Medicinal Plants and their Compounds with Therapeutic Potential in the Treatment of Cancer: an Integrative Review

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Plantas Medicinais e seus Compostos com Potencial Terapêutico no Tratamento do Câncer: Revisão Integrativa

Plantas Medicinales y sus Compuestos con Potencial Terapéutico en el Tratamiento del Cáncer: Revisión Integradora

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ABSTRACT

Introduction: The epidemiological and nutritional transitions have been contributing for the exponential growth of cancer. Thus, in order to enhance the activity of antineoplastic drugs, the number of studies using medicinal plants for cancer treatment has increased. **Objective**: To identify medicinal plants and compounds with possible action in the cancer treatment process. **Method**: An integrative review was carried out. For the bibliographic search, the descriptors "neoplasms" and "medicinal plants" and the qualifier "treatment" for the word cancer were used, specifying it. The articles were surveyed in the following databases: Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS) and Medical Literature Analysis and Retrieval System on-line (MEDLINE) from the PubMed. **Results**: The search and application of the inclusion and exclusion criteria resulted in the selection of 93 articles. The main characteristics of the studies included were in vitro assays, with breast cancer cell line and published in English. It was possible to identify six compounds that stood out due to their pro-apoptotic activity in various types of cancer such as curcumin, epicatechin, lupeol, caffeic acid, ursolic acid and berberine. **Conclusion**: The present work offers inputs so that future studies can associate the use of compounds present in medicinal plants with conventional treatment, in order to improve the prognosis of cancer patients.

Key words: Neoplasms/therapy; Plants, Medicinal/chemistry; Therapeutics; Complementary Therapies.

RESUMO

Introdução: As transições epidemiológica e nutricional têm contribuído para o crescimento exponencial do câncer. Assim, com o intuito de potencializar a atividade das drogas antineoplásicas, aumentou o número de estudos utilizando plantas medicinais para tratamento do câncer. **Objetivo:** Identificar as plantas medicinais e os compostos com possível ação no processo de tratamento do câncer. **Método:** Foi realizada uma revisão integrativa. Para a busca bibliográfica, foram utilizados os descritores "neoplasias" e "plantas medicinais" e o qualificador "tratamento" para a palavra câncer, especificando-a. O levantamento dos artigos foi feito nas seguintes bases de dados: *Scientific Electronic Library OnLine* (SciELO), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e *Medical Literature Analysis and Retrieval Sistem Online* (MEDLINE) via PubMed. **Resultados:** A busca e a aplicação dos critérios de inclusão e exclusão resultaram na seleção de 93 artigos. As principais características dos estudos incluídos eram ensaios *in vitro,* com a linhagem de células de câncer de mama e publicados em inglês. Foi possível identificar seis compostos que se destacaram em razão da sua atividade pró-apoptótica em vários tipos de câncer, a exemplo da curcumina, da epicatequina, do lupeol, do ácido cafeico, do ácido ursólico e da berberina. **Conclusão:** O presente trabalho oferece subsídios para que pesquisas futuras possam associar a utilização de compostos presentes em plantas medicinais ao tratamento convencional, com o intuito de melhorar o prognóstico de pacientes oncológicos.

Palavras-chave: Neoplasias/terapia; Plantas Medicinais/química; Terapêutica; Terapias Complementares.

