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THE EFFECT OF ANTIULCER ACTIVITY ON RAUWOLFIA SERPENTINE (ROOT)

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Abstract:
The aim of the study was to evaluate the effect of antiulcer activity on rauwolfia serpentine (root). Material and ***Method:*** *ulcer was induced by aspirin induced model in Wister albino mice. The experimental animals were divided into four groups and received subsequent treatment. Aspirin was induced 500mg/kg b.w. in 3 days by oral dose. Group 1 (control group) received normal saline 10ml/kg body weight for 5 days, group 2(test group) received low dose of rauwolfia serpentine 30mg/kg body weight for 5 days, group 3(test group) received higher dose of rauwolfia serpentine110mg/kg b.w. for 5 days and group 4 (standard group) received pantoprazole 40mg/kg b.w for 3 days. After completion of dose mice were sacrificed by cervical dislocation and stomach were cut from lesser curvature and everted. Result: - The extract of Rauwolfia serpentine (root) is show significant effect on ulcer induced by aspirin induced model. It is an effective antiulcer agent and increase ulcer protection by regeneration of mucosal layer. Rauwolfia Serpentine exhibited protection against characteristics lesion produced by aspirin administration. It is exhibited anti-inflammatory and antiulcerogenic activity.*

Keywords: *Peptic ulcer, Rauwolfia Serpentine, Aspirin induced ulcer model, Estimation of mucin, Pathophysiology.*

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INTRODUCTION:

The most common cause of stomach ulcer is a bacterium called *Helicobacter pylori*. Similarly ulcer may cause by over use of pain killers, such as aspirin and non-steroidal anti-inflammatory such as ibuprofen, naproxen etc.A peptic ulcer is essentially is a wound that affects the mucous membrane of the digestive tract. Different names are given to ulcers depending on where they are located (gastric ulcers are located in the lining of the stomach, duodenal ulcers are located in the duodenal). Many times in clinical practice we see a lack of digestive enzymes to be the root cause of the ulcer a lack of enzymes can create an imbalanced environment leading to a growth of *H.pylori* which can infect the mucous membrane. [5]

Peptic ulcer is the most common gastrointestinary disorder in clinical practice. Peptic ulcer occurs due to an imbalance between the aggressive (acid, pepsin and *Helicobacter pylori*) and the defensive (gastric mucus and bicarbonate secretion, prostaglandins, innate resistance of the mucosal cells) factors. Although a number of antiulcer drugs such as H2 receptor antagonists, proton pump inhibitors and cytoprotectants are available for ulceration all these drugs have various undesirable effects such as arrhythmias, impotence and hematopoietic changes and limitations. There are many agents in alternative medicine, which have shown promising antiulcer activity without producing above mentioned adverse reaction. The antiulcerogenic activity of many plant products is reported due to an increase in mucosal defensive factors rather than decrease in the offensive factors. [18] Peptic ulcer is one of the world's major gastrointestinal disorders and affecting. [5]

Peptic ulcer

Peptic ulcer is the most common gastrointestinal disorder in clinical practice.[18] Peptic ulcer occurs due to an imbalance between the aggressive (acid, pepsin and Helicobacter pylori) and the defensive (gastric mucus and bicarbonate secretion, prostaglandins, innate resistance of the mucosal cells) factors. Peptic ulcer disease (PUD), which includes gastric and duodenal ulcers, is the most common gastrointestinal problem and demands a well targeted therapeutic strategy. The most common sites for ulcers are the stomach and the first few centimeters of the duodenum. Peptic ulcer causes break off in the continuity of the mucosa of stomach or duodenum as a consequence of some medications like non-steroidal anti-inflammatory drugs (NSAIDS), gastric acids and pepsin, finally causing lesions[17] .Chronic peptic ulcers penetrate through the epithelial and muscle layers of the stomach wall. There are several symptoms of ulcer like changes in appetite, nausea, bloody or dark stools, weight loss, indigestion, vomiting, and chest pain. Complications of peptic ulcers include haemorrhage, perforation, pyloric stenosis and the development of malignant tumors. Poor digestion and elimination, improper metabolism, mental and physical stress, and difficult to digest food enhance the development of ulcers. [17]

