



An evidence-based review of *Morinda citrifolia* L. (Rubiaceae) fruits on animal models, human studies, and case reports

[Una revisión basada en la evidencia de los frutos de *Morinda citrifolia* L. (Rubiaceae) en modelos animales, estudios en humanos e informes de casos]

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Abstract

Context: *Morinda citrifolia* L. (Rubiaceae), commonly known as noni, is widely used as a complementary and alternative therapy in many countries due to its numerous beneficial effects on health.

Aims: To thoroughly analyze the efficacy and safety of *M. citrifolia* fruit across all reported areas.

Methods: The articles were explored on the PubMed and Cochrane Library databases using a combination of keywords: *Morinda citrifolia* AND human studies; *Morinda citrifolia* AND pharmacological activities using PRISMA guidelines.

Results: Studies in animal models revealed its activity as anti-dyslipidemia, anti-lipogenesis, anti-fungal, hepatoprotective, hypotensive, immunostimulatory, anti-alopecia, photoprotective, antitumor, antiviral, anticancer, antidopaminergic, and antimicrobial. Based on the clinical and efficacy evidence, it is apparent that *M. citrifolia* is a potentially valuable medicinal plant whose status should be upgraded from laboratory bench to bedside. The safety of *M. citrifolia* has been confirmed and proven by no occurrence of AEs or only mild gastrointestinal discomforts. However, five cases of male and female patients aged from 14 to 63 years old reported different symptoms, such as fatigue, headache, vomiting, pigmentation, or acute hepatitis, after a high-dose daily use of this supplement.

Conclusions: Taking everything into consideration, *M. citrifolia*, despite its mild adverse events, has a beneficial efficacy and safety as an antioxidant; nevertheless, caution and therapy drug monitoring is required if this plant is to be taken in a long-term period.

Keywords: adjunctive therapy; antioxidants; *Morinda citrifolia*; noni fruit; plant-based therapy.

Resumen

Contexto: La *Morinda citrifolia* L. (Rubiaceae), comúnmente conocida como noni, se utiliza ampliamente como terapia complementaria y alternativa en muchos países debido a sus numerosos efectos beneficiosos para la salud.

Objetivos: Analizar exhaustivamente la eficacia y seguridad del fruto de *M. citrifolia* en todas las áreas reportadas.

Métodos: Los artículos se exploraron en las bases de datos PubMed y Cochrane Library utilizando una combinación de palabras clave: *Morinda citrifolia* AND human studies; *Morinda citrifolia* AND pharmacological activities utilizando las guías de PRISMA.

Resultados: Los estudios en modelos animales revelaron su actividad como antidislipidémica, antilipogénica, antifúngica, hepatoprotectora, hipotensora, inmunoestimuladora, antialopecia, fotoprotectora, antitumoral, antiviral, anticancerígena, antidopaminérgica y antimicrobiana. Basándose en las pruebas clínicas y de eficacia, es evidente que la *M. citrifolia* es una planta medicinal potencialmente valiosa cuyo estatus debería elevarse de la mesa de laboratorio a la cabecera del enfermo. La inocuidad de la *M. citrifolia* ha sido confirmada y demostrada por la ausencia de EA o por la aparición de molestias gastrointestinales leves. Sin embargo, cinco casos de pacientes de ambos sexos con edades comprendidas entre los 14 y los 63 años informaron de diferentes síntomas, como fatiga, dolor de cabeza, vómitos, pigmentación o hepatitis aguda, tras el uso diario de este suplemento en dosis altas.

Conclusiones: Tomando todo en consideración, la *M. citrifolia*, a pesar de sus leves efectos adversos, tiene una eficacia y seguridad beneficiosas como antioxidante; no obstante, se requiere precaución y seguimiento farmacológico de la terapia si se va a tomar esta planta a largo plazo.

Palabras Clave: antioxidantes; fruto del noni; *Morinda citrifolia*; terapia basada en plantas; terapia coadyuvante.

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INTRODUCTION

The fruits of *Morinda citrifolia* L. of the *Rubiaceae* family, consumed as fresh juice, have been broadly studied since 1999 (Hirazumi and Furusawa, 1999). Commonly, the fresh juice of *M. citrifolia* fruit is prepared by fermenting the fruit in sealed bottles for weeks at room temperature or boiling the fruit for hours. The major phytoconstituents in the fermented fruit were phenolics, anthraquinones, and flavonoids (Motshakeri and Ghazali, 2015), such as scopoletin (coumarins), quercetin (flavonoids), naringenin (flavonoids), and ursolic acid (terpenes) (Haiqing et al., 2008; Mohd et al., 2007), and phenolic acids such as gentisic acid, *p*-hydroxybenzoic acid, and chlorogenic acid (Lin et al., 2013), as depicted in Fig. 1.

The juice of the ripe fruit, which possesses an unpleasant odor (due to the presence of sulfur compounds) and bitter taste, has been reported for its total polyphenols, ester compounds, carbohydrates, proteins, minerals, vitamins, and fat content (Ali et al., 2016). Another study described that the secondary metabolites of the fruits, both in the fresh and fermented preparation, were glycosides, polyphenols, and alkaloids, which contributed to the antibacterial and antioxidant activity (Sina et al., 2021). The fruit juice was reported could enhance neural-immune interactions and cell survival pathways and inhibit inflammatory processes. Moreover, old rats treated

with the fruit juice of *M. citrifolia* revealed an increase in lymphoproliferation, interleukin-2, and interferon- γ production, and a decrease in interleukin-6 production, lipid peroxidation, protein carbonyl formation, and the expression of *I*kappa B- α and p-NF-*kappa* B (p50) in the splenocytes (Pratap et al., 2017).

There have been many review articles on *M. citrifolia* (Abou et al., 2017; Ali et al., 2016; Chanthira et al., 2022; Pawlus and Kinghorn, 2010; Saminathan et al., 2013; Wang et al., 2002a; 202b), indicating the importance of this plant. These review articles mostly discussed the effect of fruit extracts on animal models or cell lines. However, very few articles appraised its studies in humans, and none reviewed the case reports.

Studies in humans, in essence, assure the efficacy, safety, and description of the side effects that frequently occur in humans as a result of drug delivery (Mukherjee et al., 2022). Not all herbal treatments describe the potential for adverse effects. Therefore, this evidence-based review aims to provide insights for clinicians on the efficacy, safety, outcomes, and benefits of using *M. citrifolia* in humans, including case reports, and to upgrade its status from laboratory bench to bedside. In addition, the present study intends to prove the effective dose of *M. citrifolia* for health supplement products as a single component and/or in combination with other plants.

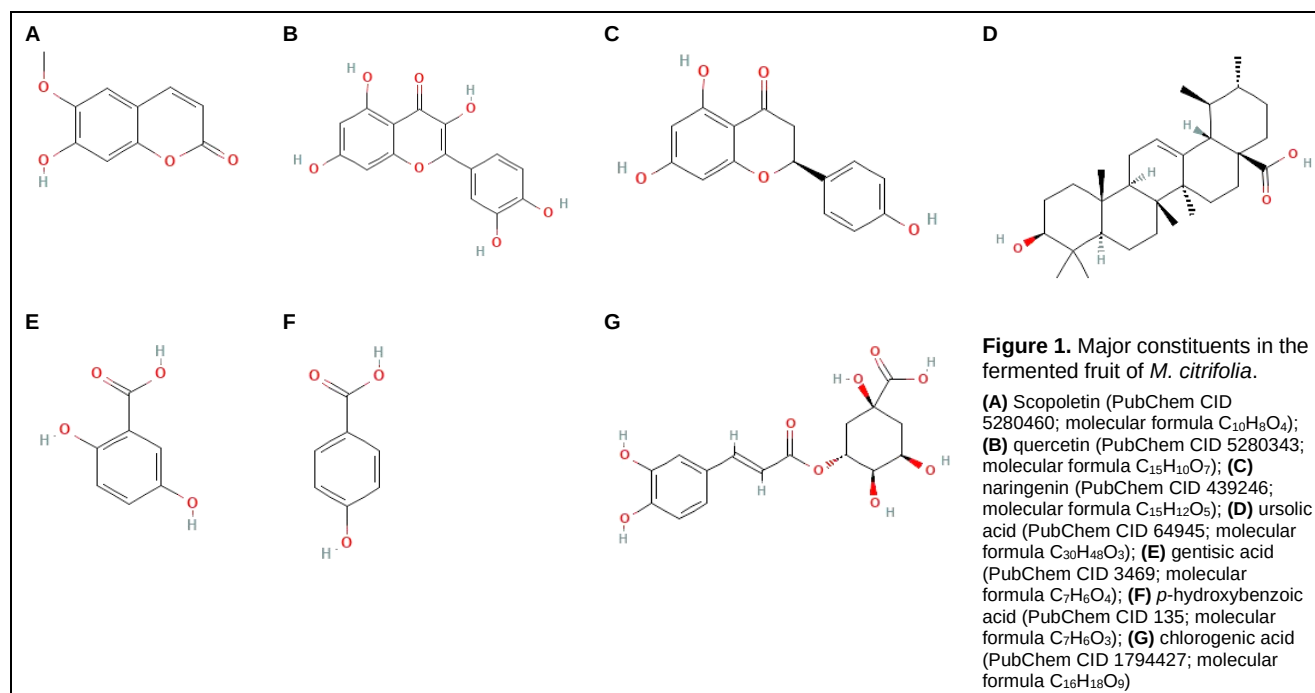


Table 1. Keywords and results of searches conducted in each database.