RESUMEN

Introducción: Las transiciones epidemiológica y nutricional han contribuido al crecimiento exponencial del cáncer. Por lo tanto, para mejorar la actividad de los fármacos antineoplásicos utilizados para tratar la enfermedad, ha aumentado el número de estudios que utilizan plantas medicinales para este propósito. **Objetivo:** Identificar plantas medicinales y compuestos con posible acción en el proceso de tratamiento del cáncer. **Método:** Se realizó una revisión integradora, utilizando los términos de búsqueda validados y utilizados: "neoplasias" y "plantas medicinales". El calificador "tratamiento" se usó para la palabra cáncer, especificándolo. Los artículos fueron encuestados en las siguientes bases de datos: Biblioteca Científica Electrónica en Línea (SciELO), Literatura Latinoamericana y Caribeña en Ciencias de la Salud (LILACS) y Sistema de Análisis y Recuperación de Literatura Médica en Línea (MEDLINE) vía PubMed. **Resultados:** La búsqueda y la aplicación de los criterios de inclusión y exclusión dieron como resultado la selección de 93 artículos. Las características principales de los estudios incluidos fueron ensayos in vitro, con linaje celular de cáncer de mama y publicados en inglés. En relación con los estudios, fue posible identificar seis compuestos que se destacaron por su actividad contra diferentes tipos de cáncer: curcumina, epicatequina, lupeol, ácido cafeico, ácido ursólico y berberina, induciendo la apoptosis por varios mecanismos. **Conclusión:** El presente trabajo, nos permite ofrecer subsidio para que la investigación futura pueda asociar el uso de compuestos presentes en plantas medicinales con el tratamiento convencional, para mejorar el pronóstico de los pacientes con cáncer.

Palabras clave: Neoplasias/terapia; Plantas Medicinales/química; Terapéutica; Terapias Complementarias.

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INTRODUCTION

Cancer is one of the most prevalent diseases worldwide and the number of harms and deaths related to this condition is growing exponentially[1]. Studies attempting to identify the substances for the treatment that can improve patients' survival and quality of life have increased in the last years[2].

In this context, medicinal plants and functional food can work as potential adjuvant in cancer therapy considering the biological properties of its bioactive compounds[3]. In addition, the medicinal plants components and functional food have low cost and are easily accessed, yet safe dosages need to be determined[4].

This study is justified in order to elucidate the use of natural compounds in cancer therapy and stimulate the development of other studies on the theme. The objective of this study was to identify the medicinal plants and compounds with possible pharmacologic action in the process of cancer treatment.

METHOD

Integrative review proposed by methodological reference[5] consisting of six phases: 1) definition of the research question; 2) search in the databases; 3) data collection; 4) critical analysis of the studies included; 5) discussion of the results; and 6) presentation of the data with unambiguous notification of the results encountered.

The hypothesis to be tested in this study adopted the PICO[6] strategy where "P" stands for population, patient, or problem, "I", interest and "Co", context of the study. Thus, the following research question was elaborated: "What are the medicinal plants and compounds most utilized in cancer treatment?"

The databases Scientific Electronic Library Online (SciELO), Latin America and Caribbean Health Sciences Literature (LILACS) and Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed were searched to find the articles.

The criteria to select the articles comprehended all the categories with abstracts and full texts available for analysis and published in Portuguese, English, and Spanish between 2015 and 2019. In addition, the articles selected should respond to the research question.

The following descriptors acknowledged by the Descriptors of Sciences of Health (DeCS) and Medical Subject Headings (MeSH) adopted in the search were: "neoplasms" and "medicinal plants". In addition, the qualifier "treatment" was used for the descriptor "neoplasm", for better definition of the aspects. The Boolean operator "AND" was used to associate the descriptors in the databases.

This study adopted the classification of the articles included per levels of evidences proposed in the literature[7].

The construction of the database was based in the tool "Instrument of data collecting of the integrative review" proposed by the authors[8], containing variables of identification of the study as well as the main results and conclusion.

RESULTS

The initial search with the descriptors encountered 22,908 articles and of these, only 172 met the inclusion criteria and responded to the research question. After refining the studies found, 77 were duplicate, in different bases and databases – with the same search tool – which reduced the number to 93 articles that formed the sample.

The results showed that the biggest number of publications were concentrated in 2017 (n=23, 24.7%) and 2018 (n=24, 25.8%). All the articles were in English (n=93, 100%). Of the types of cancer most investigated, breast cancer was quoted in 46.2% (n=43) of the articles, colon cancer in 23.6% (n=22), prostate in 20.4% (n=19), liver, in 19.3% (n=18), kidney cancer in 14% (n=13) and lung cancer in 12.9% (n= 12); in most of the articles, different studies addressed more than one cancer simultaneously.

