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Systematic Review: Anticancer Activity of *Chromolaena odorata* L.

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Abstract

Cancer is one of the leading causes of death in the world, and conventional therapies such as chemotherapy and radiotherapy often cause significant side effects. Therefore, natural ingredients are a promising alternative, one of which is *Chromolaena odorata,* which is known to be rich in flavonoids, alkaloids, and terpenoids. This study aims to systematically review the evidence of anticancer activity of *C. odorata* based on *in vitro* and *in vivo* studies. The literature review was conducted through PubMed, ScienceDirect, Google Scholar, and Web of Science databases using the PRISMA 2020 method, and ten articles were obtained that met the inclusion criteria. The analysis showed that *C. odorata* extracts and fractions have cytotoxic activity against various cancer cell lines, including breast (MCF-7, T47D, MDA-MB-231, 4T1), cervical (HeLa), liver (HepG2), colon (HT-29, WiDr, HTB), and skin keratinocyte models (HaCaT). The identified mechanisms include induction of apoptosis, arrest of the G_0-G_1 phase of the cell cycle, suppression of proliferation, and modulation of apoptosis-regulating protein expression. Kaempferide compounds emerged as the most potent candidates with low toxicity to normal cells. However, differences in the extraction method, dose, and cell type led to variations in effectiveness, and the combination with cisplatin on MDA-MB-231 cells showed antagonistic effects. This review provides integrated evidence for the anticancer potential of *Chromolaena odorata* and highlights research gaps for future pharmacokinetic and clinical investigations

Keywords:*Chromolaena odorata*, anticancer, apoptosis, kaempferide, systematic review

1. Introduction

Globally, cancer is the second leading cause of death and will account for an estimated 20 million new cases and 9.7 million deaths by 2022, with an estimated 1 in 5 people having cancer in their lifetime (International Agency for Research on Cancer, 2024). Projections by IARC show that global cancer cases are expected to exceed 35 million new cases per year by 2050, an increase of more than 75% compared to 2022 (The Guardian, 2024). In Indonesia, the cancer burden is also alarming, recording more than 396,914 new cases and 234,511 cancer deaths in 2020 (Prihantono et al., 2023). More recent data from 2022 reinforces this trend with more than 408,661 new cases and 242,099 deaths, particularly from breast, cervical, lung, colorectal, and liver cancers (Ministry of Health of the Republic of Indonesia, 2025). This demonstrates the high burden of cancer, especially in resource-limited countries, and the urgency for more effective cancer control.

Conventional therapies, such as chemotherapy and radiotherapy, are effective in controlling or inhibiting the growth of cancer cells, but cause significant side effects and affect patients' quality of life. Chemotherapy often results in chronic fatigue affecting up to 80% of patients, accompanied by nausea, vomiting, loss of appetite, and an overall decline in physical and emotional functioning (Lewandowska et al., 2020). In addition, radiotherapy, especially if repeated or applied to large volumes of tissue, can cause fatigue, hematologic damage such as bone marrow suppression, as well as ongoing psychosocial impact, especially in patients with long-term therapeutic approaches (Ahmadsei et al., 2022). With the increasing life expectancy of cancer patients, emphasis on non-cancer outcomes such as quality of life, long-term toxic effects, and psychological well-being is becoming increasingly important in determining optimal treatment strategies (Tali & Amin, 2024).

Various phytochemicals are increasingly viewed as alternatives or adjuvants for cancer therapy due to their diverse structures and molecular targets that can induce apoptosis, halt the cell cycle, stop angiogenesis, and modulate inflammatory/oxidative pathways. Historically, natural products and their analogs have even accounted for a large portion of modern cancer drugs and remain a major source of discovery for new candidates. Research by Atanasov et al. (2021) says that at the preclinical level, many phytochemicals, especially polyphenols and flavonoids, show antineoplastic activity through regulating ROS, NF-κB, MAPK, and PI3K/Akt, and have the potential to synergize with chemotherapy/radiotherapy to enhance cytotoxic effectors and overcome resistance. De Luna et al. (2023) stated that the evidence of the past decade supports the role of phytochemicals as companions to conventional therapies to improve effectiveness and suppress toxicity. However, translational challenges such as low bioavailability and extract standardization still need to be addressed through formulation design and structure-based optimization (Lin et al., 2020).

