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Print & Online, Open Access, Research Journal Available on <http://jbsd.in>

ISSN: 2229-3469 (Print); ISSN: 2231-024X (Online)

Research Article



Cytoprotective effect of *Aloe vera* gel on Cysteamine induced Duodenal ulcer in aged Mice

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Article Info

Received: 04-08-2017,

Revised: 06-11-2017,

Accepted: 09-12-2017

Keywords:

Duodenal ulcer,
Cysteamine, *Aloe vera* ,
ulcer index, Protein

Abstract

Gastro duodenal ulcer is a common disorder of the gastrointestinal tract. The present study aimed to evaluate the effect of *Aloe vera* on Cysteamine induced duodenal ulcer in aged mice. Duodenal ulcer were induced in young and old age mice using Cysteamine-HCl (40mg/100gm B.W.). The cytoprotective effect of *Aloe vera* was assessed from the measurement of body weight, ulcer index and protein content of duodenum. A significant reduction in ulcer index, increased level of body weight and increased protein content was observed in ulcer induced mice treated with *Aloe vera* gel compared to ulcerated mice.

INTRODUCTION

Peptic ulcer is major gastrointestinal disorder caused by imbalance between offensive (gastric acid, pepsinogen secretion) and defensive (mucus secretion, gastric mucosal integrity) factors (Umamaheswari *et al.*, 2007 and Smith *et al.*, 2008). Mucosal erosion of duodenum, due to multiple causes including bacteria (Marshall and Warren, 1984; Lykoudes, 1958) chewing gum, tobacco smoking, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs), steroids food allergies, poor nutrition, chronic stress (Kin *et al.*, 2007) and gender differences (Anders *et al.*, 2008) leads to duodenal ulcer. Duodenal ulcer most common type of peptic ulcer and their sensitivity increases with age (Crstensen *et al.*, 2006; Bonnevie, 1975; Ostensen *et al.*, 1985).

Several anti-ulcerogenic drugs are available to cure the peptic ulcer (Asstin, 1998) but most of these synthetic drugs produce several side effects, adverse reactions and sometime may alter biochemical mechanism of the body by chronic usage (Ariyphisi *et al.*, 1986). While the medicinal plants phytoconstituents of has effective and relatively less toxic than the synthetic drugs.

Aloe vera has been used as popular folk medicine. The colorless mucilaginous gel of *Aloe vera* contains active phytoconstituents (Naveen and Someshekhar, 2013) such as vitamins, enzymes, minerals, sugars, lignin's, saponins, salicylic acids and amino acids. *Aloe vera* leaf parenchyma is used as remedy against a variety of skin disorders (Capasso and Ganginella, 1997). *Aloe vera* has anti-inflammatory properties, wound healing, mucus stimulatory, regulation of gastric secretion and antioxidant activities (Hart *et al.*, 1990, Lee *et al.*, 1999; Sabeh F *et al.*, 1993). The present study evaluates the anti-ulcer, cytoprotective and antioxidant activity of *Aloe vera* gel in cysteamine induced ulcer in aged mice.

MATERIALS AND METHODS

Preparation of *Aloe vera* gel: The fresh aloe vera leaves were washed thoroughly with water and pulp (containing mucilaginous gel) was removed. The gel was subjected to the dialysis in glycerol for 24 hour to remove the water. The extract was obtained, which was stored in refrigerator (4°C) till use.

Animals:

Healthy Swiss strain albino mice, *Mus musculus* were used for the present investigation.

The breeding pairs were obtained from (Appasaheb Birnale College of Pharmacy, Sangli). Young mice of 2 month age weighing 24 ± 2 gm body weight and old mice of 16 to 18 month age, weighing 40 ± 2 gm body weight were used for present investigation. All animals were reared in air-conditioned departmental animal house. They were received Amrut mice feed (Pranav Agro Industries, Pvt. Ltd, Sangli) and water *ad libitum*. Body weight of control group and experimental group were recorded time to time.

Experimental Groups:

Mice were divided into three groups containing six animals in each groups:

Control group: The young and old mice were given oral administration of 0.5 ml distilled water/ day/ animal for 15 days.

Duodenal ulcer induced group: The young and old mice was given subcutaneous injection of cysteamine HCl (40mg/100gm/BW) dissolved in 0.5 ml distilled water (Szabo, 1978).

