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NATURAL PRODUCTS WITH ANTICANCER ACTIVITY: A REVIEW OF IN VITRO, IN VIVO AND MOLECULAR DOCKING ASSAYS

PRODUTOS NATURAIS COM ATIVIDADE ANTICÂNCER: UMA REVISÃO SOBRE ENSAIOS IN VITRO, IN VIVO E DOCKING MOLECULAR

PRODUCTOS NATURALES CON ACTIVIDAD ANTICANCERÍGENA: UNA REVISIÓN DE LOS ENSAYOS IN VITRO, IN VIVO Y DE ACOPLAMIENTO MOLECULAR

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ABSTRACT
Natural products are being increasingly used in scientific research to obtain new drugs for current diseases. Most of the time these substances are presenting good results, besides presenting some positive points as easy acquisition, low cost and less or none adverse effect. In this sense, the aim of this research is to perform a bibliographic survey on *in vitro*, *in vivo* and *in silico* studies of natural products to prove their antitumor activity. The study is a review research that used 31 articles to highlight the scientific findings on the antitumor activity of natural products and their derivatives. Articles were included in the time estimate between 2015 - 2021 (last six years). The search and selection of the reference studies was performed in Scielo, Science Direct, PubMed and Google Academic databases. The literature shows that natural compounds have several activities against several types of cancer, such as breast, prostate, liver, pancreas, colorectal cancer, among others. The studies found suggest that the diversity of existing compounds may trigger important steps towards the optimization of new strategies for the formulation of drugs for cancer chemotherapy. Thus, new studies may be important to elucidate even more specifically the effects of these compounds isolated and in association *in vivo* for the discovery of new treatments for cancer.

KEYWORDS: Natural Products. Antitumor Activity. *In vivo* Evaluation

RESUMO
Os produtos naturais estão sendo compostos cada vez mais usados em pesquisas científicas na tentativa de se obter novos medicamentos para as doenças da atualidade. Na maioria das vezes essas substâncias estão apresentando bons resultados, além de apresentar alguns pontos positivos como facilidade em sua aquisição, baixo custo e menos ou nenhum efeito adverso. Nesse sentido, o

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RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
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objetivo desta pesquisa é de realizar um levantamento bibliográfico sobre estudos *in vitro, in vivo* e *in silico* de produtos naturais para comprovação de sua atividade antitumoral. O estudo trata-se de uma pesquisa de revisão que utilizou 31 artigos para evidenciar os achados científicos sobre a atividade antitumoral de produtos naturais e seus derivados. Foram incluídos artigos na estimativa de tempo entre 2015 – 2021 (últimos seis anos). A pesquisa e seleção dos estudos de referência foi realizada nas bases de dados Scielo, Science Direct, PubMed e Google Acadêmico. A literatura evidencia que os compostos naturais apresentam diversas atividades frente a diversos tipos de câncer, como câncer de mama, próstata, fígado, pâncreas, efeito colorretal, entre outros. Os estudos encontrados sugerem que a diversidade de compostos existentes pode desencadear passos importantes para a otimização de novas estratégias para formulação de medicamentos para quimioterapia do câncer. Dessa forma, novos estudos podem ser importantes para que se consiga elucidar de forma ainda mais especifica os efeitos desses compostos isolados e em associação *in vivo* para a descoberta de novos tratamentos para o câncer.

PALAVRAS-CHAVE: Produtos Naturais. Atividade antitumoral. Avaliação *in vivo*

RESUMEN
Los productos naturales se utilizan cada vez más en la investigación científica en un intento de obtener nuevos fármacos para las enfermedades actuales. La mayoría de las veces, estas sustancias están presentando buenos resultados, además de presentar algunos puntos positivos como la fácil adquisición, el bajo costo y el menor o nulo efecto adverso. En este sentido, el objetivo de esta investigación es realizar un estudio bibliográfico sobre los estudios *in vitro, in vivo* e *in silico* de productos naturales para demostrar su actividad antitumoral. El estudio es una investigación de revisión que utilizó 31 artículos para destacar los hallazgos científicos sobre la actividad antitumoral de los productos naturales y sus derivados. Los artículos se incluyeron en la estimación temporal entre 2015 - 2021 (últimos seis años). La búsqueda y selección de los estudios de referencia se realizó en las bases de datos Scielo, Science Direct, PubMed y Google Academic. La literatura muestra que los compuestos naturales presentan diversas actividades contra varios tipos de cáncer, como el de mama, próstata, hígado, páncreas, colorrectal, entre otros. Los estudios encontrados sugieren que la diversidad de compuestos existentes puede desencadenar pasos importantes hacia la optimización de nuevas estrategias de formulación de fármacos para la quimioterapia del cáncer. Así pues, pueden ser importantes nuevos estudios para dilucidar aún más específicamente los efectos de estos compuestos aislados y en asociación *in vivo* para el descubrimiento de nuevos tratamientos contra el cáncer.

