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Evaluation of Anti-Ulcer Activity of *Garcinia cambogia* in Experimentally Induced Ulcer in Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Peptic ulcer is the most common gastrointestinal disorder that world faces at present. *Garcinia cambogia* is one of the folk plants used by the people to treat various ailments to attain health benefits. Every part of the plant has various activities which can eradicate maximum health issues. The present study is aimed to investigate the gastro-protective and anti-ulcerogenic activity of ethanolic extract of *Garcinia cambogia*. The ethanolic extract was tested orally in doses of 200 mg/kg and 400mg/kg which was obtained from the acute oral toxicity studies on gastric ulcerations experimentally induced by pylorus ligation and ethanol in rats. Comparison of the drug effect is done with the effect of standard drugs, omeprazole (30 mg/kg) and sucralfate (100 mg/kg). The parameters like gastric pH, gastric acid volume, total acidity, free acidity and ulcer index are assessed.The ethanolic extract showed an activity in a dose of 200 mg/kg and 400 mg/kg with a reduction in the gastric volume, total acidity, free acidity, ulcer index and raise in the gastric pH when compared to that of ulcer control group. A gastro-protective and anti-ulcerogenic activity is shown by the extract of *Garcinia cambogia* both in ethanol induced ulcer model and pylorus ligated ulcer model.At the concluding point, extract of *Garcinia cambogia* was found to possess a very good gastroprotective and anti-ulcerogenic property. The results of the study revealed the further uses of the leaves of this plant in the treatment of ulcers in the stomach.

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1. INTRODUCTION

Peptic ulcers are global problems faced by the world today. Ulcers are nothing but the deep lesions formed on the lining of the stomach or duodenum caused due to the variations between aggressive factors (H. pylori, NSAIDs and gastric acid) and defensive factors (mucin, bicarbonate and prostaglandins). It can occur in any part of the stomach. The ulcer formed in the duodenum is called the duodenal ulcer whereas in the stomach is called as gastric ulcers. There are two types of ulcers presently known: acute peptic ulcer and chronic peptic ulcer [1]. Acute ulcers are formed unexpectedly in the stomach where the patient experiences un tolerable pain after the consumption of food whereas chronic ulcers stay longer and with a symptom of pain, nausea and vomiting. Such ulcers cannot be treated soon.

In the present study fruits of *Garcinia cambogia* have been used. *Garcinia cambogia* is grown for its fruit in Southeast Asia, coastal Kerala/Karnataka, India, and west and central Africa. It survives in most moist forests. *Garcinia cambogia* is one of the several closely related *Garcinia* species from the plant family Clusiaceae. Along the west coast of South India, it is popularly termed "Malabar tamarind", and shares culinary uses with the tamarind (*Tamarindus indica*). It is called *uppage* in Kannada language and fruits are collected and dried for selling to dealers in Sirsi, Karnataka. The dried rind has been extensively used for centuries throughout Southeast Asia as a food preservative, flavoring agent and carminative, and is now used profoundly as an ingredient of dietary supplements for weight loss in developed countries. Studies have revealed that the fruit rind contains moisture (80.0 g/100 g), protein (1%), tannin (1.7%), pectin (0.9%), Total sugars (4.1%) and fat (1.4%). Malabar tamarind has been shown to contain a variety of secondary metabolites such as xanthones, flavonoids and benzophenones. Xanthones are oxygenated heterocyclic compounds present in higher plants. Xanthone nucleus is symmetric and is known as xanthen-9H-ones or 9-xanthenone or dibenzo-γ-pyrone. Hydroxycitric acid being the major constituent and is responsible for its weight lose activity.

