Dengue and drawbacks of marketed *Carica papaya* leaves supplements

Nusrat Hossain¹, Palanirajan Vijayaraj Kumar¹, Yeong Siew Wei²

¹Faculty of Pharmacy, Department of Pharmaceutical Technology, UCSI University, Kuala Lumpur Campus (South Wing), No. 1, Jalan Menara Gading, UCSI Heights (Taman Connaught), Cheras 56000, Kuala Lumpur, Malaysia, ²Faculty of Pharmacy, Department of Clinical Pharmacy, UCSI University, Kuala Lumpur Campus (South Wing), No. 1, Jalan Menara Gading, UCSI Heights (Taman Connaught), Cheras 56000, Kuala Lumpur, Malaysia

Abstract

Aim: This review is mainly focused on describing deadly disease, dengue and the main drawbacks related to marketing *Carica papaya* leaves supplements. **Materials and Methods:** Information was collected from various published research, review articles, web pages, and other online databases related to the topic. Dengue is a deadly viral disease and it has affected 40% of the world population. It can be transmitted by mosquitoes (*Aedes aegypti*) infected with one of the four dengue virus serotypes. Due to this complex virus serotype, there is no particular therapeutic treatment for dengue. Therefore, despite of the severity and deadly effects of dengue, vaccines are not available. **Results and Discussion:** As a result, the use of herbal supplementary medicines has been increased in passing time. The supplements of *C. papaya* leaves have shown promising prospect due to the platelet increasing property. However, the manufacturing techniques used in several marketed *C. papaya* leaves formulations can degrade the active phytochemicals, which will suppress the beneficial effects of the supplements. **Conclusion:** There is a need to improve the old herbal formulations for the current crisis. Therefore, the drawbacks of marketing *C. papaya* leaves supplements need to be modernized for better patient care.

Key words: *Carica papaya* leaves, dengue, supplements

INTRODUCTION

Dengue is a severe arthropod-borne viral disease which occurs mainly in tropical areas and it can cause both morbidity and mortality in humans. *Flavivirus* is the main vector for spreading dengue among human.¹ According to the survey of the World Health Organization (WHO), dengue has affected 40% of the total global population. However, dengue epidemic has extended many new countries and amplified significantly in the already affected areas.² Being a tropical country and having humid weather condition, the people of Malaysia are suffering from an increased number of dengue cases.³

According to the Health Ministry of Malaysia Guideline for the management of dengue, the frequency of Case Fatality Rate of dengue was higher in the year 2007 compared to 1999 in Malaysia.³ In 2014, the WHO declared that 80,578 dengue cases had been reported in Malaysia and among them 153 patients died.⁴ Dengue treatment can be both symptomatic and supportive. Due to the absence of any particular therapeutic treatment, dengue can be controlled with only proper supportive care and vigilant fluid administration during different phases.⁵ The main complications of dengue hemorrhagic fever are plasma leakage, hemoconcentration, and abnormalities in homeostasis. Plasma leakage occurs due to the activation of infected monocytes and T-cells. This will cause endothelial cell dysfunction and cause plasma leakage in dengue patients. Plasma leakage in dengue patients will hamper the blood clotting and it can cause death. By increasing the platelet count in the patient, the death rate can be reduced.⁶

The WHO fact data sheet, published in December 2014, stated that the people of some Asian and African countries...
depend on cultural or traditional treatments for dengue as supportive care.[7] Recently, *Carica papaya* leaves juice has become popular among the dengue suffering patients due to the platelet increasing activity of the leaves.[8,9] Various active phytochemicals (papain, flavonoids, phenols, saponins, alkaloids, ascorbic acid, etc.) had been identified in *C. papaya* leaves by the phychochemical screening process.[10-12] Based on these findings and clinical trials, physicians are advising dengue patients to take fresh *C. papaya* leaves juice while dengue treatment.[9] However, during the rainy season, dengue spreads rapidly compared to other time of the year. Tropical countries, such as Malaysia, India, Thailand, Indonesia, Sri Lanka, and the Philippines, suffer more due to the humid environment, which is preferable for the fertilization of *Aedes* mosquitoes.[13,14] Therefore, the sudden increase of patients in these areas makes the availability of fresh *C. papaya* leaves slightly difficult. Furthermore, fresh juice extraction on a daily basis and bitter taste of the juice are the main drawbacks of the treatment.