Aloe vera gel protective group: Both duodenal ulcer induced male and female mice were given oral administration of *Aloe vera* gel 300 mg/kg dissolved in distilled water/ day/ animal for 15 days (Rajasekaran S, *et al.*, 2005).

After completion of the treatment control, cysteamine HCl administered and *Aloe vera* gel treated animals were weighed and sacrificed by cervical dislocation. The pyroduodenal junctions were dissected out and cut the duodenum blotted and weighted on electronic balance and were proceed for gross morphological observation ulcer index (Szabo, 1978) and protein estimation (Lowry *et al.*, 1958).

Statistical analysis

All values are expressed as mean \pm S.D. The statistical analysis was performed using student's t 'test. A value of $P < 0.001$ was considered statistically highly significant.

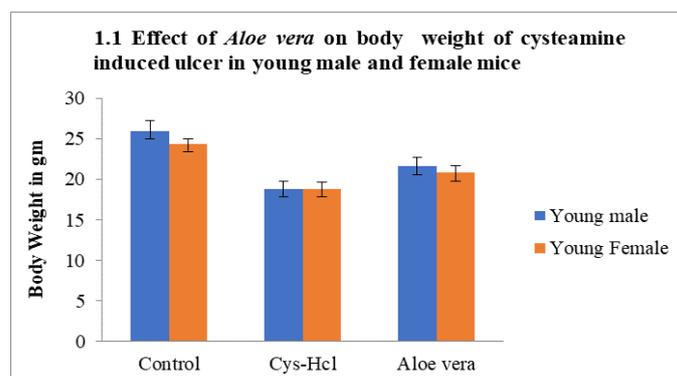
RESULTS AND DISCUSSION

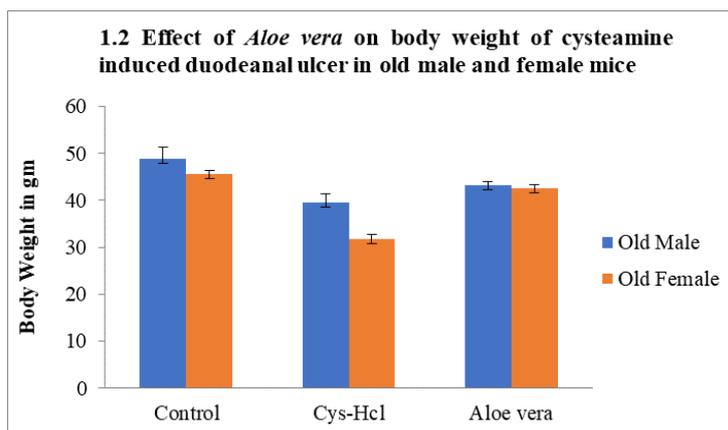
The graph (1.1 and 1.2) shows the body weight of mice from control, duodenal ulcerated and *Aloe vera* treated group.

The body weight of control young male and female mice was 26 ± 0.547 and 24.4 ± 0.547 respectively. Which was reduced to 18.8 ± 0.938 and 18.8 ± 0.873 respectively in cysteamine induced duodenal ulcer in young mice. The reduction in the body weight in cysteamine induced ulcer in mice was highly significant as compared to body weight of control group mice (1:2, $P < 0.001$). Mice receiving *Aloe vera* gel along with cys-HCl were having body weight 21.6 ± 1.140 and 20.8 ± 0.901 . The increase in the body weight of *Aloe vera* treated both young male and female mice was highly significant as compared to cysteamine induced ulcerated mice (2:3, $P < 0.001$).

The body weight of control old male and female mice was 48.9 ± 2.449 and 45.6 ± 0.680 respectively. Which was reduced to 39.6 ± 1.673 and 39.5 ± 1.000 respectively in cysteamine induced duodenal ulcer in old mice. The reduction in the body weight in cysteamine induced ulcer in mice was highly significant as compared to body weight of control group mice (1:2, $P < 0.001$). Mice receiving *aloe vera* gel along with cys-HCl were having body weight 43.2 ± 0.836 and 42.6 ± 0.818 . The increase in the body weight of *Aloe vera* treated both old male and female mice was highly significant as compared to cysteamine induced ulcerated mice (2:3, $P < 0.001$).

Graphical representation shows significant change in body weight after administration of Cysteamine HCl with respect to all control groups. There is no any significant difference between body weight of male and female mice. The control group of mice had greater body mass than Cysteamine-HCl administered. Cysteamine-HCl administration decreases the body weight but which increased by the treatment of *Aloe vera* gel.





