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Review

Recent advances and mechanism of action of *Anredera cordifolia* (Ten.) Steenis as anticancer approach: A systematic review

[Avances recientes y mecanismo de acción de *Anredera cordifolia* (Ten.) Steenis como tratamiento anticancerígeno: Una revisión sistemática]

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Abstract

Context: Cancer is one of the causes of death throughout the world. There are around 9.6 million deaths from cancer every year throughout the world, with 70% of cancer deaths occurring in developing countries in the world. Natural species like *Anredera cordifolia* is the old-world diamond flower. It is historically important in traditional Chinese medicine. It's commonly found in Indonesia, notably Java, and has gained attention for its potential anticancer effects.

Aims: To evaluate the existing research on the bioactive compounds of *A. cordifolia* leaves and their anticancer potentials.

Methods: The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), using databases like PubMed, ResearchGate, ScienceDirect, and Google Scholar via Rayyan.ai. Sixteen included primary studies were analyzed descriptively.

Results: Results revealed *A. cordifolia* active compounds acting against anticancer. Activities included anti-proliferation (induce Cav-1, reduce glycolysis pathway, p38, MAPK, and ERK 1/2), apoptosis, antioxidant effects, cytotoxicity, inhibiting tumor progression genes, reducing metastatic genes (MMP-9), and enhancing pro-apoptotic genes (BAX, P53, caspase-3, caspase-8, caspase-9, cleaved PARP).

Conclusions: According to the mechanisms studied, *A. cordifolia* extract could be showed promise as a potential anti-cancer agent.

Keywords: *Anredera cordifolia*; apoptosis; anticancer; anti-proliferative; cytotoxicity.

Resumen

Contexto: El cáncer es una de las causas de muerte en todo el mundo. Cada año, se producen alrededor de 9,6 millones de muertes por cáncer en todo el mundo, y el 70 % de las muertes por cáncer se producen en países en desarrollo. Especies naturales como *Anredera cordifolia* son las flores de diamante del viejo mundo. Es históricamente importante en la medicina tradicional china. Se encuentra comúnmente en Indonesia, especialmente en Java, y ha ganado atención por sus posibles efectos anticancerígenos.

Objetivos: Evaluar la investigación existente sobre los compuestos bioactivos de las hojas de *A. cordifolia* y sus potenciales anticancerígenos.

Métodos: La revisión siguió los elementos de informe preferidos para revisiones sistemáticas y metaanálisis (PRISMA), utilizando bases de datos como PubMed, ResearchGate, ScienceDirect y Google Scholar a través de Rayyan.ai. Se analizaron descriptivamente dieciséis estudios primarios incluidos.

Resultados: Los resultados revelaron que los compuestos activos de *A. cordifolia* actúan contra el cáncer. Las actividades incluyeron antiproliferación (inducción de Cav-1, reducción de la vía de la glucólisis, p38, MAPK y ERK 1/2), apoptosis, efectos antioxidantes, citotoxicidad, inhibición de genes de progresión tumoral, reducción de genes metastásicos (MMP-9) y mejora de genes proapoptóticos (BAX, P53, caspasa-3, caspasa-8, caspasa-9, PARP escindido).

Conclusiones: De acuerdo con los mecanismos estudiados, el extracto de *A. cordifolia* podría mostrarse prometedor como un potencial agente anticancerígeno.

Palabras Clave: *Anredera cordifolia*; apoptosis; anticancerígeno; antiproliferativo; citotoxicidad.

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INTRODUCTION

Cancer is one of the causes of death throughout the world (Li et al., 2021). There are around 9.6 million deaths from cancer every year throughout the world, with 70% of cancer deaths occurring in developing countries, including Indonesia. Based on the same data, in 2020, there were 396,914 new cases of cancer in Indonesia, with 234,511 deaths. The highest cancer in women is breast cancer (65,858 cases), followed by cervical cancer (36,633 cases). The highest cancer in men is lung cancer (34,783 cases), followed by colorectal cancer (34,189 cases) (Lyon et al., 2020).

Cancer is characterized by the uncontrolled growth and spread of abnormal cells. Cancer is a multifactorial disease where genetic factors play an important role in the occurrence of cancer and increases drastically with age. There are many types of cancer affecting different parts of the body. Cancer is generally divided into two categories based on the origin of the cells, namely carcinoma, originating from epithelial cells, and sarcoma, originating from bones and soft tissue. Carcinomas include breast, prostate, lung, and colon cancer, which are invasive to surrounding tissue and metastasize to lymph nodes and other body organs (Shahab et al., 2024). Even though there has been a lot of research on cancer, the cause of this disease is not yet fully known, and neither is the cure (Syed, 2020).

Standard drugs and chemotherapy so far have been given, but chemotherapy also affects normal cells with a fast division rate in addition to cancer cells, such as buccal mucosa cells, bone marrow, gastrointestinal (GI) mucosa, and hair follicles. This causes side effects such as vomiting, stomatitis, bone marrow suppression, and alopecia (Ullah et al., 2024). Therefore, targeted therapy with specific targets was developed to avoid side effects. Consideration of therapy is based on disease risk as assessed by cytogenetic and molecular profiles. The therapy being developed is based on the presence of mutations in genes that play a role in abnormal DNA methylation in hematological malignancies. However, chemotherapy standards also affect normal cells with fast dividing rates besides cancer cells, such as cells of the buccal mucosa, bone marrow, GI mucosa, and hair follicles. This causes side effects such as vomiting, stomatitis, bone marrow suppression, and alopecia (Burguin et al., 2021).