**MATERIALS AND METHODS**

**Search Criteria**

Information was collected from various published articles, review articles, and web pages related to the topic. Original published resources of recent research on dengue, the medicinal activity of *C. papaya* leaves and drawbacks of available supplements of *C. papaya* leaves were transferred from PubMed, Science Direct, Research gate, WHO guidelines, and other online databases. The search criteria were restricted to dengue, brief description of *C. papaya* leaves and current marketed supplements of *C. papaya* leaves.

**Dengue Virus (DV)**

Dengue is an endemic disease.[15] It has affected the normal life of people living tropical and subtropical regions. Dengue is the most common human arthropod-borne virus disease and it causes thousands of deaths every year.[16] DV is very unique in structure. It can be transmitted by mosquitoes named *Aedes aegypti*. *Aedes* mosquitoes are normally small and black with the white lines on the body and legs. The DV belongs to the Flaviviridae family and it has four different serotypes (DV-1 to DV-4).[17]

The DV is composed of mainly a nucleocapsid. It is covered by glycoproteins and totally surrounded by a lipid membrane.[15] It consists of a positive-sense genome and single-stranded ribonucleic acid (RNA). The RNA has encoded with a polyprotein precursor of the main viral proteins. This precursor can be cleaved by host and viral proteases. They are consist of three structural and seven non-structural proteins. The structural protein is capsid C, pre-membrane, and envelope E.[18] The non-structural proteins are NS1, NS2a, NS2b, NS3, NS4A, NS4B, and NS5.[19] Schematic representation of DV is shown in Figure 1.

The three structural proteins are united into the developed infective virion. However, the non-structural proteins only help in the replication of the virus. Researchers have isolated DV from the macrophages, polymorph nuclear leukocytes, dendritic cells, and others. Furthermore, it has also been identified in megakaryocyte progenitors and platelets. These findings from different journals propose that DV has the capability to react directly with megakaryocytes and platelets, which may induce thrombocytopenia.[15,20,21]

**Management of Dengue**

The *A. aegypti* mosquito is the primary vector of dengue. *A. aegypti* can control *Flavivirus* transmission. *Flavivirus* has four separate serotypes, which are DV-1, DV-2, DV-3, and DV-4. However, the DV can transmit in human beings through the bites of infected female mosquitoes. After 4-10 days of virus incubation period, an infected mosquito is capable of transmitting the virus its whole life. The illness started to build up after the incubation period. It followed three main phases-febrile, critical, and recovery. In the febrile phase, suddenly high temperature can be identified as symptoms. In critical phase, the temperature of the patient falls to 37.5-38°C or less. The afterward platelet count is reduced, and it causes plasma leakage. In the recovery stage of dengue, the patient started to recover, and proper monitoring of symptoms should be done to next following 48-72 h.[6,13] Schematic outline of different phases of dengue are shown in Figure 2.

Febrile phase in dengue can last for 2-7 days. The main symptoms are a headache, skin erythema, arthralgia, body ache, myalgia, and facial flushing. In the beginning of the critical phase, hemocrit levels may increase. However, in the critical phase platelet count started to lower down and it causes plasma leakage. In dengue patients, shock occurs due to plasma leakage. During 24-48 h of critical phase, the fluid management of the patient is very critical. After 72 h of critical phase, recovery phase started. However, in recovery phase; patient’s physical condition started to improve. In this phase, the normal appetite will return, gastrointestinal bleeding will reduce, the platelet count will increase, and blood pressure will stabilize. Bradycardia and electrocardiographic changes can be identified during the recovery stage.[22] Schematic depiction of the symptoms of dengue fever is shown in Figure 3.

