Phytochemical Screening, Antioxidant Activity, and Total Phenol Profile of *Carica pubescens* Leaves from Cangar, Batu-East Java, Indonesia

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**Abstract.** Mountain papayas (*Carica pubescens*) spread limitedly and can only adapt in the highland environment. In Malang area, *C. pubescens* is found only in the Cangar area (3000 masl). The study was carried out to determine active compounds, antioxidant activity, and total phenolic of *C. pubescens* stem and leaves methanolic extract. The samples of *C. pubescens* leaves were taken from Cangar, Batu-East Java. Afterward, the phytochemical screening analysis was conducted using LCMS (Shimadzu brand) with three types of solvent, i.e., methanol, ethyl acetate, and chloroform. The leaves and stem extract were produced by a maceration method using methanol as a solvent. The antioxidant activity of *C. pubescens* stem and leaves extract series concentration 25, 50, 75, and 100 ppm and DPPH as standard. Total phenolic content was estimated according to the Folin Ciocalteu method and Gallic acid as standard. The data of active compounds in papaya leaves were analyzed descriptively. The results showed that 62 types of active compound were dominantly identified using ethyl acetate, followed by 60 types were found by methanol, and 53 types were identified using chloroform solvent. The IC₅₀ value of *C. pubescens* leaves, and stem methanolic extract was 35.64 ppm and 62.34 ppm respectively. The total phenolic concentration also showed that leaves methanolic extract (62.1134 mg EGA/g) is higher than stem methanolic extract (30.9278 mg EGA/g). Furthermore, those results reveal that the extract from ethyl acetate produces a more active compound compared to methanol and chloroform from the *C. pubescens* leaves. Otherwise, the methanolic extract from the leaves has a higher potential antioxidant rather than the stem methanolic extract.

**Keywords:** *Carica pubescens* leaves, antioxidant activity, LCMS, total phenolic

1. **Introduction**

The use of plants for herbal medicine has been carried out for a long time worldwide. The phytochemical in a plant is the basis for discovering potential medicine. The medicinal properties derived from a plant depend on the content of its phytochemical constituents and nutritive elements such as minerals. Importantly, the effectiveness of a plant that is used as a drug depends on the concentration of those nutrient compounds [1]. Natural products, either as pure compounds or as standardized extracts, provide many benefits because of the unmatched availability of chemical diversity [2]. Phytochemical screening is also an essential process to evaluate the medicinal properties...
of plants [1]. The bioactive compounds of the plant initially come from leaves, stems, roots, flowers, fruit, or seeds. For this reason, all parts of plants potentially contain active ingredients.

Indonesia has a large variety of plant species. The papaya plant has been used by the local people as herbal medicine. Papaya belongs to the family Caricaceae. Papaya which is distributed in Indonesia consists of 2 species, Carica papaya and Carica pubescens. Papaya (C. papaya), the common papaya fruits that easily grow and spread from the lowlands to the highlands up to 1000 meters above sea level. On the other hand, another species of papaya, C. pubescens has more potentials to grow in mountainous or higher areas. In particular, for East Java area, there is a highlighted place that can modulate mountain papaya to increase namely in the Cangar, Batu-East Java Region.

In comparison with the natural papaya, most local peoples consume mountain papaya. This phenomenon attracted the specific interest of some researchers to describe and provide the primary data of the active compounds from mountain papaya leaves [3]. Papaya leaves chemical profiling have been shown so many active components such as papain, chymopapain, cystatin, tocopherol, ascorbic acid, flavonoids, cyanogenic glucoside and glucosinolates [4]. Primarily, flavonoids are the common chemical compounds found in all plant kingdoms. These compounds are generally used by the local people as an insecticide [5]. Moreover, another active compound within papaya leaves including alkaloid family; carpaine, dihydrocarpaine, nicotine, and cyanogenic glycosides [6]. Indeed, carpaine is the principal alkaloid chemical ingredient contained in the papaya leaves extract [7]. Papaya leaves also have pseudocarpaine, dehydrocarpaine I and II which related to the bitter taste from its leaves [8].