One of the standard treatments for cancer is 5-fluorouracil (5-FU), which is a pyrimidine derivative that functions as an antimetabolite and is one of the most commonly used chemotherapy agents. 5-FU works by starting with antimetabolites that enter cells and resemble molecules that play an important role in cell growth. 5-FU is cytotoxic and interferes with normal cell mechanisms by damaging genetic material, that is, DNA and RNA. 5-FU is used in chemotherapy for various carcinomas, especially cervical cancer, breast cancer, colon cancer, and skin cancer. 5-FU was approved as a drug by the FDA and widely used in chemotherapy, either alone or in combination with other drugs. 5-FU works by inhibiting enzymes involved in DNA and RNA synthesis, particularly thymidylate synthase. This enzyme is responsible for producing thymidine, one of the building blocks of DNA. By inhibiting this enzyme, 5-FU interferes with DNA replication and repair, which inhibits the growth of cancer cells. 5-FU is a pyrimidine analog, which can be interpreted as a molecule that is similar to DNA and RNA components. The use of 5-FU in cancer cells using 5-FU as a substitute for uracil or thymidine in the process of RNA and DNA synthesis will disrupt the normal function of RNA and DNA. In the process of disrupted DNA and RNA synthesis, 5-FU will cause cellular damage that can trigger cancer cell death through the process of apoptosis (programmed cell death) (Mostavi et al., 2020). Although 5-FU is effective in treating cancer, there are some drawbacks and side effects in the use of 5-FU, including mucositis, sepsis, diarrhea, stomatitis, cardiotoxicity, and decreased appetite. This is likely due to 5-FU affecting the normal cells around it. Therefore, 5-FU therapy is monitored and combined with other drugs to reduce side effects and increase the effectiveness of treatment (Li et al., 2021).

Therefore, a combination of chemotherapy with a specific target is needed to reduce side effects. Combination therapy in cancer is a treatment modality that combines two or more therapeutic agents. The combination of these anticancer drugs can increase their level of effectiveness compared to the monotherapy approach. This is because combination therapy is carried out synergistically or additively. This approach has the potential to reduce drug resistance while providing the benefits of anticancer therapy, such as reducing tumor growth and metastatic potential, inhibiting cells that are actively undergoing mitosis, reducing the population of cancer stem cells, and inducing apoptosis (Kadomoto et al., 2020). Cancer treatment usually uses medical treatments such as chemotherapy, radiation, or a combination of both. However, these treatments usually cause some side effects, such as pain, nausea, vomiting, and alopecia. In chemotherapy treatment, in addition to destroying cancer cells, the therapy can also attack normal cells. Therefore, *A. cordifolia* is one of the Indonesian plants

that has the potential to treat cancer (Febriansah and Lakshita, 2021).

Anredera cordifolia (Ten.) Steenis, family *Basellaceae*, known as binahong in Indonesia, is a plant that has medicinal properties for various diseases, including saponins, alkoloids, and flavonoids for anticancer (Dwitiyanti et al., 2019). *Boussingaultia pseudobasselloides* Haum, *Boussingaultia gracilis* and *Boussingaultia cordifolia* are the synonyms of *A. cordifolia* (Astuti et al., 2011). The effectiveness of *A. cordifolia* in terms of medical treatment is due to the various phytochemicals in the plant. Some experimental results state that *A. cordifolia* contains several compounds that have the potential as anticancers in the MMP2 pathway (Feriyani et al., 2020). Previous studies reported that *A. cordifolia* extract plays a role in healing internal and external surgical wounds and burns, improving blood circulation, restoring weak conditions, and preventing strokes (Varghese et al., 2020). Other research on this plant in India stated that in the last decade, it has shown that the compounds in the *A. cordifolia* extract have the potential to modulate tumor signaling, overcome chemoresistance, and re-educate the tumor microenvironment (TME) (El-Tanani et al., 2022). This may occur due to overexpression of one or more antiapoptotic proteins or decreased expression of proapoptotic protein groups, or even a combination of the two (Gao et al., 2021). Based on the antiproliferative effect of vitexin on the MMP2 pathway, *A. cordifolia* plant extract has the potential to be a complementary therapy for breast cancer patients. However, the studies that examine the potential of the leaf extract of *A. cordifolia* on cancer cells are limited.

A. cordifolia is an herbal plant that is most often used to cure various types of diseases in a number of Asian countries, such as Vietnam, Taiwan, China, Korea and Indonesia. The ingredients in this plant, especially the leaves, are often used as herbal medicine. Health experts in Indonesia have proven that this plant can treat diabetes mellitus, tuberculosis, rheumatism, gout, asthma, typhoid, hypertension, and hemorrhoids, and is used as a diuretic, postpartum recovery, wound healing, and post-circumcision surgery, gastritis, colitis, and cancer (Feriyani et al., 2020). *A. cordifolia* has also been used in traditional medicine by placing its leaves over wounds, and that has shown an affinity in accelerating wound healing (Febriansah and Lakshita, 2021). *A. cordifolia* reproduces vegetatively. This plant has axillary leaf tubers that function to spread species quickly. The use of natural materials as medicinal ingredients or for other purposes tends to increase. Traditional medicine commonly called "jamu" is widely used by the community in efforts to prevent a disease (preventive), healing (curative), health recovery (rehabilitative), or improving health (promotive). *A. cordifolia* has chemical content such as flavonoids, alkaloids, saponins, triterpenoids, quoin, sesquiterpenoids, and monoterpenes, while the rhizome of this plant contains flavonoids, polyphenols, tannins, and steroids. Optimal growth and productivity of *A. cordifolia* are determined by the type of plant and the content of secondary metabolites found in this plant. *A. cordifolia* can grow in both lowlands and highlands. Differences in growth locations will cause differences in the growth and development of *A. cordifolia* because there are differences in microclimates (Elekofehinti et al., 2021). *A. cordifolia* has parts consisting of leaves, stems, flowers, roots, and rhizomes that have antioxidant properties. The leaves have very short stalks, arranged alternately, and have a length of 5-10 cm and a width of 3-7 cm; green in color, heart-shaped, and have a textured, cylindrical, and smooth surface with a red stem. *A. cordifolia* is rich in vitamins E, C, and A, carotene, flavonoids, albumin, bilirubin, and ceruloplasmin, among others. These substances have the function of reducing cholesterol in the blood and can be used as anticancer agents due to the presence of terpenoids, flavonoids, and other biochemicals. In its use as a medicine, flavonoids act as anti-inflammatory, antioxidant, and hypoglycemic. Meanwhile, terpenoids help the process of recovery (repair) of body cells. In addition, terpenoids are also known to have an important role in decreasing blood cholesterol levels and anticarcinogenic substances (Astuti et al., 2011).