In that context, *Chromolaena odorata* (L.) R.M. King & H. Rob. is a tropical shrub of the Asteraceae family that originally originated in Central and South America, but is now spreading as an invasive plant in Asia, Africa, Australia, and Indonesia due to its high ecological adaptability (Budha Magar et al., 2023). This plant is known as a source of various bioactive compounds, including flavonoids (quercetin, kaempferol, acacetin, luteolin, naringenin), terpenoids, alkaloids, as well as phenolic compounds, steroids, saponins, and tannins that play an important role in its

pharmacological activities (Olawale et al., 2022; Tiamiyu & Okunlade, 2020). The presence of these secondary metabolites has been shown to support antioxidant, antimicrobial, anti-inflammatory, antihyperglycemic, and cytotoxic activities, thus making *C. odorata* a potential candidate in the development of natural ingredient-based drugs (Harfiani et al., 2022) . Interestingly, the highest concentration of phytochemicals was reported in the leaves and flowers compared to the stem, suggesting these parts are more promising to be explored in further pharmacological research (Budha Magar et al., 2023).

Preclinical studies have shown that *C. odorata* has promising anticancer potential through apoptotic and antiproliferative mechanisms. Isolation of kaempferide, one of the major flavonoids from this plant, was shown to effectively trigger apoptosis in HeLa cervical cancer cells, characterized by caspase activation and PARP cleavage, while showing pharmacological safety in normal fibroblasts (Nath et al., 2015). Furthermore, the ethyl acetate fraction can selectively reduce the viability of MCF-7 and T47D breast cancer cells, with IC_{50} values of 218.78 µg/mL and 307.61 µg/mL respectively, as well as a high selectivity index (12.77 for MCF-7 and 9.08 for T47D), signifying the ability of this extract to effectively suppress cancer cell proliferation (Yusuf et al., 2023). In addition, the ethyl acetate fraction was also shown to limit proliferation and induce apoptosis in cervical cancer cells through MTT and flow cytometry evaluation (IC_{50} around 82 µg/mL), with more than 97% of HeLa cells undergoing cellular death at IC_{50} and $2\times IC_{50}$ concentrations (Yusuf, Fahriani, & Murzalina, 2022). Although there have been no explicit reports of anti-angiogenesis effects, these findings strongly suggest kinetic and cytotoxic activities underlying the potential of *C. odorata* as a source of anticancer phytochemicals.

Research on *C. odorata* as an anticancer agent continues to evolve from in vitro tests on various cell lines (e.g., breast, cervical, colorectal) to preliminary in vivo evidence in animal models. However, so far, the studies are generally general narrative reviews (pharmacology/phytochemistry) or focus on non-cancer indications (e.g., wound healing), so there is no systematic review available that specifically summarizes and integrates the results of in vitro and in vivo anticancer tests of C. Odorata comprehensively (Ajay et al., 2021; Olawale et al., 2022). Therefore, this study aims to systematically review the anticancer activity of C. odorata across various cancer cell lines and animal models by synthesizing evidence related to cytotoxicity (IC_{50}), apoptosis/necrosis, proliferation inhibition, and tumor outcomes. Specifically, this review seeks to answer the research question: What is the overall evidence for the anticancer potential of *Chromolaena odorata* based on in vitro and in vivo studies, and what research gaps remain for future investigation?

2. Methods

This study used a systematic review approach based on the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines to ensure transparency and replicability (Page et al., 2021). A comprehensive literature search was conducted on scientific

databases such as PubMed, ScienceDirect, SpringerLink, and Google Scholar with a publication time range of 2013-2023, using the keywords: *"Chromolaena odorata"*, *"anticancer"*, *"cytotoxicity", "apoptosis", "anti-proliferation"*, and *"anti-angiogenesis"*. Articles that met the inclusion criteria were in vitro and in vivo studies that assessed the anticancer activity of extracts or bioactive compounds from *C. odorata*. Exclusion criteria included non-research articles (reviews, editorials), studies without relevant biological activity data, and publications that were not fully accessible.

The article selection process was conducted in two stages, namely title/abstract screening and full text review. To reduce bias, the literature was screened, and the selection results were discussed until consensus was reached. Data extracted included basic research information (author, year, country), type of cancer cells or test animals, test method, concentration/dose, mechanism of action (apoptosis, antiproliferation, antiangiogenesis), and main results.

