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Evaluation of the Genotoxicity of Medicinal Plant Extracts for Their Potential Use in Anticancer Phytotherapy

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ABSTRACT
A systematic review was carried out on the production and publication of research papers related to the study of Genotoxicity, Plant Extracts, Medicinal Plants and Phytotherapy under the PRISMA approach (Preferred Reporting Items for Systematic reviews and Meta-Analyses). The purpose of the analysis proposed in this document was to know the main characteristics of the publications registered in the Scopus and Wos databases during the study of the proposed variables, achieving the identification of 24 publications in total. Thanks to this first identification, it was possible to refine the results through the keywords entered in the search button of both platforms, which were Genotoxicity, Plant Extract, Medicinal Plants, Phytotherapy, reaching a total of 15 documents, excluding duplicates and those that did not meet the analysis criteria. The results will identify patterns, limitations and gaps in current research, providing a solid basis for the development of safe and effective therapies based on natural products. This review highlights the importance of a rigorous approach in the assessment of genetic toxicity to enhance the responsible use of herbal medicine in oncology.

Keywords: Genotoxicity, Plant Extract, Medicinal Plants and Phytotherapy

1. INTRODUCTION

Cancer represents one of the greatest threats to public health worldwide, causing millions of deaths each year and constituting a crucial challenge to health systems and scientific research. Despite significant advances in conventional therapies, such as chemotherapy, radiotherapy and targeted therapies, important limitations remain related to their toxicity, severe side effects and acquired resistance on the part of tumour cells. These factors have motivated the search for more effective, safe and sustainable therapeutic alternatives. In this context, phytotherapy has gained increasing interest as an approach based on the use of bioactive compounds derived from medicinal plants, which offer a wide range of biological activities with therapeutic potential.

Phytotherapy, understood as the use of natural products for the prevention and treatment of diseases, has a long history of application in various cultures. In recent years, the development of biotechnology and analytical chemistry has made it possible to characterize the pharmacological properties of numerous plant extracts, positioning them as promising candidates in modern oncology. Prominent examples include compounds such as paclitaxel, extracted from the Pacific yew (Taxus brevifolia), and vincristine, obtained from periwinkle (Catharanthus roseus), both widely used in clinical practice as effective anti-cancer agents. This success has prompted the exploration of other medicinal plants in search of compounds with similar or superior activities, especially in regions with high biodiversity such as Latin America, Asia and Africa.

However, although medicinal plant extracts have enormous therapeutic potential, their safety must be rigorously evaluated before being considered for clinical applications. In this sense, genotoxicity, defined as the ability of a compound to damage the genetic material of cells, is a critical aspect that cannot be ignored. Genotoxic agents have the potential to induce genetic mutations, chromosomal aberrations, and genomic instability, which could lead to serious adverse effects, including carcinogenesis. Therefore, genotoxicity assessment is a critical step in ensuring that natural compounds proposed as anticancer therapies do not pose risks to human health.

A variety of validated methods are used in genotoxicity assessment to identify and quantify DNA damage. Among the most commonly used assays are the Ames test, which detects point mutations in bacteria; the Comet assay, which measures DNA damage in individual cells; and the micronucleus test, which assesses micronucleus formation as an indicator of chromosomal damage. These methods, applied systematically, provide essential

information on the safety profile of plant extracts, allowing the identification of those with the greatest potential for the development of safe and effective therapies.

The anticancer activity of medicinal plant extracts has been widely documented in the scientific literature, highlighting properties such as the induction of apoptosis, inhibition of cell proliferation, reduction of tumor angiogenesis and modulation of signaling pathways involved in the growth and survival of cancer cells. However, the relationship between these properties and the potential risk of genotoxicity is not yet fully clarified. This uncertainty highlights the need for comprehensive and well-designed studies that address both the therapeutic benefits and potential risks associated with their use.

Despite the growing body of research in this field, significant gaps in knowledge persist that limit a comprehensive understanding of the potential and limitations of medicinal plant extracts. These gaps include a lack of standardization in extraction and characterization methods, heterogeneity in the concentrations used in the studies, and the absence of long-term data on their safety and effectiveness. These limitations underscore the need for a systematic approach to consolidate the available evidence and establish clear criteria for the assessment of its genetic toxicity.

In this sense, the PRISMA methodology (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) offers a robust and widely accepted framework for carrying out systematic reviews that allow the existing evidence to be identified, selected and critically analyzed. This approach ensures the transparency and reproducibility of the process, helping to generate reliable and informed conclusions that can guide future research and clinical applications.