Peptic ulcers are defects in the gastrointestinal mucosa that extend through the muscularis mucosae and they persist as a function of the acid or peptic activity in gastric juice. Peptic ulcer disease (PUD) is an important cause of morbidity, and health care costs estimate of expenditures related to work loss, hospitalization, and outpatient care (excluding medication costs) are $5.65 billion per year in the United States. [19]

Signs and symptoms:

Here in peptic ulcer diseases patients can be asympomatic or experience anorexia, nausea, vomiting, bleaching and blotting and heart burn or epigastric pain. [15]

Sinn and symptoms of peptic ulcer may include one of the following : epigastric pain (strongly correlated to mealtimes), gastroesophageal reflux, dyspepsia, and melena (presence of blood in the stool). The two most common types of indigestions are peptic ulcer disease (PUD) and nonulcer dyspepsia (NUD). NUD is aprevalent disease in several countries such as Iran. Medication therapy is an effective treatment for peptic ulcer and usually combination of drugs is required for the ultimate effect. Patients should beable to tolerate medications and adhere to the prescribed regimen.Diagonosis test fo H. pylori couldbe noninvasive methods such as stool antigen test and blood antigen test. However, the most accurate methods to detect H. pylori are invasive approaches that require histological examination after endoscopic biopsy as well as rapid urease test and microbial culture. [14]

Risk Factors

Common risk factors causes for PUD and gastritis include infection with *H.pylori*,and NSAIDs.Less common risk factors include alcohol ,smoking, cocaine, severe illness, autoimmune problems, radiation therapy and Crohn disease among others. [9]
Use of painkillers called nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, naproxen (Aleve, Anaprox, Naprosyn, and others), ibuprofen (Motrin, Advil, some types of Midol, and others), and many others available by prescription;

even safety-coated aspirin and aspirin in powered form can frequently cause ulcers.
• Excess acid production from gastrinomas, tumors of the acid producing cells of the stomach that increases acid output
• Excessive drinking of alcohol
• Smoking or chewing tobacco
• Serious illness
• Radiation treatment to the area[13]

Causes of Peptic Ulcer Disease
Common

- *H. pylori* infection
- NSAIDs
- Medications

Rare

- Zollinger-Ellison syndrome
- Malignancy (gastric/lung cancer, lymphomas)
- Stress (Acute illness, burns, head injury)
- Viral infection
- Vascular insufficiency
- Radiation therapy
- Crohn disease
- Chemotherapy

Plant description
India features a wealthy heritage of Ayurvedic Medicines and currently rush in require for plant-based drugs. Plants have showed a important role in mannaging Human health and improving human life. Rauwolfia Serpentina (Linn.) is a Medicinal Shrub or Herb from Apocynaceae family. Rauwolfia Serpentineone of well - known Antipsychotic and Tranquilizer Herb of India for Schizophrenia and Paranoia treatment as well as also control Hypertension and high blood pressure. Rauwolfia serpentine generally called 'snake root' or Sarapgandha called "Wonder drug of India". Sarapgandha has been more than few years ago that drugs of plan origin are using to cure of the diseases in Man & Animals.[2]

Scientific Classification
Kingdom: plantae
Phylum: Angiosperms
Subphylum: Eudicots
Class: Asteroids
Order: Gentianales
Family: Apocynaceae
Genus: Rauwolfia
Species: serpentine [3]

Chemical Composition
Rauwolfia contains many different Phytochemicals, Including Alcohols, Sugars, Glycosides, Fatty Acids, Flavonoids, Phytosterols, Oleoresins, Steroids, Tannins, and Alkaloids. The most important Alkaloids found within the plant are indole Alkaloids, with quite 50 of these Alkaloids having been isolated in the plant. Indole alkaloids are a gaggle of nitrogenous compounds that are derived from the aminoalkanoic acid tryptophan.[8]

In modern life science, its active constituent is employed effectively as commercial drugs. It is one of the essential compounds; It is used for the treatment of high blood sugar,[7] treatment of various CNS disorders associated with psychosis, schizophrenia, insanity, insomnia, and Epilepsy,[9] Reserpine, the principal alkaloid of Rauwolfia serpentinais traditionally used for the treatment of hypertension, sexual aggression and vertigo,[11] Due to the presence of Alseroxylon alkaloid (fat soluble, extracted from roots), it is known to cure many circulatory disorders.The root extract or decoction extracts is known to treat and relieves the abdomen, liver pain, and gastrointestinal disorders. The leaves, flower buds, and roots are dried and crushed into milk, and the crude paste is used externally on affected areas to treat burns, body aches, eczema, and scabies.[8]