The type of trial most adopted in the texts selected was *in vitro* quoted in 68.8% (n=64) of the articles, followed by review (integrative and narrative) in 18.3% (n=17). *In vivo* trials were developed in 7.5% (n=7) of the sample and 4.3% (n=4) presented *in vitro* and *in vivo* trials concomitantly. Only one study (1.1%) addressed oncologic patients (double-blind randomized clinical trial).

Regarding evidence, 80.6 % (n=75) of the articles were at level III, 18.3% (n=17) at level II and only one article (1.1%) at level I of the reference adopted.

The main botanic families quoted in the articles were Asteraceae 10.5% (n=10), Fabaceae 8.4% (n=8), Zingiberaceae 7.4% (n=7) and Theaceae 6.3% (n=6). Families as Solanaceae, Betulaceae, Euphorbiaceae, Berberidaceae, Araliaceae, Rutaceae, Malvaceae, Piperaceae, Acanthaceae, Lamiaceae, Phyllanthaceae and Acanthaceae were quoted in at least two articles of the sample.

The results of this study are presented in Tables 1 to 5 describing the plants most investigated with possible effects in cancer treatment with the respective botanic families and active principles encountered.

DISCUSSION

The studies' results concluded that the medicinal plants utilized in the treatment of different types of cancer included species and classification of many countries and that during the last years, much emphasis has been given to this kind of study. When Fabaceae, Zingiberaceae and Theaceae stand out, it is possible to notice that the

Table 1. Medicinal plants investigated in cancer treatment. Alfenas, MG, 2020

Identification of the article	Author/year	Types of cancer	Botanic family	Medicinal plant (popular name)	Active principle
1	Azadmehr et al., 2015[9]	Breast	Scrophulariaceae	*Scrophularia variegata*	Unidentified
2	Caamal-Fuentes et al., 2015[10]	Liver and lung	Fabaceae	*Aeschynomene fascicularis*	Spinochalcone A
3	Sawadogo et al., 2015[11]	Leukemia	Verbenaceae	*Lantana ukambensis (cambará-de-jardim)*	Polymethoxyflavones
4	Esmaeilbeig et al., 2015[12]	Leukemia	Lamiaceae	*Satureja hortensis* (summer savory)	Unidentified
5	Formagio et al., 2015[13]	Breast, ovary, lung, and leukemia	Annonaceae	*Annonaceae*	Unidentified.
6	Ghorbani e Hosseini, 2015[14]	Breast, colon, and liver	Zingiberacea	*Curcuma longa* (saffron)	Curcumin
7	Hosseini et al., 2015[1]	Liver	Iridaceae	*Crocus sativus* (true saffron)	Unidentified
8	Jafri et al., 2016[15]	Breast and cervical cancer	Araliaceae	*Hedera nepalensis* (ivy)	Lupeol
9	Kuete et al., 2015[16]	Breast, colon, and prostate	Unidentified	*Nauclea pobeguinii*	Unidentified
10	Kuete e Efferth, 2015[17]	Kidney and liver	Piperaceae	*Piper Capense*	Phenolic components
11	Manosroi et al., 2015[18]	Liver	Unidentified	*Ventilago denticulata*	Unidentified
12	Mohammed et al., 2015[19]	Leukemia	Acanthaceae	*Andrographis lineata*	Flavones
13	Nourazarian et al., 2015[20]	Colon	Fabaceae	*Glycyrrhiza glabra* (licorice)	Unidentified
14	Rabe et al., 2015[21]	Melanoma	Asteraceae	*Artemisia khorassanica*	Sesquiterpene lactone
15	Sung et al., 2015[22]	Stomach, breast, prostate	Lamiaceae	*Salvia miltiorrhiza* (sage)	Dihydrotanshinone I
16	Wen et al., 2015[23]	Prostate	Apiaceae	*Cnidium monnieri*	Coumarin
17	Yaacob et al., 2015[24]	Breast	Acanthaceae	*Strobilanthes crispus*	Lutein
18	Yadav et al., 2015[25]	Breast	Fabaceae	*Saraca indica* (asoka tree)	Unidentified
19	Ali et al., 2016[26]	Breast	Unidentified	*Ochradenus arabicus*	Unidentified

Caption: *Compound found in unspecified medicinal plants.