PALABRAS CLAVE: Productos naturales. Actividad antitumoral. Evaluación *in vivo*

1. INTRODUCTION

The evolution of man's knowledge about therapeutics of natural origin is gradual and parallel to the evolution of human history. Countless are the examples of species used in traditional practice that provide pharmacology with the active principles in use, a science known as ethnopharmacology. The World Health Organization itself recognizes the importance of the practice and encourages all nations to preserve and promote the rational employment of knowledge derived from folk medicine (COSTA, 2018; MUNARI et al., 2021).

Plants produce a wide variety of metabolites that are gaining importance due to their therapeutic and biotechnological applications. The production levels of these metabolites are induced by environmental and genetic factors. The ability to synthesize toxic compounds is related to defense

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

from pathogens (bacteria or fungi), herbivores such as animals or insects or suppress the growth of competitive neighboring species (NEWMAN, 2020; VOUNG, 2021; KIM et al., 2021).

Such metabolites have great potential as active ingredients, can be used directly in therapy, as precursors in chemo pharmaceutical semi-synthesis or in models for the synthesis of new principles for therapeutic use (COLONE, 2020).

Nowadays, several compounds of natural origin are used in research and for the therapy of several diseases. These products are considered privileged structures for acting on several targets, having several pharmacological activities already elucidated, such as antibacterial activity (CORDEIRO et al., 2020), antifungal (EL-HOSSARY et al., 2017), antioxidant (HUANG, 2017), antiparasitic (DE MORAES, 2015), anti-inflammatory (LIN, 2018) and antitumor (SOLTANA et al., 2019).

Researchers around the world have focused on research for the elucidation of the dynamics of natural products against cancer. Considered a major problem in the world, cancer is responsible for thousands of deaths worldwide. Natural compounds have not been used as strategies for new drugs for this disease considered complex, because they have some positive factors for their use, such as: easy handling and obtaining, low cost of acquisition and with fewer adverse effects and toxicity rates (RAYAN, 2017; NGUYEN et al., 2020; ESPINOSA-RODRIGUEZ et al., 2021).

In these review studies we addressed the use of natural products and their derivatives for investigation of antitumor activity. These studies were all results of *in vitro, in vivo* and *in silico* assays. We aimed to investigate in the current literature evidence that these compounds actually have activity against cancer.

2. METHODOLOGY

This is an integrative literature review (IRL) with descriptive allowance. In this sense, in the first moment it elaborated the following guiding question: what are the findings in the literature that can elucidate the antitumor mechanism coming from natural products and their derivatives?

The theoretical basis was based on electronic databases: International Literature in Health Sciences (MEDLINE) through the Regional Portal of the Virtual Health Library (VHL) and in virtual libraries: Scientific Eletronic Library Online (SciELO), ScienceDirect, and Google Academico.

The terms used were identified in Medical Subjects Headings (MeHS) and/or Health Science Descriptors (DeCS). Terms such as: natural products, anticancer activity, *in vivo* evaluation, were used as keywords to guide the search strategy, given the specificity of the theme. The search strategies are presented in table 1.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

Libraries and databases	Search Strategy
MEDLINE	*"Natural products AND Anticancer activity OR in vivo evaluation", "Natural products AND Anticancer activity", "Natural products OR in vivo evaluation".*
SciELO, ScienceDirect e Google Academico.	*Natural products AND Anticancer activity OR in vivo evaluation", "Natural products AND Anticancer activity", "Natural products OR in vivo evaluation"*

Table 1 - Search strategies used in the databases selected for the study.
Source: Prepared by the authors, 2021.

Inclusion criteria were primary articles that presented the use of natural products for antitumor activity, such as: theses, dissertations, clinical and randomized trials that had been published in English, Portuguese and available in full between the years 2015 and 2021 (last 6 years), due to being the years in which most of the publications disassembled on the topic of interest.

The exclusion criteria were editorials, review articles, those already selected in the search in another database, and those that did not answer the research question.

The search was conducted simultaneously by two independent researchers, who standardized the sequence of use of descriptors and cross-references in each database and then compared the results obtained. The articles in the sample were selected using the sequence: reading the title, reading the abstract, and reading the full text.

A total of 119 articles were found from the search of the descriptors and MeHS. Of this total, 18 were found in MEDLINE, 53 in SciELO, 28 in ScienceDirect, and 20 in Google Scholar. According to the eligibility criteria, 31 articles were selected for this review, as shown in Figure 1.

