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Supportive care and herbal interventions in dengue fever: A critical appraisal of hydration, nutrition, and plant-based therapies

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ABSTRACT

Dengue fever is a significant mosquito-borne viral disease in tropical and subtropical areas that causes a significant burden to public health systems and the affected communities. There is no definite antiviral treatment that can be used routinely in clinical practice, though there is growing interest in natural management, especially in endemic countries where home-based care, traditional medicine, and plant-derived adjuncts are widely used. The objective of this review is to critically evaluate evidence for natural and supportive management strategies in dengue fever, including oral hydration, nutritional support, rest, non-pharmacological symptom relief, and selected herbal interventions. A focused narrative review of clinical, preclinical, systematic-review, and guideline-based literature was conducted. Evidence supports oral hydration as the most established supportive measure in uncomplicated dengue, while nutritional support and rest may aid recovery. *Carica papaya* leaf extract may improve platelet counts, but this has not consistently translated into better clinical outcomes such as reduced bleeding, shock, hospitalization, or mortality. Evidence for other ethnomedicinal plants remains limited and largely preclinical. Overall, natural approaches may be useful only as adjuncts to standard supportive care and should not replace clinical monitoring or timely referral. Further well-designed trials are needed to clarify efficacy, safety, dosing, and standardization.

KEYWORDS: Dengue fever; Herbal; Hydration; Nutrition

1. Introduction

Dengue fever has become among the most significant viral diseases transmitted by mosquitoes in the world and has turned out to be

a significant burden to the health systems of the population in the tropical and subtropical regions[1,2]. According to the World Health Organization (WHO) report, dengue is endemic in over 100 countries, the number of reported cases has increased significantly over recent decades, and was a historic high of over 14.6 million cases and over 12 000 deaths in 2024[3,4]. Additionally, the WHO also reports that the actual burden is significantly greater than the number of surveillance counts given since a significant number of infections are either asymptomatic or mild and are treated outside of formal health care settings. This geographic proliferation, frequent outbreaks, and under-acknowledgment have transformed dengue not just into a biomedical issue, but also a social, household, and health systems issue, especially in areas where access to prompt diagnosis and follow-up treatment may be unreliable[5].

Currently, there is no antiviral therapy of dengue in routine clinical use. Both WHO and Center for Disease Control and Prevention (CDC) stress that dengue is treated using the framework of supportive care[6]. The CDC also positions the management of dengue based on supportive care and emphasizes that serious dengue is a hospitalized illness[7–9]. The new booklet by the WHO on the management of dengue cases in primary health care and home-based care reflects this fact by highlighting the natural progression of the disease, early identification, proper fluid replacement, and early referral in primary care and resource-constrained environments[10].

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Notably, home management is not positioned in this framework as an alternative system of medicine, but as a systematized continuation of evidence-based supportive care of the chosen patients who do not exhibit danger signs[11]. In actual practice however, the term natural management is much more widely applied by the layman and in the discourse of complementary medicine to include oral hydration, nutritional support, rest, traditional dietary practices, plant-based preparations, herbal juices, and folk remedies aimed at reducing fever, improving appetite, increasing platelet counts, or shortening recovery[12,13].

Early symptoms tend to be unspecific and thus are hard to diagnose, leaving room to self-treat before the disease process becomes apparent[14,15]. The CDC emphasizes that by identifying the initial symptoms of shock and initiating intensive supportive treatment using intravenous fluids, the risk of death in severe dengue can be lowered to less than 0.5%[16]. This fact is quite germane in the consideration of natural or home-based approaches. Therefore, it is not whether there are natural measures or not, but whether they are applied within a clinically appropriate window and in a way that is compatible with safe dengue triage[17]. The focus of fluid balance has been described as severe dengue being marked by high vascular permeability, and plasma leakage, especially at the acute stage[17,18]. The home-based care focusing on early recognition, fluid management, and monitoring developed by the WHO is based on the idea that dehydration and intravascular volume depletion are critical factors of clinical deterioration[19]. The CDC also suggests rest, proper oral hydration, acetaminophen in case of fever, and avoiding non-steroidal anti-inflammatory drugs (NSAIDs). These interventions might not appear very complex, but they deal with the most immediate physiological risks of uncomplicated dengue and form the basis upon which every other adjunctive strategy should be evaluated[19].

