DISCUSSION

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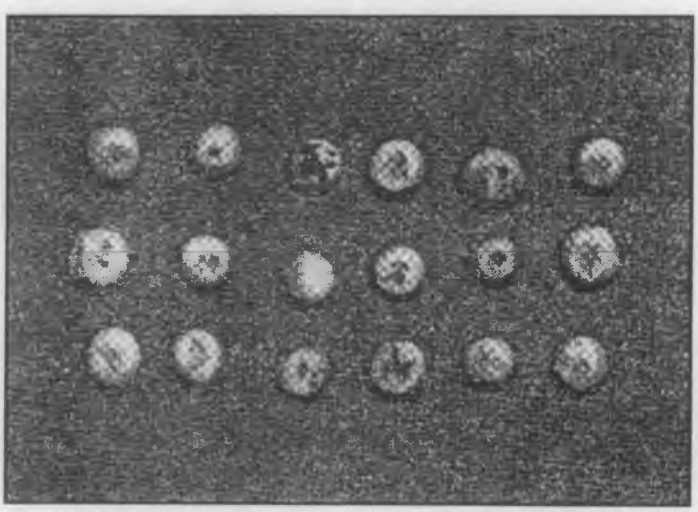
The profile of Nirmali, as revealed from Ayurvedic literature (187), is as under;

BOTANICAL NAME	:	*Strychnos potatorum* Linn.
INDIAN NAMES	:	Hindi - Nelmal
		Bengali - Nirmali
		Sanskrit - Kataka
		Punjabi - Nirmali
		Tamil - Telankottai
		Telugu - Chettu
FAMILY	:	Loganiaceae
ABOUT THE PLANT	:	Middle sized plant with branches, height up to 40 feet, oval shaped leaves with small stalk, light yellow flowers having aroma, fruits contain one / two seed (s).

Nirmali (*strychnos potatorum* Linn.) leaves



Nirmali (*strychnos potatorum* Linn.) seeds

DISTRIBUTION	:	Occurred in plenty in Bihar, Orissa and southern part of India.
MEDICINAL USE	:	Seeds are used as a local application in eye diseases, in dysentery and hyperacidity, in diabetes and gonorrhea (188).

In connection with screening experiments of various plants, fruits, seeds, roots etc. for having their anti- ulcer effect, if any, we noticed that seeds of Nirmali (*Strychnos potatorum* Linn.) exerted anti- ulcer effect on experimental ulcers induced by the drugs like aspirin and indomethacin. The observations tempted us to undertake the project in detail with a view to study the anti -ulcer effect of Nirmali (*Strychnos potatorum* Linn.) in other drug induced experimental ulcer models and to note the possible mechanism of the anti-ulcer effect. The present work, thus, was an attempt to evaluate the anti-ulcer activity of Nirmali (*Strychnos potatorum* Linn.) and its effect on various biochemical parameters in experimental ulcer models induced by the drugs like ;

1. Salicylic acid
2. Aspirin
3. Paracetamol
4. Indomethacin
5. Hydrocortisone
6. Prednisolone
7. Phenylbutazone and
8. Histamine.

Salicylic acid induced ulcers : Role of Nirmali (*Strychnos potatorum* Linn).

Brodie and Chase(15) while working on the ulcerogenic role of salicylic acid in rats, observed a dose dependent response of salicylic acid in the production of gastric ulcer. In the present study it was also noticed (Table – 1) that salicylic acid in the dose of 100 mg/kg when given to rats intraperitoneally once daily for three consecutive days produced profuse ulcers in the glandular part of stomach. Ulcers were associated with frank intragastric haemorrhage. Dodd *et al.* (19) also found the intragastric haemorrhage with ulcers induced by salicylic acid.

Conflicting reports are available in the literature regarding the effect of

salicylic acid on the volume of gastric juice, gastric acidity and peptic activity. Lish *et al.* (81) reported that salicylic acid caused a decrease in volume and acidity of gastric secretion while Winkelman and Summerskill (82) found that salicylic acid had no effect on the rate of gastric secretion and gastric acidity. In the present study it was observed that salicylic acid had no significant effect on rate of gastric secretion, gastric acidity and peptic activity (Table – 9).

Salicylic acid in the aforesaid dose was found to decrease significantly ($p < 0.025$ to $p<0.001$) the levels of gastric dissolved mucin and gastric mucosal mucus when measured its constituent carbohydrate components like total hexoses, hexosamine, methyl pentose and sialic acid (Tables – 17, 25).Kent and Allen (111) also observed a reduction in the rate of synthesis and secretion of mucus by salicylic acid. They thus said, " It is the loss of mucus barrier that permits the toxic effects of salicylic acid to produce ulcers in stomach". In addition to loss of mucus barrier we also observed that ulcerogenic dose of salicylic acid could increase ($p < 0.001$) the levels of lipid peroxides and decrease ($p < 0.001$) the amount of DNA of gastric mucosa of rats (Table – 33).