The objective of this article is to carry out a systematic review, following the PRISMA guidelines, on the genotoxicity of extracts of medicinal plants with anticancer potential. Through the integration of recent findings, it seeks to provide a comprehensive view of the current state of research, identify trends and gaps in knowledge, and establish a solid foundation for the development of safe and effective therapies based on natural products.

2. General objective

To analyze, from a bibliometric and bibliographic perspective, the production of research papers on the variables Genotoxicity, Plant Extract, Medicinal Plants and Phytotherapy, published in high-impact journals indexed in the Scopus and Wos databases during the period 2018-2023.

3. Methodology

The present research is qualitative, according to Hernández, et al., qualitative approaches correspond to research that carries out the procedure of obtaining information to review and interpret the results obtained in such studies; for this, it searched for information in the Scopus and Wos databases through the words Genotoxicity, Plant Extract, Medicinal Plants, Phytotherapy. (2015)

3.1 Research design

The design of the research proposed for this research was the Systematic Review that involves a set of guidelines to carry out the analysis of the data collected, which are framed in a process that began with the coding to the visualization of theories. On the other hand, it is stated that the text corresponds to a descriptive narrative since it is intended to find out how the levels of the variable affect; and systematic because after reviewing the academic material obtained from scientific journals, theories on knowledge management were analyzed and interpreted. (Strauss & Corbin, 2016) (Hernández, Baptista, & Fernández, 2015)

The results of this search are processed as shown in Figure 1, through which the PRISMA technique for the identification of documentary analysis material is expressed. It was taken into account that the publication was published during the period between 2018 and 2023 without distinction of country of origin of the publication, without distinction of area of knowledge, as well as any type of publication, namely: Journal Articles, Reviews, Book Chapters, Book, among others.