Table 2. Medicinal plants investigated in cancer treatment. Alfenas, MG, 2020

Identification of the article	Author/year	Types of cancer	Botanic family	Medicinal plant (popular name)	Active principle
20	Asadi-Samani et al., 2016[2]	Breast and prostate	Theaceae	*Camellia sinensis* (Indian tea)	Epicatechin
21	Chen et al., 2016[27]	Stomach and colon	Rhamnaceae	*Rhamnus davurica*	Unidentified
22	Du et al., 2016[28]	Colorectal	Thymelaeaceae	*Daphne genkwa*	Flavonoids
23	Narayanan e Antonisamy, 2016[29]	Breast	Cyatheaceae	*Cyathea spp* (tree fern)	Unidentified
24	Kim et al., 2016[30]	Colon	Brassicaceae, Apiaceae e Betulaceae	*Descurainia sophia, Peucedanum praeruptorum* (herb-sophia)	Unidentified
25	Kuete et al., 2016[31]	Breast, colon, and prostate	Annonaceae e Passifloraceae	*Annona muricata e Passiflora edulis* (soursop and passion fruit)	Eugenol and quinones
26	Leelawat e Leelawat, 2016[32]	Colangio carcinoma	Phyllanthaceae	*Phyllanthus emblica* (Indian gooseberry)	Unidentified
27	Motawi et al., 2016[33]	Breast	Unidentified	*Unspecified**	Caffeic acid
28	Prasad et al., 2016[34]	Lung, breast and gall bladder	Solanaceae, Phyllanthaceae,	*Withani somnifera, Phyllanthus amarus* (Indian ginseng and leaf flower)	Unidentified
29	Pereira et al., 2016[35]	Leukemia	Geraniaceae	*Pelargonium sidoides*	Fluorouracil
30	Sapio et al., 2017[36]	Stomach and mouth	Labiatae	*Coleus forskohlii* (boldo-brasileiro)	Forskolin
31	Subramani et al., 2016[37]	Pancreas	Meliaceae	*Azadirachta indica* (Amargosa)	Nimbolide
32	Sun et al., 2016[38]	Ovary	Rosaceae	*Pyracantha fortuneana* (Piracanta)	Polysaccharides
33	Thomas et al., 2016[39]	Leukemia, breast, and kidney	Asteraceae	*Vernonia condensata* (boldo-baiano)	Vernolide A
34	Teoh et al., 2016[40]	Breast	Acanthaceae	*Clinacanthus nutans*	Unidentified
35	Uche et al., 2016[41]	Ovary	Menispermaceae	*Triclisia subcordata*	Cicleanine
36	Zhao et al., 2016[42]	Breast	Ranunculacea, Berberidaceae	*Hydrastis canadensis, Berberis aristata* (Balisse fruit)	Berberine
37	Attar et al., 2017[43]	Ovary	Phyllanthaceae	*Phyllanthus spp*	Corilagin
38	Bhandari et al., 2017[44]	Prostate, breast, and cervical cancer	Alliaceae	*Allium wallichii* (garlic)	Terpenoids and flavonoids

Caption: *Compound found in unspecified medicinal plants.