Several previous studies have shown that the active compounds of aqueous extract of C. papaya (Caricaceae family) leaves were tannin, saponin, flavonoid, terpenoid, steroid, alkaloid [9]. However, from those six compounds, the only terpenoid which could not be detected in extract ethanol papaya leaves [10]. Identification and quantification flavonoid used chromatographic and spectroscopic methods found 7 flavonoid compounds namely quercetin, kaempferol, myricetin, quercetin 3-(2′G-rhamnosyl-rutinoside), kaempferol 3-(2′G-rhamnosyl-rutinoside), quercetin 3-rutinoside, myricetin 3-rhamnoside, and kaempferol 3-rutinoside [11]. The extraction and quantification of carpaine in papaya leaves extract yielded 63% from alkaloid total [12]. The strength of the HPLC (High-Performance Liquid Chromatography) method that has been done is to identify flavonoids and quantify carpaine which in the other analyses, e.g., qualitative analysis, it cannot detect the compound specifically. Otherwise, the weaknesses of the analysis cannot detect full compounds contained in papaya leaves extract and the material used was only extracted of C. papaya.

Plant C. papaya is one family with Carica pubescens. Previous work has only focused on the active compounds in the fruit of C. pubescens only, as for the leaves was less studied. For this reason, this paper sought to address the potential of C. pubescens leaves from Cangar by conducting an analysis of active compounds. Also, this study also examined the antioxidant, and the total phenolic activity of C. pubescens leaves extract. Furthermore, the implication of this study aimed to explore the new potential traditional medicine.

2. Methods

2.1. Plant materials
The plant materials used in this research consisted of the leaves and stems of mountain papaya (Carica pubescens) which were collected from Cangar, Batu (Indonesia) at an altitude of 3000 m above sea level. The samples were then deposited in Herbarium unit in the Biology Department, Universitas Negeri Malang. Before the analysis process, the samples were washed with water to remove dust at first. Then the leaves and stem of C. pubescens were dried by the oven at 50 °C for 3 days and crushed into powder form using a dry blender.

2.2. Preparation of plant extract
C. pubescens leaves powder was extracted by maceration method by using methanol, ethyl acetate, and chloroform as a solvent with a ratio 1:10. The mixture was filtered using Whatman filter paper,
and the extracts were evaporated to dryness using a water bath. The extract obtained was used for phytochemical screening. The C. pubescens leaves, and stem powder was extracted by maceration method using methanol as a solvent with ratio 1:10 (20 grams of simplicia dissolved in 200 mL methanol). Maceration process was performed at room temperature for 4×24 hours used shaker at 100 rpm. The mixture was filtered using Whatman filter paper and was evaporated using a water bath. The obtained leaves and stems extract were used for antioxidant and total phenol.

2.3. Antioxidant activity test
The total of 0.002 g of leaves and stem C. pubescens methanolic extract were weighed and then each extract dissolved in 20 mL methanol resulted in 100 ppm. The main liquor was taken using micropipette with the multilevel dilution to obtain the test solution concentration of 75, 50, and 25 ppm. There is 0.002 g 1,1-diphenyl-2-picrylhydrazyl (DPPH) was weighed and then dissolved in 50 ml methanol resulted in 40 ppm. Besides, 0.5 mL of each test solution was put into glass bottles and then added with 4.5 mL DPPH, and then it was shaken vigorously and incubated in the dark room for 30 min at room temperature. The absorbance of the solution was measured with a spectrophotometer of visible light at 517 nm with deionized water as a blank.

2.4. Total phenolic content
The total phenolic content was estimated using the Folin Ciocalteu. A total of 0.0025 g Gallic Acid was weighed and then dissolved in 25 mL deionized water resulted in 100 ppm. This solution was made multilevel dilution to obtain 75 ppm, 50 ppm, and 25 ppm. As much as 1 mL of each solution was put and then added with 2 mL Folin Ciocalteu and incubation 4-8 minute at room temperature. After that, the solution added 4 mL Sodium Carbonate 1 M, and then incubation 1-2 hours at room temperature. The absorbance of the solution was measured with a spectrophotometer of visible light at 765 nm. The standard curve of Gallic acid was plotted.

As much as 0.002 g of leaves and stem C. pubescens methanol extract were weighted and then each extract dissolved in 20 mL deionized water resulted in 100 ppm. Amount 1 mL of each test solution was put into glass bottles and then added with 2 mL Folin Ciocalteu and incubation 4-8 minute at room temperature. After that, the solution added 4 mL Sodium Carbonate 1 M and then incubation 1-2 hours at room temperature. The absorbance of the solution was measured with a spectrophotometer of visible light at 765 nm.