According to the guideline of the WHO, dengue management is done using three steps, which are overall assessable of the disease, diagnosing disease phase with severity, and finally, focus on the treatment of dengue. Clinical diagnosis can be done by serological testing in the febrile phase of dengue.[13]

In the febrile phase, patients are only encouraged to take paracetamol and oral fluid saline. However, in the critical
phase 0.9% saline is given to dengue patients. If the symptoms started to worsen and hematocrit level is rising, the fluid infusion rate needs to be increased. In critical phase, patients started to show more symptoms than the febrile phase. They may experience with bleeding from the gums, epistaxis, face, and vagina. At the beginning, patients’ do not require blood transfusion. However, dengue patients’ with significant bleeding need blood transfusion. It has been suggested that replacement red blood cells of 5-10 ml/kg or replacement blood of 10-20 ml/kg can be given with proper care. Non-shock dengue patients are encouraged to take oral fluid intakes and bed rest. However, transfusion of blood or fresh frozen plasma can be done in case of severe gastrointestinal bleeding. In the recovery phase, the rate of IV infusion is gradually reduced from 5 to 7 ml/kg/h for 1-2 h, and then to 3-5 ml/kg/h for 2-4 h. The IV fluid rate can be continued up to 24-48 h during the recovery phase.$^6$

Vaccines are not available for immunization in dengue.$^{[24]}$ Therefore, the use of herbal-based medicine and medicinal plants such as *C. papaya* for alternative treatment in dengue is growing.$^{[17]}$ Papaya leaves contain active components such as papain, chymopapain, ascorbic acid, flavonoids, saponin, phenolic acid, alkaloids, and quercetin, and some of them can be degraded due to heat and storage condition.$^{[25-28]}$ Therefore, the heat inducing extraction methods such as micronization, fermentation, Soxhlet extraction can degrade the heat sensitive active phytochemicals of papaya leaves.$^{[29,30]}$ However, a formulation of lyophilized *C. papaya* leaves can protect this phytochemical degradation.

**Interaction of DV with Human Antibodies**

In our body, the first immunological reaction against DV started by producing antibodies. Our immune system will produce antibodies against the envelope protein of DV. However, our body can react with DV by two different responses, which are primary and secondary responding.$^{[13]}$ An individual will show a primary response if they are affected by DV for the first time. But if an individual had suffered from previous DV infection, the secondary response can be identified. During the primary dengue infection, DV specific IgM and IgG antibodies will appear. In the secondary dengue infection, our immune system will produce a high amount of IgG antibodies as B-cells and memory B-cells will identify the virus during the onset period. However, DV will induce DNA-based immunization and the production of IgG1 and IgG3 subtypes of antibodies.$^{[31,32]}$

An individual will develop serum antibodies against both structural and non-structural protein of DV. In primary infection, researchers have identified high levels of prM and NS1 antibodies compared to secondary infection. NS1 antibodies can react with the antigens of platelets and endothelial cells. It has been also reported that the production NS1 antibodies can cause vasculature in dengue.$^{[31]}$ The primary infection pathway of DV is shown in Figure 4.

**Diagnosis of Dengue**

Different diagnosis method is used to identify dengue infection, and they have their own advantages and disadvantages. Using virus detection method, DV can be isolated from the blood plasma. However, different virus serotypes can be identified using serotype-specific monoclonal antibodies. Viral RNA detection of dengue can be done by nucleic acid amplification test using the blood tissue of the dengue patient. Furthermore, reverse transcription-polymerase chain reaction (RT-PCR) or nested RT-PCR can be used to detect the DV.$^{[34]}$
Antigen detection can be done by either NS1-based assays or immunohistochemistry. For identifying NS1-based antigen in dengue infection, enzyme-linked immunosorbent assay (ELISA) and rapid immunochromatographic assay are used. NS1-based antigen can be identified during the first 9 days of both primary and secondary dengue infection. Schematic representation of the immunological response to dengue infection is shown in Figure 5.

