International Journal of Early Childhood Special Education (INT-JECSE)
DOI:10.9756/INTJECSE/V14I5.1008 ISSN: 1308-5581 Vol 14, Issue 05 2022

A Study On Anti-Ulcer Activity Of Benincasa Hispid a Leaves In Ulcer Induced Rats

Running Title: - A Study On Anti-Ulcer Activity Of Benincasa

K Lourdhu Manoj[1], P Dhanunjaya Reddy[2], U Satya Gopi[3], C Sateesh[4], Ch Gopala Krishna[5]*, A Santi[6]

[1, 2, 3, 4, *5, 6]A.M Reddy memorial college of pharmacy, Narasaraopet, Andhra Pradesh, India
Email id:gopipharma.ch@gmail.com[5]

***Corresponding author: -**Ch Gopala Krishna.

*A.M Reddy Memorial College of pharmacy, Narasaraopet, Andhra Pradesh, India
Email id:gopipharma.ch@gmail.com

Abstract
Benincasa Hispida aqueous, ethanol leaf extract was tested for antiulcer efficacy in rats using a variety of ulcer-inducing chemicals. Methods: The Benincasa hispida certified medicine was dried in the shade and finely ground. Extraction was carried out using analytical grade solvents in accordance with normal procedure. Ethanol (64.5-65.5oc) and distilled water were used to extract the Benincasa hispida's coarse powder, which was Sox allowed to dry. Under decreased pressure, the resulting extracts were concentrated. Tests on benincasa hispida extracts in ethanol and water yielded positive results. In order to determine the numerous phytoconstituents that may be found in food. 30 minutes before to pyloric ligation, BH powder extracts or a conventional medication or a control vehicle were given. Each animal's ulcer index is the mean score for each ulcer. Different rat models (pylorus-ligation model) and dosages of aqueous and ethanol extracts i.e. 250 mg/kg and 500 mg/kg of bodyweights were used to validate the anti ulcer efficacy of BH leaves. There was a significant decrease in stomach fluid volume and an elevation in pH in the treated group (pylorus ligation model) after treatment with 8 mg/kg body weight with lansoprazole. Acidic pH was found in the aqueous and ethanol extracts treatment groups at the dosage level of 250 mg/kg and 500 mg/kg body weight. @ 500mg/kg body weight, stomach fluid volumes have reduced considerably in aqueous and ethanol extracts treated groups. In the (pylorus ligation model) investigated, BH Leaves extracts in aqueous and ethanol at doses of 500 mg/kg body weight provided better percentage protection by lowering ulcer index than standards in all treatment groups. Pylorus ligation model of Lansoprozole utilised as standard. The anti-ulcer properties of BHLeaves may be due to the anti-oxidant properties of flavonoid, which protects the mucosal barrier.

Keywords: Anti-oxidant, Anti-ulcer activity, Benincasa hispida, Flavanoid, Pylorus ligation model.

INTRODUCTION

For more than a century, peptic ulcer disease has been a major cause of morbidity andmortality. The pathophysiology of peptic ulcer has been centralized on an imbalance betweenaggressive and protective factors in the stomach such as acid-pepsin secretion, mucosal barrier,mucus secretion, blood flow, cellular regeneration, prostaglandins and epidermal growth factors.Although hospital admissions for uncomplicated peptic ulcers in developed countries had begundecrease, there was a striking rise in admissions for ulcer hemorrhage and perforation amongelderly people. This increase has been attributed to the increased use of non-steroidal anti-inflammatory drugs (NSAIDs), alcoholic beverages, cigarettes and *Helicobacterpylor i*infections[1-5].

Peptic ulcer disease represents a serious medical problem. Approximately 500,000 newcases are reported each year. Interestingly, those at the highest risk of contracting peptic ulcerdisease are those generations born around the middle of the 20th century. Ulcer disease has become a disease predominantly affecting the older population, with the peak incidence occurring between 55and 65 years of age. Inmen,duodenalulcers were more common than gastric ulcers; in women, the converse was found to be true[6-8]. Thirty-five percent of patientsdiagnosed with gastric ulcers will suffer serious complications. Although mortality rates from pepticulcer disease are low, the high prevalence and the resulting pain, suffering, and expense a revery costly[3, 9].

