INPLASY

Potential Antimelanoma of Natural Compounds Derived from Plants: A Systematic Review of In Vivo Studies

INPLASY202490019

doi: 10.37766/inplasy2024.9.0019

Received: 5 September 2024

Published: 5 September 2024

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ADMINISTRATIVE INFORMATION

Support - Brazilian Hospital Services Company (EBSERH).

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - I declare that I am not subject to any type of conflict of interest with the collaborators in the development of the research protocol entitled “Potential Antimelanoma of Natural Compounds Derived from Plants: A Systematic Review of In Vivo Studies”, whose researchers involved are: B. S. Gomes; J. F. M. de Sousa; R. L. Mendes.

INPLASY registration number: INPLASY202490019

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 5 September 2024 and was last updated on 5 September 2024.

INTRODUCTION

Review question / Objective The survey of bibliographic data through the systematic review process will have quantitative, exploratory and descriptive methodological characteristics. This study will be based on the following guiding question: How effective are natural products derived from plant species in inhibiting the growth of murine melanoma when applied as a treatment?

The research question was established using the PICOT method with the following topics: Problem: tumor activity in a murine melanoma model; Intervention: treatment with natural products derived from plant species; Comparison: positive control (standard drug), negative control (inert substance) or no intervention; Outcome: tumor inhibition rate related to the use of natural products; Type of Study: interventional study (experimental research) - pre-clinical studies in vivo.

Rationale It is relevant to develop a systematic literature review study regarding the antitumor activity of natural products derived from medicinal plants, with the aim of enabling a better understanding regarding the antineoplastic and antimetastatic action of plant species in the murine melanoma model, for through tumor induction of B16F10 cells (murine melanoma cell line). In addition to covering information about the experimental designs used to evaluate antitumor activity, as in vivo study models are crucial in the process of developing potential active principles, as well as establishing mechanisms of action of secondary metabolites in relation to the molecular behavior of the progression process of the melanoma.

Condition being studied Cutaneous melanoma, a lethal neoplasm originating from epidermal melanocytes, stands out for its resistance to conventional therapies and high metastatic rate. Among the types of skin cancer, melanoma is the least common; however, it is the most lethal due to its ability to metastasize. In 2022, the IARC estimated that there were 331,000 new cases of melanoma worldwide, of which 56,000 resulted in death. Faced with the urgent need for new therapeutic approaches, this study focuses on the antitumor potential of natural compounds derived from plants, recognized as primary sources of antineoplastic chemotherapeutics.

METHODS

Search strategy Data search was structured according to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). The databases used in this research were Science Direct, Scopus, PubMed and Embase. The data search strategy will use standardized terms selected through vocabularies registered in MESH (National Library of Medicine via Medical Subject Headings) and in the Virtual Health Library using the Descriptors in Health Sciences (DeCS). The terms to be used for the data search will be: “melanoma”, “medicinal plants” and “antineoplastic agents”. The search method will involve applying the terms to the databases in a standardized way, using the Boolean operator “AND”, defined by the following search strategy: “melanoma and (medicinal plants and antineoplastic agents)”.

Participant or population Species Mus musculus; Induction of melanoma with the B16 cell line and its sublines; In vivo studies evaluating antitumor and antimetastatic activity; In the exclusion criteria, experimental models using any animal species other than Mus musculus will be excluded, including but not limited to Rattus norvegicus, Oryctolagus cuniculus, or any other species different from Mus musculus.

Intervention Treatments with natural products derived from plant species (examples: extract, essential oil, compounds isolated from plant species, plant polymers, among others). All periods, frequencies and concentrations of treatments will be eligible for inclusion. Treatments in which natural products derived from medicinal plants are incorporated into pharmaceutical formulations (examples: cream, ointment, emulsions, syrups, liposome, nanoparticles, among others); Synthetic compounds developed from plant species; Treatments with natural products that do not indicate the plant species of origin will not be included.

Comparator Control group or model using an antitumor drug that has been validated and applied in clinical practice.

Study designs to be included Interventional studies (experimental research) - In vivo preclinical studies will be included if they have a control group and evaluate the antitumor or antimetastatic activity of natural products derived from plant species in a murine melanoma model induced by the B16F10 cell line or sublines.