Database	Keyword(s)	Item(s) searched
PubMed	“ <i>Morinda citrifolia</i> AND studies in humans”	210
	“ <i>Morinda citrifolia</i> AND pharmacological activity”	345
Cochrane Library	“ <i>Morinda citrifolia</i> AND studies in humans”	18

MATERIAL AND METHODS

For this review, the PRISMA guidelines were followed (Page et al., 2021).

Eligibility and exclusion criteria (PICOS)

All studies investigating pharmacological activity (*in vivo* and *in vitro*), plant-based medications, clinical efficacy, safety, and case studies in healthy and diseased persons were included. All studies were included regardless of comparison/control group type. Plant parts, solvents, study design, dose and concentration ranges, changes in disease severity, physiological parameters, subjective symptoms, and reported quality of life were all considered in the study. During the article selection process, no language limits were imposed. The following list highlights the PICOS criteria (Eriksen and Frandsen, 2018) used for study inclusion and exclusion in the current review:

- **P (Population):** Animal models, cell models or assays in efficacy studies, studies in healthy subjects, or patients diagnosed with disease.
- **I (Intervention):** Any plant part of *M. citrifolia* as a single herb or in combination with other plants.
- **C (Comparison):** any comparison (no treatment/placebo control, usual care, alternative treatment, or no control).
- **O (Outcome):** pharmacological activity and mechanisms of action, safety (adverse reactions, toxicity), any changes in the severity of the disease, physiological parameters, subjective symptoms, and reported quality of life.
- **S (Study Design):** any form of research design.

Information sources

The databases via PubMed and the Cochrane Library were systematically searched for relevant studies investigating the pharmacological activity (*in vivo* and *in vitro* studies), plant-based medications, clinical studies (safety and case studies) of *M. citrifolia* in various types of animals, healthy subjects, and in patients with a diagnosed disease.

Search strategy

Database searches were limited to free full-text articles, trials, and publications of the last 13 years (2010 to 2023). The following search strategy was employed, as seen in Table 1. An additional search was conducted on Google without restricting the year of publication when required.

Study selection and data collection process

Two authors worked independently on study screening and selection to identify all relevant studies, such as title, abstract screening, and full-text papers. The titles and the abstracts of the articles were further screened for their relevance to the topic of this study. Additional relevant studies were obtained from the citations in the selected articles and case reports. Disagreements were then discussed until a consensus was found. A flowchart (Fig. 2) detailed the research selection and data collection process. Data from included articles were manually retrieved, compiled in tables, and critically appraised. Table 2 depicts the inclusion and exclusion criteria used to choose studies, the research questions, and PICO aspects. When data went missing, writers were contacted by e-mail in order to recover critical information.

Data items

The following data items extracted were retrieved from the included reviews: characteristics of the study population and intervention, comparison type and assessed outcomes, study design, overall results, and the authors' conclusions.

Risk of bias in studies

Risk of bias in studies may occur due to different study designs, different aspects of trial design, conduct, reports, and incomplete data (Page et al., 2019).

Summary of measures and synthesis of results

Results were summarized in three tables: Table 3 tabulates the *in vivo* study of the pharmacology activities of *M. citrifolia*, and Tables 4 and 5 present information on human studies of *M. citrifolia* fruits and the most relevant case reports on the use of *M. citrifolia* as a supplement. The collected evidence was then discussed to arrive at a critical qualitative synthesis.

RESULTS

Summary of findings

A total of 573 articles were identified based on the search criteria described in the methodology. Upon removal of duplicates and record screening by the

abstract and title, 537 records were excluded. Of the 30 full-text articles that were screened for eligibility, 4 records were excluded because of different plant species. A final count of 26 papers met all the inclusion criteria and hence were included for analysis. Fig. 2 depicts the selection and data collection process.

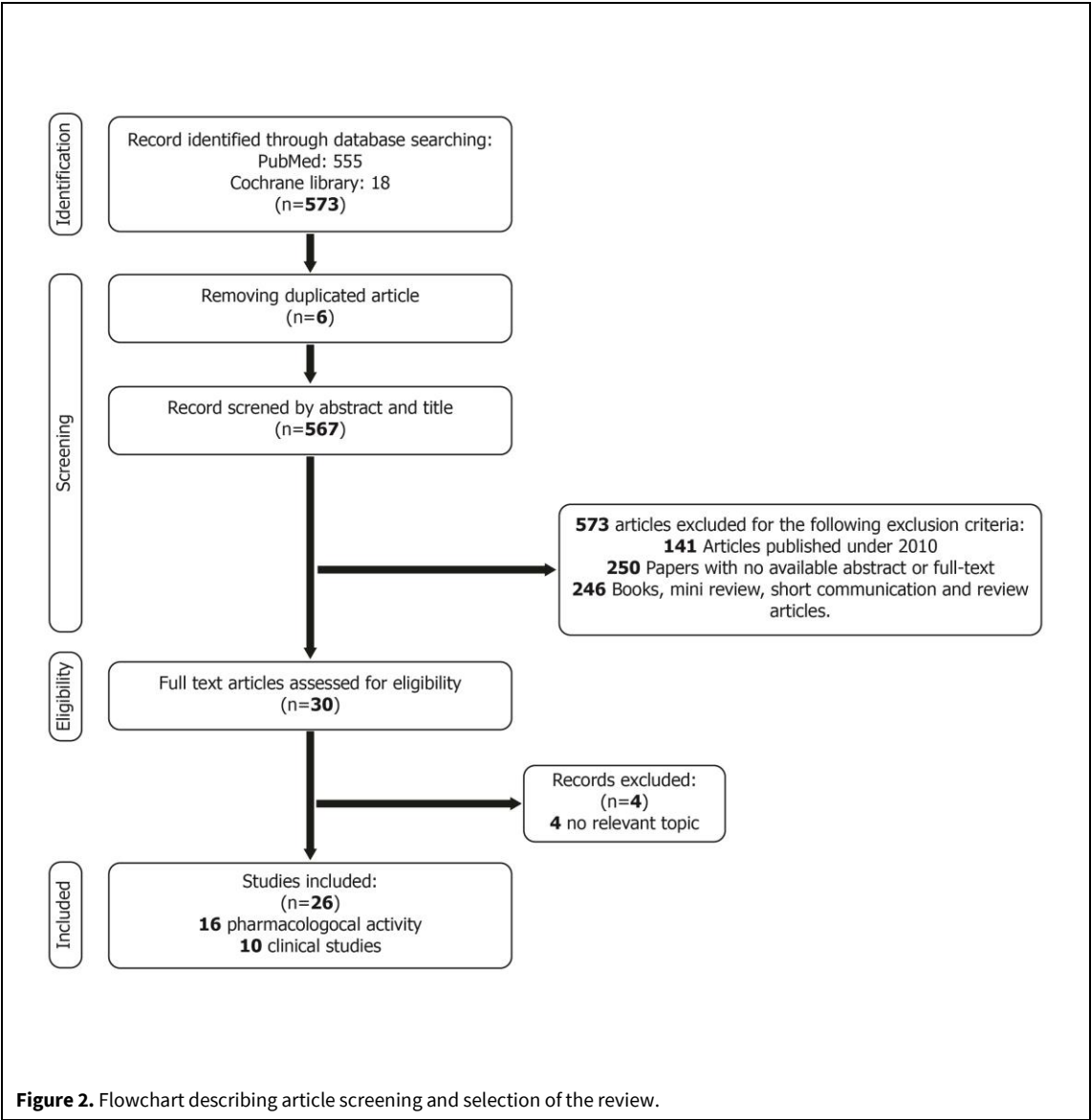


Table 2. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Plant-based drugs, <i>in vivo</i> and <i>in vitro</i> studies, and randomized control trials or human studies	1. <i>In silico</i> studies, non-plant-based
2. Papers published with title, abstract and full text	2. Papers with no available abstract or full-text
	3. Books, mini-reviews, short communication, and review articles
	4. Non-English articles
	5. Articles published under 2010

Table 3. *In vivo* study of pharmacology activities of *M. citrifolia*.

