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Anti-ulcer activity of extract of *Moringa oleifera* Lam. using Indomethacin induced gastric ulcers

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Abstract
Moringa oleifera Lam commonly known as Moringa, a native plant from Africa and Asia, and the most widely cultivated species in Northwestern India, is the sole genus in the family Moringaceae. Several studies have demonstrated the beneficial effects in humans. MO has been recognized as containing a great number of bioactive compounds. The most used parts of the plant are the leaves, which are rich in vitamins, carotenoids, polyphenols, phenolic acids, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins and saponins. The present investigation was carried out to investigate anti-ulcer activity of various extract of the plant using indomethacin induced gastic ulcer.

Keywords: moringa oleifera, anti-ulcer activity, indomethacin

Introduction
Peptic ulcers (PU) are sores or lesions in the gastrointestinal mucosa extending throughout the muscularis mucosae, typically characterized by different stages of necrosis, neutrophil infiltration, blood flow reduction, increased oxidative stress and inflammation [1]. The disease is mostly categorized based on its anatomical origins, such as gastric (found along the lesser curvature of the stomach) and duodenal (occurring in the duodenal bulb—the most exposed area to gastric acid) ulcers [2]. PU manifested as a non-fatal disease, majorly represented by periodic symptoms of epigastric pain, which are often relieved by food or alkali, besides to trigger much discomfort to patients, disrupting their daily routines and also causing mental agony [3]. Studies have shown that peptic ulcer disease (PUD) occurs because of an imbalance between aggressive injurious (e.g., pepsin, HCl) and defensive mucosa-protective factors (e.g., prostaglandins, mucus and bicarbonate barrier and adequate blood flow) [4]. All ulcers of the upper gastrointestinal tract were originally thought to be caused by the aggressive action of pepsin and gastric acid on mucosa. However, the denomination "peptic ulcer" has lately pointed to Helicobacter pylori infection, where the chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) are some of the disease-causing factors. Thus, based on the latest advances on this field and stress the fact that PUD is an important cause of morbidity and health care costs, the present study aim to provide a general overview on peptic ulcers, namely considering their epidemiology, main symptoms and clinical features, pathogenesis, where a particular emphasis will be given to H. pylori infection, pharmacological agents used in an effective management and also pointing out the latest challenges and opportunities of using plant phytochemicals as upcoming antiulcerogenic agents. Lastly, a special emphasis was given on plant products safety and security, in order to trigger the interest in deepening skills on this matter and to ensure an effective managing competence for health-related systems.

Moringa, a native plant from Africa and Asia, and the most widely cultivated species in Northwestern India, is the sole genus in the family Moringaceae. It comprises 13 species from tropical and subtropical climates, ranging in size from tiny herbs to massive trees. The most widely cultivated species is Moringa Oleifera (MO). MO is grown for its nutritious pods, edible leaves and flowers and can be utilized as food, medicine, cosmetic oil or forage for livestock. Its height ranges from 5 to 10 m. Several studies have demonstrated the beneficial effects in humans. MO has been recognized as containing a great number of bioactive compounds]. The most used parts of the plant are the leaves, which are rich in vitamins, carotenoids, polyphenols, phenolic acids, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins and saponins. The high number of bioactive compounds might explain the pharmacological properties of MO leaves. Many studies, in vitro and in vivo, have confirmed these pharmacological properties. The leaves of MO are mostly used for medicinal purposes as well as for human nutrition, since they are rich in antioxidants and other nutrients, which are commonly deficient in people living in undeveloped countries. MO leaves have been used for the treatment of various diseases from malaria and typhoid fever to hypertension and diabetes. The roots, bark, gum, leaf, fruit (pods), flowers, seed, and seed oil of MO are reported to have various biological activities, including protection against gastric ulcers, antidiabetic, hypotensive and anti-inflammatory effects [5-9].

Material and Methods
Collection of plant material and extraction procedure
Moringa oleifera Lam were collected from the botanical garden of Ram Krishna Dharmarth Foundation University Bhopal Madhya Pradesh between 28/01/2017 to 25/09/2017. Plant was authenticated by the Head of Department of botany Dr. Zia Ul Hasan Professor of Safia College of

Science Bhopal. Plant authentication no. is 346/Bot/Safia/2017 the date14/10/2017.