MATERIAL AND METHODS

Eligibility criteria

To be further analyzed in this review, eligible studies had to conduct a systematic review of the effectiveness of *A. cordifolia* as an anticancer agent compared to 5-FU; inclusion criteria included experimental studies (*in vitro*, *in vivo*, and clinical trials) comparing these two agents, using human or animal cancer cells, cancer-induced animal models, or cancer patients. Studies should involve the use of extracts or active compounds from *A. cordifolia* and 5-FU as a comparator, as well as report antiproliferative, cytotoxic, or tumor growth inhibition results, improvement in quality of life, or reduction in tumor size, and the mechanism of anticancer action. Only studies published in English within the last ten years (2012-2023) will be included. Non-comparative studies, editorials, reader letters, non-systematic literature reviews, as well as studies that do not involve cancer cells, cancer animal models, or cancer patients will be excluded. Likewise, studies that used *A. cordifolia* or 5-FU for non-cancer purposes did not report results relevant to anticancer effectiveness or were published

in languages other than English or Indonesian or before 2004, were excluded from this review (Fig. 1).

Information sources

The research process began with keyword searches across established electronic databases, i.e., PubMed, Europe PMC, Science Direct, Google Scholar, and ResearchGate. The study involved a systematic review of existing randomized controlled trials (RCTs) that assessed the activity, efficacy, and safety of natural products with *A. cordifloia* (experimental arm) versus 5-FU (control arm) in cancer patients (Fig. 1).

Search strategy

This study is a comprehensive systematic review of existing literature presented narratively. A comprehensive search strategy was devised to identify relevant studies investigating the anticancer effects of *A. cordifolia* extracts on common cancer through both *in vitro* and *in vivo* experiments, using relevant terms such as "*Anredera cordifolia*" and "anticancer" and utilizing Boolean operations (Table 1).

Table 1. The keywords used for the literature review.

Main keywords	Additional keywords
Anredera cordifolia	*Anredera cordifolia* (Ten.) Steenis; *Boussingaultia basselloides; Boussingaultia cordifolia; Boussingaultia gracilis* Miers
Anticancer	Therapy; chemotherapy; combination therapy

Selection process

The authors refined their data selection using specific inclusion and exclusion criteria. Inclusion criteria followed the PICOS framework (Table 2), encompassing cancer cells as the problem, *A. cordifolia* extract as the intervention, and outcomes related to inhibition of proliferation, cell cycle, metastasis, and apoptosis in cancer cells, using experimental study designs, both cell lines or animal models. Additionally, inclusion parameters consisted of (1) articles must be original research or experimental studies; (2) the topic must involve anticancer or *A. cordifolia*, either separately or combined; (3) articles should have been published more or less in the past ten years (2012-2023); (4) articles must be written in English; and (5) articles must be from reputable and indexed publishers, indexed in Scopus, Web of Science, and SCImago Journal Rank. Exclusion criteria passed: (1) non-open access or articles with unavailable full texts; and (2) articles not meeting quality assessment criteria based on the Preferred Reporting Items for Systematic Reviews (PRISMA) checklist (Petrelli et al., 2021).

Data collection and synthesis process

The PRISMA statement is used in selecting the literature to be used (Petrelli et al., 2021). The PRISMA guidelines for systematic reviews define a process of study identification, screening, eligibility, and inclusion and are outlined in Fig. 1. The screening process was conducted using Rayyan.ai to eliminate duplicate references. The articles considered for our analysis were of decent to high standards. Lastly, the gathered information was integrated to create a comprehensive literature review. Descriptive data analysis was utilized to present and summarize the data meaningfully and briefly.

Data items

The extracted data items obtained from the reviews encompassed details such as study population and intervention characteristics, type of comparison, primary and secondary outcomes, study design, and the conclusions drawn by the authors. The primary objective of this systematic review was to compare the activity, efficacy, and safety of *A. cordifolia* as chemotherapy in cancer patients in terms of either DFS, OS, DMFS, PFS, ORR, or pCR, and adverse events.

Bias risk assessment

The study quality was evaluated by two reviewers (SZI and AG), who evenly portioned the study using Cochrane risk of bias tools for the RCT study. Reviewer discrepancies were discussed, and ATE, EN, SP, and EW were consulted.

Table 2. PICO criteria for this review.