Name and origin of the <i>M. citrifolia</i> (Reference)	Part of the plant and solvent used for extraction	Type of study and statistical analysis	Pharmacology activity	Range of dose or concentration	Control used	Results
<i>M. citrifolia</i> fruit juice (NFJ) was supplied by Divine Noni Gold (Batch No. 44141), Chennai, India. (Pratap et al., 2017)	Fruit juice using water as the solvent.	<i>In vivo</i> on young and old male F344 rats. Statistical analysis was not described.	Immunostimulatory	NFJ 5%, 10%, and 20% per oral twice daily for 60 days.	Not described.	<i>In vitro</i> NFJ incubation of splenic lymphocytes increased Con A-induced lymphocyte proliferation, IL-2 and IFN- γ production, and expression of p-ERK, p-Akt, and p-CREB in young and old rats.
		<i>In vitro</i> on the splenocytes isolated from young and old F344 rats. Statistical analysis was not described.		0.0001–1% concentrations of NFJ for a period of 24 h.	Not described.	<i>In vivo</i> treatment of old rats with NFJ increased lymphoproliferation, IL-2 and IFN- γ production, the expression of p-TH, NGF, and NO production, and suppressed IL-6 production, lipid peroxidation, protein carbonyl formation, and the expression of I κ B- α and p-NF- κ B (p50) in the splenocytes.
<i>M. citrifolia</i> fruit juice was supplied by Alwa's Ayurvedic Pharmacy, Moodbidre, and Mangalore, India. (13.0614407,74.9767726) (Shoeb et al., 2016)	Fruit juice using water as the solvent.	<i>In vivo</i> on male Wistar albino rats (n = 40). The data were presented as mean $\pm$ standard error of the mean (SEM), and were analyzed using one-way ANOVA followed by Tukey's post-hoc test. The p<0.05 was considered as statistically significant.	Anti-dyslipidemia	50 and 100 mg/kg BW with a duration of 31 days.	Atorvastatin 10 mg/kg BW was given as a suspension in 0.1% w/v Tween-80.	The total cholesterol, triglyceride, and VLDL-cholesterol levels significantly decreased in rats treated with both doses of extract (p<0.05). A decrease of LDL-cholesterol levels in rats treated with a dose of 100 mg/kg.
Fruits of <i>M. citrifolia</i> were individually selected and harvested in the municipality of Campo Grande, Mato Grosso do Sul, Brazil. (20°27'04.5" S and 54°36'04.3" W) (Inada et al., 2020)	<i>M. citrifolia</i> fruits were extracted with 400 mL of deionized water (AE) for 3 days and continued with fractionation in 1.5 mL cryogenic tubes. They were maintained at -80°C to avoid oxidation.	<i>In vivo</i> on Swiss adult male mice (n = 42). The data were expressed as the mean $\pm$ standard error of the mean (SEM), and the differences were determined using Student's unpaired <i>t</i> -test for independent samples or ANOVA, followed by Tukey's post-test (for one-way ANOVA) or Bonferroni's post-test (for two-way ANOVA), to compare more than two groups, using GraphPad Prism, version 8.3.0. Differences were considered statistically significant when p $\leq$ 0.05.	Anti-lipogenesis	250 and 500 mg/kg BW with a duration of 16 days.	Not described.	Seventeen metabolites were identified in the fraction, including iridoids, noniosides, and rutin. The dose of AE 500 mg/kg BW could improve glucose tolerance; however, neither dose had effects on the other metabolic and histological parameters. The dose of AE 500 mg/kg BW could downregulate the PPAR- α , PPAR- γ , SREBP-1c, and fetuin-A mRNA in the liver and upregulated the PPAR- α mRNA in white adipose tissue.

Table 3. *In vivo* study of pharmacology activities of *M. citrifolia* (continued...)

Name and origin of the <i>M. citrifolia</i> (Reference)	Part of the plant and solvent used for extraction	Type of study and statistical analysis	Pharmacology activity	Range of dose or concentration	Control used	Results
Ripe fruits of <i>M. citrifolia</i> were collected in Madurai, a city in the southern part of Tamil Nadu, India. (9.9179737,77.9751613) (Barani et al., 2014)	Not described.	<i>In vitro</i> on <i>Candida albicans</i> using the disk diffusion method on MHA medium. Data were analyzed using an independent t-test. The level of significance was set at 0.05.	Anti-fungal	1000, 500, 250, 100 µg/mL with a duration of 24 hours.	Amphotericin B (10 µg/disc).	<i>M. citrifolia</i> extract at 1000 µg/mL effectively inhibited the growth of <i>C. albicans</i> (16.6 ± 0.3) (p<0.05) compared to the positive control- amphotericin B (20.6 ± 0.6).
<i>M. citrifolia</i> leaves were collected in Bukit Expo, Universiti Putra Malaysia. (2.9868698,101.7080204) (Chong et al., 2019)	The leaves were extracted with 70% ethanol.	<i>In vivo</i> on female Sprague Dawley rats (n = 38). The data were presented as mean ± standard error (SEM). Statistical significance level was set as p<0.05, and was analyzed using one-way ANOVA followed by post hoc Tukey.	Hepatoprotective	500, 1000 mg/kg BW with a duration of three months.	Simvastatin 10 mg/kg BW was given as a suspension in tap water.	The leaf extract prevented hepatic steatosis by significantly increasing (p<0.05) the liver antioxidant enzyme SOD and GPx, significantly increasing (p<0.05) ALP, decreasing liver lipids infiltration, preventing mitochondrial damage, and overall maintaining the normal liver histology and ultrastructure.
<i>M. citrifolia</i> leaves and fruits were collected in Sendangguwo, Semarang, Central Java, Indonesia. (7.0245522,110.3346619) (Wigati et al., 2017)	The leaves and fruits were extracted with 96% ethanol.	<i>In vivo</i> on rats (n = 30) The data were analyzed by one-way analysis of variance and descriptive analysis.	Hypotensive	500 mg/kg BW with a duration of 14 days.	Captopril 10 mg/kg BW.	The leaf extract, the fruit extract, and its combination significantly decreased the blood pressure of hypertensive rats by 16.71 ± 3.95%, diastolic pressure by 21.49 ± 7.90%, and mean arterial blood pressure by 19.58 ± 6.35%.
<i>M. citrifolia</i> (Nonitri®) and β-glucan were provided by COSMAXNBT Inc. Korea. (37.4046237,127.0993002) (Kim et al., 2022)	The fruits were extracted with 10% ethanol at 80°C for 4 h.	<i>In vivo</i> on male C57BL/6 mice (n = 45). Data were expressed as the mean ± standard error. A p<0.05 was considered statistically significant.	Immunostimulator	50 and 200 mg/kg BW with a duration of 30 days.	Polymyxin B 40 µg/mL diluted with DMSO in the culture medium.	The ethanolic extract significantly increased the population of NK cells among these numerous types of immune cells (including Tc (cytotoxic T cells), Th (T helper cells), NK, and dendritic cells, as well as macrophages).
		<i>In vitro</i> on RAW264.7 cells, YAC-1 cells, and T-cell lymphoma. Data were expressed as the mean ± standard error. A p<0.05 was considered statistically significant.		50 and 200 g/mL with a duration of 24 hours.	β-glucan 50 g/mL diluted with DMSO in the culture medium.	Western blot analysis showed that the extract enhanced the phosphorylation levels of nuclear factor (NF)- <i>kappa</i> B and activator protein (AP)-1 subunits in RAW264.7 cells. The extract increased the population of splenic NK cells and subsequent upregulation of its cytotoxic activity.
Ripe fruits of <i>M. citrifolia</i> were collected in Lampung, Indonesia. (4.9421449,103.5720907) (Susanti et al., 2022)	The fruits were extracted with 96% ethanol at room temperature and then fractionated: water, ethyl acetate, and n-hexane.	<i>In vivo</i> on male white rabbits (n = 18). Statistical analysis was not described.	Anti-alopecia	5%, 15%, and 25% with a duration of 21 days.	Minoxidil Dosage not described.	The fractions could potentially act as anti-alopecia with high follicle density and increased anagen phase. The ethyl acetate fraction showed large numbers of anagen follicles with an anagen/telogen (A/T) ratio of 1.64/1 compared to the vehicle group of 1/1.50 and Minoxidil control of 1.39/1.

Table 3. *In vivo* study of pharmacology activities of *M. citrifolia* (continued...)

Name and origin of the <i>M. citrifolia</i> (Reference)	Part of the plant and solvent used for extraction	Type of study and statistical analysis	Pharmacology activity	Range of dose or concentration	Control used	Results
<i>M. citrifolia</i> leaves were collected in Sao Cristovao, Sergipe, Brazil. (10°18'20.7" S; 36°39'7.2" W) (Serafini et al., 2014)	The extract was prepared by boiling dry leaves in distilled water (7,5% w/v) for 15 minutes.	<i>In vivo</i> on male CF1 mice (n = 50) Data were expressed as mean ± standard error of the mean (SEM) or ± standard deviation (SD) and were analyzed using one-way ANOVA followed by Tukey's post-hoc test. Data analyses were performed using the GraphPad Prism 5.0 software. A p<0.05 was considered statistically significant.	Photoprotective	10%, 15% w/w with a duration of 7 days of study.	Not described	The <i>M. citrifolia</i> leaf extract formulations protected the skin against UV-induced damage.
<i>M. citrifolia</i> leaves were collected from Kg. Tanjung Keramat, Langkap, Perak, Malaysia. (4.1249005,101.1430965) (Abu et al., 2018)	Nordamnacanthal was isolated from the root of <i>M. citrifolia</i> by solvent fractionation.	<i>In vivo</i> on 4T1-bearing BALB/c mice (n = 12). Data were expressed as mean ± standard deviation (SD) and were analyzed using one-way ANOVA followed by Duncan post-hoc test.	Antitumor	50 mg/kg BW with a duration of 28 days.	Not described	50 mg/kg BW of nordamnacanthal successfully delayed the progression of 4T1 tumors in Balb/C mice after 28 days of treatment. Treatment with nordamnacanthal increased tumor immunity as evidenced by the immunophenotyping of the spleen and YAC-1 cytotoxicity assays.
		<i>In vitro</i> on MCF-7 and MDA-MB231 cells Data were expressed as mean ± standard deviation (SD) and were analyzed using one-way ANOVA followed by Duncan post-hoc test.	Anticancer	MTT assay: 30 µg/mL to 3.75 µg/mL Flow cytometry analyses of cell death (cell cycle and Annexin V): 10 µg/mL for 48 h.	Not described	Nordamnacanthal induced cell death in MDA-MB231 and MCF-7 cell lines
The fresh unripe fruit <i>M. citrifolia</i> was collected in Malacca, Malaysia. (2.2375482,102.1691004) (Pandy et al., 2017)	The fruits were extracted with methanol.	<i>In vivo</i> on male ICR mice (n = 42). Data were expressed as mean ± standard error of the mean (SEM) and were analyzed using one-way ANOVA followed by post hoc comparison using Tukey's multiple comparison test. Stereotyped behavior was analyzed by the Kruskal-Wallis test followed by Dunn's multiple comparison tests because nonparametric statistics are needed with all or none or rating scale scores. All data analyses were conducted using GraphPad Prism 5 statistical software. A p<0.05 was considered statistically significant.	Anti-dopaminergic	5, 10, 25, 50, 100 mg/kg BW with a duration of 15 days.	Apomorphine 5 mg/kg BW was given with normal saline containing sodium metabisulphite 0.125% w/v, or methamphetamine injection 5 mg/kg BW with normal sterile saline.	Low dose (25 mg/kg BW) significantly attenuated the apomorphine-induced climbing time and climbing behavior in mice. Dose of 5 and 10 mg/kg BW significantly inhibited methamphetamine-induced stereotyped behavior in mice.

