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Efficacy and Safety of *Morinda citrifolia* L. (Noni) as a Potential Anticancer Agent

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Abstract

Cancer is a major cause of morbidity and mortality worldwide and therefore there has been interest in discovering the phytoconstituents of medicinal plants exhibiting anticancer activities. *Morinda citrifolia* L., commonly known as Noni, has shown anticancer properties in in vitro, in vivo, and in clinical studies. A systematic review was conducted to collate scientific evidence on the anticancer properties of *M. citrifolia* using pre-determined keywords on 5 electronic databases: MEDLINE, CENTRAL, LILACS, Web of Science, and EBSCOHost. A total of 51 clinical and preclinical studies comprising 41 efficacy and 10 safety studies were included in this review. Our findings showed that *M. citrifolia* demonstrated various anticancer properties in different cancer models, via multiple mechanisms including antitumor, antiproliferative, pro-apoptotic, antiangiogenesis, antimigratory, anti-inflammatory, and immunomodulatory activities. *M. citrifolia* is deemed to be a potentially valuable medicinal plant in the treatment of cancer through its many intrinsic pathways. More well-designed and reported preclinical efficacy and safety studies are needed to allow for better translation into future clinical studies which could further substantiate the role of *M. citriflolia* in cancer treatment.

Keywords

Morinda citrifolia, noni, cancer, tumor, neoplasm, chemotherapy

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Introduction

Cancer is a major cause of morbidity and mortality worldwide, accounting for nearly 10 million deaths in 2020. The highest incidence (in terms of new cases of cancer) in 2020 was seen in breast (2.26 million cases) followed by lung, colon and rectum, and prostate cancer. Among these, lung cancer contributed the most mortality (1.8 million deaths).[1,2] Meanwhile in Malaysia, according to the Malaysia Cancer Registry Report, a total of 115 238 new cancer cases were diagnosed for the period of 2012 to 2016 with breast cancer (19.0%) reported as the most common cancer among all Malaysians, as well as the most prevalent cancer among women, followed by colorectal cancer (13.5%), the most prevalent cancer among males.[3,4] Despite the various cancer treatment modalities, efficacy, and safety remains a concern. Therefore, there is a need to explore novel strategies for the treatment of cancer.

There has been long-standing interest in the use of plant materials for cancer treatment due to their scalability and sustainability, as well as potential therapeutic benefits.[5,6] Many in vivo and in vitro studies have shown naturally occurring phytoconstituents found in medicinal plants exhibiting anticancer activities via antiproliferative, pro-apoptotic, antimetastatic, antiangiogenic, autophagy regulation, multidrug resistance reversal, and immunomodulatory properties, as well as the potential to enhance chemotherapy as adjuvants. The bioactive compounds that have been popularly studied in cancer models include curcumin

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(polyphenol compound extracted mainly from the rhizomes of eg, *Curcuma longa*), epigallocatechin gallate (main polyphenol in green tea [*Camellia sinensis*], berberine [isoquinoline alkaloid mainly extracted from medicinal plants such as *Coptidis chinensis* Franch], artemisinin [sesquiterpene peroxide derived from annual wormwood (*Artemisia annua* L.)], and ursolic acid [ursane-type pentacyclic triterpenic acid found in the berries and leaves of a series of natural medicinal plants, including cranberry (*Vaccinium macrocarpon* Ait)]).[7]

Morinda citrifolia L. (Noni), a member of the Rubiaceae family, is a small evergreen tree or shrub. It is native in regions of Southeastern Asia to Australia and currently has a pantropical distribution.[8] In Malaysia, *M. citrifolia* is commonly known as noni or mengkudu with other common names such as Indian mulberry, hai ba ji (China), and nuna (India).[9] *M. citrifolia* has been traditionally used to treat various ailments where the fruits, leaves, root, stem, and bark can be applied externally as a poultice or consumed orally as a decoction or in the form of fermented fruits.[10,11] Some of the reported traditional uses are to relieve sore throat, carbuncle, peeling or cracking of the toes and feet, treating stomach ulcer, hypertension,[12,13] enlarged spleen, nausea, colic and fever, diabetes, liver disease, hemorrhage, and coughs.[11] In pharmacological studies, *M. citrifolia* has showed anticancer activities on various cell lines such as lung, cervical, and breast cancer cells.[14] Modern studies also showed that *M. citrifolia* possess antioxidant, antimicrobial, antifungal, antiangiogenic, antidyslipidemic, hypoglycemic, hepatoprotective activity, and immunomodulatory properties.[15]

The ongoing interest in the anticancer effect by *M. citrifolia* is evidenced through many published articles either from in vitro, in vivo, or clinical studies as well as several narrative reviews of its general potential pharmacological properties.[14,16-18] However, there is no recent review focusing specifically on the anticancer activity of *M. citrifolia* since in the past decade, with the most recent narrative review published by Brown.[14] Therefore, the aim of this study is to produce an updated, extensive and systematic review on the anticancer properties of *M. citrifolia*. This review presents the current anticancer evidence for *M. citrifolia* and its bioactive phytoconstituents at all levels in humans, animals, and cells.

Methodology

Research Questions

This review was conducted based on the primary research question "What are the anticancer properties of *Morinda citrifolia*?" This primary question was further expanded to secondary research questions including the following:

i. What is the scientific evidence available with regards to the anticancer properties of *M. citrifolia*?
ii. What is the effective dose of different plant parts of *M. citrifolia* in treating different types of cancer?
iii. What are the possible anticancer mechanisms of action of *M. citrifolia*?

Table 1. Population, Intervention, Comparison, and Outcomes (PICO) Framework.

Elements	Details
Population	1. Human patients of all ages with diagnosed cancer 2. Animal models in anticancer efficacy studies 3. Cell models or assays in anticancer efficacy studies
Intervention	Any plant part of *Morinda citrifolia* as a single herb, in any form (including phytoconstituent-based) of any formulation
Comparison	1. No treatment/placebo control 2. Standard treatment for cancer
Outcomes	*Primary outcome* 1. Anticancer efficacy and mechanisms of action *Secondary outcome* 1. Safety (adverse reactions, toxicity)

The following Population, Intervention, Comparison, and Outcomes (PICO) framework was applied to address the review's research questions as shown in Table 1. Three main population categories were targeted to answer the 3 secondary research questions.

Search Strategy

A systematic search was conducted by 2 independent investigators for published literature and ongoing trials with predetermined keywords. In general, a combination of keywords consisting of "*Morinda citrifolia*," "noni," "cancer," "tumor," "neoplasm," "apoptosis," and "chemotherapy" was used, catered, and adapted to each search engine. An example of the keywords search used for MEDLINE is presented in the Supplemental Appendix S1. A total of 5 electronic databases including MEDLINE, CENTRAL, LILACS (Latin American and Caribbean Health Sciences Literature), Web of Science (WoS), and EBSCOHost were searched since inception until September 2021. Additional relevant studies were also identified from the reference list of related review papers found during the initial search. All searches were performed and matched by 2 independent investigators. Search results were managed using bibliographic software (EndNote X9), and duplicates were removed. Investigators of ongoing clinical trials were contacted to obtain relevant interim information if necessary.

Article Inclusion

Title, abstract screening, and full-text paper inclusion were performed by 2 independent investigators. A third investigator was involved in cases of disagreements. Studies were selected based on the inclusion and exclusion criteria with

Table 2. Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
1. Clinical and preclinical (in vivo and in vitro) primary articles reporting on the anticancer effects and safety of *M. citrifolia* in any formulation	1. In vitro studies that only performed cytotoxic analysis without additional investigation on other anticancer properties or mechanisms of action
2. Articles that investigated *M. citrifolia* as a medicinal plant (including any plant part)	2. Articles that investigated *M. citrifolia* or its derived phytoconstituents as part of a mixture containing other potentially active ingredients (eg, herb mixtures)
3. Articles that investigated *M. citrifolia* derived phytoconstituents for example, damnacanthal	3. Pharmacokinetic or formulation optimization studies without efficacy evidence
	4. Articles that investigated the role of *M. citrifolia* in alleviating chemotherapy related adverse effects
	5. Non-English articles

reference to the research questions identified and PICO elements as depicted in Table 2. Only English language articles were included. This paper reviewed both *M. citrifolia* as a medicinal plant and *M. citrifolia* derived phytoconstituents, adhering to the study objectives. Articles investigating *M. citrifolia* in combination (as mixtures) with other interventions were excluded to facilitate causal relationship analysis between reported effects and anticancer efficacy of *M. citrifolia* or its derived phytoconstituents. Specifically for in vitro studies, we excluded studies that reported solely on cytotoxicity screening or evaluation of the intervention without additional information on potential anticancer mechanisms. This is to ensure that this review includes studies of more robust models to allow for better translation of anticancer efficacy from the scientific evidence.