Population	Patients with cancer diagnosed (early-stage cancer without metastasis, grade II/III, anthracycline-resistant and invasive cancer stage T2-3, N0-3, and M0)
Intervention	*Anredera cordifolia* treatment that is either given following or prior to other chemotherapy medication
Comparison	Another chemotherapy or standard drug in cancer, one of which is 5-fluorouracil (5-FU)
Outcome	Several pairs of parameters are used to evaluate effectiveness, including as disease-free survival (DFS), overall survival (OS), progression-free survival (PFS), distant metastasis-free survival (DMFS), objective response rate (ORR), and pathological complete response (pCR). Safety is determined by monitoring adverse effects.

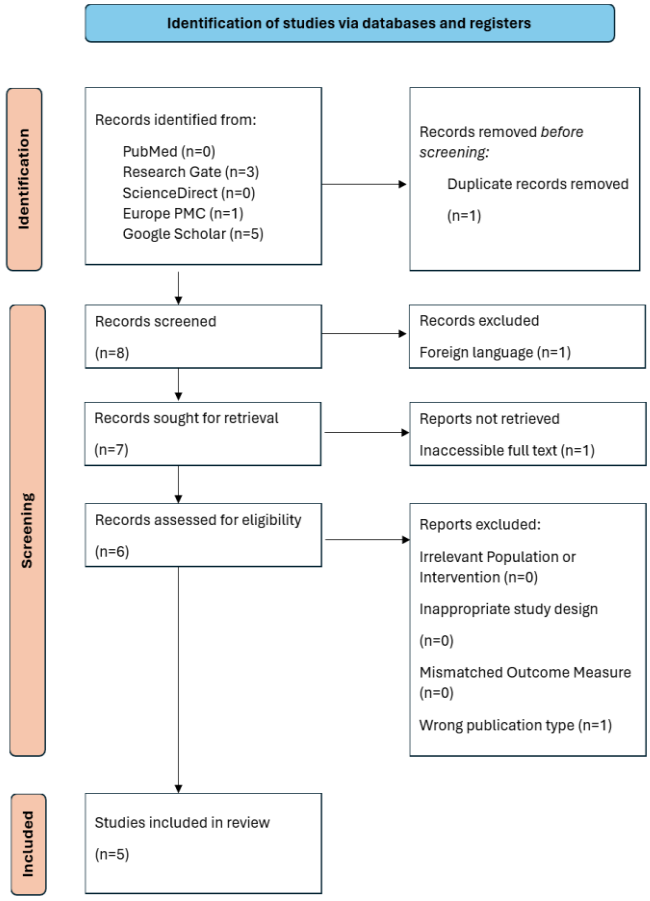

Figure 1. PRISMA 2020 flow diagram systematic reviews.

RESULTS

Study selection

The initial search across electronic databases yielded a total of records. After removing duplicates, record screening with exclude foreign language articles. A total of eight unique records were screened for eligibility based on titles and abstracts. Following this preliminary screening, seven full-text articles were retrieved for detailed assessment against the predefined inclusion and exclusion criteria. Through a meticulous review of the full-text articles, five studies were identified as meeting the criteria for inclusion in this systematic review. The reasons for excluding studies after full-text retrieval (Fig. 1).

Risk of bias studies

Four eligible studies were evaluated for their quality and risk of bias. In this screening, the overall bias risk of each study was low. Therefore, these five studies were included in the review process. Details of risk assessment are mentioned in Table 3. While all the studies had a relatively low risk of bias, only one study reported a risk of bias due to missing results that can arise from reporting biases.

Results of individual studies

After conducting a quality assessment using the PRISMA checklist for both Systematic Reviews and original articles, five articles were found feasible for further systematic review (Table 4). These articles contained the active compounds in *A. cordifolia* that affect the cancer cells.

DISCUSSION

The traditional medicinal plant *A. cordifolia*, which has been used for many therapeutic purposes, has attracted interest recently because of its possible use as an anticancer agent, especially when combined with other therapies. *A. cordifolia* has the potential to improve treatment efficacy while lowering negative effects when used with other complementary medicines or conventional cancer treatments. The goals of integrative medicine, which aims to improve patient outcomes by combining traditional and complementary medicines, are in line with this strategy. By utilizing *A. cordifolia*'s synergistic effects in conjunction

Table 3. Risk of bias assessment using Cochrane risk of bias tools.

Author (year)	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participant and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Overall bias risk
Sozianty and Febriansah (2020)	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	**Low risk**	**54% low risk**
Utami and Januarti (2012)	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	**Low risk**	**55% low risk**
Virginia et al. (2019)	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	**Low risk**	**57% low risk**
Yuliani et al. (2015)	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	**Low risk**	**47% low risk**
Febriansah and Lakshita (2021)	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	**Low risk**	**52% low risk**

with conventional cancer therapies like radiation therapy or chemotherapy, researchers hope to enhance patient survival rates and overall treatment response rates (Yuliani et al., 2015).