Table 3. *In vivo* study of pharmacology activities of *M. citrifolia* (continued...)

Name and origin of the <i>M. citrifolia</i> (Reference)	Part of the plant and solvent used for extraction	Type of study and statistical analysis	Pharmacology activity	Range of dose or concentration	Control used	Results
<i>M. citrifolia</i> leaves were collected in Okinawa Prefecture, Japan. (24.663741,107.5234162) (Ratnogliik et al., 2014)	The leaves were extracted with methanol at room temperature and then fractionated: water, ethyl acetate, and n-hexane.	<i>In vitro</i> on HCV cells. Data were expressed as mean $\pm$ standard error of the mean (SEM). Statistical significance was evaluated by Student's t-test. A $p < 0.05$ was considered statistically significant.	Antiviral	100, 30, 10, 3, and 1 $\mu\text{g/mL}$ with a duration of 2 days.	Not described	The methanol extract, n-hexane fraction, and ethyl acetate fraction had anti-HCV activity with IC_{50} values of 20.6, 6.1, and 6.6 $\mu\text{g/mL}$, respectively. In the methanol extract, two metabolites, pheophorbide a and pyropheophorbide a, were identified as having anti-HCV activity with IC_{50} values of 0.3, and 0.2 $\mu\text{g/mL}$, respectively. The CC_{50} of pheophorbide a and pyropheophorbide a were 10.0 and 7.2 $\mu\text{g/mL}$, respectively, their selectivity indexes (SI) being 33 and 36, respectively.
The fruits of <i>M. citrifolia</i> were collected in the campus of the State University of Santa Cruz, Bahia, Brazil. (24.1168996,105.9733891) (Candida et al., 2014)	The fruits were extracted with 70% ethanol.	<i>In vitro</i> on B16-F10 cells. The data were presented as mean $\pm$ standard deviation (SD) and were analyzed using one-way ANOVA followed by the Student–Newman–Keuls Multiple Range Test. GraphPad Prism v.3.0 software was used. A $p < 0.05$ was considered statistically significant.	Antitumor	1-80 mg/mL with a duration of 8 days.	Not described	The ethanol extract (10 mg/mL) decreased cellular activity and inhibited 45% of the rate of cell proliferation of B16-F10 melanoma, with an IC_{50} value = 14.69.
		<i>In vitro</i> on <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> bacterial. The data were presented as mean $\pm$ standard deviation (SD) and were analyzed using one-way ANOVA followed by the Student–Newman–Keuls Multiple Range Test. GraphPad Prism v.3.0 software was used. A $p < 0.05$ was considered statistically significant.	Antimicrobial	10, 1, and 0.1 mg/mL with a duration of 2 days.	Ampicillin Dosage not described.	The ethanol extract reduced the growth of both <i>S. aureus</i> and <i>E. coli</i> bacteria with MICs ranging from 1 mg/mL to 10 mg/mL, showed greater effectiveness against <i>S. aureus</i> strains where it exhibited a similar pattern to that caused by the antibiotic inhibition Ampicillin.
The fresh unripe fruits of <i>M. citrifolia</i> were collected from Malacca, Malaysia. (2.2375482,102.1691004) (Pandy et al., 2014)	The fruits were extracted with methanol.	<i>In vivo</i> on SD male rats ($n = 24$). Data were expressed as mean $\pm$ standard error of the mean (SEM). Statistical significance was evaluated by unpaired Student's t-test and one-way ANOVA followed by Dunnett post hoc test. A $p < 0.05$ was considered statistically significant.	Anti-dopaminergic and antiadrenergic	20, 40, 60, 80, and 100 mg/mL with a duration of 15 days.	Haloperidol 1.6, 12.8, 128, and 500 $\mu\text{g/mL}$ and prazosin 0.01, 0.1, and 1.6 $\mu\text{g/mL}$ were prepared fresh in double distilled water.	The methanol extract at higher doses (60–100 mg/mL) showed a dose-dependent contractile response in rat vas deferens, which was partially inhibited by high doses of haloperidol but not by prazosin. These findings showed that the methanol extract had biphasic effects on the dopaminergic system, with lower dosages (40 mg/mL) having an antidopaminergic effect and higher concentrations (> 60 mg/mL) having an agonistic effect.

Table 3. *In vivo* study of pharmacology activities of *M. citrifolia* (continued...)

Name and origin of the <i>M. citrifolia</i> (Reference)	Part of the plant and solvent used for extraction	Type of study and statistical analysis	Pharmacology activity	Range of dose or concentration	Control used	Results
<i>M. citrifolia</i> fruit were collected from a local fruit farm (Xuejia District, Tainan City, Taiwan). (23.2547554,120.1517782) (Lin et al., 2017)	The fruit was stored in a stainless-steel bottle and fermented at room temperature for one year.	<i>In vivo</i> , on male Wistar rats (n = 50). Data were expressed as mean ± standard error of the mean (SEM) and were analyzed using one-way ANOVA. A p<0.05 was considered statistically significant.	Hepatoprotective	2.51, 5.02, and 7.52 mg/mL with a duration of 2 month.	Not described.	The fermentation of <i>M. citrifolia</i> manifests a protective potential on liver fibrosis via the enhancement of antioxidant capacities, decreasing endoplasmic-reticulum stress, inflammatory cytokines, collagen accumulation, and MMP-2 and MMP-9 activities (p<0.05), as well as TIMP-1 and TIMP-3 in livers.
<i>M. citrifolia</i> leaf and fruit samples were collected in the city of Hilo, HI, United States. (19.7132052, -155.106248) (Wu et al., 2015)	The leaf and fruit were immersed in 95% ethanol, 2% NaClO, and 70% ethanol, then fermented at room temperature (25°C) for 4–6 weeks.	<i>In vitro</i> on human carcinoma cell lines SK-LU-1, PC-3, and MCF-7. Statistical analysis was not described.	Anticancer	50 µg/mL with a duration of 3 days.	Ellipticine Dosage not described.	Twelve distinct endophytic fungal species were obtained from the leaves and three from the fruit. Three of the leaf endophytes inhibited the growth of human carcinoma cell lines LU-1, PC-3, and MCF-7 with IC ₅₀ values of ≤10 µg/mL. Meanwhile, three fruit endophytes inhibited the growth of human carcinoma cells LU-1, PC-3, and MCF-7 with IC ₅₀ values >50 µg/mL.

B16F10: a murine melanoma cell line from a C57BL/6J mouse; CC₅₀: 50% cytotoxic concentrations; CF1 mice: non-Swiss albino outbred mice; GPx: glutathione peroxidase; HCV: hepatitis C virus; IC₅₀: 50% inhibitory concentrations; ICR mice: is a strain of albino mice originating in SWISS and selected by Dr. Hauschka to create a fertile mouse line originated from the Institute of Cancer Research in the USA, the strain was named ICR after the initial letters of the institute; IFN: interferon; IL: interleukin; MCF-7: a human breast cancer cell line with estrogen, progesterone and glucocorticoid receptors derived from the pleural effusion of a 69-year-old Caucasian metastatic breast cancer; MDA-MB-231: is an epithelial, human breast cancer cell line that was established from a pleural effusion of a 51-year-old Caucasian female with a metastatic mammary adenocarcinoma; MHA: Muller Hinton agar; MMP-2 and MMP-9: matrix metalloproteinase; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a yellow tetrazolium salt commonly used to measure cell viability, proliferation, and cytotoxicity; NaClO: sodium hypochlorite; NGF: nerve growth factor; NO: nitric oxide; PC-3: a prostate cancer cell line obtained from bone metastasis in a 62-year-old Caucasian male with grade IV prostate cancer; PPAR: peroxisome proliferator-activated receptor; RAW264.7 cells: a macrophage-like, Abelson leukemia virus-transformed cell line derived from BALB/c mice; SD: Sprague-Dawley rats is an outbred multipurpose breed of albino rat used extensively in medical research, developed by Sprague Dawley, Inc. SD rats were first generated by Robert S. Dawley during the 1920s by breeding Wistar rats to hybrids of laboratory derived and wild stocks; SK-LU-1: epithelial cells isolated from the lungs of a female with adenocarcinoma; SOD: super oxide dismutase; SREBP-1c: sterol regulatory element binding protein 1c; TIMP-1 and TIMP-3: tissue inhibitors of metalloproteinase; YAC-1: a fibroblast cell that was isolated from the lymphoblast of a mouse with lymphoma.

Table 4. Human studies of *M. citrifolia* fruits.