Assessment of study quality is done using assessment tools appropriate to the type of study. For in vitro studies, quality is assessed based on transparency of methodology, replication of tests, and controls used (Tran et al., 2021). As for in vivo studies, *SYRCLE's Risk of Bias Tool* was used to evaluate aspects of randomization, blinding, sample size, and clarity of data reporting (Hooijmans et al., 2014) . Articles with low quality or high risk of bias were noted but treated with caution in the synthesis of results.

Data from each study were analyzed narratively and, where possible, compared between studies based on cancer cell types, active compounds, and reported mechanisms of action. This approach is expected to provide a comprehensive picture of the anticancer potential of *C. odorata* and the direction of future research.

3. Result and Discussion

3.1 Study Selection

A literature search on four major electronic databases, namely PubMed, ScienceDirect, ProQuest, and Google Scholar, yielded a total of 845 articles related to *C. odorata* and its anticancer activity. After removing 135 duplicates, 710 unique articles were screened based on title and abstract, at this stage of screening, 634 articles were excluded because they were not relevant to the research topic, such as general review articles, reports that did not involve *C. odorata*, or studies that did not evaluate anticancer effects. Thus, only 76 articles proceeded to the full-text review stage. Of these, 66 articles were excluded because they did not meet the inclusion criteria, such as the use of non-cancer models, incomplete data, or inappropriate research design. Finally, 10 articles were eligible and included in this systematic analysis.

3.2 Characteristics of Included Studies

The ten included studies evaluated the potential of *C. odorata* against various types of cancer, both through *in vitro* approaches using cancer cell cultures and *in vivo* with experimental animal models. Many *in vitro* studies used breast cancer cell lines (MCF-7, T47D, MDA-MB-231, and 4T1), cervical cancer (HeLa), liver cancer (HepG2), colon cancer (HT-29, WiDr, and HTB), and skin keratinocyte model (HaCaT). Meanwhile, *in vivo* studies used Wistar rats induced carcinogenesis. The most commonly tested extract types are ethanol extract and the ethyl acetate fraction of *C. odorata* leaves, although some studies have also reported the isolation of specific flavonoid compounds, such as kaempferide. The results of the article selection process using the PRISMA 2.0 method are presented in Figure 1.