Using the serological method, the production of IgM, IgG, and IgA can be identified. IgM antibody production is higher in primary dengue infection and, in contrast, IgG antibody level is higher in secondary dengue infection. During primary dengue infection, almost 93% of the patient produces a detectable IgM level of antibodies. Therefore, ELISA-based IgM assay is used to identify the primary dengue infection. IgG-based assay method can be used to identify both past and current dengue infection. Using this method; the level of infection (either primary or secondary) can be recognized.

Botanical Descriptions of *C. papaya*

Papaya plant is normally found in tropical areas around the world. The family name is Caricaceae, and the botanical name is *C. papaya*. Papaya is a tree like a plant and it can be 16-33 feet tall. The leaves are 50-70 cm in diameter with deep seven lobes. *C. papaya* tree comes into fruiting within 5 months and lives for 4-5 years. Usually, male and female flowers are on different trees, but some flowers are bisexual. *C. papaya* leaves are spirally arranged. They are clustered near apex of the trunk; the petiole is up to 1 m long, hollow, greenish, and 25-75 cm in diameter. In Figure 6, grown up *C. papaya* tree is shown.

Plants used in Dengue Treatment

In a review article (2013) of potential anti-dengue medicinal plants, Siti et al. mentioned that *Boesenbergia rotunda* (Chinese ginger), *Andrographis paniculata* (Hempedu Bumi), *Azadirachta indica* (neem), *C. papaya* (papaya), *Cladosiphon okamuranus* (seaweed), *Gymnogongrus griffithsiae* (red seaweed), *Momordica charantia* (bitter melon), *Quercus lusitanica* (oak), *Euphorbia hirta* (tawa-tawa), *Rhizophora apiculata* (Bakau), *Ocimum sanctum* (Tulsi), etc., were reported to be used for traditional treatment of dengue. Among these plants, papaya leaves have been used in several studies for the treatment of dengue. Several animal and human clinical trials had been conducted with *C. papaya* leaves juice for elaborating the toxicity and platelet inducing activity.

**Phytochemical Constituents of *C. papaya* Leaves**

The medicinal effects of *C. papaya* leaves extracts can be recognized due to the presence of several active components such as papain, chymopapain, alkaloids, glycosides, tannins, saponin, L-tocopherol, ascorbic acid, riboflavin, flavonoids, and minerals (such as calcium, iron, magnesium, potassium, sodium, and zinc). The phytochemical constituents of *C. papaya* leaves in different solvents and mineral composition are shown in Tables 1 and 2.

Afzan et al., 2012 has done the phytochemical analysis of *C. papaya* by UPLC-Triple TOF-ESI-MS (ultra-performance liquid chromatography time-of-flight mass analyzer with an electrospray ionization source) fingerprinting. Canini et al., 2007 has identified the phenolic compounds of *C. papaya* using gas chromatography. High-performance liquid chromatography was also used for the analysis of *C. papaya* leaves and extracts.

Table 1: Phytochemical constituent of *Carica papaya* leaves in mg/10 g residue of different solvents

<table>
<thead>
<tr>
<th>Phytochemicals</th>
<th>Solvent extraction (ethanol) mg/10 g residue</th>
<th>Solvent extraction (hot water) mg/10 g residue</th>
<th>Solvent extraction (acetone) mg/10 g residue</th>
<th>Solvent extraction (chloroform) mg/10 g residue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenols</td>
<td>0.7</td>
<td>0.7</td>
<td>0.64</td>
<td>0.56</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>10.0</td>
<td>0.0</td>
<td>0.21</td>
<td>0.22</td>
</tr>
<tr>
<td>Saponins</td>
<td>0.8</td>
<td>0.04</td>
<td>0.04</td>
<td>0.4</td>
</tr>
<tr>
<td>Alkaloids</td>
<td>0.6</td>
<td>0.01</td>
<td>0.02</td>
<td>0.54</td>
</tr>
<tr>
<td>Glycosides</td>
<td>0.7</td>
<td>0.01</td>
<td>0.3</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Adapted from references [40-42]