Mineral composition
Rauwolfia is additionally known to contain an outsized number of macro and micro-nutrients and therefore the most abundant macro nutrient is calcium. The potential of R. serpentina to prevent bleeding and its use in treating wounds are often thanks to its high calcium content, because it helps in blood clotting . R. serpentina contains low sodium content which will be another advantage thanks to the direct relationship of sodium intake with hypertension in human. The presence of zinc shows that plant can play valuable roles within the management of diabetes, which result from insulin malfunction. The plant R. serpentina is additionally a superb source of ascorbic acids, riboflavin, thiamin and niacin. Ascorbic acid is vital for body performance as it plays an important role in normal wound healing, and lack of it impairs the normal formation of intercellular substances throughout the body (including collagen, bone matrix and tooth dentine).[4]

Material
Plant Material :- Root of *Rauwolfia serpentine* were purchased from Akhand Aushdhi bhandar Indore and authentify by department of botany Janata PG college A.P.S. university Rewa,M.P.

Animals
The Wister albino mice (20 - 30g) were taken from the animal house of swami vivekanand college of pharmacy,Indore (M.P.) and kept according to the international guidelines of animal handling by placing them individually in cages under temperature (23±20°C) with free access to water ad libitum and fed standard diet.[1] Institutional Animals Ethics Committee (IAEC) approved the experimental protocol and care of animals was taken as per guidelines of CPCSEA, Department of Animal Welfare and Government of India.[12]

Drug and Chemicals
Aspirin (USV), Pantaprazole
Method
Procedure for Extraction:- 40 grams of ground powder of root of rauwolfia serpentina was extracted with 360 ml of distilled water for 15-18 hrs by soaking method and filtered through Whatman no. 1 filter paper. The filtrate was evaporated by heating mental at 100 for 10 min till filtrate was remaining 10⁄ of volume then evaporate on water
bath at 100°C for 5 min.

Phytochemical testing-
1) Tests for Alkaloids: - 1 ml of extract was taken and added 1 ml hydrocholoric acid, to this few drops of Wagner's reagent was added.. A brown precipitate was found that indicated the presence of alkaloids.

2) Test for Anthraquinones:- To 1 ml extract, added FeCl3 (1 ml) and concentrated HCl (0.5ml) were added. Boiled during a water bath for 3 min , filtered it and the filtrate was treated with ether and concentrated ammonia. Pink colour was not found.

3) Tests for Carbohydrates (Fehling's Test) :- 2 mg extract was taken shaken with water (10 ml), then Fehling's solution A and B (1ml) were added and boiled , red colour precipitate was found which indicated the presence of the sugar.

4) Test for Cardiac Glycosides (Keller-Killani Test) :- 5 ml extract was taken and added glacial acetic acid (2 ml) mixed with two drops of ferric chloride solution. Then concentrated sulphuric acid (1ml) was added. A brown ring was observed that indicated presence of cardiac glycoside.

5) Test for Resins: - 1 ml extract was dissolved in acetone (1 ml), and added distilled water (2 ml). Turbidity was found that indicated the presence of resins.

6) Test for Flavonoids (Alkaline Reagent Test) :- 1 ml extract was treated with 3-5 drops of 20% sodium hydroxide solution. Observed formation of yellow colour, indicated the presence of flavonoids.

7) Test for Saponins (Foam Test) :- 1 ml extract was shaken with 2 ml of water. Foam was observed that indicated the presence of saponins **.**

8) Test for Phenols (Ferric Chloride Test) :- 1 ml of extract was taken and 5-6 drops of aqueous FeCl3 was added. The blue colour was found that indicated the presence of phenols.

9) Test for Tannins: - 1 ml of extract was taken and added 1 ml of ferric chloride. The light green colour was found that indicated the presence of tannins.