Data Charting

Three different data extraction tables were specifically designed for: (1) clinical studies, (2) preclinical studies (in vivo), and (3) preclinical studies (in vitro), to comprehensively capture the required information from the included articles. In general, the categories of main data extracted include the following:

(i) Article identifier: designated number; title; and author
(ii) Article characteristics: year; country; type of study (randomized controlled trials, case series, in vivo, in vitro, etc.); and objectives
(iii) Study subjects: sample size; animal model (age, gender, species)
(iv) Intervention: plant part used; formulation; dose; route; duration
(v) Comparator: formulation; dose; route; duration
(vi) Outcome measures: efficacy, safety, mechanism of action

Data extraction was performed independently by 2 investigators with disparities addressed by a third investigator. All investigators were briefed and trained on using the data extraction tables prior to initiation of data extraction to ensure consistency.

Data Analysis

Qualitative analysis was presented descriptively and numerically based on the type of study (clinical, preclinical in vivo, and preclinical in vitro), intervention (plant-based or phytoconstituent-based), cancer type, overall efficacy summary by cancer type, and mechanism of action.

In the absence of randomized controlled clinical trials, pooled quantitative analysis was only performed on preclinical in vivo studies. Quantitative analysis was performed using Cochrane Review Manager (RevMan, version 5.4) software[19] to generate pooled effect analysis involving 3 or more in vivo studies investigating the same quantifiable outcome. The reported mean ± standard deviation (SD) or standard errors of mean (SEM) values and the number of subjects per group comparing *M. citrifolia* (in any formulation or isolated phytochemical constituents) against comparator (control or standard treatment) were extracted for analysis. Pooled outcome estimates for continuous data were reported as standardized mean differences (SMD) and 95% confidence intervals (CI), with random effects model applied for all outcomes analyzed in view of the different species and methodologies used to induce the same experimental cancer model. All SEM values were converted into SD values using the in-built calculator of the RevMan software. The I^2 statistic was used to assess heterogeneity among pooled studies. Further subgroup analysis was conducted for studies that investigated between compound (phytoconstituent) or plant extract/juice, high or low dose, and comparator type (negative control and other treatments) where appropriate.

Risk of bias assessment was only conducted on in vivo animal studies since there were no randomized controlled clinical trials identified. The risk of bias assessments was conducted by 2 independent investigators, with disparities

addressed by a third investigator. The RevMan 5.4 software and Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool for animal interventions studies were used for this purpose.[20] This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist[21] (Supplemental Appendix S2 and S3).

Results

Summary of Findings

A total of 2602 articles were identified based on the search criteria described in the methodology. Upon removal of duplicates and record screening by the abstract and title, 2207 records were excluded. Of the 106 full-text articles that were screened for eligibility, 55 records were excluded for having no outcome measures, different plant species, drug-herb interactions and for being in a foreign language. A final count of 51 papers met all the inclusion criteria and hence were included for analysis. Figure 1 depicts the selection process and Table 3 presents the details of the included studies.

Efficacy

Clinical evidence. A Phase I clinical trial[22] and 2 case reports of gastric cancer[23] that utilized noni as part of the treatment for cancer were included in this review. A summary of the clinical findings is described in Table 4.

Preclinical Evidence

Quantitative analysis. Experimental breast cancer, lung cancer, and leukemia met the pre-specified criteria for meta-analysis. Subgroup analysis was performed where appropriate based on the outcome measures stated in Table 5 to address heterogeneity potentially due to differences in intervention or dose.

i. Experimental breast cancer

Pooled estimates from 3 studies[24-26] showed that noni administration did not result in significantly different effects on tumor volume in experimental breast cancer (SMD −1.67, 95% CI −3.70-0.35) when compared to controls. Subgroup analysis according to intervention type (noni fruit juice; 2 studies and phytoconstituent; 1 study) also did not show any significant difference in effects (Figure 2). Abu et al[24] used 4T1-bearing BALB/C mice, Ali et al[25] used Swiss albino mice inoculated with Ehrlich cancer cells while Clafshenkel et al[26] used female mouse mammary tumor virus (MMTV)-*neu* transgenic mice as experimental breast cancer models. Two studies (Ali et al and Clafshenkel et al) compared noni treatment against a negative control group while 1 study (Abu et al) did not report details of the intervention used in the control group.

ii. Experimental lung cancer

Pooled estimates from 3 studies[27-29] showed that noni administration significantly reduced experimental lung cancer tumor volume compared to overall control (SMD −1.31, 95% CI −2.50-−0.13) (Figure 3). Subgroup analysis revealed significant effects of noni administration in reducing tumor volume when compared to negative controls that is, saline or vehicle (SMD −2.70, 95% CI −3.50-−1.90) but no significant difference when compared to other treatments including oxaliplatin and erlotinib (SMD −0.39, 95% CI −2.11-1.33). These findings are shown in Figure 4. However, all 3 studies, Lim et al[27,28] and Ma et al[29] reported vastly different values for tumor volume for high and low dose noni treated groups which may have contributed toward high heterogeneity $I^2 = 91\%$. Further sub-analysis did not show any significant difference between high dose noni versus other treatment (SMD −1.73, 95% CI −3.65-0.19) and low dose noni vs other treatment (SMD 0.21, 95% CI −2.10-2.52) (Figure 5). Two articles, Lim et al[27,28] used standardized ethanolic leaf extract (300 and 150 mg/kg) while 1 study, Ma et al[29] reported on fermented noni fruit juice (0.2 mL/10 g and 0.4 mL/10 g). All 3 studies used male BALB/c mice inoculated with A549 cells as the experimental lung cancer model.

iii. Experimental leukemia

Pooled estimates showed that noni administration did not exert significantly different effects when compared to controls on neutrophil (SMD −1.59, 95% CI −3.59-0.41), lymphocyte (SMD −0.29, 95% CI −0.88-0.30), erythrocyte (SMD 0.65, 95% CI −0.11-1.40), and leukocyte (SMD −1.01, 95% CI −2.67-0.66) counts in experimental leukemia (total studies = 3 for each parameter). Hazilawati et al[30,31] used 8-week-old male Sprague Dawley rats in both studies (leukemia model induced by N-methyl-N-nitrosourea) while Ahmadi et al[32] used 1.5-month-old male BALB/c mice injected with WEHI-3B cells as experimental leukemia models. Both studies by Hazilawati et al investigated on dried fruit while the study by Ahmadi et al investigated noni leaf extract. As shown in Figure 6, subgroup analysis according to intervention type (dried fruit, 2 studies; leaf extract, 1 study) showed no significant difference in all outcomes (data not shown) although Hazilawati et al explained that the significant differences in effect reported in both studies could be explained by a dose-dependent effect of the dried fruit administration (5000 vs 3000 mg/kg as part of food ration) in the individual studies. The intervention details in the control group were unclear for both studies by Hazilawati et al while Ahmadi et al compared noni against All-Trans-Retinoic-Acid (ATRA).