Figure 1.
Diagram of PRISMA procedure as a literature search and review process·

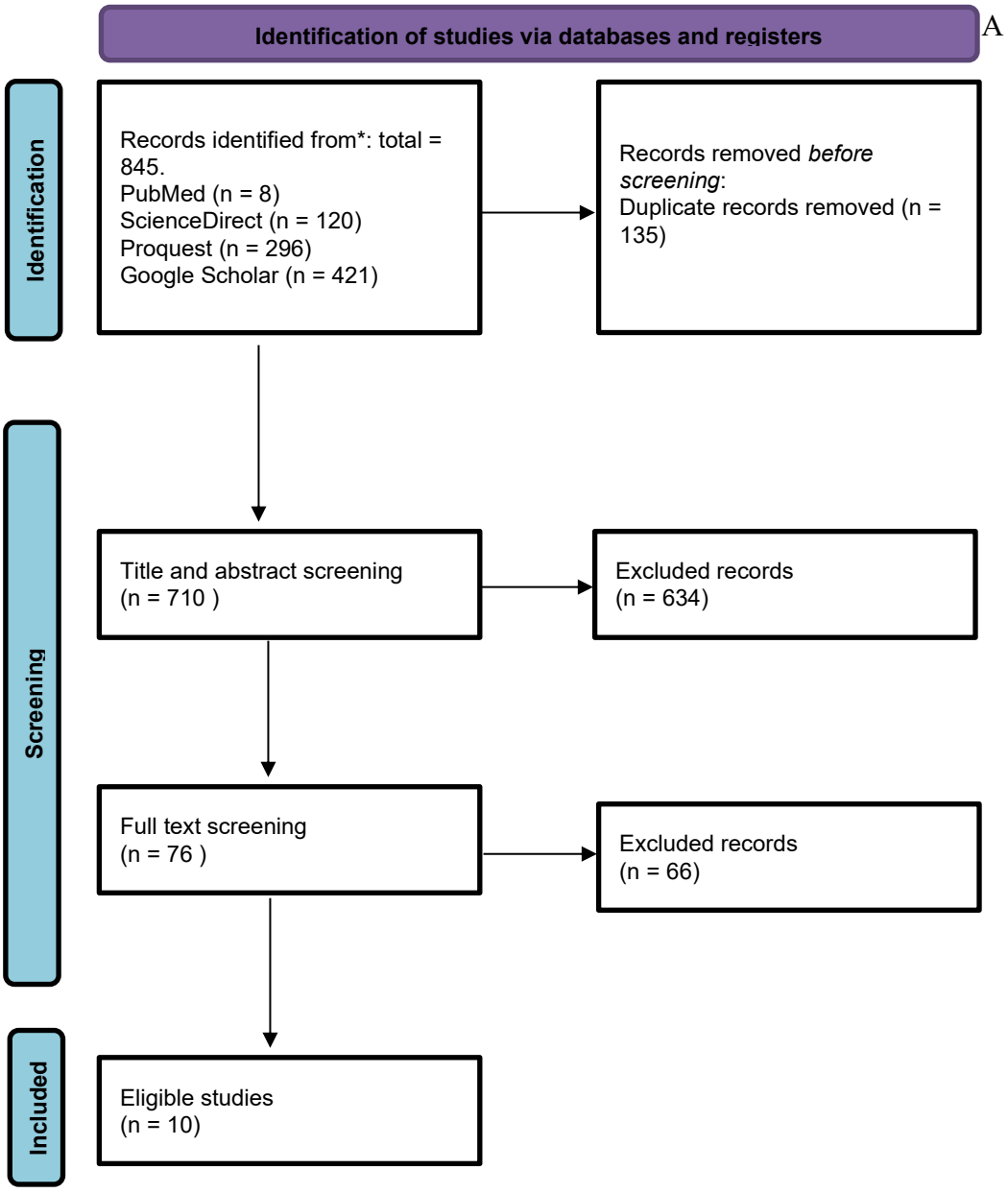

Table 1. Data extraction

Author, Publication Year	Research Design	Cell Type/Animal Model	Treatment	Treatment Concentration/ dose	Treatment Duration	Parameters	Research Results
Hanifah Yusuf, Hijra Novia, Marhami Fahriani	In vitro	MCF-7, T47D, and Vero Cells	*C. Odorata* (leaf) Ethyl acetate extract	50-400 µg/mL (test range, IC_{50}: 218.78 µg/mL for MCF-7 and 307.61 µg/mL for T47D)	24, 48, 72 hours	Cell viability (MTT assay) - Apoptosis/necrosis (flow cytometry) - Selectivity index (SI)	IC_{50} indicates cytotoxic activity: MCF-7 is more sensitive than T47D - Viability decreased significantly after IC_{50} treatment according to the above duration - High apoptosis/necrosis: T47D = 83.35%, MCF-7 = 95.15% (both cells mostly entered necrosis) - Selectivity Index is relatively high: MCF-7 = 12.77, T47D = 9.08 → indicates EACO is quite selective against cancer cells compared to normal cells
Hanifah Yusuf, Marhami Fahriani, Cut Murzalina, 2022	In vitro experimental study	HeLa	*C. Odorata* (leaf) Ethyl acetate extracts	15,625, 31.25, 62.5, 125, 250, and 500 µg/mL; IC_{50} = 82.41 ± 6.73 µg/mL	24, 48, 72 hours	Cell viability (MTT assay) - Cell proliferation (doubling time assay) - Apoptosis/necrosis (double staining & flow cytometry)	IC_{50} = 82.41 ± 6.73 µg/mL - Cell death >97% at doses of IC_{50} & $2\times IC_{50}$ ($p < 0.05$) - Cell proliferation was significantly inhibited at doses of ½ IC_{50}, IC_{50}, and $2\times IC_{50}$ within 24 hours ($p < 0.05$)
Hanifah Yusuf, Reno Keumalazia Kamarlis, Yusni Yusni, Marhami Fahriani, 2021	Experimental in vivo	Wistar rats *(Rattus norvegicus)*	Oral *C.Odorata* (Leaf), Ethanol extract of	500, 1000, 2000, and 4000 mg/kg BW	16 weeks	Number of cancer nodules, Nodule volume, Weight of cancer nodules, Body weight of mice, AgNOR count (cell proliferation indicator)	Significant reduction in the number, volume, and weight of cancer nodules at all doses ($p < 0.001$) - The 2000 mg/kg dose showed lower nodule weight than the doxorubicin group ($p < 0.0001$) - Significant increase in body weight of rats at week 11 ($p < 0.05$) and week 16 ($p < 0.001$) dose-dependently