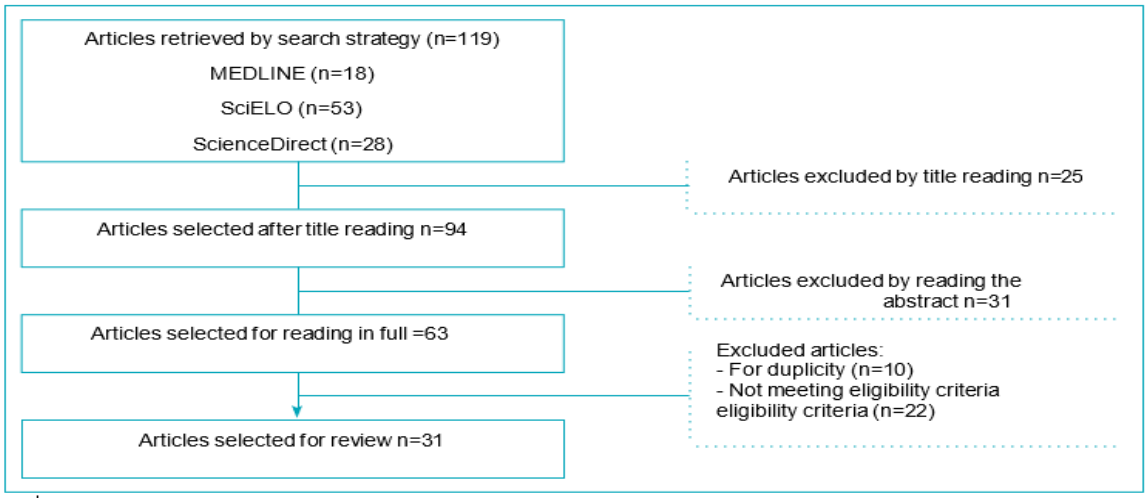


Figure 1. Flowchart of the number of articles found and selected after applying the inclusion and exclusion criteria.
Source: Prepared by the authors, 2021.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
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3. RESULTS AND DISCUSSION

3.1 Evaluation of natural products *in vitro* studies

Table 2. Summary of data on in vitro studies

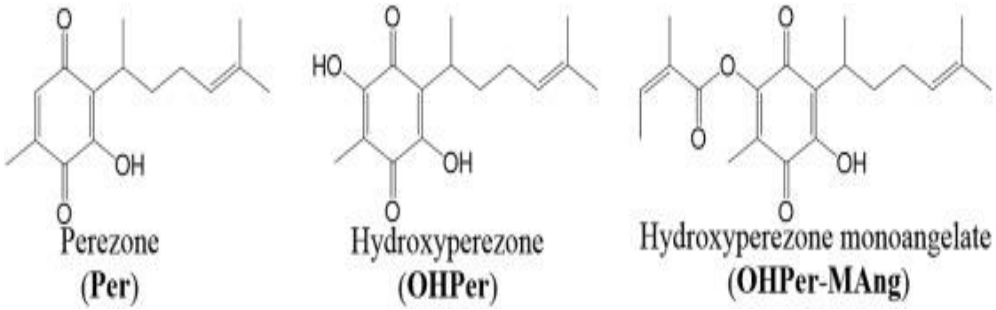
Manuscript title	Periodical	Objective
In vitro and computational studies of natural products related to perezone as anti-neoplastic agents	Biochimie	To evaluate two perezone (Per)-related phytochemicals as anti-cancer agents: hydroxyperezone (OHPer) and its monoangelate (OHPer-MAng).
Structure Identification and In Vitro Anticancer Activity of Lathyrol-3-phenylacetate-5,15-diacetate	Molecules	Evaluate the antitumor activity of some natural products from the genus *Euphorbia*.
Phytochemical Screening and In-Vitro Antibacterial and Anticancer Activity of Crude Extract of *Matricaria aurea*	Current Pharmaceutical Design	To evaluate the antibacterial and anticancer activities of the crude extract of *Matricaria aurea*
Activation of JNK and p38 in MCF-7 Cells and the In Vitro Anticancer Activity of *Alnus hirsuta* Extract	Molecules	To evaluate *in vitro* the antitumor activity of *Alnus hirsuta*
In Vitro Anticancer and Radio sensitizing Activities of Phlorethols from the Brown Alga *Costaria costata*	Molecules	Investigating the anticancer and radio sensitizing effects of high molecular weight chloretols isolated from the brown algae of *Costaria costata*

Source: Prepared by the authors (2021).