Plants and other natural substances have been used as the rich source of medicine. Allancient civilizations have documented medicinal uses of plant in their own ethnobotanical texts.Thelist of drugs obtained from plant sourceis fairly extensive[10, 11]. In view of this, the present study is taken up to investigate the possible anti-ulcer role of benincasahispida leaves. So this study is essentialand justifiable. The present study was aimed to investigate antiulcer

activity of aqueous, ethanol extractof *Benincasahipsida*byusing various ulcer induced agents in rats.

MATERIAL AND METHODS

Plants

The whole plant mixture of*BENINCASA HISPIDA*used for the investigation were collected from were collected from GUNTUR. The plan therbarium specimen was identified andauthenticated by Dr. p satyanarayana rajuplant taxonamist, Department of Botany, acharyanagarjunauniversity, Guntur-522510, AndhaPradesh.

Animals

Albino wistar rats of either sex weighing between 150 to 200 gm were procured form registered breeders theanimals were housed under standard conditions of temperature (25 □ 2^0C) andrelative humidity (30-70%) with a 12:12 light-dark cycle. The animals were fed with standardpelletdiet

Plant Extraction

The authenticated drug benincasa hispida was dried in shade and powdered coarsely.Extraction was done according to standard procedure using analytical grade solvents. The coarsepowder of the benincasa hispida was Sox let extracted with the solvents with increasing order ofpolarity i.e.Ethanol (64.5-65.5^{oc}), and distilled water. The extracts obtained were concentrated underreduced pressure.

Qualitativ echemicaltest:

Preliminary phytochemical investigation of extract:

Qualitative chemical tests were conducted forchloroform extract ofbenincasa hispida. Toidentify the various phytoconstituents. The various tests and reagents used are given below andobservationsarerecorded and tabulated.

Tests for Carbohydrates:

Molisch's test(General test):

To 2-3 ml aqueous extract, few drops of □-naphthol solution in alcohol was added, shaken andconcentrated H_2SO_4 was added from the sides of the test tube. It was observed for violet ring atthe junctionoftwo liquids.

For Reducing Sugars:

A. **Fehling's test:**1 ml Fehling's A and 1ml Fehling's B solutions was mixed and boiled for onemin. Equal volume of test solution was added. Heated in boiling water bath for 5-10 min andobservedfor ayellow, then brick red precipitate.

B. **Benedict's test:**Equal volume of Benedict's reagent and test solution (T.S.) in test tube weremixed.Heated in boiling water bath for 5 min.Solution may appear green, yellow or reddependingon amount ofreducing sugar present in test solution.

TestforMonosaccharides:

Barfoed'stest:

Equal volumes of Barfoed's reagent and test solution were added. Heated for 1-2 min, in boilingwaterbathand cooled. Observed for red precipitate.

TestforHexoseSugars:

Cobalt-chloride test: 3 ml of test solution was mixed with 2ml cobalt chloride, boiled and cooled.AddedfewdropsofFeCl3andNaOHsolution.Solutionwasobservedforgreenishblue(glucose), purplish (Fructose) or upper layer greenish blue and lower layer purplish (Mixture ofglucoseand fructose).

TestsforNon-ReducingSugars:

a) TestsolutiondoesnotgiveresponsetoFehling'sandBenedict'stest.
b) Tannicacidtestforstarch:With20%tannicacid,testsolutionwasobservedforprecipitate.