Reference	Sample size	Gender	Age (years)	Clinical conditions	Intervention (formulation, route, dosage)	Length of therapy (days)	Control drug	Efficacy or clinical outcomes	Safety evaluation	Adverse events
	(Patients)	M/F								
(Yilmaz et al., 2020)	178	94/84	>18	Patients with systolic BP ≤ 140 mmHg and/or diastolic BP ≤90 mmHg and a normal eGFR (≥90 mL/min). Excluded: patients taking an ACEI or ARBs, with obesity (BMI >30 kg/m²), dyslipidemia (total cholesterol >280 mg/dL, fasting TG >180 mg/dL), renal failure, (eGFR <90 mL/min), nephrotic syndrome (urinary protein excretion >3000 mg/day), a history of CVD (medical history, abnormal electrocardiogram, smoking and/or currently or within the last 3 months taking statins).	<i>M. citrifolia</i> AAL 3 mL once per day, omega-3 AIC 3 capsules once per day, and an extract of Alaskan blueberry and 21 different red-purple fruit vegetables AOL 30 mL once per day.	84	Not described	ADMA, MDA, PTX3, HOMA index, hsCRP, eGFR, SBP, DBP, HbA1c, TC, TG, and LDL-C levels were significantly decreased and serum albumin, FMD, CuZn-SOD, GSH-Px, HDL-C, vitamin B12, 25OHVD, and folic acid levels were significantly increased. The eGFR and BMIs of the patients did not change significantly during the study period.	Analysis of serum ADMA, MDA, CuZn-SOD, GSH-Px, hsCRP, and PTX3 concentrations and basal insulin levels, TC, TG, HDL-C, and FPG.	Not reported
(Palleschi et al., 2017)	80	42/38	18	Patients with negative urine examination and negative urine culture. Excluded: history of recent hematuria (within 3 months), presence of indwelling catheter or nephrostomy or suprapubic catheter or ureteral stent, recent urological, gynecological or pelvic surgery (within 3 months), neoplastic disease, diagnosis of interstitial cystitis, pathological findings at physical examination.	Oral administration of two vials/day of Ausilium NAC® (phytoterapic product) for 7 days starting from the day of the examination. Each vial contains D-mannose 500 mg, N-acetylcysteine 100 mg, and <i>M. citrifolia</i> fruit extract 300 mg.	7	Prulifloxacin 400 mg/day orally for 5 days starting from the day before the procedure.	7.89% of the control and 5.4% of the test group developed UTIs (p = 0.671).	Urine examination and urine culture.	No patient reported side effects in both groups.

Table 4. Human studies of *M. citrifolia* fruits (continued...)

Reference	Sample size	Gender	Age (years)	Clinical conditions	Intervention (formulation, route, dosage)	Length of therapy (days)	Control drug	Efficacy or clinical outcomes	Safety evaluation	Adverse events
	(Patients)	M/F								
(Kharaeva et al., 2022)	188	95/93	36 to 69	Patients confirmed with delta variant of virus 157, with omicron 31. Excluded: endocrine pathology, acute illnesses, heart diseases, uncontrolled hypertension, current use of hypnotics, or any treatment for breathing disorders.	Oral administration of standardized fermented tropical fruits papaya (<i>Carica papaya</i> Linn.) and <i>M. citrifolia</i> syrups a 14 g (a plastic spoon) BioRex <i>M. citrifolia</i> , in the morning after breakfast and 14 g of BioRex Papaya (a plastic spoon) after supper.	20	Not described	Clinical symptoms, IL-6, IL-8, and nitric oxide metabolites diminished significantly compared to the placebo group and their background expression. The polymorphonuclear leukocyte (PMN) capacity to phagocyte, antioxidant activity (AOA), and ATP content remarkably increased. The oral-nasal-pharyngeal microbiota were unchanged.	Analysis of hematological and biochemical parameters (erythrocytes, Hb, leukocytes, and platelets), differential count of leukocytes, urea, creatinine, electrolytes, glucose, alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, troponin, ferritin, hsCRP, pro-calcitonin, coagulation factors, D-dimer, and IL-6. Questionnaire and regular physical examinations, Dynamics of electrocardiography before and after add-on intervention.	Not reported
(Sasnan et al., 2014)	30	16/14	<40 and >40	Patients with hypercholesterolemia with an increased TC >200 mg/dL and LDL-C >130 mg/dL, in males and females, and aged over 30 years. Excluded: the use of supplements or drugs that will interfere with cholesterol metabolism, pregnant and breast feeding women, women with hormone replacement therapy, and patients with chronic disease.	Oral administration of two capsules <i>M. citrifolia</i> capsule (MCC) (each capsule contains 500 mg extract containing 90% dry extract of MC fruits and 10 % filler) 3 times daily.	14	Not described	There was a significant decrease in TC and LDL-C on day 14 compared to the control (placebo group). Reduction in TC and LDL-C was 13.8 and 15.5 %, respectively.	Analysis of serum concentration levels of TC, LDL-C, HDL-C, and TG before and after add-on intervention.	Mild gastrointestinal symptoms such as flatulence and abdominal distention after the first few doses but the symptoms subsided within a week in all subjects.

Table 4. Human studies of *M. citrifolia* fruits (continued...)

Reference	Sample size	Gender	Age (years)	Clinical conditions	Intervention (formulation, route, dosage)	Length of therapy (days)	Control drug	Efficacy or clinical outcomes	Safety evaluation	Adverse events
	(Patients)	M/F								
(Shashikumar et al., 2022)	96	52/44	30 to 60	Patients with chronic periodontitis (ChP), having the presence of >2 nonadjacent sites per quadrant with probing depths (PDs) >5 mm, bleeding on probing (BOP) <10%, and radiographic bone loss >30% of the root length. Excluded: patients who had taken any anti-inflammatory or antimicrobial drug in the past 6 months and pregnant or lactating women who used any vitamin supplements or mouthwashes in the past 6 months.	Rinse with 10 mL of <i>M. citrifolia</i> mouthwash twice daily.	90	Not described	Clinical parameters PI (Plaque index), GI (Gingival index), CAL (Clinical attachment level), BOP (Bleeding on probing), and PD (Probing depth) reduced significantly in groups B, C, and D posttreatment 3 months follow-up. However, the intergroup comparison did not show any significant difference (p>0.05). Salivary TAOC level was higher in groups B, C, and D when compared with healthy control group A, and it was significantly reduced in all three groups B, C, and D post 3 months of therapy (p<0.05). Intergroup comparison of salivary TAOC levels between groups B, C, and D did not show any significant difference (p>0.05).	The levels of PI, GI, CAL, BOP, and PD were measured as indicators of recovery.	Not reported
(Ardiansyah et al., 2020)	56	0/56	51 to 55	Women who were diagnosed with OAB based on OAB symptom scores (OABSS) and the results of urinalysis. Excluded: consuming hormone replacement therapy, suffering from diabetes mellitus, suffering from UTIs, taking anti-depressant drugs, smoking, consuming alcohol, and damaged samples.	<i>M. citrifolia</i> fruit extract capsules at a dose of 500 mg (8–16 mg/kg body weight), one capsule a day for 30 days.	30	5 mg of solifenacin capsules, one capsule daily for 30 days.	The administration of <i>M. Citrifolia</i> fruit extract has the same effect as giving solifenacin to decrease the degree of OAB in women.	Analysis levels of hs-CRP urine before and after add-on intervention.	Not reported

Table 4. Human studies of *M. citrifolia* fruits (continued...)

Reference	Sample size	Gender	Age (years)	Clinical conditions	Intervention (formulation, route, dosage)	Length of therapy (days)	Control drug	Efficacy or clinical outcomes	Safety evaluation	Adverse events
	(Patients)	M/F								
(Sabu et al., 2021)	20	N/A	30 to 55	Patients diagnosed as having chronic generalized periodontitis as per the 1999 classification of periodontal disease with periodontal pockets of ≥5 mm and radiographic evidence of vertical bone loss and patients with good general health and without any history of systemic disease or under medication. Excluded: patients showing unacceptable oral hygiene during the presurgical (Phase I) period. Smokers, pregnant women, and lactating mothers.	Open flap debridement and the placement of <i>M. citrifolia</i> fruit extract.	180	Not described	From the values of clinical parameters, there was a mean reduction in probing pocket and gain in attachment level, and a 27.7% increase in bone fill in the experimental group compared to the control group, which was 14.50% from CBCT analysis.	The levels of Gingival index, probing pocket depth, relative attachment level, and CBCT were measured as indicators of recovery.	Not reported
(Fletcher et al., 2013)	80	0/80	18	Patients with dysmenorrhoea. Excluded: Patients with a history of previous surgery, pelvic surgery, hypersensitivity to <i>M. citrifolia</i> , liver disease, and suspected pregnancy.	Oral administration of one capsule twice daily for five days, beginning 2 days before the onset of the menses and half an hour before meals. Each capsule contained calcium sulfate, gelatin, silica, vegetable magnesium stearate, and 400 mg of pure milled <i>M. citrifolia</i> herb powder.	90	Not described	Both bleeding and pain scores gradually improved in both groups as the women were observed over three menstrual cycles; however, the improvement was not significantly different in the <i>M. citrifolia</i> group when compared to the controls. The mean bleeding score was 70.93 for the placebo and 87.70 for <i>M. citrifolia</i> , while the mean maximal pain there was a marginal decrease in the mean maximal pain in the <i>M. citrifolia</i> group compared to the placebo group with pain scores of 6.59 and 7, respectively.	Analysis of bleeding and pain scores, hemoglobin, PCV or hematocrit, and ESR before and after add-on intervention.	Not reported

Table 4. Human studies of *M. citrifolia* fruits (continued...)

