

Antitumor Effects of *Myrmecodia pendans*: a Scoping Review

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Abstract

The most commonly used cancer treatments were surgical therapy, radiotherapy, and/or chemotherapy, all of which have significant side effects that can reduce a patient's quality of life. Flavonoids, an antioxidant thought to be involved in tumor growth and apoptosis, are found in ant nest plants, also known as *Myrmecodia pendans*.

The goal of this study was to see how effective ant nest flavonoids are at inducing apoptosis in cancer cells and providing physiological death mechanisms. The study was a review of the literature within articles that met the inclusion criteria: experimental controlled trial of ant nest plant extract biological therapy and its effect on cancer cell apoptosis activity. Search engines such as Google Scholar, ProQuest, ScienceDirect, and Wiley Online Library were used with strategic keywords. The final review included 7 of the 4869 articles discovered through database searching. Flavonoids, tannins, polyphenols, and glycosides, all of which have antioxidant properties, were discovered in ant nests.

Flavonoids have the ability to influence apoptotic pathway signalling via two mechanisms: Suppressing pro-apoptotic proteins and activating anti-apoptotic proteins and caspases. Ant nest extract has been shown to be a promising alternative in cancer treatment.

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Introduction

Cancer is a disease that is triggered by impaired function and cellular homeostasis. Cancer progression is the result of uncontrolled cell growth and differentiation resulting in a massive expansion of the neoplastic cell population.¹ Controlling or stopping the uncontrolled growth of cancer cells is one strategy of cancer treatment. The most effective method is to use the mechanism of cell death, also known as apoptosis.² Because apoptosis inhibition is the "heart" of tumor development, tumor cell death is required to eliminate malignant cells while maintaining healthy cells.³

Treatments that target apoptosis are the most successful non-surgical cancer treatments and can be used on all types of cancer.²

Surgical therapy, radiotherapy, and/or chemotherapy are the most commonly used cancer treatments today.^{4,5} However, these therapies frequently have serious side effects that can have an impact on the patient's psychological, physical, and social conditions, while also affecting their emotional and quality of life.⁶ Cancer treatment can cause nausea, vomiting, loss of appetite, fatigue, and hair loss, and also affect normal body cells.^{4,5} Extensive surgery on tumors in the cavity mouth and maxillofacial region can affect facial aesthetics, swallowing, speaking, and sense of smell and taste.^{6,7} Furthermore, the high cost of treatment and other expenses during cancer treatment can be extremely expensive for the patient.⁷ This is unfortunate because the final treatment should not cause new problems. As a result, more and more research is being conducted on natural

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substances that can be used as alternative cancer therapies with minimal side effects.^{4,5}

Herbal extracts that target tumor cells have been widely reported.⁸ Ant nest (*Myrmecodia pendans*) is a Southeast Asian native plant that belongs to the Rubiaceae family and has been widely used for disease treatment in its native area.⁹ Flavonoids are the active substances found in ant nests. Ants nest plant is effective as an antibacterial contained in flavonoids and tannins.¹⁰ Flavonoid antioxidants are believed to be capable of warding off free radicals that contribute to tumor or cancer formation. Flavonoids have been shown to inhibit angiogenesis, inactivate carcinogens, act as antiproliferative agents, inhibit the cell cycle, induce apoptosis and differentiation, and inhibit angiogenesis. Flavonoids have also been shown in vivo to inhibit protein kinase activity, which is involved in apoptosis.¹¹ These properties are expected to inhibit tumor growth, allowing flavonoids to be considered as anticancer drug candidates.

However, there is still little literature describing ant nests' antitumor potential. As a result, the authors decided to conduct a scoping review to provide a descriptive overview of *Myrmecodia pendans*' antitumor effect. Google Scholar, Proquest, ScienceDirect, and Wiley Online Library were the sources examined. There are no restrictions on language or year of publication. The goal of this review is to develop natural resources as a safe and effective alternative cancer treatment using these findings.

