Nutrition and Food Sciences Research Vol 8, No 2, Apr-Jun 2021, pages:11-18

Original Article

Effect of Kokum (*Garcinia Indica*) Rind Extract With Honey on Chronic Gastritis: A Randomized Controlled Trial

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Received: August 2020 **Accepted:** October 2020

ABSTRACT

Background and Objectives: Chronic gastritis is a chronic inflammation of gastric mucosa associated with various degrees of damages to superficial and glandular epithelia. Garcinia species are evergreen tropical shrubs, cultured in North-Eastern India and Southeast Asia. In Indian traditional medicine, the kokum fruit rinds are used to treat various inflammatory diseases such as gastric ulcers and bowel complaints caused by *Helicobacter pylori* infection. The objective of this study was to assess effects of kokum rind extract with honey on symptoms and life quality of individuals with chronic gastritis as well as their effects on gastric myoelectrical activity.

Materials and Methods: 60 chronic gastritis patients were randomly gategorized into two groups. Experimental group (n = 30) received 10 g of kokum rind extract with 18 g of honey twice a day and control group (n = 30) received 200 ml of warm water twice a day for three weeks. Electrogastrogram, Izumo scale questionnaire and gastrointestinal symptom questionnaire were used at the baseline and on Day 21. Data analysis was carried out using R Statistical Software v.3.6.0.

Results: Significant decreases in gastrointestinal symptoms were observed in experimental group verified by gastrointestinal symptom questionnaire ($p < 0.0001$), compared to control group ($p = 0.2879$). Izumo scale questionnaire for quality of life assessment showed significant improvements with $p < 0.0001$ in experimental group. The mean decreases in dominant frequency of electrogastrogram were higher in experimental group ($p < 0.0001$), compared to control group ($p = 0.1511$), which suggested improvements in gastric myoelectric activity.

Conclusions: Kokum rind with honey is a cost-effective treatment to decrease symptoms of chronic gastritis, which can be considered as a safe home remedy.

Keywords: Kokum rind extract, Honey, Chronic gastritis, EGG, GISQ

Introduction

Functional gastrointestinal diseases are considered as major problems to public health because they are significantly common and induce major socioeconomic burdens. The severity of these diseases is affected by intestinal and extra-intestinal symptoms, psychological distresses and quality of life (QoL) (1). Chronic gastritis is a chronic inflammation of gastric mucosa, which is associated with various degrees of damages to superficial and glandular epithelia (2). Globally, more than half of people may have chronic gastritis. *Helicobacter* (*H*) *pylori* infection in childhood is the major cause of chronic gastritis (3). There are numerous other causes such as viral and bacterial infections, reactive inflammations due to bile and pancreatic juice refluxes, non-steroidal anti-inflammatory drugs (NSAID), alcohol consumption, chemotherapy and autoimmune responses against parietal cells as well as other rare causes such as post-radiation and stress-induced inflammations (4). Proton pump inhibitors (PPIs) have been used as effective therapies in management of chronic gastritis. Sufficient evidence reveal that PPIs are associated with serious adverse effects, especially at high doses. Majorly, PPIs are metabolized by hepatic microsomal enzymes with inhibitory effects (5). Acid peptic disease is more common in age groups of 18–59 years (6). In India, almost 80% of the population are infected by *H. pylori*, mostly by ten years. Triple therapy

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[DOR: 20.1001.1.23830441.2021.8.2.5.5]

[DOI: 10.52547/nfsr.8.2.11]

[Downloaded from nfsr.sbmu.ac.ir on 2026-11-01]

[DOR: 20.1001.1.23830441.2021.8.2.5.5]

[DOI: 10.52547/nfsr.8.2.11]

now fails because of the bacterial resistance. Hence, newer remedies and agents are needed to fight increasing prevalence of *H. pylori* linked gastritis (7). Garcinia species are evergreen tropical shrubs, which are grown in North-Eastern India and Southeast Asia (8). *Garcinia indica* (kokum) fruit rind can be one of these alternative therapies, which includes potential anti-inflammatory, anti-bacterial and anti-ulcer activities (9).