Author, Publication Year	Research Design	Cell Type/Animal Model	Treatment	Treatment Concentration/ dose	Treatment Duration	Parameters	Research Results
Hanifah Yusuf, Marhami Fahriani, Cut Murzalina, Rumaisa Dhifa Mawaddah, 2022	In vitro experimental	HepG2	*C.odorata* (leaf), Ethanol extracts	(11,72), (23,44), (46,88)	24, 48, and 72 hours	Total flavonoid abundance and identification of major phytochemicals (LC-MS) - Cell viability (MTT assay) - Cell proliferation (number reduction) - Cell cycle analysis (flow cytometry, G0-G1 phase accumulation)	Extracts and fractions significantly reduced HepG2 cell proliferation after 72 hours of incubation with ½ IC_{50}. - There was an accumulation of HepG2 cells in the G0-G1 phase, indicating cell cycle arrest - The extract contains flavonoids (1.95%); major compounds such as pentamethoxyflavonone and other alkaloids were identified through LC-MS
Hanifah Yusuf, Fauzul Husna, Basri A. Gani, 2021	In vitro experimental	(WiDr) and (HTB and 4T1)	*C.odorata* (leaf), Ethanol extract	7.8-(62.5), 125, 250, 500 µg/mL	24 hours	Cytotoxicity, Cell viability	Cytotoxicity increased with dose; at 500 µg/mL, toxicity was >80% in all cells; significant effect ($p<0.05$). IC_{50} values not reported numerically.
Adedapo, Adeolu A.; Oyagbemi, Ademola A.; Fagbohun, Olusegun A.; Omobowale, Temidayo O.; Yakubu, Momoh A., 2016	In vitro experimental	HT-29	C.odorata (leaf), Ethanol extracts of	100-700 µg/m, 200 µg/mL and 800 µg/mL	24, 48, and 72 hours	Cell viability (Cell Titer 96 MTT assay) - Mitogen effects (VEGF, ET-1) on extract activity	MLECO extract significantly suppressed HT-29 proliferation after 72 hours, the effect was stronger at high concentration (800 µg/mL). - When mitogens (VEGF or ET-1) were combined, a concentration of 200 µg/mL with ET-1 showed a more dominant proliferative effect, reducing the anticancer effect of the extracts

Author, Publication Year	Research Design	Cell Type/Animal Model	Treatment	Treatment Concentration/ dose	Treatment Duration	Parameters	Research Results
Lekshmi R. Nath; Jaggaiah N. Gorantla; Sophia Margaret Joseph; Jayesh Antony; Sanu Thankachan; Darsan B. Menon; S. Sankar; Ravi S. Lankalapalli; Ruby John Anto, 2015	Experimental in vitro	HeLa	*C.odorata* (leaf) extract, hexane, dichloromethane, ethyl acetate, and methanol p	25, 50, 100, 250 µg/mL	72 hours	1. Cell viability (MTT assay) 2. Apoptosis (morphology, Annexin V staining, FACS) 3. Activation of caspases & PARP cleavage (Western blot) 3. 4. Toxicity to normal fibroblasts 4. 5. In vivo examination - acute and chronic toxicity 5.	1. Kaempferide showed the most potent cytotoxicity against HeLa with IC_{50} = 16 µM, equivalent to curcumin (~16.67 µM). 2. - Non-toxic to fibroblast cells up to 100 µM. 3. Triggers apoptosis (typical morphology, Annexin V+, caspase & PARP cleavage). 4. Minimal in vivo toxicity in acute and chronic studies
Hanifah Yusuf; Marhami Fahriani, 2022	In vitro experimental	HepG2	*C.Odorata* (leaf) Ethanol extracts	7.8, 15.6, 31.25, 62.5, 125, 250, 500 µg/mL	72 hours	Cell viability (MTT assay) - Cell proliferation (cell number) - Cell cycle arrest (flow cytometry, accumulation of G_0-G_1 phase) - Apoptosis induction (flow cytometry)	1. Crude ethanol extract was most potent (IC_{50} = 23.44 µg/mL), followed by n-hexane fraction (84.52 µg/mL), ethanol (88.51 µg/mL), and ethyl acetate fraction (167.49 µg/mL) 2. Treatments at ½ IC_{50} and 2× IC_{50} significantly inhibited proliferation and triggered arrest of G_0-G_1 cells, as well as increased apoptosis compared to controls