Reference	Sample size	Gender	Age (years)	Clinical conditions	Intervention (formulation, route, dosage)	Length of therapy (days)	Control drug	Efficacy or clinical outcomes	Safety evaluation	Adverse events
	(Patients)	M/F								
(Prapaitrakool, 2010)	100	0/100	18 to 65	Patient with had controlled systemic disease and were to undergo elective surgery under general anesthesia and who also had at least 3 of 4 predictors of PONV (female gender, history of PONV, non-smoking, and opioid use). Excluded: No patients who received antiemetics within 24 hours, had a full stomach, underwent neurological/bowel surgery, did not expect to extubate after surgery, had potential morbidity associated with PONV or had hyperkalemia.	150 mg of <i>M. citrifolia</i> extract, which is equivalent to 5 g of dried fruit (M1 group), 300 mg of extract, which is equivalent to 10 g of dried fruit (M2 group), and 600 mg of extract, which is equivalent to 20 g of dried fruit (M3 group) in the form of two identical capsules taken orally with a sip of water 1 hour before surgery.	Not described	Not described	Significantly fewer patients who had received the 600 mg <i>M. citrifolia</i> extract experienced nausea during the first 6 hours. compared to the placebo group (48% for the 600mg <i>M. citrifolia</i> group and 80% for the placebo group, p = 0.04).	Monitoring nausea and vomiting.	Not reported
(Nima et al., 2012)	20	10/10	18 to 45	Patients with complete haemogram, liver function tests, renal function tests, basic blood chemistry tests, routine urine examination, and a coagulogram screening test. Excluded: Patients with a history of allergy or known hypersensitivity to ranitidine; use of other drugs within 14 days before or during the trial (except for acetaminophen); a history of CVD or pulmonary disorders, DM, or any other disease or condition that might interfere with the study results; a recent history of drug abuse or a positive urine drug screen for drugs of abuse; and inability to communicate or co-operate with the investigator due to language problems, poor mental development or impaired cerebral function.	<i>M. citrifolia</i> aqueous fruit extract or drinking water was administered orally 30 min prior to a single oral administration of ranitidine (300 mg).	14	Not described	The area under the plasma ranitidine concentration–time curve and the maximal plasma ranitidine concentration were significantly increased after pretreatment with <i>M. citrifolia</i> aqueous fruit extract (p=0.001).	Monitoring profile pharmacokinetic parameter.	Not reported

AAL: anti-atherosclerotic liquid; ACEI: angiotensin-converting enzyme inhibitor; ADMA: asymmetric dimethylarginine; AIC: anti-inflammatory capsule; AOL: antioxidant liquid; ARB: angiotensin II receptor blocker; BP: blood pressure; BMI: body mass index; CBCT: cone-beam computed tomography; CVD: cardiovascular disease; DBP: diastolic blood pressure; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; FMD: flow-mediated dilatation; FPG: fasting plasma glucose; GSH-Px: glutathione peroxidase; HbA1c: glycated hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; HOMA: homeostasis model assessment; hs-CRP: high sensitivity C reactive protein ; LDL-C: low-density lipoprotein cholesterol; MDA: malondialdehyde; M/F: male/female; N/A: Not applicable; OAB: overactive bladder; PCV: packed cell volume; PONV: postoperative nausea and vomiting; PTX3: Pentraxin-related protein 3; SBP: systolic blood pressure; TAO: total antioxidant capacity; TC: total cholesterol; TG: triglyceride.

Table 5. Case reports on the use of *M. citrifolia* as supplement.

Presentation of the patient	Treatment	Outcome	Reference
A 14-years male patient with a 1-week history of fatigue and a 2-day history of scleral icterus. Initial presentation demonstrated that: - alanine aminotransferase (ALT): 2860 U/L. - total bilirubin: 4.4 mg/dL. - direct bilirubin: 3.4 mg/dL. - aspartate aminotransferase (ALT): 1584 U/L. - γ-glutamyl transferase 141 U/L. - normal ammonia of 22 μmol/L. - elevated prothrombin time at 19.4 seconds and international normalized ratio of 1.7. The patient has taken 10 bottles (600 mL total) of an OTC antioxidant supplement drink during 2 months for improving energy. The last ingestion of the supplement occurred on the day of admission to the hospital. Ingredients of the antioxidant supplement were aloe vera, acai berry, muscadine grape, mangosteen, <i>M. citrifolia</i> (approximately 91 mg/kg), gogi berry, pomegranate, blueberry, green tea extract, and plant-derived vitamins and minerals. Examination of viral hepatitis panel, CMV/Epstein-Barr virus PCR, serum ceruloplasmin and copper, serum iron, α-1-antitrypsin genotype, HIV, HSV, anti-nuclear antibody, anti-smooth muscle antibody, and anti-liver-kidney-microsome antibody, was negative. An abdominal ultrasound with Doppler indicated hepatitis and did not reveal any signs of biliary tree obstruction. The liver biopsy revealed acute hepatitis with portal inflammation and periportal necrosis, hepatocellular cholestasis with focal ductular proliferation, and presence of numerous eosinophils.	The antioxidant supplement was stopped.	After 2 months without taking the antioxidant supplement, the patient has recovered without symptoms of liver disease. It should be taken aware that there may be an association between long-term <i>M. citrifolia</i> juice consumption and acute hepatotoxicity.	(Yu et al., 2011)

Table 5. Case reports on the use of *M. citrifolia* as supplement (continued...)

Presentation of the patient	Treatment	Outcome	Reference
A 38-years female patient with headache was diagnosed with intracranial aneurysm and experienced successful surgery. Liver tests before surgery were within normal range. Based on pathological electroencephalogram postoperatively, PB was initiated for the prevention of seizures. During 9 months of follow-up, clinical and liver function tests remained normal, and the patient started taking the recommended daily doses (60 mL) of <i>M. citrifolia</i> juice, and 1 week after she jaundiced. On admission, laboratory tests showed: • bilirubin: 165.3 µmol/L (normal 2–20). • AST: 925 U/L (normal 8–30). • alanine aminotransferase (ALT): 813 U/L (normal 10–36). • γ-glutamyl transpeptidase: 933 U/L (normal 9–35). • alkaline phosphatase (AP): 532 U/L (normal 54–119). • international normalized ratio 2.61, indicating hepatocellular injury (ratio ≥5) according to the DILI classification. • The PB level was below the therapeutic range (77 µmol/L; normal 86–173). • Genotyping of CYP2C19 and CYP2C9 polymorphisms identified CYP2C9*1/*1 and CYP2C19*1/*1, fast metabolic genotypes. There was no evidence of biliary or vascular obstruction on ultrasound. Viral hepatitis (A, B, C), CMV, Epstein-Barr virus, HIV, HSV, autoimmune hepatitis (anti-nuclear antibody, anti-smooth muscle antibody, anti-liver-kidney microsome antibody), hemochromatosis and Wilson's disease tested negative. The level of bilirubin peaked at 366 µmol/L, whereas other liver tests did not deteriorate significantly. A percutaneous liver biopsy revealed mixed pattern of injury with predominant hepatocellular form. Hepatocellular zonal necrosis mostly in the perivenular zone with massive necrosis of one lobule accompanied by sinusoidal lymphocytosis. An intrahepatic hepatocanalicular cholestasis with portal tract inflammatory infiltrate rich in eosinophils was obtained. Qualitative histochemical staining of copper and iron was negative.	Both PB and <i>M. citrifolia</i> juice were stopped. Treatment with steroids was initiated and gradually tapered for 3 months until discontinuation. A control liver biopsy 3 months after discharge revealed preserved architecture of lobules with mild mixed type of sinusoidal inflammation in only one lobule and also mild canalicular type of cholestasis. In the portal tracts mild mixed type of inflammation was found with no signs of ductular type cholestasis.	Two months later, the liver enzymes, bilirubin and international normalized ratio were normal, and the patient remained asymptomatic.	(Mrzljak et al., 2013)
A 49-years male patient has been treated with phenytoin sodium 600-700 mg/day in combination with lamotrigine 400 mg/day was also added because the patient still had seizures despite the therapeutic phenytoin levels. The patient was adhering to his medication, but he showed poor seizure control (the level of blood phenytoin fell into the very <10 mg/L). After a thorough inquiry of his daily foods, the patient admitted that he took <i>M. citrifolia</i> fruit juice daily.	The patient was suggested to stop his daily <i>M. citrifolia</i> fruit juice supplement for one period, restart with his usual daily consumption at the next period. The patient was treated with lamotrigene 400 mg/day and lorazepam 3 mg if any major seizure occurs. Clobazam treatment was added.	During the “stop period” with phenytoin 600 mg/day therapy, the level of phenytoin raised to 25.34 mg/L. Even after phenytoin dose was reduced to 500 mg/day, the drug level continued to elevate to 33.26 mg/L.	(Kang et al., 2015)

Table 5. Case reports on the use of *M. citrifolia* as supplement (continued...)