2. Determination of Ulcer Index:

The results of the effect of *Aloe vera* gel have significantly reduced the ulcer index (Table No.1, 2, 3,4). Ulcer index was severe in the old age than

young mice . Maximum inhibition of ulcer index was observed in the animals treated with *Aloe vera* gel.

Table No.2.1 Effect of *Aloe vera* gel on ulcer index of cysteamine induced duodenal ulcer in young male mice.

Group	Experimental Mice	Ulcer in Percentage					
		%	Superficial	Deep	Perforated	Mean severity	Ulcer index
Young male mice	Young mice with Cysteamine-HCl	100	08	64	23	3.10	5.00
	Young mice with Cysteamine-HCl+ <i>Aloe vera</i> gel	100	20	50	20	2.9	4.08

Table No.2.2 Effect of *Aloe vera* gel on ulcer index of cysteamine induced duodenal ulcer in young female mice.

Group	Experimental Mice	Ulcer in Percentage					
		%	Superficial	Deep	Perforated	Mean severity	Ulcer index
Young female mice	Young mice with Cysteamine-HCl	100	08	64	23	3.10	5.00
	Young mice with Cysteamine-HCl + <i>Aloe vera</i> gel	100	32	48	20	2.9	4.66

Table No.2.3 Effect of *Aloe vera* gel on ulcer index of cysteamine induced duodenal ulcer in old male mice.

Group	Experimental Mice	Ulcer in Percentage					
		%	Superficial	Deep	Perforated	Mean severity	Ulcer index
Old male mice	Old mice with Cysteamine-HCl	100	08	74	18	3.33	5.3
	Old mice with Cysteamine-HCl+ <i>Aloe vera</i> gel	100	25	67	08	3.0	4.8

Table No. 2.4. Effect of *Aloe vera* gel on Ulcer index of Cysteamine induced duodenal ulcer in old female mice.

Group	Experimental Mice	Ulcer in Percentage					
		%	Superficial	Deep	Perforated	Mean severity	Ulcer index
Old Female mice	Adult mice with Cysteamine-HCl	100	10	70	20	3.1	6.2
	Adult mice with Cysteamine-HCl + <i>Aloe vera</i> gel	100	14	70	16	3.2	5.14

Animal treated with *Aloe vera* gel showed few signs of mucosal injury and percentage of damage as compared to groups treated with cysteamine. Old mice injected with the Cyste-amine showed higher ulceration as compared to young ulcerated mice, while treated with *Aloe vera* gel ulceration is slow and animal becomes recovered. These changes significantly reduced in ulcer treated with *Aloe vera* gel.

III) Determination of Protein content

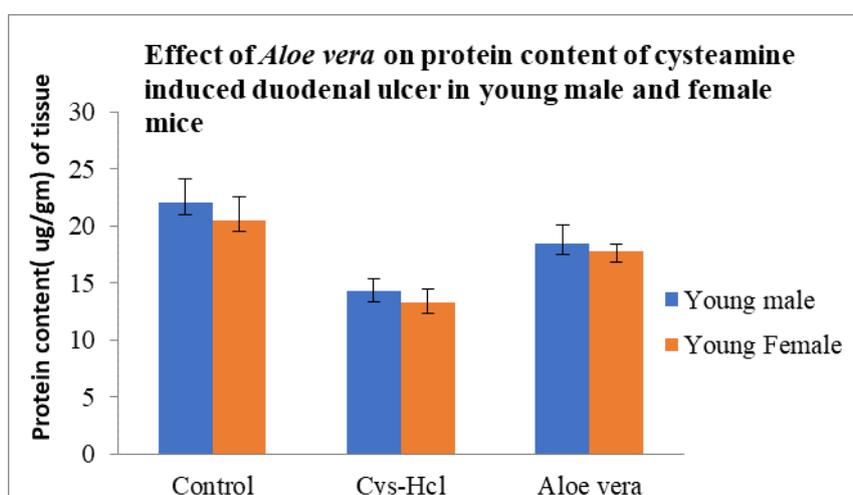
The graphs (3.1 and 3.2) shows the protein content of mice from control, duodenal ulcerated and *Aloe vera* treated group.

