Review Article

Carica papaya L. Leaf: A Systematic Scoping Review on Biological Safety and Herb-Drug Interactions

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Introduction. The Carica papaya L. leaf is gaining interest as a potential therapeutic agent for alleviating dengue- and non-dengue-associated thrombocytopaenia. In that regard, safety considerations are as important as efficacy potential. The safety evaluation of botanical products for human use is complicated by variable formulations, complex phytochemical composition, and extrinsic toxicants. This review aimed to systematically collate related safety clinical and preclinical data, as well as reports on herb-drug interactions of C. papaya leaf consumption.

Methods. A systematic search using predetermined keywords on electronic databases (MEDLINE, Cochrane Library Central, LILACS, and Web of Science) and grey literature was conducted. Relevant clinical and preclinical studies were identified, screened, and analysed to present an overall safety profile of C. papaya leaf consumption.

Results. A total of 41 articles were included (23 clinical, 5 ongoing trials, and 13 preclinical) for descriptive analysis on study characteristics, adverse reactions, toxicity findings, and herb-drug interactions, from which 13 randomised controlled and quasiexperimental trials were further assessed for risk of bias and reporting quality. Overall, C. papaya leaf consumption (in the form of juice and standardised aqueous extract) was well tolerated by adult humans for short durations (< five days) while one randomised controlled trial reported safe consumption of C. papaya leaf standardised aqueous extract in children (aged 1–12 years). Minor gastrointestinal side effects were most commonly reported. There are concerns about hepatotoxicity and reproductive toxicity in long-term use, supported by animal studies. Unfavourable herb-drug interactions with metformin, glimepiride, digoxin, ciprofloxacin, and artemisinin were accounted.

Conclusion. C. papaya leaf consumption in adults is generally safe for short-term use though cautioned in pregnancy and people with liver impairment. It has potential herb-drug interactions with oral hypoglycaemic agents, p-glycoprotein substrates, and antibiotics with cation chelating properties.

1. Introduction

Carica papaya L. is a common medicinal plant used in folk medicine [1]. Traditionally, the leaves of C. papaya, in decoction or infusion form, are consumed orally to reduce blood pressure and sugar levels. The juice of C. papaya leaf is used for irregular menstruation while infusion of young leaf is used for fever [2, 3]. There is long standing interest in the use of C. papaya leaf as an adjunctive treatment to the standard care for improving platelet counts, especially in cases of dengue fever [4], or more recently, in cancer treatments [5]. Among the most important clinical findings on the efficacy of C. papaya leaf is its use in thrombocytopaenia management during dengue infection [6], a common and potentially life-threatening complication during the course of infection [7]. Such clinical benefits and potential mechanisms of action have also been investigated and backed by preclinical data [8–10]. Other efficacy evidence of C. papaya leaf includes hypoglycaemic [11], hypolipidaemic [12], gastrophrotective [13], antimicrobial [14], antimalarial [15], and wound healing properties [16]. C. papaya leaf has been reported to contain several important phytochemical compounds including flavonoids, alkaloids, tannins, quinones, and steroids which may collectively contribute towards its biological activities [17, 18]. In addition to the abundance of phenolic compounds with antioxidant properties identified in a methanol extract of C. papaya leaf [19], the alkaloid carpine was reported to be a
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2. Materials and Methods

This review was conducted according to the York Framework of scoping studies by Arskey and O’Malley [26], advanced by Levac et al. [27]. This framework serves as a guide for a standardised and systematic approach in conducting scoping studies to address new or broad research questions of complex or heterogeneous nature. As the safety profile of C. papaya leaf encompasses heterogeneous clinical and preclinical evidence, including data on herb-drug interactions, this methodological framework is suited to be applied. All five stages of scoping review, namely, (1) identification of research question (s), (2) identification of relevant studies, (3) selection of studies, (4) data charting, and (5) collation, summarisation and reporting of findings, were undertaken. This review was not registered with PROSPERO as scoping reviews are currently not accepted for registration [28].

2.1. Research Questions. This review was conducted based on the primary research question “How safe is the oral consumption of C. papaya leaf for humans?” This primary question was further expanded to secondary research questions including the following:

(i) What is the documented safe dose range of C. papaya leaf consumption in humans?
(ii) What is the safety profile of C. papaya leaf in animal toxicity studies and how does it potentially translate into negative effects in humans?
(iii) What are the potential herb-drug interactions of C. papaya leaf?

The following Population, Intervention, Comparison, and Outcomes (PICO) framework was applied to address the study’s research questions (Table 1). Three main population categories were targeted to answer the three secondary research questions.

2.2. Search Strategy. A systematic search was conducted by two independent investigators for published and grey literature with predetermined keywords. In general, a combination of keywords consisting of “papaya,” “leaf,” “leaves,” “side effect,” “health effect,” “adverse effect,” “toxic,” “safety,” “herb interaction,” and “drug interaction” was used, catered, and adapted to each search engine. An example of the keywords search used for MEDLINE is presented in the supplementary material (S1 Appendix). For published papers and ongoing trials, electronic databases MEDLINE, Cochrane Library Central, LILACS (Latin American and Caribbean Health Sciences Literature), and Web of Science were searched for the period since inception until October 2020. Additional grey literature related to safety reports were searched for from the websites of FDA Medwatch, U.S.A National Toxicology Program, European Food Safety Authorities, ProQuest Dissertations & Theses Global, and the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) bulletin. Details on Adverse Drug Reaction (ADR) reports related to C. papaya leaf consumption in Malaysia from the MADRAC database were further obtained via an official application [30] to the Pharmacovigilance Section, Centre for Compliance and Quality Control,
Table 1: Population, Intervention, Comparison, and Outcomes (PICO) framework.

| Elements          | Details                                                                                                                                 |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Population        | 1. Human patients of all ages and diseases, healthy and unhealthy                                                                     |
|                   | 2. Animal models in toxicity studies                                                                                                    |
|                   | 3. Animal models, cell models, or assays in herb-drug interaction studies                                                               |
| Intervention      | C. papaya leaf as a single herb, in any form of any formulation. Only studies utilizing the leaf part of the plant were included       |
| Comparator        | Placebo, no treatment, or control treatment                                                                                            |
| Primary outcome   | 1. Safe dosage range and formulations documented                                                                                        |
|                   | 2. Intrinsic toxicity data including adverse events and serious adverse events reported in clinical trials or studies which may or may not be related to treatment |
| Outcome           | 3. Toxicity findings from animal toxicity studies                                                                                       |
|                   | 4. Reports on herb-drug interaction                                                                                                     |
| Secondary outcome | Reporting quality of randomised controlled and quasieperimental trials specific to quality of herbal medicine interventions (Consolidated Standards of Reporting Trials (CONSORT) extension for herbal trials, item No. 4 [29]), an indirect indicator of extrinsic toxicity of the test item |

National Pharmaceutical Regulatory Agency Malaysia. Additional relevant studies (if any) were also identified from the reference list of related review papers found during the initial search. All searches were performed and matched by two independent investigators. Search results were managed using bibliographic software (EndNote X8.1), and duplicates were removed. For ongoing clinical trials, attempts were made to contact the investigators for relevant information.

