Carica papaya Leaf Extract

Subjects: Biochemical Research Methods

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Carica papaya (papaya) leaf extract has been used for a long time in a traditional medicine to treat fever in some infectious diseases such as dengue, malaria, and chikungunya. The development of science and technology has subsequently made it possible to provide evidence that this plant is not only beneficial as an informal medication, but also that it has scientifically proven pharmacological and toxicological activities, which have led to its formal usage in professional health care systems.

Carica papaya leaf extract herbal medicine

1. Introduction

Carica papaya (papaw or papaya) is one of the tropical and subtropical trees that are well known for having the entirety of its parts utilized. As a tropical species, this plant grows continuously during winter, although growth slows down and fruit production ceases during the colder months [1]. In Indonesia, the export demands for papaya come from Germany, Hong Kong, Japan, Malaysia, Singapore, Taiwan, and the USA; despite still being high, the export volume decreased from 2009 to 2020 [2]. This could indicate the preservation of this crop becoming less intensive, leading to a reduction in its productivity.

2. Extraction

The extraction of papaya leaf is carried out by means of various methods, from traditional maceration, percolation, and Soxhlet approaches to the use of more advanced instruments such as microwaves and ultrasonic cleaners. **Table 1** presents the extraction methods used for papaya leaf along with the solvents involved in these methods. The leaves are mostly extracted using a maceration method that employs 96% ethanol as the solvent. The reason for maceration being the most common method could be that it is simpler and less expensive compared to other methods. The leaf has a soft texture; therefore, it is easier for the solvent to penetrate the leaf cells while extracting the phytoconstituent. However, this method has a disadvantage in terms of the equilibrium state between the outside and inside of the cell since the solvent does not move. This causes the extraction to stop, and the residues of filtrate need to be re-macerated using a new solvent [3][4]. On the other hand, 96% ethanol and water are used as the two most common solvents. The main reason for choosing these solvents is the fact that they have fewer toxic properties compared to others [5]. Most likely, the flavonoid glycoside, as well as alkaloids in a salt form, would be easily extracted from the leaf cells due to their suitable polar character in relation to the solvents. Appropriately in light of the above, these two solvents are the most recommended by the National Agency of Drug and Food Control.

Table 1. The extraction method for papaya leaves along with the solvents used.

Extraction Method	Solvents	References
Ultrasonic cleaner	Methanol 96% ethanol	[6] [7]
Hot presser	Water	[8]
Blender	Water	[9][10][11][12]
Maceration	70% ethanol 96% ethanol 70% methanol 80% methanol Water	[13][14] [15][16][17][18][19][20][21][22][23] [24][25] [26][27] [28]
Mixer	cold water, hot water, cold ethanol, 70%	[29][30]
Microwave	methanol, 70% ethanol and water	[31]
Soxhlet	hexane, acetone, 60% ethanol, 40% ethanol and water	[32]

3. Safety

A full safety study was conducted to evaluate papaya leaf extract in both pre-clinical and clinical settings [33]. Male Wistar rats were given up to 1500 mg/kg of a methanolic papaya leaf extract via gavage, which resulted in no observed mortality [34]. An aqueous papaya leaf extract with a dose of 2000 mg/kg BW led to greater LD_{50} values than those given the methanolic dose in the aforementioned study [35]; meanwhile, there were no mortalities observed when a methanolic papaya leaf extract was administered to Wistar mice in doses of up to 3200 mg/kg [36]. A further study was carried out by giving Wistar rats with a methanolic papaya leaf extract (400 mg/kg bw/d) via gavage for 28 days, it was found that the rats exhibited reduced aspartate aminotransferase activity, enhanced blood urea nitrogen levels, and moderate hyperaemia in the kidney and heart muscles [34]. Another study showed that no extract-related effects were indicated when green papaya leaf extract (up to 2000 mg/kg/day) was administered to Sprague-Dawley rats for 28 days via gavage [37]. Similarly, no adverse effects were shown when Wistar mice were administered a methanolic papaya leaf extract (up to 3200 mg/kg/day) for 60 days [36]. The safety of aqueous papaya leaf extract was evaluated in pregnant Wistar rats via gavage on days 12–18 of gestation with a dose of 60 or 120 mg/kg [38]; deformities were observed in the morphometry of foetuses, while 100% resorption was noted in rats treated with 120 mg/kg of the extract. Other effects of papaya leaf extract on the reproductive system were noted in a study conducted on male Wistar rats [39] given 500 mg/kg BW extract orally for 21 days. This exposure resulted in significant reductions in mean values of sperm count, motility, viability, and serum testosterone concentration, compared to control rats.

Papaya leaf extracts that were mixed with 96% ethanol, followed by partitioning into hexane, ethyl acetate, and water fractions, were evaluated for their cytotoxicity against T47D, a breast cancer cell line, using an MTT assay. The cytotoxicity assay showed that the extract does not interrupt the growth of T47D cells. However, the hexane,

ethyl acetate, and water fractions showed reduced viability of T47D cells with IC_{50} values of 2231.30, 557.33, and 2112.81 µg/mL, respectively. These results showed that the ethanolic extract of papaya leaves and all of its partitions have no potential cytotoxicity in T47D cells due to their high IC_{50} values [23].

Recently, a juice and standardized aqueous extract of papaya leaf were reported to be well tolerated by adult humans for short durations (<five days), while one randomised controlled trial reported its safe consumption in children (aged 1–12 years). The most common side effects were minor uncomfortable gastrointestinal feelings. Hepatotoxicity and reproductive toxicity were concerns in relation to long-term use, which was supported by in vivo animal studies. Some unfavourable herb-drug interactions were indicated with metformin, glimepiride, digoxin, ciprofloxacin, and artemisinin. In conclusion, papaya leaf consumption by adults is most likely safe for short-term use but should be carefully managed when it is given to pregnant women and people with liver impairments. Furthermore, potential herb-drug interactions could occur with oral hypoglycaemic agents, P-glycoprotein substrates, and antibiotics with cation-chelating properties [40]. As previously mentioned, a papaya leaf extract produced by Sido Muncul showed non-sub-chronic toxicity even for long periods of consumption when it was evaluated in an animal study.

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