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Research Article

EVALUATION OF ANTIULCER ACTIVITY OF *WEDELIA CALENDULACEA* AQUEOUS EXTRACT IN RODENTS

Gindi Sumalatha[2], Hwisa T Nagiat[1], Chandu Babu Rao[1]* and Katakam Prakash[1]
[1]Faculty of Pharmacy, University of Zawia, Al-Zawia, Libya
[2]Hindu college of Pharmacy, Guntur 522017, India
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ABSTRACT
The present study was focused to evaluate the protective activity of the *Wedelia calendulacea* (WC) whole plant aqueous extract against aspirin-pylorus ligation, HCl-ethanol and water immersion stress induced ulcers. In the present study aspirin-pylorus ligation induced gastric ulcer was adopted to screen the antisecretory activity of plant extract. WC extract produced 61.76% ulcer inhibition at 400mg/kg body weight, when compared to that of standard (ranitidine, 50mg/kg) which produced 62.6% ulcer inhibition. In HCl-ethanol induced ulcer model 400mg/kg body weight of WC produced 88.87% ulcer inhibition when compared that of standard (sucralfate, 100mg/kg) which produced 90.80% ulcer inhibition. In water immersion-stress induced ulcer model 400mg/kg body weight of WC, produced 96.34% ulcer inhibition when compared to that of standard (omeprazole, 20mg/kg) which produced 99.30% ulcer inhibition. WC showed significant percentage of ulcer inhibition in the three models tested. The glycosides which are present in the aqueous extract could be responsible for their antiulcer properties.
Keywords: Ulcer, Pylorus ligation, *Wedelia calendulacea*, aqueous extract

INTRODUCTION

Gastric ulcer is a chronic and most common health problem that most of the population experience with excruciating stomach burning. A bleeding gastric ulcer is a potentially life-threatening condition and may represent a major health challenge that needs to be solved. Although ulcer is one of the oldest known diseases of mankind and affects a large population of the world, no significant progress has been made in achieving a permanent cure. Administrations of allopathic antiulcer agents do not show permanent solution and the use of NSAIDs is unavoidable in clinical practice. Therefore there is a need for development of safer alternatives to existing synthetic drugs.

As per World Health Organization estimates the indigenous plants are being used by 75-80% of the world for primary health care because of better acceptability and compatibility by human body with lesser side effects[1]. Plants and herbs have been used since ancient times to treat different gastrointestinal illnesses, including peptic ulcers[2]. Even though the etiology of gastric ulcers is still debated, it is accepted that ulcers are caused due to net imbalances in mucosal offensive and defensive factors[3]. Newer ulcer therapy is now mainly focused on the search safer drugs which protect the gastric mucosa from damaging agents without influencing acid secretion or neutralizing intra-gastric acidity. The search for novel molecules has been extended to herbal drugs that offer better protection and decreased relapse. Numerous medicinal plants were found to exhibit antiulcer activity and found useful in the treatment of peptic ulcer.

Wedelia calendulacea (WC) Less (Syn., W. chinensis Merrill) of the family Asteracea, known as "pitabringi" (Sanskrit), "Pila bhangra" (Hindi), "kalsarji, Gargari" (Kannada) is a procumbent, perennial herb found in wet and marshy places India. The plant has been extensively studied for its hepatoprotective activity, skin diseases, anticancer and immunomodulatory activity[4]. In the present investigation the crude aqueous extract of WC was tested for their antiulcer activity in rodents using three models.

MATERIALS AND METHODS

Identification of the selected medicinal plant

The plant was authenticated by Prof.V. Jaya, Head, Botany Department, Hindu College, Guntur, Andhra Pradesh, India. The plant specimen was deposited in the College herbarium (HCOP 27/2012) at Hindu College of Pharmacy, Guntur-522001, Andhra Pradesh, India.

Preparation of aqueous extract

The whole plant was collected, shade dried and powdered coarsely with a multi-mill. The coarse powder was decocted in purified boiling water in the ratio of 1:16. The decoction was then filtered, weight /ml was estimated randomly and was administered freshly to the animals by gastric intubation.