Figure 4: Schematic representation of infection pathway of the dengue virus. Adapted from reference [33]
liquid chromatography (HPLC)-based activity profiling of C. papaya has been done by Julianti et al.\textsuperscript{[45]} High-performance thin layer chromatography phytochemical screening has been done by Anjum et al., 2013 using different extracts of C. papaya leaves. However, fingerprinting was done by determining the r\textsubscript{f} values of the prepared extracts.\textsuperscript{[46]} Flavonoids of C. papaya leaves have been investigated using aqueous and ethanolic extract using HPLC method. In the HPLC, rutin and lycopene (between 190 and 700 nm) were used as a standard. In this research, 95% methanol and 5% water was used as a mobile phase. However, 1% phosphoric acid was also added to maintain the pH range within 4.0. All the solvents were degassed before use by sonication.\textsuperscript{[47]}

In a recent study, Fadare et al., 2015 attenuated total reflectance Fourier transform infrared spectroscopy (FTIR) and HPLC spectroscopic studies have been done using both C. papaya leaves and flowers. For HPLC analysis, they have used mobile phase containing 90% phosphate buffer, 8% acetonitrile, and 2% methanol. In FTIR spectrum, they identified the functional groups of C. papaya leaves and discovered the active components based on the absorption band values in the region of infrared radiation.\textsuperscript{[48]}

**Medicinal Activity of the Phytochemicals of C. papaya Leaves**

Researchers found that phytochemicals of C. papaya leaves like Vitamin C had the capability of treating idiopathic thrombocytopenia.\textsuperscript{[49]} Otsuki et al., 2010 found the anti-tumor activity of C. papaya leaves in an animal model.\textsuperscript{[50]} In a recent study, Panzarini et al., 2014 explained the beneficial use of C. papaya leaves extracts as an antioxidant and anticancer agent.\textsuperscript{[51]} Juárez-Rojop et al., 2014 identified the hypoglycemic activity of papaya leaves in diabetic rats.\textsuperscript{[52]} The anti-inflammatory effect of C. papaya leaves extracts in a murine model was found by Gamulle et al., 2012\textsuperscript{[53]} and the anti-plasmodial effect of papaya leaves are also identified by HPLC-based activity profiling.\textsuperscript{[45]}

Owoyele et al., 2008 has identified the anti-inflammatory action of Carica papaya leaves using a cold maceration extraction method using 2 L of ethanol.\textsuperscript{[54]} C. papaya leaves were individually extracted using 95% of cold ethanol, cold methanol, and pure water to identify the antimicrobial activity by Anibijuwon and Udeze in 2009.\textsuperscript{[62]} Cardiovascular Effects of C. papaya leaves have been studied using alcoholic extract by Gupta et al., 1990. They have identified that leaves extract between the doses of 100 and 200 mg/kg can give total protection against electroshock-induced spasms in rats.\textsuperscript{[55]} Lyophilized C. papaya leaves juice (2.6% w/w yield) have been used to determine the toxicity using Sprague-Dawley rats. In the study, Sprague-Dawley rats at doses around 0.01, 0.14, and 2 g/kg of C. papaya leaves extract were administered. After administering the dose, mainly general behavior, clinical signs, hematological parameters, serum biochemistry, and histopathology changes were analyzed. A dose until 2 g/kg was found to be safe among the rats.\textsuperscript{[43]}