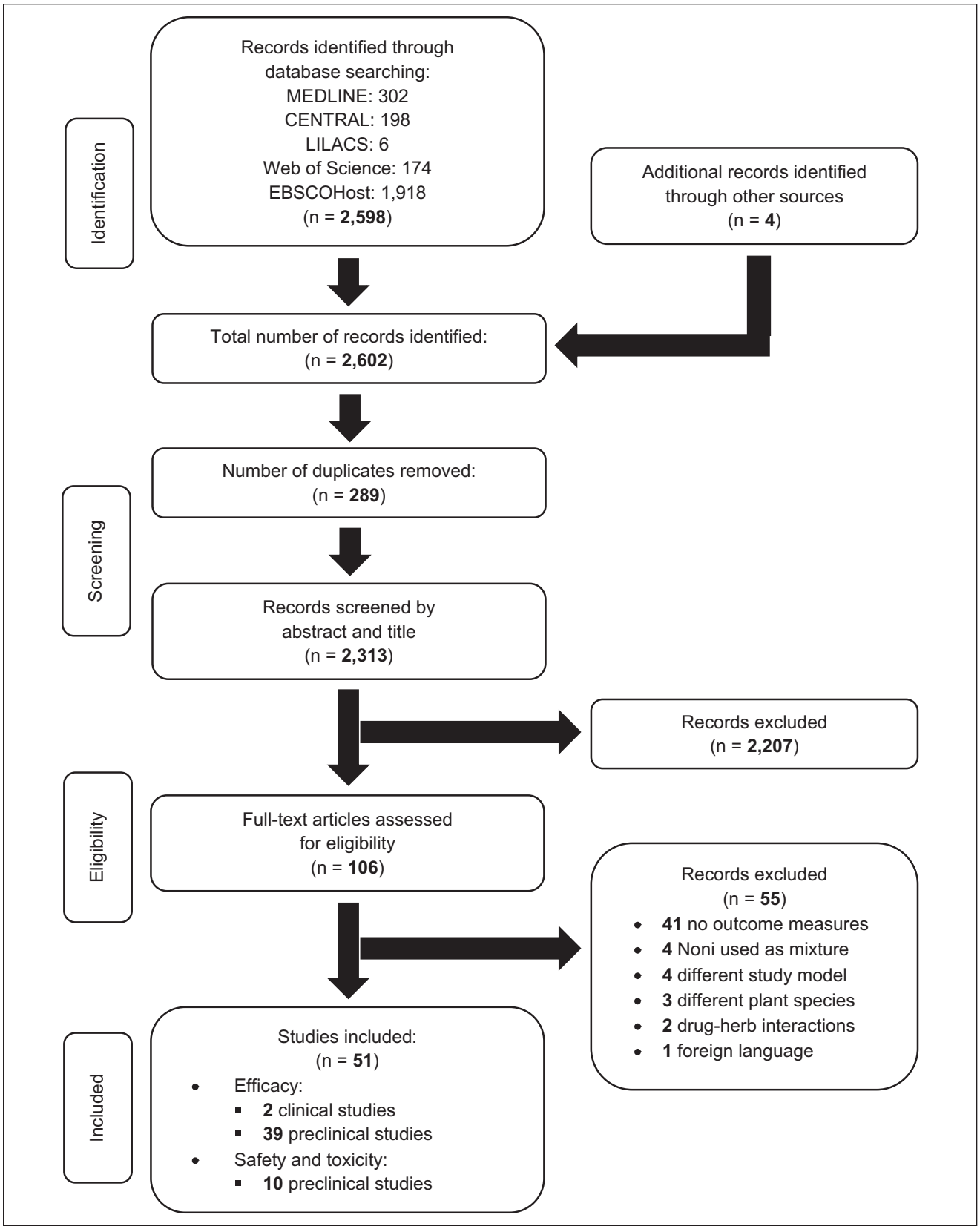

Figure 1. PRISMA flow chart.

Table 3. (a) Details of Included Efficacy Studies.[22-62]

Evidence level	Number (%)
Clinical	
Case report and clinical trial	2 (4.9)
Preclinical	
In vivo	11 (26.8)
In vitro	24 (58.5)
In vivo + in vitro	4 (9.8)
Total	41 (100)
Cancer type	
Breast cancer	15 (36.7)
Lung cancer	6 (14.6)
General cancer pathogenesis	5 (12.2)
Cervical cancer	3 (7.3)
Leukemia	3 (7.3)
Colon cancer	3 (7.3)
Others (oral, liver, prostate, skin, eye)	6 (14.6)
Total	41 (100)
Intervention	
Plant parts-based	
Fruit	15 (36.7)
Leaf	5 (12.2)
Seed	1 (2.4)
Unspecified	7 (17.1)
Phytoconstituent-based	
Damnacanthal	6 (14.6)
Nordamancanthal	4 (9.8)
Morindone	1 (2.4)
Glycosides	1 (2.4)
Polysaccharides	1 (2.4)
Total	41 (100)

(b) Details of Included Safety and Toxicity Studies.[24,63-71]

Evidence level	Number (%)
Preclinical	
In vivo	6 (60.0)
In vitro	3 (30.0)
In vivo + in vitro	1 (10.0)
Total	10 (100)
Intervention	
Plant parts-based	
Fruit	5 (50.0)
Leaf	2 (20.0)
Fruit and leaf	2 (20.0)
Phytoconstituent-based	
Nordamnacanthal	1 (10.0)
Total	10 (100)

Descriptive Analysis

Noni had been studied in breast cancer, lung cancer, leukemia, and general cancer pathogenesis mainly by utilizing mice and rat models. There were 4 studies on breast cancer which used plant extract and 1 study which used nordamnacanthal, a naturally occurring anthraquinone in noni. Lung cancer and leukemia studies used plant extracts in 4 and 3 studies, respectively. Three studies on general cancer pathogenesis made use of plant extract. A summary of these findings is shown in Tables 6a and b. The efficacy summary reported in the table is generalized to Noni exceeding the activity of comparator or adjuvant, unless stated otherwise. Detailed outcome measures are presented in the Supplemental Appendix S4 and S5.

Quality of Other In Vivo Studies: Risk of Bias (ROB) Assessment Summary

Risk of bias assessment (ROB) was performed on 15 in vivo studies using the RevMan 5.4 software to establish transparency of evidence synthesis on results and their findings. The summary of the ROB analysis is depicted in Figure 7.

All studies reported unclear risk for selection bias in terms of sequence generation and allocation concealment. The procedure on allocation sequence for the selection of animals in respective treatment group were not generated. Information on allocation concealment was not reported by personnel involved in the studies. All studies had unclear risk of performance bias as the information on random housing of animals and blinding of intervention groups was not reported. Detection bias for random outcome assessment of animals in different treatment groups and blinding of the accessor was reported as unclear for all the animal studies due to an absence of information provided in the individual papers included.

The baseline characteristics of animals for the selection bias category, that is, age, weight, gender, breed, and number of animals, were reported in 4 studies (26.7%). Other studies had not provided at least one of the required parameters. A majority of the studies (73.3%) were reported as high risk for attrition bias due to missing or incomplete outcome data reported in the results section. Most of these studies lacked pivotal information on either the initial number of animals included in the study or the final number of animals included in the analysis. Besides, the reasons for the number of animals excluded for result analysis also was not clearly justified. The pattern of analysis of reporting bias for selective outcome reporting is similar to the attrition bias for incomplete data except for an additional study by Abu et al.[24] Although all the animals were accounted for in this study, reporting bias was present as the creatinine and albumin levels were monitored but unreported. Consequently, 12 out of 15 studies (80%) exhibited reporting bias. Financial conflict of interest constitutes other bias reported in studies. About 60% of the studies were sponsored by either the government, university, or nonprofitable organization; hence were categorized as low risk. Two of the studies were reported as high risk due to

Table 4. Clinical Findings Related to Use of Noni in Cancer Patients.

Author	Study design	Sample size	Cancer type	Intervention (formulation, route, dose, duration)	Outcome	Limitations
Issell et al[22]	Phase 1 (for dose selection for Phase 2 study)	51 advanced cancer patients (n = 12 dropouts)	Colorectal (n = 9), ovarian (n = 6), lung (n = 4), pancreatic (n = 3), others (n = 17)	500 mg freeze dried noni fruit extract per capsule, oral consumption, 2 to 10 g for 28 days	• No toxicity • Improved physical functioning, pain improvement, and fatigue score • No measured tumor regressions	No measurable parameter for toxicity analysis meant for safety study
Wong[23]	Case report	1 Patient	Stomach	• Homemade noni juice,[a] consumed orally, dose and duration unclear • Other treatment: none	No worsening of cancer (through biopsy examination) up to 6 year	No qualitative or quantitative analytical details of the noni juice consumed were provided
Wong[23]	Case report	1 Patient	Stomach	• Homemade noni juice,[a] consumed orally, dose and duration unclear • Other treatment: multiple surgical dilation procedures to relieve benign stricture	No symptoms of recurrence for 16 year	No qualitative or quantitative analytical details of the noni juice consumed were provided

[a]Plant part used was not reported.

Table 5. Outcome Measures for Meta-Analyses.

Experimental cancer	Outcome measure
Breast	Tumor volume
Lung	Tumor volume
Leukemia	Neutrophil count
	Lymphocyte count
	Erythrocyte count
	Leukocyte count

being sponsored by industry, namely Alnoni Ltd, Antalya, Turkey[32] and Morinda, Inc., Utah, USA.[36] Four studies did not provide any funding information.

In Vitro Findings

The in vitro studies were performed by utilizing both the plant extracts and also the phytoconstituents on the respective cancer cell lines such as for breast, lung, cervical, oral, and colon cancers. A summary of the included studies is shown in Tables 7a and b. The efficacy summary reported in the table is generalized to Noni exceeding the activity of comparator or adjunct, unless stated otherwise. Detailed outcome measures are presented in the Supplemental Appendix S6 and S7.