Effect of Nirmali (*Strychnos potatorum* Linn.) on salicylic acid induced gastric ulcers in rats was not reported in the available literature. We have noted that powdered seeds of Nirmali (*Strychnos potatorum* Linn.) in the oral dose of 1 g /kg/day for three consecutive days along with salicylic acid could prevent gastric ulcer induced by salicylic acid (Table – 1).This anti-ulcer effect of Nirmali (*Strychnos potatorum* Linn.) was not related with gastric secretion, gastric acidity and peptic activity (Table – 9) but had relation with mucus secretion, lipid peroxidation and DNA content of the stomach. We had seen that Nirmali (*Strychnos potatorum* Linn.) could increase the amount of gastric mucus (Tables – 17, 25), decrease lipid peroxides and increase DNA content of gastric mucosa (Table – 33) and thus exerted its anti – ulcer effect. All changes were found statistically significant ($p < 0.025$ to $p < 0.001$).

Aspirin induced ulcers : Role of Nirmali (*Strychnos potatorum* Linn).

Table – 2 showed that aspirin in the dose of 100 mg/kg/day when given to rats intraperitoneally for three consecutive days induced profuse ulcers in glandular part of stomach and the stomachs were invariably accompanied by frank intragastric haemorrhage - an earlier observation made by Brodie and Chase (15), Djahanguiri (16) using different doses of aspirin in experimental animals.

While studying the effect of aspirin on the rate of gastric secretion, gastric acidity and peptic activity Paul *et al.* (80) observed that aspirin causes a decrease in volume and acidity of gastric secretion while Lynch (79) observed an increase, no change or a decrease in gastric secretion and gastric acidity by aspirin depending on the dose and species studied. We, however, observed no significant change in volume, acidity and peptic activity of gastric secretion by the dose of aspirin (100 mg/kg/day intraperitoneally for three consecutive days) we used in albino rats (Table – 10).

That aspirin reduces the secretion of gastric mucus was an earlier observation made by different workers (110, 111). We also found that aspirin reduced the amount of dissolved gastric mucin as well as gastric mucosal mucus. The constituent carbohydrate components of dissolved gastric mucin and mucosal mucus viz. total hexoses, hexosamine, methyl pentose, sialic acid etc. showed a significant decrease ($p < 0.025$ to $p < 0.001$) in levels when compared to that of control values. The amount of dissolved mucin and mucosal mucus as represented by total carbohydrate (110) also showed a significant decrease ($p < 0.001$) by aspirin. (Tables – 18, 26).
We have also noted that aspirin increased the concentration of lipid peroxides and decreased the amount of DNA of gastric mucosa (Table – 34). Results were statistically significant ($p < 0.001$) when compared to that of control values. Best *et al.* , however, observed (189) that aspirin had no effect on DNA content of gastric mucosa.

Effect of Nirmali (*Strychnos potatorum* Linn.) on aspirin induced gastric ulcers in albino rats was not reported in the available literature. We have noted that powdered seeds of Nirmali (*Strychnos potatorum* Linn.) in the oral dose of 1 g /kg/day for three consecutive days along with aspirin could prevent gastric ulcer induced by aspirin(Table – 2). Ulcer index came down from 23 to 7.3. This anti-ulcer effect of Nirmali (*Strychnos potatorum* Linn.) was not related with gastric secretion, gastric acidity and peptic activity (Table – 10) but had relation with mucus secretion, lipid peroxidation and DNA content of the stomach. We had seen that Nirmali (*Strychnos potatorum* Linn.) could increase the amount of gastric mucus (Tables – 18, 26), decrease lipid peroxides and increase DNA content of gastric mucosa (Table – 34) and thus exerted its anti – ulcer effect. All changes were found statistically significant ($p < 0.025$ to $p < 0.001$).

Paracetamol induced ulcers : Role of Nirmali (*Strychnos potatorum* Linn).

Studies on paracetamol for its ulcerogenic potency are few in the available literature. Proudfoot and Wright (22) when studied the cases of acute paracetamol poisoning noticed gastrointestinal haemorrhage. We found the presence of massive ulcers at the glandular part of the stomach of rats when the animals were treated with paracetamol (100 mg/kg/day intraperitoneally for three consecutive days). Most of the ulcers were associated with haemorrhage(Table – 3) . We also found that the ulcerogenic dose of paracetamol could not change significantly the rate of gastric secretion, gastric acidity and peptic activity (Table – 11) but could decrease the gastric mucus as well as DNA content of gastric mucosa (Tables – 19, 27, 35) and could increase the level of lipid peroxides (Table – 35) . All the changes were statistically significant ($p < 0.025$ to $p < 0.001$).