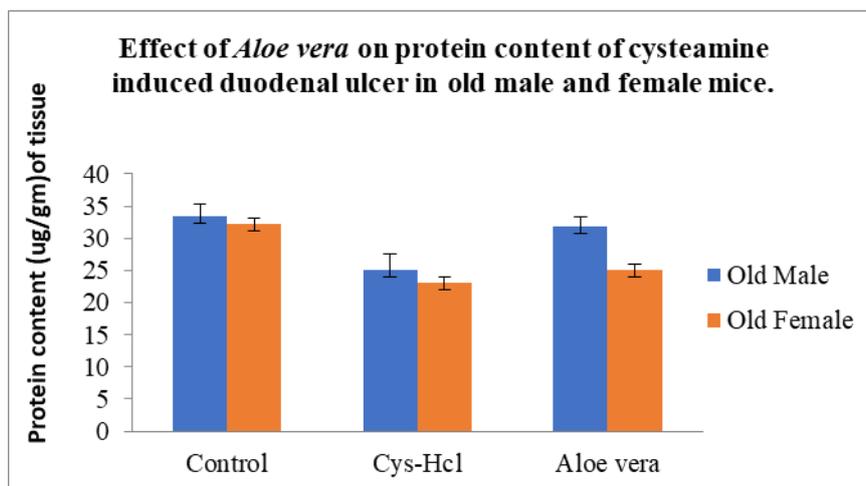
The protein content of control young male and female mice was 22 ± 2.092 and 20.50 ± 2.092 ug/gm of tissue respectively, where as it was reduced to 14.30 ± 1.095 and 13.30 ± 1.151 ug/gm of tissue in cysteamine induced duodenal ulcer group (1:2, $P < 0.001$). After the treatment of *Aloe*

vera gel protein content was increased upto 18.50 ± 1.571 and 17.80 ± 0.570 ug/gm of tissue (2:3, $P < 0.01$). The increase in the protein content in duodenum of *Aloe vera* treated both male and female mice was highly significant as compared to cysteamine induced ulcerated mice.

The protein content of control old male and female mice was 33.40 ± 1.973 and 32.15 ± 0.6519 ug/gm of tissue respectively. Where it was reduced to 25.00 ± 2.500 and 23.00 ± 2.0917 ug/gm of tissue in cysteamine induced duodenal ulcer group (1:2, $P < 0.001$). After the treatment of *Aloe vera* gel protein content increased upto 31.8 ± 1.483 and 25.00 ± 2.5000 ug/gm of tissue (2:3, $P < 0.001$). The increase in the protein content in duodenum of *Aloe vera* treated both old male and female mice was highly significant as compared to cysteamine induced ulcerated mice.

The content was found to be almost equal in both male and female mice.





Animal treated with *Aloe vera* gel showed few signs of mucosal injury and percentage of damage was less as compared to duodenal ulcerated group. The ulcer index was markedly reduced in comparison to control group. The analysis of chemical composition of *Aloe vera* revealed the presence of various active phytoconstituents, anthraquinones including aloein, Aloe-emodin, organic acid, polyphenols, vitamins, salicylic acid, aldehydes, indole, alkaloids, fatty acids, laxative which readily accounts for the medicinal value of *Aloe vera* in many organism (Hamman, 2008; Josephs and Raj, 2010). When old mice injected with the Cyste-amine showed higher ulcer severity as compared to young mice, while all groups animals treated with *Aloe vera* gel showed complete recovery as compared to duodenal ulcerated group. These changes significantly reduced in ulcer induced animal treated with *Aloe vera* gel.

The ulcerogenic effect of cysteamine is both rapid and constant (Szabo *et al.*, 1977 and Pascaud *et al.*, 1993). The possible mechanism of duodenal ulcerogenesis includes hypersecretion of gastric acid, deterioration of mucosal resistance and promotion of gastric emptying (Szabo *et al.*, 1979 and Briden S *et al.*, 1985). In the present work, mice administered with Cys-HCl showed highly significant decrease in body weight and less weight gain than the control group throughout the experiment periods, and this reduction may be due to the reduction of food utilization (Grant and Butler, 1989) or may also be due to increased level of stress in the body leading to increased catabolic process in the body. Body weight drops due to a reduction in the food consumption and absorption (Trentacoste *et al.*, 2001).