Author, Publication Year	Research Design	Cell Type/Animal Model	Treatment	Treatment Concentration/ dose	Treatment Duration	Parameters	Research Results
Nurliana Abd Mutalib; Zulhilmi Mohamad Bakri; Khairuddin Abdul Jalil; Normala Abd Latip, 2023	In vitro experimental	MDA-MB-231 and MCF-7	*C.odorata* (leaf), Ethanol extract	0.078, 0.156, 0.313, 0.625, 1.250, 2500, Mg/ml	72 hours	Cell viability (MTT), Combination Index (CI), isobologram	The combination of extract + cisplatin was antagonistic (CI>1) in both cells.
Karlina Amir Tahir; Erwin Hafid; Muh. Fitrah; Ahmad Lalo; Nurul Fadilah; Syamsuri Syakri; Syatirah Jalaluddin; Katsuyoshi Matsunami, 2024	In vitro experimental	HaCaT	*C.odorata* (leaf), Ethanol extracts	20 µg/mL, 50 µg/mL, and 100 µg/mL	24 hours	Cell viability of HaCaT keratinocytes was measured using the MTT assay.	Ethyl acetate fraction reduced HaCaT cell viability up to 48% at a concentration of 100 µg/mL.

Based on a systematic review of 10 articles that met the inclusion criteria, it was found that *Chromolaena odorata (C. odorata*) shows a broad spectrum of anticancer activity in various cancer cell models and experimental animals. The most widely used extracts are ethanol and ethyl acetate fractions of the leaves, which are known to be rich in flavonoids and phenolic compounds. Research results consistently show that *C. odorata* is able to suppress proliferation, reduce viability, induce apoptosis, and, in some models, cause cell cycle arrest. These activities appear to be selective to cancer cells compared to normal cells, and in *vivo* models have been shown to significantly suppress tumor growth.

3.3 Anticancer Activity by Cancer Type

3.3.1 Breast Cancer

In breast cancer cells (MCF-7, T47D, MDA-MB-231, and 4T1), the ethyl acetate extract of *C. odorata* exerted cytotoxic effects with IC_{50} values of 218.78 µg/mL (MCF-7) and 307.61 µg/mL (T47D)(Yusuf et al., 2023). This effect was followed by high apoptosis/necrosis (MCF-7: 95.15%; T47D: 83.35%) and good selectivity index against normal Vero cells (12.77 and 9.08) (Yusuf et al., 2023). In 4T1 triple-negative breast cancer cells, the ethanol extract decreased viability in a dose-dependent manner up to concentrations ≥500 µg/mL, confirming the anticancer potential even in the aggressive subtype (Yusuf et al., 2021). Meanwhile, the combination with cisplatin in MDA-MB-231 cells showed an antagonistic effect (Combination Index > 1), indicating that the interaction of phytochemicals with conventional chemotherapy needs to be further investigated to find the optimal dosing scheme (Mutalib et al., 2023).

3.3.2 Cervical Cancer

In cervical cancer cells (HeLa), ethyl acetate extract showed strong antiproliferative activity with an IC_{50} value of 82.41 µg/mL (Yusuf, Fahriani, & Murzalina, 2022). Exposure at a dose of ½-2×IC_{50} inhibited proliferation significantly ($p<0.05$) and induced cell death by 97%, suggesting that the apoptotic mechanism became the main pathway (Yusuf, Fahriani, & Murzalina, 2022). Further research isolating flavonoids from *C. odorata* leaves found kaempferide as the most active compound, capable of triggering DNA fragmentation and caspase activation, with low toxicity in animal tests (Nath et al., 2015). This makes kaempferide a strong candidate to be developed as a *lead compound* in cervical cancer therapy.

3.3.3 Liver Cancer

In liver cancer cells (HepG2), two studies reported that the ethanol extract of *C. odorata* leaves decreased proliferation significantly (Yusuf et al., 2022). This cytotoxic effect occurred in a dose-dependent manner (IC_{50} about 23.44 µg/mL) and was attributed to the mechanism of cell cycle arrest in the G_0-G_1 phase as well as increased apoptosis (Yusuf & Fahriani, 2022). The flavonoids, alkaloids, and phenolic contents in the extract are thought to contribute to these

anticancer effects through oxidative inhibition pathways and modulation of cell cycle regulatory protein expression (Yusuf et al., 2022).