Extraction of leaves and fruits

The leaves and fruits were shade dried and reduced to coarse powder in a mechanical grinder and passed through sieve No. 40. The powdered material obtained was then subjected to successive extraction in batches using petroleum ether, chloroform, and acetone and methanol solvents in a Soxhelet extractor. The different extracts obtained were evaporated in rotary evaporator to get a semisolid mass. The extracts thus obtained were subjected to phytochemical analysis.

Experimental Animal

Animals

Male albino Wistar rats weighing between 200-250 gm were used. The experiment protocol was approved by the Institutional Animal Ethics Committee (IAEC), Vedica College of B Pharmacy, RKDF University, and Bhopal. The Animals were housed and maintained in animal house of the institute, Animals were kept in cages while maintaining a temperature 26±2°C with 12 hours: 12 hours' dark and light cycles. They were fed standard diet and water *ad libitum* given. Animals that were subjected for administration of standard drugs used and selected extracts, were fasted for 18 hours before administration of drugs to the experimental animals. All animals were maintained under standard conditions in an animal house approved by Committee for the Purpose of Control, and Supervision on Experiments on Animals (CPCSEA).

Acute toxicity study

The acute oral toxicity study was performed according to the OECD guidelines (Organisation for Economic Co-operation and Development) (Office of prevention, pesticide and toxic substance) Up and Down procedure (Health Effect Test Guideline 2004). The different extracts were suspended using 0.5% sodium carboxy methylcellulose and were administered orally. The concentration was adjusted in such a way that it did not exceed 1ml/kg b/w of the animal.

Indomethacin induced gastric ulcers

The gastric ulcers were induced by administering indomethacin (5mg/kg. p.o.) for 5 days during this period the animals were fed normally.The animals were then treated either with misoprostol (100 µ/kg, *p.o*) or with different extracts of *Moringa oleifera* Lam (500 mg/kg *p.*o) once daily for 5 days after induction of ulcer while the control group received only vehicle. The last dose of indomethacin was considered as 0^{th} day. Rats were sacrificed on the 0^{th} day and 5^{th} day, 6 hours after the last dose of the drug treatment. The stomachs were removed and they were cut open along the greater curvature and ulcer score and ulcer index were determined. The glandular portion of the stomach was taken and was used for estimation of mucin content, total proteins, antioxidant factors like super oxide dismutase activity, total tissue sulfhydryl groups and catalase activity [10].

Statistical analysis

The statistical significance was assessed using one-way analysis of variance (ANOVA) followed by Dunnet comparison test. For comparing nonparametric ulcer scores, ANOVA followed by non-parametric Dunn posttest was used. The values are expressed as mean ±SEM and $p<0.05$ was considered significant.

Results and Discussion

The acetone and methanolic extracts of *Moringa oleifera* Lam and misoprostol showed a significant reduction in ulcer index when compared to control ($p<0.01$). The petroleum ether extract did not show significant reduction in ulcer index when compared to control. The acetone and methanolic extracts of *Moringa oleifera* showed a significant increase in the mucus content when compared to control ($p<0.01$). The petroleum ether extract and misoprostol showed a non-significant increase in mucus content when compared to control (Table: 1). None of the treatments produced any significant effect on total proteins and anti-oxidant factors like SOD activity, total tissue sulfhydryl group (glutathione) and catalase activity (Table: 2). The animals became very weak after 5 days of administration of indomethacin (5mg/kg p.o.) and they showed symptoms of severe diarrhoea and their stools were black in colour.

Table 1: Effect of *Moringa oleifera* different extracts on mucin content, ulcer index and total proteins

Treatment	Mucin content	Ulcer index	Total proteins
Control	14.05±4.54	0.1023±0.007	21.83±7.11
Misoprostol	37.25±3.722	0.0323±0.010**	29.41±1.13
Petroleum ether flower extract	34.89±7.690	0.1050±0.020	32.52±2.14
Acetone flower extract	50.10±9.70**	0.0262±0.003**	35.47±3.82
Methanol flower extract	48.91±7.73*	0.0421±0.0062*	36.03±8.11
Chloroform flower extract	43.24±7.532	0.2031±0.011	33.33±1.17
Petroleum ether fruits extract	40.08±8.66**	0.0353±0.005**	34.32±2.76
Acetone fruits extract	49.83±8.64*	0.0622±0.0054*	34.06±7.24
Methanol fruits extract	33.62±7.452	0.203±0.031	23.43±3.14
Chloroform fruits extract	33.26±3.723	0.0333±0.021**	24.40±1.17
Petroleum ether seeds extract	31.82±7.381	0.1134±0.033	32.63±1.17
Acetone seeds extract	37.23±4.24	0.0123±0.022**	38.40±2.14
Methanol seeds extract	33.82±7.791	0.1059±0.031	33.44±2.19
Chloroform seeds extract	41.09±8.88**	0.0243±0.005**	36.38±3.75