Eligibility criteria Inclusion: Studies published between 2013-2023 in English, Portuguese, or Spanish.
Exclusion: Systematic reviews, case studies, clinical studies, meta-analyses, conference abstracts, or any other types of publication that are not experimental research. Additionally, studies that are not available in full text, that use different cell lines for melanoma induction, or that use synthetic products developed from plant species will be excluded."

Information sources The databases used in this research were Science Direct, Scopus, PubMed and Embase.

Main outcome(s) Tumor inhibition data; Tumor volume; Tumor weight / relative tumor weight; Tumor inhibition rate; Survival rate; Number of metastatic nodules in the lung; Lung metastasis inhibition rate; Do not report data on tumor inhibition parameters, including: tumor volume, tumor weight, relative tumor weight, tumor inhibition rate, survival rate, number of metastatic nodules in the lung or lung metastasis inhibition rate.

Data management
Data to be extracted from the selected studies:
Information to be extracted:
Language/country of origin; Natural product; Part of the plant; Plant species; Route of tumor induction; Strain of animal model; Sex of the animals; Sample number; Experimental groups; When treatment was started; Treatments administered; Routes of administration of the treatments; Concentrations / doses of treatments; Frequency of treatments; Duration of treatments - period; Parameters assessed: tumor volume, tumor weight, relative tumor weight, tumor inhibition rate, survival rate, number of metastatic nodules in the lungs and metastatic inhibition rate in the lungs.

Quality assessment / Risk of bias analysis Tumor growth inhibition: Data will be extracted in the format of tumor volume in mm^3 (continuous data).
Tumor regression rate: Extracted as the percentage of animals whose tumors regressed after treatment with the natural product (dichotomous data).
Survival rate: Extracted as the percentage of animals surviving throughout the study period after treatment with the natural product (dichotomous data).
Pulmonary metastasis inhibition: Extracted as the percentage reduction of tumor nodules in response to treatment with the natural product (continuous data).

Strategy of data synthesis The results will be organized using the data extraction form and presented through narrative synthesis;
Inhibition of tumor growth: Narrative synthesis: The effectiveness of the treatment will be evaluated using of tumor size reduction, involving summarizing findings from individual studies and discussing observed patterns or trends. Tumor regression rate: Narrative synthesis: Tumor regression will be assessed through the percentage of animals whose tumors regress after treatment, involving summarization of findings from individual studies and discussion of observed patterns or trends. Survival rate: Narrative synthesis: Will be assessed through the survival of the animals during the study period, involving the summary of findings from individual studies and the discussion of observed patterns or trends.
Inhibition of lung metastases: Narrative synthesis: It will be evaluated through the percentage of reduction of tumor nodules in response to treatment, involving the summary of findings from individual studies and the discussion of patterns or trends observed.
Differences in response between sexes: Narrative synthesis: Will be carried out to compare the effectiveness of treatment between male and female animals. This will involve summarizing findings from individual studies and discussing observed patterns or trends in response to treatment based on the sex of the animals.
Adverse effects: Narrative synthesis: Adverse effects will be qualitatively summarized narratively. This approach will involve the systematic extraction and summarization of information on adverse reactions observed in studies, including their nature, frequency and severity.
Toxicity associated with route of administration: Narrative synthesis: Similar to adverse effects, toxicity associated with different routes of administration will be qualitatively summarized narratively. This will involve summarizing information about any observed toxicity related to each route of administration in the studies.
Efficacy of treatment by route of administration: Narrative synthesis: The effectiveness of treatment by route of administration will be evaluated through a narrative synthesis. This will involve summarizing findings from individual studies and discussing observed patterns or trends in treatment effectiveness based on route of administration.
Biological activity of metabolites: Narrative synthesis: The biological activity of metabolites will be qualitatively summarized narratively. This will involve the systematic extraction and summarization of information on the biological activity of secondary metabolites observed in studies, including their potential contribution to antitumor and antimetastatic effects.

Subgroup analysis None planned.

Sensitivity analysis None planned.

Country(ies) involved Brazil.

Keywords Skin melanoma; Medicinal plants; Antineoplastics; Natural product; Secondary metabolites.

Dissemination plans The systematic review produced by this protocol will be published in a scientific journal, and will also be used as basic research for establishing experimental designs to evaluate antimelanone activity (in vivo).

Contributions of each author
Author 1 - Bruna Gomes - Author 1 is a reviewer and wrote the submission protocol. They will be responsible for structuring the manuscript for publication.
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