The leaves and fruits are sour, astringent, thermogenic, constipating and digestive. The herbal preparations made out of Garcinia rinds are used in the treatment of inflammatory ailments, for rheumatic aches and bowel disturbances. The fruit is known to be anti-helmintic and cardio tonic. The juice (sherbet) made out of the fruit rind is used for piles, haemorrhoids, colic problems, ulcers, inflammations, treat sores, dermatitis, diarrhoea, dysentery, ear infection, to facilitate digestion and to prevent over perspiration or hyper perspiration . Garcinia natural antacid and the preparation rind, yogurt and salt are supposed to relieve gastric ulcerations and burning sensation. The Garcinia butter is also used in dysentery, diarrhoea, phthisis pulmonalis and scorbutic disease [2].

In the present study the fruits of *Garcinia cambogia* contains proteins, flavonoids, tannins and steroids hence theres a chance of anti-ulcer activity due to these constituents. The constituents from *Garcinia cambogia* were extracted by using ethanol and this ethanolic extract was subjected for preliminary chemical tests. The ethanolic extract was then evaluated for anti-ulcer activity by ethanol induced ulcer model and pylorus ligated ulcer model.

2. MATERIALS AND METHODS

2.1 Plant Material Collection and Preparation

The fruits of *Garcinia cambogia* were collected from Kerala, India during the month of August. The plant was then authenticated by DR. Jyothi Miranda, Department of Botany St. Aloysius College, Mangalore, Karnataka. The fruits are then dried and coarse powdered for extraction. The powdered dry fruit materials are subjected for repeated extraction. Ethanol is used as the solvent for successive extraction. The dried, coarse powdered material was kept in an extraction chamber along with the ethanol as the extracting solvent for around 7 days with occasional stirring. This content is then filtered by using a muslin cloth and the filtrate obtained is subjected to distillation under minimum pressure to remove the ethanolic fractions from the filtrate. The concentration of the drug left behind is further concentrated to obtain a thick slurry. This

slurry is further dried and then stored in desiccators for future use.

2.2 Selection of Animals

Albino Wistar rats of either sex, 4 - 6 weeks old weighing about 180-250 g was taken. Animals are obtained from the central animal house, NCARE, Paneer, Mangalore. These rats were properly housed in different cages under the temperature conditions in dark and light for 12 hours. Animals were provided with standard food and water ad libitum.

2.3 Drug Treatment and Acute oral Toxicity Studies [3]

In order to assess the acute pharmacological and drug safety, an initial pharmacological study was conducted. Acute oral toxicity studies were carried out to determine the lethal dose, i.e., LD50 of the extract of *Garcinia cambogia*. These studies were conducted on albino Wistar rats of 150-200g body weight by using “Up and Down Method” as per OECD 425 guidelines. The procedure of the test minimizes the number of animals required to estimate the acute oral toxicity studies of the extract. The suspension of extract (2000 mg/kg) was administered orally to the rats which were fasted overnight. These animals are watched once in 30 minutes interval for about 4 hours in order to check any behavioral and neurological changes and finally till the death after 24 hours of administration.

2.4 Selection of Doses

To evaluate the anti-ulcer activity of *Garcinia cambogia* fruit, two dose levels have to be selected. Let the two doses to be mid dose and a higher dose. Selecting the mid dose from the acute toxicity studies, the mid dose will be 1/10th of the maximum dose given in the acute oral toxicity studies which is 2000 mg/kg.so, 1/10th of 2000 mg/kg will be 200 mg/kg of rat body weight which is taken as mid dose. The higher dose will be double that of 1/10th dose, that is, 400 mg/kg body weight of rat.

2.5 Ethanol Induced Ulcer Model [4]

2.5.1 Experimental design

Albino Wistar rats weighing about 180-200 g were randomly divided into 6 groups containing 6 rats each. The animals were categorized into different groups are described in the table below:

The animals were fasted overnight before conducting the experiment. Absolute alcohol was administered irrespective of the weight of animal, orally at a dose of 1 ml per animal one hour after the administration of the drugs. These animals are sacrificed after one hour of ethanol administration and their stomachs were isolated and cut opened along the greater curvature then pinned on thermocol board. This isolated stomach was exposed and examined for ulcerations and the ulcer index was determined.