The other factor that makes this topic a matter of close consideration is the fact that the general discourse about the management of dengue is usually narrowed down to thrombocytopenia[20]. One of the most apparent laboratory alterations of dengue is the decline in platelet counts; hence, it has turned into a significant focus of plant-based and over-the-counter treatments, namely, papaya leaf preparations. Nevertheless, the platelet count is not a defining feature of clinical severity in dengue[21,22]. The clinical framing of the CDC focuses on signs of warning, plasma leakage, hemodynamic compromise, severe bleeding, and organ involvement, and not thrombocytopenia alone. This implies that even an intervention that can increase the number of platelets without affecting the overall disease process can still lack clinical benefit[23,24]. The platelet-centric story can also be a false reassurance, making the families proceed with self-treatment despite

the changing vascular leakage or early shock. A stringent review is thus needed to get the discussion out of the single surrogate markers to more impactful results of deterioration, hospitalization, bleeding events, duration of symptoms, tolerability, and safety[25,26].

This review critically analyzes supportive care for dengue with a specific focus on safe home-based care, fluid maintenance, nutritional support, symptomatic care, surveillance of warning signs and the judicious use of natural/plant-based supplements in the context of evidence based clinical practice. This review takes a more holistic and safety-based approach to dengue care as opposed to prior reviews which have largely focused on general clinical care, hospital-based fluid resuscitation or the use of individual herbal remedies such as papaya leaf extract. This review aimed to address a key gap in knowledge, specifically the lack of a clinically-balanced review explaining which natural or supportive strategies might be recommended, which have less evidence to support them, and how the use of those that appear to be effective might be misguided and forestall prompt medical evaluation during this critical period of the disease known as dengue. Therefore, this review sets out to close this gap between community-level care for dengue and its scientific support, evaluating natural methods of management as complementary to normal supportive treatment.

2. Natural supportive management in mild dengue

2.1. Hydration based natural support

Early and sufficient oral hydration is the most repeatedly advocated supportive intervention in patients with mild dengue and no warning signs, as it aids in maintaining intravascular volume, decreases the probability of dehydration, and potentially the decrease in the risk of clinical worsening. Oral rehydration solution (ORS) contains glucose along with sodium, so this product helps to increase the water absorption into the intestine by the sodium glucose co-transport system and may thus be more effective in maintaining circulating volume than simple water. This is in line with clinical evidence that oral isotonic solution was associated with less nausea and vomiting, greater oral intake, more positive fluid balance, relatively stable mean arterial pressure and a tendency towards rapid defervescence, but this was not statistically significant. The interventional and observational studies indicate that there is evidence to this. Harris *et al.* reported that the predictive value of high fluid intake in the 24 hours preceding a clinical assessment in patients with dengue fever was significantly important including the reduction of hospitalization in patients with dengue fever, reflecting the practical protective

value of early oral fluid intake in ambulatory care[27]. More recent prospective primary-care evidence found by Besnard *et al.* indicated that at least five glasses of liquid in the past 24 hours was strongly related to a lack of dengue warning signs, which again confirms that proper hydration could influence the development of clinical progression in uncomplicated dengue. Interventional evidence also supports oral hydration as a reasonable frontline strategy when oral intake is possible[28]. In a comparative clinical trial, it is found that oral hydration seemed equally effective as intravenous fluid replacement in non-shock dengue haemorrhagic fever in adults who could drink well, and showed no evidence of shock, indicating that oral fluid therapy could be clinically adequate in selected stable patients who are able to drink satisfactorily[29]. Equally, an oral isotonic solution was also well tolerated by dengue patients and had a good trend over plain water, with less nausea and vomiting and better fluid balance though the differences were statistically insignificant[30]. Combined, results of various studies advocate the most research-based natural supportive intercession of frequent oral fluids, and, more particularly, of ORS or electrolyte-bearing liquids, for mild dengue[31]. Meanwhile, the proper management of home care involves meticulous attention to the micturition, thirst, light-headedness, fatigue, vomiting and capacity to continue oral food and beverage consumption, as in hydration failure or onset of any warning symptoms should signal an emergency medical re-evaluation, rather than a continuation of the home care regimen[28]. ORS should not be considered as a treatment for dengue, but as a practical supportive treatment that is better suited to treat dehydration and fluid/electrolyte losses than plain water, especially in children, elderly patients and in patients who are vomiting or have poor oral intake. Mild dengue involves no warning signs and is managed with oral hydration, moderate dengue may involve warning signs or poor oral intake requiring medical reassessment, and severe dengue (*e.g.*, shock or haemorrhagic fever) may necessitate supervised intravenous fluid replacement in patients who cannot drink adequately. The current WHO guidelines are based on severity-based fluid management. Patients who are not presenting with warning signs should be encouraged to drink plenty of fluids orally and be monitored closely, while those who present with a warning sign, persistent vomiting, poor oral tolerance, decreased urinary output, or clinical deterioration should be medically reassessed and may require supervised intravenous fluid replacement with isotonic crystalloids (*e.g.* normal saline or Ringer's lactate).