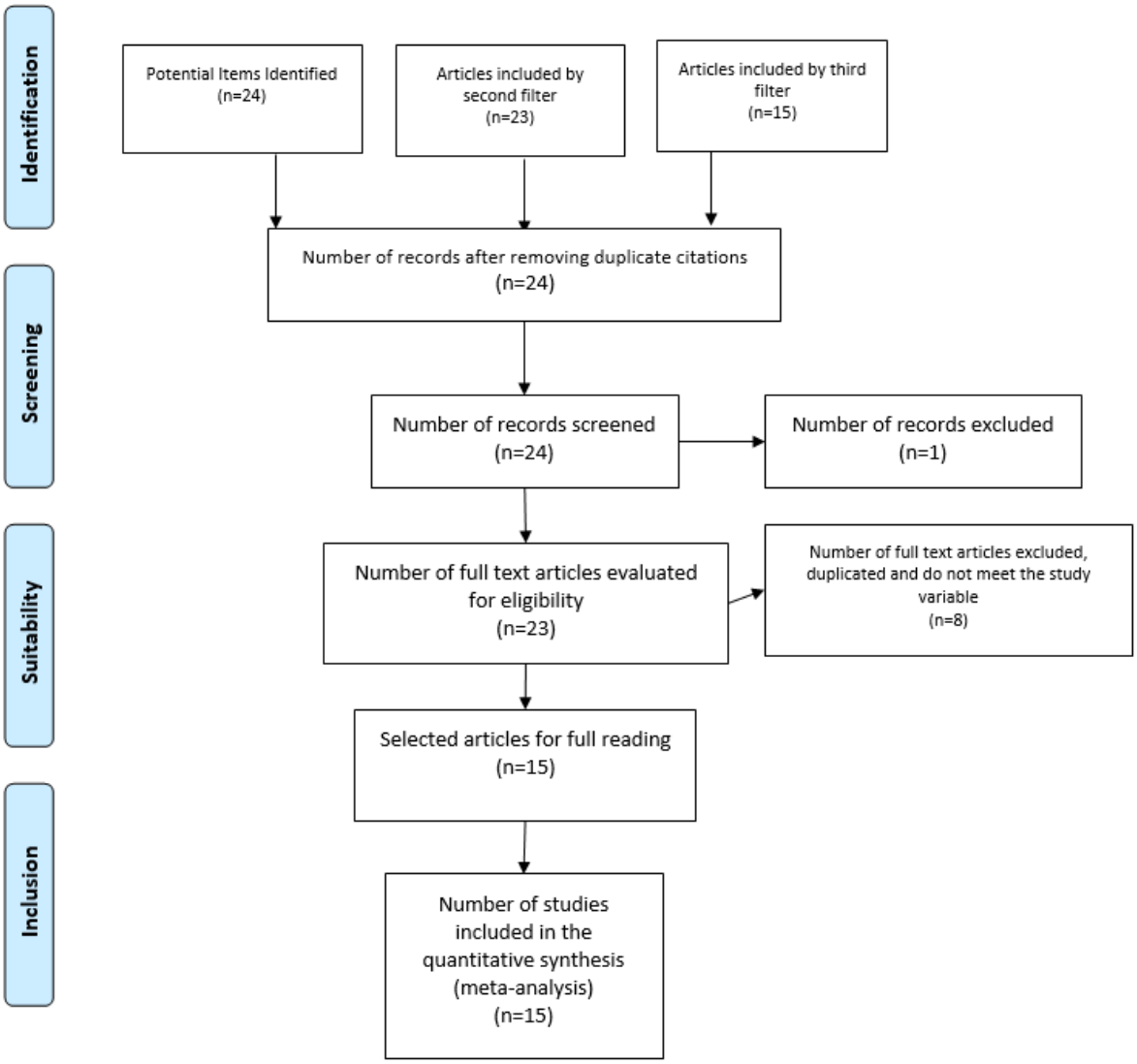

Figure 1. Flowchart of a systematic review carried out under the PRISMA technique (Moher, Liberati, Tetzlaff, Altman, & Group, 2009)
Source: Authors; Based on the proposal of the Prisma Group (Moher, Liberati, Tetzlaff, Altman, & Group, 2009)

4. RESULTS

Table 1 shows the results after applying the search filters related to the methodology proposed for this research, after recognizing the relevance of each of the referenced works.

Table 1. List of articles analyzed

No.	RESEARCH TITLE	AUTHOR/YEAR	Country	Type Of Study	Indexing
1	Evaluation of the cytogenotoxic potential of Zingiber officinale Roscoe, Zingiberaceae (ginger); [Assessment of the cytogenotoxic potential of Zingiber officinale Roscoe	Cardoso, Elisa Dos Santos to Send mail to Cardoso E.S.; Rossi, Ana Aparecida Bandini to; Pedri, Eliane Cristina Moreno De	Brazil	Qualitative	Scopus

	(ginger), Zingiberaceae]; [Evaluation of the cytogenotoxic potential of Zingiber officinale Roscoe Zingiberaceae (ginger)]	to; da Rocha, Vinícius Delgado b; Rodrigues, Alex Souza to; Fagundes, Patrícia Ana De Souza A (2019)			
2	Neurovascular glial unit: A target of phytotherapy for cognitive impairments	Trujillo Villarreal, L. A. (2022).	Mexico	Qualitative	Scopus
3	Medicinal Plants for the Treatment of Mental Diseases in Pregnancy: An in Vitro Safety Assessment	Spiess, D. , Winker, M. , Chauveau, A. , ... Gründemann, C. , Simões-Wüst, A.P. (2022)	Switzerland, Germany	Qualitative	Scopus
4	Antigenotoxic, antiproliferative and antimetastatic properties of a combination of native medicinal plants from Argentina	Carabajal, M.P.A. , Piloto-Ferrer, J. , Nicollela, H.D. , ... Isla, M.I. , Zampini, I.C. (2021)	Argentina, Cuba, Brazil.	Qualitative	Scopus
5	Genotoxic Assessment of the Dry Decoction of Myracrodruon urundeuva Allemão (Anacardiaceae) Leaves in Somatic Cells of Drosophila melanogaster by the Comet and SMART Assays	de Amorim, É.M., de Santana, S.L., da Silva, A.S., ... Ximenes, R.M., Rohde, C. (2020)	Brazil	Quantitative	Scopus
6	Persicaria hydropiper (L.) Delarbre: A review on traditional uses, bioactive chemical constituents and pharmacological and toxicological	Ayaz, M. , Ahmad, I. , Sadiq, A. , ... Khalil, A.T. , Devkota, H.P. (2020)	Pakistan, China, Arabia Saudi	Qualitative	Scopus