Presentation of the patient	Treatment	Outcome	Reference
A 29-years male patient with acute hepatitis after treatment of an upper respiratory tract infection with paracetamol (4 g daily for 5 days followed by lower doses over 4 weeks, cumulative dose of 40 g) associated with reduced food intake. Laboratory analysis: • Bilirubin: 26.3 mg/dL (normal: 0.1-1.2 mg/dL). • AST 2926 U/L (normal: < 35 U/L). • ALT 2665 U/L (normal: < 45 U/L). • γ-Glutamyl transpeptidase: 75 U/L (normal: < 55 U/L). • Alkaline phosphatase: 209 U/L (normal: 40-130 U/L). The patient had allergic asthma treated with inhalative β2-agonists and glucocorticoids and eosinophilia of up to 12% in his peripheral blood smear. Viral hepatitis, autoimmune hepatitis, hemochromatosis, α1-antitrypsin deficiency, Wilson’s disease as well as other infections (leptospirosis, toxoplasmosis, coxsackie, and brucellosis) were ruled out and his abnormal liver tests were interpreted as low-dose paracetamol toxicity facilitated by fasting. Three weeks priorly, the patient consumed 1.5 L of <i>M. citrifolia</i> juice and for 9 days before admission, approximately 7 g/day of a Chinese herbal mix containing bupleuri, pinellia, scutellaria, codonopsis, glycyrrhizae, schizonepeta, and paeonia. He denied any other medication over the past year. Other etiologies for acute liver failure, such as fulminant hepatitis A or B, acute Wilson’s disease, mushroom poisoning, and Budd-Chiari syndrome were ruled out. A transjugular liver biopsy was performed and revealed acute hepatitis consistent with an idiosyncratic drug reaction.	Over the next 3 days, liver failure progressed rapidly. On day-4, the patient fulfilled King’s College criteria for emergency liver transplantation and was listed for urgent liver transplantation. On day-6, liver transplantation was performed. On day-11, hepatic artery thrombosis necessitated retransplantation.	During the “resumption” period, the drug level fell to 17.82 mg/L under the same dose of 500 mg/day. The patient recovered completely and was discharged on day-30.	(Stadlbauer et al., 2005)
A 62-years female patient with vomiting and diarrhea and laboratory analysis revealed acute hepatitis with: • AST: 1415 U/L. • ALT: 2381 U/L. • γ-Glutamyl transpeptidase: 241 U/L. • Alkaline phosphatase: 292 U/L. • Bilirubin 2.9 mg/dL. She had been diagnosed with chronic B-cell leukemia, which was treated with fludarabine resulting in remission. Throughout that time, liver function tests were normal, and the patient did not take any other regular medication. Recently, she consumed 2 L of Tahitian <i>M. citrifolia</i> juice. Viral hepatitis, autoimmune hepatitis, hemochromatosis, α 1-antitrypsin deficiency, and Wilson’s disease were ruled out. There was no evidence of biliary obstruction or Budd-Chiari syndrome on ultrasound. The patient did not take any other potentially hepatotoxic drugs during that period. A percutaneous liver biopsy revealed acute hepatitis consistent with an idiosyncratic drug reaction.	<i>M. citrifolia</i> juice was discontinued.	Laboratory values peaked at AST 2022, ALT 3570 U/L, and bilirubin 4.9 mg/dL and gradually improved over the next 30 days (ASAT 194, ALAT 645 U/L, and bilirubin 3.9 mg/dL). Nine months later, aminotransferases and bilirubin normalized and the patient remained asymptomatic.	(Stadlbauer et al., 2005)
A 63-years Japanese female patient with gray-brownish pigmentation on her lower part of face for 7 years. She admitted that there was no history of hyperpigmentation or contact dermatitis. Patch testing using the Japanese Standard Allergen series showed positive results of nickel, fragrance mix, and thiuram mix. Despite avoiding intake or contact with these substances, her pigmentation worsened. The patient has been taking <i>M. citrifolia</i> juice nearly four times the recommended daily dose (approximately 100 mL/day) for 7 years. She also said that she used to wrap the juice-soaked towel around her neck for 2 weeks, one year before her hospital visit.	The patient was suggested to discontinue <i>M. citrifolia</i> juice.	The pigmentation reduced within a month after stopping noni juice consumption. This was a rare case of hyperpigmentation possibly related to the consumption of <i>M. citrifolia</i> juice.	(Mizuno et al., 2022)

CMV: Cytomegalovirus; HSV: Herpes simplex virus; PB: Phenobarbital.

Pharmacology activities

Numerous *in vivo* studies (Table 3) reported different pharmacology activities of *M. citrifolia* fruits (Barani et al., 2014; Candida et al., 2014; Inada et al., 2020; Pandey et al., 2017; Pandey and Vijeepallam, 2017; Pratap et al., 2017; Shoeb et al., 2016; Susanti et al., 2022; Wigati et al., 2017), with a specific description of ripe fruits (Barani et al., 2014; Susanti et al., 2022), unripe fruits (Pandey et al., 2014; 2017), and leaves (Abu et al., 2018; Chong et al., 2019; Pandey and Vijeepallam, 2017; Ratnoglik et al., 2014; Wigati et al., 2017). The plants were mostly collected in Malaysia (Abu et al., 2018; Chong et al., 2019; Pandey et al., 2014; 2017), Brazil (Candida et al., 2014; Inada et al., 2020; Serafini et al., 2014), Indonesia (Susanti et al., 2022; Wigati et al., 2017), India (Barani et al., 2014), Japan (Ratnoglik et al., 2014), Taiwan (Lin et al., 2017), USA (Wu et al., 2015). Studies on *M. citrifolia* nutraceutical products were also reported (Pratap et al., 2017; Shoeb et al., 2016; Kim et al., 2022).

Pharmacological studies have shown the ability of this plant as an anti-dyslipidemia (Shoeb et al., 2016), anti-lipogenesis (Inada et al., 2020), anti-fungal (Barani et al., 2014), hepatoprotective (Chong et al., 2019; Lin et al., 2017), hypotensive (Wigati et al., 2017), immunostimulatory (Kim et al., 2022; Pratap et al., 2017), anti-alpecia (Susanti et al., 2022), photoprotective (Serafini et al., 2014), antitumor (Abu et al., 2018; Candida et al., 2014), antiviral (Ratnoglik et al., 2014), anticancer (Abu et al., 2018; Wu et al., 2015), anti-dopaminergic (Pandey et al., 2017; Wu et al., 2015), and antimicrobial (Candida et al., 2014). However, not all studies reported the use of standard drugs as the control.

Studies in humans

There are ten articles from ten different countries worldwide reported on the efficacy and safety of *M. citrifolia*. The articles analyzed were published from 2010 to 2023. The total number of participants involved was 848 patients, with the patients being male gender (30%) and female (70%). The age of the participants ranged from 18-69 years old. The duration of the studies ranged from 7 to 180 days. Several studies used standard care drugs, such as antispasmodics (solifenacin 5 mg) and antibiotics (prulifloxacin 400 mg).

Researchers from Turkey evaluated the effect of *M. citrifolia* as an anti-atherosclerotic liquid on inflammation, oxidative stress, and endothelial dysfunction determined by flow-mediated dilatation (FMD) and asymmetric dimethylarginine (ADMA) levels in patients with chronic disease (Yilmaz et al., 2020). A study conducted in Italy compared the administration

of D-mannose association, N-acetylcysteine (NAC), and *M. citrifolia* extract versus antibiotic therapy in the prophylaxis of urinary tract infections (UTIs) (Palleschi et al., 2017). Meanwhile, researchers from Russia examined the effect of two fermented food supplements (FFS) in syrup form based on *Carica papaya* and *M. citrifolia* for the treatment of post-COVID symptoms (Kharaeva et al., 2022). Indonesian researchers reported the effect of *M. citrifolia* capsules (MCC) on total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemia patients (Sasnan et al., 2014) and the effect of *M. citrifolia* extract on overactive women's bladder (OAB) through observation of high-sensitivity C-reactive protein (hs-CRP) urine level (Ardiansyah et al., 2020). Researchers from India evaluated the effect of *M. citrifolia* mouthwash in the maintenance of periodontal health in patients with type 2 diabetes mellitus (T2DM) with chronic periodontitis (ChP) (Shashikumar et al., 2022), and the bone fill efficacy of *M. citrifolia* fruit extract in the periodontal bone defect (Sabu et al., 2021). Other researchers from Jamaica described the efficacy of *M. citrifolia* in women with dysmenorrhea (Fletcher et al., 2013). Researchers from Thailand evaluated the efficacy of *M. citrifolia* for the prevention of postoperative nausea and vomiting (PONV) in patients after various types of surgery (Prapaitrakool and Itharat, 2010) and the study was to investigate the gastrokinetic activity of *M. citrifolia* aqueous fruit extract (AFE) in human subjects (Nima et al., 2012).

Most of the studies reported a reduction of symptoms or faster recovery in the intervention group (*M. citrifolia*, and/or a combination of *M. citrifolia* with other plants) compared to the control group. Moreover, seven studies indicated the safety of *M. citrifolia* and/or a combination of *M. citrifolia* with other plants, as proven by no adverse effects observed in the intervention group of patients. Number of trials, gender, age, clinical conditions, intervention, length of therapy, clinical outcomes, and adverse events are tabulated in Table 4.

Efficacy and safety of *M. citrifolia* in human studies

Efficacy was evaluated by measuring the complete hematological and biochemical examination (five articles), and/or measuring the levels of inflammatory responses, either IL-6, IL-8, and nitric oxide (one article), and/or measuring the periodontal parameters (two articles) and/or prevention of postoperative nausea and vomiting, and gastrokinetic activity (two articles).

It is interesting to find out that the use of *M. citrifolia* (anti-atherosclerotic liquid- AAL), omega-3 (anti-inflammatory capsules- AIC), and extract with Alaskan blueberry (antioxidant liquid- AOL) for 12 weeks

can significantly reduce levels of ADMA (1.3 μ mol/L), MDA (2.2 nmol/mL), and PTX3 (2.2 ng/mL) as well as the inflammatory marker (hs-CRP 3 mg/L) levels compared to the baseline in improvement in endothelial functions in patients with chronic diseases. Asymmetric dimethylarginine (ADMA), malondialdehyde (MDA), and serum pentraxin 3 (PTX3) were the markers responsible for the improvement of endothelial dysfunction in patients using these three products with anti-inflammatory, antioxidant, and anti-atherosclerotic properties (Yilmaz et al., 2020). Another interesting thing about the use of *M. citrifolia* fruit extract on intraosseous defects in periodontitis patients proven to be efficacious in terms of relative attachment level and amount of bone filling. *M. citrifolia* fruit extract showed a statistically significant ($p < 0.05$) gain in attachment level and a 27.7% increase in bone filling compared to the control group (Sabu et al., 2021). Moreover, two capsules of *M. citrifolia* (each capsule contains 500 mg dry extract of the fruits) showed a statistically significant ($p < 0.05$) reduction in total cholesterol (TC) 13.8% (33.0 mg/dL) and LDL-C 15.5% (26.6 mg/dL) levels compared to that of the placebo group in patients with hypercholesterolemia. However, *M. citrifolia* capsule has caused mild gastrointestinal discomfort in the patients, such as flatulence and abdominal distention after the first few doses, but the symptoms subsided within a week in all subjects (Sasnan et al., 2014). Another study that examined the influence of *M. citrifolia* capsules (containing calcium sulfate, gelatin, silica, vegetable magnesium stearate, and 400 mg of pure milled *M. citrifolia* herb powder) in reducing menstrual pain or bleeding in women with dysmenorrhea reported a not clinically significant result compared to the placebo group, the bleeding and pain scores gradually improved in both groups when the women were observed for three menstrual cycles (Fletcher et al., 2013).