Materials and methods

Google Scholar, Proquest, ScienceDirect, and Wiley Online Library are the search engines used. There are no restrictions on the language or the year of publication. The Boolean operator (tumor*) AND (*Myrmecodia pendans* OR ant nest OR anthill plant) AND were the keywords used in the search strategy (apoptosis). PRISMA guidelines were used to develop and report on this scoping review. Data extraction will be performed on studies that meet the inclusion criteria. (Figure 1). The criteria for inclusion and exclusion, information sources, and search strategy will be discussed in greater detail below. Inclusion criteria: Experimental controlled trial study with Population: tumor cells; Intervention: biological therapy of ant nest extract

(*Myrmecodia pendans*), which can impact the apoptotic activity of tumor cells; Comparison: without giving ant nest extract; Outcomes: differences in tumor cell apoptotic activity.

Exclusion criteria: Non-experimental articles, namely reviews, conferences, commentaries, and research that did not mention the observation period and the unclear conditions of the control and treatment groups, were excluded.

Data Extraction & Collection Two reviewers were responsible for article selection. After screening titles and abstracts for a more in-depth review of the article as a whole to determine inclusion and exclusion criteria, the selected articles were those approved by the two reviewers. If the two parties cannot agree, it will be decided by a third reviewer.

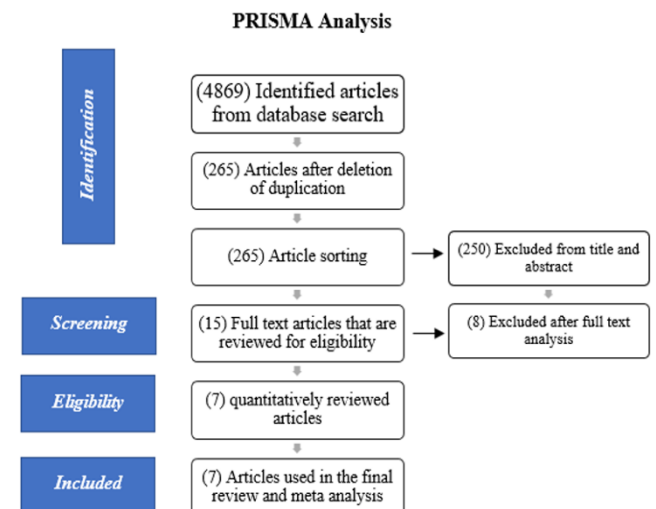


Figure 1. PRISMA Analysis Chart.

The following information was extracted from each article: author, year of publication, sample characteristics, biologic therapy and method of administration, study group description, period of observation, and final results. The information is then compared.

Results

7 papers were included in the final review out of 4869 articles found through database searching based on inclusion and exclusion criteria. According to the reviewed publications, ant nest extract may have anticancer properties by triggering apoptosis and repressing the proliferation of several cancer cell types (Table 1).

