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

Daniel Lopes Araújo, Emanuel Osvaldo de Sousa, Lucas Clementino da Silva Sousa, Beatriz Gomes Sousa, Diego Bruno Brito Cerqueira, Eduardo Fellipe Capini de Almeida Tavares, José Leandro da Silva Menezes Diniz, Karol Arias Fernandes, Ingrid Mikaela Moreira de Oliveira, Gabriela Lais da Silva, Mateus de Melo Terra, Elisa Morais Barcelo, Ludmilla Rafaela Marinho da Silva, Maria Isabelli Leite Figueiredo, Tiago Tavares Gonçalves

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 toward 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
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 colo-retal, 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 específica 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, colorectal, 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
from pathogens (bacteria or fungi), herbivores such as animals or insects or suppress the growth of competitive neighboring species (NEWMAN, 2020; YOUNG, 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.
NATURAL PRODUCTS WITH ANTICANCER ACTIVITY: A REVIEW OF IN VITRO, IN VIVO AND MOLECULAR DOCKING ASSAYS

Daniel Lopes Araújo, Emanuel Osvaldo de Sousa, Lucas Clementino da Silva Sousa, Beatriz Gomes Sousa, Diego Bruno Brito Cerqueira, Eduardo Felipe Capini de Almeida Tavares, José Leandro da Silva Menezes Diniz, Karol Arias Fernandes, Ingrid Mikaela Moreira de Oliveira, Gabriela Lais da Silva, Mateus de Melo Terra, Elisa Marise Barcelo, Ludmilla Rafaela Marinho da Silva, Maria Isabelly Leite Figueiredo, Tiago Tavares Gonçalves

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 - Ciências Exatas e da Terra, Sociais, da Saúde, Humanas e Engenharia/Tecnologia
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      | 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 Lathyril-3-phenylacetate-5,15-diacolate | 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 *Marrubia avara* | Current Pharmaceutical Design     | To evaluate the antibacterial and anticancer activities of the crude extract of *Marrubia avara*.                                      |
| 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 Chlorophytre from the Brown Alga *Costania costate* | Molecules                         | Investigating the anticancer and radio sensitizing effects of high molecular weight chlorophytre isolated from the brown algae of *Costania costate*. |

**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).
Natural products with anticancer activity: a review of in vitro, in vivo and molecular docking assays

Daniel Lopes Araújo, Emanuel Osvaldo de Sousa, Lucas Clementino da Silva Sousa, Beatriz Gomes Sousa, Diego Bruno Brito Cerqueira, Eduardo Fellipe Capini de Almeida Tavares, José Leandro da Silva Diniz, Karol Arias Fernandes, Ingrid Mikaela Moreira de Oliveira, Gabriela Lais da Silva, Mateus de Melo Terra, Elisa Morais Barcelo, Ludmilla Rafaela Marinho da Silva, Maria Isabelly Leite Figueiredo, Tiago Tavares Gonçalves

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

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-phenylacetate-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.

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...
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 activities 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.

![Graphical summary of the experiment](image)

**SOURCE:** 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.
3.2 EVALUATION OF NATURAL PRODUCTS FOR ACTIVITY 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.
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.
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.
3.3 EVALUATION OF NATURAL PRODUCTS FOR ANTITUMOR ACTIVITY IN 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.
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.
ACKNOWLEDGMENTS

The main author of this manuscript would like to thank the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel) for the financial support in the form of a master’s degree scholarship.

REFERENCES

AHMAD, Irfan et al. Phytochemical screening and in-vitro antibacterial and anticancer activity of crude extract of Matricaria aurea. Current Pharmaceutical Design, v. 27, n. 1, p. 69-79, 2021.

COLONE, Marisa; CALCABRINI, Annarica; STRINGARO, Annarita. Drug delivery systems of natural products in oncology. Molecules, v. 25, n. 19, p. 4560, 2020.

CORDEIRO, Laísa Vilar et al. Association of carvacrol with ceftazidime and cefepime against Klebsiella pneumoniae. Research, Society and Development, v. 9, n. 7, p. e264974089-e264974089, 2020.

COSTA, Ana Carla Ferreira; CAVALCANTE, Giani Maria. Atividade antitumoral in vitro de prosopis juliflora frente a células de câncer de mama e câncer de ovário. Acta Biomédica Brasiliensia, v. 9, n. 1, p. 130-136, 2018.

DE MORAES, Josué. Natural products with antischistosomal activity. Future Medicinal Chemistry, v. 7, n. 6, p. 801-820, 2015.

EL-HOSSARY, Ebba M. et al. Antifungal potential of marine natural products. European journal of medicinal chemistry, v. 126, p. 631-651, 2017.

ESPINOSA-RODRIGUEZ, Bryan Alejandro et al. Comparative Anticancer Activity and Molecular Docking of Different Isatin-Based Scaffolds. Anticancer Research, v. 41, n. 10, p. 4969-4977, 2021.