Honey is a natural product with antibacterial and healing properties (10). Kokum juice is used as a natural remedy for stomach and liver disorders (11).In Indian traditional medicine such as Ayurveda, fruit rinds and leaves are used to treat various inflammatory diseases such as gastric ulcers and bowel complaints. Chemical studies have shown that the herbal rinds contain proteins, tannin, pectin, sugars, fats, ascorbic acid, organic acids (22.8%) such as hydroxy citric acid, hydroxy citric acid lactone and citric acid, anthocyanins (2.4%), cyanidin-3-glucoside and cyanidin-3-sambubioside, garcinol and iso-garcinol and 30% of moisture contents (12). Kokum juice is mixed with yogurt and salt to make a natural antacid (13).Garcinol present in the rinds shows potential antimicrobial activities. It plays important roles in treatment of gastric ulcers caused by *H. pylori* chronic infections (14). Honey naturally shows , protectections against gastrointestinal infections, healing properties on ulcers (peptic ulcer disease) and antibacterial, antiviral, antifungal and anti-inflammatory activities and acts as a prebiotic and an antioxidant. Gluconic acid, acetic acid, formic acid and citric acid are detected in honey, controlling inflammations and promoting healings (15).These organic acids are responsible for the acidic properties of honey (16). Studies have verified that honey with the triple therapy has shortened necessary times to eliminate *H. pylori* infections (17). Considering limited studies in this area and lack of clinical trial-based evidence, the current study investigated efficiencies of honey and kokum rind extract on symptoms and QoL in individuals with chronic gastritis.

Materials and Methods

Study design: This randomized, controlled trial study included three weeks in Nature Cure Hospital, Shanthivana, Dharmasthala, Karnataka, India. The study received the institutional ethics committee approval (Registration No. EC-219). All the patients were provided with written informed consents in their local language.

Patients: Totally, 100 pre-diagnosed chronic-gastritis patients were screened. Of these patients, 60 patients of 20–50 years old, (6) from both genders participated in the study based on inclusion and exclusion criteria. The participants were categorized into experimental (n = 30) and control (n = 30) groups using the lottery method of randomization. These participants were recruited from Out-Patient Facility, SDM College of Naturopathy and Yogic Sciences, Ujire, as well as suburbs of Ujire, Dharmasthala and Venoor (Karnataka). Participants were assessed using gastrointestinal symptoms questionnaire (18) and their detailed histories were collected. Patients with the following conditions were excluded from the study: peptic ulcers, administrated antacids for the past two months, inflammatory bowel disease (IBD) and gastric and colorectal cancers. Furthermore, patients with other co-morbid conditions such as diabetes mellitus and renal diseases and those who were not willing to participate in the study were excluded from the study.

The mean age of the participants included 34.33 ±9.02 years in experimental and 28.40 ±9.81 years in control groups. In total, 24 (40%) males and 36 (60%) females participated in the study. In general, 30 participants were set in each group that ten males and 20 females were in experimental and 14 males and 16 females in control groups.

Sample size: A few preliminary studies have included 30 participants as the minimum sample size in each group, which was suggested based on the thumb rule and central limit theorem (19). Therefore, 30 participants in each group were set as the sample size of the present study.

Intervention: Participants in experimental group received kokum rinds**,** which were collected from Dakshina Kannada District, then it was dried by solar drying method (20) Honey was collected from honey society, Puttur, Dakshina Kannada District. In general, 10 g of kokum rinds were soaked in 200 ml of water for 7–8 h. Then, the soaked water was mixed with 18 g of honey and consumed at early mornings and evenings (21, 22). Instructions included fasting half an hour before and after drinking the juices. Control group was asked to drink 200 ml of warm water twice a day (23). No adverse events were recorded during the study.

Assessment: The assessed variables included severity of symptoms of the disease, QoL and gastric myoelectric activity.

Gastrointestinal symptoms questionnaire: The questionnaire was used to assess changes in the symptoms linked to chronic gastritis (18). Izumo scale questionnaire (including 15 items in five domains of reflux, pain, fulness, constipation and diarrhea with three items in each domain(24)) was used to QoL in gastrointestinal disease patients (25).