2.2. Nutritional and dietary support

Nutritional support in mild dengue is considered as a general supportive therapy and not a disease specific one. In the febrile stage, a lot of patients experience poor appetite, nausea, abdominal

pain or vomiting and hence the practical objective is to sustain light, frequent, and easily absorbed oral intake instead of struggling to intake large meals[32]. Clinical management literature based on review studies typically suggests soft foods and easy oral feeding, including foods that are simple to digest and palatable to the patient, as well as ongoing fluids, since ongoing intake may aid in preventing weakness, recovering, and further nutritional impairment under ongoing acute illness[32]. In a wider sense, nutritional adequacy can be of interest, since host nutritional status seems to be an important determinant of dengue: paediatric evidence indicates that abnormal baseline nutritional status, especially overweight or obesity, could be a predictor of higher dengue severity, although the results of studies are not entirely consistent[33]. This justifies a tentative conclusion that proper nutrition applies to general resilience and recovery even in the absence of any particular food that has been shown to have a direct impact of changing the trajectory of mild dengue[34]. Notably, assertions regarding specific immunomodulatory foods or nutritional supplements sought to be maintained in a low-profile way[35]. The clinical significance of protein intake is that febrile acute illness increases metabolic needs, and reduction in serum albumin has been suggested to be associated with dengue-febrile illness and plasma leakage, but there is a lack of evidence to support the use of high-protein therapy as a specific treatment for dengue. Micronutrient reviews on dengue state the evidence is sparse and inconsistent, and even with the most debated adjuncts like papaya leaf preparations. Systematic and scoping reviews essentially state that the available evidence is still unable to substantiate general therapy claims or even generally recommend it as a food-based therapy[36]. Thus, during mild dengue, the most justifiable dietary guidance is to promote small, well-tolerated meals and nutritionally sufficient intake, with exaggerated claims that a certain food can enhance immunity to the extent that it will cure dengue[37]. The current evidence shows that a balanced, protein-adequate and micronutrient-rich diet, and correction of known deficiencies, if necessary, is beneficial but there is no compelling evidence that any food, fruit juice, papaya preparation, vitamin or mineral supplement consistently improves platelet count, reduces plasma leakage or influences the natural course of dengue alone.

2.3. Rest and physical activity restriction

The early recovery phase and febrile period are typically treated with a supportive recovery setting that is based on rest, lack of vigorous physical exercise and basic comfort interventions to treat the fever[38]. Surveys of the primary-care management of dengue report that bed rest can be used to alleviate physical suffering during the febrile stage, and that outpatient management should focus on close observation and low risk supportive interventions, as opposed

to excessive activity[39]. Clinical evidence confirming that dengue is a disease often linked to fatigue: a systematic review and meta-analysis published in 2025 found that approximately 59% of acute dengue patients experienced fatigue and approximately 20% post-infectious dengue patients did so. Previous prospective studies and burden of disease studies showed that fatigue could last for weeks after apparent recovery and impair the patient's ability to work or return to normal activity[40]. The most justifiable advice is that mild dengue patients must rest in the acute and early stage of recovery, shun intense physical activity until strength and hydration returns, and use non-medical temperature-comfort interventions sparingly, and re-evaluate in case of warning signs, incessant vomiting, bleeding, and progressive weakness.

3. Herbal and plants based adjunct of dengue fever

Herbal and medicinal plants have received significant attention in the context of the management of dengue because of their potential antiviral, immunomodulatory, antioxidant, and hematological properties especially in areas where practice of traditional medicine is common[41]. The use of herbal and plant-based adjuncts for dengue should be assessed based on the level and nature of evidence available and should be clearly differentiated between laboratory and clinical effects[42]. There is low level of clinical evidence for most of the medicinal plants like *Azadirachta indica*, *Andrographis (A.) paniculata* and *Euphorbia (E.) hirta* which are supported primarily on the preclinical evidence obtained from *in vitro* or animal studies. The evidence for humans is strongest with *Carica (C.) papaya* leaf extract, as in some small clinical trials, it improved platelet recovery, but not necessarily reduced bleeding, shock, hospitalisation or

mortality. Overall evidence is low to moderate. The existing studies have several significant drawbacks, such as small sample sizes, variations in preparation and dosage, inadequate standardization, lack of blinding, and short follow-up periods, as well as use of surrogate outcomes (Table 1). Thus, at present, it is best to consider herbal therapies only as a complement to the established supportive therapies.