Possible Mechanisms of Action

All the included in vivo and in vitro studies were analyzed for reporting on possible mechanisms of action to better illustrate the potential of noni as an anticancer agent. The majority of the studies displayed pro-apoptotic, antiangiogenesis, antimigratory, antitumor, and antiproliferative effects which facilitate the elimination of cancer cells. The proposed mechanisms of action and supporting evidence are summarized in Table 8.

Safety and Toxicity Assessment

Ten studies[24,63-71] reported on the safety and toxicological assessment of *M. citrifolia.* Table 9 describes the safety implications of Noni investigated on animal toxicity, chronic, and subchronic toxicities as well as cell toxicity studies.

Discussion

Overall, *M. citrifolia* demonstrated various anticancer properties in different experimental cancers, via several mechanisms including antitumor, antiproliferative, pro-apoptotic, antiangiogenesis, antimigratory, anti-inflammatory, and immunomodulatory activities. The scientific evidence gathered were mostly confined to preclinical studies. This review provides a comprehensive evaluation including subgroup analysis and risk of bias assessment of available evidence and it is one of the first systematically conducted reviews on the efficacy and safety of *M. citrifolia* as an anticancer agent.

Focusing on the included preclinical studies, the role of *M. citrifolia* was mostly studied in experimental breast cancer, lung cancer, and leukemia. Various mechanisms of action have been found to modulate the anticancer properties of *M. citrifolia* in animal and cell cancer models most notably through pro-apoptotic, anti-migratory, and cell proliferation disruption properties. The proliferation of cancer cells may be inhibited through the suppression of the AKT/NF-κB signaling pathway leading to apoptosis.[29] In addition, downregulation of cell proliferation Ki67 and PCNA proteins, inhibition of anti-apoptotic protein Bcl-2 expression, and the upregulation of apoptotic caspase-3 protein enhances the apoptotic pathway to eliminate the tumor cells.[29] Furthermore, Noni has demonstrated the ability to disrupt cell migration to inhibit metastasis, halting the progression of tumor cells.[43,45] Despite positive outcomes reported in individual studies, most of the selected studies for pooled and subgroup analysis showed no significant differences between treatment and comparator groups, with the exception for experimental lung cancer whereby the administration of *M. citrifolia* resulted in significant reduction in lung tumor volume. However, the heterogeneity was very high ($I2 = 97\%$). Further subgroup analysis revealed significant difference in reducing tumor volume between the *M. citrifolia* treated group and negative control/untreated group (with acceptable heterogeneity of $I^2 = 29\%$), while this significant effect was not identified when compared to groups treated with other treatment intervention (erlotinib and oxaliplatin).[29-31] Different formulation of *M. citrifolia*, comparator (drug), and treatment duration could have contributed to the high heterogeneity being observed.

In terms of safety, there have been several case reports on the potential association of *M. citrifolia* with adverse kidney[72] and liver injuries.[73-75] However, these studies were not included in this review as the study population did not have cancer and furthermore had other underlying conditions. There were 2 compounds isolated from *M. citrifolia* which have been associated with hepatotoxicity; anthraquinones (dose-dependent) and coumarins (idiosyncratic), however such causality needs to be further evaluated.[74] Although some of these events have raised concerns on the potential hepatotoxic effect of *M. citrifolia*, many important confounding factors could not be accounted for including the contribution of contamination or adulterants, dose, and formulation related effects. As phytoconstituent profiles of finished or processed herbal formulations largely depend on the agroclimatic factors and processing methods (eg, different solvents and drying methods resulting in different phytochemical composition[76]) of raw materials, it is inherently

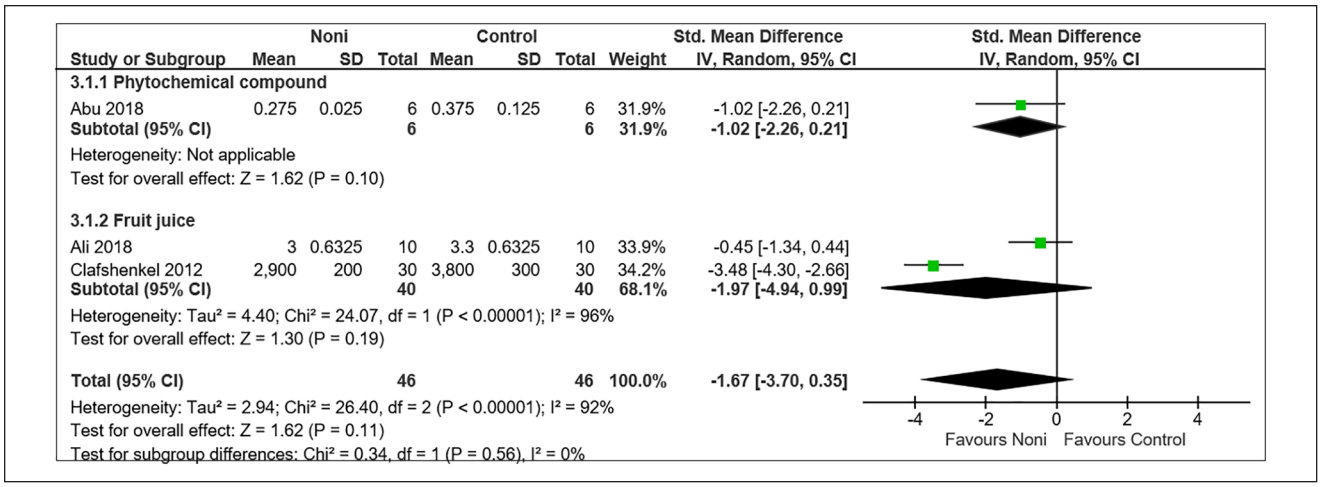

Figure 2. Pooled effect size of noni treatment on tumor volume in experimental breast cancer.

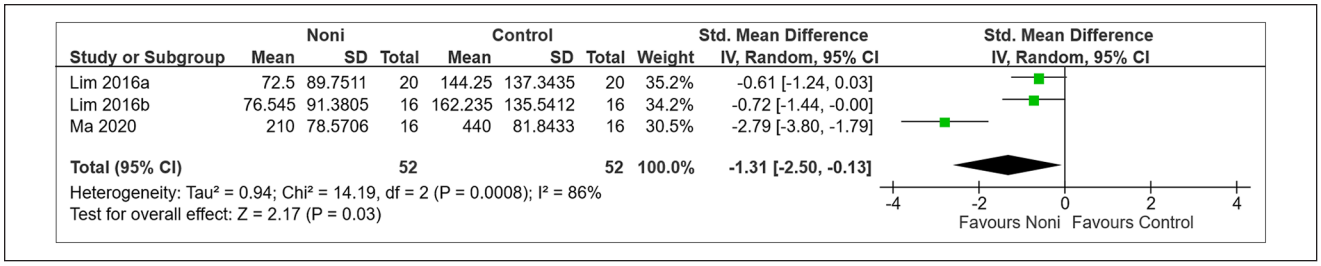

Figure 3. Overall pooled effect size of noni treatment on tumor volume in experimental lung cancer.

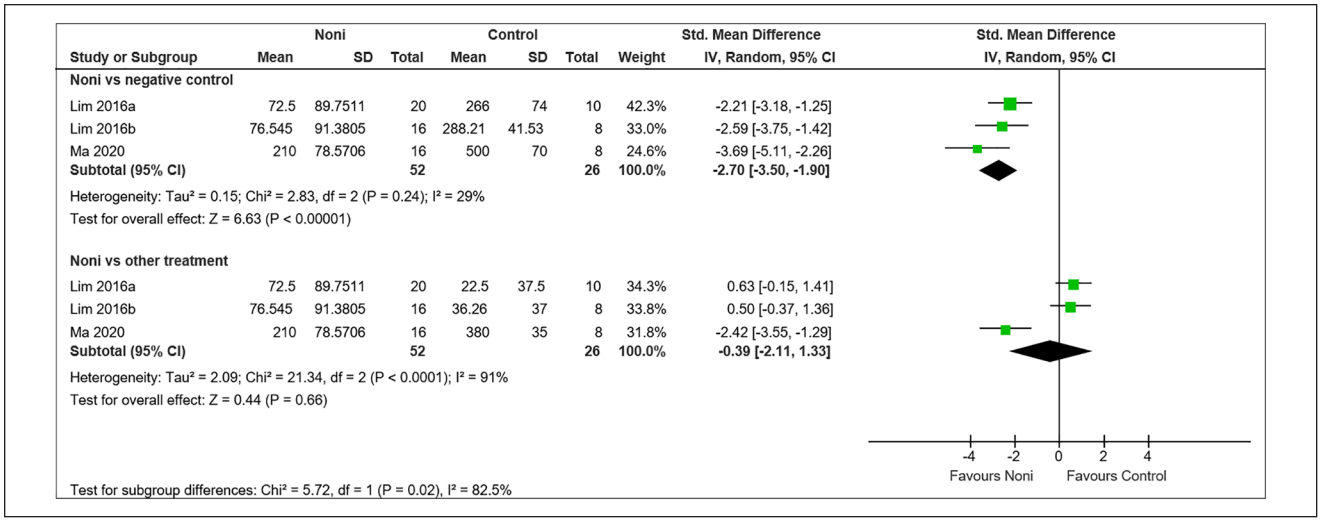

Figure 4. Subgroup analysis on pooled effect size of noni treatment on tumor volume in experimental lung cancer based on comparator (negative control and other treatment).