Electrogastrogram: Electrogastrogram (EGG) is an accurate measurement of the gastric slow waves and represents gastric motility changes. Frequency of the normal slow waves is three (2 ±4) cycles per minute (CPM) and abnormal data may deviate from 1 to 9 CPM. All EGG recordings were carried out after skin preparation and placement of three electrodes on the abdominal skin. The EGG signals were recorded using standard Ag/AgCl cutaneous electrodes. The first electrode was positioned

above the antrum (located 1 cm ±3 to the right and midway between the xiphoid and the umbilicus). The second electrode was positioned 45 degrees to the left, 5 cm above the first electrode. The reference electrode was positioned on the right flank under the rib cage (26, 27). Moreover, EGG recorder and software analysis (Biopac Student Lab System, Biopac Systems, Aero Camino Goleta, CA, USA) were used to record the EGG signals using BIOPAC BSL 4.0 MP 36, Montana, USA. For the evaluation of EGG records, the following parameters were included: 1) dominant frequency, reflecting frequency of the gastric slow waves (normal range of 2–4 CPM); and 2) proportion of gastric dominant frequency, dividing into three ranges of normogastria, tachygastria (4–10 CPM) and bradygastria. In healthy participants, the normal slow-wave proportion was ≥ 70% of the recording time. Fast Fourier transforms (FFT) analysis was carried out to assess EGG changes. Recording was carried out for 30 min.[28] Baseline data were collected and tests were repeated after 20 days of intervention.

Statistical analysis

Shapiro-Wilk test was used to check normal distribution of data. Data analysis was carried out to assess mean differences within the baseline (pre) and endpoints (post). One-tailed two-sample paired t-test and paired t-test were used for normally distributed variables and Wilcoxon signed-rank test for variables with no normal distributions. For the comparison of data between the experimental and control groups, one-tailed two-sample t-test, one-tailed Welch's t-test and Mann-Whitney test were used. Data were analyzed using R Statistical Software v.3.6.0. Significance was reported if $p \leq 0.05$.

Results

Continuous variables were represented in mean ±SD (standard deviation). To check normality, Shapiro-Wilk's test was used. For the mean comparisons, t-test/paired t-test, Welch's two-sample t-test was used. For data that were not under normal distribution, Wilcoxon/Mann-Whitney test was used. Table 1 shows the baseline assessment of demographic variables such as age and gender, which indicated that the mean of age was significantly greater in experimental group, compared to control group. Furthermore, no significant differences were seen in distribution of genders in the two groups. No significant differences were reported between pre-EGG and duration of disease within the two groups using two-tailed two-sample t-test. Furthermore, no significant differences were reported between pre-GISQ and within the two groups using Welch's t-test.

Table 1. Baseline assessments of age, gender, disease duration, GISQ and electrogastrogram

		Group		P value
		Experimental	Control	
Age		34.33 ± 9.02	28.40 ± 9.81	0.0089*
Gender	Male	10	14	0.291^{Ch}
	Female	20	16	
Pre-EGG		7.25 ± 1.25	6.77 ± 1.44	$0.157^{\#}$
Pre-GISQ		43.30 ± 18.21	38.23 ± 8.38	0.086^{Wt}
Disease duration (year)		0.89 ± 0.31	0.87 ± 0.30	$0.773^{\#}$

Abbreviations: *:one tailed two sample t-test, Wt: Welch's t-test, t: t-test, Chi-sq: Chi-square, #:two tailed two sample t-test

Table 2 shows statistical significance ($p < 0.05$) for all the variables. The table shows significant decreases in symptoms of gastritis; thus, proving efficacy of the interventions in the experimental group. Moreover, EGG demonstrates statistical significances with $p < 0.0001$, meaning that the gastric motility was normalized after the interventions.

