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RESUMEN

Antecedentes: el cáncer constituye un severo problema de salud pública global y nacional, siendo la segunda causa de muerte a nivel mundial y una de las principales en Chile; con una preocupante estimación de incremento superior al 60% para el 2040. Esta afección corresponde a un crecimiento descontrolado de células anormales; lo que es promovido por factores genéticos (tales como RAS, MYC, TP53 y RB1), epigenéticos y ambientales; con la capacidad de invadir otros tejidos mediante la alteración y evasión de mecanismos reguladores de la proliferación celular y la apoptosis; permitiéndole a las células tumorales evolucionar clonalmente y adaptarse a su microambiente, presentando un crítico desafío al diagnóstico y tratamiento a causa de la heterogeneidad tumoral. Metodología: se condujo una minirevisión con enfoque cualitativo mediante el protocolo PRISMA. La búsqueda se limitó a las bases de datos Scopus y PubMed, cubriendo el periodo 2010 y 2025, enfocándose en publicaciones sobre plantas nativas y/o endémicas de Chile. Resultados: se seleccionaron y analizaron seis artículos enfocados en las especies *Azorella compacta, Phycella cyrtanthoides, Escallonia spp., Ephedra chilensis, Leptocarpha rivularis,* y *Cryptocarya alba*. Estas plantas presentan compuestos, como diterpenoides, alcaloides y flavonoides, con potente actividad citotóxica por inducción de la apoptosis y la producción de especies reactivas de oxígeno. Discusión: Estos resultados destacan la biodiversidad de la flora nativa chilena con gran potencial farmacológico y terapéutico en la búsqueda de nuevos agentes antineoplásicos. No obstante, los estudios analizados en este trabajo en su mayoría se realizaron con pruebas in vitro, lo que limita aun su escalabilidad terapéutica, lo que destaca la necesidad de una mayor inversión en ciencia aplicada para el desarrollo de terapias contra el cáncer más efectivas y accesibles.
Palabras clave: Plantas nativas de Chile; Compuestos Antineoplásicos; Actividad Citotóxica; Especies Bioactivas.

ABSTRACT.

Background: cancer constitutes a severe public health issue at the global and national level, being the second leading cause of death worldwide and one of the principal causes in Chile; with a worryingly estimated increasing incidence of over 60% by 2040. This illness corresponds to an uncontrolled growth of abnormal cells, promoted by genetic factors (such as RAS, MYC, TP53, and RB1), epigenetics and environmental factors; with capability to invade other tissues through the alteration and escape from regulatory mechanisms of cell proliferation and apoptosis; allowing tumor cells to evolve clonally and adapt to their microenvironment, which presents a critical challenge to diagnosis and treatment due to tumor heterogenicity. ***Methodology****: a qualitative mini-review was conducted utilizing the PRISMA protocol. The search strategy was limited to the Scopus and PubMed databases, covering from 2010 to 2025. The focus was exclusively on publication concerning native or endemic plants from Chile.* ***Results****: six articles were selected and analyzed six articles focused on the following species Azorella compacta, Phycella cyrtanthoides, Escallonia spp., Ephedra chilensis, Leptocarpha rivularis and Cryptocarya alba. These plants contains compounds, such as diterpenoids, alkaloids and flavonoids, which exhibit strong cytotoxic activity through the induction of apoptosis and the production of reactive oxygen species (ROS).* ***Discussion****: these results highlight the biodiversity of native chilean flora showcasing its pharmacological and therapeutics potential as a source antineoplastic agents. But, between the studies analyzed most were conducted in vitro, which suggests a limited therapeutical scalability; this, in turn, undescores the urgent for greater investment in applied science to develop more effective and accesible therapies against cancer.*
Keywords: *Native plants of Chile; Antineoplastic compounds; Cytotoxic activity; Bioactive species.*

SUMMARY

Cancer is a disease characterized by the uncontrolled growth of abnormal cells with invasive and metastatic potential, which differentiates it from other proliferative conditions. Its origin lies in genetic mutations that affect cell cycle regulation, apoptosis, and other essential mechanisms. Hereditary, environmental, and epigenetic factors contribute to its development and progression. Tumor cells evolve in a clonal pattern, adapting

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to the microenvironment, which complicates diagnosis and treatment. Genes such as RAS, MYC, TP53, and RB1 play crucial roles in malignant transformation. Genomic instability, cellular plasticity, and immune evasion mechanisms also contribute to tumor aggressiveness. Furthermore, cancer represents a global epidemiological problem, being the second leading cause of death worldwide and the leading cause in Chile. Given this reality, the therapeutic potential of Latin American medicinal plants is being explored. Six studies focused on native or endemic Chilean species, including Azorella compacta, Phycella cyrtanthoides, Escallonia spp., Ephedra chilensis, Leptocarpha rivularis, and Cryptocarya alba, were reviewed. These plants showed compounds with significant cytotoxic activity, mainly diterpenoids, alkaloids, and flavonoids, which induce apoptosis and reactive oxygen species production. However, most studies are in vitro, limiting clinical projection without further preclinical and clinical trials. This mini-review highlights Chilean biodiversity as a promising source of new antineoplastic agents, underscoring the need for greater scientific investment to advance toward more effective and accessible cancer therapies.

