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ANTITUSSIVE AND EXPECTORANT PROPERTIES OF MALE PAPAYA FLOWERS (*CARICA PAPAYA* L.) ON MICE

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Summary

Carica papaya is a plant originating from America that was introduced to Vietnam a long time ago, with the main purpose of being a fruit tree. Though it is also used in traditional medicine for some diseases. This study aimed to scientifically validate the traditional use of male papaya flowers for their antitussive (cough-suppressing) and expectorant properties. The results showed that the ethanol extract of male papaya flowers at a dose of 400 mg/kg had a significant antitussive effect compared to the model group in the ammonia-induced cough model ($p < 0.05$). Meanwhile, the extract at both doses of 200 mg/kg and 400 mg/kg showed the expectorant effect by increasing the phenol red level secreted from the mouse trachea (37.9% and 26.1%, respectively, compared to the model group). Thus, the ethanol extract of male papaya flowers possesses expectorant activities and potential in the treatment of cough.

Keywords: *Carica papaya* L.; *Antitussive; Expectorant.*

1. Introduction

Carica papaya is a plant originating from America that was introduced to Asia, including Vietnam. Papaya plants grow in three different genders, namely male, female, and hermaphrodite. This hermaphrodite has male and female reproductive organs, which have flowers and can bear fruit [1]. According to Indian folk medicine, ripe papaya is a digestive, diuretic, and flatulence remedy; syrup and wine made from papaya have expectorant, sedative, and tonic effects; the leaves treat neuralgia, reduce elephantiasis, and the juice cures malaria; Indonesians use papaya fruit to treat tuberculosis. Fresh male papaya flowers are antitussive in children, antipyretic, and treat jaundice [2]],[[3]. Researches on *C. papaya* are mainly on chemical compositions of leaves, radix, flowers, and some biological effects such as antioxidant, cytotoxic, antibacterial, antidiabetic, antihyperlipidemic, and analgesic properties [4]],[[5]],[[6]],[[7].

Cough is a natural reflex of the body when exposed to irritants. A prolonged cough causes discomfort, affecting daily activities. Cough with phlegm is a very common respiratory disease in both adults and children, so it needs to be treated promptly. Drugs for treating cough, expectorants are not much, such as: Dextromethorphan and codeine; acetylcysteine, ambroxol, or guaifenesin which have been used for a long time with adverse effects. Some traditional medicines have been researched and put into use, but their effects are still limited, so it is still necessary to discover potential medicinal herbs that can reduce cough with few side effects.

As a traditional remedy, male papaya flowers have been used for antitussive, but there is no research to prove this effect. So, in this study, we evaluated the cough-suppressing and expectorant effects of the ethanol extract of male papaya flowers in mice to elucidate the uses of this herb.

2. Materials and Methods

2.1. Materials

2.1.1. Sample:

Male papaya flowers were harvested in Lai Chau Province in September 2023.Male papaya flowers were dried at a temperature of below 60°C until they reached the humidity below 13 % and then ground, sieved through a 5 mm sieve. The powder of male papaya flowers was refluxed with ethanol 80 % during 1.5 hours at boiling temperature, the ratio of herb and ethanol

solution was 1:7, the procedure was repeated 2 times. Recover the ethanol in the extract solution by distilling it in a rotary evaporator, dry the condensed extract in a vacuum oven at 60°C until the dry extract. The ethanol extract of male papaya flowers (HDD) had an extraction efficiency of 16.5% and a moisture content of 4.7%.

The oral doses for mice in this study were 200 mg and 400 mg/kg based on the traditional dose that male papaya flowers are used to treat cough in children at a dose of 10-20 g/day [1].

2.1.2. Animals:

Swiss mice weighing 23±2 g, both male and female, were obtained from the National Institute of Hygiene Epidemiology. Mice were acclimatized in the animal room at a temperature of 25 ± 1°C for 1 week before the experiment with chow and water ad libitum.

2.2.3. Chemicals:

Ammonium hydroxide (Xilong-China), phenolsulfonphthalein–PSP (Sigma), $NaHCO_3$, ethanol 96 % (Vietnam), Codeine (Terpincodein-F 5mg codeine, TV Pharm) was used as a positive control of the antitussive model, and acetylcysteine (Trade mark Acemuce 200 mg, Sanofi-synthelabo) was used as a positive control of the expectorant model.