TestsforProteins:

a. **Biurettest**(Generaltest):To3mlT.S.added4%NaOHandfewdropsof1%CUSO4solutionand observed for violet or pink colour.

b. **Millon'stest**(forproteins):Mixed3mlT.S.with5mlMillion'sreagent,whiteprecipitateobtained.Precipitatewarmedturns brick redor precipitatedissolvesgiving red colour.

c. Xanthoproteintest(Forproteincontainingtyrosineortryptophan):Mixed3mlT.S.with1mlconcentratedH_2SO_4,observed for whiteprecipitate.

d. Testforproteincontainingsulphur: Mixed 5 ml T.S. with 2 ml 40% NaOH and 2 drops10%lead acetatesolution.Solution was boiled,turns blackor brownishdueto PbSformation.

e. Precipitationtest: Thetestsolutionwasobservedforwhitecolloidalprecipitatewithfollowingreagents:

i. Absolutealcohol
ii. 5%mercuricchloridesolution
iii. 5%cupricsulphate solution
iv. 5%leadacetate
v. 5%ammoniumsulphate

TestsforSteroids: SalkowskiReaction:To2mlofextract,2mlchloroformand2mlconcentrated H_2SO_4 was added.Shook well, whether chloroform layer appeared red and acidlayershowed greenish yellow fluorescencewas observed.

a) Liebermann-Burchard Reaction: Mixed 2ml extract with chloroform.Added 1-2 ml aceticanhydride and 2 drops concentrated H_2SO_4 from the side of test tube, observed for first red,thenblueand finally green colour.
b) Libermann's reaction:Mixed 3 ml extract with 3 ml acetic anhydride.Heated and cooled.Addedfew drops concentrated H_2SO_4,observed forbluecolour.

TestsforAmino Acids:

a) **Ninhydrin test** (General test): 3 ml T.S. and 3 drops 5% Ninhydrin solution were heated inboilingwaterbath for10min and observedfor purple orbluish colour.
b) **TestforTyrosine:**Heated3mlT.S.and3dropsMillion'sreagent.Solutionwasobservedfordarkred colour.
c) **Testfortryptophan:**To3mlT.S.addedfewdropsglycoxalic acidandconcentratedH_2SO_4observedfor reddish violet ring at junction ofthetwo layers.

TestsforFlavonoids:

a) **Shinodatest:**Todriedpowderorextract,added5ml95%ethanol,fewdropsconcentratedHCland 0.5 g magnesium turnings. Pink colourwas observed.
b) Tosmallquantityofresidue,addedleadacetatesolutionobservedforYellowcoloredprecipitate.
c) Additionofincreasingamountofsodiumhydroxidetotheresiduewasobservedastowhetherit showedyellow colouration,which wasdecolourised afteraddition ofacid.
d) **Ferricchloridetest:**Totestsolution,addedfewdropsofferricchloridesolutionobservedforintensegreen colour.

TestsforAlkaloids:

a) **Dragendroff'stest:**To2-3mlfiltrateaddedfewdropsDragendroff'sreagentandwasobservedfor orangebrown precipitate.
b) **Mayer'stest:**2-3mlfiltratewithfewdropsMayer'sreagentwasobservedforprecipitate.
c) **Hager'stest:** 2-3mlfiltratewithHagersreagentwasobservedforyellowprecipitate.
d) **Wagner'stest:**2-3mlfiltratewithfewdropsofWagner'sreagentwasobservedforreddishbrownprecipitate.

TestsforTanninsandPhenolicCompounds:-

To2-3mltestsolution,addedfewdropsoffollowingsolutions and was looked forrespectivecoloration orprecipitate:

a) 5%Ferricchloridesolution:-Deepblue-blackcolored.
b) Leadacetatesolution: - Whiteprecipitate.
c) Gelatinsolution: -Whiteprecipitate.
d) Brominewater:-Decolorationofbrominewater.
e) Aceticacidsolution:-Redcoloursolution.
f) Potassiumdichromate:-Redprecipitate.
g) Diluteiodinesolution:-Transientredcolour.
h) DiluteNitricacid:-Reddishto yellowcolour.