3.1. *Carica (C.) papaya*

The extract of *C. papaya* leaves has been the subject of a lot of interest as a complementary supportive therapy in dengue especially dengue associated thrombocytopenia (DAT). Generally, the results of systematic reviews and meta-analyses indicate that papaya leaf preparations may promote platelet recovery in certain patients, but the number of available studies is small; the studies are heterogenous, and many suffer from methodological limitations. In 2019, a systematic review synthesizing of 7 of 9 studies was published, which found an increase in platelet counts in those who received *C. papaya* extract and one study found no significant improvement[22]. According to reviews published between 2024 and 2025, the main proposed benefit of this extract is platelet recovery acceleration. The mechanistic hypotheses are the generation of thrombopoiesis by *ALOX12* and *PTAFR* gene activation, potential immunomodulatory effects, membrane-stabilizing effect, and limited experimental antiviral effect, although these mechanisms are not fully proven in humans[43,52]. Clinically, shock, plasma leakage, severe bleeding and/or mortality are endpoints commonly included in human studies relying on platelet measurements, rather than the outcomes that truly matter to the clinical study[53]. In 2024, a meta analysis also found that papaya preparations had the potential to

Table 1. Summary of herbal plants investigated for dengue fever management.

Herbal plant	Mechanism of action	Evidence level	Experimental outcome	Adverse effects	Major research limitations	Ref.
<i>Carica papaya</i> leaf extract	Could stimulate thrombopoiesis <i>via</i> ALOX12/PTFR; Immunomodulatory and membrane stabilizing effects	Low to moderate clinical evidence	May improve platelet recovery	Usually, mild gastrointestinal effects	Variable preparations/ dose, limited safety data	[43,44]
<i>Euphorbia hirta</i>	Hemostatic, platelet enhancing, anti-inflammatory	Low, mainly ethobotanical and animal	Experimental platelet and clotting benefits	Gastrointestinal disturbance and allergy	No standardized dosing or preparations, no randomized control trials	[45,46]
<i>Andrographis paniculata</i>	Andrographolide and related compounds may inhibit dengue viral replications	Preclinical only; Mainly <i>in vitro</i>	Antiviral activity against several dengue serotypes in laboratory	Allergic reactions, gastrointestinal tract disturbance, diabetic medication interaction	No clinical trials, lack of pharmacokinetic profile in humans, non standardized extracts dosing	[47,48]
<i>Chondrus crispus</i> / carrageenans	Sulfated carrageenans can inhibit viral attachment and viral entry by mimicking the heparan sulfate	<i>In vitro</i> evidence	Inhibit DENV-2 and DENV-3 in cell culture	Hepatotoxicity, gastrointestinal tract disturbance	Lack of human and animal trials, no studies about pharmacokinetics	[49,50]
<i>Boersenbergia rotunda</i>	Panduratin A derivatives may inhibit the viral NS2B-NS3 protease and disrupt viral replication	mainly <i>in silico</i> and enzyme assay evidence	Experimental protease inhibition	No major side effects	Limited <i>in vitro</i> evidence	[51]

increase platelet counts and reduce hospital stay, though the studies included were small and methodologically limited[54]. Evidence in the trial level is promising but not conclusive because platelet count trends are useful for monitoring disease progression, but their improvement should not be interpreted as a standalone indicator of clinical recovery. Clinical outcomes depend on multiple factors, including vascular integrity, fluid status, and end-organ perfusion, and platelet counts alone have limited predictive value for patient prognosis. One example is a randomized placebo-controlled pilot study in adults with severe thrombocytopenic dengue, which administered 1 100 mg tablets three times a day for 5 days. The study noted a faster platelet recovery, reduction of transfusion, and high short-term tolerability, but no evident reduction in hospitalization length[43,55]. The key shortcomings of the literature are the lack of homogeneity in formulation (fresh juice, aqueous extract, tablets, capsules), lack of consistency in the dosing schedule, small sample size, lack of proper safety evaluation, and high or not adequately studied risk of bias; reported adverse effects are generally mild and typically gastrointestinal, yet standardization, pharmacovigilance, and herbal product quality control remain lacking[56]. Thus, *C. papaya* leaf extract can be negotiated as a promising supportive adjunct in dengue related thrombocytopenia, but not in dengue *per se*, and should not be used in place of recommended supportive care or clinical surveillance for severe dengue.