Table 3. Medicinal plants investigated in cancer treatment. Alfenas, MG, 2020

Identification of the article	Author/year	Types of cancer	Botanic family	Medicinal plant (popular name)	Active principle
39	Chandel et al., 2017[45]	Uterus and colon	Rubiaceae	*Anthocephalus cadamba*	Alkaloids
40	Rodrigues et al., 2017[46]	Prostate and melanoma	Combretaceae	*Terminalia fagifolia* (Caatinga-de--porco)	Unidentified
41	Dushimemaria et al.,2017[47]	Breast, melanoma, and kidney	Fabaceae	*Guibourtia coleosperma*	Unidentified
42	Harsha Raj et al., 2017[48]	Breast	Myrtaceae, Musaceae	*Eugenia jambolana, Musa Paradisiaca.* (Indian blackberry and banana tree)	Unidentified
43	Kooti et al., 2017[49]	Breast, colon, and liver	Theaceae, Amaryllidace, Zingiberaceae	*Camellia sinensis, Allium sativum, Curcuma longa* (Indian tee, garlic, saffron)	Epicatechin, allicin and curcumin
44	Kuete et al., 2017[50]	Lung, liver and breast	Asteraceae	*Elephantopus mollis* (tobacco weed, soft elephantsfoot erva-moli)	Flavonoids and polyphenols
45	Mbaveng et al., 2017[51]	Breast, prostate, colon	Piperaceae	*Piper capins*	Unidentified
46	Liang et al., 2017[52]	Leukemia, liver and uterus	Nyctaginaceae, Brassicaceae	*Bougainvillea spectabilis, Brassica campestres* (três-marias turnip, wormseed)	Unidentified
47	Mbele et al., 2017[53]	Prostate, kidney, and gall bladder	Zingiberaceae	*Zingiber officinale* (ginger)	Unidentified
48	Nguyen et al., 2017[54]	Pancreas, colon, ovary, lung, and skin	Rutaceae	*Paramignya trimera*	Ostruthin
49	Okubo et al., 2017[55]	Leukemia	Ranunculaceae and Rutaceae	*Coptis japonica e Phellodendron amurense*	Berberine
50	Pandey, 2017[56]	Melanoma	Fabaceae	*Bauhinia variegata* (pata-de-vaca)	Flavonoids
51	Rahman et al., 2017[57]	Prostate	Boraginaceae	*Cordia dichotoma*	Flavonoids
52	Rajavel et al., 2017[58]	Lung	Malvaceae	*Grewia tiliaefolia*	Unidentified
53	Roman Junior et al., 2017[59]	Breast and lung	Zingiberaceae	*Alpinia zerumbet* (false cardamom)	5,6-Dehydrokavain

to be continued

Table 3. continuation

Identification of the article	Author/year	Types of cancer	Botanic family	Medicinal plant (popular name)	Active principle
54	Thakor et al., 2017[60]	Kidney	Unidentified	Unspecified*	Maslinic acid
55	Torquato et al., 2017[61]	Breast, prostate, colon, liver	Zingiberaceae and Theaceae	*Curcuma longa* e *Camellia sinensis* (saffron and Indian tea)	Curcumin and Epigallocatechin -3
56	Xia et al., 2017[62]	Breast, colon, and prostate	Lamiaceae	*Scutellaria baicalensi* (Baikal skullcap)	Baicalin
57	Yadav et al., 2017[4]	Breast	Asteraceae	*Eclipta alba* (erva-botão)	Unidentified
58	Zhang et al., 2017[63]	Breast	Ranunculaceae	*Aconitum coreanum* (Wolfsbane Potion)	Polysaccharides
59	Zhong et al., 2017[64]	Lung, breast, liver, cervical and prostate.	Dryopteridaceae	*Dryopteris fragrans*	Unidentified
60	Abu-Darwish e Efferth, 2018[65]	Breast, prostate and kidney	Solanaceae	*Withania somnifera* (Indian ginseng)	Unidentified

Caption: *Compound found in unspecified medicinal plants.

Table 4. Medicinal plants investigated in cancer treatment. Alfenas, MG, 2020

Identification of the article	Author/year	Types of cancer	Botanic family	Medicinal plant (popular name)	Active principle
61	Al-Dabbagh et al., 2018[66]	Liver	Apocynaceae	*Rhazya stricta*	Flavonoids
62	Asadi-Samani et al., 2018[67]	Prostate	Euphorbiaceae and Asteraceae	*Euphorbia szovitsii* e *Achillea wilhelmsii*	Unidentified
63	Bonam et al., 2018[68]	Breast, kidney, liver and colon	Zingiberaceae	*Curcuma longa* e *curcuma zedoaria* (saffron and zedoária)	Curcumin
64	Chen et al., 2018[69]	Uterus, melanoma	Berberidaceae	*Gênero Epimedium*	Icaritin
65	Dong et al., 2018[70]	Pancreas	Fabaceae	*Pao Pereira* (pau-pereira)	Unidentified
66	Escher et al., 2018[71]	Colon, liver and lung	Asteraceae	*Centaurea cyanus* (escovinha)	Chlorogenic, caffeic and ferulic acids
67	Esghaei et al., 2018[72]	Colon	Theaceae	*Camellia sinensis* (Indian tea)	Epicatechin
68	Fort et al., 2018[73]	Prostate	Euphorbiaceae	*Cnidosculus chayamansa*	Unidentified
69	Gomes et al., 2018[74]	Breast, kidney and prostate	Asteraceae	*Solidago chilensis* (Brazilian arnica)	Diterpene solidagenone