Hernandez-Rodrigues and co-workers (2020) aimed to evaluate two perezone (Per)-related phytochemicals as anti-cancer agents: hydroxyperezone (OHPer) and its monoangelate (OHPer-MAng). The molecules in this study were tested *in vitro* on six cancer cell lines, they were: (K562, MCF-7, MDA-MB-231, HeLa, U373, A549) and non-malignant cells determine their cytotoxicity. *In vitro* and computational studies provided the inhibition of PARP-1 and its potential binding mode. Cell proliferation assays demonstrated that OHPer-MAng treatment significantly induces apoptosis in the triple negative breast cancer cell line (TNBC) (MDA-MB-231 IC50 = 3.53 μM) and is particularly less cytotoxic to Vero cells (IC50 = 313.92 μM), human lymphocytes (IC50 = 221.46 μM) and mouse endothelial cells (IC50=> 400 μM).

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

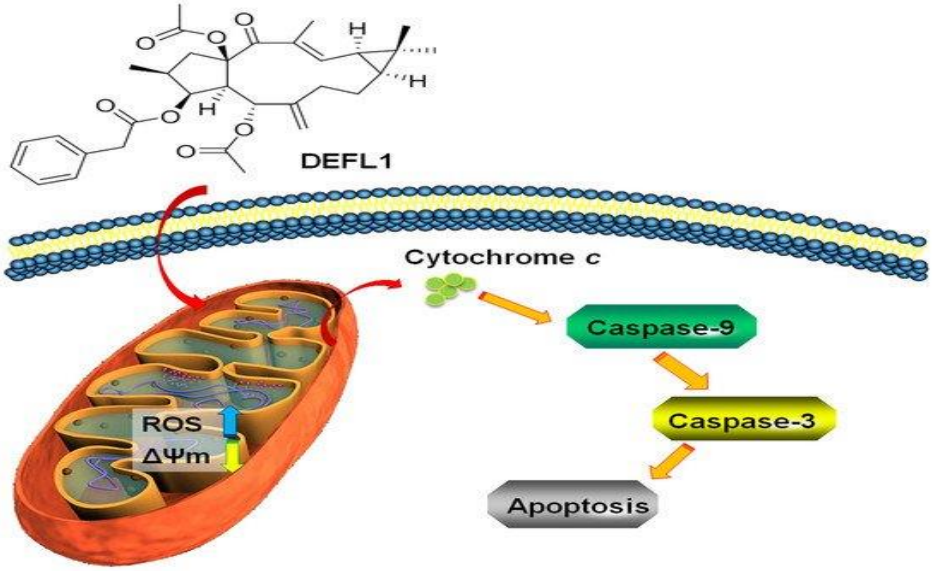
Figure 2. Natural compounds related to perezone employed in the study.



SOURCE: HERNANDEZ-RODRIGUES et al., (2020).

In the study by Zhang et al., (2017), their aim was to evaluate the antitumor activity of some natural products from the genus *Euphorbia*. In the study, they used the compound lathyrol-3-phenyl-acetate-5,15-diacetate (deoxy Euphorbia factor L1, DEFL1). DEFL1 showed potent inhibition against lung cancer A549 cells, with an IC50 value of 17.51 ± 0.85 μM. Furthermore, DEFL1 suppressed the healing of A549 cells in a concentration-dependent manner. Mechanistically, DEFL1 induced apoptosis, with involvement of increased reactive oxygen species (ROS), decreased mitochondrial membrane potential (ΔΨm), cytochrome c release, increased caspase-9 and 3 activity.

Figure 3. Graphical summary of the experiment.



SOURCE: ZHANG et al., (2017).

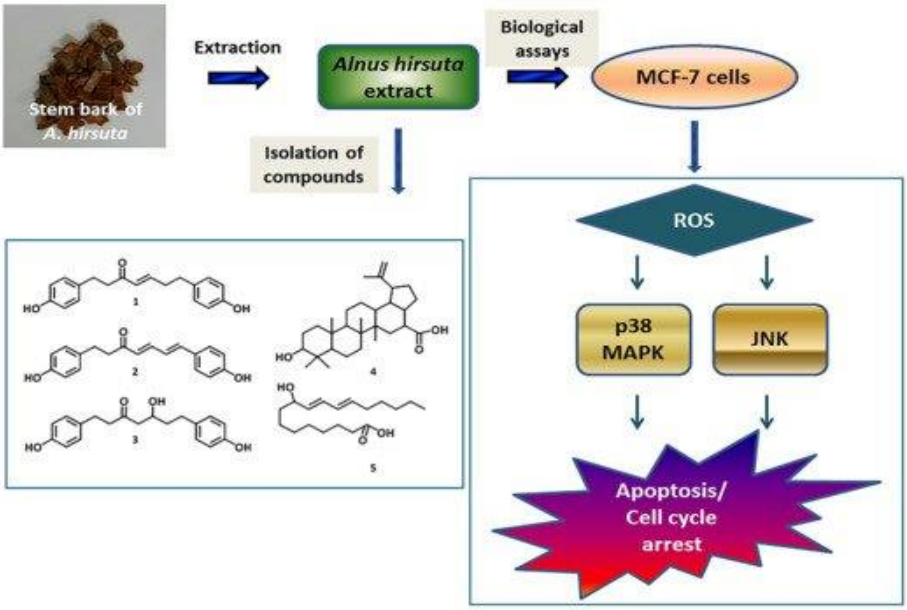
In the study by Ahmad and co-workers (2021), the antibacterial and anticancer activities of the crude extract of *Matricaria aurea* were investigated. The data showed that the *M. aurea* extract had