challenging to apply a blanket rule on *M. citrifolia* induced hepatoxicity based on case reports, unless a bioactive causative phytoconstituent is identified. A Phase 1 clinical study administered escalating doses of 500 mg of dehydrated noni fruit to advanced cancer patients and it was found that the acute toxicity was not dependent on the dose though liver function analysis was not reported in this study.[22] On the other hand, 9 preclinical studies conducted in animals

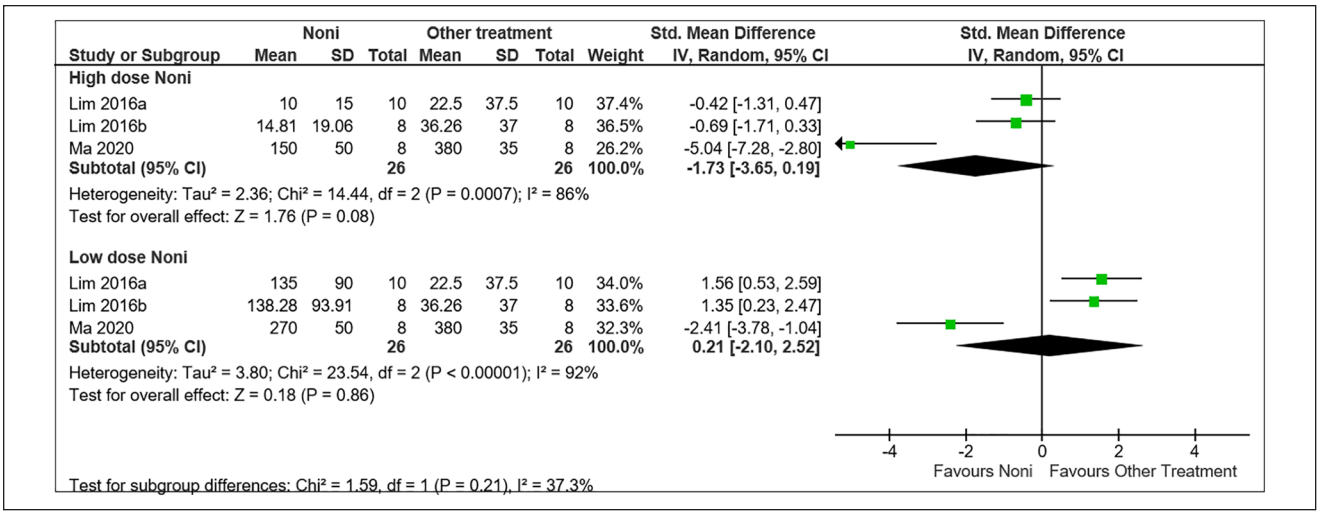

Figure 5. Subgroup analysis of high or low dose noni treatment vs other treatment on tumor volume in experimental lung cancer.

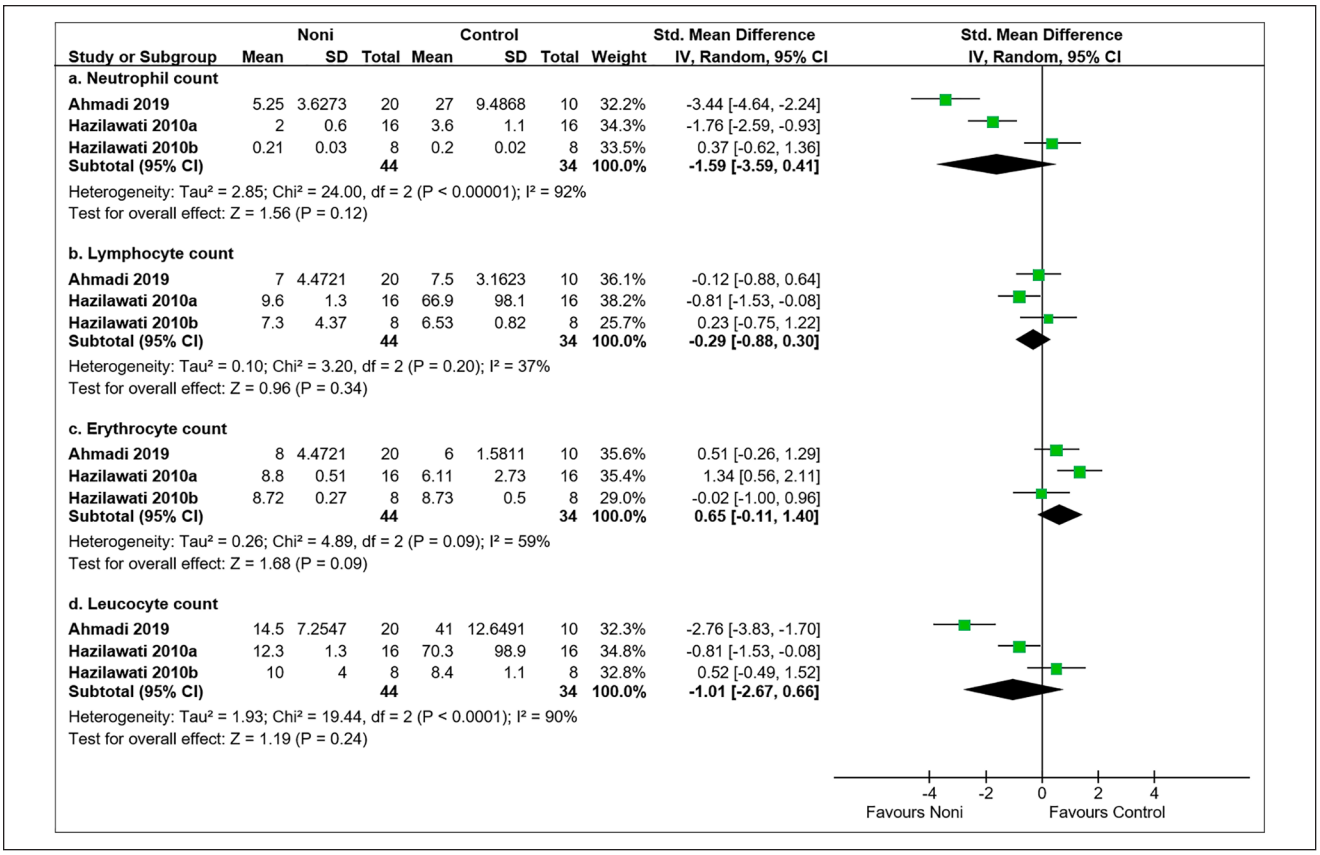

Figure 6. Pooled effect size of noni treatment on (a) neutrophil, (b) lymphocyte, (c) erythrocyte, and (d) leukocyte count in experimental leukemia.

showed normal hematological and biochemical parameters with no signs of mortality and toxicity except for a study by Mohamad Shalan et al[66] which utilized leaf and fruit extract. In fact, a study by Rosly et al[65] which utilized a comparably larger sample size and a higher dose of dried fruit also reported no mortality and liver injuries. Moreover, several safety studies in which the patient (s) consumed Tahitian Noni Juice® also did not report any adverse events.

Table 6. (a) Summary of In Vivo Preclinical Evidence (Plant Extract).