A comparison of pre-test and post-test variables of the control group in Table 3 shows no significances at 5% level of significance as *p*-value was greater than 0.05. It also shows no differences in symptoms within the control group. The EGG was almost constant after the interventions ($p = 0.1511$). In this study, significant differences were seen in the mean decreases of EGG scores from the the experimental group using Welch's t-test, compared to control group ($p < 0.0001$) (Table 4). This reveals that treatments were effective in the experimental group. The mean decreases of tachygastria was significantly less in the control group than the experimental group using two-sample t-test ($p < 0.0001$). The mean increases of normogastria scores were significantly less in the control group than the experimental group using two-sample t-test ($p < 0.0001$). The mean decreses of total Izumo scores were significantly less in the control group than the experimental group. Significant differences were reported in decreases of heartburn, gastralgia, postprandial fullness, constipation, diarrhoea and GISQ of the experimental group using Mann-Whitney test, compared to the control group. This demonstrates decreses in symptoms of gastritis and effectiveness of the interventions in the experimental group.

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[DOI: 10.52547/nfsr.8.2.11]

Table 2. Comparisons of pre-test and post-test parameters in the experimental group

Parameter	Timepoint	Mean± SD/Median (Range)	p-value
EGG	Pre	7.25±1.12	< 0.0001[pt]
	Post	3.44±0.68	
Tachygastria	Pre	66.34±8.99	<0.0001[#pt]
	Post	53.07±11.52	
Normogastria	Pre	10.22±5.75	<0.0001[#pt]
	Post	21.99±12.47	
Heartburn	Pre	4 (0,14)	<0.0001[W]
	Post	0 (0,2)	
Gastralgia	Pre	5 (2,13)	<0.0001[W]
	Post	0 (0,2)	
Postprandial fullness	Pre	6 (1,15)	<0.0001[W]
	Post	0 (0,2)	
Constipation	Pre	3.5 (0,15)	<0.0001[W]
	Post	0 (0,2)	
Diarrhea	Pre	1 (0,11)	0.000196[W]
	Post	0 (0,1)	
Total Izumo score	Pre	22.63±10.71	<0.0001[#pt]
	Post	1.83±1.44	
GISQ	Pre	43.3±18.21	<0.0001[#pt]
	Post	2.7±1.88	

Abbreviations: #pt: One-tailed two-sample paired t-test; pt: paired t-test; W: Wilcoxon-sign rank test

Table 3. Comparisons of pre-test and post-test parameters in the control group

Parameter	Timepoint	Mean±SD/Median (Range)	p-value
EGG	Pre	6.77±1.44	0.1511[pt]
	Post	6.97±1.61	
Tachygastria	Pre	53.89±13.62	0.0764[#pt]
	Post	60.78±11.16	
Normogastria	Pre	16.07±8.58	0.0845 [#pt]
	Post	13.11±10.8	
Heartburn	Pre	5 (0,11)	0.7728[W]
	Post	5 (0,11)	
Gastralgia	Pre	5.9±1.4	0.1033[pt]
	Post	6.03±1.47	
Postprandial fullness	Pre	4 (2,10)	0.2755[W]
	Post	4.5 (2,11)	
Constipation	Pre	4 (0,7)	0.2365[W]
	Post	4 (0,8)	
Diarrhea	Pre	3 (1,6)	0.2986[W]
	Post	3 (1,6)	
Total Izumo score	Pre	23.1±3.36	0.06154[pt]
	Post	23.6±3.98	
	Post	34.3±10.69	
GISQ	Pre	38.23±8.38	0.2879[pt]
	Post	37.63±8.18	

Abbreviations: #pt: One-tailed two-sample paired t-test; pt: paired t-test; W: Wilcoxon sign rank test.