5-FU is a simple form of uracil but is fundamentally different in that it has an additional fluorine atom on carbon 5 instead of a hydrogen atom. At room temperature, 5-FU is a colorless solution that is buffered with NaOH and is administered intravenously. dihydropyrimidine dehydrogenase is the most sensitive protein to FU breakdown and is primarily located in the liver. Approximately 80% of 5-FU is converted to inactive metabolites, and 5-20% is excreted by the kidneys. Given that 5-FU only accounts for about 1-3% of clinical efficacy, 5-FU penetrates cells quickly after treatment. Similar to uracil, 5-FU is transported into cells by human nucleoside transporters (hNTs). Human nucleoside transporters include three enriched components (hCNT 1, 2, 3) and four equilibrium transporters (hENT 1, 2, 3, 4). 5-FU is transported by hENT 1 and 2. In cells, 5-FU undergoes phosphorylation into three major dynamic metabolites, including fluorouridine triphosphate (FUTP), fluorodeoxyuridine triphosphate (FdUTP), and fluorodeoxyuridine monophosphate (FdUMP) (Tavazoie et al., 2018). These dynamic metabolites activate the anticancer effects of 5-FU through different pathways. 5-FU metabolites and DNA damage cause disruption of DNA repair and replication by inhibiting the production of thymidylate synthase (TS) and thymidine. Thymidine may be a molecule involved in DNA repair and replication. TS is an enzyme involved in the production of thymidine. The efficacy and clinical application of 5-FU are limited by the development of drug resistance, which commonly occurs after cancer chemotherapy. The combination of 5-FU as the main chemotherapy agent with natural bioactive compounds is an attempt as a way to reduce the effective dose and thus reduce harmful side effects (Zhang et al., 2020).

Understanding the therapeutic potential of *A. cordifolia* and directing future research directions require an understanding of the possible mechanisms of action behind its anticancer activities. Numerous potential mechanisms have been proposed by preclinical research, including the induction of apoptosis, antioxidant activity, anti-inflammatory effects, suppression of angiogenesis, and modification of signaling pathways implicated in the growth of cancer. Together, these processes enable the plant to suppress tumor growth, encourage the death of malignant tumor cells, and maybe stop metastases. To completely understand these mechanisms and determine their applicability in therapeutic situations, more research is required (Joubert et al., 2020).

Compound extract of *A. cordifolia* significantly inhibited proliferation and induced apoptosis of high-metastatic breast cancer cell lines MDA-MB-231 and MDA-MB-453, while having no obvious cytotoxic effect on multiple nonmalignant cells. Furthermore, *A. cordifolia* remarkably suppressed the migration and invasion capacities of the above breast cancer cells by modulating the matrix metalloproteinases (MMPs) and the epithelial-mesenchymal transition (EMT) pathway (Rachmi et al., 2020).

Table 4. The summarized research on *Anredera cordifolia* and their phytochemicals potential anticancer, including *in silico*, *in vitro*, and *in vivo* studies.

No.	Author, year	Treatment	Target	Effect	Measurement
1	Sozianty and Febriansah (2020)	*Anredera cordifolia* extracts	MCF-7 breast cancer	**[Molecular docking]** The docking score showed that the interaction of Bcl-2 protein and the 8-glucopyranosyl-4',5,7 trihydroxyflavone compound was more negative with a docking score of -7.5 kcal/mol compared with doxorubicin of -4.8 kcal/mol, it means that the compounds require less energy to bind with Bcl-2 protein than doxorubicin to form a stable bond. HER-2 protein also binds with 8-glucopyranosyl-4',5,7 trihydroxyflavone and showed that it has a smaller energy than doxorubicin. HER-2 protein bind with 8-glucopyranosyl-4',5,7 trihydroxyflavone has a docking score of -8.0 kcal/mol, which means more negative when compared with doxorubicin that has a docking score of -6.9 kcal/mol. Both Bcl-2 and HER-2 proteins have more stable bond to the test active compound when compared with the doxorubicin drug. Therefore, the 8-glucopyranosyl-4',5,7 trihydroxyflavone compound has a good potency in inhibiting the overexpression of Bcl-2 and HER-2 proteins. **[Flavonoid identification]** The flavonoid compounds in the *A. cordifolia* extract were identified using thin-layer chromatography. Flavonoid compounds are possible because the spots showed yellow under visible light after evaporating the plate using ammonia. **[Antioxidant test with DPPH method]** The IC_{50} value of *A. cordifolia* extract is 4940 µg/mL, which means it has weak potency as an antioxidant. This is compared with quercetin, which has an IC_{50} value of 6.8 µg/mL, which means it has strong antioxidant activity. **[Cytotoxic and Selectivity Analysis]** The relationship between cell viability and cell concentration obtained a linear regression equation that was used to calculate an IC_{50} value. The IC_{50} value of *the A. cordifolia* compound was 486 µg/mL, which has a moderate toxic effect on MCF-7 breast cancer cells. Vero cells have a low cytotoxic effect with an IC_{50} value of 1073 µg/mL. Selectivity Index (SI) values compared between IC_{50} value on normal Vero cells with IC_{50} value on MCF-7 breast cancer cells. The result showed that the SI value was 2.15, it means that *A. cordifolia* extract has selective activity in inhibiting breast cancer cells.	**[Molecular docking]** Using Autodock Vina. This interpreted the minimum deviation from the interaction and the bonding between tested compounds and proteins. **[Thin layer chromatography]** The analyses of chemical contents of *A. cordifolia* extract using the TLC method with silica gel GF254 as stationary phase. **[Antioxidant test with DPPH method]** The ability of *A. cordifolia* extract to reduce 50% DPPH. If the IC_{50} value obtained is very high, it means the ability of the compound as a weak antioxidant. The antioxidant activity of a compound is considered weak in the range of >150 µg/mL. **[Cytotoxic and selectivity analysis]** The absorbance is a quantitative method that could be read using an ELISA reader at a wavelength of 595 nm. The absorbance data obtained are put into a linear regression equation to get the IC_{50} value. The compounds are quite toxic in the range of 101-500 µg/mL, and it does not have cytotoxic activity in the range of >1000 µg/mL. The selectivity of compounds can be measured using the selectivity index (SI); a compound has a selective activity in cancer cells if the SI value is >2.