3.2. *Euphorbia (E.) hirta*

E. hirta is also considered as one of the most extensively utilized medicinal plants in treating dengue in Philippines where ethnobotanical surveys have revealed that the plant is widely used as a supportive household medicine, especially by women in dengue-infested areas[57]. It is also reportedly commonly used in Agoo, La Union, where it was found to be one of the most prevalent taken remedies by dengue patients. Traditionally *E. hirta* is typically used as a decoction of the leaves or aerial parts and its easy availability in home gardens has probably made it popular as a home-prepared remedy[46]. However, this traditional decoction lacks standardized formulation, as the concentration of active phytochemicals varies considerably depending on plant source, preparation time, and extraction method, making reproducible dosing nearly impossible in household settings. Subacute administration of *E. hirta* leaf or whole-plant in experimental rats and rabbits has proposed a potential platelet-supportive and a hemostatic effect of *E. hirta* leaf on platelet count, bleeding time, and clotting reaction, suggesting a role in dengue-related thrombocytopenia and bleeding disposition. Platelet augmentation in thrombocytopenic rabbits was noted in 24 hours but

the effect was also noted to be less significant compared to that of *C. papaya* leaf extract[57]. There is also a lack of clinical support that *E. hirta* can elevate platelet counts and decrease flu-like symptoms in dengue patients with symptomatic improvement reported in almost 70% of patients, potentially resulting from its anti-inflammatory effect[45]. Despite this reported improvement, no established dosage recommendations exist for human use, as current clinical data are derived from a single study without a validated dose-response curve or standardized therapeutic regimen. Phytochemical analyses have detected alkaloids, glycosides, saponins, phytosterols, phenolic compounds and flavonoids in *E. hirta* and phenolics and flavonoids have been suggested as the primary platelet enhancing and symptom reducing agents[58]. Regarding safety, potential adverse effects such as gastrointestinal disturbances, and allergic reactions have been anecdotally reported, but systematic documentation is absent, and the plant's safety profile in vulnerable populations such as pregnant women, children, and patients with comorbidities remains entirely unexamined. However, the current evidence is still tentative and a new prospective clinical and ethnobotanical research is required to verify its effectiveness, safety and the generalizability of the results to clinical practice as an adjunct in dengue treatment[59]. Furthermore, the lack of rigorous pharmacokinetic and pharmacodynamic studies means that even if efficacy were confirmed, the absence of standardized formulations and evidence-based dosing would continue to limit its integration into formal clinical protocols.

3.3. *Andrographis (A.) paniculata*

A. paniculata has demonstrated good anti-dengue potential in *in vitro* research especially due to its major secondary metabolite, andrographolide[60]. However, it is critical to emphasize that most of this evidence derives from laboratory-based *in vitro* studies and animal models, and no established clinical efficacy has been confirmed in human dengue patients. Andrographolide, antiviral properties of andrographolide have already been linked to various viruses such as hepatitis B virus, herpes simplex virus, influenza virus, hepatitis C virus, chikungunya virus, and dengue virus serotypes 2 (DENV-2) and DENV-4[61]. Anti-dengue properties of methanolic extracts of *A. paniculata* were also reported in the previous literature, in Vero E6 and HepG2 cell lines, against DENV-1[47]. The highest nontoxic concentration (MNTD) of andrographolide in C6/36 cells was determined as 15.62 µg/mL; antiviral was examined by real-time PCR using Taqman probes and showed 97.23% inhibition of DENV-2. These results suggest that andrographolide is a potent *in vitro* anti-dengue candidate and can be a good lead molecule in future drug development although