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Table 4. Comparisons of the parameters between the groups

Parameter	Time point	Mean± SD/Median (Range)	p-value
EGG[R]	Experimental	3.81±1.14	< 0.0001[#Wt]
	Control	-0.2±0.75	
Tachygastria[R]	Experimental	13.26±11.74	<0.0001[#t]
	Control	-6.88±11.67	
Normogastria[I]	Experimental	13.34±10.57	<0.0001[#t]
	Control	-9.72±10.48	
Heartburn [R]	Experimental	4 (0,13)	<0.0001[MW]
	Control	0 (-1,1)	
Gastralgia[R]	Experimental	4.5 (2,11)	<0.0001[MW]
	Control	0 (-1,1)	
Post prandial fullness[R]	Experimental	5 (0,14)	<0.0001[MW]
	Control	0 (-2,1)	
Constipation[R]	Experimental	3.5 (-1,14)	<0.0001[MW]
	Control	0 (-3,1)	
Diarrhoea[R]	Experimental	1 (0,11)	<0.0001[MW]
	Control	0 (-1,1)	
Total Izumo score[R]	Experimental	20.8±10.03	<0.0001[#Wt]
	Control	-0.5±1.41	
	Control	-5.03±6.63	
GISQ[R]	Experimental	37.5 (21,106)	<0.0001[MW]
	Control	0 (-6,13)	

Abbreviations: #t: One-tailed two-sample t-test; #Wt: One-tailed Welch's t-test; MW: Mann-Whitney test. '*R*' indicates reduction was observed from pre-test to post-test and '*I*' indicates increment observed from pre-test to post-test.

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Discussion

This study showed significant beneficial effects of kokum rind extract with honey on symptoms of chronic gastritis, which were evident from significant decreases in tachygastric waves in EGG as well as improvements in symptoms and QoL as shown by GISQ and Izumo scale questionnaire, respectively. The improvements might be due to the neutralizing and antacid activity of garcinia, as shown in a previous study by Panda et al. They showed that neutralizing effects of *Garcinia indica* extract (GIE) were significantly better ($p < 0.01$) than those of water, compared to standard sodium bicarbonate in modified artificial stomach models. They also showed significant, consistent acid-neutralizing effects of GIE. Antacids neutralize gastric acid and thus help heal inflammations (13). A comparative study by Deore et al. demonstrated significant antiulcer activities of *Garcinia* extracts in Wistar rats ($p < 0.01$), compared to placebo. The rat ulcers were induced using indomethacin. Fruit rinds include anthocyanin, polyphenols such as garcinol, flavonoids and ascorbic acid as major chemical compounds, which are responsible for their antiulcer activities (29). In the present study, significant improvements were seen in symptoms associated to gastritis. Therefore, it can be concluded that garcinol in kokum rinds with other polyphenols includes excellent anti-ulcer activities. Yamaguchi et al. have previously shown that garcinol suppressed indomethacin induced gastric injuries in rats (30). Another study on intestinal cell lines demonstrated that garcinol significantly inhibited release of arachidonic acid from macrophages and intestinal cells with > 50% of inhibition. Garcinol inhibited nuclear factor-kappa B (NFkB) activation and cyclooxygenase 2 (COX_2) expression. Furthermore, it significantly inhibited nitric oxide synthase (iNOS) expression in macrophages and thus helped decrease inflammations (31).

The *H. pylori* is one of the major causes of gastritis, peptic ulcer and gastric cancer (32). Previous comparative studies showed similar or better bactericidal activities of garcinol against *H. pylori* at 6 and 12-h incubation times, compared to clarithromycin. Results indicated potential roles for this antioxidant in treatment for *H. pylori* infections. Garcinol plays important roles in treatment of gastric ulcers caused by *H. pylori* (33). This could be one of the reasons why improvements were seen in symptoms of chronic gastritis in the current study, as verified by GISQ. Honey is known for its antibacterial and healing properties. It includes glucose oxidase, which liberates hydrogen peroxide when diluted. The hydrogen peroxide includes bactericidal activity and enhances epithelial proliferation. The acidic pH of honey is a factor preventing the growth of *H. pylori* (10). This was shown in previous studies, where honey in combination with triple therapy was helpful to