Cancer type	Animal model	Intervention description	Comparator/ combination	Effective dose	Duration	Efficacy summary	Ref
Breast	Swiss albino mice	Fruit juice	Cisplatin hydrochloride[b] 5 mg/kg	0.35 mL/mouse	14 days	• Increased mean survival time and life span • Reduced tumor volume, cell viability and body weight with adjuvant therapy • Myeloprotective and hepatoprotective effect in CP challenged mice	Ali et al[25]
	Female MMTV-*neu* transgenic mice	Fruit juice	UV purified drinking water	10% v/v	Up to 12 months	• Decreased tumor volume • Reduced metastatic progression	Clafshenkel et al[26]
	Female BALB/c mice	Noni juice[a]	Doxorubicin[b] 3 mg/kg	0.5 mL/bw	14 days	• Reduced tumor size and cell proliferation and increased apoptotic activity in individual and combination treatment group	Taşkin et al[32]
	Male Swiss albino mice	Fruit juice	Hydroalcoholic mixture (1:10) and water	100 mg/kg	60 days	• Improved survival rate compared to control group	Torres et al[33]
Lung	Male BALB/c mice	50% ethanol leaf extract	Erlotinib 50 mg/kg	150 mg/kg 300 mg/kg	21 days	• Reduced lung tumor volume significantly than erlotinib • Reduced inflammation in lungs and livers • Induced activation of pro-apoptotic, anti-inflammatory, antioxidant gene expression, and downregulating pro-tumorigenesis genes	Lim et al[27]
	Male BALB/c mice	50% ethanol leaf extract	Erlotinib 50 mg/kg	150 mg/kg 300 mg/kg	21 days	• Decreased lung tumor volume significantly than erlotinib • Extract suppressed of expression of pro-inflammatory gene, enhanced tumor suppressor gene and inhibited tumor growth cellular gene	Lim et al[28]
	Male BALB/c nu/nu mice	Fermented fruit juice	Oxaliplatin 10 mg/kg	0.2 mL/10 g 0.4 mL/10 g	Every other day until Day 46	• Decrease in tumor volume and weight • Inhibition of expression of cell proliferation proteins and anti-apoptotic protein • Enhanced apoptotic protein expression • Inhibition of AKT/NF-κB signaling pathway	Ma et al[29]
	Male and female C57BL/6 mice	Fruit juice	Cisplatin[b] Adriamycin[b] Vincristine[b] Methotrexate[b] 5-Fluorouracil[b]	0.8 mg/mouse	Up to 50 days	• Fruit juice prolonged the life span with concomitant treatment of sub-optimal dose of chemotherapeutic drugs except methotrexate • Stimulated the release of immune mediators from effector cells	Hirazumi and Furusawa[34]
Leukemia	Male Sprague Dawley rats	Dried fruit	Not stated	5000 mg/kg	Unclear	• Lymphocytosis is reduced to normal range • Anemic state is corrected	Hazilawati et al[30]
	Male Sprague Dawley rats	Dried fruit	Not stated	3000 mg/kg	Unclear	• Reduced the incidence of early-stage leukemia	Hazilawati et al[31]
	Male BALB/c mice	50% ethanol leaf extract	ATRA 5 mg/kg	100 mg/kg 200 mg/kg	4 week	• Suppressed growth of leukemic cells, comparable to ATRA • Upregulation of anti-cancer, anti-inflammatory and downregulation of pro-cancer and pro-angiogenic genes, almost similar to ATRA	Ahmadi et al[35]
General cancer pathogenesis	Male and female DBA/2, C57BL/6, BALB/c mice	Fruit juice	13 Chemotherapeutic drugs[b]	0.5 mg/mouse	Prophylactic: 10 days (4-5 injections) Treatment: 5 days (4 injections)	• Fruit juice produced cured rate of 27% to 31% (therapeutic treatment) and 45% to 53% (prophylactic treatment) • Anti-tumor activity abolished with macrophage, T cell, and NK cell inhibitors • Increased survival rate with IFN-ɣ, imexon immunomodulators and several chemotherapeutic drugs (cisplatin, adriamycin, mitomycin-C, bleomycin, etoposide, 5-fluorouracil, vincristine, and campotethecin)	Furusawa et al[36]

(continued)

Table 6. (continued)

Cancer type	Animal model	Intervention description	Comparator/ combination	Effective dose	Duration	Efficacy summary	Ref
	Female C57BL/6J, Nu/B6 nude, beige KO mice	Fruit (fermented exudate)	LPS and PBS	500 μL/ mouse/day	3 days	• Complete tumor rejection in normal C57BL/6J mice, partial tumor rejection in nude mice lacking functional lymphocytes, and no tumor rejection in NK cell deficient beige mice • Tumor rejection in C57BL/6J mice when re-challenged • Increased percentage of innate immune cells (granulocytes and natural killer cells)	Li et al[37]
	Female C57BL/6J mice	Fruit (fermented exudate)	PBS	0.2 mL/mouse	Prevention: 14 days (2 injections) Treatment: 3 days (3 injections)	• fNE rejected tumor challenge (75%) and completely eliminated existing tumor • Butanol fraction of fNE completely rejected tumor challenge and eliminated existing tumor • Ethyl acetate fraction of fNE eradicated 75% of existing tumor	Li et al[38]

Abbreviations: CP: cisplatin; bw: body weight; UV: ultraviolet; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NK: natural killer; IFN-γ: interferon gamma; ATRA: all-trans-retinoic-acid; fNE: fermented noni exudate; LPS: lipopolysaccharide; PBS: phosphate buffered saline.
[a]Plant part used was not reported.
[b]Noni given as combination or adjuvant to conventional treatment.

(b) Summary of In Vivo Preclinical Evidence (Phytochemical).

Cancer type	Animal model	Phytochemical	Comparator	Effective dose	Duration	Efficacy summary	Ref
Breast	Female BALB/c mice	Nordamnacanthal	Not stated	50 mg/kg	24 days	• Reduced tumor volume and weight • Regulated immune markers	Abu et al[24]

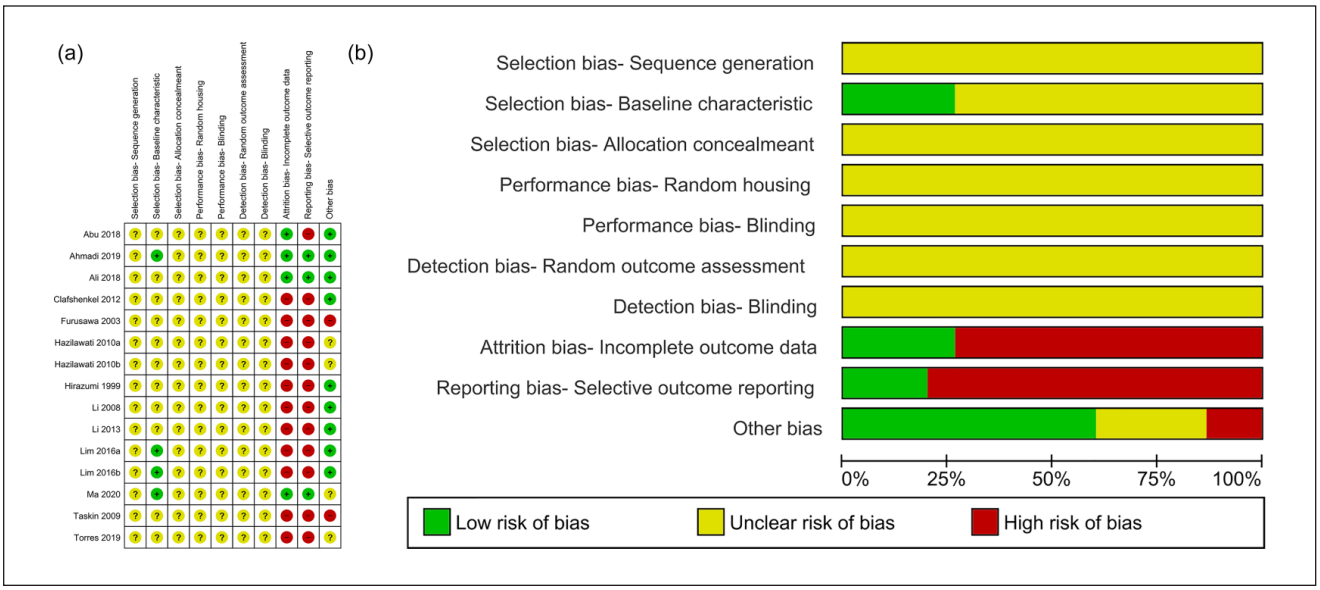

Figure 7. (a) Risk of bias assessment of each included study and (b) risk of bias assessment summary of all studies.