its clinical applicability remains to be validated by animal models and clinical trials[48,62]. Despite these promising *in vitro* findings, it is essential to avoid overstating their translational value, as cell-based assays do not account for complex *in vivo* pharmacokinetics, bioavailability, metabolism, and immune interactions that determine actual therapeutic outcome. It was reported that the antiviral effect was largely due to flavonoids but other ethanol-extractable phytochemicals like terpenes, flavonoid and polyphenols could also play a role[63–65]. The translation of these laboratory observations into a clinically viable treatment is further hindered by the absence of standardized extracts, well-defined dosing regimens, and safety data in humans, all of which are prerequisites for clinical application. Besides flavonoids, the effects of diterpenes that can be found in *A. paniculata*, namely andrographolide, 14-deoxyandrographolide, and 14-deoxy-11,12-didehydroandrographolide, must be regarded as significant as well. These are the compounds found in methanolic extracts which are active against DENV-1, and which have been reported previously to have an antiviral effect against other viral systems, including anti-HIV effects[66,67]. Therefore, while *A. paniculata* and its phytoconstituents represent a scientifically interesting lead for anti-dengue drug discovery, well-designed, randomized, placebo-controlled human clinical trials are urgently needed before any recommendation can be made for its use as an adjunct or definitive therapy in dengue management.

3.4. *Chondrus (C.) crispus*

An example of a red seaweed is *C. crispus* (Irish moss or carrageen moss), of the family Gigartinales, a major natural source of carrageenan, a family of naturally occurring sulfated polysaccharides, commonly used in the food and pharmaceutical industries. Red seaweeds are commonly known carrageenophytes and synthesize three major types of carrageenans, *i.e.*, kappa-, iota-, and lambda- carrageenans, among which there is an interest due to their reported antiviral effects[49]. Carrageenans have been promising in experimental studies, especially against DENV-2 in the context of dengue. Studies by Talarico *et al.* revealed that lambda- and iota-carrageenans (polymerized chains of sulfated galactopyranosyl) had the potential to suppress the proliferation of DENV-2 and DENV-3 in Vero cells and HepG2 cells. One of these findings was the antiviral effect, which was markedly more robust against DENV-2; this implies serotype-specific variations in susceptibility. The carrageenan antiviral effect seems to take place at the viral entry point in a mechanistic manner[68]. Specifically, the proposed mechanism involves the highly sulphated nature of carrageenan, which allows it to mimic heparan sulfate, a cell

surface glycosaminoglycan that dengue virus exploits for initial attachment, thereby competitively blocking viral adsorption to host cell membranes and preventing subsequent endocytosis and fusion. This was confirmed by the fact that no viral growth inhibition was observed when the normal entry step was evaded by DENV-2 RNA transfection, which shows that lambda-carrageenan does not mainly inhibit intracellular viral replication once the viral genome has invaded the host cell. Rather, it probably works earlier, attaching to prevent virus attachment or penetration. The mechanism is biologically plausible, as dengue virus is known to bind with heparan sulfate, a sulfated glycosaminoglycan on the surface of host cells, in the early stages of binding. Carrageenans, also being highly sulfated polysaccharides may rival or disrupt such an interaction between the virus and the cell, thus disrupting the early processes of viral entry. In general, the available data indicate that carrageenans of *C. crispus* and associated red seaweeds have a promising anti-dengue potential, especially as inhibitors of entry[69,70]. However, it is important to underscore that this evidence is entirely derived from *in vitro* cell culture models, and no clinical studies have been conducted to evaluate the safety, pharmacokinetics, or antiviral efficacy of carrageenans from *C. crispus* in dengue patients, meaning that clinical effectiveness has not yet been demonstrated.

3.5. *Boesenbergia (B.) rotunda*

B. rotunda is a medical species of the family Zingiberaceae that has been of interest as a possible natural source of anti-dengue due to its inhibitory properties on the dengue virus protease cascade[71]. The proposed antiviral mechanism centers on the competitive inhibition of the dengue virus NS2B-NS3 serine protease, an essential enzyme for viral polyprotein processing and subsequent replication, thereby disrupting the viral life cycle at the post-entry stage. Among isolated constituents of *B. rotunda*, panduratin A and 4-hydroxypanduratin A had the strongest activity, each inhibiting approximately 65% of the protease activity at a concentration of 80 mg/L meaning these two compounds are the major bioactive anti-dengue constituents of the plant[51]. Kinetic analysis also revealed that the two compounds have a competitive mode of inhibition, with K_i values of $(25 \pm 8) \mu\text{M}$ and $(21 \pm 6) \mu\text{M}$ respectively, indicating a high binding affinity to the viral enzyme. On the contrary, pinostrobin and cardamomin inhibited the protease in a non-competitive mechanism with K_i values of $(345 \pm 70) \mu\text{M}$ and $(377 \pm 77) \mu\text{M}$ respectively, which demonstrates less potent inhibitory ability. Even though pinocembrin and cardamomin were not very active alone, the combination of the two was significantly stronger, which indicates potential synergy in action against DENV-2 protease[51]. Despite these promising