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improve elimination rate of *H. pylori* in gastritis and duodenal ulcer patients (17). Gluconic acid, a product of glucose oxidation, is the major organic acid of honey that contributes to its acidic pH (3.2–4.5) (34). A study on antibacterial effects of three commercial brands of honey on *H. pylori* showed that all brands included potentially bactericidal effects on *H. pylori*, which could successfully be used in treatment of peptic ulcers (35). These factors contributed to the activity of honey against *H. pylori* growth and thus helped decrease symptoms and severity of chronic gastritis. This was shown in the present study as significant improvements were reported in symptoms of gastritis in the experimental group (GISQ) (p = 0.0001). A previous survey on Japanese patients with chronic gastritis demonstrated greater decreases in QoL of the patients with greater numbers of abdominal symptoms, using Izumo scale questionnaire (24). In the present study, improvements were recorded in all the five domains of Izumo scale questionnaire in the experimental group (Table 3). The *p*-values of the Izumo scale questionnaire total scores for the experimental and control groups included 0.0001 and 0.062, respectively. It has shown that kokum rind extract in combination with honey helps improve QoL in patients with gastritis.

In this study, EGG changes were statistically significant in the experimental group after interventions (p < 0.0001). The FFT results showed that the dominant frequency component was improved in the experimental group after interventions (Fig. 1), showing that gastric slow waves were normalized after consumption of kokum juice with honey.

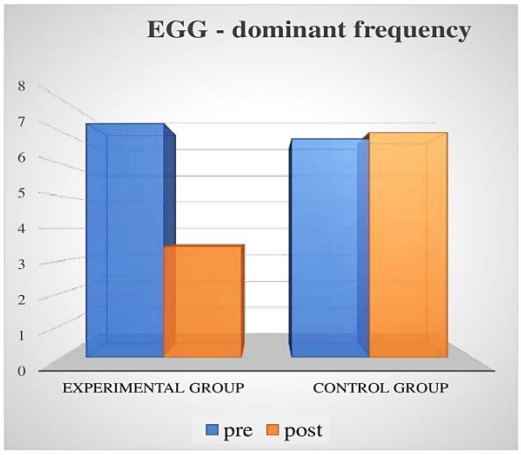


Figure 1. Comparisons of the mean values of electrogastrogram (EGG) waves (dominant frequency)

In a previous study on gastric motility in 198 Japanese patients with histologic gastritis, histologic gastritis with severe inflammation were shown to possibly inhibit gastric motility (36). Another study on dysfunctions in gastric myoelectric and motor activity in *H. pylori* positive gastritis patients reported increases in tachygastria and antral hypomotility of the patients. Gastric hypomotility is linked to increased tachygastria. In patients with gastritis, higher rares of tachygastria are usually seen (37). The present study showed decreses in tachygastric and improvements in normogastric waves in the experimental group after the interventions, suggesting that consumption of kokum rind extract with honey helps improve gastric wave regularity and stability. Findings of the current study revealed that use of kokum rind extract with honey by chronic gastritis patients is beneficial to decrese severity of symptoms and improve QoL of the patients. The exact mechanism includes prevention of *H. pylori* growth, enhancement of digestion and hence prevention of further complications due to the bacteria that may lead to gastric ulcers and cancers. These effects occur due to the antibacterial, anti-inflammatory, antioxidant and bactericidal activities of kokum and honey. The strength of the present study was that this study was the first study on humans to assess effects of kokum rind extract on chronic gastritis. Use of kokum rinds is a cost-effective treatment for gastritis that can be used with no usuall side effects. No dropouts and no adverse effects occurred during the interventions of the current study. Although kokum extract and honey included antibacterial activities against *H. pylori* in this study, the bacterial activity could not be checked.

Future prospects

Study can be carried out using a larger sample size.

Long-term effects of kokum rind extract can be checked.

Variables such as hydrogen breath test and serum IgG can be assessed in future studies.

Conclusion

In conclusion, consumption of kokum rind extract with honey in empty stomach for 20 days can improve symptoms of gastritis, including heartburn, gastralgia and post-prandial fullness as well as improvements in QoL of the patients. Kokum rind with honey is a cost-effective safe home-remedy to decrease symptoms of chronic gastritis

Acknowledgement

The authors express their deep gratitudes to the President of SDM Educational Society for his valuable supports. This study was self funded.

Financial disclosure

The authors declare no conflicts of interest.

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[DOI: 10.52547/nfsr.8.2.11]

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