2.3. Article Inclusion. Title and abstract screening, as well as full-text paper inclusion, was performed by two independent investigators. A third investigator was involved in cases of disagreements. Studies were selected based on the inclusion and exclusion criteria with reference to the research questions identified and PICO elements (Table 1). The inclusion and exclusion criteria are presented according to the three main questions of this study (Table 2). Similar but specific inclusion and exclusion criteria were applied for each question to optimise data inclusion with the aim of building a well-rounded safety profile for C. papaya leaf consumption. This paper only reviewed C. papaya leaf as a whole, adhering to the study objective, and did not take into account compound-based interventions. C. papaya leaf is often consumed as a whole leaf extract for therapeutic use in cases of thrombocytopenia. The effect of medicinal plants is often due to the collective contribution of several phytochemicals present in the plant; thus, studies on single compounds may not sufficiently represent the real-world usage of C. papaya leaf as a whole plant part for therapeutic purposes. Articles investigating C. papaya leaf in combination (as mixtures) with other interventions were also excluded to aid in the analysis of any causal relationship between reported effects and C. papaya leaf as the main contributor. Only English language articles were included.

2.4. Data Charting. Data extraction was carried out and then agreed on by two independent reviewers while disparities were reviewed by a third. Four different data extraction tables (supplementary material: S2 Appendix) were specifically designed for (1) clinical, (2) animal toxicity, (3) pharmacodynamic herb-drug interaction, and (4) pharmacokinetic herb-drug interaction articles to comprehensively capture the required data for different types of study and outcome. All investigators were briefed and trained on using the data extraction tables beforehand to ensure accurate and consistent data extraction.

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 (randomised controlled trials, case series, in vivo, in vitro, etc.); and objectives

(iii) Study population: sample size; drop outs; and details of study population (age, gender, comorbidities, diagnosis, animal model, cells, and assay)

(iv) Intervention: plant part used; form; formulation; quality details, e.g., quantitative analysis, chemical fingerprinting, standardisation, voucher specimen, and source; dose; duration; and cointervention

(v) Comparator: intervention description; formulation; dose; duration; and cointervention

(vi) Outcomes: adverse events or reactions; herb-drug interaction; mechanism of herb-drug interaction; and method of assessment

(vii) Others: limitations; funding details; other reference identified (for tracing of additional papers); and remarks (reasons for exclusion must be stated)

For unpublished ADR reports, the following information was requested from the official providers to enable critical appraisal and descriptive analysis of causality:

(i) Name and details of the ingested C. papaya leaf formulation/product (plant name, plant part, formulation details, dose, frequency, and duration)

(ii) Purpose of C. papaya leaf consumption

(iii) Details of concomitant intervention

(iv) Description of an adverse event
Table 2: Inclusion and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| a) Clinical articles and reports on primary human data | a) Review papers or reports on secondary data |
| b) Articles that investigated C. papaya leaf as an intervention in all types of formulations including as raw plant, extracts, juice, tablet, capsule, powder, and syrup, as a single herb | b) Articles that investigated isolated compounds as intervention, including C. papaya-leaf-derived compounds |
| c) Articles that included patients of all ages and health status as study population | c) Articles that investigated mixture formulations which contain C. papaya leaf as one of their components, along with other active ingredients |
| d) Articles that investigated plant parts of C. papaya apart from leaves | d) Articles that investigated plant parts of C. papaya apart from leaves |

2B: animal toxicity studies

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| a) Primary articles of in vivo animal toxicity studies | a) Review papers or reports on secondary data |
| b) Articles that investigated C. papaya leaf as an intervention in all types of formulations including as raw plant, extracts, juice, tablet, capsule, powder, and syrup, as a single herb | b) Articles that investigated isolated compounds as interventions, including C. papaya-leaf-derived compounds |
| c) Articles that investigated mixture formulations which contain C. papaya leaf as one of their components, along with other active ingredients | c) Articles that investigated mixture formulations which contain C. papaya leaf as one of their components, along with other active ingredients as the main intervention (this does not refer to the herb/drug in which potential for interaction was investigated) |
| d) Articles that investigated plant parts of C. papaya apart from leaves | d) Articles that investigated plant parts of C. papaya apart from leaves |
| e) Non-in-vivo papers such as in vitro and in silico studies | f) Efficacy papers |

2C: herb-drug interaction studies

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| a) Articles and reports on the primary data of any potential herb-drug interaction | a) Review papers or reports on secondary data |
| b) All study types including clinical (inclusive of all ages and health status) and preclinical (in vivo, in vitro, in silico, and assay-based) papers | b) Articles that investigated isolated compounds as interventions, including C. papaya-leaf-derived compounds |
| c) Articles that investigated C. papaya leaf as an intervention in all types of formulations including as raw plant, extracts, juice, tablet, capsule, powder, and syrup, as a single herb | c) Articles that investigated mixture formulations which contain C. papaya leaf as one of their components, along with other active ingredients as the main intervention (this does not refer to the herb/drug in which potential for interaction was investigated) |
| d) Articles that investigated plant parts of C. papaya apart from leaves | d) Articles that investigated plant parts of C. papaya apart from leaves |

(v) Causality score/assessment

(vi) Patient demographics (age, gender, comorbidities, and diagnosis)

2.5. Data Analysis. Due to the versatility in types of studies and results acquired, descriptive numerical analysis was carried out for the country and type of study. A list of ongoing studies and their latest status were tabulated. The toxicity profile of C. papaya leaf was built on collating and descriptively summarising results on safe doses used in clinical settings, adverse reactions reported in clinical articles, and animal toxicity data, as well as evidence of both pharmacokinetic and pharmacodynamic herb-drug interactions.

Specifically for randomised controlled and quasiexperimental trials, the reporting quality of the herbal intervention investigation was assessed using the Consolidated Standards of Reporting Trials (CONSORT) extension for herbal trials, item No. 4 [29]. This was also an indirect representation of data transparency and awareness on declaring potential extrinsic toxicities of the investigated test items by the original authors. Risk of bias assessment was conducted by two independent investigators, with disparities addressed by a third, using the Cochrane Review Manager (RevMan, version 5.4) software, on all randomised controlled and quasiexperimental trials included. This scoping review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-SCRs) checklist (S3 Appendix) [31].

3. Results

3.1. Study Inclusion. From a total of 322 records identified from the initial search, final 41 articles were included in this scoping review for descriptive analysis, from which 13 randomised controlled and quasiexperimental trials were analysed for risk of bias and test item (herbal intervention) reporting quality (Figure 1). Five registered ongoing trials were also identified. The details of these trials can be found in supplementary material S1 Table. Three related ADR reports from the MADRAC database were successfully retrieved (official information provided through e-mail by the Head of Pharmacovigilance Section, Centre for Compliance and Quality Control, National Pharmaceutical Regulatory Agency, Malaysia). Two out of three ADR reports were included in this review while one was excluded as it involved consumption of an herbal mixture containing C. papaya and other unidentified herbs.
3.2. Demographics of Included Articles. Table 3 presents the characteristics of all included articles. Among the 23 clinical articles (21 published and 2 unpublished) included, most were randomised controlled trials on dengue patients, with India being the leading country (52.17%). All five of the ongoing trials identified also investigated the effects of *C. papaya* leaf in dengue patients (S1 Table). Both general and specific toxicity studies on rodents and nonrodents were published, mostly reported by Malaysian authors. Few herb-drug interactions were studied at the preclinical level while there were no clinical reports on these interactions (Table 3).