in vitro enzyme inhibition data, it is critical to recognize that most of the evidence for *B. rotunda* originates from molecular docking simulations, *in silico* modelling, and cell-free enzymatic assays, which do not account for bioavailability, metabolic degradation, or off-target effects in a complex biological system. On the whole, the results indicate that *B. rotunda* and specifically panduratin A and 4-hydroxypanduratin A could be an excellent source of lead molecules in the design of anti-dengue agents that would affect the activity of the viral protease[72]. Nevertheless, no human clinical trials have been performed to date, and the clinical effectiveness of *B. rotunda* or its isolated compounds against dengue fever, dengue hemorrhagic fever, or dengue shock syndrome has not yet been established in any patient population.

4. Discussion

The reviewed literature shows that in mild dengue, the most effective and most reliable support is still basic supportive care as compared to the use of other medical interventions. In both outpatient and primary-care research, early oral intake recognition, monitoring of warning signs, and maintenance are the most clinically defensible strategies[28]. The oral fluid intake seems to be especially significant: Studies found that the more fluid was consumed before clinical evaluation, the less likely it would be to be hospitalized[27]; whereas Besnard *et al.* discovered that the better hydration was, the fewer warning signs were observed at primary care. Concurrently, in practice, primary-care reviews have strongly focused on the fact that when patients are not suffering any warning conditions, timely home-based supportive management can decrease the progression and unwarranted deterioration[73]. Combined with the above results, there is a hierarchy of evidence where supportive care has better real-life support compared to adjunctive phytotherapy[74]. When critically comparing the available herbal interventions, *C. papaya* leaf extract emerges as the most clinically investigated with some human trial data, whereas *E. hirta* relies heavily on preclinical animal studies, and *A. paniculata*, *C. crispus*, and *B. rotunda* are supported almost exclusively by *in vitro*, *in silico*, and molecular docking evidence, creating a stark gradient of evidence quality that precludes direct comparative effectiveness rankings. Substantial inconsistencies exist among published studies, including variable extraction methods, differing plant parts used, lack of standardized control groups, and conflicting results on platelet recovery timelines, making it difficult to synthesize findings into a coherent evidence base.

Within this supportive framework, hydration remains the clearest cornerstone, whereas nutrition, rest, and environmental comfort

appear useful mainly as conservative adjuncts. There is some clinical evidence indicating that oral hydration can be adequate in some stable dengue patients[75]. Studies have found oral hydration to be equivalent to intravenous fluid replacement in adults with non-shock dengue hemorrhagic fever, and oral isotonic fluids are better tolerated and with more favorable trends than plain water[38]. These research findings are not in any way a recommendation to be cured, but rather they reaffirm the practical importance of oral supportive care under the conditions that the patients are well able to drink and are closely monitored[76]. Equally, the literature on primary care and clinical management endorses rest, symptom-directed home care, and observation at the febrile and the initial recovery stages instead of unnecessary exercise and violent treatment[30,75]. A major methodological limitation across nearly all clinical trials of herbal interventions for dengue is the small sample size, lack of blinding, absence of placebo controls, short follow-up durations, and reliance on surrogate endpoints such as platelet counts rather than clinically meaningful outcomes like hospitalization rates, bleeding episodes, plasma leakage, or mortality.

C. papaya leaf extract is the most frequently studied herbal adjunct and is the most reported herb in the clinical literature, focusing mainly on platelets[21,43]. Clinical studies have demonstrated effects on platelet counts; and reviews have described potential anti-thrombocytopenic and immunomodulatory effects[77]. Another herbal plant *E. hirta* use in dengue endemic regions has seen it emerge as an important ethnomedicinal plant and reviews have cited both antiviral and platelet activity[78]. But much of the evidence is preclinical information, small case studies or non-randomised human trials[45]. Other plant extracts, such as *A. paniculata*, *Cymbopogon* (*C.*) *citratus*, *Citrus* (*C.*) *limon* and associated phytochemicals, are even more experimental[61]. The evidence for these therapies often rests upon their *in vitro* and *in silico* screening, enzyme inhibition, molecular docking, or other preclinical evidence rather than clinical studies[40]. For instance, methanolic extracts of *A. paniculata*, *C. citratus* and *C. limon* have been found to have anti-dengue effects in cell-based screening models, and isolated andrographolide has demonstrated anti-dengue effects *in vitro* and *in silico*[79]. One of the most critical unresolved challenges is the standardization of herbal preparations, as the concentration of bioactive compounds varies widely depending on plant cultivar, geographic origin, harvesting season, drying method, extraction solvent, and processing technique, making batch-to-batch consistency nearly unattainable without good manufacturing practice compliance and rigorous quality control protocols.