3.3.4 Colon Cancer

In colon cancer cells (HT-29, WiDr, HTB), anticancer activity was also confirmed. In HT-29, the ethanol extract suppressed proliferation significantly with a maximal effect at a concentration of 800 µg/mL after 72 hours (Adedapo et al., 2016). Interestingly, when cells were exposed to mitogens such as VEGF and ET-1, the antiproliferative effect of the extract decreased, which confirmed the involvement of the angiogenesis pathway in the mechanism of colon cell growth (Adedapo et al., 2016). In WiDr and HTB lines, ethanol and methanol extracts also showed dose-dependent cytotoxic effects, with a significant decrease in viability starting from a concentration of 500 µg/mL, although IC_{50} values were not explicitly listed (Yusuf et al., 2021).

3.3.5 Skin Cancer

The HaCaT (skin keratinocytes) model was used to assess the potential protection against skin cancer. In this model, the ethyl acetate fraction of the ethanol extract of *C. odorata* leaves reduced viability to 48% at 100 µg/mL, indicating an ability to prevent neoplastic transformation in epidermal tissue (Amir Tahir et al., 2024). Although not a malignant cancer model, these findings provide a basis for further exploration of skin cancer associated with exposure to environmental carcinogens.

3.4 Overall Synthesis and Interpretation

Overall, evidence from 10 studies showed that *Chromolaena odorata* has consistent multi-targeted anticancer activity on various cancer cell types (breast, cervical, liver, colon, and skin), with the main mechanisms being proliferation inhibition, viability reduction, apoptosis induction, and cell cycle arrest. These findings are reinforced by *in vivo* data confirming the antitumor potential in animal models. However, the reported antagonistic effect when combined with cisplatin suggests that the interaction of *C. odorata* with conventional drugs still needs to be carefully explored. These results support the potential of *C. odorata* as a source of bioactive compounds for the development of more effective and safe herbal-based anticancer therapies.

The results of this systematic review show that *C. odorata* has broad anticancer activity on various cancer cell types through mechanisms involving apoptosis, proliferation inhibition, and cell cycle control. The effectiveness of the extracts varied between cell types, reflecting the heterogeneity of the cancer itself as well as differences in the active phytochemical content of the extracts used. In breast cancer cells, for example, ethyl acetate extract of *C. odorata* leaves gave significant cytotoxic effects with IC_{50} values of 218.78 µg/mL in MCF-7 cells and 307.61 µg/mL in T47D cells. These cytotoxic effects were accompanied by high apoptosis rates, namely 95.15% in MCF-7 and 83.35% in T47D, as well as quite good selectivity index (SI) values against normal Vero cells of 12.77 and 9.08, respectively (Yusuf et al., 2023). These findings are in line with

recent studies emphasizing that flavonoids and phenolic compounds in plant extracts are able to suppress breast cancer growth by increasing apoptosis and significantly reducing cell proliferation (Bonta, 2020). However, the combination of *C. odorata* ethanol extract with cisplatin on MDA-MB-231 triple-negative breast cancer cells actually showed an antagonistic effect with a Combination Index value > 1, indicating that the use of herbs together with chemotherapeutic agents does not always result in positive synergy (Mutalib et al., 2023).

More potent cytotoxic activity was seen in cervical cancer, where the ethyl acetate fraction extract from *C. odorata* leaves showed an IC_{50} of 82.41 ± 6.73 µg/mL against HeLa cells, and treatment at ½-2×IC_{50} was able to inhibit proliferation significantly ($p<0.05$) with a cell death rate of up to 97% after 24 hours of treatment (Yusuf et al., 2022). Further research successfully isolated the flavonoid kaempferide from the ethanol extract of *C. odorata* leaves, which showed higher activity with an IC_{50} of 16 µM on HeLa cells, triggering DNA fragmentation and caspase activation, but remained safe against normal fibroblasts up to a concentration of 100 µM (Nath et al., 2015). This confirms that kaempferide can be considered as a *lead compound* in the development of nature-based cervical cancer therapy.

In addition to breast and cervical cancer, the anticancer activity of *C. odorata* was also consistently found in liver cancer. In hepatocarcinoma cell line HepG2, ethanol extract of *C. odorata* leaves was reported to have a strong cytotoxic effect with a low IC_{50}, around 23.44 µg/mL, and was able to arrest the cell cycle in the G_0-G_1 phase and induce apoptosis. This mechanism is most likely influenced by the presence of flavonoids, alkaloids, and phenolics, which are known to increase the expression of cell cycle regulatory proteins such as p21, while suppressing the anti-apoptotic protein Bcl-2, so that the intrinsic apoptotic pathway is more dominantly activated (Yusuf et al., 2022). The higher effectiveness in HepG2 cells compared to MCF-7 or T47D suggests that compounds in *C. odorata* may better target signaling pathways predominant in hepatocarcinoma, which are associated with oxidative stress and cellular metabolism.