TestsforVitamins:

a. Test for Vitamin A:- Dissolve a quantity equivalent to 10-15 units in 1ml chloroform and add5mlof

antimonytrichloridesolution, atransient bluecolour is producedimmediately.

b. Test for vitamin C (Ascorbic acid):- Dilute 1 ml of 2% w/v solution with 5 ml of water andadded 1 drop of freshly prepared 5% w/v solution of sodium nitroprusside and 2 ml diluteNaOH solution. Added 0.6 ml of hydrochloric acid drop wise and stir, the yellow color turnsblue.
c. Test for Vitamin D:- Dissolved a quantity equivalent to about 100 units of Vitamin D,activating in chloroform and added 10 ml of antimony tricohloride solution, a pinkish-redcolourappearedat once.

TestsforGlycosides:
Generaltest forGlycosides:
PartA:
To 2-3 ml of extract dil. H_2SO_4 was added and heated on a water bath for 1-2 mins. Neutralizewith 10% NaOH,check with litmus paper and to resulting solutionadd Fehling's A & B.Increasedred precipitatein this caseshows glycosides arepresent.

PartB:
To 2-3 ml of extract, water was added and heated. According to need, NaOH was added forneutralization and also added equal quantity of water. To the resulting solution added Fehling's A&B. Increased red precipitate in this case showed glycosidesareabsent.ComparePartA andB.

TestsforCardiacGlycosides:
a. Baljet'stest:Thetestsolutionwas observedfor yellowtoorangecolourwith sodiumpicrate.
b. Legal'stest(Forcardenoloids):Toaqueousoralcoholictestsolution,added1mlpyridineand1 ml sodium nitroprusside, observed for pinkto red colour.
c. Test for deoxysugars (Kellar Killani test): To 2 ml extract added glacial acetic acid, one dropof 5% $FeCl_3$and concentrated H_2SO_4,observed for reddish brown colour at junction of thetwoliquid and upper layers bluish green.
d. Libermann's test (For bufadenolids): Mixed 3 ml extract with 3 ml acetic anhydride. Heatedandcooled. Added few drops concentrated H_2SO_4observedforbluecolour.

TestsforSaponin Glycosides:-
a. **Foamtest**:Thedrugextractordrypowderwasshakenvigorouslywithwater.Persistentfoamwas observed.
b. **Hemolytictest**:Addedtestsolutiontoonedropofbloodplacedonglassslide.Hemolyticzonewhether appeared was observed.
c. **TestsforCoumarinGlycosides:**Testsolutionwhenmadealkaline,observedforblueorgreenfluorescence.

Antiulceractivity:
Pilorusligationmethod:

Albino wistar rats of either sex weighing between (150-200gms) were divided into six groupsofsix animals in group.
1. Group-I–Control(2% gumacacia)
2. Group-II–Standard(Lansoprazole8mg/kg in2%gumacacia).
3. Group-III–Aqueousextractof*BH*leaves (250mg/kgp.o.).
4. Group-IV–Aqueousextract *BH*leaves(500mg/kgp.o.).
5. Group-V–Ethanolic extract*BH*leaves(250mg/kgp.o.).
6. Group-VI– Ethanolicextract*BH*leaves(500mg/kg p.o.).

Inthismethodalbinoratswerefastedinindividualcagesfor24hr.carewastakentoavoidcoprophagy.BHpowderextractsorstandarddrugorcontrolvehiclewasadministered30min.prior topyloric ligation.Under lightether anesthesia, give anincisionof 1cmlong intheabdomen just below the sternum. Expose the stomach pass a thread around the pyloric sphincterand apply a tight knot. While putting the knot care was taken so that no blood vessels are tiedalong the knot. The abdomen was sutured clean the skin from any blood spots and bleeding.Apply collodion over the wound. At the end of 4 hr. after ligation the animals were sacrificedwith excess of anesthetic ether. Open the abdomen and tie the oesophageal end (cardiac end) ofthe stomach. Cut and removed the entire stomach from the body of the animal. Gastric juice wascollected into graduated centrifugation tube and was centrifuged at 1000 rpm for 10 min. andgastric volume was noted. The p^H of the gastric juice was recorded by P^H meter. Open thestomach along the greater curvature and washed with running water to see for ulcers in glandularportionof thestomach.

