Research Article

Prevention of Functional Dyspepsia with Carica Papaya Extract

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Abstract | Functional dyspepsia (FD) is a set of relapsing or chronic dyspeptic symptoms in the absence of structural organic lesions. Approximately 15-20% of the general population in many developed countries suffers from dyspeptic symptoms at any time in a year, whereas in Pakistan, 14-22 % of general population suffers from FD.

Objective: This study was designed to evaluate the effectiveness of carica papaya extract (CP) in preventing functional dyspepsia in human volunteers.

Methodology: A community based, placebo-controlled, double -blind, multi-centered, and randomized clinical trial through systematic random sampling was conducted in Lahore urban community. After initial diagnostic investigations in 200 patients diagnosed as cases of FD fulfilling Rome III criteria were recruited after taking written consent and randomly assigned to one of 2 treatment groups (CP extract group or placebo) in equal number. A 7 days medication free period was observed before the start of trial. Each patient received the treatment for 6 weeks. The primary outcome variable was the improvement in gastrointestinal symptom score (GIS) consisting of evaluation of 10 dyspeptic symptoms rated on Likert scale. Dyspeptic symptoms were assessed at the start of trial then after 2, 4 and 6 weeks.

Results: In this trial, 200 patients fully participated in this study (age 36.31±9.711 years, range 18-55, 60% female). Compared with placebo, Carica papaya extract (CP group) showed a clinically significant improvement. The GIS significantly decreased in CP group during the first 2 weeks, compared to the placebo ($p < 0.05$). During the second and third 2-week period, symptoms further improved in CP group ($p < 0.05$). After 6 weeks, 95.7% on CP treatment and 3.1% on placebo were completely relieved of FD symptoms ($p < 0.001$).

Conclusions: CP extract was significantly effective gastro-protective as compared with placebo.

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Introduction

Dyspepsia refers to a heterogeneous group of symptoms that are localized in the epigastric region. Typical dyspeptic symptoms include post-prandial fullness, early satiation, epigastric pain and epigastric burning, but other upper gastrointestinal symptoms such as nausea, belching or abdominal bloating often occur. Functional dyspepsia is defined as the presence of dyspeptic symptoms in the absence of an organic cause that readily explains them.[(1)]

Functional gastrointestinal disorders (FGIDs) are prevalent and affect individuals with poor quality of

life. These disorders are different from other gastrointestinal (GI) disorders because structural abnormalities are subtle or cannot be demonstrated by formal investigation. Therefore the diagnosis of FGIDs has mainly relied on the use of self-report questionnaires[2,3].

The FGIDs are diagnosed and classified using the Rome criteria. The 2006 Rome III criteria comprised of one or more of the following symptoms:

a. Post-prandial fullness, which was an unpleasant sensation such as the long persistence of food in the stomach
b. Early satiation, which was a feeling of overfilling of stomach in spite of little food intake
c. Epigastric pain.
d. Epigastric burning, which was expressed as sensation of heat

No evidence of structural or organic disease for the last 3 months with the onset of symptom at least 6 months prior to diagnosis.[4,5] The criteria changed over time as new scientific data emerged. The Rome IV was released in May 2016 in which Rome III criteria were amended as Rome IV. Minor changes were introduced, mainly to improve the specificity. Among the major symptoms of FD, not only post-prandial fullness, but also bothersome epigastric pain, epigastric burning, and early satiation were taken into consideration.[6,7]

Population-based studies on true functional dyspepsia (FD) are scarce due to the logistic difficulties of excluding structural disease in large numbers of people. Globally, the prevalence of uninvestigated dyspepsia (UD) varied between 7%-45%, depending on definition used and geographical location, whilst the prevalence of FD had been noted to vary between 11%-29.2%.[8] According to another report the prevalence of functional dyspepsia ranged from 5 to 11 percent worldwide.[9,10] Among Asian population, 8%-23% suffered from FD.[11]

According to one study, the prevalence of dyspepsia in West part of Iran was 54.6%.[12] A study from India reported prevalence of dyspepsia to be 30.4%.[13] Though very common in Pakistan, no exact data was available so far. Functional dyspepsia consisted of 11-15% of a physician's practice in Pakistan [14]. Prevalence of FD ranged from 14% to 22% in different studies conducted in Pakistan.[15]

In a study on patients with dyspepsia, functional dyspepsia was found in 76% patients.[16] No specific cause was found in 50 % of patients, and the dyspepsia was considered to be idiopathic. Evaluation of dyspepsia included a thorough history and physical examination, with significance given to symptoms that suggested the presence of serious disease. Hurry, worry and curry were detrimental for stomach health and unluckily these are very frequent here in Pakistan.