3.3. Clinical Evidence on Safety Profile. Details of clinical evidence on the safety profile of *C. papaya* leaf consumption are presented in Table 4. Among the published papers, 28.6% of the papers, including 25% of published randomised control trials, did not explicitly report safety-related findings [6, 36, 42].

3.4. Adverse Reactions. Based on published clinical evidence, overall, no major adverse reactions related to *C. papaya* leaf consumption were reported across a wide range of formulations, doses, and durations [5, 6, 32–50]. The most commonly reported side effects were gastrointestinal disturbances, comparable to control groups [5, 37, 39, 41, 50]. Cases of rash observed solely in the *C. papaya*-leaf-administered group of patients were also reported in two papers, highlighting a risk for allergic reactions [32, 41] (Table 4).

Two cases of unpublished ADR reports retrieved from the MADRAC database reported hepatic enzyme derangements, with a MADRAC causality score [51] of “possible.” At the time of reporting, one of the patients was recovering (Alanine Transaminase (ALT) and Aspartate Transaminase (AST) normalisation) after cessation of the *C. papaya* leaf extract capsule while the other had not (Table 5).
3.5. Herbal Intervention/Test Item Reporting Quality, Selection, Dosage Range, and Duration. Analysis of reporting quality on the herbal intervention/test item based on CONSORT checklist item No. 4 is presented in S4 Appendix. Nearly all of the published randomised controlled and quasiexperimental trials did not report on most of the recommended important reporting items pertaining to the test item quality. Only one paper (7%) [6] reported that heavy-metal levels were within allowable limits. Factors that may contribute towards extrinsic toxicities such as purity testing for heavy-metal or other contaminant testing were not reported in the other 12 papers. Although the brand name Caripill was mentioned in a few papers, the name of the manufacturer (Microlabs), details on extract (aqueous extract), and the standardised content of 40% glycoside were not specifically reported in text. However, based on the collective understanding of the investigators and information available online [52], all trials involving Caripill tablet and syrup reported here were assumed to be manufactured by Microlabs for further descriptive and risk of bias analysis.