However, these studies were not reported in this review due to the intervention being a mixture of noni, grape and blueberry juice.[77-79] Therefore, to address the uniqueness of herb-based products, regulators often require comprehensive preclinical toxicity data explicit to the product or test items of interest prior to approval for use in humans.[80,81]

Table 7. (a) Summary of In Vitro Preclinical Evidence (Plant Extract).

Cancer type	Cell model	Intervention description	Comparator/ combination	Efficacy summary	Ref
Breast	Human breast tumor explant	Noni juice[a]	Not stated	• Inhibition of capillary growth and degenerate newly formed vessels	Hornick et al[39]
	CYP 2C19 enzymes isolated from human recombinant Sf9 insect cells	Fruit juice	Not stated	• Dose-dependently inhibited CYP 2C19 aromatase enzyme which decreases estrogen production	Palu et al[40]
	MDA-MB-231 human breast cancer carcinoma	Unclear (butanol extract)	LPS	• Induced apoptosis through interaction with TLR4	Parker et al[41]
	• MCF-7 human breast cancer cell MDA-MB-231 human breast cancer carcinoma	Fractionation of 90% ethanolic fruit extract	Paclitaxel (cytotoxicity assay)	• Arrested cell proliferation and cell cycle • Induced apoptosis • Increased caspase activities • Decreased ROS production and mitochondrial membrane potentials	Sharma et al[42]
	MCF-7 human breast cancer cell	95% ethanolic leaf extract	Not stated	• Inhibited cell migration	Boontha et al[43]
	MCF-7 human breast cancer cell	95% ethanolic leaf extract	Not stated	• Suppressed migration of cancer cells	Boontha et al[44]
Lung	• A549 human lung adenocarcinoma cells • LL2 mouse Lewis lung carcinoma cells	50% ethanolic leaf extract	Erlotinib 50 mg/kg	• Extract inhibited cell proliferation and induced apoptosis Induced cell cycle arrest and activated caspase apoptotic activity	Lim et al[28]
	A549 human non-small cell lung cancer (NSCLC)	Fermented fruit juice	Not stated	• Induced apoptosis, inhibited proliferation, invasion, and migration of cells • Downregulated phosphorylation of AKT, p50, and STAT3 protein	Ma et al[29]
	A549 human lung carcinoma cells	Fruit juice	Not stated	• Inhibited the manganese-induced HIF-1α protein expression • Interfered with manganese's signaling to activate PKB, ERK-1/2, JNK-1, and S6 • Repressed the induction of HIF-1α protein by desferoxamine or IL-1β	Jang[45]
	A549 human lung cancer	Dried seeds	Not stated	• Induced intracellular nuclear damage • Induced apoptosis and cell cycle arrest • Accumulation of ROS production and disruption of mitochondrial potential	Rajivgandhi et al[46]
Cervical	Human cervical cancer cell HeLa (HPV18+) SiHa (HPV16+)	Noni juice[a]	Cisplatin[b] 10 μg/mL	• Combination treatment induced cell death • Upregulation of p53 and pro-apoptotic proteins, downregulation of the anti-apoptotic proteins and survivin • Increase in caspase activity	Gupta et al[47]
	Human cervical cancer cell HeLa (HPV18+) SiHa (HPV16+)	Noni juice[a]	Cisplatin[b] 10 μg/mL	• Combination treatment decreased lipid peroxidation and enhanced catalase activity	Gupta and Singh[48]
	Human cervical cancer cell SiHa (HPV16+)	Noni juice[a]	Cisplatin[b] 10 μg/dL	• Enhanced expression of DNA repair genes with noni treatment by itself or combination with cisplatin	Gupta et al[49]
Eye	Y79 retinoblastoma cell	Fruit extract	Not stated	• Apoptotic morphology observed • Modulated caspase activation	Gangadharan et al[50]
Leukemia	Jurkat cells (human T lymphocytes)	50% ethanol leaf extract	Not stated	• Induce apoptosis and cell cycle arrest • Enhanced caspase activities	Ahmadi et al[35]

Abbreviations: CYP2C19: cytochrome P450 2C19; TLR: toll-like receptor; ROS: reactive oxygen species; HIF: hypoxia-inducible factor; AKT/PKB: protein kinase B; ERK: extracellular-regulated protein kinase; JNK: c-Jun N-terminal kinase; IL: interleukin; STAT: signal transducer and activator of transcription.

[a]Plant part used was not reported.

[b]Noni given as combination or adjuvant to conventional treatment.

(b) Summary of In Vitro Preclinical Evidence (Phytochemical).

Cancer type	Cell model	Phytochemical	Comparator/ combination	Efficacy summary	Ref
Breast	• 4T1 mouse breast cancer cell • MCF-7 human breast cancer cell • MDA-MB-231 human breast cancer carcinoma	Nordamnacanthal	Not stated	• Increased population of early apoptotic and late apoptotic cells • Induced cell cycle arrest	Abu et al[24]
	MCF-7 human breast cancer cell	Damnacanthal	Not stated	• Induced apoptosis and stimulate cell cycle arrest • Activation of caspase activity • Enhanced expression of pro-apoptotic genes and proteins	Aziz et al[51]
	MCF-7 human breast cancer cell	Damnacanthal	Doxorubicin[a] (0.2-0.55 μg/mL)	• Induced cell cycle arrest and apoptosis in combination treatment • Upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins in combination treatment	Aziz et al[52]
	MCF-7 human breast cancer cell	Polysaccharides	Not stated	• Induced DNA damage by apoptosis through activation of p53 and caspase-3 proteins	Srinivasahan and Durairaj[53]
Oral	Human oral squamous cell carcinoma (OSCC) • H103, H400, H413, H357, H376, H314	Damnacanthal Nordamnacanthal	Not stated	• Triggered apoptosis • Increase in caspase activities • Induced cell cycle arrest • Disrupted mitochondrial potential	Shaghayegh et al[54]
	Human oral squamous cell carcinoma (OSCC) • H103, H400, H413, H357, H376, H314	Damnacanthal Nordamnacanthal	Not stated	• Reduced cell proliferation • Induced early apoptosis • Inhibited cell migration • Exhibited morphological changes and signs of programed cell death	Shaghayegh et al[55]
Colon	HCT116 human colon carcinoma cell	Anthraquinones	Not stated	• Morindone inhibited polymerase activities and cell growth	Kamiya et al[56]
	Human colon carcinoma cell • HCT-116, SW480, LoVo	Damnacanthal	Not stated	• Inhibited proliferation and induce apoptosis • Induced cell cycle arrest • Enhanced caspase activities	Nualsanit et al[57]
Liver	Hep G2 human hepatocellular carcinoma	Damnacanthal	Not stated	• Affected cell survival • Inhibited growth and clonogenic potential • Induced apoptosis • Inhibited cell migration	García-Vilas et al[58]
Skin	MUM-2B human melanoma cell	Damnacanthal	Not stated	• Inhibited proliferation and increased apoptotic rate • Increased caspase activities • Upregulated pro-apoptotic protein	Zhang et al[59]
Colon, prostate, and breast cancer	• HCT-116 human colon cancer cell • HT-29 human colorectal adenocarcinoma cell • PC-3 human prostate cancer cell • MCF-7 human breast cancer cell	Damnacanthal	Not stated	• Suppression of cell growth • Affected cell cycle regulation	Sukamporn et al[60]
General cancer pathogenesis	K-ras^{ts}-NRK epithelial cell	Damnacanthal	Not stated	• Induced normal morphology and cytoskeletal structure • Inhibition of macromolecule synthesis	Hiramatsu et al[61]
	JB6 mouse epidermal cells	Glycosides	Not stated	• Suppression of TPA- or EGF-induced cell transformation and associated AP-1 activity • Inhibited of TPA- or EGF-induced phosphorylation of c-Jun	Liu et al[62]

Abbreviations: TPA, 12-O-tedtradecanoylphorbol-13-acetate; EGF, epidermal growth factor; AP1, inducible eukaryotic transcription factor.
[a]Noni given as combination or adjuvant to conventional treatment.

Table 8. Summary of Preclinical Evidence (Potential Mechanistic Studies).