Role of plants may not be ignored as far as treatment of human diseases was concerned .They had been in use as source of modern drug therapy since long.[17] There is no doubt that traditionally about 25% of modern medicines have been prepared from plants. In African countries near about 80% of the population used traditional medicine for common ailments and primary health care. In Europe, North America, and other industrialized regions, about half of the population was in habit of using traditional medicines. About 70% Canadians and 90% Germans had consumed traditional medicine in some part of their life. According to the World Health Organization (WHO), majority of the world's population (80%) depended on traditional medicine for their primary health care needs .[18]

Papaya effectively improved all types of digestive and abdominal disorders. It was described as a medicine for dyspepsia and hyperacidity[19]. In one study the anti-ulcerogenic activity of aqueous extract of Carica papaya fruit was observed in aspirin – induced ulcer in rats [20].Similarly in another study anti-ulcerogenic activity of aqueous extract of Carica papaya seeds was demonstrated on indomethacin-induced peptic ulcer in male albino rats.[21]

Ethanol extract of the leaves of carica papaya afforded protection against aspirin-induced gastric ulcer in rats in one study. [22] Gastroprotective effect of C. papaya was also revealed in a study on rats conducted by R Gadekar, et al.[23] One study showed anti-ulcer activity of Carica papaya seed extracts in indomethacine induced ulcers in rats. [24] In a study published in Ethnobiol Ethnomed Journal in the year 2010 , the efficacy of C. papaya fruit in the treatment of gastritis was also documented. [25] Aqueous extract of unripe carica papaya fruit was investigated for its anti-ulcer, mucus secretion, anti-acid secretory and pepsin binding effects in indomethacin induced ulcers in rats and it was found that the extract had positive effects on

the normal function of the stomach.[26]

In one study carried out in humans papaya preparation contributed to the maintenance of digestive tract physiology. [27]

No study was conducted so far revealing the efficacy of carica papaya extract used in very little quantity producing instant effect and without any side effect in humans. As we are aware that eating habits in our societies are not up to the mark so there is dire need to develop a solution for instant relief and prevention of functional dyspepsia on a long-term basis.

Material and Methods

Carica papaya (CP) extract was prepared from fresh papaya fruit purchased from market. One kilogram fresh papaya fruit yielded 500 grams innermost pulp. The pulp yielded 50 grams of powder after dessication. For obtaining extract micro-prevention technique (anaerobic sublimation followed by ethanolic-aqueous extraction) was used. 200 grams powder obtained from 4 Kg fruit was processed through anaerobic sublimation resulting into 20 grams residue which was undergone ethanolic-aqueous extraction. The resultant extract was dissolved in water to prepare 0.2 ppm solution (1 microgram extract in 5 ml). Control group was given 5 ml orally placebo whereas Intervention group was given orally 5 ml extract of CP extract diluted in 100 ml of water thrice a day after every meal for a period of 6 weeks. CP extract and placebo were identical in colour, taste, smell and dose.

A double-blind, randomized, placebo-controlled, multicenter trial (RCT) was conducted in Allama Iqbal town-a Lahore urban community randomly selected out of 10 towns in Lahore through simple random sampling, for a period of 6 weeks with the help of randomly selected leading family physicians practicing in the above mentioned community. Thus, randomly selected ten (10) out of fifty (50) family physicians participated in the study. Sample size for this trial was estimated through this formula:

$$ne = nc = \{(Z_{\alpha/2} + Z\beta)2\delta 2(\lambda+1)/\lambda\}/(\mu c - ue)^2$$

In this study, the ratio (λ) of C. papaya group to placebo group was 1:1 and keeping power of 80% (1 - λ) at significance level of 5% (λ), a sample size of $ne = nc =$ 100 patients per treatment group was taken. As there was control group also, so total sample size was 200.

Regarding safety and ethical use, *C. papaya* extract has been extensively used in various research studies specially to increase platelet count in dengue patients.[28] The family physicians selected FD patients attending their clinics through systematic random sampling and after taking written consent for participation in the trial and with the help of questionnaire recorded their presentations. Epigastric pain, nausea, vomiting, postprandial fullness, early satiation, heart burn, regurgitation, epigastric burning, belching and bloating were the variables studied in the trial.

2006 Rome III criteria was applied for induction of participants and cases of FD fulfilling the following criteria were enrolled in the trial after taking written consent to participate.