| Demographic categories | Frequency (n) | Percentage (%) |
|------------------------|--------------|----------------|
| Clinical evidence (published and unpublished) (n = 23) | | |
| **Type of article** | | |
| Randomised controlled trial | 12 | 52.17 |
| Quasiexperimental trial | 1 | 4.35 |
| Retrospective audit | 1 | 4.35 |
| Case report/series | 7 | 30.43 |
| Other unpublished reports | 2 | 8.70 |
| **Indication** | | |
| Dengue | 15 | 65.22 |
| Chemotherapy-induced thrombocytopenia | 3 | 13.04 |
| Cancer | 1 | 4.35 |
| Chronic immune thrombocytopenia purpura | 1 | 4.35 |
| Febrile thrombocytopenia | 1 | 4.35 |
| General health | 1 | 4.35 |
| Neonatal thrombocytopenia | 1 | 4.35 |
| **Country** | | |
| India | 12 | 52.17 |
| Malaysia | 3 | 13.04 |
| Pakistan | 3 | 13.04 |
| U.S.A | 2 | 8.70 |
| Bangladesh | 1 | 4.35 |
| Indonesia | 1 | 4.35 |
| Sri Lanka | 1 | 4.35 |
| **Preclinical in vivo toxicity studies (n = 7)** | | |
| **Type of study** | | |
| General toxicity | 5 | 71.43 |
| Specific toxicity | 1 | 14.29 |
| Combination (general and specific) | 1 | 14.29 |
| **Animal model** | | |
| Rodent | 5 | 71.43 |
| Nonrodent | 2 | 28.57 |
| **Country** | | |
| Malaysia | 3 | 42.86 |
| Nigeria | 2 | 28.57 |
| Ghana | 1 | 14.29 |
| Brazil | 1 | 14.29 |
| **Herb-drug interaction studies (n = 6)** | | |
| **Type of study** | | |
| Pharmacokinetic | 2 | 33.33 |
| Pharmacodynamic | 4 | 66.67 |
| **Study model** | | |
| In vivo | 3 | 50.00 |
| In vitro | 2 | 33.33 |
| Combination (in vitro and in vivo) | 1 | 16.67 |
| **Country** | | |
| Nigeria | 3 | 50.00 |
| Italy | 2 | 33.33 |
| Japan | 1 | 16.67 |
| Author, year [ref.] | Study design | Recruited sample size, n (analysed sample size, n) | Sample description (age; gender; comorbidities) | Indication for *C. papaya* leaf | Intervention details (formulation; dose; frequency; duration) | Comparator/ cointervention | Safety data reported (yes/no) | Adverse reactions (number, n, OR percentage patient in analysed population, %) |
|---------------------|--------------|--------------------------------------------------|-----------------------------------------------|-------------------------------|-------------------------------------------------------------|---------------------------|-----------------------------|--------------------------------------------------------------------------|
| Hettige, 2008 [32]  | Case series  | 12 (12)                                          | 5–44y; 50% M, 50% F; NS                       | Dengue                        | Fresh *C. papaya* leaf juice; 2.5–5mL; 2 doses 8 hours apart | NA/ Routine dengue supportive treatment except steroids, blood products, and nonsteroidal anti-inflammatory drugs | Yes                         | Rash (n = 5)*                                                            |
| Ahmad, 2011 [33]    | Case report  | 1 (1)                                            | 45y; M; NS                                    | Dengue (diagnosed based on signs and symptoms and risk factors, without a serology test) | Fresh *C. papaya* leaf juice; 25mL; Twice daily; 5 days CPLE syrup; 5mL; Twice daily; 5 days | NA/ Broad-spectrum antibiotics and antimalarial drugs                  | No                          | —                                                                        |
| Assir, 2012 [34]    | RCT          | 39 (NS)                                          | Adult (age NS); 72% M, 28% F; NS              | Dengue                        | Placebo/ NS                                                 | Yes                       | No significant adverse event occurred in either group                  |
| Kala, 2012 [35]     | Case series  | 5 (5)                                            | 19–52y; NS; NS                                | Dengue (diagnosed based on signs and symptoms and risk factors, without a serology test) | Fresh *C. papaya* leaf juice; 30mL; 3 times daily; NS (but the observation duration was 2 days) | NA/ Not mentioned          | No                          | —                                                                        |
| Yunita, 2012 [36]   | RCT          | 80 (80)                                          | 15–34y; 56% M, 44% F; NS                      | Dengue                        | *C. papaya* leaf 70% ethanolic extract in capsule; 1100 mg; 3 times daily; 5 days | Control group without placebo/routine dengue supportive treatment | No                          | —                                                                        |
| Subenthiran, 2013 [6]| RCT          | 290 (228)                                        | Mean 28.4y ± SD 8.8; 85% M, 15% F; None       | Dengue                        | Fresh *C. papaya* leaf juice; 50 g leaves; Once daily; 3 days | Control group without placebo/routine dengue supportive treatment | No                          | —                                                                        |
| Author, year [ref.] | Study design | Recruited sample size, n (analysed sample size, n) | Sample description (age; gender; comorbidities) | Indication for C. papaya leaf | Intervention details (formulation; dose; frequency; duration) | Comparator/ cointervention | Safety data reported (yes/no) | Adverse reactions (number, n, OR percentage patient in analysed population, %) |
|---------------------|--------------|---------------------------------------------------|-------------------------------------------------|-------------------------------|---------------------------------------------------------------|-----------------------------|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Gowda, 2014 [37]    | RCT          | 30 (30)                                           | 18–55y; 73% M, 27% F; NS                       | Dengue                        | CPLE tablet (Caripill, Microlabs); 1100 mg; 3 times daily; 5 days Fresh C. papaya leaf juice | Control group without placebo/routine dengue supportive treatment | Yes                           | Gastrointestinal disturbances, e.g., nausea and vomiting which were similar across groups |
| Siddique, 2014 [38] | Case report  | 1 (1)                                             | 23 y; M; None                                   | Dengue                        | 150 mL (1 and a half leaf); Once daily; 5 days               | NA/ Commercial fruit juices (NS) | No                            | —                                                                                                                                  |
| Abhishek, 2015 [39] | RCT          | 60 (60)                                           | 18–55y; 73% M, 27% F; NS                       | Dengue                        | CPLE tablet; 1100 mg; 3 times daily; 5 days                  | Control group without placebo/Routine dengue supportive treatment | Yes                           | Gastrointestinal disturbances, e.g., nausea and vomiting which were similar across groups |
| Gadhwal, 2016 [40]  | RCT          | 400 (400)                                         | >16y; 69% M, 31% F; NS                         | Dengue                        | Dried C. papaya leaf crude aqueous extract in capsule; 500 mg; Once daily; 5 days | Control group without placebo/routine dengue supportive treatment (antipyretic paracetamol, intravenous 0.9% normal saline, antiemetic) | Yes                           | None                                                                                                                             |
| Kasture, 2016 [41]  | RCT          | 300 (292)                                         | 18–55y; 55% M, 45% F; NS                       | Dengue                        | CPLE tablet (Caripill, Microlabs); 1100 mg; 3 times daily; 5 days | Placebo/ Routine dengue supportive treatment except corticosteroids | Yes                           | Nausea (n = 26) and vomiting (n = 17) which were evenly distributed across groups |
| Singhai, 2016 [42]  | RCT          | 80 (NS)                                           | >18y; NS; NS                                    | Febrile thrombocytopenia      | CPLE capsule; 2 capsules (strength NS); 3 times daily; 9 days | NS/none reported | No                            | —                                                                                                                                  |
| Author, year [ref.] | Study design | Recruited sample size, \(n\) (analysed sample size, \(n\)) | Sample description (age; gender; comorbidities) | Indication for \(C.\ papaya\) leaf | Intervention details (formulation; dose; frequency; duration) | Comparator/ cointervention | Safety data reported (yes/no) | Adverse reactions (number, \(n\), OR percentage patient in analysed population, %) |
|---------------------|--------------|----------------------------------------------------------|-------------------------------------------------|----------------------------------|---------------------------------------------------------------|-----------------------------|--------------------------------|---------------------------------------------------------------|
| Adarsh, 2017 [43]   | RCT          | 100 (100)                                               | 21–65 y; 45% M, 55% F; NS                       | Dengue                           | CPLE capsule; 500 mg; 3 times daily; 5 days                   | Placebo/ Routine dengue supportive treatment (intravenous fluids, paracetamol, antacids, platelet transfusion, and inotropic agents) | Yes                            | No severe adverse events; Gastrointestinal disturbances, e.g., nausea and vomiting reported in both treatment and control groups |
| Hussain, 2017 [44]  | Quasiexperimental trial | 60 (58)                                               | 28–80 y; 66% M, 34% F; Malignancy, ischaemic heart disease, chronic obstructive pulmonary disease, diabetes, and others (NS) | CIT                              | Fresh papaya leaf granules in capsule; 290 mg; Twice daily; 5 days | Control group without placebo/ Chemotherapy, single or in combination of 5-fluorouracil, bleomycin, etoposide, ifosfamide, cyclophosphamide, paclitaxel, docetaxel, carboplatin, oxaliplatin, gemcitabine, capecitabine, and cisplatin with radiation | Yes                            | None; No significant changes in haematological and biochemical (NS) values; No treatment-related deaths |
| Sundarmurthy, 2017 [5] | RCT          | 40 (40)                                                 | Mean 42.5 y ± SD 10.2; 62.5% M, 37.5% F; Solid tumour malignancy and others (NS) | CIT                              | CPLE tablet (marketed product, brand (NS)); 1100 mg; 3 times daily; 7 days | Control group without placebo/NS | Yes                            | Diarrhea (15%), dizziness (10%), vomiting (15%), headache (10%), and dysgeusia (20%) the in intervention group; Comparable to the control group |
| Rahmat, 2018 [45]   | Case report  | 1 (1)                                                    | 76 y; M; Prostate cancer, hypertension, IgG2/ IgG4 subclass deficiency | Prostate cancer                  | CPLE tea and elixir; 4 g tea, 5 mL elixir; Twice daily (morning tea, night elixir); NS | NA/ None reported, though having a strong history of using natural products | Yes                            | None                                                                        |
| Author, year [ref.] | Study design | Recruited sample size, n (analysed sample size, n) | Sample description (age; gender; comorbidities) | Indication for C. papaya leaf | Intervention details (formulation; dose; frequency; duration) | Comparator/ cointervention | Safety data reported (yes/no) | Adverse reactions (number, n, OR percentage patient in analysed population, %) |
|---------------------|-------------|------------------------------------------------|-------------------------------------------------|-------------------------------|-------------------------------------------------|-----------------------------|-----------------------------|------------------------------------------------|
| Hampilos, 2019 [46] | Case series | 4 (4) | 21–67 y; 50% M, 50% F; Chronic immune thrombocytopaenic purpura, hyperlipidaemia, hypothyroidism, and ulcerative colitis | Chronic immune thrombocytopaenic purpura | C. papaya leaf 10:1 glycerin extract (in liquid and capsule); 600 mg–1200 mg; 3 times daily; Up to ten months | NA/ Steroids (prednisolone), gemfibrozil, and levothyrdoxine | Yes | Increased glucose levels (n = 1); lymphopaenia (n = 1) **; Increased appetite (n = 1) |
| Pandita, 2019 [47] | Case report | 1 (1) | Neonate (30 weeks preterm 23 days of life); M; None | Sepsis thrombocytopaenia | CPLE syrup (Caripill, Microlabs); 20 mg/kg; 3 times daily; 19 days (tapered off) | NA/ Hospital resuscitative support | Yes | None; Baby healthy up to 18 months of age at follow-up |
| Srikanth, 2019 [48] | RCT | 294 (285) | Mean 7.75 y ± SD 3.27; 50% M, 50% F; NS | Dengue | CPLE syrup (Caripill, Microlabs); 275–550 mg; 3 times daily; 5 days | Control group without placebo/ Routine dengue supportive treatment | Yes | None; Baby healthy up to 18 months of age at follow-up |
| Sathyapalan, 2020 [49] | RCT | 50 (50) | Mean 52.5 y ± SD 15; 61% M, 39% F; NS | Dengue | Placebo/ Routine dengue supportive treatment | Yes | No serious adverse events reported up to 2 weeks after intervention cessation |
| Sreelatha, 2020 [50] | Single-arm retrospective audit | 50 (50) | 19–75 y; 50% M, 50% F; Solid tumour malignancy and others (NS) | CIT | CPLE tablet; 1100 mg; 3 times daily; Up to 2 weeks | NA/temozolomide, paclitaxel, docetaxel, gemcitabine, doxorubicin, cyclophosphamide, rituximab, vincristine, 5-fluorouracil, cisplatin, carboplatin, oxaliplatin, and capcitabine | Yes | Dysgeusia and nausea |