Cancer type	Proposed mechanism of action	Intervention (formulation/phytoconstituent)	Study type	
			In vitro	In vivo
Breast	Antitumor	Unclear	√[24]	√[32]
		Fruit juice		√[25,26]
		Nordamnacanthal		√[24]
	Antiproliferative	Unclear	√[42]	√[32]
		Fruit extract	√[51]	√[24]
		Damnacanthal	√[24]	
		Nordamnacanthal		
	Pro-apoptotic	Unclear	√[41]	√[32]
		Fruit extract	√[42]	√[24]
		Damnacanthal	√[51]	
		Nordamnacanthal	√[24]	
		Polysaccharides	√[53]	
	Antimigratory	Leaf extract	√[43,44]	
	Antiangiogenesis	Fruit juice	√[40]	
	Immunomodulatory	Nordamnacanthal	√[24]	√[24]
Lung	Antitumor	Fruit juice	√[29]	√[29,34]
		Leaf extract	√[28]	√[27,28]
	Antiproliferative	Leaf extract	√[28]	√[27,28]
		Dried seed	√[46]	√[29]
		Fruit juice	√[29]	
	Anti-inflammatory	Leaf extract	√[28]	√[27,28]
	Pro-apoptotic	Dried seed	√[46]	√[28]
		Leaf extract	√[28]	√[29]
		Fruit juice	√[29]	
	Antimigratory	Fruit juice	√[29]	√[29]
	Immunomodulatory	Fruit juice		√[34]
Leukemia	Antiproliferative	Dried fruit	√[30]	√[35]
		Leaf extract	√[35]	
	Pro-apoptotic	Leaf extract	√[35]	√[35]
	Anti-inflammatory	Leaf extract	√[35]	√[35]
	Antiangiogenesis	Leaf extract	√[35]	√[35]
Cervical	Antiproliferative	Fruit juice	√[48]	
	Pro-apoptotic	Fruit juice	√[48]	
Eye	Pro-apoptotic	Fruit extract	√[50]	
Oral	Antiproliferative	Damnacanthal	√[55]	
		Nordamnacanthal	√[54,55]	
	Pro-apoptotic	Damnacanthal	√[54,55]	
		Nordamnacanthal	√[54,55]	
	Antimigratory	Damnacanthal	√[55]	
		Nordamnacanthal	√[55]	
Colon	Antiproliferative	Morindone	√[56]	
		Damnacanthal	√[57]	
	Pro-apototic	Damnacanthal	√[57]	
Liver	Antiproliferative	Damnacanthal	√[58]	
	Pro-apoptotic			
	Antimigratory			
Skin	Antiproliferative	Damnacanthal	√[59]	
	Pro-apoptotic			
Colon, prostate, breast	Antiproliferative	Damnacanthal	√[60]	
General cancer pathogenesis	Antitumor	Fruit juice		√[36]
		Fermented fruit exudate		√[37,38]
	Immunomodulatory	Fruit juice		√[36]
		Fermented fruit exudate		√[37]

Numbers in superscript indicate the cited reference.

Table 9. Safety and Toxicity Assessment of *Morinda citrifolia*.

Type of safety study	Animal/cell model	Duration	Intervention description	Dose	Safety summary	Ref
Animal toxicity						
General safety	Female Sprague Dawley rats	28 week	Fruit juice	10% of 5 mL/rat/day	Decreased lipid peroxidation, increased catalase and SOD activity, normal hematological parameter, liver, and kidney function test.	Saminathan et al[63]
Subchronic toxicity						
Oral toxicity	Male and female Sprague Dawley rats	90 days	Fruit extract	1.72 g/kg bw 3.43 g/kg bw 6.86 g/kg bw	No histopathological, haematological, and biochemical profile changes. NOAEL was established as greater than 6.86 g/kg bw.	West et al[64]
	Male and female Sprague Dawley rats	13 week	Dried fruit	2000 mg/kg bw/day 5000 mg/kg bw/day	No significant differences in hematological and biochemical parameters. NOAEL was determined to be greater than 500 mg/kg bw/day.	Rosly et al[65]
	Male BALB/c mice	28 days	Nordamnacanthal	10 mg/kg/day 50 mg/kg/day	No mortality and sign of toxicity. No changes in liver profile.	Abu et al[24]
Chronic toxicity						
Oral toxicity	Female ICR mice	6 month	Leaf and fruit extract	1 mg/mL 2 mg/mL	No signs of toxicity or death in animals treated with leaf extract. Low dose fruit extract showed low toxicity, high dose resulted in toxicity, 40% mortality and liver injury.	Mohamad Shalan et al[66]
Cell toxicity						
Genotoxicity	Human lymphocytes	3 h	Fruit juice	3.1-100 mg/mL	Not genotoxic but displays cytotoxicity at highest concentration.	Ratanavalachai et al[67]
Mutagenicity	*Salmonella typhimurium*	2 days	Acetone leave extract	0.8-3.2 µg/plate	Exhibit strong inhibition of the revertant colony, thereby display antimutagenicity potential.	Nuntatovattana and Tongyonk[68]
Clastogenicity	Male ICR mice	2 week	Leaves Fruit juice Fruit powder	12.5% and 25% 10 and 20 mL/kg 100 and 500 mg/kg	Leaves inhibited formation of micronucleus in peripheral blood induced by MMC and DMBA effectively compared to fruit juice and powder.	Kupradinun et al[69]
Cytogenotoxicity	Human lymphocytes	3 h	Aqueous leave extract	0.8-50 mg/mL	Not genotoxic but displays cytotoxicity at highest concentration.	Ratanavalachai et al[70]
	Male and female Wistar albino rats	3 days	Aqueous fruit extract	2.5-10 mg/kg	Induced genotoxicity in white blood cells, cytotoxicity and mutagenicity in liver and kidney cells; in dose dependent manner.	de Moraes et al[71]
Hepatotoxicity	HepG2 liver cells	48 h	Fruit extract	150 µg/mL	No inhibition of cell growth. Neutral lipid accumulation and phospholipidosis was not induced.	West et al[64]

Abbreviations: SOD, superoxide dismutase; NOAEL, no-observed-adverse-effect-level; bw, body weight; MMC, mitomycin C; DMBA, 7,12-dimethylbenz[a]anthracene.

The present review had identified an additional 22 studies as compared to a previous review by Brown.[14] In addition, our review paper enabled better translation of anticancer efficacy of *M. citrifolia* due to excluding studies that solely reported on in vitro cytotoxicity results without further exploration of other anticancer mechanisms or activities. From our findings, it can be observed that new preclinical studies have been consistently conducted on *M. citrifolia*, which remains a popular medicinal plant investigated for cancer. Although the anticancer properties of *M. citrifolia* were substantially studied in preclinical studies, it is vaguely translated into clinical trials as only a single Phase 1 study, conducted more than a decade ago, was identified.[22] There may be many reasons that could have contributed toward the slow progress made toward human clinical trials such as a lack of funding, scarcity of sufficient data on safety and efficacy, challenges in consistent raw material sourcing, among others. The assessment on reporting quality of included preclinical studies performed in this review raises significant concerns on the current reporting quality of published animal studies on this topic. As the translation to clinical research will depend on the quality of preclinical data available, there is a need to improve the awareness of guidelines on the internal validity of individual animal experiments, good reporting practices, as well as the potential risk of bias concerning animal studies among researchers.[20,82]

This review included English papers hence evidence from other languages may be excluded. Although we attempted to pool a few studies for quantitative analyses, the high heterogeneity and small number of studies suited for meta-analysis are inherent limitations of this review. Further improvements in study design such as baseline characteristics (ie, age, body weight, environmental factors), comparator group, and treatment duration should be considered to achieve homogeneity in order to reach a conclusive data. The purpose of excluding herbal products containing a mixture of *M. citrifolia* with other active herbal ingredients was to eliminate confounding factors, which resulted in the exclusion of several clinical and preclinical papers that reported on Tahitian Noni Juice®, which is made up of a combination of noni, grape, and blueberry juices.[77-79] To enable a better understanding of the role of *M. citrifolia* in mixtures, future reviews can be conducted to assess the safety, herb-herb, and herb-drug interactions data available for *M. citrifolia*.

Conclusion

Based on currently available clinical and preclinical efficacy evidence, it is apparent that noni is a potentially valuable medicinal plant in the treatment of cancer. The anticancer activities of *M. citrifolia* is evidently shown in breast and lung cancer models in which the tumor volume is significantly decreased through apoptosis as well as disruption in cell migration and proliferation pathways. Although several hepatotoxicity cases were reported, there is insufficient evidence to adequately assess the causality of Noni as the causative agent. More well-designed and reported preclinical efficacy and safety studies are needed to allow for better translation into future clinical studies.

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Author Contributions

The first 2 authors contributed equally to this work. All authors provided critical feedback and helped shape the final version of the manuscript for publication.

Data Availability Statement

The authors declare that (the/all other) data supporting the findings of this study are available within the article (and its supplementary information files).

Declaration of Conflicting Interests

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Supplemental Material

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