3. Results
The phytochemical screening results found in methanol, ethyl acetate, and chloroform extracts from C. pubescens leaves using Shimadzu brand LCMS i.e 2,3 butanediene, Diacette alcohol, Isopropyl butyrate, Coumarin, Benzyl thioctanate, 3,4 dihydroxybenzoic acid, Benzylthioure, Caffeic acid, Citric acid, Isopentyl benzoate, Ferulic acid, 5 Deoxykaempferol, Kaempferol, Prunasin, Sambunigrin, Quercetin, Dicoumarol, 4p Coumaroylquinic acid, Chlorogenic acid, Benzyl glucosinolate, β Sitosterol, β Amyrin, Lupeol, α Tocopherol, Luteoindin 5 glucoside, Isovitexin, Vitexin, Kaempferol 3 rhamnoside, Kaemferol 3 O D glucoside, Kaemferol 7 O β glucoside, Luteolin 7 glucoside, Betulinic acid, Isoquercitrin, Dehydrocarpaine II, Dehydrocarpaine I, Quercitruron, Carpane, Pseudocarpaine, β Carotene, and Naringin. The active compound was found only in methanolic extract of C. pubescens leaves, i.e., Niacin, Glucose, Galactose, Pantothenic acid, Thiamin, Riboflavin, Folic acid, Procyanidin, Prodelphinidin B and only in chloroform extract was Linalool Oxide. The active compound was found in ethyl acetate and chloroform extract of C. pubescens, i.e. Ocimene, α Termipene, α Phellandrene, Myrcene, Linalool, Caryophyllene, Phytofluene, 15 cis Phytoene, Cryptoxanthin, Carotene 5,6 epoxide, and Anteraxanthine.

Based on the phytochemical screening, the total of active compounds was found in extracts (methanol, ethyl acetate, and chloroform) from C. pubescens leaves using Shimadzu brand LCMS are presented in Table 1.
Table 1. Total Active compounds in methanol, ethyl acetate, and chloroform extract of *C. pubescens* papaya leaves

| No. | Kind of Extract               | The Total Number of Active Compound |
|-----|-------------------------------|-------------------------------------|
| 1.  | Leaves Methanolic extract     | 60                                  |
| 2.  | Leaves Ethyl Acetate extract  | 62                                  |
| 3.  | Leaves Chloroform extract     | 53                                  |

The number of active compounds detected using LCMS showed that *C. pubescens* leaves extract using ethyl acetate solvent produced the highest number (62 compounds) and the lowest number was found in chloroform extract. Among the active compounds identified were 10 active compounds which were the highest percentage in the extract (Table 2).

Table 2. Active Compounds contained in the methanol, ethyl acetate, and chloroform extract of *C. pubescens* leaves which have the highest percentage

| No. | Name of compound | Extract | Class of Secondary metabolite |
|-----|------------------|---------|-------------------------------|
| 1.  | Gallic acid      | PM 5.69 | Phenolic                      |
|     |                  | PE 4.81 |                                |
|     |                  | PK -    |                                |
| 2.  | Kaemferol        | PM 3.50 | Phenolic (Flavonoid)           |
|     |                  | PE 3.96 |                                |
|     |                  | PK 4.51 |                                |
| 3.  | Quercetin        | PM 3.93 | Phenolic (Flavonoid)           |
|     |                  | PE 4.48 |                                |
|     |                  | PK 5.15 |                                |
| 4.  | Benzyl glucosinolate | 4.39 | Phenolic                      |
|     |                  | PE 5.02 |                                |
|     |                  | PK 5.82 |                                |
| 5.  | Carpaine         | PM 3.50 | Alkaloid                       |
|     |                  | PE 3.95 |                                |
|     |                  | PK 4.51 |                                |
| 6.  | Psedocarpaine    | PM 3.26 | Alkaloid                       |
|     |                  | PE 3.67 |                                |
|     |                  | PK 4.16 |                                |
| 7.  | Dehydrocarpaine I | 2.21 | Alkaloid                       |
|     |                  | PE 2.35 |                                |
|     |                  | PK 2.53 |                                |
| 8.  | Dehydrocarpaine II| 2.28| Alkaloid                       |
|     |                  | PE 1.37 |                                |
|     |                  | PK 1.33 |                                |
| 9.  | Isoquercitrin    | -       | Phenolic (Flavonoid)           |
|     |                  | PE -    |                                |
|     |                  | PK 4.17 |                                |
| 10. | Luteolin 7 glucoside | 3.58 | Phenolic (Flavonoid)           |
|     |                  | PE -    |                                |
|     |                  | PK -    |                                |

PM: *C. pubescens* leaves methanolic extract; PE: *C. pubescens* leaves ethyl acetate extract; PK: *C. pubescens* leaves chloroform extract

Table 2 shows that alkaloid was detected in all extracts. Phenolic compounds were also found in all three extracts, however different kinds of compounds identified in each type of extract. Isoquercitrin compounds found highest percentage detected in chloroform extract. Luteolin 7 glucoside compounds found the highest percentage in papaya leaves methanolic extract. Testing of antioxidant activity of leaves methanolic extract and stem of *C. pubescens* leaves was conducted by DPPH method (Table 3).