Experimental design
The experimental animals were divided into the following groups and received the subsequent treatments accordingly. [49]
Group 1(control) – Normal saline (10 ml/kg) orally for 5 days
Group 2(test) – Extract (30 mg/kg) orally for 5 days
Group 3(test) – Extract (110mg/kg) orally for 5 days
Group 4(standard) – Pantaprazole (40 mg/kg) i.p. for 3 days

Fig.3. Administration of Pantoprazole i.p.

Induction of gastric ulcer (aspirin induced ulcer model)

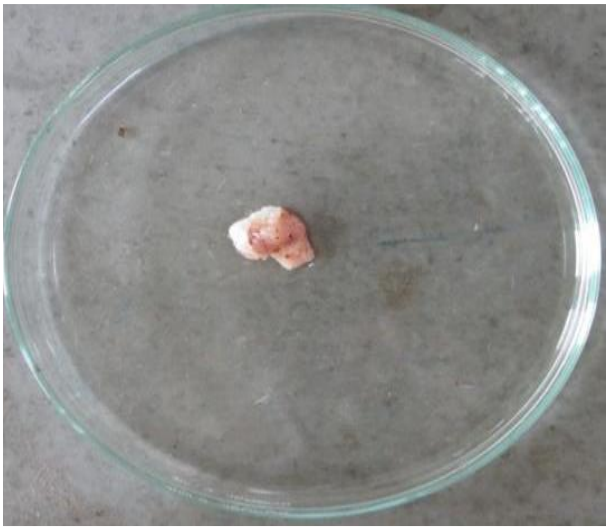
Mice were has kept in metabolic cages with raised floors of broad mesh to avoid coprophagy, which affects the entrance of peptic ulceration. The animals were lent for 36 h to empty the stomach of food and increase the gastric acid level, thereby facilitating gastric injury upon aspirin administration. One hour before the experiments, water was also withheld. Gastric mucosal injury was induced by a oral dose of acetyl salicylic acid (500 mg/kg body weight) in 3 days.

The animals were sacrificed after dose completion by use of anesthesia and the stomach was then excised and cut along the greater curvature, rinsed gently with saline to get rid of the gastric contents and blood clots. Ulcer index was then calculated by adding the total number of ulcers and calculate ulcer index.[51]

Method of gastric fluid collection:
• Mice was oblation and dissected.
• Pylorus portion was tied care of a thread.
• Stomach was isolated , pylorus portion was cut.
• A syringe crammed with water was skilled oesophagous and gastric fluid oozed out from pyloric section.

Determination of gastric pH
After the collection of digestive juice from stomach in tube. Add 1-2 drops phenolphthalein indicator. And titrate with 0.01 N NaoH. Titrate the answer until the color changes from purple to colourless.
Note the volume of NaoH consume from the burette.
Acidity= Volume of NaoH × Normality of NaoH ×100 mEq/lit/100 g /0.1

Estimation of mucin
Mucin estimation was performed using Alcian Blue method. Briefly, digestive juice specimen were taken in test tubes and diluted with water . Then 1% solution of Alcian blue in 50mm sodium acetate buffer was pair and was incubated at temperature under continuous anxiety for 30min. After incubation, specimen were centrifuged for 20min at 3000 rpm. Then one ml of 95% ethanol was added and vortexed for 10sec. After 5min, the specimen were centrifuged for 20min at 3000 rpm. Then Aerosol OT (1:2 dilutions with distilled water) was added followed by addition of equal quantity of ether under emphatic shaking. The specimen were centrifuged for 15min at 3000 rpm then the optical density was gauge at 605nm. Concentration of mucin was then enumeration from the quality graph.



