

Bioactives of noni plant (*Morinda citrifolia L.*) as anti-cancer herbals: A scoping review

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ABSTRACT

Literature Review

ARTICLE INFO

Keywords:

noni,
active compounds,
anti-cancer

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DOI: 10.20885/JKKI.Vol14.Iss2.art10

History:

Received: July 11, 2022

Accepted: April 12, 2023

Online: August 31, 2023

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In Indonesia, the noni plant (*Morinda citrifolia L.*) has gained popularity as an alternative treatment for various diseases. Cancer is the second cause of death worldwide, with chemotherapy as the primary treatment. There is growing interest in exploring phytochemicals found in noni plants such as anthraquinones, chitosan, phenols, and flavonoids. These antioxidant compounds hold potential as alternative treatments for cancer. This study explores the active compounds in noni plants that exhibit anti-cancer properties. This study employed a scoping review approach. Previous original articles were retrieved from Scopus, Science Direct, ClinicalKey, Springer Link, and Google Scholar with keywords in *Morinda citrifolia L.*, component, bioactive, antioxidant, anti-inflammatory, and anti-cancer. We included 34 articles that met the inclusion criteria. The findings of this study highlight the anti-cancer activity of several phytochemicals found in noni plants. Damnacanthal has been shown to reduce the number of MCF-7 cells. Nordamnacanthal inhibited the development of the H400 cell cycle by increasing the activity of Cytochrome C, Caspase-9, and Caspase 3/7 and induced the death of MDA-MB231 and MCF-7 cells. Chitosan nanoparticles can inhibit the growth of A549 cells. Scopoletin can inhibit cancer cell proliferation by inducing cells in the G0 / G1 and S phases. Epicatechin can inhibit the growth of PC-9 cells. Damnacanthal, nordamnacanthal, chitosan nanoparticles, scopoletin, and epicatechin are active compounds presented in noni plants that can act as anti-cancer.

Latar Belakang: Di Indonesia, tanaman mengkudu (*Morinda citrifolia L.*) telah populer sebagai pengobatan alternatif untuk berbagai penyakit. Kanker merupakan penyebab kematian kedua di seluruh dunia, dengan kemoterapi sebagai pengobatan utama. Terdapat perkembangan minat dalam mengeksplorasi fitokimia yang ditemukan dalam tanaman mengkudu, seperti antrakuinon, kitosan, fenol, dan flavonoid. Senyawa antioksidan ini memiliki potensi sebagai pengobatan alternatif untuk kanker.

Tujuan: Studi ini bertujuan untuk mengeksplorasi senyawa aktif dalam tanaman mengkudu yang memiliki sifat anti kanker.

Metode: Studi ini menggunakan pendekatan scoping review. Artikel penelitian sebelumnya diambil dari portal Scopus, Science Direct, ClinicalKey, Springer Link, dan Google Scholar dengan menggunakan kata kunci *Morinda citrifolia L.*, komponen, bioaktif, antioksidan, antiinflamasi, dan anti kanker. Terdapat 34 artikel yang memenuhi kriteria inklusi.

Hasil: Temuan dari penelitian ini menyoroti aktivitas anti kanker dari beberapa fitokimia yang ditemukan dalam tanaman noni. Damnacanthal telah terbukti mengurangi jumlah sel MCF-7. Nordamnacanthal menghambat perkembangan siklus sel H400 dengan meningkatkan aktivitas Sitokrom C, Caspase-9, dan Caspase 3/7 serta menyebabkan kematian sel MDA-MB231 dan MCF-7. Nanopartikel kitosan dapat menghambat pertumbuhan sel A549. Selain itu, scopoletin menghambat proliferasi sel kanker dengan menginduksi sel ke dalam fase G0/G1 dan S, sementara epikatekin efektif menghambat pertumbuhan sel PC-9.

Kesimpulan: Damnacanthal, nordamnacanthal, nanopartikel kitosan, scopoletin, dan epikatekin adalah senyawa aktif yang terdapat dalam tanaman noni dan memiliki potensi sebagai agen anti kanker.