Phytochemical analysis

The crude extract was subjected to preliminary phytochemical screening to test the presence of alkaloids, carbohydrates, reducing sugars, glycosides, proteins, amino acids, steroids, triterpenoids, phenolic compounds, tannins, flavonoids, fixed oils, fats, volatile oils, gums and mucilages[5,6]

Animals

Sprague dawley (SD) albino rats weighing 100-200 g and albino mice weighing 24-30 g of either sex were used for the present study. They were housed in groups of four in standard laboratory conditions (25 ±1^{0}C, relative humidity 55 ±5% and 12.00:12.00 h dark : light cycles), fed with standard pellet diet and water *ad libitum*. The experiments were performed as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. The Institutional

Animal Ethics Committee approved the study protocol (IAEC/HCOP/01/2009).

Acute toxicity studies

Healthy adult albino rats of Wistar strain (procured from national Institution of Nutrition, Hyderabad, registered with CPCSEA) were taken and maintained at 22^{O}C ± 3^{O}C, 50-60% relative humidity, 12:12 hour time cycle of light and dark and were housed individually with standard pellet diet and water *ad libitum*. Rats were fasted overnight with water *ad libitum* prior to the test.

They were divided into five groups each containing six animals. Group-I animals were treated with distilled water (2 ml/kg/p.o.) and Group-II to Group-V animals received 1, 2, 4 and 8 g/kg/p.o. of the plant extract by gastric intubation using a soft catheter[7].

The animals were observed continuously after 2 h and then intermittently at gaps of one hour and at the end of 48 h for their behavioral, neurological and autonomic profiles blindly by two qualified observers during acute toxicity studies.

Experimental Design

Aspirin-pylorus ligation induced gastric ulcer in albino rats

The SD albino rats weighing 100-200 g of either sex were divided into 4 groups each consisted of 6 animals. All the animals received 200 mg/kg p.o. of aspirin once daily for three days. Group I served as control and received water. Group II was treated with 50 mg/kg, p.o. of ranitidine as standard. Group III and IV were treated with aqueous plant extract of 200 and 400 mg/kg p.o. respectively. On the fourth day pylorus part was ligated following 36h fasting[8]. Four hours after the pyloric ligation the animals were sacrificed by cervical dislocation. The stomach was opened and the ulcer index was determined[9]. The gastric content was titrated against 0.01 N NaOH to find out the free acidity and total acidity[10]. The number of ulcers was counted using a magnifying glass and the diameter of the ulcers was measured using vernier calipers. The following arbitrary scoring system[11] was used to grade the incidence and severity of lesions: (i) 10 = denuded epithelium; (ii) 20 = petechial and flank haemorrhages; (iii) 30 = one or 2 ulcers; (iv) 40 = multiple ulcers and (v) 50 = perforated ulcers.

Ulcer index (UI) was then calculated from the above scorings as follows:

$$UI = (UN + Us + Up \times 10) - 1$$

Where, UN is average number of ulcers per animal, Us is mean severity of ulcer score and Up is percentage of animals with ulcer incidence. The percentage inhibition was calculated by the following formula.

$$\% \text{ inhibition} = \frac{\text{UI control} - \text{UI treated}}{\text{UI control}} \times 100$$

HCl - ethanol induced ulcer in albino mice

Albino mice weighing 24-30 g of either sex were divided into 4 groups, each group consisted of 6 animals. Group I served as a control and received water. Group II received 100 mg/kg, p.o. sucralfate as standard. Group III and IV have received aqueous plant extract of 200 and 400 mg/kg p.o. respectively. After 1h all the animals were treated with 0.2 ml of HCl - Ethanol mixture p.o. (0.3 M HCl and ethanol 60%) to induce gastric ulcer. Animals were sacrificed by cervical dislocation at one hour after administration of HCl - ethanol mixture. The stomach was excised and lesion index was determined by measuring each lesion in mm along its greater length[12].