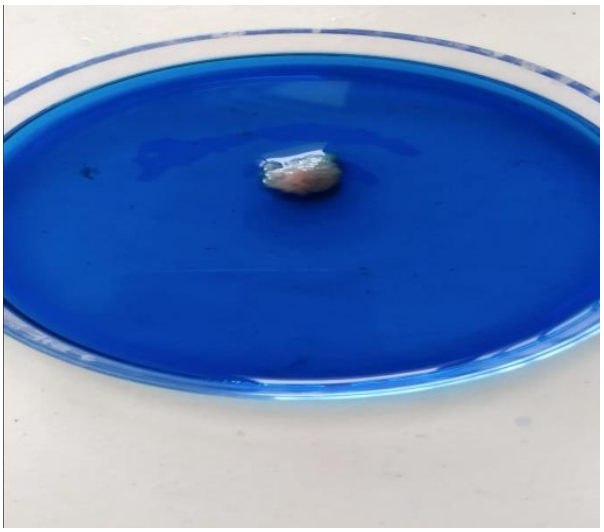


Fig 4. 1) Everted stomach for estimation of mucin **2) Everted stomach dipped in alcian Blue for estimation of mucin.**

Histopathology analysis
Histological studies were performed by taking a small piece of tissue, including ulcers, were embedded in paraffin and sectioned at 5µm in an automated microtome. Haematoxylin and eosin staining was done and tissue was observer under microscope.

RESULT:

Rauwolfia serpentine are well known herbal plant with its various medicinal uses and dietary supplement.It contain various types of chemical constituents those are useful in the treatment of various diseases and formulation in various herbal drugs. The result phytochemical screening of *Rauwolfia serpentine* root extract shown in table 1.In table 2 shown result of aspirin induced ulcer in mice with standard drug and test dose of *Rauwolfia serpentine*.

Table 1. Phytochemical analysis of *Rauwolfia Sepentina*

Phytochemical constituents	**Qualitative analysis**
Alkaloids	Positive
Carbohydrates	Positive
Resin	Positive
Cardiac glycoside	Positive
Flavonoids	Positive
Tannins	Positive
Saponins	Positive
Phenol	Positive
Anthraquinone	Negative

Table 2. Aspirin induced ulcer in mice

S.No.	**Treatmet**	**Red coloration (0.5)**	**Spots (1)**	**Streaks (1)**	**Hemorrahage (0.5)**	**Perforation (5)**	**Ulcer index**
1.	**Control group**						
a.	1st animal	3	2	2	2	1	11.5
b.	2nd animal	2	1	2	2	2	15.0
c.	3rd animal	2	3	3	1	1	12.5
d.	4th animal	1	2	0	1	2	13.0
e.	5th animal	1	0	1	2	2	12.5
		Average Ulcer Index					12.9
2.	**Standard group**						
a.	1st animal	0	0	0	0	0	0
b.	2nd animal	0	0	0	0	0	0
c.	3rd animal	0	0	0	0	0	0
d.	4th animal	0	0	0	0	0	0
e.	5th animal	1	0	0	0	0	0.5
		Average Ulcer Index					0.04
3.	**Test group**						
3.1	**Lowdose**						
a.	1st animal	2	1	2	1	1	9.5

b.	2nd animal	2	1	2	3	1	10.5
c.	3rd animal	1	2	0	2	2	13.5
d.	4th animal	3	2	2	1	1	11.0
e.	5th animal	2	2	1	0	1	9.0
		Average Ulcer Index					10.7
3.2	**Highdose**						
a.	1st animal	1	2	0	0	0	2.5
b.	2nd animal	2	0	1	1	0	2.5
c.	3rd animal	0	0	1	2	0	2.0
d.	4th animal	1	0	0	0	1	5.5
e.	5th animal	2	0	1	2	0	3.0
		Average Ulcer Index					3.1