The number of ulcersper stomachwasnoted andsevarityof the ulcers of the ulcersscoredmicroscopically with thehelp of hand lens(10X)and scoringwas doneas following.

0=normalstomach.
0.5=redcoloration.
1.0=spotulcers.
1.5=hemorrhagic streaks.
2.0=ulcer>3but < 5.
3.0=ulcer >5

Mean ulcer score for each animal is expressed as ulcer index. The percentage protection wascalculatedusing theformula, Percentage protection = 100 - $U_t/U_C \times 100$Where, U_t = ulcer index oftreated group.U_C=ulcer index ofcontrol group.

Statisticalanalysis:-
Statistical analysis were performed by simple graph.

RESULTS

Table1:Preliminaryphytochemicalscreening

s.no	Type of phytochemical constituents	Petroleum ether extract	Chloroform Extract	Ethanolic Extract	Aqueous Extract
1	Carbohydrates	_	+	+	+
2	Proteins	_	_	+	+
3	Flavonoids	_	-	+	+
4	Steroids	+	+	+	_
5	Tannins	_	_	+	+
6	Saponin glycosides	_	_	+	+
7	glycosides	_	+	+	+
8	Alkaloids	_	_	+	_

Note:-Absent,+Indicatespresence,

Acutetoxicity(LD50)studies:-
Acute toxicity studies for chloroform extracts of benincasa hispida were conducted as perOECDguidelines420usingalbinoswissmice.Eachanimalwasadministeredchloroformextracts by oral route. The animals were observed for any changes continuously for the first 2 hrsand up to 24 hrs for mortality. There were no mortality and noticeable behavioral changes in allthegroups tested. The extractswerefound to besafeup to 2000 mg/kgbody weight.

An attempt was made to identify LD_{50} of aqueous, ethanolic, benincasa hispida leaves. Since nomortality was observed at 2000 mg/kg. It was thought that 2000 mg/kg was the cut off dose.Therefore, 1/8 and 1/4 dose i.e. 250 mg/kg. and 500 mg/kg. Were selected for all further in vivostudies.

PylorusligationulcerModel:
Effect of aqueous, ethanolic, benincasa hispida leaves On pH of gastric secretion followingpylorusligation in rats:
At 250 mg/kg&500mg/kg the pH was remained unchanged when compared with control.The influence on the pHin pylorus ligation of Lansoprazole (8mg/kg); aqueous, ethanolic,benincasahispidaleaves(250,500mg/kg) ismentioned in the following table.

Table2:pH ofgastricsecretion

Group no	Treatment	Dose	pH
1	Control	-	1.3
2	Lansoprazole	8mg/kg	5.717
3	Aq.Extract 250mg	250mg/kg	1.56
4	Aq.Extract 500mg	500mg/kg	2.10
5	Ethnolic Extract 250mg	250mg/kg	1.26
6	Ethonolic extract 500mg	500mg/kg	1.90

Effectofaqueous,ethanolic,benincasahispidaleavesonvolumeofgastricsecretionfollowingpylorus ligation inrats:
At500mg/kgthevolumeofgastricjuicesecretionwassignificantlyreducedbychloroform extract of BH leaves in dose dependant manner when compared with control. Theinfluence on the volume of gastric juice secretion in pylorus ligation of Lansoprazole (8mg/kg);chloroformextract ofBH(250,500mg/kg).

Table3:gastric volume table

Group no	Treatment	Dose	Volume of gastric juice
1	Control	-	6.35
2	Lansoprazole	8mg/kg	1.03
3	Aq.Extract 250mg	250mg/kg	6.51
4	Aq.Extract 500mg	500mg/kg	4.91
	Ethanolic Extract 250mg	250mg/kg	5.51
	Ethanolic Extract 500mg	500mg/kg	4.71

Effectofaqueous,ethanolic,benincasahispidaleavesonulcerindexandtheir%protectioninpylorus ligation induced ulcerationinrats.
At 250&500mg/kg the ulcer index had significantly reduced by **aqueous, ethanolic, benincasahispidaleaves** indosedependantmannerwhencomparedwithcontrolandpercentageprotection is comparable to lansoprazole.