Any case comprising of one or more of the following symptoms:

a. Post-prandial fullness which was an unpleasant sensation like the long persistence of food in the stomach
b. Early satiation, which was a feeling of overfilling of stomach in spite of little food intake
c. Epigastric pain.
d. Epigastric burning which was expressed as sensation of heat

No evidence of structural or organic disease for the last 3 months with the onset of symptom at least 6 months prior to diagnosis.

After selection, all patients were explained about the use of the medicine. After a washout of 7 days, the patients were randomized to 6 weeks treatment period with either CP extract or placebo. They were given free supply of extract as well as free lab tests as incentives for follow up. The trial period was for six weeks and the efficacy was evaluated at week 2, 4 and 6 after administration.

Any case who was not fulfilling the following criteria or suffering from was not enrolled in the trial:

a. 2006 Rome III criteria
b. chronic irritable bowel syndrome,
c. any heart disease,
d. any lung disease,
e. any liver disease,
f. any kidney disease,

g. Participants in any another clinical trial during the last 3 months.
h. Participants who were surgical operated during last 6 months except appendicectomy
i. Pregnant and lactating mothers
j. Allergy,
k. Drug abuse,
l. Existing intestinal or extra-intestinal organic disease,
m. Severe organic or psychiatric illness
n. Chronic malabsorption
o. Diseases for which participants have been using any antibiotic, proton-pump inhibitor, bismuth salt, prokinetic agents, drugs with an anti-kinetic action (e.g.: beta-blockers, calcium antagonists, anti-cholinergic drugs, anti-convulsants).
p. Patients using any sort of other herbal medicines.
q. Patients with the complaints of abrupt weight loss or black stool
r. Patients refusing to participate were also excluded

The selected family physicians enrolled FD patients in the trial in a randomized way. Out of FD patients attending their clinics, it was decided through simple random sampling about the selection of first/second/third or any order patient followed by enrolling the incoming FD patients in the order decided. If the selected or enrolled patient was not fulfilling the laid down criteria then the next patient fulfilling the same criteria was selected .They placed FD patients in CP group or control group according to the order decided. For example some of them selected every second FD patient attending their clinic and they placed in CP group then they placed every third FD patient in control group. So equal number of participants in CP group and control group were enrolled.

As the study was double blind, so the researchers (Family physicians) were neither aware of the actual extract and placebo nor the patients as both samples of extract and placebo were of same colors and were supplied in bottles of same size, shape and color. Only the code numbers were written on the bottles.

Data was collected and compiled throughout the course of trial. At the start of trial, demographic features of study population were recorded. For demographic profile, frequency table was prepared. Means and standard deviations were calculated (Table 1).

Assessment of FD symptoms was made using GIS system, which evaluated the severity of 10 symptoms of FD. Symptoms (epigastria pain, nausea. vomiting, post prandial fullness, early Satiation, heartburn, regurgitation, epigastric burning, belching, bloating. FD Patients were evaluated on the basis of symptoms using the following Likert scale, 1 No symptom, 2 minimal problem (ignorable without effort). 3. Mild problem (ignorable with effort), 4.Moderate problem (Not ignorable but not affecting daily life activities), 5.Moderately severe problem (cannot be ignored and occasionally limits my daily activities). 6.Severe(Not ignorable but limiting daily life activities) 7. Very severe problem (Not ignorable and markedly limiting daily life activities and often requires rest).

Table 1: *Demographic pofile frequency*

Parameter	Result			
Age	36.31±9.711			
Minimum age limit	18 years			
Maximum age limit	55 years			
Gender	Male	80(40%)	Female	120(60%)

The baseline parameters of the participants were similar among the groups (see Table 2).

Routine laboratory investigations (CBC, lipid profile, renal profile, total protein and serum albumin), were carried out in the CP group before and after intervention. During the trial period, after 2 and 4 weeks, the efficacy of CP extract and placebo was evaluated by observing change in Gastrointestinal Symptom (GIS) scale and at the end of trial along with final assessment of FD symptoms using GIS system. Data was collected, compiled and analyzed through SPSS 21. For Comparison of Blood parameters before and after intervention in CP group and for efficacy results at baseline, after 2, 4 and 6 weeks on GIS Scale, paired t-test was applied (Table 2 and 3).

For difference in the findings of CP group and control groups at base line and after 6 weeks independent sample t-test was applied (SeeTable 4). Statistical significance was set at $p \leq 0.5$. Though an extract of fruit in very minute quantity was used in the study, the participants were clearly informed about the composition of extract, its mechanism of action and its dosage.