Water immersion stress induced ulcer in albino rats

Stress ulcers were induced by forced swimming in the glass cylinder[13] (height 45 cm, diameter 25 cm) containing water to the height of 35 cm maintained at 25°C for 3h. Animals were fasted for 24h prior to the experiment and divided in to 4 groups with 6 animals in each group. Group I received water and served as control and group II treated with 20 mg/kg, p.o. omeprazole as standard. Group III and IV have received aqueous plant extract of 200 and 400 mg/kg p.o. respectively. After the treatment the animals were allowed to swim in water for 3 h. The stomach of each animal was removed and the extent of gastric damage was assessed as described by Alphine and Word[14].

Statistical analysis

The statistical analysis of all the results was carried out using one-way ANOVA followed by post hoc Dunnet's multiple comparisons and all the results obtained in the study were compared with the control group.

TABLE 1. EFFECT OF AQUEOUS EXTRACT OF *WEDELIA CALENDULACEA* ON GASTRIC SECRETION, ACIDITY, pH, ULCER INDEX AND PERCENTAGE OF ULCER INHIBITION

Groups	Volume of gastric secretion (ml/100)	Free acidity (mEq/l/100g)	Total acidity (mEq/l/100g)	pH	Ulcer index	% ulcer inhibition
Control	2.633 ± 0.071	206.7 ± 1.5	587.7 ± 1.3	2.20 ± 0.12	28.30 ± 0.33	-
Ranitidine (50mg/kg)	1.733 ± 0.056	144.3 ± 1.5	491.2 ± 2.7	3.55 ± 0.16	10.58 ± 0.17	62.60%
***W.C.* (200mg/Kg)**	1.550 ± 0.161	144.2 ± 1.2	496.8 ± 1.2	2.47 ± 0.13	15.33 ± 0.42	45.83%
***W.C.* (400mg/Kg)**	1.078 ± 0.051	143.2 ± 1.3	548.8 ± 0.9	2.48 ± 0.04	10.82 ± 0.12	61.76%

***P<0.001 *vs* control group analyzed by one way ANOVA followed by post hoc Dunnet's test;
W.C- *Wedelia calendulacea.* All values are mean ± S.D. (n=6).

TABLE 2. EFFECT OF AQUEOUS EXTRACT OF *WEDELIA CALENDULACEA* AGAINST HCL - ETHANOL INDUCED ULCER IN MICE

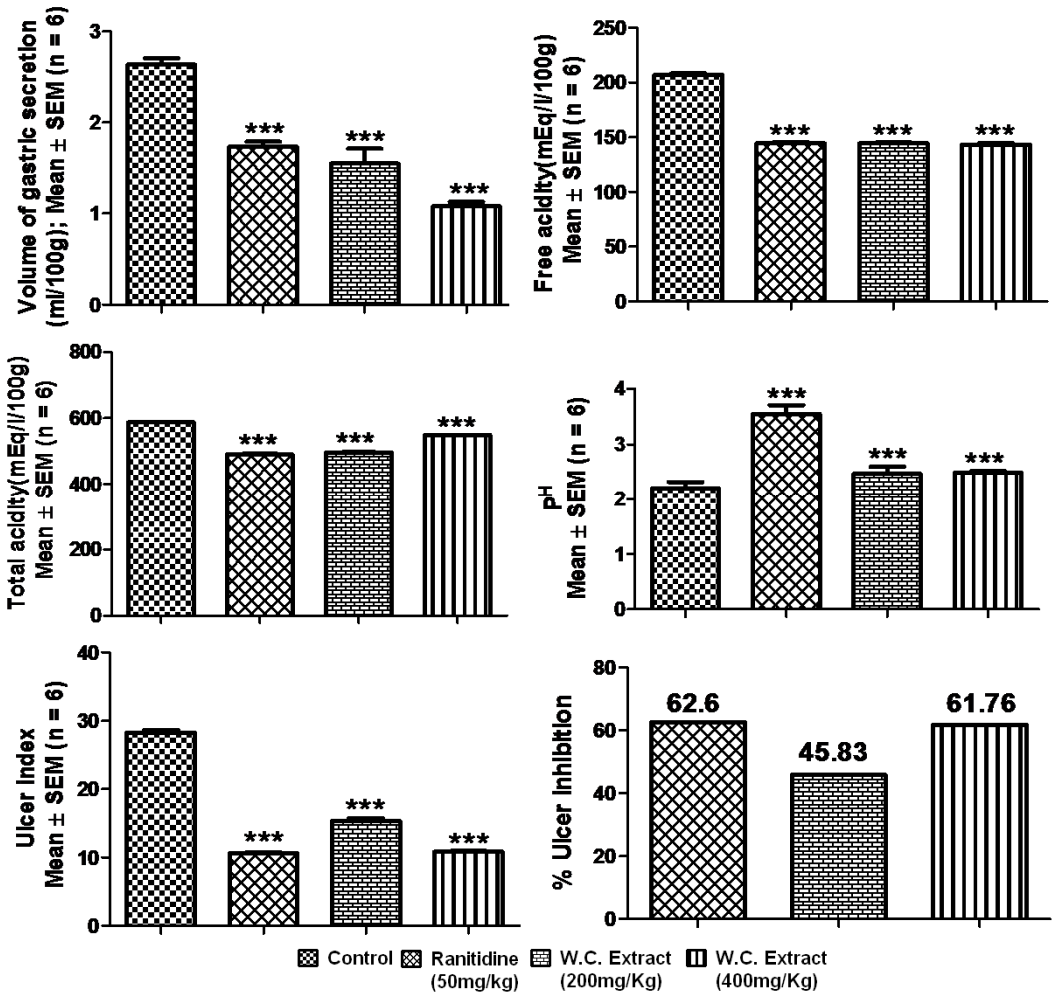
Groups	Gastric lesions	% Ulcer inhibition
Control	22.48 ± 0.21	-------
Sucralfate (100mg/kg)	2.05 ± 0.09	90.80
***W.C.* (200mg/kg)**	4.40 ± 0.12	80.42
***W.C.* (400mg/kg)**	2.50 ± 0.08	88.87