* Diagnosed as haemorrhagic skin rash due to disease instead; ** thought to be not related to C. papaya leaf treatment but steroid treatment instead; CIT = chemotherapy-induced thrombocytopaenia; CPLE = C. papaya leaf extract; F = female; M = male; NA = not applicable; NS = not specified; SD = standard deviation; y = years.
Overall, 61% of the included articles mentioned the type of extract used as an intervention. The most commonly investigated formulation in the clinical articles included was juice (26%) followed by a commercialised standardised aqueous extract of C. papaya leaf containing 40% glycosides (Caripill, Microlabs) (21.7%). There were no reports on specifying the type of extract. In general, C. papaya leaf juice was reportedly given at doses ranging from 2.5 mL in children to up to 150 mL a day in adults (Table 4). The youngest patient to be safely administered with 20 mg/kg C. papaya leaf extract was a preterm neonate at 23 days of life [47]. In terms of duration, C. papaya leaf extract and juice were administered only for a short duration of three to five days in randomised controlled and quasiexperimental trials, mostly in dengue patients. A longer duration of consumption of a 10:1 glycerin extract, for up to ten months, was reported in case reports of patients with chronic immune thrombocytopenic purpura (Table 4).

For the two unpublished ADR reports of liver enzyme derangements, the dose of C. papaya leaf extract capsule administered was 600 mg once daily over a short duration of three to six days, with incomplete details on the type of extract and concomitant medications, as well as underlying comorbidities and preexisting hepatic impairment risk factors of the patients (Table 5).

### 3.6. Risk of Bias Analysis

Risk of bias analysis (Figure 2) of 13 randomised controlled and quasiexperimental trials showed that proper blinding of participants and personnel was only achieved in 15.4% (n = 2/13) of the studies. Performance bias was the most highly rated bias in the included articles (61.54%, n = 8/13). Most of these studies did not include administration of a formulated placebo in the control group. Although reported as randomised controlled trials, only four papers explicitly reported the details of randomisation methods (computer generated table, online randomisation software, odd-even method, and block-of-10) to achieve low selection bias while randomisation methods were not specified for the remaining 9 studies. Reporting bias was found to be equally low and high in 38.5% (n = 5/13) of the studies. Five studies were categorised as containing high reporting bias due to missing reports on safety data including biochemical investigations of renal and hepatic function. Three papers were categorised as having high risk of other biases were either industry sponsored or authored by personnel from the company who manufactured the herbal intervention/test item. A summary on risk-of-bias analysis for individual papers is presented in Figure 3.

### 3.7. Animal Toxicity Studies

Details and findings of animal toxicity studies of the oral C. papaya leaf are presented in Table 6. In general, C. papaya leaf juice and aqueous extract are non-toxic at high doses up to 2000 mg/kg in rats administered as a single dose [55, 57]. There was also no mortality reported in any animal toxicity studies regardless of dose (up to 2000 mg/kg), duration (up to 24 weeks), and formulation [53–59]. However, there are some concerns on the hepatotoxic effects of long-term administration. In rats administered with freeze-dried C. papaya leaf juice for 21 days, raised ALT and Alkaline Phosphatase (ALP) levels

### Table 5: Details of unpublished adverse drug reaction (ADR) reports of C. papaya leaf consumption in humans.

| Report no. | Gender | Age (years) | ADR description | Indication for C. papaya leaf | Intervention details (formulation; dose; frequency; duration) | Additional laboratory evaluation (adulteration and heavy-metal analysis) | Potential confounding factors (e.g., concomitant medications/comorbidities) | MADRAC causality assessment |
|------------|--------|-------------|-----------------|-----------------------------|---------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------|
| 1          | Male   | 17          | Deranged liver enzymes after 6 days of consumption reported in a patient diagnosed with dengue fever | Dengue | C. papaya leaf extract; 600 mg; Once daily; 6 days | Negative detection for paracetamol and nonsteroidal anti-inflammatory drugs; heavy-metal levels within allowable limits | Not specified | Possible |
| 2          | Female | 37          | General health   | C. papaya leaf extract; 600 mg; Once daily; 3 days | Negative detection for steroids; heavy-metal levels within allowable limits | Not specified | Possible |

Source: Pharmacovigilance Section, Centre for Compliance and Quality Control, National Pharmaceutical Regulatory Agency, Malaysia; ADR = adverse drug reaction; MADRAC = Malaysian Adverse Drug Reactions Advisory Committee.
Figure 2: Risk of bias analysis of included randomised controlled and quasiexperimental trials (n = 13).