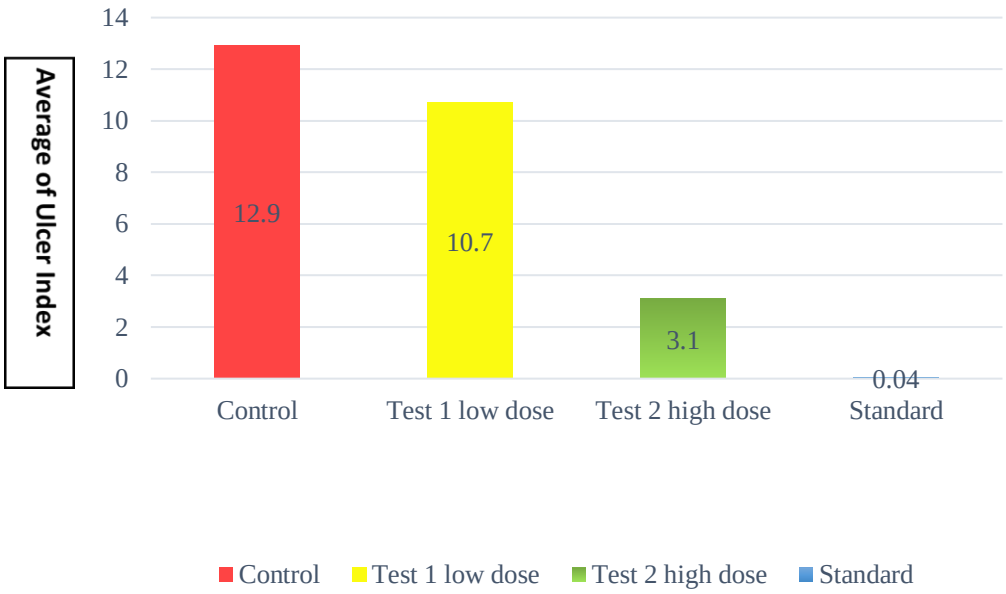


Fig.1 Graph Average of Ulcer Index

Table 3. Estimation of mucin

Group	Treatment	No of animal used	Dose	Mean ± SD
1.	control	5	10ml/kg	528±5.338
2.	Low dose	5	30mg/kg	543±3.708
3.	High dose	5	110mg/kg	579±8.717
4.	Standard	5	40mg/kg	600±1.322