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

significant antimicrobial activity against the tested strains. The SRB assay data provide the potential anticancer activity through cell death.

Ryu (2020) evaluated the antitumor activity of *Alnus hirsuta in vitro*. In the study, biological ctivities of A. hirsuta extract associated with regulation of apoptosis and JNK and p38 in MCF-7 breast cancer cells were reported. The authors manage to elucidate the antitumor mechanism of the compound cited and further suggest that the antitumor effect of *A. hirsuta* extract is achieved by promoting apoptosis and cell cycle arrest mediated by the activation of JNK and p38 signaling pathway through ROS generation.

Figure 4. Graphical summary of the experiment.



SOUCE: RYU, (2020).

Malyarenko (2020) investigated the anticancer and radio sensitizing effects of the high molecular weight chloretols CcPh (Mw = 2520 Da) isolated from the brown algae of *Costaria costata*. CcPh at non-toxic concentrations inhibited colony formation in colon cancer cells and significantly increased their sensitivity to low non-toxic X-ray irradiation. The combinatorial effect of radiation and CcPh was synergistic (Combination index < 0.7). Algae chloretols may be potential candidates as radiosensitizers to improve the radiation therapy regimen.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

3.2 EVALUATION OF NATURAL PRODUCTS FOR ACTIVITY IN VIVO STUDIES

Table 3. Summary of data on in vivo studies

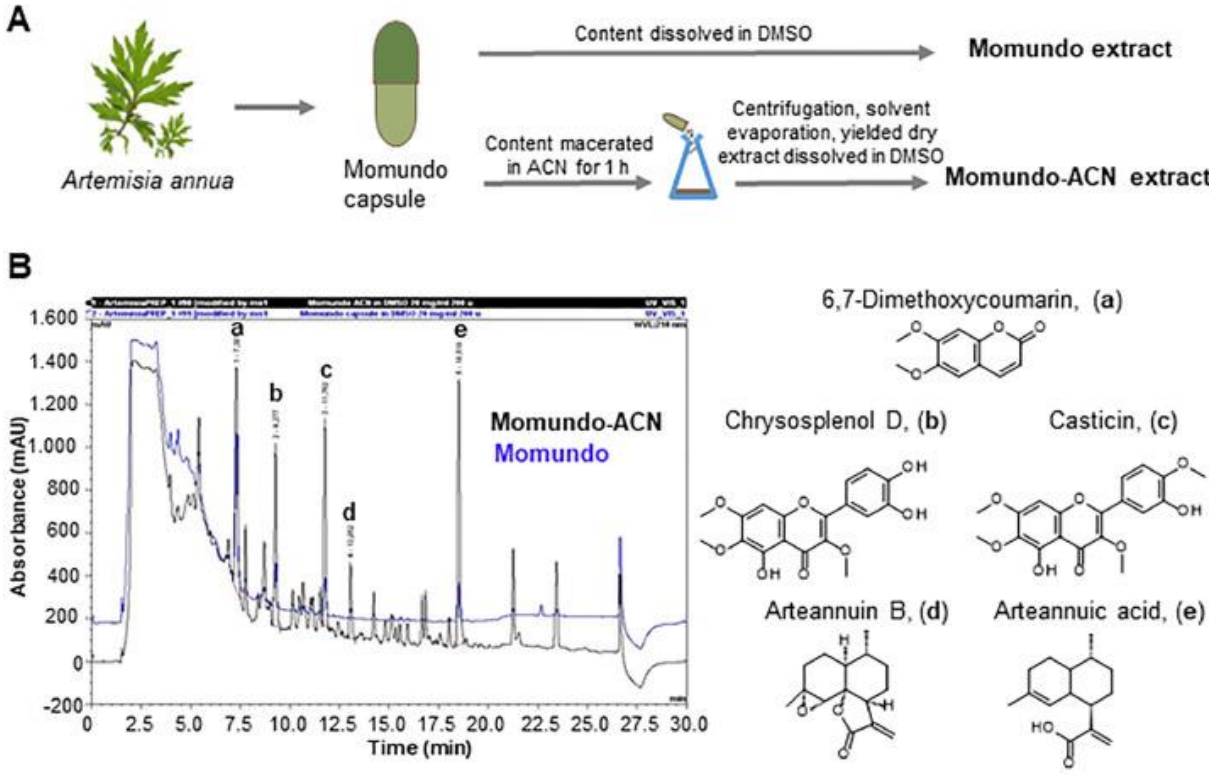
Manuscript title	Periodical	Objective
Antitumor activity of an *Artemisia annua* herbal preparation and identification of active ingredients	Phytomedicine	To investigate *in vitro* and *in vivo* the anticancer efficacy of an *Artemisia annua* extract marketed as an herbal preparation
Antimicrobial, anticancer and antioxidant activities of nano-heart of *Phoenix dactylifera* tree extract loaded chitosan nanoparticles: In vitro and in vivo study	International Journal of Biological Macromolecules	Perform evaluation of the antimicrobial, antitumor and antioxidant activity of chitosan nanoparticles from *P. dactylifera (*HP).
Evaluation of anticancer activities of *Poria cocos* ethanol extract in breast cancer: *In vivo* and *in vitro*, identification and mechanism	Journal of Ethnopharmacology	To verify the anticancer efficacy of *P. cocos* ethanol extract (PC) in breast cancer, as well as to investigate its most active compound and its underlying molecular mechanism *in vivo* and *in vitro.*
In vitro and *in vivo* anti-cancer activity of dichloromethane fraction of *Triticum aestivum sprouts*	Biomedicine & Pharmacotherapy	To investigate *in vitro* and *in vivo* the mechanism underlying the anticancer effects of a *Triticum aestivum* (TA) fraction