Figure 3: Risk of bias analysis summary for individual randomised controlled and quasiexperimental trials (n = 13). Green and “+” = low risk, yellow and “?” = unclear risk, and red and “−” = high risk.
| Author, year [ref.] | Animal model (species; gender) | Intervention details (formulation; dose; frequency; duration; quantitative analysis of content) | Comparator | Quantitation of toxic/safe dose | Description of toxicity findings |
|----------------------|---------------------------------|-------------------------------------------------|------------|-----------------------------|--------------------------------|
| Akinloye, 2010 [53]  | Rat (Wistar; Male)              | Air-dried *C. papaya* leaf decoction; 500 mg/kg; Daily; 21 days; NS | 0.9% sodium chloride | NA                          | (i) Male reproductive toxicity |
|                      |                                 | *C. papaya* leaf aqueous extract; 200 mg/kg; Daily; 24 weeks; NS |            | Water                       | (i) Transient elevation of liver enzymes (ALP, GGT, and bilirubin) at initial periods of treatment (3 to 5 weeks); (ii) Risk of bile duct obstruction |
| Omonkhua, 2011 [54]  | Rabbits (New Zealand; NS)       | Freeze-dried *C. papaya* leaf aqueous extract; 5, 50, 300, and 2000 mg/kg; Once; Single dose; NS | Water     | NA                          | (i) No mortality and acute adverse events at all doses; (ii) Raised HGB, HCT, RBC, TG, and total protein levels at 2000 mg/kg; (iii) No relative organ weight and gross histopathology changes (i) No mortality and acute adverse events at all doses; (ii) No abnormalities in serum haematology; (iii) Raised ALT and ALP levels at 10 mg/kg and 140 mg/kg (male and female); (iv) Raised total protein, AST, and HDL at 140 mg/kg (female); (v) No relative organ weight and histopathology changes (i) No mortality and acute adverse events, no changes in body weight and food and water intake at all doses; (ii) No abnormalities in serum haematology; (iii) Raised LDH at 2000 mg/kg (male); (iv) Raised albumin at 140 mg/kg (male); (v) Raised protein and albumin at 140 and 2000 mg/kg (female); (vi) Reduced creatinine at 2000 mg/kg (male and female); (vii) No relative organ weight and histopathology changes |
| Halim, 2011 [55]     | Rat (Sprague Dawley; female)    | Lypophilised fresh *C. papaya* leaf juice; 10, 140, and 2000 mg/kg; Daily; 28 days; NS | Water     | NS                          |                                |
| Afzan, 2012 [56]     | Rat (Sprague Dawley; male and female) | Freeze-dried fresh *C. papaya* leaf juice; 10, 140, and 2000 mg/kg; 13 weeks; NS | Water     | NOAEL = 2000 mg/kg (male and female) |                                |
were observed at 10 mg/kg and 140 mg/kg for males and females, respectively. Elevated total protein and AST were also observed in female rats administered with 140 mg/kg freeze-dried *C. papaya* leaf juice in the same study. However, there were no histopathological changes in the liver post-mortem [56].

3.8. Herb-Drug Interactions. Six preclinical studies reported several differential herb-drug interactions between oral administration of *C. papaya* leaf with oral hypoglycaemic agents (metformin and glimepiride), antimalarial (artemisinin), antibiotic (ciprofloxacin), and cardiovascular drug (digoxin). No specific compounds or biomarkers of *C. papaya* leaf were objectively identified as the main contributor of interaction (Table 7).

### Table 6: Continued.

| Author, year [ref.] | Animal model (species; gender) | Intervention details (formulation; dose; frequency; duration; quantitative analysis of content) | Comparator | Quantitation of toxic/safe dose | Description of toxicity findings |
|----------------------|--------------------------------|-------------------------------------------------------------------------------------------------|------------|-------------------------------|----------------------------------|
| Ansah, 2015 [58]     | Rat (Sprague Dawley; male and female) | Air-dried *C. papaya* leaf decoction;  
Acute:  
100–5000 mg/kg; Once;  
Single dose; NS  
Subacute:  
10–500 mg/kg; Once daily; 2 weeks; NS  
Reproductive:  
10–500 mg/kg; Once daily; 2 weeks (male); throughout the gestation period (female, duration NS); NS | Distilled water | LD$_{50}$ > 2000 mg/kg | (i) No mortality and acute adverse events;  
(ii) No abnormalities in serum haematology;  
(iii) Hepatotoxicity: abnormalities in liver enzymes and histology (subacute, male and female);  
(iv) Male and female reproductive toxicity |
| Nghonjuyi, 2016 [59] | Chicks (Kabir; male and female) | Air-dried *C. papaya* leaf 70% hydroethanolic extract;  
Acute:  
40–5120 mg/kg; Once; Single-dose; NS  
Subchronic:  
0–640 mg/kg; Once daily; 6 weeks; NS | Distilled water | LD$_{50}$ > 5120 mg/kg | (i) No mortality and acute adverse events, no changes in body weight, food, and water intake at all doses;  
(ii) Transient raised WCC at 640 mg/kg (male, subchronic);  
(iii) No abnormalities in serum biochemistry |

3.8. Herb-Drug Interactions. Six preclinical studies reported several differential herb-drug interactions between oral administration of *C. papaya* leaf with oral hypoglycaemic agents (metformin and glimepiride), antimalarial (artemisinin), antibiotic (ciprofloxacin), and cardiovascular drug (digoxin). No specific compounds or biomarkers of *C. papaya* leaf were objectively identified as the main contributor of interaction (Table 7).

### 4. Discussion

Thrombocytopenia in dengue fever remains the most investigated indication of *C. papaya* leaf in clinical studies [6, 32–41, 43, 48–50]. This is also reflected in the list of registered ongoing clinical trials (S1 Table). A majority of both published and ongoing studies are conducted by countries (e.g., India, Malaysia, and Pakistan) with interest in utilising *C. papaya* leaf for diseases of high local prevalence such as dengue [66, 67]. Arachidonate 12-lipoxygenase
(ALOX12) gene activity enhancment is thought to be one of the important mechanisms of improving platelet counts by *C. papaya* leaf [6]. Hence, in recent years, there is growing interest in the use of *C. papaya* leaf for non-dengue-infection-related thrombocytopaenia such as chemotherapy-induced thrombocytopaenia [5, 44].

### 4.1. Intrinsic Toxicity

#### 4.1.1. Clinical Evidence

Oral consumption of *C. papaya* leaf is generally well tolerated across a variety of formulations (mostly as juice and aqueous extract) in adults though high-quality and comprehensive safety data has not been well documented. *C. papaya* leaves were mostly administered for a short duration of up to five days [6, 32–34, 36, 37, 39–44, 48,49], though longer durations of administration have been reported to be tolerable [46]. Based on the published literature, mild gastrointestinal disturbances were most commonly reported [5, 6, 32–50]. Rash was reported in two papers in the *C. papaya* leaf juice and aqueous extracts intervention group solely [32, 41]. Although there may be some concerns on allergic reactions, no serious adverse events such as cases of anaphylaxis were reported in all included clinical articles.

Two cases of liver enzyme derangements were identified from unpublished local ADR reports, which documented a "possible" causal relationship of *C. papaya* leaf extract with the adverse event. These two reports involved consumption of a locally registered product within the recommended dose.