	activities				
7	Modulation of inflammatory pathways, medicinal uses and toxicities of Uvaria species: potential role in the prevention and treatment of inflammation	Jalil, J. , Attiq, A. , Hui, C.C. , Yao, L.J. , Zakaria, N.A. (2020)	Malaysia	Qualitative	Scopus
8	Phytochemical study, molecular docking, genotoxicity and therapeutic efficacy of the aqueous extract of the stem bark of Ximenia americana L. in the treatment of experimental COPD in rats	Sousa Carvalho, G.F. , Marques, L.K. , Sousa, H.G. , ... Rai, M. , Uchôa, V.T. (2020)	Brazil	Quantitative/Qualitative	Scopus
9	Tapinanthus species: A review of botany and biology, secondary metabolites, ethnomedical uses, current pharmacology and toxicology	Wang, L., Kong, D., Tian, J., ... Tian, J., Zhou, H. (2022)	China	Qualitative	Scopus
10	Screening of phytochemicals and toxicity of medicinal plants, Dillenia species, reveals potential natural product resources	Thooptianrat, T., Chaveerach, A., Sudmoon, R., ... Liehr, T., Babayan, N. (2018)	Thailand	Qualitative	Wos
11	An in vitro Study on the DNA Damaging Effects of Phytochemicals Partially Isolated from an Extract of Glinus lotoides	Demma, J; El-Seedi, H; (...); Hellman, B	Switzerland, Ethiopia	Qualitative	Wos

12	Biogenic synthesis of noble metal nanoparticles using Melissa officinalis L. and Salvia officinalis L. extracts and evaluation of their biosafety potential	Manolescu, D; Uta, G; (...); Avram, S (2022)	Romania	Qualitative	Wos
13	Toxicological, chemopreventive, and cytotoxic potentialities of rare vegetal species and supporting findings for the Brazilian Unified Health System (SUS)	Silva, JD; Monçao, NBN; (...); Ferreira, PMP (2020)	Brazil	Qualitative	Wos
14	Preliminary Research Regarding The Cytotoxicity And Antioxidant Activity Of Arbutus Unedo L. Leaves	Anghel, AI; Ancuceanu, R; (...); Nencu, I (2021)	Romania	Qualitative/Quantitative	Wos
15	Enhancing Therapeutic Efficacy of Donepezil, an Alzheimer's Disease Drug, by Diplazium esculentum (Retz.) Sw. and Its Phytochemicals	Inthachat, W; Chantong, B; (...); Temviriyanukul, P	Thailand	Qualitative	Wos

Source: Own elaboration

4.1 Co-occurrence of words

Figure 2 shows the relationship between the keywords used to search for the study material for the elaboration of the systematic analysis proposed for this research.

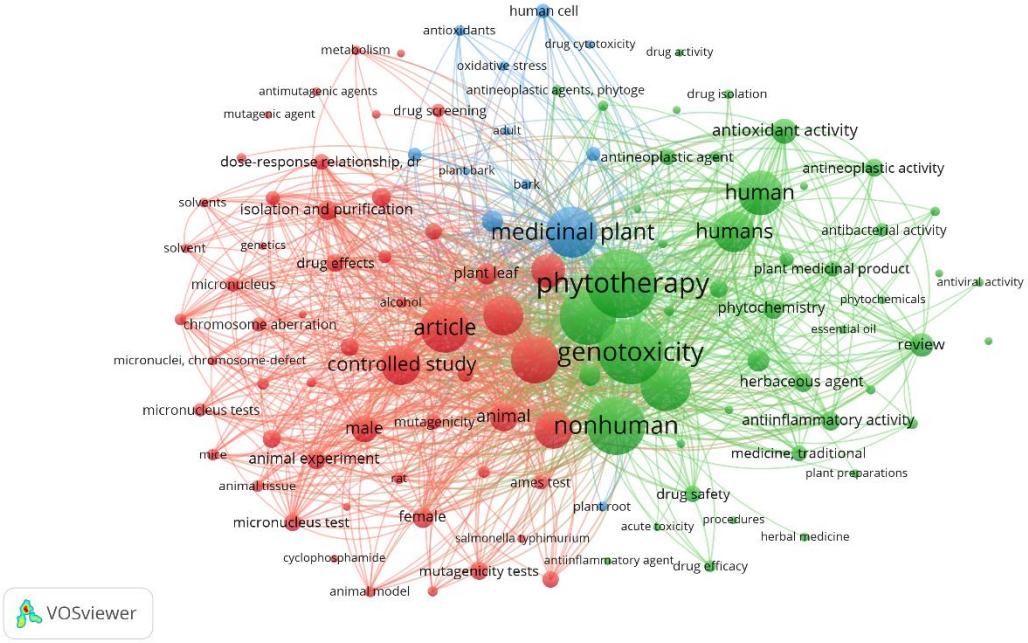

Figure 2. Co-occurrence of keywords.
Source: Own elaboration

The graph generated from an analysis of co-occurrence of keywords reveals important relationships between terms that highlight the central focus in the study of the "Genotoxicity" of compounds derived from medicinal plants, with potential applications in "Phytotherapy". At the core of the network, the words "Medicinal Plant", "Phytotherapy", and "Genotoxicity" form a robust interconnection, indicating their relevance as the main topics in the field of research.