Source: Prepared by the authors (2021).

Lang and co-workers (2019) conducted a study in order to investigate *in vitro* and *in vivo* the anticancer efficacy of an *Artemisia annua* extract marketed as an herbal preparation. The *Artemisia annua* extract, inhibited the viability of breast (MDA-MB-231 and MCF-7), pancreas (MIA PaCa-2), prostate (PC-3), non-small cell lung cancer (A459) cells. In addition, the extract inhibited cancer cell proliferation, decreased tumor growth, and induced apoptosis in vivo in TNBC MDA-MB-231 xenografts cultured in CAM.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

Figure 5. Graphical summary of the experiment.



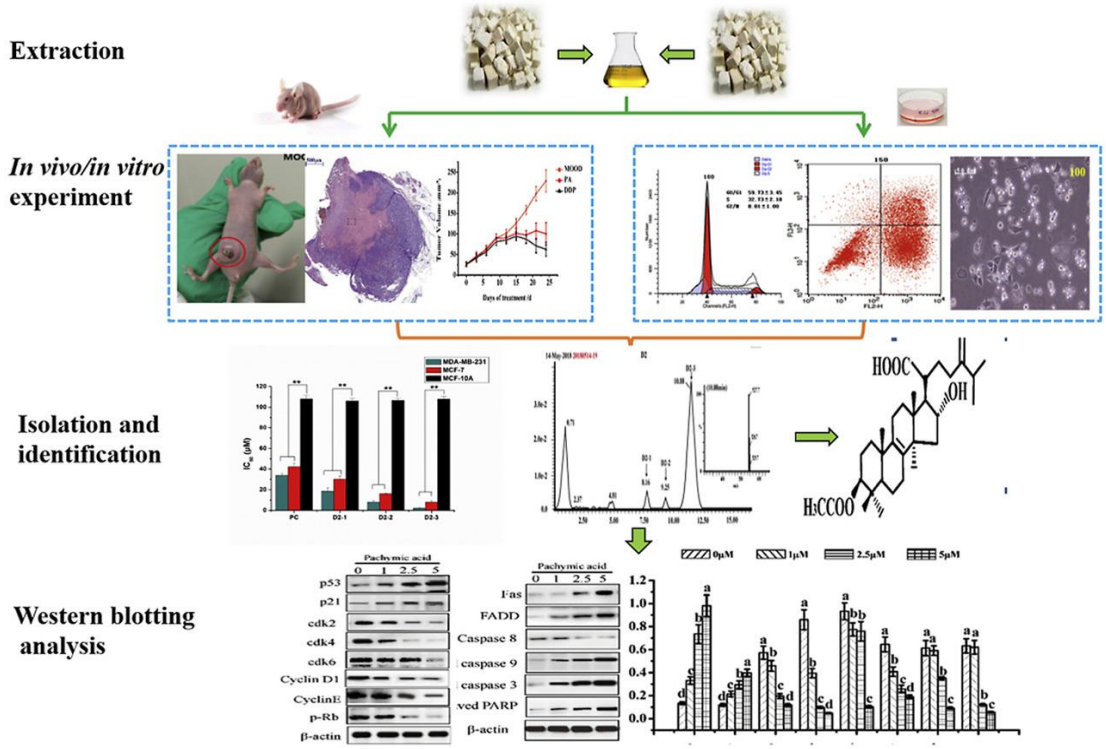
SOURCE: LANG et al., (2019).