| Author, year [ref.] | Study type (animal model, if any) | *C. papaya* formulation details (formulation; dose; frequency; duration; biomarker) | Drug candidate(s) of interaction | Outcome of interaction | Proposed type of interaction |
|---------------------|----------------------------------|----------------------------------------------------------------------------------|---------------------------------|------------------------|-----------------------------|
| Fakeye, 2007 [60]   | *In vivo* (rat)                  | Dried *C. papaya* leaf 96% ethanolic extract; 5mg/kg and 10mg/kg; 3 and 7 days; NS | Metformin, glimepiride          | Enhanced hypoglycaemic effect | Pharmacokinetic + pharmacodynamic |
| Sanella, 2009 [61]  | *In vitro*                       | Dried *C. papaya* leaf decoction; 100 and 150μg/mL; NA; | Artemisinin                    | Synergism in inhibiting growth of *Plasmodium falciparum* | Pharmacodynamic |
| Onaku, 2011 [62]    | *In vivo* (mouse)                | Fresh *C. papaya* leaf crude aqueous extract; 50–200mg/kg; NS | Artemisinin                    | Antagonism in percentage reduction of parasitaemia (*P. berghei*) | Pharmacodynamic |
| Oga, 2012 [63]      | *In vitro*                       | Dried *C. papaya* leaf decoction of aqueous extract; 0.02–20mg/mL; Single dose; NA; NS | Digoxin                        | Inhibition of p-glycoprotein transport of digoxin | Pharmacokinetic |
| Ukpo, 2017 [64]     | *In vivo* (rabbit)               | Freeze-dried crude *C. papaya* leaf aqueous extract; 500mg/kg; Single dose; NA; NS | Ciprofloxacin                  | Reduced absorption and serum half-life of ciprofloxacin | Pharmacokinetic |
| Sanella, 2019 [65]  | *In vivo* (mouse) and *in vitro*| Dried *C. papaya* leaf decoction; 100 and 150μg/mL (in *in vitro*), 250mg/kg/day (in *in vivo*); 14 days (in *in vivo*); Total flavanoids (expressed as rutin) | Artemisinin                    | Subsynergism in inhibiting *P. falciparum* growth | Pharmacodynamic |

NA = not applicable, NS = not specified.
of the specific product for short duration of time (three to six days). Additional laboratory quality assessments also ruled out heavy-metal contamination and product adulteration. Hepatic side effects of C. papaya leaf were not reported in any other published clinical evidence regardless of formulation, age, dose, and duration of exposure. However, in most of the randomised controlled studies, patients with underlying liver impairments and abnormal liver enzymes were already excluded from participation [5, 6, 37, 39–41, 48, 49]. It is inherently challenging to make accurate causality assessments in voluntary ADR reporting due to the anecdotal nature of ADR reports. Furthermore, outcomes of causality assessment are heavily influenced by an individual reporter’s judgement. For example, factors such as knowledge and familiarity with the ADR reporting form components can vastly affect causality scorings [51]. In both reports, the contribution of confounding factors such as concomitant medications or underlying medical conditions was unclear.

In herbal medicine development, it is well established that several confounding factors such as the agroclimatic factors and types of extraction solvent used can influence the final phytochemical composition of a formulation, which may, in turn, affect efficacy and toxicity [68–70]. Therefore, acceptable safe dose range and duration based on clinical trials are only specific to each formulation as reported in the literature, e.g., 1100mg three times daily for standardised aqueous extract to 40% glycoside for up to 5 days [49]. In published trials, there is insufficient reporting and data transparency on the quantitative analysis of the composition of most test items. Reporting bias with missing data of safety-related laboratory investigations such as biochemical test results of renal and liver functions was also observed. Therefore, with currently available evidence, it is challenging to deduce a safe dose of C. papaya leaf specific to its phytochemical composition. Specifically in paediatric cases, only one randomised controlled trial among dengue-infected children was conducted and published [48], while one case series [32] and one case report [47] documented the safe administration of C. papaya leaf extract in young children. Future trials with detailed quantitative assessment of phytochemical analysis, specialised investigations in paediatric population, and improved ADR reporting are needed to strengthen safety findings. Such data are valuable in providing input for the development of comprehensive clinical guidelines.

4.1.2. Animal Studies. Extrapolating from animal toxicity studies, elevated liver enzymes have been reported in rats and rabbits administered with repeated doses of C. papaya leaf juice and aqueous extracts, as well as decoction [54, 56–58]. One paper reported histopathological fatty changes and fibrosis in the liver, as well as haemorrhage and inflammation in the hepatic portal tract of rats administered with air-dried C. papaya leaf decoction (140 mg/kg for two weeks) [58]. Time-course evaluation of the effects of C. papaya leaf aqueous extract (200 mg/kg, 24 weeks) on rabbit hepatic enzymes revealed transient elevation of ALP, GGT, and bilirubin at initial phases of treatment possibly due to bile obstruction which subsided over time (after 5 weeks) without cessation of intervention [54]. In subacute and subchronic toxicity studies conducted on rats (fresh C. papaya leaf juice, up to 2000 mg/kg) according to the Organization for Economic Cooperation and Development (OECD) Guidelines for Testing of Chemicals, although elevated liver enzymes were observed, no histopathological changes were detected in the liver postmortem [56, 57]. In a single-dose acute toxicity study of C. papaya leaf aqueous extract, no death, acute adverse events, and biochemical abnormalities were detected at doses up to 2000 mg/kg [55]. Among the major compounds identified in C. papaya leaf are rutin, carpaine, manghaslin, papain, and clitorin [56, 71]. Currently, there is little evidence available on the hepatotoxicity of these individual compounds. Among these, rutin has, in fact, demonstrated hepatoprotective properties possibly via antioxidant and anti-inflammatory effects [72, 73], while an in silico docking study predicted that carpaine has low-risk hepatotoxic potential [74]. The mechanism of hepatotoxicity of C. papaya leaf remains to be elucidated. In view of concerns on hepatotoxicity, C. papaya leaf consumption should be cautioned in patients with underlying hepatic impairment while safety in long-term consumption remains to be ascertained. Future clinical trials should also include assessments and detailed reports on liver function tests to further ensure its safety specific to the investigated formulation. Insufficient reporting on the effects of investigated C. papaya leaf formulations on serum liver enzymes was found to be one of the contributing factors of reporting bias in the randomised clinical trials included here.

Reproductive side effects have also been reported in animal studies [53, 58]. At doses above 60 mg/kg, air-dried C. papaya leaf decoction administered throughout the gestational period negatively impacted the length of gestation and fertility index, as well as litter size and birth weight of female rats [58]. Male reproductive toxicity of C. papaya leaf decoction (10 to 500 mg/kg, 14 to 21 days), evidenced by impairment in all investigated andrological parameters including semen analysis, serum follicle stimulating hormone (FSH), luteinising hormone (LH), and testosterone levels, as well as degenerative changes of the seminiferous tubule epithelium, was observed in two animal studies [53, 58]. As there are insufficient data on the effects of short-term consumption of C. papaya leaf on the reproductive system, pregnant women are often excluded from clinical trials; the risk of consumption during human pregnancy cannot be ruled out and should, therefore, be avoided.

4.1.3. Herb-Drug Interactions. In clinical trials, C. papaya leaf was commonly administered with routine supportive treatment of dengue fever which often includes antipyretics and antiemetics. No unfavourable outcomes were explicitly reported with short durations of coadministration with these drugs, though it was not within the trials’ objectives to investigate herb-drug interactions [6, 34, 36, 37, 39–41, 43, 48, 49]. In preclinical studies, C. papaya leaf
demonstrated significant herb-drug interaction with several drugs including metformin, gliclazide, digoxin, ciprofloxacin, and artemisinin [60–65]. Herb-drug interaction investigations revealed complex interactions between 96% C. papaya leaf ethanol extract and other oral hypoglycaemic agents (metformin and gliclazide) [60]. As a single intervention, C. papaya leaf reported hypoglycaemic activity [75, 76]. When given in combination with metformin, 96% C. papaya leaf ethanol extract initially reduced metformin’s hypoglycaemic effect at two hours but subsequently enhanced its effect at 24 hours. For coadministration with gliclazide, the same extract delayed the onset of hypoglycaemic effect but eventually enhanced it at 24 hours. The mechanism of interaction was not elucidated, but combined pharmacokinetic (reduced absorption) and pharmacodynamic interactions (differential effects seen with oral hypoglycaemic agents with different mechanisms of action) were proposed [60].