Using 400 mg/kg C. papaya leaves in a rat model, it was found that it can significantly increase the platelet count and decrease the blood clotting time in 7 days.\textsuperscript{[38]} In a recent docking study, Senthilvel et al., 2013 found that flavonoids (quercetin, protocatechuic acid, p-coumaric acid, caffeic acid, chlorogenic acid, kaempferol, and 5, 7-dimethoxycoumarin) from C. papaya inhibits NS2B-NS3 protease and can prevent dengue viral assembly. Complex formation between NS3 and

**Table 2: Mineral composition of the Carica papaya leaves on dry weight basis (mg/kg)**

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Green leaf (mg/kg)</th>
<th>Yellow leaf (mg/kg)</th>
<th>Brown leaf (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>8612.50</td>
<td>3762.50</td>
<td>4362.50</td>
</tr>
<tr>
<td>Magnesium</td>
<td>67.75</td>
<td>28.55</td>
<td>35.35</td>
</tr>
<tr>
<td>Sodium</td>
<td>1782.00</td>
<td>567.00</td>
<td>324.00</td>
</tr>
<tr>
<td>Potassium</td>
<td>2889.00</td>
<td>819.00</td>
<td>468.00</td>
</tr>
<tr>
<td>Iron</td>
<td>90.50</td>
<td>147.50</td>
<td>79.50</td>
</tr>
<tr>
<td>Manganese</td>
<td>9.50</td>
<td>5.00</td>
<td>4.50</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>162.9</td>
<td>96.2</td>
<td>112.6</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>1.3</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Thiamine</td>
<td>9.4</td>
<td>4.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Adapted from reference [39]

\[\text{Figure 5: Schematic representation of immunological response to dengue infection. Adapted from reference [36]}\]

\[\text{Figure 6: Carica papaya tree. Adapted from reference [12]}\]
NS2B co-factor is needed for virus replication. The active components of *C. papaya* leaves can control this process.\(^{[56]}\) *C. papaya* leaves have membrane-stabilizing properties, and they can control the damage of blood cells.\(^{[41]}\)

**Papaya Leaf Extract in Dengue Treatment**

Ahmad *et al.* have done a study using the case report of a 45-year-old male patient, suffering from dengue. It was observed that the platelet count increased from \(55 \times 10^3/\mu L\) to \(158 \times 10^3/\mu L\) in the patient by administering 25 ml of *C. papaya* leaves extract for 5 days.\(^{[57]}\) Dharmarathna *et al.* found that papaya leaves can increase the platelet and RBC count in the test group compared to the control group of animal.\(^{[8]}\) Toxicological studies of *C. papaya* leaves extract had been done using Sprague-Dawley rats by Afzan *et al.*, 2012. The results suggest that *C. papaya* leaves extract up to 2 g/kg was safe for traditional use in the animal model.\(^{[43]}\)

A patent had been done by Stanbridge *et al.*, 2014 about the application of *C. papaya* leaves extract inhibiting hypoxia-inducible factor activity. In the research, it was proved that papaya leaves can treat hypoxia-related conditions or diseases such as inflammatory diseases, vascular diseases, cancer, and infections.\(^{[58]}\)

**Arachidonate 12-lipoxygenase (ALOX 12) Gene Expression in Platelet Production**

In humans, normal platelet count ranges from 150,000 to 350,000. Thrombocytopenia occurs if platelet count reduces and it may cause plasma leakage in dengue patients. Megakaryocyte is responsible for the production of blood platelets, and ALOX 12 genes are strongly expressed in megakaryocytes. ALOX 12, which is also known as platelet-activating factor receptor (PTAFR), plays an important role in platelet aggregation. It means that PTAFR gene can be a precursor for platelet production.\(^{[59]}\)

In a clinical trial, *C. papaya* leaf juice was given to 228 dengue patients, and the RNA was extracted for further investigation. It was found that ALOX 12 gene activity increased 15-fold in the experimental groups compared to the control days in 3 days.\(^{[9]}\)

**Marketed Formulation of *C. papaya* Leaves**

Papaya leaf extract formulations are available on the global market as supplements under Rochway,\(^{[60]}\) Iowa Select Herbal, Herbal Papaya,\(^{[61,62]}\) and SidoMuncul Herbal.\(^{[63]}\) However, they are formulated using micronization, fermentation, and liquid extraction. Marketed *C. papaya* leaves supplements were shown in Table 3.