to be continued

Table 4. continuation

Identification of the article	Author/year	Types of cancer	Botanic family	Medicinal plant (popular name)	Active principle
70	Hong et al., 2018[75]	Breast	Unidentified	Unspecified*	Apigenin and luteolin
71	Kuete et al., 2018[76]	Breast, liver and colon	Unidentified	*Ptycholobium contortum*	β-amirine and lupeol
72	Maciel et al., 2018[77]	Liver, colorectal and lung	Malvaceae	*Hibiscus sabdariffa*	Anthocyanins and flavonoids
73	Malvicini et al., 2018[78]	Colon	Poaceae	*Deschampsia antarctica* (Antarctic hair grass)	Antartina
74	Ogunlaja et al., 2018[79]	Breast and colon	Moraceae	*Ficus burtt-davyi*	Catechin and lupeol
75	Saeed et al., 2018[80]	Breast, colon, and liver	Betulaceae	*Betula pendula* (White birch)	Betulinic acid
76	Santos et al., 2018[81]	Liver, colorectal	Fabaceae, Theaceae Aquifoliaceae	*Aspalathus linearis,Camellia sinensis e Ilex paraguariensis*	Kaempferol, catechin, epicatechin
77	Sethi et al., 2018[82]	Breast, kidney, and colon	Fabaceae	*Trigonella foenum-graecum* (feno-grego)	Diosgenin
78	Sodrul et al., 2018[83]	Breast, kidney and colon	Araliaceae	*Panax ginseng* (ginseng)	Ginsenosides
79	Soyingbe et al., 2018[84]	Breast, uterus and colon	Apiaceae, Canellaceae e Curtisiaceae	*Centella asiatica, Warburgia salutaris e Curtisia dentata*	Unidentified

Caption: *Compound found in unspecified medicinal plants.

Table 5. Medicinal plants investigated in cancer treatment. Alfenas, MG, 2020

Identification of the article	Author/year	Types of cancer	Botanic family	Medicinal plant (popular name)	Active principle
80	Nguyen et al., 2019[3]	Pancreas	-	*Paramignya trimera*	Gallic acid and caffeic acid
81	Tayeh e Ofir, 2018[85]	Lymph nodes	Asteraceae	*Asteriscus graveolens* (rue)	Unidentified
82	Uen et al., 2018[86]	Mouth	Solanaceae	*Solanum nigrum* (nightshades)	Unidentified
83	Zhang et al., 2018[87]	Uterus	Asteraceae	*Dryopteris fragrans*	Unidentified
84	Asl et al., 2018[88]	Stomach	Linaceae	*Linum álbum* (fedegoso)	Unidentified
85	Aumeeruddy e Mahomoodally, 2019[89]	Breast	Piperaceae, Piperaceae and Ranunculaceae	*Piper nigrum, Piper longum e Nigella sativa* (black pepper)	Piperine, Sulforaphane and thymochinone
86	Cordeiro et al., 2019[90]	Lung	Lythraceae	*Lafoensia pacari* (pacari)	Procyanidin

to be continued

Table 5. continuation

Identification of the article	Author/year	Types of cancer	Botanic family	Medicinal plant (popular name)	Active principle
87	De et al., 2019[91]	Lung and cervical cancer	Dilleniaceae	*Dillenia pentagyn* (elephant apple)	Unidentified
88	Iqbal et al., 2019[92]	Skin	Zingiberaceae	*Curcuma longa* (saffron)	Curcumin
89	Lim et al., 2019[93]	Colon, breast cancer and leukemia	Amaryllidaceae	*Crinum amabile* (açucena-do-brejo)	Unidentified
90	Mfengwana et al., 2019[94]	Prostate, breast	Asparagaceae and Asteraceae	*Asparagus laricinus e Senecio asperulus* (aspargus)	Unidentified
91	Sinha et al., 2019[95]	Kidney	Unidentified	Unspecified*	Lupeol
92	Wang et al., 2019[96]	Leukemia	Meliaceae	*Melia azedarach* (cinnamon)	Unidentified
93	Zahra et al., 2019[97]	Breast, liver and larynx	Zingiberaceae	*Alpinia zerumbet* (false cardamom)	Unidentified