2.6 Pylorus ligation Induced Ulcer Model [5]

2.6.1 Experimental design

Albino Wistar rats of weight 180-200 g are arbitrarily divided into 5 groups of 6 animals each. The different groups are given in the table below:

The albino Wistar rats were fasted overnight. During this time, the rats were sheltered in individual cages with raised bottoms of wide wire mesh in order to avoid coprophagy and cannibalism. Access to drinking water ad libitum was provided. The rats were anaesthetized after one hour of drug treatment and the mid line incision of 1cm long is made in the abdomen below the sternum. The stomach is identified and the pyloric sphincter is tied with a sterile thread and a knot is applied, which was done without causing any damage to the blood supply of the stomach. The abdomen wall was sutured and these rats were allowed to recover back and were stabilized in single cages. Animals were deprived of water during post-operative period. Group 1 animals are served as normal. These animals were sacrificed by cervical decapitation method, 6 hours after the pylorus ligation. The stomachs were removed and cut along the greater curvature and observed for the ulcerations. The gastric juice of the stomach is collected. Its volume, pH, free acidity and total acidity are determined. The pH is determined using pH meter. The ulcerations in the stomach was observed and noted. With the help of hand lens (10x), the severity of the ulcer scores were recorded macroscopically and is compared with that of the standard drug. The ulcer index is determined.

Table 1. Experimental design of ethanol induced ulcer model

Group	Treatment
Group I	Normal control
Group II	Ulcer control (Absolute alcohol, 1 ml) p.o
Group III	Standard (sucralfate , 100mg/kg) p.o
Group IV	*Garcinia cambogia* extract (200mg/kg)
Group V	*Garcinia cambogia* exract (400mg/kg)

Table 2. Experimental design of pylorus ligation induced ulcer model

Group	Treatment
Group I	Normal control
Group II	Ulcer control (Absolute alcohol, 1 ml) p.o
Group III	Standard (Omeprazole 30mg/kg) i.p
Group IV	*Garcinia cambogia* extract (200mg/kg)
Group V	*Garcinia cambogia* exract (400mg/kg)

2.7 Biochemical Estimations

2.7.1 Estimation of Ulcer Index (UI) [6]

The abdomen was removed and cut open along the greater curvature, pinned on a soft board. The severity of ulcer scores is observed and noted with the help of hand lens (10X) and the standard ulcer scores are given below.

Table 3. Scores for ulcer index

Observation	Score
Normal stomach	0
Red colouration	0.5
Spot ulcer	1.0
Hemorrhagic streaks	1.5
Ulcers	2.0
Perforations	3.0

He ulcer index was calculated by using the formula:

$$UI = UN + US + UP \times 10\text{-}1$$

Where,
UI - Ulcer Index.
UN - Average of number of ulcers per animal.
US - Average of severity scores.
UP – Percentage animals with ulcers.
Then the percentage of ulcer protection was determined as given:

$$\%\text{protection} = \frac{\text{control mean ulcer index} - \text{test mean ulcer index} \times 100}{\text{Control mean ulcer index}}$$

2.7.2 Estimation of free acidity and total acidity [7]

The stomach was removed, cut along the greater curvature and the gastric juice was collected in a test tube. It was then centrifuged at 3000 rpm (rotation per minute) for about 10 minutes. From this, 1 ml of the supernatant (gastric juice) was pipetted into a 100 ml conical. The collected supernatant was diluted with 10 ml of distilled water. The pH of the solution is noted and to that 2-3 drops of topfers reagent (dimethyl-amino-azo-benzene with phenolphthalein) is added. This solution was titrated against 0.01 N NaOH till the solution turns to orange as end point. The quantity of alkali added was recorded which gives the free acidity. The titration is further continued to obtain total acidity. The titration is continued further till the solution regains pink color. The complete volume of NaOH is noted, which corresponds to the total acidity.