***P<0.001 *vs* control group analyzed by one way ANOVA followed by post hoc Dunnet's test ; W.C: *Wedelia calendulacea*

TABLE 3 EFFECT OF AQUEOUS EXTRACT OF *WEDELIA CALENDULACEA* AGAINST WATER IMMERSION STRESS INDUCED ULCER IN ALBINO RATS

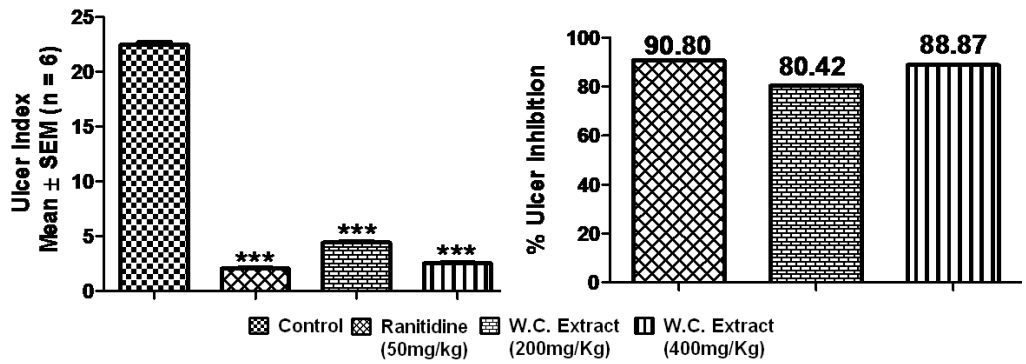
Groups	Mean ulcer score	% Ulcer inhibition
Control	145.0 ± 0.45	-------
Omeprazole (20mg/kg)	0.93 ± 0.08	99.30
***W.C.* (200mg/kg)**	6.90 ± 0.13	95.20
***W.C.* (400mg/kg)**	5.30 ± 0.14	96.34

. ***P<0.001 *vs* control group analyzed by one way ANOVA followed by post hoc Dunnet's test; W.C.- *Wedelia calendulacea*