Table 4. The summarized research on *Anredera cordifolia* and their phytochemicals potential anticancer, including *in silico*, *in vitro*, and *in vivo* studies (continued...)

No.	Author, year	Treatment	Target	Effect	Measurement
2	Utami and Januarti (2012)	Ethanol and ethyl acetate extracts of *Anredera cordifolia* leaves	Cervical cancer cell lines (HeLa)	**[Cytotoxic assay]** Ethanol and ethyl acetate extract of *A. cordifolia* leaves have cytotoxic effects on HeLa cervical cancer cell lines. MTT assay obtained the result that ethanol and ethyl acetate extract of *A. cordifolia* leaves significantly reduced the viability and proliferation of HeLa cervical cancer cell lines in a concentration-dependent manner. The IC_{50} value of ethanol extract is 21.84 µg/mL, and the IC_{50} value of ethyl acetate extract is 127.93 µg/mL. It means that the ethanol extract of *A. cordifolia* leaves has higher cytotoxic potency than ethyl acetate extract. **[Detection Apoptotic Cells by double staining method]** Apoptotic and necrotic cells in ethanol are 21.84 µg/mL, and in ethyl acetate is 59.98 µg/mL after acridine orange/ethidium bromide staining. Ethanol and ethyl acetate from *A. cordifolia* leaves induced apoptotic in HeLa cell lines.	**[Cytotoxic assay]** The absorbance is quantitative method that could be read using ELISA reader at a wavelength of 550 nm. The absorbances were correlated with viable cells. **[Detection of apoptotic cells by double staining method]** Apoptosis was detected by morphological analysis after acridine orange/ethidium bromide (AO/EB) staining (1:1). The apoptosis was observed by fluorescence microscopy.
3	Virginia et al. (2019)	*Anredera cordifolia* leaves extract	HeLa cells	**[MTT cytotoxicity assay on Vero cells]** The cytotoxic effect of *A. cordifolia* extract was found at a concentration above 1000 g/mL, with an IC_{50} = 1302 µg/mL. Cisplatin showed a strong cytotoxic effect, with an IC_{50} = 64 µM on Vero cells. SI was calculated based on the IC_{50} values of extract (75 g/mL) and cisplatin (40 µM or 11.9 g/mL) on HeLa cells. *A. cordifolia* extract had a higher selectivity to HeLa cells than cisplatin. **[Flowcytometric assay]** The cells accumulated more in the G0/G1 phase in the extract treatment (compared with untreated cells). Cisplatin accumulation in the G2/M phase. **[Immunocytochemistry Assay]** Bcl-2 protein is significantly overexpressed in cervical cancer than normal cells. Bcl-2 expression was suppressed by extract and cisplatin on HeLa cells. Anti-apoptotic activity of Bcl-2 is prevented by Bax activity, a dominant pro-apoptotic protein of the Bcl-2 family.	**[MTT cytotoxicity assay]** The MTT assay was used to determine the cytotoxicity of *A. cordifolia* extract compared with cisplatin. The secondary antibody was diluted from the Starr Trek HRP universal detected system. The absorbance could be read using an ELISA reader at a wavelength of 595 nm. **[Flowcytometric assay]** To analyze the cell cycle of HeLa cells, the flow cytometry analysis was carried out using a propidium iodide kit (BD Bioscience Cat). The cells were transferred into a flow cytometry vial and analyzed by a FACS Calibur flow cytometer. **[Immunocytochemistry assay]** The Intensity of Bcl-2 expression was observed under an inverted microscope.

Table 4. The summarized research on *Anredera cordifolia* and their phytochemicals potential anticancer, including *in silico*, *in vitro*, and *in vivo* studies (continued...)