Interesting results were also found in colon cancer cell lines. The ethanol extract of *C. odorata* leaves suppressed the proliferation of HT-29 cells significantly, with the maximum effect at a concentration of 800 µg/mL after 72 hours. However, when cells were exposed to growth factors such as VEGF and ET-1, the antiproliferative activity of the extract was reduced, suggesting that the tumor microenvironment plays an important role in modulating the effectiveness of this herbal extract (Adedapo et al., 2016). This phenomenon emphasizes that angiogenesis mechanisms and paracrine factors could be additional targets to be considered in drug development strategies from *C. odorata*. In other colon cell lines, such as WiDr and HTB, both ethanol and methanol extracts decreased viability in a dose-dependent manner starting at a concentration of 500 µg/mL, although IC_{50} values have not been explicitly reported (Yusuf et al., 2021).

The protective potential of *C. odorata* was also identified in a human keratinocyte model (HaCaT). Although not malignant cancer cells, the ethyl acetate fraction of the ethanol extract of *C. odorata* leaves was able to reduce viability to 48% at a concentration of 100 µg/mL, indicating an ability to prevent neoplastic transformation in epidermal tissue (Amir Tahir et al., 2024). This finding opens up opportunities for further research in the context of environmental carcinogen-

induced skin cancer, in line with reports that other tropical medicinal plants, such as *Centella asiatica* and *Curcuma longa,* also have protective potential against DNA damage due to UV radiation and carcinogenic compounds.

Overall, the results of this systematic review confirm that the main strength of *C. odorata* lies in the multi-target nature of its bioactive compounds, which can intervene in various cancer signaling pathways simultaneously. However, differences in extraction methods, doses used, and the heterogeneity of cancer cells lead to considerable variations in their effectiveness. Therefore, future research needs to focus on the isolation of key active compounds such as kaempferide, bioavailability, and pharmacokinetic testing through *in vivo* models, and long-term safety evaluation. In addition, the interaction with conventional chemotherapeutic agents should be further investigated to ascertain whether the combination can be synergistic or antagonistic. With this approach, *C. odorata* has a great opportunity to be developed as a complementary therapy or as a source of new candidate molecules in cancer treatment. Considering the important role of angiogenesis and cell proliferation pathways in lung cancer, further research on the potential of *C. odorata* to key receptors such as VEGFR is highly recommended, so as to open up opportunities for the development of innovative therapies for lung cancer, which still has a high mortality rate.

4. Conclusion

Based on a systematic review of ten studies, *Chromolaena odorata* was shown to have consistent anticancer potential in various cancer cell lines, including breast, cervical, liver, colon, and skin keratinocyte models. The main mechanisms underlying this activity are apoptosis induction, cell cycle arrest, proliferation suppression, and modulation of regulatory protein expression. Bioactive compounds such as flavonoids, alkaloids, terpenoids, and especially kaempferol play an important role in producing these effects, with relatively good selectivity against normal cells. These findings strengthen *C. odorata*'s position as a source of new candidate molecules for nature-based cancer therapy.

Nonetheless, the variation in results between studies is influenced by the extraction method, dosage, cancer cell type, and micro-environmental conditions. The majority of evidence still comes from *in vitro* tests, while *in vivo* data are still limited and do not cover pharmacokinetics, bioavailability, and chronic toxicity. The fact that combinations with conventional chemotherapeutics can lead to antagonistic effects suggests the need for further research on drug-phytochemical interactions. Thus, *C. odorata* can be positioned as a complementary therapy or a source of new *lead compounds*, but its clinical implementation requires standardized preclinical trials, molecular mechanism testing, and human clinical trials.

This systematic review demonstrates that *C. odorata* possesses notable anticancer potential through mechanisms such as apoptosis induction, cell cycle arrest, and inhibition of proliferation across multiple cancer cell lines, with kaempferide and other flavonoids identified as key bioactive

compounds. Despite promising results, variations in extraction methods and limited in vivo data restrict direct comparison and clinical translation. Future studies should focus on standardized compound isolation, pharmacokinetic evaluation, and expanded testing, including lung cancer models. Overall, this review provides integrated evidence supporting *C. odorata* as a promising natural source for developing safe and accessible anticancer therapies.

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