Results

This study included 200 patients with functional dyspepsia diagnosed according to the Rome III criteria. All the patients belonged to adults (mean age, 36.31,

SD 9.71 years). Overall, 60 percent of the patients were female (Table 1).

At base line the patients were not having any significant difference between FD symptoms but after 2 weeks after initiating intervention, significant improvement was observed (p<0.0001) in the CP group though there was improvement also in the control group. After 4 weeks, FD symptoms further improved in CP group (p<0.0001) but deterioration was found in control group. After completion of 6 weeks intervention, significant improvement (p-value<0.0001) was observed in CP group (Table 3).

Significant difference (p<0.01) was found in all the symptoms in CP group after completion of 6 weeks as compared to all the symptoms in Placebo group in which no improvement was found in FD symptoms (p>0.05). There was found significant difference (<0.0001) in the two groups after completion of trial i.e. after 6 weeks. (see Table 4).

Table 2: *Comparison of blood parameters before and after intervention in CP group (paired 't' Test)*

	At base line	After 6 weeks	p-value
Parameter	**Mean±SD**	**Mean±SD**	**>0.05(Not significant)**
hemoglobin	13.26±1.47	13.51±1.49	>0.05(Not significant)
total leucocyte count	7909±1900	8120±1967	>0.05(Not significant)
platelets	252710±42887	255860±41650	>0.05(Not significant)
polymorphs	60.53±1.98	59.42±1.77	>0.05(Not significant)
lymphocytes	33.45±1.64	32.12±1.48	>0.05(Not significant)
monocytes	3.16±1.47	2.87±1.34	>0.05(Not significant)
eosinophils	2.87±.84	2.77±.81	>0.05(Not significant)
blood sugar random	116.07±17.51	131.87±17.51	>0.05(Not significant)
bilirubin	.575±.20	.612±.22	>0.05(Not significant)
alanine transaminase	27.45±8.03	26.32±7.87	>0.05(Not significant)
alanine transphosphatase	29.89±7.64	27.76±7.32	>0.05(Not significant)
alkaline phosphstase	121.67±14.13	124.82±15.23	>0.05(Not significant)
blood urea	25.49±12.89	23.31±11.54	>0.05(Not significant)
Serum creatinine	.719±.08	.673±.06	>0.05(Not significant)
serum cholesterol	163.44±9.49	165.28±10.21	>0.05(Not significant)
serum triglycerides	149.53±16.10	153.65±16.34	>0.05(Not significant)
high density lipoprotein	43.95±6.15	41.12±5.87	>0.05(Not significant)
low density lipoprotein	136.16±11.40	141.78±12.91	>0.05(Not significant)

Table 3: Efficacy results at baseline, after 2,4 and 6 weeks on GIS scale (unpaired t-test)

Symptoms	Baseline		After 2 weeks			After4 weeks			After 6 weeks		
	CP extract	Placebo	CP extract	Placebo	Difference	CP extract	Placebo	Difference	CP extract	Placebo	Difference
Epigastric pain	6.8	6.8	0.6	3.7	<0.05	0.2	3.8	<0.05	0	4.9	<0.05
Nausea	6.2	6.2	0.9	4.3	<0.05	0.1	4.6	<0.05	0	4.6	<0.05
Vomiting	4.5	4.5	1.2	2.1	<0.05	0	2.3	<0.05	0	2.1	<0.05
Postprandial fullness	5.9	5.9	1.4	4.2	<0.05	1.2	4.4	<0.05	0.2	5.3	<0.05
Early satiation	5.4	5.4	1.1	4.3	<0.05	0.6	4.7	<0.05	0	4.9	<0.05
Heart burn	6.3	6.3	0.3	4.6	<0.05	0	5.1	<0.05	0	5.4	<0.05
Regurgitation	5.8	5.8	0.8	4.9	<0.05	0.2	5.0	<0.05	0	5.3	<0.05
Epigastric burning	6.9	6.9	0.6	3.5	<0.05	0	4.1	<0.05	0	5.4	<0.05
Belching	6.7	6.7	0.8	4.2	<0.05	0.2	4.7	<0.05	0	4.9	<0.05
Bloating	5.9	5.9	0.9	4.8	<0.05	0.2	5.1	<0.05	0	5.8	<0.05

Table 4: *Difference in the findings of experimental and control groups at base-line and after 6 weeks (paired t-test)*