The green group highlights words associated with the biochemical and pharmacological activities of plant compounds. Terms such as "Antioxidant Activity", "Antineoplastic Agent", "Antibacterial Activity", and "Antiviral Activity" highlight the therapeutic potential of these extracts. The strong connection between "Phytotherapy" and "Antioxidant Activity" suggests that antioxidant effects are fundamental for their therapeutic application, particularly in the prevention of genotoxic damage and as anti-cancer agents.

In the red group, the keywords focus on methodological and experimental aspects, such as "Controlled Study", "Micronucleus Test", "Chromosome Aberration", and "Ames Test". These connections reflect the importance of preclinical trials and genotoxic testing in "Nonhuman" models, such as "Animal Experiment," to assess the safety of extracts before considering their application in "Human" subjects. In addition, terms such as "Dose-Response Relationship" and "Drug Effects" highlight the need to establish specific parameters to ensure safety and efficacy.

The blue group, though less prominent, includes terms related to specific compounds and their sources, such as "Plant Bark," "Plant Leaf," and "Plant Root." This shows that different parts of plants can be evaluated to determine their therapeutic activity and genotoxic impact. The connection to "Oxidative Stress" suggests that plant extracts can be investigated for both their antioxidant capabilities and their potential to induce or mitigate DNA damage.

At the intersection of all groups, the word "Human" is strongly linked to terms such as "Phytochemistry", "Herbal Medicine", and "Drug Safety", reflecting a growing interest in translating the findings of preclinical studies into clinical applications. The presence of "Review" indicates that there is a considerable volume of reviewed literature that consolidates these findings, emphasizing the need for systematic reviews such as the present research.

In conclusion, the graph shows an interdisciplinary structure in the research of the "Genotoxicity" of medicinal plants, integrating both experimental studies and theoretical reviews. This highlights the importance of comprehensively addressing both the therapeutic benefits and genotoxic risks of plant compounds for use in phytotherapy.

4.2 Discussion

The research of Cardoso et al. (2019), which evaluates the cytogenotoxic potential of Zingiber officinale (ginger), offers an important precedent for this study. The evaluation of genotoxicity in an extract widely used in

traditional and modern medicine underscores the relevance of addressing the genetic risks associated with the therapeutic use of medicinal plants. This study demonstrates that even plants recognized for their benefits must undergo rigorous analysis before being applied in cancer treatments, establishing a basis for future research on their safety and viability as anticancer agents.

Trujillo Villarreal (2022) provides an alternative approach by exploring the impact of phytotherapy on the glial neurovascular unit to treat cognitive deficits. While its primary focus is not genotoxicity, this study highlights the ability of plant extracts to modulate specific molecular pathways. This reinforces the importance of understanding how plant compounds interact with the human body, especially in a context as sensitive as cancer treatment, where genotoxic effects could compromise patient safety.

The work of Spiess et al. (2022) on medicinal plants used during pregnancy highlights the importance of in vitro testing to assess the safety of extracts prior to use in vulnerable populations. This approach is also critical for anti-cancer phytotherapy, as it allows potential genotoxicity risks to be identified early in product development. The methodology described in this study could be adapted to evaluate extracts with anticancer activity, ensuring that their safety profile meets the required standards.

The research by Carabajal et al. (2021), focused on the antigenotoxic, antiproliferative and antimetastatic properties of medicinal plants native to Argentina, offers a comprehensive view of the therapeutic potential of these extracts. This study is particularly relevant to the present research, as it combines genetic safety tests with efficacy evaluations against tumour processes. This shows that it is possible to develop treatments that are not only effective against cancer, but also safe from a genetic perspective.

The study by De Amorim et al. (2020), which uses Comet and SMART assays to assess the genotoxicity of Myracrodruon urundeuva, establishes a robust methodological model that could be applied in this research. These techniques make it possible to assess DNA damage and chromosomal aberrations in somatic cells, providing accurate data on the safety of plant extracts. This quantitative approach, combined with anti-cancer efficacy evidence, could be key to ensuring that proposed extracts meet safety and efficacy standards.