No	Authors	Samples	Final result
1	Lestari et al ¹² (2019)	<ul style="list-style-type: none"> HSC-3 (Human Oral Squamous Cell Carcinoma) Cell culture In Vitro Ant nest water extract (2,5 mg/ml, 5 mg/ml, and 7,5 mg/ml) Incubation for 24 and 48 hours 	Administration of ant nest extract induces apoptosis of HSC-3 cells via the proapoptotic Bax and antiapoptotic BCL-2 pathways
2	Sumarno ¹³ (2011)	<ul style="list-style-type: none"> Samples of 28 C3H mice inoculated with mammary adenocarcinoma tumor In Vivo Ants Nest Powder Extract 4 mg/day, 8 mg/day, and 16 mg/day Treatment for 3 weeks, the extract was administered using a micropipette 	Administration of myrmecodia pendans extract can induce apoptosis and reduce cancer cell proliferative activity. Increasing the dose is not followed by an increase apoptotic index.
3	Achmad et al ¹⁴ (2016)	<ul style="list-style-type: none"> Tongue cancer cell culture (SP-C1) In Vitro Flavonoid fraction ethyl acetate extract (7812, 18625, 3125, 625, 125, 250, 500, 1000 and 0 µg/mL) Incubation for 24 hours 	Ant nest extract has antitumor activity on multiple molecular targets via the Akt pathway and nuclear factor-kappa B (NF-κB) in tongue cancer cells, and induces apoptosis (Caspase -3, -9)
4	Irfanita et al ¹⁵ (2019)	<ul style="list-style-type: none"> HSC-3 cell culture In Vitro Ant nest extract 5 mg/ml and 3 mg/ml Incubation for 24 hours and 48 hours 	Ant nest-induced apoptotic activity was detected, so ant nest could potentially be an oral cancer treatment
5	Bashari et al ¹⁶ (2020)	<ul style="list-style-type: none"> Breast cancer cell cultures (MCF-7, HCC1954) and cervical cancer (Hela) In Vitro ant nest Extract of methanol, ethyl acetate, and n-hexane fraction Incubation for 0, 24,48, and 72 hours 	The n-hexane ant nest extract has the most potential to induce breast cancer cell apoptosis and has been shown to inhibit cervical cancer cell migration
6	Medawati et al ¹⁶ (2020)	<ul style="list-style-type: none"> Burkitt's Lymphoma cancer cell culture In Vitro Ant nest ethyl acetate extract (37.5, 75, 112.5, 150 and 300 mg/mL) Incubation for 24 hours 	The ethyl acetate fraction of ant nests has potent antitumor activity on oral cancer cells of Burkitt's lymphoma by inhibiting cell cycle induction and apoptosis by lowering the levels of E-CDK-2 complex.
7	Yuletnawati et al ¹⁷ (2016)	<ul style="list-style-type: none"> Oral Carcinoma (KB) cell culture In Vitro Ant nest ethanol extract (0, 62.5, 125, 250, 500, 1000 µg/ml) Incubation for 24 hours 	The administration of ant nest ethanol extract could inhibit the proliferation of KB cells by 84.2% and increase apoptotic activity by 84.2%.

Table 1. Reviewed Publication on Ant Nest Extract.

Discussion

Cancer prevention is one of the functions of apoptosis. Loss of apoptotic function causes cancer cells to last longer and allows time for the possibility of accumulation of mutations, thereby increasing tumor progression to a more invasive direction, stimulating angiogenesis, taking over the proliferation process and disrupting the differentiation process.² Inhibition of apoptosis is the "heart" of development. tumor, then tumor cell death is necessary to eliminate malignant cells and maintain healthy cells. Targeting the apoptotic pathway has been shown to have

potential as a therapeutic intervention against cancer.^{2,3} One way of treating cancer is to control or as much as possible stop the uncontrolled growth of cancer cells. The most effective method is to use the cell death mechanism itself. Treatments that target apoptosis are the most successful non-surgical cancer treatments and can be effective in all types of cancer.²

Targeting apoptosis in cancer treatment is getting more and more interesting to study. Drugs or treatment strategies that can restore the signaling function of the apoptotic pathway to normal conditions have the potential to eliminate cancer cells that are struggling to survive. Various studies have opened new doors to new anti-cancer drugs.¹⁸

The active substances found in ant nests are flavonoids, tannins, polyphenols and glycosides which have antioxidant functions. Besides having anticancer properties, these active compounds also have antimicrobial and antidiabetic properties. Antiproliferation, cell cycle inhibition, apoptosis induction, carcinogen inactivation, and angiogenesis inhibition are all mechanisms of action for flavonoids. The study showed that there was a significant reduction in the number of Burkitt lymphoma cells observed after treatment with ethyl acetate extract from ant nests. There was a significant relationship between extract concentration, incubation period and the number of cells that survived after administration of ethyl acetate extract.¹⁹ According to Yi et al, flavanols and tannin fractions were able to inhibit cell growth up to 50% at concentrations of 70-100 and 50-100 L/mL.²⁰