INTRODUCTION

Morinda citrifolia L. is an Indonesian plant species known as noni.¹ Noni is a plant from the Rubiaceae family and the sub-family Rubioideae.^{2,3} Noni plants have different names in tropical and subtropical regions, such as Tahiti, Hawaii, Polynesia, India, and Argentina. Nunaakai (Tamil), dog dumplings (Barbados), apatite (Philippines), pace (Java), noni (Hawaii), and kumudu (Bali) are various names for noni in some regions.^{1,4.}

The noni plant, thriving at an altitude of 1300 meters above sea level, holds significant value in health and general applications. In the general field, the noni plant contains secondary metabolites comprising triterpenes, polyphenols, and saponins, which can be toxic. As a result, they are commonly utilised as vegetable insecticides for *Aedes aegypti* mosquitoes.^{1,5,6} Additionally, noni fruit serves as a natural coagulant in latex processing. Coagulation, also known as freezing, is a chemical process that aims to bind rubber granules in the latex liquid, producing solid lumps. Due to its acidic nature with a pH of 3.6-4.3, noni fruit has become a viable alternative material for coagulation, replacing the use of formic acid.^{7.}

The noni plant has been considered an alternative treatment for various diseases for over 2000 years, including cancer, atherosclerosis, acquired immunodeficiency syndrome (AIDS), hypertension, and diabetes.¹ This plant also acts as an immunomodulator for modifying the immune system response,⁸ protects the liver and heart,⁹ anti-cancer,¹⁰⁻¹² and is a natural antioxidant for diabetic people.^{13,14} Phytochemicals in noni plants include anthraquinones, chitosan, phenols and flavonoids. Anthraquinone compounds have derivatives in the form of damnacanthal and nordamnacanthal, which are proven to have cytotoxic properties.¹⁵ Chitosan is a derivative

of chitin. Chitosan has chitosan nanoparticles that can have a toxic effect on cancer cells.¹⁶ Phenols and flavonoids, as organic compounds with antioxidant properties, have derivative compounds that can fight the growth of cancer cells in the form of scopoletin and epicatechin.^{17,18}

Cancer is a non-communicable disease that is the second leading cause of death worldwide.¹⁹ Chemotherapy remains the primary approach in treating various types of cancer. Chemotherapy aims to kill cancer cells with cytotoxic anti-cancer drugs. However, repeated chemotherapy can worsen the patient's functional status.²⁰ The noni plant harbours numerous active ingredients that hold potential in the health sector, particularly in cancer treatment, where finding alternative therapies without side effects is challenging. This study explores the active compounds in all parts of the noni plant that exhibit anti-cancer properties. It is hoped that this work will contribute to the advancement of herbal cancer treatment approaches.