What is Cancer?

Cancer is a pathology characterized by an uncontrolled growth of abnormal cells that can divide and multiply, and invade adjacent tissues; also, can disseminate to all body organs due processes named metastasis. This invasive capability of cancer distinguishes this from other normal proliferative cell forms (SEOM, 2019).

In pathophysiological view, cancer come from genetic mutations of cell cycle regulatory genes, apoptosis, angiogenesis, and another vital mechanism. Factors such as hereditary, environmental, infectious agents or epigenetic can promote or cause cancer. Progressive cumulation of these mutations can generate cells whit proliferative advantages, and immune response evasiveness, that facilitate its expansion and heterogenicity (Shlyakhtina et al., 2021).

Additionally, tumoral development is not a linear process, in fact, consider a clonal evolution where subpopulations of tumoral cells compete and adapt to microenvironmental. This implicate a hard challenge for diagnostic and therapeutic strategies, due the tumor are commonly heterogenous or biologically diverse, even in the same patient.

Genetic and Molecular Basis of Cancer.

the current knowledge about cancer biology has allowed understand it as complex, multifactor and evolutive disease, in this pathology is combination of genetic, epigenetic, environmental that promote adaptability of tumors to diverse tissue environment and strategies of chemotherapy.

Mutations of protooncogenes RAS and MYC, or tumor suppressor genes such as PT53 and RB1 have key role to understand cancer origins; due its key roles on cell proliferation, apoptosis, repair-correct DNA. cell differentiation and senescence. Dysregulation of its pathways can promote the malignant transformation (Hu & Zhang, 2016; Shlyakhtina et al., 2021). The work of Rout et al. (2025), by bioinformatic approach show the role of proteins as PI3K-Akt, p53, MAPK into apoptosis and cytokines signals. Key networks for new therapies development.

Additionally, genomic instability, aneuploidy and cell plasticity can give to tumor a higher capability, joined to its intrinsic variability, to evolve in clonal pattern even front therapy. Proteogenomic analysis has shown this. even in cells with severe damage at genetic or chromosomal levels (Bökenkamp et al., 2025). This adaptation considers control mechanisms for misfolding proteins, metabolic changes and modifications of signal pathways, shaping a molecular resilient network.

According to previous, three proteins that act as suppressor of tumor are key actors into the cancer way (Chen et al., 2020). The retinoblastoma protein (pRb1) was the first "tumor suppressor gene" identified. pRb is an antiproliferative regulator acting as inhibitor for E2F transcription factor; its function is lose in 98% of childhood malignancies

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retinoblastoma, analysis showed that exist (Mandigo et al., 2022). Its inactivation is based on deletions, methylation of its promotor, or mutations that result in nonfunctional protein.

Additional to pRb1 role, the protein p53 is the most relevant tumor suppressor known. Experiments in murine models has shown that p53 loss activity made cells more vulnerable to permanent genetic damage and neoplastic transformation. Data show that in 50% of human cancers, p53 have some mutation (Liu, Tavana & Gu, 2019).

Another aspect of tumor develop is the growing role of non-coding RNA (ncRNA). Its role as post-transcriptional control, epigenetic regulation and cell to cell communication are highlighted. Some micro-RNA (miRNA) act as oncogenes or tumoral suppressor, and its dysregulation can contribute to beginning, progression and metastasis in diverse cancer types (Absalan & Vaziri, 2025).

Other points to consider is the immune modulation and pharmacological resistance exhibit by tumors. respect to immune modulation, has been shown that tumor can manipulate this by expression of immune cell inhibitory ligand or until to recruiting immunosuppressor cell (as Treg cells). This immune evasion has several and direct implications over efficacy of current immunotherapy (Czajka-Francuz et al, 2023).

Epidemiological Aspects of Cancer.

Cancer constitute one of main public health issues on worldwide level. According to World Health Organization (WHO, 2022) this pathology is the second death cause over world, causing ten million yearly. Most common cancer forms are breast, lung, colon, rectum, prostate and stomach. Social charge of this disease varies significantly accord economic status, environmental and demographic factors, but with more observed incidence in high- or medium-income countries.

