin being the predominant polyphenol representing more than 90% of the total polyphenolic content of this fruit and the literature reports that this class of biomolecules presents antitumor activity, as it inhibits and retards the growth of colon cancer cells, in addition to presenting pro-apoptotic and anti-proliferative functions in leukemic cells [59]. The açaí oil extracted from the fruit's pulp is rich in anthocyanin phenols, such as phenolic acids and procyanidins [60]. The açaí pulp has about 90 bioactive substances, including polyphenols, which have the ability to modulate different stages of the apoptotic process and/or expression of regulatory proteins, including downregulation of NF-kB, caspase-3 cleavage, downregulation of anti-apoptotic Bcl-2 and Bcl-XL expression, and increased expression of the proapoptotic Bax [59]. Anthocyanins belong to the class of polyphenols and have excellent antioxidant properties acting as scavengers of reactive oxygen species from oxidative stress, and cyanidin-3-glycoside (the most abundant anthocyanin in açaí) has an antiproliferative effect in studies carried out with cancer cells of breast [61-62]. The literature also reports that açaí oil in nanoemulsion has activity against melanoma skin cancer cells observed in studies involving experimental models in vitro and in vivo [63] and in non-melanoma cells in vitro and in vivo [64] and that different açaí extracts, using the fruit, the bark and/or the seed, show antitumor activity against MCF-7 cell lines, thus showing the biological and therapeutic potential of this plant [65]. The analyzes referring to the evaluation of the pharmacological potential of açaí still need to be extensively expanded by carrying out epidemiological, toxicological studies and other more detailed *in vitro* and *in vivo* experiments, in order to build a more robust database that represents its biological effects in a more detailed way. more accurate, since the polyphenols present in açaí oil are poorly soluble in aqueous solutions, which makes their administration and absorption by the body difficult [66]. In this context, the encapsulation of these phytochemical compounds in nanostructures becomes a plausible alternative to modulate their bioavailability and biodistribution, thus enhancing their biological effects [67]. More information on the biological effects of *Euterpe oleracea* is summarized in Table 1.

3.2.7 Anacardium occidentale (Cajueiro)

A plant of Brazilian origin, this tree is responsible for producing the pseudofruit (cajú or cashew), where the fruit (cashew nut) is trapped [68]. Cashew juice is very common in the daily lives of many Brazilians and its main chemical component is anacardic acid (AA), 2-hydroxy-6-pentadecylbenzoic acid, which is a type of phenolic lipid that has attracted great interest in recent years. years. times due to its antitumor, antibiotic, gastroprotective, and antioxidant properties [69]. Approximately 90% of the seed extract is composed of AA, the rest being composed of other components related to AA such as cardanol, cardol, and 2-methyl-cardol [70]. AA and its derivatives have the biological activity of inhibiting proliferation and inducing death in various types of tumor cells such as melanomas, colon, prostate, lung, cervix, kidney, and breast cancer [71]. The antitumor activity of AA is due to the inhibition of histone acetyltransferase p300, responsible for regulating the DNA repair and transcription system. Furthermore, AA blocks the transcription factor NF-κβ, responsible for controlling the expression of more than 400 different gene products necessary for the survival and expansion of tumor cells [72]. AA was identified as the first natural product that inhibits the activity and can be considered a natural biological compound of great value for the development of new drugs for the treatment and/or prevention of cancer [73]. More information

on the biological effects of *Anacardium occidentale* is summarized in Table 1.

4. Final considerations

Faced with the financial, economic, and cultural reality of certain developing countries, including Brazil, and in view of the examples described throughout this review, it is evident the importance of including a healthy diet based on foods of plant origin that help directly or indirectly the patient with cancer to have an improvement in his clinical picture or simply in the reduction of the pathological symptoms expressed by this type of individuals. However, the use of products of plant origin for medicinal purposes must be accompanied by scientific proof of their therapeutic effect, in addition to observing that they are exempt from toxicity and possible drug interactions that they may present.

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