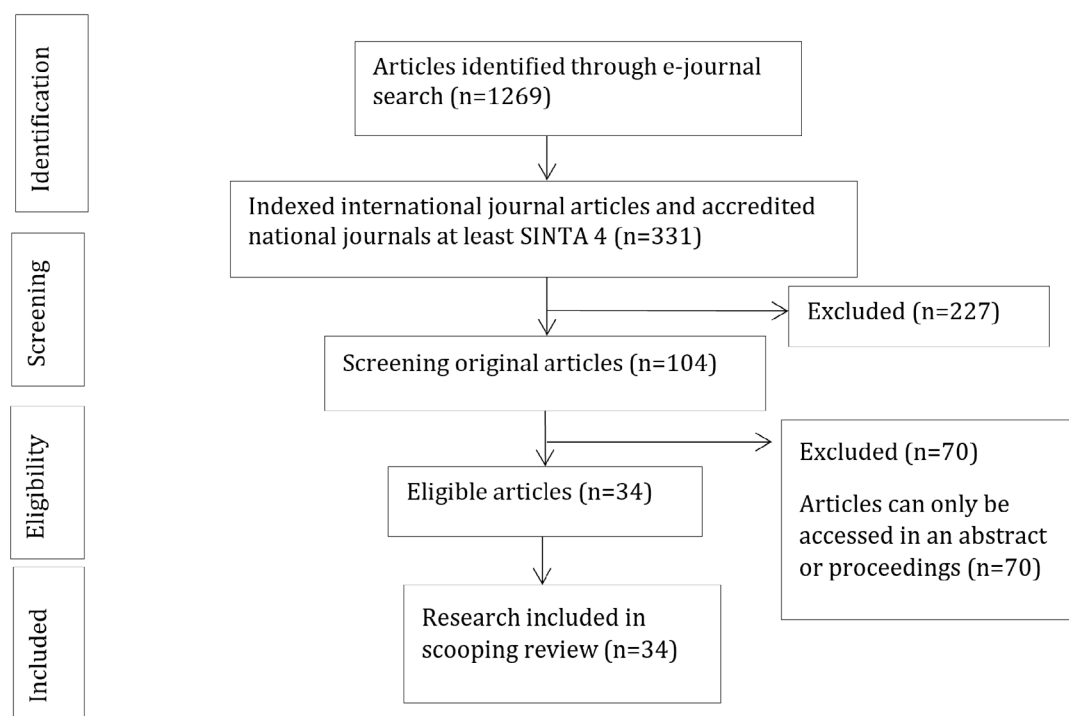
METHODS

This study employs a scoping review approach from December 2020 to January 2021. Available original articles were retrieved from Scopus, Science Direct, Clinicalkey, Springer Link, and Google Scholar portals with keywords: *Morinda citrifolia L.*, component, bioactive, antioxidant, anti-inflammatory, and anti-cancer, as listed in Table 1 and displayed in Figure 1.

The articles were evaluated according to the inclusion and exclusion criteria (Table 1). In Figure 1, it was described that 1269 articles were found, 331 articles discussed the content of *Morinda citrifolia L.* and its health benefits, and only 104 articles were published in 2011-2021. A total of 65 original articles can be accessed on indexed international journal portals and

Table 1. Inclusion and exclusion criteria for previous original articles

Inclusion Criteria	<ul style="list-style-type: none"> - Original articles on the active ingredients of <i>Morinda citrifolia L.</i>, and its functions in the health sector - Published in 2011-2021 - Original article - Accessible on international and national journal portals - Indexed international journals - Minimum accredited national journal SINTA 4
Exclusion Criteria	<ul style="list-style-type: none"> - Only accessible in abstract and proceedings

Figure 1. Article Selection Flowchart²¹

accredited national journals with a minimum of SINTA 4. A total of 31 articles can only be accessed in the abstract. A total of 34 articles met the inclusion and exclusion criteria so that they were used in writing this scoping review consisting of 7 articles on Scopus, seven articles on Science Direct, three articles on the ClinicalKey, ten articles on the Springer Link, and seven articles on the Google Scholar.

The articles were assessed based on predefined inclusion and exclusion criteria (see Table 1). Figure 1 summarises the search results, indicating that initially, 1269 articles were identified. Of these, 331 articles focused on the content of *Morinda citrifolia L.* and its health benefits, and only 104 were published between 2011 and 2021. From this pool, 65 original articles were accessible through indexed international journal portals and accredited national journals with a minimum SINTA 4 rating. On the other hand, 31 articles were only accessible in abstract form. Ultimately, after careful evaluation, 34 articles were found to meet the inclusion and exclusion criteria, making them suitable for this scoping review. Among these articles, seven were sourced from Scopus, seven from Science Direct, three from ClinicalKey, ten from Springer Link, and seven from Google Scholar.

RESULTS

Most parts of the noni plant contain bioactive compounds, including roots, stems, seeds, fruits and leaves. The active compounds of each part are presented in Table 2. The roots of the noni plant contain damnacanthal, nordamnacanthal, and monotropein. On the other hand, the stem only contains nordamnacanthal. Noni seeds are a source of pioglitazone and chitosan nanoparticles. Furthermore, noni leaves contain scopoletin, epicatechin, and catechins.

According to Table 2, the majority of bioactive compounds contained in noni plants is antioxidant properties. Additionally, other compounds present in noni have various beneficial effects, including anti-inflammatory, anti-cancer, anti-hepatotoxic, anti-bacterial, anti-tuberculosis, anti-fungal, anti-dopaminergic, anti-diabetic, anti-osteoporotic, and anti-hyperlipidemic properties. The antioxidant properties of the noni plant are particularly noteworthy, as they play a crucial role in supporting the body's antioxidant requirements. Antioxidants are active compounds that help counteract the harmful effects of oxidants in the body. *Morinda citrifolia L.*, a traditional medicinal plant native to Indonesia, is rich in antioxidants, making it an excellent natural source to combat free radicals and inhibit the growth of cancer cells. The highest antioxidants in noni plants are phenol (14.44±0.82

Table 2. Types of bioactive compounds based on their properties.