Sahyon (2020) performed evaluation of antimicrobial, antitumor and antioxidant activity of chitosan nanoparticles from *P. dactylifera* (HP) through *in vitro* and *in vivo* assays. The *in vivo* study demonstrates reduced cardiac and renal apoptosis with increased programmed cell death protein-1 (PD-1); as the main anticancer pathway (doxorubicin) is free radical release with decreased PD-1 levels and induction of apoptosis. In conclusion, HP-ChNPs, at a very small dose, may be a promising supplement to avoid doxorubicin toxicity with enhancement of antioxidant enzymes without affecting its anticancer activity.

Jiang (2020) conducted a study in order to verify the anticancer efficacy of *P. cocos* ethanol extract (PC) in breast cancer, as well as to investigate its most active compound and its underlying molecular mechanism *in vivo* and *in vitro*. The in vivo experiment revealed that PC could significantly inhibit tumor development and the average final tumor weight of mice in the PC group (0.51 ± 0.12g) was significantly lower than that of the model group (1.22 ± 0.45g). Notably, compared with first-line anticancer cisplatin, PC showed fewer side effects on vital organ function and muscle strength of the mice.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

Figure 6. Graphical summary of the experiment.

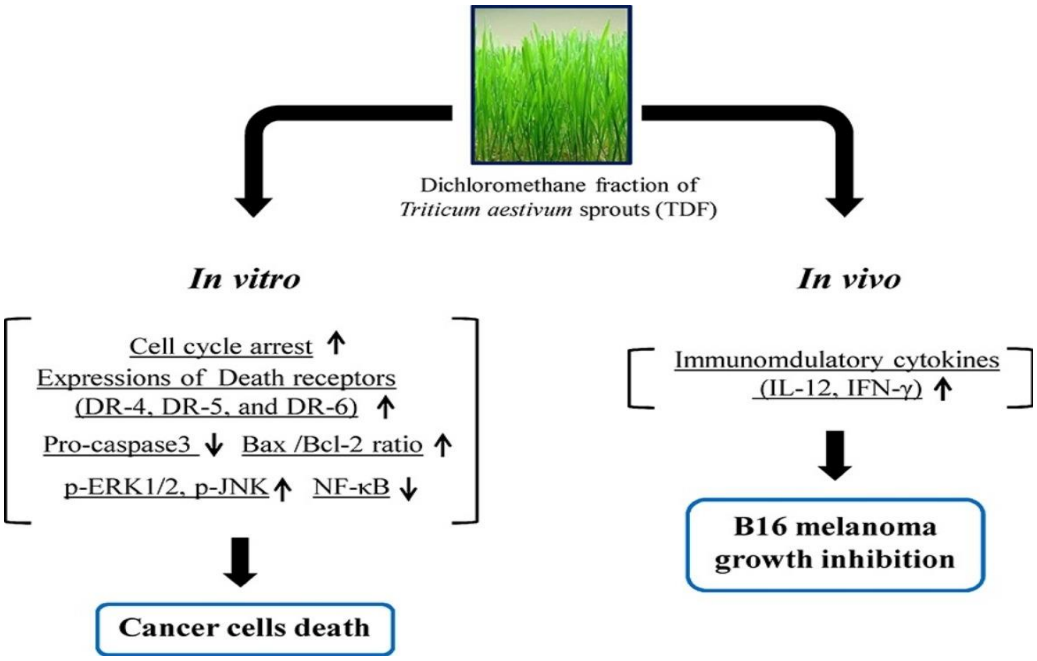


SOURCE: JIANG, (2020).