In general cysteamine administration induces the disturbances in hormonal balance cytotoxicity and stress, that restraint stress suppresses food intake and body weight gain in rodents and animal models. But controversial, mice treated with *Aloe vera* gel showed increase in body weight and phytoconstituents of *aloe vera* overcome stressed condition by its antioxidant property, which improves duodenal functions. Several hypotheses have been given for the mechanism of cytoprotection, namely increased mucus synthesis, increased mucosal blood flow and increased phospholipid content of the mucosal lining (Yusuf *et al.*, 2004). Therefore, one potential explanation of these data is that older, lighter animals may be generally less healthy, manifesting in lowered body weight which is recovered by treatment of *aloe vera* gel.

The *aloe vera* gel possess gastroprotective activity as evidenced by its significant inhibition in the formation of ulcers induced by cysteamine. Experimental duodenal ulcer assessed on the basis of number of mucosal lesions. In the present study a significant increase in the number of lesions in duodenal mucosa observed in old aged cysteamine HCl administered mice compared with young and adult cysteamine HCl administered. The treatment of *aloe vera* resulted in the significantly reduction in the number of lesions in the duodenal mucosa of group III mice as compared to group II mice indicating the protective effect of *Aloe vera*. Accordance with an earlier reports showed that cysteamine-HCl, impaired mucosal integrity leads to stress, such stress induced lesion formation may be multifactorial with status of gastric flow contributing significantly to the hemorrhagic as well as the necrotic aspects of the tissue injury.

It may be occurred by the neutralization of HCl excessively secreted into duodenum. Raise in the rate of acid in the ulcerated mice might be a consequence of enhanced permeability the mucosa important step in the development of ulcer. The present study investigated the effect of *Aloe vera* on cysteamine induced duodenal ulcer healing by assessing an ulcer index and an ulcer area. These parameter former indicates the ulcer area while the later gives idea about the morphology of the ulcerated area. *Aloe vera* extract inhibits acid secretion may be due to the presence of lectins in the plants have the ability of direct action on the acid producing cells (Takeuchi *et al.*, 1987). Neutralization or inhibition of an acid secretion into stomach as well as in duodenum accelerates the ulcer healing.

The decrease in protein level was due to trap of protein from the alimentary tract or due to mucosal necrosis as a result of Cysteamine administration to albino rats (Said *et al.*, 1992). Thus it's interpreted that the protein reduction is due to physiological acclimation of the mice to overcome stress situation using protein catabolism to supply high energy demand. Such hypoproteinemia may be due to direct effect of the utilization of body protein as an energy supply to meet the increasing physiological demands to overcome the stress. Ethanol induced damage the gastric mucus by the mechanical injury (Pratyusha S. *et al.*, 2012) leads to increased total protein and carbohydrate level initially later on decreased during ulcerogenesis. *Aloe vera* juice and *Amala* fruit juice enhance the gastric mucosal offensive factor and protect the gastric mucosa from necrotizing substances (Kelly Samara de Lira Mota *et al.*, 2009).

In our study the level of protein was decreased in the Group II (Cysteamine administered) animal as compared to that of control animal. This exhibited that Cys-HCl acute stress caused the erosion of duodenal mucosal cells. The net effect would be the accumulation of losted protein. The oral administration of *Aloe vera* reduces the Cys-HCl stress induces disruption of mucosa and mucosal erosion of protein the of Group III (*Aloe vera* treated) mice. An *aloe vera* may increase the level of protein content this indicates that the *aloe vera* heal the ulcer erosion due to flavonoids protects the stomach of rat from peptic ulcer occurred by oxidative stress (Roa *et al.*, 2003). Flavonoids have been reported as antiulcer agent (Lewis *et al.*, 1999; Mohan Kumar M, *et al.*, 2006;

and Moury *et al.*, 2012). Therefore protection from ulcer and enhanced level of protein due to *aloe vera* treatment afforded by disintegration of protein and carbohydrates from tissues was prevented and the dissolution of protein in the duodenum reduced. *Aloe vera* gel were shown to be as efficacious as sucralfate on acetic gastric ulcer and induced healing (Mahattanadul, 1995). The findings suggested that *Aloe vera* gel exerts an Anti-duodenal ulcer action by directly protecting the gastric and duodenal mucosa and by exerting cytoprotective activity resulting in an enhancement of local healing process.

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How to cite this article

Tate A. B. and Bodare R. D., 2018. Cytoprotective effect of *Aloe vera* gel on Cysteamine induced Duodenal ulcer in aged mice. *Bioscience Discovery*, 9(1): 59-65.