Petroleum ether leaves extract	42.92±7.56*	0.0631±0.0065*	34.06±6.12
Acetone leaves extract	34.42±7.691	0.1056±0.021	33.55±2.17
Methanol leaves extract	31.22±7.581	0.1048±0.032	33.53±2.16
Chloroform leaves extract	34.35±2.32	0.0123±0.021**	38.30±1.15

All values are mean ± SEM, n = 5-6. *p<0.05, **p<0.01, ***p<0.001 when compared to control group

Table 2: Effect of *Moringa oleifera* different extracts on anti-oxidant factors in indomethacin induced ulcers

Treatment	SOD Units/mg of proteins of proteins	Glutathione Units/mg	Catalase Units/mg of proteins
Control	134.85±42.31	0.112±0.013	104.15±51.03
Misoprostol	68.50±2.84	0.108±0.042	71.27±9.65
Petroleum ether flower extract	61.72±3.65	0.080±0.052	32.13±7.34
Acetone flower extract	58.70±5.22	0.264±0.070	40.63±15.21
Methanol flower extract	63.82±18.54	0.031±0.003	34.87±5.83
Chloroform flower extract	62.63±6.63	0.072±0.061	33.28±5.38
Petroleum ether fruits extract	64.69±3.33	0.164±0.075	30.50±14.24
Acetone fruits extract	55.73±17.68	0.044±0.005	33.66±4.65
Methanol fruits extract	71.63±4.63	0.051±0.032	22.27±4.45
Chloroform fruits extract	64.69±6.24	0.532±0.03	50.40±16.21
Petroleum ether seeds extract	53.73±17.58	0.022±0.007	24.86±5.17
Acetone seeds extract	63.63±3.63	0.071±0.071	34.18±6.39
Methanol seeds extract	54.75±5.33	0.233±0.074	34.60±14.20
Chloroform seeds extract	61.83±17.56	0.032±0.008	35.86±5.86
Petroleum ether leaves extract	63.74±3.65	0.083±0.053	32.16±7.35
Acetone leaves extract	62.73±3.43	0.084±0.061	32.12±7.35
Methanol leaves extract	57.79±5.22	0.253±0.076	41.60±15.10
Chloroform leaves extract	63.84±18.57	0.034±0.006	34.83±5.87

All values are mean ± SEM, n = 5-6. *p<0.05, **p<0.01, ***p<0.001 when compared to control group

Conclusion

Indomethacin is known to produce erosions and ulcers in the G.I.T of experimental animals such as rats and guinea pigs. A layer of mucus that apparently forms a barrier covers the gastric mucosa. The gastric mucus production is stimulated by prostaglandins. Prostaglandin deficiency has been regarded to be primarily responsible for ulceration. The administration of indomethacin results in the production of gastric mucosal damage mainly in the glandular portion of the stomach. Indomethacin is a known prominent inhibitor of prostaglandin synthesis that in turn damages the mucosal barrier; the damage in the mucosal barrier causes the permeation of sodium ions from the mucosa in to the lumen. The agents having cytoprotective effect are effective in preventing the ulcers induced by indomethacin. Like in the ethanol induced gastric ulcers, the acetone and methanolic extracts of *Moringa oleifera*flowers were effective in reducing ulcer index and both extracts significantly increased the mucus content. This model confirmed the cytoprotective effect of these extracts. However, the flower extracts of *Moringa oleifera* were not effective in altering the antioxidant factors like SOD activity, total tissue sulfhydryl group (Glutathione) and catalase activity suggesting that the healing of ulcers or prevention of development of gastric ulcers
in different models is not due to antioxidant action.

In indomethacin induced ulcers the acetone and methanolic extracts of *Moringa oleifera* (500mg/kg.p.o) were significantly effective in reducing ulcer index and both extracts significantly increased the mucus content.

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