The influence on the ulcer index in pylorus ligation of Lansoprazole (8mg/kg); **aqueous,ethanolic, benincasa hispida leaves** 250,500mg/kg. Along with the percentage protection thathadsignificant changes aresummarized in Table 4.

Table4: Ulcerindex

Group no	Treatment	Dose	Ulcer index	% protection
1	Control	-	7.33	0%
2	Lansoprazole	8mg/kg	1	86.35%
3	aqueous Extract 250mg	250mg/kg	2.31	68.48%
4	aqueous Extract 500mg	500mg/kg	1.81	75.30%
5	ethanolic Extract 250mg	250mg/kg	2.31	68.48%
6	ethanolic Extract 500mg	500mg/kg	1.81	75.30%

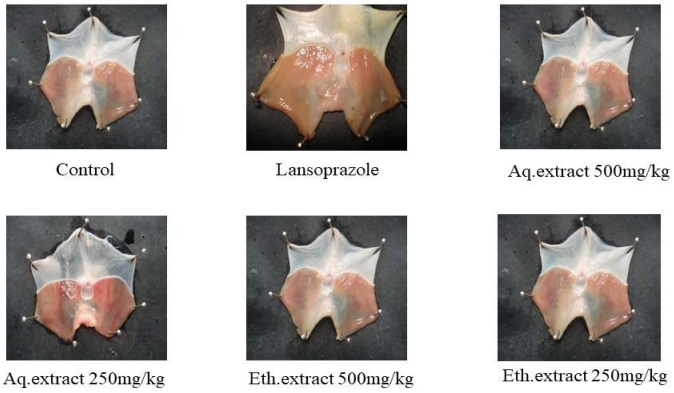

Fig1: Effectofaqueous,ethanolic,benincasahispidaleavesonulcerhealinginpylorusligationmodel.

DISCUSSION
Peptic ulcer is a chronic and dominant among the world's diseases. Gastric ulcers are results because of an imbalance between aggressive factors i.e.acid,pepsinandmucosaldefencemechanism. Ulcers found inpylorusligationmethodare due toimbalance betweenaggressivefactors, defensive mechanism and an increase in acid pepsin secretion as the animals are fastedand localization of that acid secretion by ligation of pylorus part of the stomach [10, 11].The pylorusligation increases lipid peroxidation and free radical generation due to reduced GSH levels ofgastricmucosa.All thesefactorscontributetodigestionofthegastric mucosaand causesulcer.

Differentparametersstudiedwere: From the table and fig. P^H of both aqueous and ethanol extracts when comparedtocontrol remain unchanged andin theacidicrangewhencomparedwith lansoprazole**.** From the table and fig For aqueous and ethanol extracts 500 mg/kg the volume of gastric contents were raised significantly when compared to lansoprazole[12, 13]. This indicates that lansoprazole has antisecretory activity, inhibits acid secretion by inhibiting the proton pump andpH was changed to slightly neutral when compared with control group. The drug may not have a

significant antisecretory activity but there may beincrease in the volume of gastric contents when compared with lansoprazole due to increased prostaglandin synthesis therefore increases mucus production which provid[14, 15]ed a protective effect by lining the stomach.Thismaybeattributed to the presence of flavonoids, whose gastro protective action involves endogenousPAF,increasing themucus[16-18].

From the table and fig when compared with control group the lansoprazole, aqueousand ethanol extracts 250mg/kg,500mg/kg group showedsignificant difference in ulcer index.When compared with lansoprazole. aqueous and ethanol extracts 500 mg/kg offered maximumprotection when compared with standard lansoprazole[4, 19]. This may be attributed to the formationof mucosal layer as a protective barrier even though the pH of the gastric remained acidic.Theinhibition of lipid peroxidation and protective effect of BH was may be due to the antioxidantactivityof flavonoidsagainst thedamaging free radicals producedduring pylorousligation.

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