2.2. Methods

2.2.1. Mouse model of ammonia-induced cough:

Application of the method of Ellis et al. [8] with slight modifications. The animals were divided into 4 groups: Model group (vehicle treated and ammonium hydroxide exposed), HDD 200 group (HDD at the dose of 200 mg/kg treated and ammonium hydroxide exposed), HDD 400 group (HDD at the dose of 400 mg/kg treated and ammonium hydroxide exposed) and Codeine group (positive control: Codeine at the dose of 20 mg/kg and ammonium hydroxide exposed).

Mice were treated with vehicle, test extract, or codeine during 6 days (once/day, in the morning). On the 7th day, after administering the sample for 1 hour, mice were put into a 4.5 L glass bottle saturated with 2 mL of 7% ammonium hydroxide solution. The latency time (time from beginning to first cough) and the number of coughs were recorded and measured in 5-minute observations. The cough in mice was defined by opening of the mouth and contraction of the thoracic abdominal muscles. Compare the latency time and the number of coughs between groups by using the formula:

% increase the latency time compared to the model group (Lt)

$$Lt = (t_{sample}-t_{model})/t_{model} \times 100$$

Where: t_{sample}: the latency time of the test extract or codeine group

T_{model}: the latency time of the model group

% Inhibit the number of cough (I)

$$I = [(C_{model} - C_{sample})/ C_{model}]x100$$

Where: C_{model}: the cough number of the model group

C_{sample}: the cough number of the test extract or codeine group

2.2.2. Mouse model of phenol red secretion:

Application of the method of Engler and Szelenyi [9] with slight modifications. The animals were divided into 4 groups: Model group (vehicle treated and PSP injected), HDD 200 group (HDD at the dose of 200 mg/kg treated and PSP injected), HDD 400 group (HDD at the dose of 400 mg/kg treated and PSP injected) and Acetylcysteine group (positive control: acetylcysteine at the dose of 200 mg/kg and PSP injected).

Mice were treated with vehicle, test extract, or acetylcysteine during 6 days (once/day, in the morning). On the 7th day, after administration of vehicle, test extract, or acetylcysteine for 30 minutes, a single dose of 500 mg PSP/kg (in saline) was injected intraperitoneal with 0.2 mL/10 g in volume. After thirty minutes of PSP injection, all mice were sacrificed by cervical dislocation without damaging the trachea. After isolation from adjacent organs, the trachea was removed from the main stem bronchi and the thyroid cartilage and put into 1 mL $NaHCO_3$ 5 %, shaken in a horizontal shake instrument for 30 minutes, centrifuged at 3000 rpm/10min. The optical density of the fluid was measured at 557

nm. Establish a standard curve of PSP in 5% $NaHCO_3$ to calculate the concentration of PSP. The equation of the standard curve: **PSP (µg/mL) = 1,466 x OD + 0,0015.**

The PSP levels of mice were calculated using the formula:

PSP (µg %) = [PSP] x V x 100/m

Where:

[PSP]: concentration of PSP calculated by the equation of the standard curve.

V: the volume of $NaHCO_3$ 5 % (1 mL) used to extract PSP

m: weight of mouse

2.2.3. Statistical analysis:

The experimental data are expressed as mean ± standard error (SE). The data were analyzed by one-way ANOVA followed by the Dunnett or the least-significant differences multi-comparison (LSD) test (In case of no significant deviations). In case of significant deviations, the significantly different groups were defined using the Mann–Whitney U (MW) test. SPSS Ver. 23.0 was used to conduct the statistical analyses. The differences were considered significant at $p < 0.05$.

3. Results

3.1. Effect of extract on ammonia-induced cough in mice

The latency time and the number of coughs in mice are presented in Table 1. The HDD 200 group showed a 13.1 % increase in the latency time (prolonging the onset of cough), and the number of coughs decreased by 26.1% compared to the control group, but the difference was not significant ($p > 0.05$). In the HDD 400 group, the latency time increased by 44.3% compared to the control group; however, there was no prominent difference ($p > 0.05$). The latency time of cough in the HDD 400 group was equivalent to that of the positive control codeine group (20 mg/kg). The HDD 400 group reduced the number of coughs by 74.8% compared to the model group; the difference was significant with $p < 0.05$, equivalent to the number of coughs in the positive control group.

Table 1. Effect on prolonged latency time and reducing cough times of HDD in mice

Group	Number of mice	Latency time		Coughs	
		Time (seconds)	% increase compared to the model group	Number	suppression (%)
Model	11	65.0 ± 11.5		63.1 ± 20.6	
HDD 200	11	73.5 ± 14.9	13.1	46.6 ± 13.9	26.1
HDD 400	10	93.8 ± 19.6	44.3	15.9 ± 1.8*	74.8
Codeine	10	79.3 ± 12.1	22.0	16.9 ± 4.6*	73.2

(*: $p < 0.05$ compared to a model group).