GALÚCIO, João Marcos et al. In silico identification of natural products with anticancer activity using a chemo-structural database of Brazilian biodiversity. Computational biology and chemistry, v. 83, p. 107102, 2019.

HERNÁNDEZ-RODRÍGUEZ, Maricarmen et al. In vitro and computational studies of natural products related to perezone as anti-neoplastic agents. Biochimie, v. 171, p. 158-169, 2020.

HUANG, Gangliang; MEI, Xinya; HU, Jinchuan. The antioxidant activities of natural polysaccharides. Current drug targets, v. 18, n. 11, p. 1296-1300, 2017.

HUANG, Yuzhou et al. Structure-based virtual screening of natural products as potential stearoyl-coenzyme a desaturase 1 (SCD1) inhibitors. Computational biology and chemistry, v. 86, p. 107263, 2020.

IQBAL, Tahseen et al. Natural products based crown ethers: synthesis and their anticancer potential. Journal of Asian Natural Products Research, p. 1-9, 2021.

JIANG, Yu; FAN, Liuping. Evaluation of anticancer activities of Poria cocos ethanol extract in breast cancer: In vivo and in vitro, identification and mechanism. Journal of ethnopharmacology, v. 257, p. 112851, 2020.
KHAN, Abdul Q.; UDDIN, Shahab. Anticancer Activity of Natural Compounds. Asian Pacific Journal of Cancer Prevention, v. 21, n. 2, p. 1-2, 2021.

KI, Hyeon-Hui et al. In vitro and in vivo anti-cancer activity of dichloromethane fraction of Triticum aestivum sprouts. Biomedicine & Pharmacotherapy, v. 96, p. 120-128, 2017.

KIM, Michael et al. Screening and Evaluation of Natural Product Derivative Library for Anticancer Activity in Human Prostate Cancer Cells. The FASEB Journal, v. 35, 2021.

LANG, Sophia J. et al. Antitumor activity of an Artemisia annua herbal preparation and identification of active ingredients. Phytomedicine, v. 62, p. 152962, 2019.

LIN, Tzu-Kai; ZHONG, Lily; SANTIAGO, Juan Luis. Anti-inflammatory and skin barrier repair effects of topical application of some plant oils. International journal of molecular sciences, v. 19, n. 1, p. 70, 2018.

MALYARENKO, Olesya S.; IMBS, Tatiana I.; ERMAKOVA, Svetlana P. In Vitro Anticancer and Radiosensitizing Activities of Phlorethols from the Brown Alga Costaria costata. Molecules, v. 25, n. 14, p. 3208, 2020.

MUNARI, Eduarda Laís et al. Potencial antitumoral de extratos de Eugenia involucrata DC: uso de produtos regionais para tratar um problema mundial. [S. l.: S.n], 2021.

NEWMAN, David J.; CRAGG, Gordon M. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. Journal of Natural Products, v. 83, n. 3, p. 770-803, 2020.

NGUYEN, Ngoc Hong et al. Anticancer activity of novel plant extracts and compounds from Adenosma bracteosum (Bonati) in human lung and liver cancer cells. Molecules, v. 25, n. 12, p. 2912, 2020.

RAYAN, Anwar; RAIYN, Jamal; FALAH, Mizied. Nature is the best source of anticancer drugs: Indexing natural products for their anticancer bioactivity. PloS one, v. 12, n. 11, p. e0187925, 2017.

RYU, Mina et al. Activation of JNK and p38 in MCF-7 Cells and the in vitro anticancer activity of Alnus hirsuta extract. Molecules, v. 25, n. 5, p. 1073, 2020.

SAHYON, Heba A.; AL-HARBI, Sami A. Antimicrobial, anticancer and antioxidant activities of nanohemat of Phoenix dactylifera tree extract loaded chitosan nanoparticles: In vitro and in vivo study. International Journal of Biological Macromolecules, v. 160, p. 1230-1241, 2020.

SAIKIA, Surovi et al. Marine steroids as potential anticancer drug candidates: In silico investigation in search of inhibitors of Bcl-2 and CDK-4/Cyclin D1. Steroids, v. 102, p. 7-16, 2015.

SOLTANA, Hala et al. Antitumoral activity of Ficus carica L. on colorectal cancer cell lines. Cellular and Molecular Biology, v. 65, n. 6, p. 6-11, 2019.

SUBBURAJ, Saranyadevi et al. Discovery of anaplastic lymphoma kinase inhibitors from natural product library: A holistic in silico approach. Biotechnology and Applied Biochemistry, 2020.

VUONG, Thu V. Natural Products and Their Derivatives with Antibacterial, Antioxidant and Anticancer Activities. Antibiotics (Basel), v. 13, n.1, p. 70, 10 jan. 2021.

WAKS, Adrienne G.; WINER, Eric P. Breast cancer treatment: a review. Jama, v. 321, n. 3, p. 288-300, 2019.
ZHANG, Jian-ye et al. Structure identification and in vitro anticancer activity of lathyrol-3-phenylacetate-5, 15-diacetate. *Molecules*, v. 22, n. 9, p. 1412, 2017.