The safety of *M. citrifolia*, and a combination of *M. citrifolia* with other plants was evaluated in 10 studies, by analyzing the hematological and biochemical parameters (erythrocytes, Hb, leukocytes, and platelets), differential count of leukocytes, urea, creatinine, electrolytes, glucose, alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, troponin, ferritin, hs-CRP, pro-calcitonin, coagulation factors, D-dimer, and IL-6, and/or serum ADMA, MDA, CuZn-SOD, GSH-Px, and PTX3 concentrations and basal insulin levels, serum concentration levels of TC, LDL-C, HDL-C, and triglyceride, and/or dynamics of electrocardiography, and/or physical examination (heart rate, respiratory rate, SpO₂, and dyspnea), and/or periodontal parameters (plaque index, gingival index, clinical attachment level, bleeding on probing, cone-beam computed tomography, and probing

depth), and/or monitoring nausea and vomiting, monitoring profile pharmacokinetic parameter (AUC, T_{1/2}, C_{max}, T_{max}, CL/F, V_d/F), and/or by monitoring the AEs, before and after add-on intervention. None of the studies reported severe side effects. All studies confirmed the safety of *M. citrifolia*, and a combination of *M. citrifolia* with other plants.

A previous study in 96 healthy participants consuming one of four daily quantities of *M. citrifolia* fruit juice: 0 mL (placebo), 30 mL, 300 mL, or 750 mL for 6 weeks described those participants in the *M. citrifolia* groups experienced 20-50% fewer total AEs compared to those in the placebo group. A significant reduction in the AEs experienced by the volunteers was observed in the 300 mL *M. citrifolia* group. This study revealed that administering up to 750 mL/day of *M. citrifolia* fruit juice is safe (West et al., 2009).

Case reports on *M. citrifolia* use as supplement

The tendency of a "Back to nature" lifestyle causes the use of traditional medicines, herbal medicines, and food supplements to increase, which occurs in both developed and developing countries (Sumarya et al., 2020), including Indonesia. Responding to this condition, many traditional medicine industries that produce traditional medicines often state "no side effects" because they are "natural", while drug failures and side effects are not reported (Larramendy and Soloneski, 2016). Although they are often called safe, it is recorded that many medicinal plants have the intrinsic potential to be toxic or interact with fellow traditional medicines or with conventional medicines (Ghosh and Mukherjee, 2019). *M. citrifolia* is often used in treating several diseases. Several cases of the use of *M. citrifolia* have been reported globally and summarized in Table 5.

DISCUSSION

Overall, the *M. citrifolia* plant has considerable potential to be developed because of its benefits in the health sector. In the included preclinical studies, the role of *M. citrifolia* was largely studied in various pharmacological activities. The scientific evidence collected focuses on preclinical studies (pharmacological activity *in vivo*) and human clinical studies (case reports). This evidence-based review aims to comprehensively analyze the efficacy and safety of *M. citrifolia* fruit in light of the existing evidence. Because it reports the outcomes of *in vivo*, *in vitro*, and subsequent human investigations, our review study allows for a better translation of *M. citrifolia*'s efficacy and safety. According to our findings, both preclinical and clinical investigations have been undertaken on *M. citrifolia*, which has remained a popular medicinal plant explored in recent decades.

In terms of safety, there are several case reports regarding the potential association of *M. citrifolia* with acute hepatotoxicity marked by increased serum enzymes. The mechanism of liver intoxication of *M. citrifolia* is still unrevealed. It was thought that due to the multiple components of *M. citrifolia* extract, which are anthraquinones in small levels, damage to the liver arises. Anthraquinones belong to the anthracenes and have been reported for their cytotoxicity in two human liver cell lines (HepG2/C3A and HuH-7) (Lin et al., 2017). Although anthraquinones possess many biological activities, hepatotoxicity (Wang et al., 2022b), cardiotoxicity (Chen et al., 2023), and carcinogenicity (National Toxicology Program, 2005). National Toxicology Program technical report series are among the disadvantages that have also been reported (Qu et al., 2013). Anthraquinones may cause hepatic intoxication via multiple mechanisms, e.g., endoplasmic reticulum stress and mitochondrial dysfunction due to the excess production of ROS and cytochrome-C release mediated apoptosis (Kang et al., 2022; Qu et al., 2013). In whatever way, *M. citrifolia* has gained approval as a safe supplement in the European Union because anthraquinones are present in a very low quantity to be of any toxicological significance. It was decided that *M. citrifolia* anthraquinones lacked chemical structures capable of being reduced to the toxic anthrone radicals, which were accused of herbal hepatotoxicity (West et al., 2009).

Furthermore, it was reported that iridoids were found in *M. citrifolia* fruit (Pawlus and Kinghorn, 2010). Although there have been no reports of skin lesions linked to *M. citrifolia*, consumption of *Gardenia jasminoides* (sanshishi), a plant belonging to the same *Rubiaceae* family, has been linked to a few occurrences of pigmentation-related skin lesions (Akihisa et al., 2012). The primary component of *G. jasminoides*, geniposide, a form of iridoid, induces mesenteric phleboscrosis, which is shown by the intestinal membrane's bronze coloring. Although the precise mechanism of action is unknown, genipin, a metabolite of geniposide, is thought to be involved. Blue particles are created by the spontaneous reaction of genipin with proteins and amino acids (Brauch et al., 2016). When exposed to norepinephrine, geniposide encourages melanogenesis in the epidermis (Lan et al., 2008). The clinical applications of geniposide are mainly in traditional Chinese dosage forms, not geniposide monomers (Zhou et al., 2019). Additionally, geniposide toxicity has been reported, including instances of hepatotoxicity (Ding et al., 2013; Wei et al., 2014) and chronic geniposide oral toxicity in rats that altered serum biochemistry, urinalysis, hematological parameters, and relative organ weights (Tian et al., 2018). Moreover, when administered at large doses (100 mg/kg for 26 weeks), it has clearly manifested patho-

logical problems in the liver and renal tissues (Tian et al., 2018). However, other studies reported that genipin, an aglycone of geniposide, has significant gastroprotective effects and might be useful for treating and preventing gastric lesions (Sohn et al., 2017).

Because this review only considers publications written in English, evidence written in other languages may be disregarded. Although we attempted to pool several papers for quantitative analysis, the review's intrinsic shortcoming is considerable heterogeneity. Further improvements in preclinical study design, such as baseline parameters (such as age, weight, and environmental factors), comparison groups in preclinical and clinical study, and treatment duration, should be considered to ensure homogeneity in order to obtain definitive evidence. Using references from the last 13 years (2010-2023), this review article intends to update the references utilized, which resulted in the publication of multiple preclinical and clinical articles documenting the use of *M. citrifolia* and/or its combination with other plants. A future review might be conducted to investigate the available herb-herb interaction data and herb-drug interactions for *M. citrifolia* to understand better its role in becoming one of the medicinal plants with great development potential.

CONCLUSION

Based on currently available clinical and efficacy evidence, it is apparent that *M. citrifolia* is a potentially valuable medicinal plant in the treatment of various diseases. This plant has aroused curiosity, as proven by many studies and reviews focusing on it. Numerous studies reported the major phytoconstituents in the fermented fruit were phenolics, anthraquinones, and flavonoids, such as quercetin and naringenin, coumarins, such as scopoletin, terpenes such as ursolic acid, and phenolic acids such as gentisic acid, *p*-hydroxybenzoic acid, and chlorogenic acid, which contribute to its pharmacological activities.

The chosen articles in the present review have demonstrated the heterogeneous design of studies, and almost all studies reported significant statistical analysis results, indicated by $p < 0.05$. Nevertheless, not all articles narrated their procedures in detail, thus limiting our interpretations. In whatever way, the safety of *M. citrifolia* has been confirmed and proven by no occurrence of adverse events or mild gastrointestinal discomforts. However, it should be taken more considered while administering the fruit juice of this plant to patients with certain medications, e.g., phenytoin, phenobarbital, antiepileptics, paracetamol, and other drugs, due to the potential hepatotoxicity induced by herbal-drug interactions. Caution and ther-

apy drug monitoring is required if this plant is to be taken over a long-term period. This review is advantageous for clinicians and patients for an add-on therapy and to upgrade the status of *M. citrifolia* from laboratory bench to bedside.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Sadino A	Levita J	Saptarini NM	Fristiohady A
Concepts or ideas	x	x	x	x
Design	x	x		
Definition of intellectual content	x	x	x	x
Literature search	x	x		
Experimental studies	x	x		
Data acquisition	x	x	x	x
Data analysis	x	x	x	x
Statistical analysis	x	x		
Manuscript preparation	x	x		
Manuscript editing	x	x		
Manuscript review	x	x	x	x

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