Ki and co-workers (2017) present a study to investigate the effect of TDF *in vivo*, where C57BL/6 mice were injected with B16 melanoma cells and orally administered TDF. TDF markedly inhibited cancer cell growth and induced cell morphological changes, cell cycle arrest and apoptosis, and enhanced the expressions of death receptors (DR)-4, 5, and 6 in the cell lines. In addition, TDF up-regulated the expressions of proteins linked to mitochondrial apoptosis and induced caspase-dependent cell death. It also significantly enhanced the phosphorylation of ERK1/2 and JNK, but not p38, while inhibiting NF-κB activation in cancer cells. In our mouse model, TDF significantly suppressed B16 melanoma growth to a similar extent as cisplatin (reference control) and increased immunomodulatory cytokines. In summary, this study presents the mechanism responsible for the anticancer effects of TDF *in vitro* and *in vivo.*

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

Figure 7. Graphical summary of the experiment.



SOURCE: KI et al., (2017).

3.3 EVALUATION OF NATURAL PRODUCTS FOR ANTITUMOR ACTIVITY IN IN SILICO STUDIES

Table 3. Summary of data on in silico studies

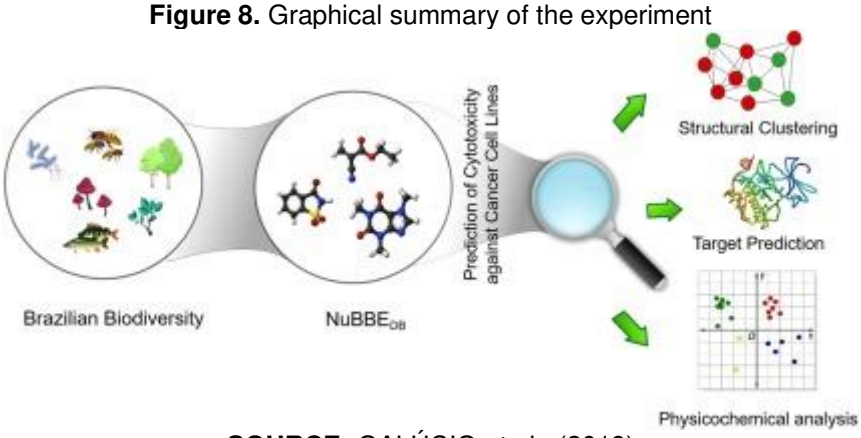
In silico identification of natural products with anticancer activity using a chemo-structural database of Brazilian biodiversity	Computational Biology and Chemistry	Evaluation against cancer cells of 2221 compounds from the Nucleus of Bioassays, Ecophysiology and Biosynthesis of Natural Products Database (NuBBEDB)
Marine steroids as potential anticancer drug candidates: *In silico* investigation in search of inhibitors of Bcl-2 and CDK-4/Cyclin D1	Steroids	Search for bioactive molecules from natural sources

Source: Prepared by the authors (2021).

Galucio and co-workers (2019) studied several compounds with possible antitumor activity using computational methods. In the present study, 46 families comprising potential anticancer compounds and at least 19 molecular targets involved in oncogenesis. To the best of our knowledge, this is the first large-scale study conducted to evaluate the potential of NPs from Brazilian biodiversity as anticancer agents using in silico approaches. The authors of the manuscript also suggest that this structural diversity of compounds can be used as strategies for optimization in the development of new drugs for cancer treatment.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

Figure 8. Graphical summary of the experiment



SOURCE: GALÚCIO et al., (2019)

Saikia and co-workers (2015) screened 182 natural steroids from star fishes occurring in different parts of the world and their 282 soft derivatives by *in silico* methods. Their physicochemical properties, drug availability, binding potential with selected targets, ADMET (absorption, distribution, metabolism, toxicity) were predicted. In addition, the results were compared with those of existing steroidal and nonsteroidal drugs and inhibitors of Bcl-2 and CDK-4/Cyclin D1. The results are promising and reveal that some of these steroids may be potent leads for cancer treatments.

3.4 FUTURE PROSPECTS

It is very true that studies involving the topic of cancer are of paramount importance, not only scientific importance, but also social importance (WAKS, 2019). We know that experiments seeking alternative and novel therapies for cancer are growing every day and will be so for years to come. As seen in this review study, compounds of natural origin may occupy much of the cancer research (KHAN, 2021; IQBAL et al., 2021).

In vitro and in vivo studies are quite important in this process, and one complements the other. In silico studies, on the other hand, are also very necessary since one can get a sense of the activities of certain compounds by means of computational methods alone (SUBBURAJ et al., 2020; HUANG et al., 2020).

4. CONCLUDING REMARKS

Therefore, in view of the results that were explained in this review, it is noticeable that natural compounds have antitumor activity in several cancer lines. The studies and assays discussed here are important for the elucidation of the mechanism of these compounds. We hope that this review study provides, in some way, an insight to guide future research involving this theme.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

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RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
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