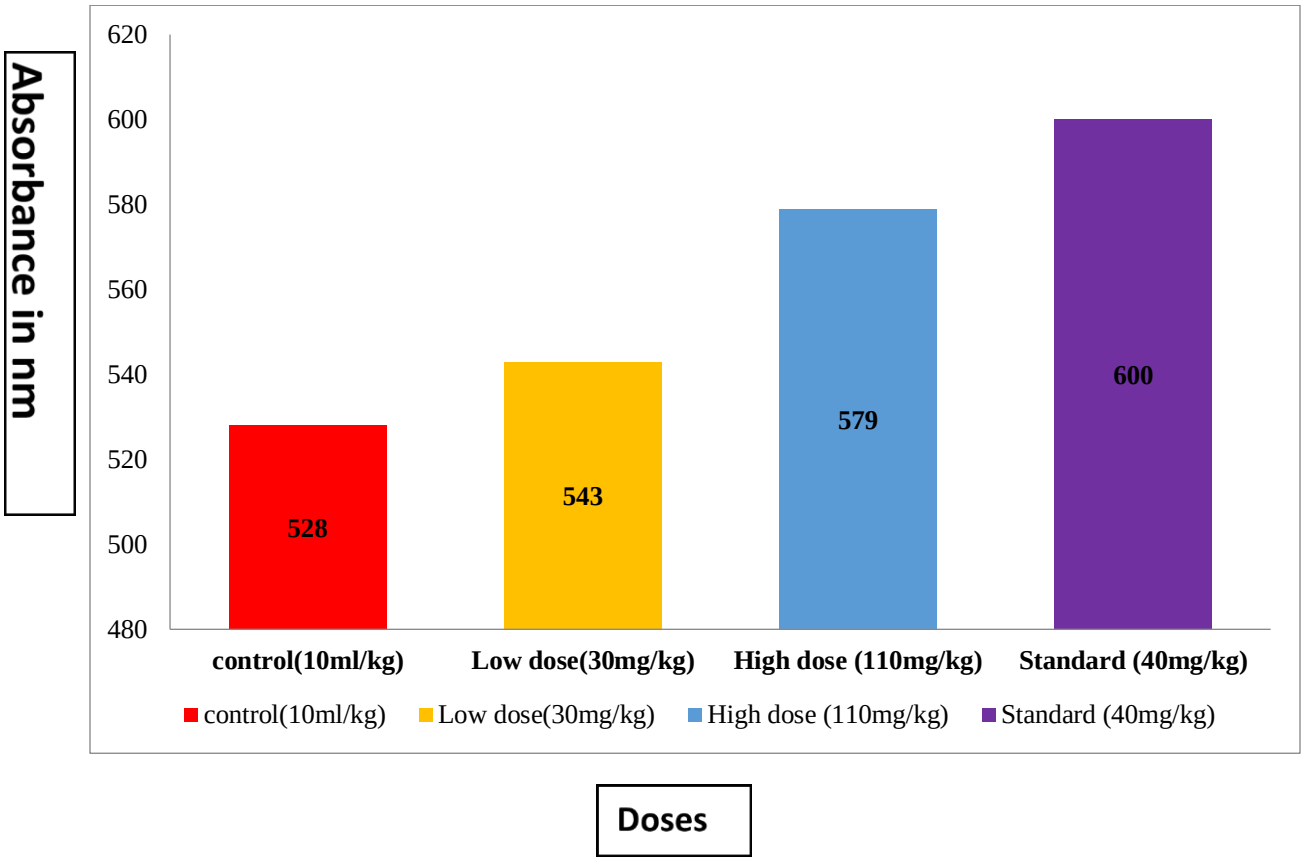


Fig.2 Graph Estimation of mucin

Histopathology

Effect of *Rauwolfia serpentine* extract administration on the histopathology

The results of haematoxylin and eosin staining are shown in fig. The control mice exhibited marked mucosal damage. The mucosal lining appears to be completely eroded in the lesion area. *Rauwolfia serpentine* extract administration appears to have preserved the intestinal preserved. Photomicrographs of representative tissue section are shown in.

Control group

Figure 2 shows normal mucosal tissue in which the intestine was cut and then placed in formalin solution (10%) which when examined through microscope showed more ulcer. Histopathological analysis showed beginning of necrosis, sloughing manifested as shortning of villi with infiltration of inflammation cell in mucosa at 10x.

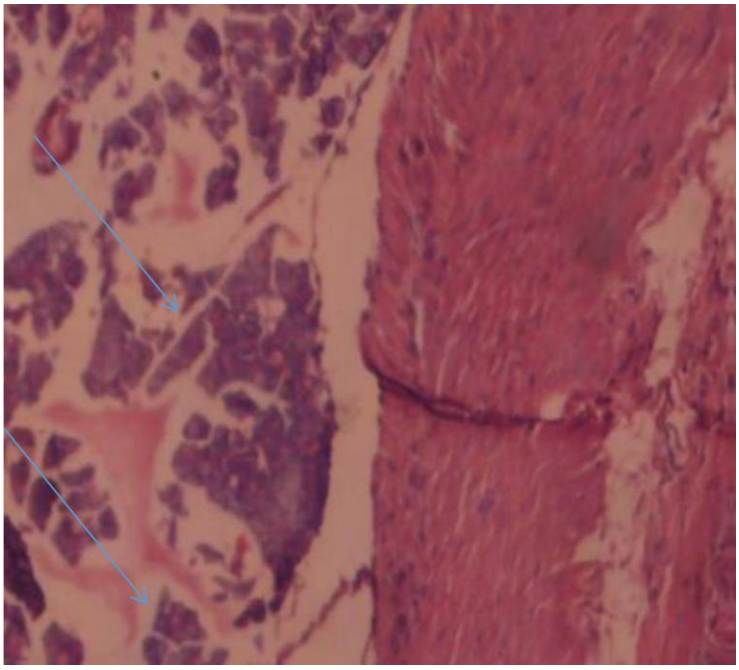


Fig 1 Photograph (Histopathology) of duodenum of the mice of control group.

A) Histologic section (10x) acute ulcer shows beginning of necrosis, sloughing manifested as shortning of villi with infiltration of inflammation cell in mucosa.

Low dose Of *R. Serpentine*

Fig 2 shows test group section in which effect of *R.serpentine* of low dose (30 mg/kg) on aspirin induced ulcer was seen and that did not show any change in ulcer.