**Problems with Micronized *C. papaya* Leaves Formulations**

Rochway is one of the leading herbal supplements manufacturers of Australia and SidoMuncul is a fully-modernized herbal company in Indonesia. Both companies are currently producing micronized *C. papaya* leaves capsules. However, extraction methods such as milling and supercritical fluids used in micronization can cause mechanical stress, and it can modify the active compounds of any herbal product. The mechanical forces such as milling and grinding during micronization can also cause physical stress and degradation of the product. Specially, during micronization thermal stress occurs and this can degrade the heat sensitive compounds.\(^{[64]}\) However, micronization with supercritical fluids such as CO\(_2\) can be difficult, due to oxidative stresses.\(^{[65]}\) The most noticeable drawback of supercritical fluids is the fact that several molecules (specially flavonoids) are not soluble in

<table>
<thead>
<tr>
<th>Company name</th>
<th>Brand name</th>
<th>Dosage form</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochway</td>
<td>Papaya leaf extract capsules</td>
<td>Each capsule contains 100% natural ingredients micronized papaya dry leaves</td>
<td>Supplement</td>
</tr>
<tr>
<td>Rochway</td>
<td>Papaya leaf extract – 500 ml</td>
<td>100% bio-fermented dry <em>Carica papaya</em> leaves extract</td>
<td>Supplement</td>
</tr>
<tr>
<td>Herbal Papaya</td>
<td>Papaya Leaf (Paw Paw Twig) Extract (alcohol-free)</td>
<td>60 Veggie capsules of dry papaya leave</td>
<td>Supplement</td>
</tr>
<tr>
<td>Iowa Select Herbs LLC</td>
<td>Papaya leaf extract 4 oz (120 ml)</td>
<td>Liquid extract of papaya leave</td>
<td>Supplement</td>
</tr>
<tr>
<td>SidoMuncul Herbal</td>
<td>Sari Daun Pepaya</td>
<td>Each capsule contains 500 mg of dry <em>Caricae folium</em> (papaya leaf) extract</td>
<td>Supplement</td>
</tr>
<tr>
<td>Celebration Herbs</td>
<td>Herbal tea, papaya leaf, caffeine free, 24 tea bags, 1.33 oz (38 g)</td>
<td>Tea bags (fermented papaya leaves)</td>
<td>Supplement</td>
</tr>
<tr>
<td>Micro lab limited</td>
<td>Caripill</td>
<td>Tablet containing dry <em>Carica papaya</em> leave extract</td>
<td>Supplement</td>
</tr>
</tbody>
</table>

Adapted from reference [60-63]
CO$_2$ [66] One way to overcome this problem is to change the supercritical fluid. However, this is not possible as the other supercritical fluids, for example, N$_2$O, light hydrocarbon, etc., is much more lethal and less environmental friendly than CO$_2$ [67].

Vandana et al., 2014 has mentioned that the main disadvantages of micromanization technique could be controlling the uniform particle size of formulation and avoiding hydrophilic particles to form agglomeration. [68] Therefore, the marketed products of Rochway named micronized papaya leaf extract capsules and SidoMuncul Herbal capsules might face the problems regarding thermal degradation.