Gastric acidity can be expressed by using the formula given below:

$$\text{Acidity} = \frac{\text{volume of NaOH} \times \text{Normality of NaOH} \times 100}{\text{mEq/L/100g } 0.1}$$

2.8 Statistical Analysis

All the datas exhibited as, Mean ± SEM and were subjected to the one – way Analysis Of Variance test (ANOVA). This was followed by the Post hoc Scheffe's test using SPSS computer software version 10. The p value < 0.05 is considered as statistically significant.

3. RESULTS AND DISCUSSION

The preliminary phytochemical analysis of ethanolic extract of *Garcinia cambogia* extract indicated the presence of alkaloids, tannins, flavonoids, carbohydrates, saponins, proteins.

The *Garcinia cambogia* extract was subjected for toxicity studies. The extract was found to be nontoxic up to 2000mg/kg body weight given orally. The animals are found to be stable after 24 hours of drug administration. There was no mortality or any signs of toxicity. Hence, the extract is found to be safe. So, for the present study, the two dose levels i.e, 200mg/kg, 400mg/kg body weight were selected.

The ethanolic extract of *Garcnia cambogia* at a dose of 200 and 400 mg/kg produced a significant activity in a dose dependent manner with a maximum percentage of inhibition (13.90% and 53.50% protection respectively) in comparison to the normal control group. It was found that there was a significant and dose dependent reduction in the ulcer index (9.69 and 5.63) at a dose of"200 and 400mg/kg respectively when it was compared to normal control group. Sucralfate (100mg/kg) which was chosen as a reference standard exhibited a potent anti-ulcer activity significantly at all the parameters.

3.1 Ethanol Induced Ulcer Model

Ethanol is a strong solvent which digests the gastric mucosa forming lesions in the mucosal barrier. It also inhibits the release of bicarbonates and synthesis of mucus. The impacts can be because of the various activities taking place in the biological system like lipid peroxidation, depolarization, free radical generation and intracellular oxidative stress. Oral administration of alcohol can produce a necrotizing effect on the gastric mucosa. Pathogenesis of ethanol induced gastric ulcers include mediators like lipoxygenase, oxygen derived free radicals and cytokinins. [8,9] The result of this study revealed that the fruit extract produced significant antiulcer activity because of the chemical content present in it. It was understood that the *Garcinia cambogia* fruit extract reduced the gastric ulcerations (table 1) in rats. Extract 200mg/kg and 400mg/kg produced an ulcer index of 9.69and 5.23 when compared with ulcer control group (11.26). The percentage protection produced by extracts 200mg/kg and 400mg/kg is 13.90% and 53.50% respectively and standard sucralfate (30mg/kg) produced 83.4% protection on ethanol induced ulcers in rat (Table 4).

3.2 Pylorus Ligation Induced Gastric Ulcer in Rats

The most acceptable model for the evaluation of gastric ulcer is pylorus ligation induced gastric ulcer in rats. Pylorus ligation leads to the accumulation of large quantity of gastric acid which results in the production of gastric volume, free acidity, total acidity and reduction in the gastric pH. The accumulation of large volume of gastric juice leads to the self-digestion of the gastric mucosa and lead to breakdown of the mucosal barrier forming gastric ulcers. [10-12] *Garcinia cambogia* fruit extract produced an anti-ulcerogenic activity in a dose dependent manner. Doses 200mg/kg and 400 mg/kg produced a good antiulcer activity by reducing the gastric acid volume, free Acidity total acidity and rise in gastric pH. The extract 200mg/kg and 400mg/kg produced an ulcer index of 5.76 and 3.83 when compared with ulcer control group (9.06) and standard group treated with omeprazole (1.63). At a dose of 200 and 400mg/kg, the extract produced a percentage protection of 36.4% and 57.7% respectively whereas the standard drug omeprazole produced a percentage protection of 82%. The result reported that the extract at 400mg/kg produced a significant effect than 200mg/kg. (Table 5)

Table 4. Effect of ethanolic extract of *Garcinia cambogia* on Ethanol induced ulcer model