Caption: *Compound found in unspecified medicinal plants.

substances encountered in the plants of these families may lead to remarkable findings for cancer treatment with important antiproliferative effects both *in vitro* and *in vivo*. Therefore, this review attempted to guide future studies with other species of these families in order to detail the mechanisms of action and application in cancer[4] treatment.

The type of cancer most described in this survey was breast cancer, associated with extracts of medicinal plants in cells cultures mainly. According to some authors[15,70], breast cancer is one of the main causes of death in women worldwide and the use of alternative therapies with natural products may increase the survival of these patients effectively and safely.

Some investigators reported the necessity of identifying the compounds found in medicinal plants responsible for the antineoplastic effect[65]. In this review, it was possible to evaluate that the compounds curcumin, epicatechin, lupeol, caffeic acid, ursolic acid and berberine stood out because of their activity against several cancer types, especially in *in vitro* studies where these compounds were isolated from medicinal plants used in assays. Curcumin can be encountered in *Curcuma longa* mainly and demonstrated effect on the reduction of the cellular viability of breast and colon cancer by promoting accumulation of reactive oxygen species (ROS), which can promote cellular stress and trigger the process of apoptosis[32,81].

Another study described that curcumin is a potent inhibitor of NF-kß (nuclear factor kappa ß), and anticancer agent since this protein complex (NF-kß) is related to the response to stress stimuli and its deregulation is connected to the development of tumors[12,76]. In addition, curcumin was associated with the cell cycle arrest in phase G2/S, inducing apoptosis. These findings associated with easy access and low cost of the plant may indicate the possibility of application of curcumin in the therapy of prostate, breast, and colon tumors, potentializing the effect of conventional therapy[81]. It is important to highlight that most part of the studies analyzing the action of this component was carried out with *in vitro* and *in vivo* assays and although these assays show the concentration of the extract utilized, it is difficult to extrapolate to human beings in what concerns the determination of the dosage; more clinical trials and study of mathematical models that potentially may determine the posology to be used to reach the expected results are necessary[1].

Epicatechin, a flavonoid that can be found in plants as *Camellia sinensis*, known as India tea, green tea, white tea, red tea among other popular names was evaluated for inhibiting the growth of cancer cells with low toxicity for healthy cells[2,61]. The mechanism of action of this substance was associated with the increase of the concentration of caspases, that can be defined as essential and constitutive proteases of the apoptosis process.

The alternative treatment with medicinal plants was able to increase the concentration of initiator caspases (as numbers 8 and 9), whose function is to cleavage the inactive preformed caspases and the concentration of effector caspases (as number 3, for instance), that cleavage other substrates, triggering the apoptotic cascade[46].

This characteristic allows the use of the compound in anticancer therapy because it is safe for normal cells and exerts antiproliferative effect in tumor tissues[33].

Lupeol of the class of pentacyclic triterpenes encountered in common fruits as olive, mango and fig showed promising effects in cancer treatment[72]. Studies[41,42] demonstrated that this compound was able to develop several functions, among them, inhibition of proliferation, migration and invasion of kidney carcinoma and gallbladder, further to inducing cells to apoptosis.

Possibly, lupeol-induced cellular death mechanism is related with the suppression of matrix metalloproteinases (MMP-9), an enzyme that degrades the basal membrane, allowing that factors involved with the carcinogenic process invade the blood flow, giving origin to metastases. This compound can be encountered in the plant of the species *Hedera nepalensis* and the ethanolic extract was able to inhibit the growth in more than 60% of cells culture of breast and cervical cancer, indicating possible application in oncologic therapy[87].