Problems with Fermented C. papaya Leaves Formulations

Rochway is one of the leading manufacturers of probiotics and herbal supplements in Australia. They have marketed bio-fermented C. papaya leaves extract named papaya leaf extract - 500 ml. However, the existing fermentation scale-up process cannot meet adequately the advance technical and economic demands of the modern industry. Therefore, alternative methods are developed for better commercialization. [69] However, in the fermented products hazardous microbial contamination always exists. David et al. found that the traditional fermentation process of fresh leaves of Cassia obtusifolia (known as sicklepod or Chinese senna) can decrease proteins, total fibers, and volatile fatty acid content. [70]

Therefore, marketed product of Rochway named papaya leaf extract - 500 ml might have the disadvantage of low active phytochemicals. However, purification of end products, balancing the yields, and biomass estimation are also major problems of the fermentation process, which influence the researchers to find other solutions for extraction. [71]

Problems with Liquid Extract of C. papaya Leaves

Herbal Papaya, Iowa Select Herbs, Hawaii Pharm, Rochway, etc., are producing C. papaya leaves liquid extract as supplements. The general liquid extraction techniques of the medicinal plant include hot continuous extraction (soxhlet), aqueous-alcoholic extraction, supercritical fluid extraction, and distillation techniques (water distillation, steam distillation, phytonic extraction with hydrofluorocarbon solvents). [72] However, different solvents are recommended for extracting specific active components. For example, ethanolic solutions are suggested for extracting tannins, polyphenols, polyacetylenes, flavonoids, terpenoids, sterols, alkaloids, and chloroform solutions are suggested for extracting specific active components. For example, ethanolic solutions are suggested for extracting tannins, polyphenols, polyacetylenes, flavonoids, terpenoids, sterols, alkaloids, and chloroform solutions are suggested for extracting terpenoids, flavonoids, phenols, etc. [73] In a previous comparison study of different extraction methods on spearmint leaves (Mentha spicata L.), Bimakr et al. found that total active flavonoid yield can be effected by the temperature. [74] In a review article, Shah et al. mentioned that for protecting the natural components of plant different modernized extraction methods need to be developed. Because the traditional drying techniques had various limitations such as lengthier extraction timeline, large solvent volumes, and degradation of thermolabile components. [75]

Therefore, it can be postulated that marketed liquid extracts of companies such as Herbal Papaya, Iowa Select Herbs, Hawaii Pharm, and Rochway might face all these limitations and the main drawback of the liquid extract will be the bitter taste of C. papaya leaves.

Problems with of C. papaya Leaves Tablets

Tablets are the most commonly used dosage form. Because, during large manufacturing simplicity and economic condition need to be considered. Therefore, recently Micro Lab Limited has introduced C. papaya leaves tablet (Caripill) in the market. Despite several advantages sometimes, certain herbal substances resist compression pressure and need a special formulation technique for improving bioavailability. For avoiding these problems, punching pressure or percentage of excipients is increased. However, high punching pressure may degrade the thermolabile active components of herbal extract, and excess binding agent may slow the dissolution and disintegration of the formulation. [76, 77]

In 2014, Pushpalatha et al. mentioned the detailed formulation process of Ashoka tablets with an industrial perspective. They have added microcrystalline cellulose, maize starch, colloidal silicon dioxide, and talc and magnesium stearate for preparing better granulating solutions. However, they dried the solution at 60°C and blended in high speed for several hours. [78] However, drying the herbal extract for long time can make them brittle and loose active components. [79]

However, similarly, the recently marketed C. papaya leaves tablet (Caripill) might face these problems during manufacture. Therefore, the company did not reveal any formulation process to the public. The use of excipients, punching pressure, and phytochemical protection was also not mentioned.

CONCLUSION

In recent years, dengue has become an epidemic in tropical countries. Unfortunately due to the absence of proper treatment method, the death rate is increasing. Researchers from several organizations and companies (example-Bill and Melinda Gates Foundation) are trying to discover a new vaccine for dengue. In 2014, Sanofi Pasteur released results of phase three trial having almost 10,275 children aged from 2 to 14 years in Indonesia, Malaysia, Philippines, Thailand, and Vietnam. But meanwhile, we need to improve the old
herbal formulations for the current crisis. Therefore, the drawbacks of marketed C. papaya leaves supplements need to be modernized for better patient care.

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Source of Support: Nil. Conflict of Interest: None declared.