In Latin America, the problem has the same concerning. The Pan-American of Health Organization (PAHO, n.d.) warn that the cases of cancer are increasing, and estimated for 2040 that the charge of this disease will be increased more than 60% into the region. In Chile this outlook is very critical. In agreement with Parra-Soto et al. (2023) cancer has transformed into the first death cause, exceed the cardiovascular pathologies. Researchers highlight the worrying increasing tendence about some cancer type, such as lung, colon and breast, also the incidence on young people.

This epidemiological reality suggests challenges for public health systems, not only about early detection and treatment., if prevention policies, improvement of oncological treatment access, and scientific information generation that allow science-based decision making.

Phytochemical Therapeutic Approaches

The research about the medicinal use of plants from Latin America has make a growing due the great biodiversity and ancient knowledge from ethnic communities, that promise be a source of new therapeutic agents against cancer, the main death cause around the world (WHO, 2022).

Tauchen et al. (2019) researched the potential of Peruvian plants. They tested the antiproliferative effects from eight plant species used in Peruvian traditional medicine on diverse human cancer lines, identifying *Dysphania ambrosioides* has moderated antiproliferative activity.

Carvalho et al. (2019) investigate by systematic revision diverse plants used in traditional medicine in Brazil. They found that the species *Jacaranda decurrens*, *Campomanesia adamantium*, *Senna velutina*, and *Stryphnodendron adstringens* are capable to kill malignant cells from melanoma and leukemia inducing apoptosis. Complementary, the work of Da Silva et al. (2016) studied eighteen plants from northeastern of Brazil, identified that the species *Byrsonima sericea*, *Duranta repens*, *Himatanthus bracteatus*, *Ipomoea purga*, *Ixora coccinea*, *Mabea piriri*, *Ocotea longifolia* and *Psychotria capitata* showed promising potential due its cytotoxic activity.

Cuevas-Cianca et al. (2023) show, in its review about Mexican medicinal plants, that *Justicia spicigera*, *Rhus trilobata*, *Annona muricata* and Veronica americana have promising properties against breast, cervix and colon cancer, and also

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evidence cytoprotective properties, that demonstrates a very interesting potential use.

Review Objective

This work, a minireview with qualitative scope, is focused in show potential of native or endemic Chilean plants as source of novel antineoplastic, antitumoral or cytotoxic compounds with projections for new therapeutics against the main death cause currently in Chile, Latin-American and worldwide.

METHODOLOGY AND RESULTS

Oriented by the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) on databases Scopus, Scielo, ProQuest, PubMed and Web of Science. Considering articles publicized between January 2010 and march 2025. Was applied selection criteria such as only articles open access, from research focus in cancer. This results in selection of six articles for depth analysis.

Figure 1 show that the six articles was published between 2016 and 2024. The journal BMC Complementary Medicine and Therapy concentrate the mayor articles selected. The figure 2 show that Flavonoids were the main compounds referred as active chemical present into the plants studied.

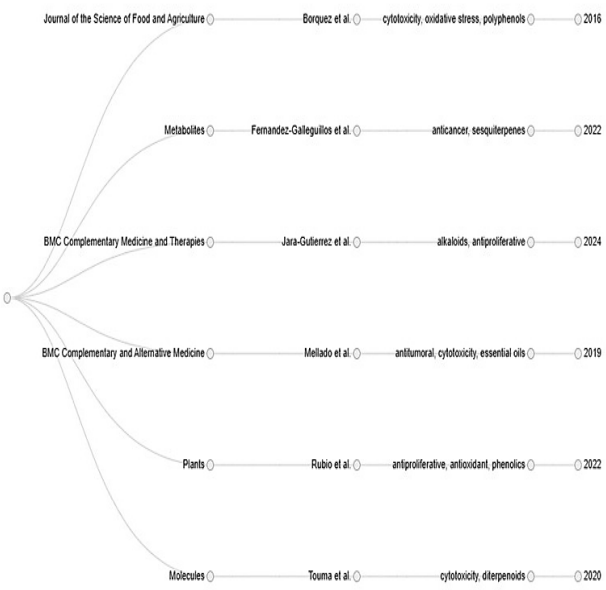

Figure 1. Dendrogram resulting from consider journal, authors, year of publication and keywords used in these.