Differential interaction effects were also reported between two C. papaya leaf formulations with the antimalarial, artemisinin. When administered in combination with artemisinin, isobologram analysis shows subsynergism or additive antimalarial effects of C. papaya leaf decoction against Plasmodium falciparum [61, 65]. C. papaya leaf reported antimalarial properties as a single intervention [65, 77, 78], which may contribute towards some pharmacodynamic additive effects, though the mechanisms remain unclear. On the other hand, C. papaya leaf crude aqueous extract demonstrated antagonistic antimalarial effects against artemisinin in Plasmodium berghei-infected mice [62]. Antagonistic activities were thought to be attributable to the pharmacological properties of these two agents [62]. C. papaya leaf has reported antioxidant activities due to the presence of phenolic compounds [79] which may oppose the antimalarial activity of artemisinin achieved through free-radical production [80]. The exact factors that contributed towards such contrasting findings of herb-drug interaction between C. papaya leaf and artemisinin remain unclear. Still, these findings further strengthen the evidence on the presence of variable phytochemical composition in different formulations of the same plant, resulting in different activities [69].

An in vitro pharmacokinetic interaction study reported that dried C. papaya leaf decoction of aqueous extract inhibits p-glycoprotein transport of digoxin in a dose-dependent manner, hence potentially impeding intestinal absorption and bioavailability of digoxin [63]. However, the mechanism and nature of inhibition were not investigated. C. papaya leaf aqueous extract, given 30 minutes prior to ciprofloxacin, also resulted in decreased absorption and shorter serum half-life of ciprofloxacin in rabbits [64]. As ciprofloxacin is well known to chelate with cations such as Ca²⁺ [81], reduced absorption of ciprofloxacin was thought to be partly due to binding with low levels of minerals and heavy metals present in the investigated formulation [64].

One of the most common pathways of herb-drug interaction is through the effect on cytochrome (CYP) enzymes, a major group of liver metabolising enzymes of many drugs [82]. At present, there is limited information on the effects of C. papaya leaf on these enzymes, though in silico prediction on individual phytochemical compounds present in C. papaya leaf have reported potential inhibitory effects [74]. Future studies on the effects of C. papaya leaf on various CYP enzymes are useful in improving the understanding of its safety profile and governance of its clinical administration.

4.2. Extrinsic Toxicity. No conclusive findings on extrinsic toxicity can be drawn as most of the required quality data to assess extrinsic toxicity were not sufficiently reported based on the CONSORT reporting checklist for herbal interventions, item No. 4 [29]. It was observed that adherence to recommended reporting guidelines was suboptimal in the included clinical papers of this review, similar to previous findings of systematic reviews assessing the reporting quality of herbal trials [83, 84]. There is insufficient reporting on the chemical fingerprinting and qualitative evaluation of phytochemical composition or other foreign materials, e.g., pesticide in most randomised controlled and quasieperimental trials. Only one paper reported that the heavy-metal levels of the investigated test item were within allowable limits [6].

Heavy-metal contamination from soil and the presence of pesticides in raw plants of herbs used in formulating the final herbal medicine product are important factors to consider when evaluating extrinsic toxicity [85]. It has been reported that heavy metals and pesticides are commonly detected in various plants and herbs [86, 87]. It is commonly understood that quality data specific to the investigated test item are required by regulatory authorities of several countries for approval of product registration and conducting clinical trials [88, 89]. Therefore, this may explain our observation on the lack of reporting as test items may be assumed to be of sufficient quality as regulated by individual authorities. However, to allow for meaningful data pooling and analysis of future studies, there is still a need to improve awareness of the availability and compliance to such reporting standards for published articles, specific to herbal medicine trials [29].

4.3. Limitations. There are several limitations of this review. Firstly, only English articles were included. However, our paper took into account all previously published randomised controlled trials which were included in the two most recent systematic reviews on efficacy and safety of C. papaya leaf in dengue patients [24, 25], with additional published papers on other medical condition apart from dengue, as well as articles from grey literature. Hence, we still think that this review adequately represents the bulk of the available safety and herb-drug interaction evidence specific to C. papaya leaf consumption. Quantitative analysis to pool incidence of reported adverse reactions was not possible in this review due to the lack of data on actual incidence of each adverse event in both treatment arms reported. Insufficient reporting on quantitative analysis on the phytochemical composition of an
individual test item further contributed towards the difficulty in performing meaningful data comparison. Furthermore, as only three out of thirteen trials administered a placebo in the control group, there is a high risk for performance bias for such analysis. Lastly, this review was unable to critically evaluate the risk of extrinsic toxicity due to limited reporting on the quality of test items/herbal interventions investigated.

5. Conclusions

In conclusion, *C. papaya* leaf consumption in adults is generally safe for short-term use though cautioned in pregnancy and people with liver impairment. Gastrointestinal disturbances and rash are the most commonly reported side effects. The most frequent investigated formulation is leaf juice at doses of 2.5 mL in children to 150 mL in adults per day followed by standardised aqueous extract (40% glycosides) tablets at 1100 mg three times daily. *C. papaya* leaf has potential herb-drug interactions with oral hypoglycaemic agents, p-glycoprotein substrates, and antibiotics with cation chelating properties; hence, coadministration of these agents should be avoided. Postmarketing surveillance to monitor the safety of *C. papaya* leaf administration in the larger populations is warranted, with special focus recommended on hepatic side effects.

### Abbreviations

- ADR: Adverse drug reaction
- ALOX12: Arachidonate 12-lipoxygenase
- ALP: Alkaline phosphatase
- ALT: Alanine transaminase
- AST: Aspartate transaminase
- CONSORT: Consolidated Standards of Reporting Trials
- CYP: Cytochrome
- FSH: Follicle stimulating hormone
- GGT: Gamma-glutamyl transferase
- LH: Luteinising hormone
- LILACS: Latin American and Caribbean Health Sciences Literature
- MADRAC: Malaysian Adverse Drug Reactions Advisory Committee
- OECD: Organization for Economic Cooperation and Development
- PICO: Population, Intervention, Comparison, and Outcomes
- PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- PRISMA-SCR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
- WHO: World Health Organization

### Data Availability

All data used to support the findings of this study are included within the article and supplementary information files.

### Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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### Supplementary Materials

S1 Table. Details of ongoing trials. S1 Appendix. Sample search strategy and keywords. S2 Appendix. Data extraction tables. S3 Appendix. PRISMA-ScR checklist. S4 Appendix. CONSORT checklist for herbal trials, item No. 4. (Supplementary Materials)

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