Ayaz et al. (2020) offer a comprehensive review of Persicaria hydropiper, highlighting the need to integrate toxicological studies into phytotherapy research. This work emphasizes that bioactive compounds should be evaluated not only for their therapeutic efficacy, but also for their impact on genetic stability. The integration of ethnopharmacological data with modern toxicological analyses reinforces the holistic approach needed to evaluate extracts with anti-cancer potential.

The research of Jalil et al. (2020) on Uvaria species highlights the importance of analyzing both the therapeutic properties and the associated risks. This multidimensional approach is crucial for research such as the present one, where extracts must demonstrate not only their ability to modulate inflammatory and tumor pathways, but also their genetic safety. This work reinforces the need to combine genotoxic tests with efficacy analyses.

Sousa Carvalho et al. (2020) present an integrated approach that combines phytochemical studies, molecular coupling, and genotoxicity assessment in Ximenia americana extracts. This model represents a practical guide for similar research, as it addresses both therapeutic benefits and genetic risks in a coherent framework. The inclusion of molecular and experimental data improves the understanding of mechanisms of action and potential adverse effects.

The work of Wang et al. (2022), which reviews the pharmacological and toxicological properties of Tapinanthus species, underscores the importance of identifying secondary compounds with therapeutic potential. The relationship between these properties and genotoxicity is not always clear, highlighting the need for additional studies to assess the associated genetic risks. This article reinforces the relevance of considering both efficacy and safety when developing phytotherapeutic extracts.

Finally, Thooptianrat et al. (2018), in their analysis of phytochemicals and toxicity in Dillenia species, demonstrates the importance of thorough screening to identify promising and safe compounds. This approach is directly applicable to the research topic, where genotoxic risks must be evaluated along with therapeutic benefits to ensure that selected extracts are viable for clinical use.

CONCLUSIONS

The analysis of the selected studies highlights the importance of evaluating the genotoxicity of medicinal plant extracts as a fundamental step to ensure their safety in clinical applications, particularly in the treatment of cancer. Despite widespread recognition of the therapeutic properties of many plant species, the risks associated with genetic damage are still insufficiently explored in several cases. This study underscores that any extract with anti-cancer potential must undergo thorough genetic safety evaluations before being considered for use in humans.

Current studies were identified as applying a variety of methodologies, such as Comet assays, micronucleus tests, and SMART analysis, to determine the presence of DNA damage or chromosomal aberrations. These techniques offer a robust and reproducible framework for assessing genotoxicity, as evidenced in works such as those by De Amorim et al. (2020) and Sousa Carvalho et al. (2020). These tools should be integrated into future research to ensure the quality and accuracy of the data obtained, setting clear standards in the field.

The reviewed evidence also highlights the dual potential of plant extracts: while some compounds exhibit genotoxic effects under certain conditions, others show antigenotoxic, antiproliferative, and antimetastatic activities, as demonstrated by the study by Carabajal et al. (2021). This indicates that, in addition to assessing risks, researchers should explore the mechanisms by which certain extracts can protect healthy cells from genetic damage, optimizing their therapeutic application.

A key takeaway is the need for a multidimensional approach in anticancer phytotherapy research. In addition to assessing genotoxicity, it is essential to characterize the bioactive compounds present in the extracts, as suggested by Ayaz et al. (2020) and Wang et al. (2022). This approach allows not only to identify possible risks, but also to maximize therapeutic benefits, developing extracts with acceptable safety profiles and high efficacy.

The results also emphasize the importance of combining in vitro, in vivo, and bioinformatic analyses, as observed in the works of Spiess et al. (2022) and Thooptianrat et al. (2018). This comprehensive approach allows for a better understanding of the extracts' mechanisms of action, as well as their interactions with DNA and other cellular components. By integrating multiple methodologies, more robust and relevant conclusions can be generated for clinical applications.

Despite advances in the field, the studies reviewed also expose significant gaps in current knowledge, particularly in the lack of standardization of methodologies, the scarcity of long-term studies on genetic safety, and the limited extrapolation of in vitro results to human models. These challenges must be addressed in order to move towards the development of therapies based on plant extracts that are safe and effective in the treatment of cancer.

In conclusion, this study reaffirms the need for a rigorous and systematic approach to evaluate the genotoxicity of medicinal plants with potential use in anticancer phytotherapy. Integrating standardized methodologies, comprehensive therapeutic efficacy analyses, and long-term studies is essential to ensure that selected extracts meet the safety and efficacy standards necessary for application in clinical practice. This work lays the groundwork for future research, providing a clear framework for the development of safe and effective phytotherapeutic agents in the fight against cancer.

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