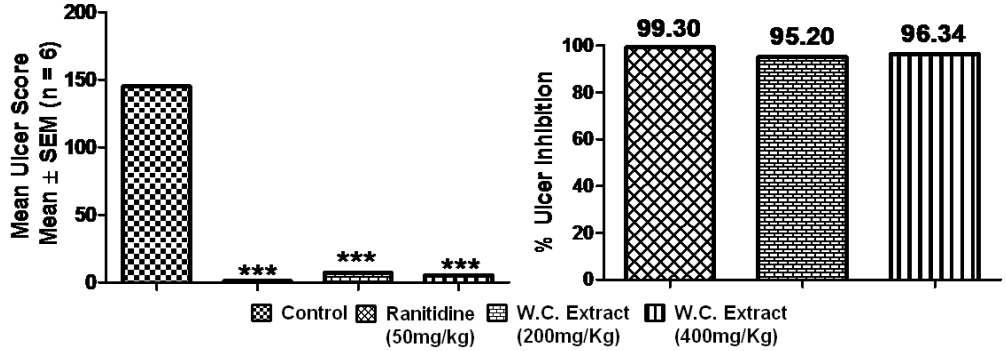
***P<0.001 *vs* control group analyzed by one way ANOVA followed by post hoc Dunnet's test; W.C- *Wedelia calendulacea*

Figure 1. Effect of aqueous extract of *Wedelia calendulacea* on gastric secretion, acidity, pH, ulcer index and ulcer % inhibition



***P<0.001 *vs* control group analyzed by one way ANOVA followed by post hoc Dunnet's test ; W.C: *Wedelia calendulacea.*

Figure.2 Effect of aqueous extract of *Wedelia calendulacea* against HCl - ethanol induced ulcer in mice



***P<0.001 *vs* control group analyzed by one way ANOVA followed by post hoc Dunnet's test; W.C- *Wedelia calendulacea*

Figure 3. Effect of aqueous extract of *Wedelia calendulacea* against Water immersion stress induced ulcer.

RESULTS

Wedelia calendulacea showed the presence of glycosides in preliminary phytochemical studies. Acute toxicity studies revealed that aqueous extracts were safe even at the dose of 8 g/kg body weight. The animals did not show any significant gross behavioral changes except for an increase in urination. From the acute toxicity studies, the doses for further studies were chosen in logarithmic progression of 200 and 400 mg/Kg body weight as suggested by Turner[7].

Effect of all the aqueous extract on gastric secretion, acidity, pH, ulcer index and percentage of ulcer inhibition were screened. In the present study aspirin - pylorus ligation induced gastric ulcer was adopted to screen the antisecretory activity of plant extract. WC extract produced 61.76% ulcer inhibition at 400mg/kg body weight, when compared to that of standard drug ranitidine 50mg/kg body weight, which has produced 62.6%. The results are shown in Table1 and the comparison between the plant extract and control and standard are shown in Figure 1. Effect of the aqueous extract on gastric lesions and % inhibition were screened by using HCl - Ethanol induced ulcer in albino mice. In this model 400mg/kg body weight of WC has produced 88.87% ulcer inhibition when compared to that of the standard (Sucralfate 100mg/kg body weight) which has produced 90.80% ulcer inhibition. The results are summarized in Table 2 and Figure 2. Effect of all the aqueous extract on mean Ulcer score and % inhibition were screened by using Water immersion stress induced ulcer in albino rats. The results are shown in Table 3 and Figure 3. In this model 400mg/kg body weight of WC has produced 96.34% ulcer inhibition when compared to that of standard (Omeperazole 20mg/kg body weight) that has produced 99.30% inhibition of ulcer. WC showed significant % ulcer inhibition in all the models.

DISCUSSION

Gastric ulcers arise due to net imbalances in mucosal offensive and defensive factors[15]. Ulcer therapy is now mainly focused on limiting the deleterious effects of offensive acid secretion. Newer drugs are aimed at protecting the gastric mucosa from damaging agents without influencing acid secretion or neutralizing intra gastric acidity. It is well known that the gastric mucosa can resist auto digestion although it is exposed to numerous noxious stimuli like aggressive secretions of hydrochloric acid, pepsin, reflex of bile, spicy food, microorganisms, formation of free radicals, stress, alcohol, 5-hydroxy tryptamine, substance P, slow releasing substance, irritant receptors and platelet activating factor.