Groups	Treatment	Ulcer index	%Protection
Group I	Normal control	0^{b}	-
Group II	Ulcer control	11.26 ± 0.2^{ac}	-
Group III	Sucralfate(100 mg/kg)	1.86 ± 0.2^{b}	83.40%
Group IV	Extract(200 mg/kg)	9.69 ± 0.5^{ac}	13.90%
Group V	Extract(400 mg/kg)	5.23 ± 0.2^{abc}	53.50%

The values are expressed as Mean ± SEM, (n=6). a = p<0.05 when compared to Normal Control group, b = p<0.05 when compared to the Ulcer Control group, c = p<0.05 when compared to Standard group.

Table 5. Effect of ethanolic extract of *Garcinia cambogia* on pylorus ligated ulcer model

Group	treatment	Gastric volume	Gastric pH	Free acidity (mEq/L)	Total Acidity (mEq/L	Ulcer index	% protect ion
Group I	Normal control	1.43±0.12^{b}	3.66±0.17^{bc}	48±2^{bc}	73.66±1.2^{bc}	0^{bc}	-
Group II	Ulcer control	4.4±0.4^{bc}	2.36±0.08^{ac}	92.6±2.4^{ac}	95.66±1.4^{ac}	9.06±0.08^{ac}	-
Group III	Omeprazole (30mg/kg)	2.3±0.2^{b}	5.53±0.23^{ab}	22±1.5^{aB}	44.66±1.7^{ab}	1.63±0.08^{ab}	82
Group IV	Extract(200mg/kg)	2.25±0.15^{b}	4.15±0.16^{bc}	40.66±2.9^{bc}	62.66±1.4^{abc}	5.76±0.3^{abc}	36.40
Group V	Extract(400mg/kg)	1.4±0.09^{bc}	5.2±0.19ab	33.16±2.4^{abc}	54.33±2.2^{abc}	3.83±0.17^{abc}	57.70

The values are expressed as Mean ± SEM, (n=6). a = p<0.05 when compared to Normal Control group, b = p<0.05 when compared to the Ulcer Control group, c = p<0.05 when compared to Standard group

Further study can be conducted to confirm which among these might be responsible for the action shown study was undertaken to investigate the anti- ulcerogenic activity of ethanolic extract of *Garcinia cambogia* from the preliminary phytochemical investigation, [13,14] the extract of *Garcinia cambogia* was found to contain flavonoids, alkaloids, reducing sugars, proteins, steroids, saponins and tannins [15-17]. The ethanolic extract of the drug is proved to be safe up to 2000mg/kg from acute oral toxicity studies. The dose of the drug extract showed a significant activity in a dose dependent manner in both ethanol induced gastric ulcer model and pylorus ligated gastric ulcerations in rats. At a dose of 400mg/kg of the extract, there was a reduction in the gastric volume, total acidity, free acidity, ulcer index and an increase in the gastric pH when compared to standard drug. The result clearly reveals that the drug has got some significant amount of antiulcer activity. Thus, according to the proof from the study, it can be concluded that the ethanolic fruit extract of *Garcinia cambogia* possesses a significant activity; hence can be utilized as an anti-ulcerogenic drug for its gastro protective and anti-ulcer activity [18].

4. CONCLUSION

These observations lend a pharmacological proof and support on the traditional use of *Garcinia cambogia* as an anti-ulcer agent. In future, this work can be extended by adding more number of ulcer models to confirm the anti-ulcer potency of *Garcinia cambogia* fruits plus the isolation and characterization of the phyto constituents responsible for the pharmacological activity can also be attempted. Toxicological studies can also be done to know more about the toxic and non-toxic nature of the drug.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The further investigations were carried out according to the CPCSEA (Committee for Purpose of Control and Supervision of Experiments on Animals) and the research work was permitted to be carried out by the Institutional Animal Ethics Committee (IAEC No. NGSMIPS/IAEC/MARCH-2018/72)

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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