No.	Author, year	Treatment	Target	Effect	Measurement
4	Yuliani et al. (2015)	*Anredera cordifolia* leaf extract	HeLa cervical cancer	**[MTT Cytotoxic assay]** *A. cordifolia* extract is potent as an anticancer agent against cervical cancer cells, with an IC_{50} value of 75 µg/mL. However, the Cytotoxic activity of *A. cordifolia* extract was weaker than that of cisplatin, with an IC_{50} value of 40 µM or 12 µg/mL. The cytotoxic activity of both *A. cordifolia* extract and cisplatin could be related to a molecular mechanism that induces apoptosis. **[Apoptosis assay]** Apoptosis of *A. cordifolia* extract better than cisplatin against HeLa cells. **[Immunocytostaining of p53]** p53 protein was responsible for the apoptosis process of cisplatin in cervical cancer cells. p53 protein is tumor suppressor gene to observe in relation between *A. cordifolia* extract cytotoxicity and apoptosis pathway. Expression of p53 was indicated by brown cell color. *A. cordifolia* extract did not increase p53 expression in HeLa cells. On the other hand, cisplatin has a slight increase in protein p53 expression. The molecular mechanism of *A. cordifolia* extract with anticancer activity was the p53 pathway.	**[MTT cytotoxic assay]** Measured by ELISA reader at a wavelength of 595 nm. **[Apoptosis assay]** An apoptosis assay was determined using Annexin V, which is able to bind phosphatidylserine residue in the outer plasma membrane as a consequence of apoptosis and was measured with a flow cytometer.
5	Febriansah and Lakshita (2021)	n-hexane fraction of *Anredera cordifolia*	WiDr colon cancer cell line	**[Phytochemical screening using TLC]** The TLC method is a qualitative test for chemical compounds in the n-hexane fraction of *A. cordifolia* using the silica gel GF254 as a stationary phase and the chloroform as a mobile phase. The result showed that under UV light 254, brown spots observed under UV light 366 showed a purple glow. Flavonoid compounds show blackish-brown spots under 254 nm UV, and under 366 nm UV, the spots show luminescence. N-hexane fraction of *A. cordifolia* contained flavonoids. **[Antioxidant test using DPPH method].** The antioxidant test obtained the IC_{50} values of the n-hexane fraction of *A. cordifolia* and quercetin (positive control) of 2851 and 6.87 µg/mL, respectively. **[MTT cytotoxic assay]** At the lowest concentration of 31.25 µg/mL, the n-hexane fraction of *A. cordifolia* could kill WiDr cells (29.91%), while at the highest concentration (500 µg/mL) of n-hexane fraction of *A. cordifolia* could kill WiDr cells (100%) and the 5-fluorouracil obtained was 311 µg/mL. ***[MTT cytotoxic assay in combination]*** n-Hexane fraction of *A. cordifolia* effect in combination with 5-fluorouracil. A combination of ½, ¼, 1/8, and 1/16 $IC_{50,}$ either n-hexane fraction of bandotan (NFB) or 5-fluorouracil, showed a synergistic effect to inhibit WiDr cell growth, scoring 0.8 (CI<1). It means that the compounds of NFB had the potency to be developed as co-chemotherapeutic agents on WiDr colon cancer cells. **[*In silico* using molecular docking]** In colon cancer, IKKB induces the activation of NF-κB in intestinal epithelial cells. Blocking the IKK and COX-2 signaling pathways could represent the potential 4', 6,7-trihydroxyaurone compound in the n-hexane fraction of *A. cordifolia*.	**[Phytochemical Screening using TLC]** After the application of the sample, the cells kept in TLC chambers. The mobile phase was allowed to move through the absorbent phase up pf the plate. Identification of the plate carried out under 254 and 366 nm UV lights. **[MTT cytotoxic assay]** Formazan complex measured by ELISA reader at 595 nm visible wavelength. **[MTT cytotoxic assay in combination]** The combination was designed to investigate the encouragement of one extract when the dose of the other extract remained fixed. It was measured by an ELISA reader at 595 nm, a visible wavelength. **[*In silico* using molecular docking]** This value interpreted the minimum deviation from the interaction and bonding between tested compounds and proteins. The bond between protein and ligand was visualized in 3D using DS Visualizer.