3.2. Effect of extract on mucus expectoration in mice

Table 2. Effect of HDD on mucus expectoration in mice

Group	Number of mice	PSP secretion	
		µg %	% increase
Model	10	0.68 ± 0.04	
HDD 200	11	0.94 ± 0.08*	37.9
HDD 400	11	0.86 ± 0.07*	26.1
Acetylcysteine	10	0.89 ± 0.07*	31.0

(*: $p < 0.05$ compared to a model group).

After one week of treatment, the PSP levels in both groups of HDD 200 and HDD 400 increased by 37.9 % and 26.1 % compared with the model group, respectively, with significant differences ($p < 0.05$). A comparable effect was observed in the positive control group treated with acetylcysteine at a dose of 200 mg/kg (Table 2). These findings indicated that HDD extract at both doses of 200 and 400 mg/kg exerts a stimulatory effect on PSP secretion in the trachea.

4. Discussion

The mechanism of action of mucolytic agents is commonly by increasing moisture and secretory volume, thereby reducing sputum viscosity, making it more transparent, and facilitating its clearance from the respiratory tract. The expectorant activity of a drug is typically assessed through its ability to enhance mucus secretion, with PSP excretion in the trachea serving as a relatively simple and reliable evaluation method [10]. Accordingly, this model was utilized to investigate the expectorant effect of HDD.

To evaluate the antitussive effect in animal models, including mice, ammonia solution is commonly used as a cough-inducing agent, which stimulates the respiratory mucosa to induce coughing. This is a simple and effective experimental method that is often applied in research [11]. Therefore, in this study, we used ammonia solution to evaluate the antitussive effect of HDD.

Sputum is a mixture of bronchial mucosal secretions, inflammatory cells, microorganisms, dust, and mucus proteins. When the mucosa is inflamed, mucus secretion increases, phlegm becomes thick, sticky, and difficult to expel, causing coughing. Cough is a neural reflex induced by secretions or foreign substances stimulating the respiratory mucosa to expel the secretions from the airways [10]. Sputum tenacity, which results in adhesiveness and cohesiveness of sputum, considerably influences the clearance of sputum. An expectorant is a drug that is thought to increase the hydration of either mucus or the periciliary fluid. Although increasing hydration of the sputum itself will not improve clearance in the case of depleted airway surface liquid, improving the hydration of this surface fluid may detach secretions from the epithelium, thus decreasing tenacity and improving transportability and clearance of sputum. Therefore, there is an increasing demand for drugs that promote antitussive and expectorant activities [12]. In the case of HDD, the extract exhibited both antitussive and expectorant effects. However, these two effects tend to act in opposite directions with respect to dosage, suggesting that the antitussive effect may not result from the expectorant action, and that different chemical constituents may be responsible for HDD effects. Thus, HDD has the potential to be used for both dry and productive coughs.

Cough suppression and expectoration are interrelated. Conventional medicines usually act either as antitussives or as expectorants, whereas certain medicinal herbs possess both cough-relieving and expectorant effects [13].

Neither the chemical constituents nor the bioactive of HDD have been documented as the antitussive or expectorant effects in any reports up to now. A review of existing studies on HDD indicated that investigations into both their chemical composition and pharmacological properties remain limited. The identified constituents of male papaya flowers include flavonoids, alkaloids, proteins, and phenolic compounds, which have been associated with antioxidant activity, inhibition of certain cancer cell lines, antimicrobial effects, analgesic properties, hypoglycemic and hypolipidemic effects, as well as xanthine oxidase inhibitory activity [5],[6]. Those findings suggest that papaya flowers are abundant in flavonoid and phenolic compounds, which are the key contributors to their medicinal properties [14], so

maybe these compounds are responsible for antitussive and expectorant effects in male papaya flowers. However, to verify this, more detailed studies on the fractional extracts and main active ingredients are needed.

5. Conclusion.

Our study showed that the ethanol extract of male papaya flowers at both doses of 200 and 400 mg/kg showed antitussive effect on the mouse model of ammonia-induced cough and increased phenol red secretion of the mouse trachea. These findings provide scientific evidence supporting the traditional use of male papaya flowers for alleviating cough and expectorant.

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