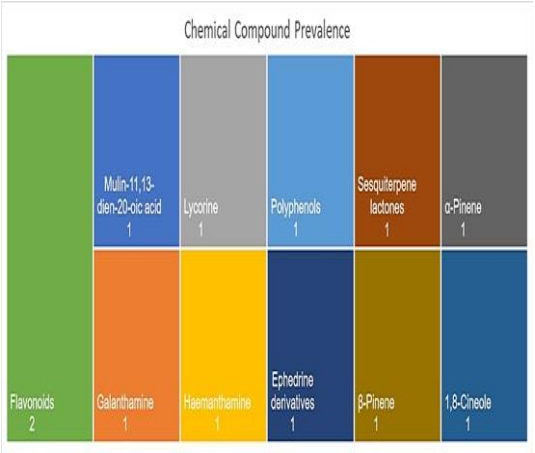

Figure 2. Tree map that shows the compounds identified and mentioned in the articles selected for review.

In congruence order of figure 1; *Azorella compacta* was studied by Bórquez et al. (2016). *A.compacta*, popularly named "yareta", is a camephite native from South-America, live in Andean region between Bolivia, Perú, Chile and Argentina; inhabits 3200 meters above sea level. The study identified 13 compounds as diterpenoids, but only four show very good cytotoxic activity against colon, lung, breast and prostate cancer cells; being 13α,14α-dihydroxymulin-11-en-20-oic acid or mulinolic acid the most active. The activity as antineoplastic was characterized as promoter of the apoptosis by mitochondrial pathway and ROS production.

Fernandez-Galleguillos et al. (2022) investigated the potential of *Phycella cyrtanthoides*, commonly named as "añañuca de fuego". *P.cyrtanthoides* is an endemic plant from central zone of Chile. The study identified alkaloids as active compounds against proliferation of lung, cervix, gastric, colon and breast cancer cells. A total of 70 alkaloids was identified by UHPLC. The activity was compared with the standard drugs used as antitumoral therapy, cisplatin, showing similar effectivity. The mechanism of antiproliferative activity was characterized as inhibitor of cell

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cycle progression (arrest of G2/M phase) and DNA damage.

Jara-Gutierrez et al. (2024) analyzed extracts from four species of the *Escallonia* genus (*E.illinita, E.rubra, E.revoluta* and *E.pulverulenta*). *E.pulverulenta*, commonly named "corontillo", is a native plant from coast and inland valleys from Coquimbo to La Araucanía region. *E.rubra*, named as "ñipa roja", is endemic from south of Chile and argentinian zones; grow over slopes of the Andes Mountains. *E.illinita*, known as "barraco", is finded from Coquimbo to Biobio region. *E.revoluta*, named as "siete camisas", is an endemic tree from Coquimbo to Los Rios region. 36 extract was obtained from plants, but only six showed cytotoxicity effects on cell tested (colon, breast, prostate human cancer cells and human embryo kidney cells), comparative study with doxorubicin.

Ephedra chilensis (Mellado et al., 2019), popularly known as "pingo-pingo", is an herbal plant endemic of Chile, from Atacama to Ñuble region, and some places of Argentina. Diverse organic extracts from *E.chilensis* were quantified for the anthraquinone, flavonoid, phenolic contents; and in other assay, the antioxidative and cytotoxic effect on some cancer cell lines (breast, colon, prostate). The non-polar (hexane and dichloromethane) was very active against the cancer cells, including more effectivity than doxorubicin against breast and prostate cancer cells.

The work of Rubio et al. (2022) analyzes the properties of *Leptocarpha rivularis*. This plant is an endemic shrub, commonly named "palo negro", that grow from Maule to Los Lagos region. The study analyzed extract obtained from cell cultures of *L.rivularis*. Was identified sesquiterpenes lactones (e.g., leptocarpin) with activity against breast, ovarian and prostate cancer cells.

Finally; Touma et al. (2020) studied extract from Cryptocarya alba, and endemic tree that grow between Coquimbo to Araucanía regions. The main compounds found in the essential oil from C. alba were α-terpineol and eucalyptol. This was assay against murine mammary tumor cells, showing good inhibitory activity.

DISCUSSION.

The evidence from six articles shows that a common mechanism of cytotoxicity, especially referred as the apoptosis induction and ROS production. Related with this, alkaloids and terpenoids are the most effective compounds with potent effects.

But, only one study (Touma et al., 2020) tested in vivo validity, which imposes limits on its prospection without major and complex effectiveness versus toxicity tests. Nosrati et al. (2017) and Cuevas-Cianca et al. (2023) refer to various mechanisms by which bioactive compounds from plants can interfere with key events in cancer progression; such as inhibition of cell proliferation, induction of apoptosis, suppression of angiogenesis.

From regional perspective, many studies has shown the therapeutic potential from plant species of Latin-America (Calderón et al., 2006; Orrego, 2015; Quintero-Rincón et al., 2025). It only takes putting hands and resources to work.

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