Table 3. Antioxidant activity of *C. pubescens* leaves and stem methanolic extract

| Sample        | Concentration (ppm) | Antioxidant activity | IC<sub>50</sub>* |
|---------------|---------------------|----------------------|------------------|
| Leaves extract| 25                  | 0.154                | y = 0.0014x + 0.1065 |
|               | 50                  | 0.158                | R<sup>2</sup> = 0.9197 |
|               | 75                  | 0.214                | IC<sub>50</sub> = 35.64 |
|               | 100                 | 0.253                |                  |
| Stem extract  | 25                  | 0.148                | y = 0.0008x + 0.125 |
|               | 50                  | 0.163                | R<sup>2</sup> = 0.9481 |
|               | 75                  | 0.176                | IC<sub>50</sub> = 62.34 |
|               | 100                 | 0.209                |                  |

IC<sub>50</sub>: half maximal inhibitory concentration
The results of the antioxidant activity test for leaves extract and stem showed different results. IC$_{50}$ value of papaya leaves extract = 35.64 ppm and papaya leaves stem extract = 62.34 ppm. Assuming this, these data reveal that papaya leaves extract has robust antioxidant activities, while stem extract is strong. Gauging phenol content from leaves extracts and leaves stems of *C. pubescens* were carried out using gallic acid as a standard (Table 4).

Table 4. Total Phenolic of *C. pubescens* leaves and stem methanolic extract

| Sample            | Absorbance | Phenol Concentration (mg/mL) | Phenol Concentration (mgEAG/g) |
|-------------------|------------|-----------------------------|--------------------------------|
| Leaves extract    | 0.165      | 6.2113                      | 62.1134                        |
| Stem extract      | 0.1045     | 3.0928                      | 30.9278                        |

The phenol of each extract is expressed as Equivalent of Gallic Acid (EAG)/g. Gallic acid is used as a standard with the standard curve equation $y = 0.0194x + 0.0445$ with $R^2 = 0.9978$. The phenolic concentration calculation results from papaya leaves extract were higher than those contained in stem extract.

4. Discussion

The phytochemical screening of *Carica pubescens* papaya leaves extract showed that papaya leaves contain many active compounds. The active compound detected in leaves extract of *C. pubescens* between 53-62 compounds. The number of active compounds detected using ethyl acetate solvent produced the highest number (62 compounds), and the lowest number was found in chloroform extract (53 compounds). Three types of solvents (ethyl acetate, methanol, and chloroform) have been carried out on phytochemical screening extract of female papaya leaves [13]. The results showed that the extract of ethyl acetate from papaya leaves was found in 6 active compounds, i.e., alkaloids, saponins, glycosides, phenolics, flavonoids, and tannins. Methanol extract detected only 4 compounds (saponins, glucosides, flavonoids, terpenoids) and chloroform extract detected 3 compounds (alkaloids, phenolic, and tannins). Based on the research results showed that more active compounds were detected with ethyl acetate solvents.

In the analysis process, the critical factor in detecting active compounds contained in extract optimally is the used solvent in the extraction process. The choice of a solvent is affected by the nature of the solvent such as having low toxicity, is easily evaporated at low temperatures, does not interfere with the bioassays used and depends on the targeted compounds [13]. Also, the results of *C. pubescens* papaya leaves extract with different solvent compounds using the LCMS method produced different amounts of active compounds identified (starting from the highest number of ethyl acetate extracts, methanolic extract, and chloroform extract). The active compounds found in all three types of extracts, but certain compounds were only identified in two kinds of extracts or just one type of extract. The difference in the number of active compounds identified is due to the nature of the active compound which is polar or tends to be non-polar. Polar active compounds are quickly dissolved in polar solvents. Otherwise, the non-polar active compounds are quickly dissolved in non-polar solvents. The difference in extract material affects the active compounds detected.