Symptoms	CP Group				Placebo Group			
	At base line	After completion	Difference	p-value	At base line	After completion	Difference	p-value
Epigastric pain	6.8	0	6.8	<0.01	6.8	4.9	1.9	>0.05
Nausea	6.2	0	6.2	<0.01	6.2	4.6	1.6	>0.05
Vomiting	4.5	0	4.5	<0.01	4.5	2.1	2.4	>0.05
Postprandial fullness	5.9	0.2	5.7	<0.01	5.9	5.3	0.6	>0.05
Early satiation	5.4	0	5.4	<0.01	5.4	4.9	0.5	>0.05
Heart burn	6.3	0	6.3	<0.01	6.3	5.4	0.9	>0.05
Regurgitation	5.8	0	5.8	<0.01	5.8	5.3	0.5	>0.05
Epigastric burning	6.9	0	6.9	<0.01	6.9	5.4	1.5	>0.05
Belching	6.7	0	6.7	<0.01	6.7	4.9	1.8	>0.05
Bloating	5.9	0	5.9	<0.01	5.9	5.8	0.1	>0.05
Mean difference			6.033				1.300	.000

Discussion

Functional (non-ulcer) dyspepsia is a highly prevalent disorder. [8,9,10] However, unfortunately, there is no permanent cure for the majority of patients because of many reasons such as worries, bad food habits, poor life style, impure and contaminated food stuff and many more and the available treatments relieve symptoms in only a proportion of patients.[11,12] Apart from traditional medicines, there have been many attempts to use fruits, vegetables and herbal preparations to check the nuisance presentation of FD and out of them some have been proved quite fruitful.[13] In the present study, focus was given to innovate a novel remedy for FD which should be having instant effect, safe, very economical and in very minute dosage and above all should be having powerful protective role.

Present study revealed the reduction of gastric inflammation which is also shown by a study published in 2008 [19]. Results of improvement recorded in this study are similar to those published in Internet Journal of Toxicology.[20] Similarly results of present study endorse the results of a previous study.[21,22] Digestive problems have been well controlled in the present study simulating the results of studies conducted in the past. Gastro-protective effect of C. papaya was also revealed in a study conducted by R Gadekar, et al [23] Regarding treatment of gastritis, the results of present study are quite similar to those in a study published in Ethnobiol Ethnomed Journal [25] . The current study is unique in many aspects. Firstly CP extract was used in very minute quantity (in micrograms) as compared with the amount of papaya used itself or its extract in past researches. Secondly its instantaneous effect in relieving FD symptoms could not be highlighted in previous studies. Thirdly a new technique i.e. micro-prevention technique was used to prepare the extract and for the first time ethanolic-aqueous extract after anaerobic sublimation was used in humans to manage FD and it might explain the instant efficacy of the extract. And lastly it opens the doors for further research for human health regarding other parts of carica papaya like flowers, leaves or roots.

We evaluated and compared the effects CP extract with placebo and found that in this six-week trial significant improvement was observed in CP extract group as compared with placebo.

As compared with all available medicines being used to treat FD, CP extract was unique in many aspects for being colorless, odorless, not having any side effects, no change in blood chemistry, locally prepared and much more economical. In reality, the response to therapy was considerably better. Extensive trials may be required to evaluate the efficacy of CP extract.

In summary, it was evident that CP extract was much more effective in relieving the symptoms of FD as compared with placebo. However, follow up studies might be required to establish the usefulness of CP extract. The exact mechanism, efficacy and optimal duration of treatment with CP extract in different communities for improving FD symptoms might be established.

Conclusion

Functional dyspepsia has become a social disease now a day due to our life style. Papaya has a good track record for treating FD. Many formulations of papaya have been tried in the past. This study opens a new door for research as first time ethanolic-aqueous extract of papaya fruit (CP extract) was studied in humans. Effect of CP extract in reducing symptoms of FD was significantly superior to placebo. Compared with placebo, CP group showed a clinically significant improvement. After a period of 6 weeks near about all patients on CP treatment and very few on placebo were completely relieved of FD symptoms.

During this trial there was no change recorded in vital parameters and no adverse effects reported. As a matter of fact adverse effects were practically nil in CP group as compared with placebo group. This might be a good addition in the library of remedies for FD and characterized by natural, instant relief, easy to use, micro dosage, without taste or smell, very economical, and without side effects even after prolonged use.

Author's Contribution

Maaz Ahmad: Designed the study, reviewed the literature, analysed and interpreted the results
Mussab Ahmad and Tehreem Munir: Assitsted in designing the study, literaturer eview, sampling of population, data collection, analysis and interprettation of the results

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