Similarly, both *C. crispus* and *B. rotunda* show promise as potential sources of anti dengue agents although the mechanisms of action

are very different. Red seaweed *C. crispus* contains carrageenans that are highly sulfated polysaccharides that mimic heparan sulfate and competitively inhibit viral attachment and entry into host cells. In contrast, *B. rotunda* targets a later stage of the viral life cycle by inhibiting the NS2B-NS3 serine protease, a crucial enzyme for viral replication, with panduratin A and 4-hydroxypanduratin A identified as potent competitive inhibitors[51]. Both natural products exhibits encouraging antiviral activity, *C. crispus* interfering at viral entry and *B. rotunda* disrupting post entry replication.

Perhaps the most common issue in the herbal dengue literature is a fixation with platelet count. While low platelets are a hallmark of dengue, severe disease is a result of a complex interplay of plasma leakage, inflammation, bleeding, and fluid balance. An intervention that increases platelet count does not necessarily stop plasma leakage, shock, major bleeding, or hospitalization. That's why supportive therapy, particularly fluid management, surveillance, and escalation of care in the presence of warning signs, remains the preferred approach to manage mild dengue[80]. Adopting herbal interventions to the clinic requires that they meet the standards set by their regulatory authorities, such as product registration, pharmaceutical quality and controlled-trial data, and the compliance to regulations, such as WHO and FDA. Polypharmacy is a major concern in dengue endemic regions; herb-drug interactions with analgesics or anticoagulants could result in increased bleeding and organ toxicity through modulation of the CYP450 system. Most of the phytochemicals, however, have not been studied extensively for their hepatotoxic and nephrotoxic profile; although many have been the subject of scientific concern in the past, very little systematic toxicology data exist. Rigorous randomized trials, pharmacokinetic/pharmacodynamic studies, reference materials, extensive toxicity testing, interactions and national adverse-event registries are among the future priorities. In conclusion, absence of long-term safety data, especially on cumulative hepatic and renal effects, continues to be a significant hurdle in the adoption of herbal medicine in practice, especially in children, the elderly, pregnant women, and those with underlying organ impairment.

5. Conclusions

Best evidence for natural supportive care in mild dengue includes fluid replenishment, oral nutrition as tolerated, rest and a conducive environment for recovery, allowing for observation and timely reassessment. It must be unequivocally stated that the current body of evidence for any herbal intervention in dengue remains profoundly limited, with most data derived from preclinical models, small uncontrolled case series that lack the rigor required to establish definitive therapeutic efficacy. Natural adjuncts, and particularly

C. papaya leaf extract, are scientifically intriguing and potentially adjunctively useful, but still require research whose findings are hampered by variability, lack of standardization and lack of focus on clinical outcomes. *E. hirta* and other plant products should be regarded as experimental for the time being. Given these substantial evidence gaps, it would be premature and clinically irresponsible to issue any definitive recommendations endorsing the routine use of these herbal preparations in dengue management, and any discussion of their potential role must be framed with explicit caution regarding their unproven status. Consequently, the best thing for a review article to do is not dismiss or overpromote but critically review based on the quality of the evidence, and supportive care remains the mainstay of treatment of dengue fever. Therefore, using herbal medicine in clinical practice is not warranted until high quality multicenter trials with patient-centered outcomes, standardized extracts, human pharmacokinetic data, pharmacovigilance systems and collaborative research networks are available.

Conflict of interest statement

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Data availability statement

The manuscript does not contain any new or generated data. All the data obtained from other work are properly cited and permission was obtained where required.

Authors' contributions

B.A. conceptualized the review, performed the literature search, analyzed the data, synthesized the findings, drafted the manuscript, supervised the project and handled project administration. M.I. designed the methodology, validated the references and critically revised the manuscript. S.J.A.S. screened the literature, extracted the data, identified gaps and prepared the tables. M.H. assessed the studies, interpreted the evidence and contributed to the discussion. H.S. organized the references, formatted the manuscript and handled the revisions. B.A., M.I., S.J.A.S., M.H., and H.S. contributed to the final version of the manuscript. B.A. supervised the project.

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