The solubility of an active compound depends on its ability to form hydrogen bonds [14]. Methanol is a polar compound, so the active compounds contained in papaya leaves extract, and polar tend to form hydrogen bonds. Ethyl acetate is a semi-polar compound so that it can attract polar and non-polar active compounds. As a result of the nature of the ethyl acetate compound, the most compounds were identified in the ethyl acetate extract. Chloroform is a non-polar solvent, so that non-polar compounds can dissolve in chloroform. As a result of this condition, the number of active compounds in the chloroform extract of papaya leaves were identified at least (53 compounds).

The active compounds of papaya leaves extract which has the highest percentage were alkaloid compounds (carpaine, pseudocarpaine, Dehydrocarpaine I and II). In the same way, the identified
alkaloid compounds in mountain papaya are the same as the active compounds contained in the *Carica papaya* leaves [7]. Another active compound is phenolic compounds (flavonoids) namely kaempferol and quercetin identified in all three types of extracts. Quercetin and kaempferol are recognized as a source of antioxidants. Flavonoid compounds, on the other hand, are common compounds found in all plant kingdoms. Furthermore, these compounds are generally also used as an insecticide [5]. Polyphenol compounds contribute to antioxidant properties [15].

Besides, the test results of the antioxidant activity of leaves methanolic extract and stem of *C. pubescens* presented that IC$_{50}$ of papaya leaves = 35.64 ppm and IC$_{50}$ papaya stems = 62.34 ppm. Based on the level of antioxidant strength, papaya leaves have a powerful antioxidant ability (IC$_{50}$ < 50 ppm) and papaya stems have a strong antioxidant capacity (IC$_{50}$ = 50-100 ppm). Regarding these criteria, it shows that the lower the IC$_{50}$ value, the higher the antioxidant ability IC$_{50}$ which mean the concentration of the sample needed to reduce 50% of the oxidation activity of free radicals. All the same, the results of measurements of total phenol in leaves methanolic extract and stem of *C. pubescens* showed gallic acid equivalent in *C. pubescens* leaves extract (62.1134 mg EGA/g) higher than in stem methanolic extract (30.9278 mg EGA/g). The antioxidant activity of methanolic extract of several different parts of the papaya plant (leaves, bark, root, peels, seeds, and pulp) showed that the highest antioxidant activity was found in leaves methanolic extract (54.28 mg EGA/g) [16]. This indicated that papaya leaves contained higher phenol compounds than other parts.

The other analysis in this study reveals a relationship between antioxidant activity and total phenolic. Accordingly, the high total phenolics was followed by a high antioxidant activity. Phenolic compounds are a source of hydrogen atoms. The hydrogen Atom was bound to the Nitrogen atom contained in the DPPH. The active compounds in the leaves extract of *C. pubescens* donated Hydrogen atoms so that free radicals change to non-radical [17]. Ultimately, this study also showed that methanolic extract of *C. pubescens* leaves had high antioxidant potential compared to extract of methanol from *C. pubescens* stem. *C. pubescens* leaves extract exhibited antioxidant activity with IC$_{50}$ of 35.64 mg/mL which is lower than *C. papaya* leaves to extract IC$_{50}$ of 13.31 mg/mL [20]. *C. pubescens* stem extract showed also scavenging activity on DPPH with IC$_{50}$ of 62.34 mg/mL. This number is lower than *C. papaya* stem extract with IC$_{50}$ 39.54 mg/mL [20]. However, both *C. pubescent* leaves and stem extract still is classified as a powerful and robust antioxidant. This replication is affected by the content of secondary metabolites of each plant part, species and population, which of them have different amounts and types of secondary metabolites [18]. Assuming that, methanol is the best solvent to extract antioxidant from *C. pubescens* leaves and stem [16].

5. Conclusion
In summary, our research findings highlighted the phytochemical screening results using LCMS from *C. pubescens* papaya leaf extracts with three different solvents (methanol, ethyl acetate, and chloroform) resulted in the differences of the types of active compounds identified. The highest active compounds were identified using ethyl acetate solvent (62 types), followed by methanol solvent (60 types), and at least with chloroform solvent (53 types). The methanolic extract of *C. pubescens* leaves had high antioxidant activity (IC$_{50}$ = 35.64 ppm, total phenolic = 62.1134 mg EGA/g) compared to *C. pubescens* stem methanolic extract (IC$_{50}$ = 62.34 ppm, total phenolic = 30.9278 mg EGA/g). Based on the identified active compounds, papaya leaves of *C. pubescens* from Cangar have the potential as a source of antioxidants.

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