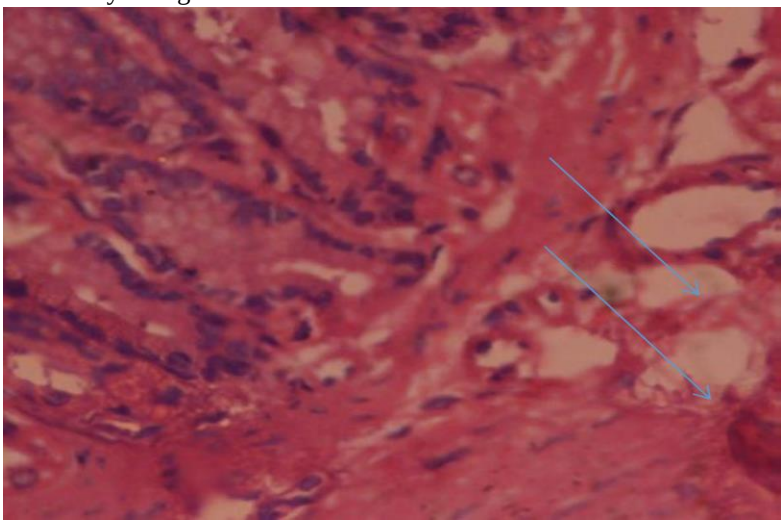


Fig 2 Photograph (Histopathology) of duodenum of the mice of Low dose of *Rauwolfia Serpentine.*

A) Histologic section (10x) of acute ulcer shows beginning of necrosis, sloughing manifested as shortning of villi with infiltration of inflammation cell in mucosa

High dose of R. serpentina (110mg/kg)

Fig 3 shows test group section effect of in which effect of *Rauwolfia serpentine* high dose (110mg/kg) on aspirin induced ulcer was seen and that showed change i.e exacerbation in ulcer**.**

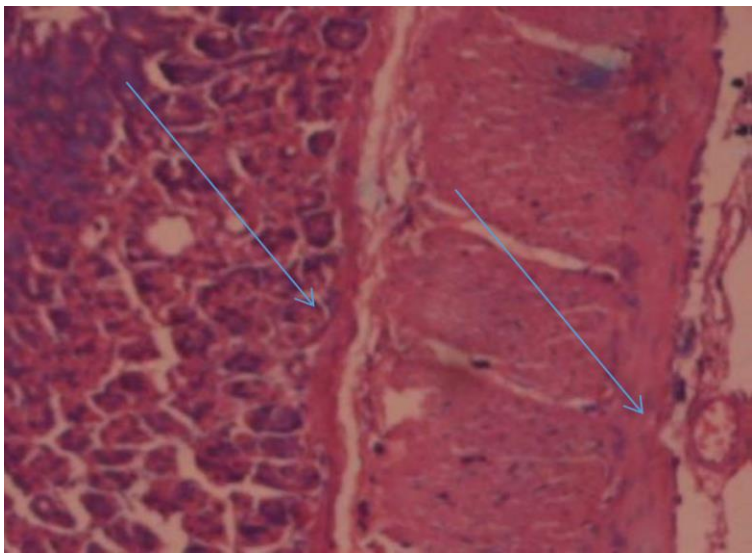


Fig 3 Photograph (Histopathology) of duodenum of the mice of high dose of *Rauwolfia Serpentine*.

A) Histologic section (10x) of acute ulcer shows beginning of necrosis, sloughing manifested as shortning of villi with infiltration of inflammation cell in mucosa.

DISCUSSION:

Rauwolfia serpentine are very useful plant for various study because of its several bioactive compound those were used in herbal treatment. It is well known drug for healing and protection of various diseases.

The phytochemical testing of root extract of R. serpentine was determined. The result was found to be Alkaloids, carbohydrates, resin, cardiac glycoside, flavonoids, tannins, saponins was positive whereas phenol and anthraquinone was negative. Recently investigation evaluated the antiulcer activity of *Rauwolfia serpentine* (root). In this study the ulcer was produced by oral administration of aspirin. The result was seen the ulcerated animals showed decrease of the mucosal thickness, loss of gastric juice and erosion of the surface epithelial cells. Standard drug treated animals showed any no damage. Then test drug (R. serpentine) treated animals showed healing its mucosal thickness, increase gastric juice and cure erosion of the surface epithelial cells.

CONCLUSION:

The present study concludes the extract of *Rauwolfia serpentine* (root) is show significant effect on ulcer induced by aspirin induced model. It is an effective antiulcer agent and increase ulcer protection by regeneration of mucosal layer. *Rauwolfia Serpentine* exhibited protection against characteristics lesion produced by aspirin administration. It is exhibited anti-inflammatory and antiulcerogenic activity.

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