Compound Properties	Type of Bioactives					References
	Root	Stem	Seed	Fruit	Leave	
Antioxidant				Scopoletin, ACP3 Isolate, Catechins, Flavonoids, Anthocyanins, Phytochemicals		Firmansyah, Winingsih and Manobi, 2021; Rabima, Harlim and Sogandi, 2020; Sahib, et al., 2012; Nowak, et al., 2018; Lim et, al., 2016
anti-inflammatory				Andrographolide		Salim, Kumolosasi, and Jantan, 2014
Anti-cancer	Damnacanthal, Nordamnacanthal	Nordamnacanthal	Chitosan Nanoparticles		Scopoletin, Epicatechins	Shaghayegh et al., 2016; Günay et al., 2016; Nualsanit et al., 2012; Rajivgandhi et al., 2020; Lim et, al., 2016
Anti-hepatotoxic				Scopoletin		Firmansyah, Winingsih and Manobi, 2021
Anti-bacterial				Scopoletin		
Anti-tuberculosis				Scopoletin		
Anti-fungal				Scopoletin		
Anti-dopaminergic				Methamphetamine		Pandy, Narasingam and Mohamed, 2012
Anti-diabetic			Pioglitazone			Elmaci and Altinoz, 2016
Anti-osteoporotic					Catechins	Shalan, Mustapha and Mohamed, 2017
Anti-hyperlipidemic					Catechins	Hui et al., 2020

mg/g extract) and flavonoids (5.69±0.21 mg/g extract).³² It is important to note that the human body's natural antioxidant defences might not be sufficient to combat free radicals effectively. Therefore, obtaining antioxidants from external sources, such as noni, becomes essential.^{14,33} With the combination of high antioxidants and its anti-cancer properties, the noni plant is considered capable of inhibiting the growth of some cancer cells.

Table 3 provides evidence that damnacanthal,

nordamnacanthal, chitosan nanoparticles, scopoletin, and epicatechin, found in noni plants, exhibit potent anti-cancer properties. These bioactive compounds not only prevent and inhibit the growth and spread of cancer cells but also effectively destroy them in various types of cancer. This outcome strongly suggests that the noni plant shares similarities with chemotherapy in terms of its ability to act as a cytotoxic agent against cancer cells, capable of both inhibiting and eradicating them.

Table 3. Anti-cancer function based on the type of bioactive compounds in noni plants

Type of Bioactive compounds	Sample	Test Method	Function	Anti-cancer	References
Damnacanthal	Root	In vitro on MCF-7 cells	Cytotoxic to cancer cells, inhibits the growth of cancer cells	Breast cancer	Aziz et al., 2016
Nordamnacanthal	Root	In vitro on H400 cell	Anti-cancer, cytotoxic to cancer cells, and contains antioxidants	Carcinoma	Shaghayegh et al., 2016
Nordamnacanthal	Stem	In vitro on MDA-MB231, MCF-7, and 4T1 cells	Inhibits the growth of cancer cells	Breast cancer	Abu et al., 2018
Chitosan Nanoparticles	Seed	In vitro on A549 cells	Increases anti-cancer activity on A549 cancer cells and impairs cancer cell growth	Lung cancer	Rajiv Gandhi et al., 2020
Scopoletin	Leave	In vitro on G0/G1 and S phases cell	Cancer cell proliferation inhibitor	Lung Cancer and Liver Cancer	Lim et al., 2016
Epicatechin	Leave	In vitro on PC-9 cells	Increases O2-detoxification capabilities	Lung cancer	Lim et al., 2016

DISCUSSION

Chemotherapy plays a crucial role in treating different types of cancer, utilising cytotoxic anti-cancer drugs to target and eliminate cancer cells.²⁰ Results of this review demonstrated that almost every part of the noni plant contains bioactive compounds comprising damnacanthal, nordamnacanthal, chitosan nanoparticles, scopoletin, and epicatechin that have cytotoxic properties against cancer cells that can inhibit and destroy cancer cells.

Damnacanthal

Damnacanthal is an anthraquinone derivative compound reported to have antiviral, anti-bacterial, and anti-cancer properties. Damnacanthal can inhibit the growth and division of colon, lung, and leukaemia cancer cells. The combination of damnacanthal with doxorubicin also reduced the number of MCF-7 cells with fewer side effects compared to using doxorubicin alone as an anti-tumour. DNA cell cycle and annexin V-FITC/PI staining, this natural product and drug combination targets MCF-7 cells through induction of apoptosis. Damnacanthal at IC₂₅ and IC₅₀ levels reduced the IC₅₀ value of doxorubicin to MCF-7 cells from 5.5 to 4.0 and 2.0 µg/mL. Doxorubicin 0.2 µg/mL and damnacanthal 8.2 µg/mL activated the genes most related to apoptosis.³⁴ This report suggests the potency of damnacanthal as a co-

chemotherapeutic agent to doxorubicin in breast cancer.