Similarly, other studies demonstrated that lupeol has cytotoxic activity for lineages of breast, liver and colon cancer and can be a promising candidate as drug for therapy against cancer because of the modulation of the mitochondrial dynamic influencing processes that interfere in the integrity of the membrane, provoking apoptosis. However, posology evaluation will be necessary in future studies for application in human beings as the articles address *in vitro* and *in vivo* trials[28,84].

Another compound identified in the studies of this review was caffeic acid, a phenolic acid whose property is its binding to other compounds with important antiproliferative and antioxidant activity. This acid activated the process of apoptosis in breast cancer cell through modulation of caspases and fragmentation of DNA, destroying tumor cells[72].

In addition, it was associated with the control of the cellular cycle related to the genes of the family Bcl-2 and to the proteins originated from said genes. These compounds belong to the family of antiapoptotic proteins (Blc2, for example) as well as by proapoptotic proteins (like Bax), the compound was able to regulate Bcl-2 negatively and reduce the relation Bcl2/Bax[45]. Therefore, the application of the caffeic acid as adjuvant in cancer treatment can be viable since this compound also demonstrated low cytotoxicity to normal cells and can preserve healthy tissues in patients with cancer[3].

The ursolic acid, a pentacyclic triterpenoid identified in the epicuticular waxes of the apples and widely found in fruits peels and medicinal plants was able to induce the apoptosis of skin cancer cells by increasing the concentration of caspases in special effector caspases number 3 responsible for substrate cleavage, promoting sequencing that leads to cellular death[76]. The results encountered showed dose-dependent efficacy, which suggests that the adjuvant application in cancer treatment should be done with the compound isolated in order to potentialize the effects of the conventional therapy[91].

Finally, the compound berberine, a natural benzylisoquinoline alkaloid extracted from rhizomes and roots of several plants, as the species *Berberis aristata,* evaluated as opposed to breast cells cancer. This compound was effective in preparing the cells to cisplatin (antineoplastic) with activation of pro-apoptotic factors also related to the increase of caspases, specially caspase 9 responsible for the initial phases of the apoptosis process[66]. It can be indicated as adjuvant therapy to the clinical treatment, mainly in patients with cancer who suffered metastasis because of its potentializing activity of the effects of antimetastatic drugs[49].

Considering the findings of the present integrative review, studies of *in vitro* and *in vivo* dosages are relevant and necessary to support its potential application in human beings according to a study where four patients with liver cancer who used 100 mg/day of encapsulated dry saffron (*Crocus sativus)* were compared with the placebo group, associated with chemotherapy. The observations showed that in the group treated with saffron, two patients responded partially or completely to the elective treatment and in the placebo group, no response was observed, which can suggest a possible application of these compounds in the protocol of treatment of patients with malignant neoplasms[1].

The discoveries and information presented in the studies selected and included in the analysis of this review can bring elements for new studies related to the identification of active principles of the medicinal plants as adjuvant therapy in human beings in order to potentialize the effects of the conventional therapy to prepare the cells to absorb the drugs utilized and increase the rate of cancer cellular death, leading to better prognosis and reversing the course of the disease.

CONCLUSION

The results of the studies included in this review allowed to conclude that the substances most investigated in the medicinal plants for cancer treatment are curcumin, epicatechin, lupeol, caffeic aid, ursolic acid and berberine. These compounds have been evaluated mostly in *in vitro* and *in vivo* assays due to their antineoplastic potential and specific effects as cellular antiproliferation, increase of pro-apoptotic proteins and reduction of factors that lead tumor cells to metastasize.

With this, the studies provide elements for future studies to associate the use of the compounds found in the medicinal plants to the conventional treatment (radio or chemotherapy) in order to potentialize the effects of this treatment and improve the prognosis of oncologic patients.

Future studies with different methods must be carried out to define better the mechanisms of action through which these components act, safe doses for human beings and potential adverse effects.

CONTRIBUTIONS

The authors contributed equally for the study conception and/or design, collection, analysis and interpretation of the data, wording, critical review and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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