Cancer cells are resistant to apoptosis. There are two apoptotic signalling pathways, namely extrinsic - associated with the large Tumor Necrosis Factor (TNF) family with the main protein caspase 8; and intrinsic - which involves the mitochondria, where proteins of the Bcl-2 family activate caspases 9, 3, and 7. In cancer, there is overexpression of the oncogenic gene (c-Myc), leading to cellular proliferation and p53 suppression, and activation of the anti-apoptotic proteins of the Bcl family. -2 in cancer cells, while pro-apoptotic proteins and caspases decreased activity. Flavonoids can affect the signaling of the apoptotic pathway by two mechanisms, namely activating anti-apoptotic proteins and caspases, and suppressing pro-apoptotic proteins (Figure 2).²¹

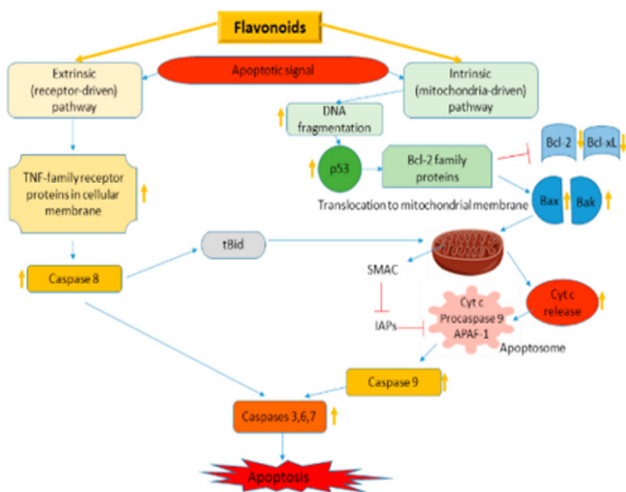


Figure 2. Flavonoids target in extrinsic and intrinsic pathways (yellow arrow).

In the extrinsic pathway, flavonoids increase the TNF family receptor on cellular membranes, resulting in an increase in caspase 8 expression which then activates the executor caspase, namely caspase 3,6,7, then apoptosis occurs. In addition, caspase 8 also has a role in the intrinsic apoptotic pathway through the role of tBid. This is where the extrinsic and intrinsic pathways meet.²

The effect of flavonoids on the intrinsic pathway of apoptosis is that it can increase DNA fragmentation and increase p53 expression. After that, anti-apoptotic Bcl-2 family proteins (Bcl-2 and Bcl-xL) decreased, while Bax and Bak proteins increased in expression. Furthermore, Bax and Bak proteins undergo a location shift to the mitochondrial membrane, combine with tBid (truncated Bid), then increase the release of cytochrome c. In addition, in the mitochondrial membrane there is also SMAC which then inhibits apoptosis-inhibiting proteins (IAPs), so that the apoptosome consisting of cytochrome c, procaspase 9, and APAF-1 can increase the expression of caspase 9, which in turn activates the executor caspase (caspase 3, 6, 7) and apoptosis occurs.²¹

In addition to suppressing tumor growth through apoptotic signaling, flavonoids act as pro-oxidants that can prevent cancer cell proliferation by inhibiting epidermal growth factor receptor/mitogen activated protein kinase (EGFR/MAPK), phosphatidylinositide 3-kinases (PI3K), protein kinase B (Akt), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).²¹

Conclusions

Ant nest extract is proven to be a potential alternative in the treatment of tumors and cancer. In addition, with the presence of anti-tumor and antiproliferative properties against tumor cells, the risk of surgical treatment will be reduced and reduce the possibility of physical disability. Further research is still needed on the effectiveness of ant nest extract, especially in vivo so that it can be further developed.

Declaration of Interest

No conflicts of interest are disclosed by the authors.

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