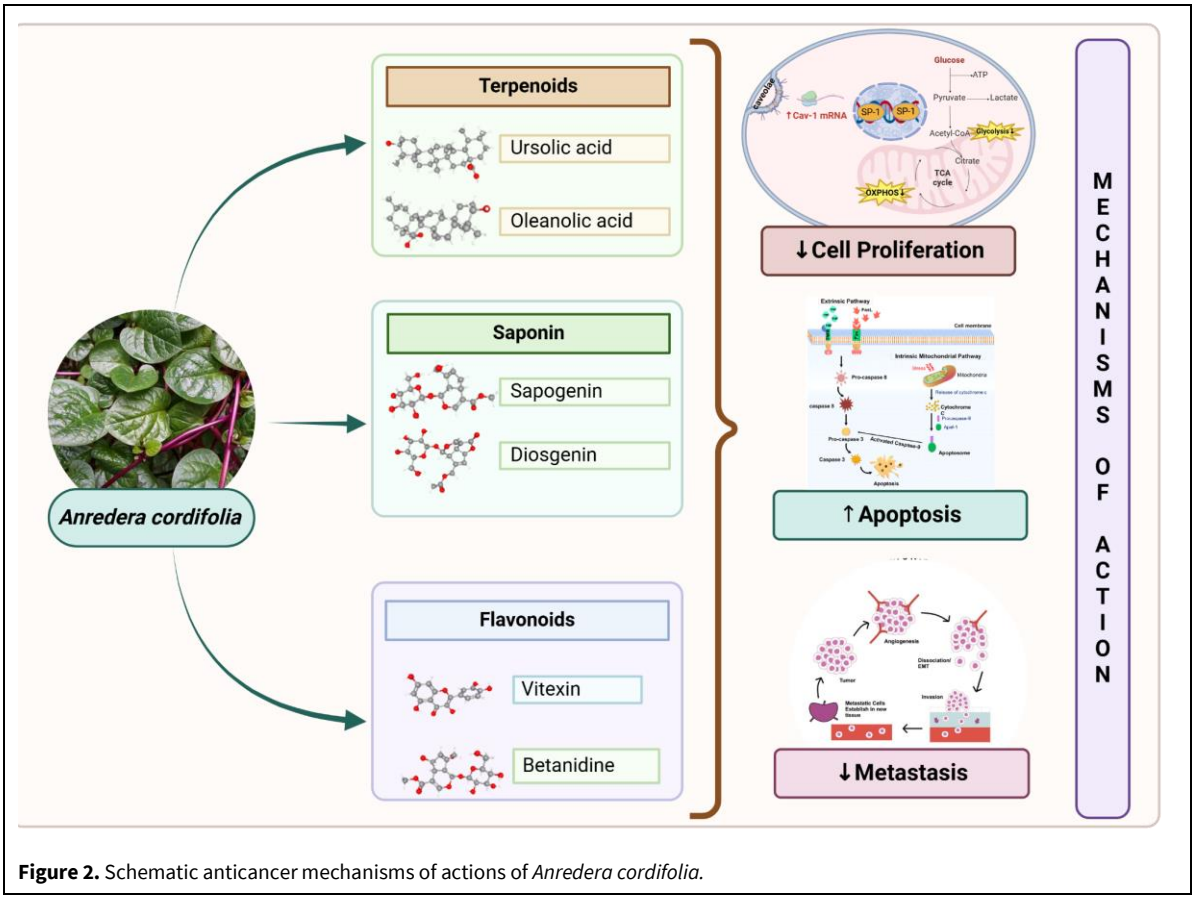

Figure 2. Schematic anticancer mechanisms of actions of *Anredera cordifolia.*

In Fig. 2, the compound-target associations in *A. cordifolia,* most of these active candidates in *A. cordifolia* have been validated to display potent anticancer biological activities. For instance, quercetin (MOL000098) could down-regulate the expressions of p-Akt, MMP-2, and MMP-9 and subsequently inhibit the metastatic potential of human liver cancer HCCLM3 cells. Stigmasterol (MOL000449) could induce apoptosis in human hepatoma HepG2 cells and also exerted its chemo-preventive effect on 7, 12-dimethylbenz[a]anthracene (DMBA)-induced skin cancer in swiss albino mice. p-Coumaric acid (MOL000771) exerted anticancer effects by inhibiting stress-related protein GRP78 and activating unfolded protein response (UPR) in colon cancer. These findings suggested that *A. cordifolia* also harbored inhibitory potential against cancer diseases, particularly metastatic carcinomas (El-Tanani et al., 2022).

In the present study, we also delineated the molecular mechanism of *A. cordifolia* compound Cav-1, MMP-2, and MMP-9 in breast cancer cells. Metastatic breast cancer is almost incurable, and medical herbs have been particularly acknowledged as a crucial source for the discovery and development of novel anticancer drugs. With proven efficacy and safety, *A. cordifolia* has been used as one of the most frequently prescribed medical herbs for breast cancer treatment in Traditional Chinese Medicine (Dwitiyanti et al., 2019). Multiple independent researchers have suggested that Cav-1 usually exhibited decreased expression in breast cancer cells than normal cells. While Cav-1 losses usually predicate a poor clinical outcome for breast cancer patients. In this early part of the process of angiogenesis, MMPs play an important role in the degradation of the extracelullar matrix (ECM). Therefore, MMP inhibitors have attracted attention as antiangiogenic agents and have been shown to have antiangiogenic activity. MMP-2 (gelatinase A) and -9 (gelatinase B) particularly degrade type IV collagen, constituting the major structural component of the basement membrane and ECM, and they are believed to be crucial in invasion by malignant tumors (Shahab et al., 2024).

A. cordifolia has been shown to have anticancer qualities in preclinical investigations; however, converting these discoveries into therapeutic applications is difficult and necessitates thorough research. To assess the safety, effectiveness, and ideal dose schedules of combination medicines based on *A. cordifolia* for different cancer types, clinical trials are required. The effective incorporation of *A. cordifolia* into cancer therapy protocols also depends on research examining possible drug interactions and patient-specific variables that may affect treatment outcomes. To op-

timize the potential benefits of *A. cordifolia* for cancer therapy and to further our understanding of its role, traditional medicine practitioners, oncologists, pharmacologists, and researchers need to collaborate together (Elekofehinti et al., 2021).

This review has implications for practice, policy, and future research. This study found that *A. cordifolia* potentially has anticancer properties, which could lead to clinical trials to evaluate its efficacy and safety in human patients. Clinicians may then consider it as a complementary or alternative treatment option, depending on the results. Clinicians need to understand the safe dosage and potential side effects of using *A. cordifolia*. This involves considering its interactions with other medications and its overall impact on the patient's health. The results obtained from this study can influence policy decisions, leading to increased funding for further research on *A. cordifolia*. Governments and health institutions can allocate resources to further investigate the potential benefits and mechanisms of action of *A. cordifolia* in cancer cells. Further research could identify gaps in the current knowledge based on *A. cordifolia* that lead to new research exploring mechanisms of action of *A. cordifolia*, optimal dosages, and efficacy in different types of cancer. Regarding future research, positive evidence from this review may encourage further preclinical studies and clinical trials to confirm the anticancer properties of *A. cordifolia*, involving laboratory tests and clinical settings to establish the safety and efficacy of *A. cordifolia*. Future research could focus on understanding the biochemical and molecular mechanisms by which *A. cordifolia* exerts its anticancer effects, leading to its effects on cancer cell pathways and tumor growth

CONCLUSION

The present review was carried out using a range of published materials, specifically focusing on the bioactive compounds of *Anredera cordifolia* plants and their potential applications in cancer. Additionally, alternative uses of the bioactive constituents found in *Anredera cordifolia* plants are also discussed that are used for anticancer activity such as apoptosis, antioxidant effects, cytotoxicity, inhibiting tumor progression genes, reducing metastatic genes (MMP-9), and enhancing pro-apoptotic genes (BAX, P53, caspase-3, caspase-8, caspase-9, and cleaved PARP).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Concepts or ideas	x	x	x	x	x	x	x	x
Design	x	x	x					x
Definition of intellectual content	x	x	x	x	x	x	x	x
Literature search	x	x	x	x	x	x	x	x
Experimental studies	x	x	x	x	x	x	x	x
Data acquisition	x	x	x	x	x	x	x	x
Data analysis	x	x	x	x	x	x	x	x
Statistical analysis								
Manuscript preparation	x	x	x	x	x	x	x	x
Manuscript editing	x	x	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x	x	x

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