Gastric ulcer is a break in the tissue lining of the stomach. Most ulcers can be cured without complications; however, in some cases peptic ulcers can develop, such as in penetration, perforation, bleeding (hemorrhage), and obstruction[16,17]. Ethanol and aspirin-induced gastric ulcer models have been widely used for the evaluation of gastroprotective activity. Acute treatment with ethanol increases oxidative stress, DNA damage, xanthine oxidase activity and malondialdehyde levels, and decreases the total glutathione content in gastric mucosal cells[18].

Aspirin-induced ulcer is mediated through tissue damaging free radicals which are produced from the conversion of hydroperoxyl to hydroxy fatty acids, which leads to cell destruction[19]. It has been found that oxygen-derived free radicals are implicated in the mechanism of acute and chronic ulceration in the gastric mucosa and scavenging these free radicals can play an appreciable role in healing the ulcer[20]. Before the introduction of potent antiulcerogenic agents, i.e., H_2 receptor antagonist, proton pump inhibitors, etc., plant remedies were widely employed for the treatment of various symptoms of peptic ulcer.

The genesis of ethanol-induced gastric lesions is multifactorial with the depletion of gastric wall mucous content as one of the involved factors. It is also associated with significant production of free radicals, leading to an increased oxidative stress and damage to the cell and cell membrane[21]. Aspirin causes a dose-dependent reduction in mucosal prostaglandin E_2 and prostaglandin I_2 biosynthesis accompanied by an increase in the mean of gastric ulceration. It is therefore reasonable to assume that the observed gastric mucosal lesion induced by aspirin is due to deficiency of mucosal prostaglandin[22].

Pylorus ligation induced ulcer is one of the most widely used methods for studying the effect of drugs on gastric secretion. Agents that decrease gastric acid secretion and/or increase mucus secretion are effective in preventing the ulcers induced by this method. The ligation of the pyloric end of the stomach causes accumulation of gastric acid in the stomach, leading to the development of ulcers in the stomach. The original Shay rat model involves fasting of rats for 72 h, followed by ligation of the pyloric end of the stomach for 19 h[23]. In the present study, the modification of Shay rat model described by Kulkarni was followed, which involves fasting of the animals for 36 h and pyloric ligation only for six hours[10]. Ranitidine significantly decreased the secretion of gastric aggressive factors, free acidity, total acidity and pepsin content, and increased the mucus secretion, which is cytoprotective.

Ethanol and HCl induced gastric ulcer were employed to study the cytoprotective effect of plant extract. It rapidly penetrates the gastric mucosa, causing cell and plasma membrane damage, leading to increased membrane permeability to sodium and water. It also produces massive intracellular accumulation of calcium, which represents a major step in the pathogenesis of gastric mucosal injury. This leads to cell death and exfoliation in the surface epithelium[24,25].

The pathophysiology of stress-induced ulcers is complex; the ulcers are produced due to the release of histamine, leading to an increase in acid secretion and a reduction in mucus production[26,27]. Stress also causes an increase in gastrointestinal motility, which causes folds in the gastrointestinal tract. The folds in the stomach are more susceptible to damage, when they come in contact with acid. The stress also brings the central nervous system into play. Agents that decrease G.I. motility, gastric secretion or those having central actions are helpful in reducing ulcers due to stress.

In the present study aspirin - pylorus ligation induced gastric ulcer was adopted to screen the antisecretory activity of plant extract. At a dose of 400mg/kg, the WC extract has produced similar ulcer inhibition comparable that of the standard drug ranitidine (50mg/kg body weight) which indicates that it is as effective as standard drug. Similarly the same dose was as effective to that of sucralfate (100mg/kg) in HCl - ethanol induced ulcer model which indicates that the extract is showing cytoprotective activity. Further this dose of WC was efficient as proton pump inhibitor comparable to that of omeperazole (20mg/kg) in water immersion stress induced ulcers. In all the three models WC has showed significant % ulcer inhibition. The glycosides which are present in the aqueous extract could be responsible for their antiulcer properties.

CONCLUSIONS

The present study confirms the antiulcer activity of WC as it produced significant antiulcer property by their antisecretory, cytoprotective and proton pump inhibitory properties. Further studies are needed to isolate the chemical moiety responsible for the antiulcer activity of this extract.

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