Nordamnacanthal

Nordamnacanthal is another anthraquinone derivative compound with high antioxidant activity against free radicals. In addition, nordamnacanthal also plays a cytotoxic effect against cancer cells.³⁵ This compound reported an inhibition effect on the H400 cell cycle development by increasing cytochrome C, caspase-9, and caspase 3/7 activities.¹⁵ Furthermore, a previous in vitro study reported a cytotoxic effect of nordamnacanthal, from noni stems, against MDA-MB231, MCF-7 and 4T1 cells, through reduction of cells' viability. In addition, based on the cell cycle and Annexin V results, nordamnacanthal successfully induced the death of MDA-MB231 and MCF-7 cells.¹⁰ Nevertheless, these studies offer the potency of nordamnacanthal to be developed as an anti-cancer agent.

Chitosan Nanoparticles

Chitosan is a form of deacetylated chitin. Notably, chitosan nanoparticles effectively encapsulate various bioactive molecules, including antimicrobials, anti-cancer drugs, antioxidants, and plant-derived antibiotics. The results of observations on the cytotoxic effect of noni seed essential oil containing chitosan nanoparticles

on A549 cells demonstrated inhibition of A549 cell growth of 54% at 40 g/ml-1. Using an in vitro morphological modification, the incidence of nuclear damage, reactive oxygen species formation, and cell cycle arrest of A549 could be observed using fluorescence microscopy and flow cytometer analysis. This finding demonstrates that *Morinda citrifolia L.* essential oil containing chitosan nanoparticles is a valuable biomaterial due to its ability to fight A549 cancer cells.¹⁶

Scopoletin

The scopoletin substance is included in the largest content of the noni plant.³⁶ Phenol coumarin compounds derived from the phenylpropanoid process produce the bioactive scopoletin. In a previous in vitro study, scopoletin substances have many functions as anti-bacterial, anti-fungal, anti-tuberculosis, and antioxidant agents. Antioxidants in scopoletin potentially functioned as an anti-cancer.¹⁷ Scopoletin inhibits cancer cell proliferation by inducing cells in the G0/G1 and S phases. Extracts from the noni plant focused on JAK2 gene mutations resulted in the loss of protein transcription factors from the STAT family, namely STAT3/STAT3A. The effect of scopoletin extract in noni plants is more effective for indications of advanced lung cancer that persists and metastasises.⁹

Epicatechin

Epicatechin belongs to the flavonoid group with an antioxidant property.¹⁸ The epicatechin content also inhibits fatty acid synthase activity, which can reduce blood sugar and cholesterol levels.^{2,27} Sahib et al.²⁶ have demonstrated a robust positive correlation between epicatechin and antioxidant activity, establishing epicatechin as a potent antioxidant. In the case of lung cancer, a previous in vitro study demonstrated that epicatechin is an anti-cancer lung, especially in PC-9 cells. The epicatechin and catechin belong to the strong cytotoxic group compared to other catechin members (ECG), error catechins (CG), epigallocatechin gallate (EGCG) and epigallocatechin (EGC). Epicatechin content positively impacts lung and liver tissue with cancer because it can increase the detoxification of O₂. Epicatechin protects against nerve damage caused by NFE2L2-HOI.^{12,29}

CONCLUSION

Noni plants are rich in antioxidant compounds, particularly phenolics and flavonoids. The active compounds, namely damnacanthal, nordamnacanthal, chitosan nanoparticles, scopoletin, and epicatechin, serve as antioxidants and exhibit potent anti-cancer properties. They play a crucial role in preventing and inhibiting the growth and metastasis of cancer cells, effectively combating various types of cancer. However, this scoping review uses original articles but is still in vitro studies. Nevertheless, further study is warranted, especially in vivo studies. Moreover, the development of biopharmaceuticals requires in silico study to evaluate the anti-cancer activity of noni plants more comprehensively.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

ACKNOWLEDGEMENT

Thanks to Diponegoro University, which has facilitated us in accessing various journals.

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