Effect of Nirmali (*Strychnos potatorum* Linn.) on paracetamol induced gastric ulcers in albino rats was not reported in the available literature. We have noted that powdered seeds of Nirmali (*Strychnos potatorum* Linn.) in the oral dose of 1 g /kg/day for three consecutive days along with paracetamol could prevent gastric ulcer induced by paracetamol (Table – 3). This anti-ulcer effect of Nirmali (*Strychnos potatorum* Linn.) was not related with gastric secretion, gastric acidity and peptic activity (Table – 11) but had relation with mucus secretion, lipid peroxidation and DNA content of the stomach. We had seen that Nirmali (*Strychnos potatorum* Linn.) could increase the amount of gastric mucus (Tables – 19, 27), decrease lipid peroxides and increase DNA content of gastric mucosa (Table – 35) and thus exerted its anti – ulcer effect. All changes were found statistically significant ($p < 0.025$ to $p < 0.001$) when compared to that of paracetamol group.

Indomethacin induced ulcers : Role of Nirmali (*Strychnos potatorum* Linn).

In animal experiments, Djahanguri (8) and Lee et al. (9) showed that indomethacin caused gastric, duodenal, antral and jejunal ulcerations, haemorrhage and perforation. On studying this ulcerogenic property, Nicoloff (78) showed that ulcerogenic effect of indomethacin did not seem to be related to acid hypersecretion. On the other hand, Menguy (110) and Goel *et al.*(140) observed that ulcerogenic effect of indomethacin was related to mucus secretion as it lowered the rate of mucus secretion and diminished the amount of carbohydrate incorporation into the

mucosubstances which helped the drug to exert its toxic effect to damage the mucosa.

In our experiment we observed that indomethacin in the dose of 25 mg/kg when given to rats intraperitoneally once daily for three consecutive days formed several ulcers at the glandular region of stomach (Table – 4). Formation of ulcer was not related with acid-peptic digestion as indomethacin with the said dose had no effect on rate of gastric secretion, gastric acidity and peptic activity (Table – 12). On the other hand, we observed, indomethacin had a relation with gastric mucus secretion since it decreased the levels of total hexoses, hexosamine, methyl pentose and sialic acid (the constituent carbohydrate components of mucin) and thus the levels of dissolved gastric mucin and gastric mucosal mucus (Tables – 20, 28). In addition, indomethacin increased the levels of gastric lipid peroxides and decreased DNA content of gastric mucosa (Table – 36). All changes were found statistically significant ($p < 0.025$ to $p < 0.001$) when compared to that of control values. Naito *et al.* (131), Joseph *et al.* (190) and Pandit *et al.* (162) also showed that indomethacin induced gastric ulcer in albino rats was mediated by increasing gastric lipid peroxidation.

Effect of Nirmali (*Strychnos potatorum* Linn.) on indomethacin induced gastric ulcers in albino rats was not reported elsewhere. We have noted that powdered seeds of Nirmali (*Strychnos potatorum* Linn.) in the oral dose of 1 g /kg/day for three consecutive days along with the said dose of indomethacin could prevent gastric ulcer induced by indomethacin (Table – 4). Ulcer index came down from 22 to 8. This anti-ulcer effect of Nirmali (*Strychnos potatorum* Linn.) was not related with gastric secretion, gastric acidity and peptic activity (Table – 12) but had relation with mucus secretion, lipid peroxidation and DNA content of the stomach. We observed that Nirmali (*Strychnos potatorum* Linn.) could increase the amount of gastric mucus (Tables – 20, 28), decrease lipid peroxides and increase DNA content of gastric mucosa (Table – 36) and thus exerted its anti – ulcer effect. All changes were found statistically significant ($p < 0.025$ to $p < 0.001$) when compared to that of indomethacin group.

Hydrocortisone induced ulcers : Role of Nirmali (*Strychnos potatorum* Linn).

Ulcerogenic potency of hydrocortisone in man as well as in experimental animals has been studied elsewhere (38, 39, 43, 44). We also observed that

hydrocortisone acetate in the dose of 50 mg/kg/day when given to rats intraperitoneally for three consecutive days produced massive ulcers of different sizes at the glandular region of stomach (Table – 5). Most of the ulcers were associated with haemorrhage. We found that this ulcerogenic dose of hydrocortisone had no effect on the rate of gastric secretion, gastric acidity and peptic activity (Table – 13) but decreased the levels of dissolved gastric mucin and gastric mucosal mucus (Tables – 21, 29). All carbohydrate components of mucus like total hexoses, hexosamine, methyl pentose and sialic acid were found decreased significantly($p < 0.025$ to $p < 0.001$) in gastric juice and gastric mucosa after the administration of hydrocortisone in comparison to the control values. Seyle (48) observed a steady decrease in mucus secretion in gastric juice after hydrocortisone administration in albino rats.

Ulcerogenic property of hydrocortisone has not been explained earlier in terms of lipid peroxidation. We, however, noted that hydrocortisone in the said dose could increase the level of lipid peroxides and decrease the amount of DNA of gastric mucosa in albino rats (Table – 37). Results were statistically significant ($p < 0.001$) when compared to that of control values.

Effect of Nirmali (*Strychnos potatorum* Linn.) on hydrocortisone induced gastric ulcers in albino rats was not reported in the available literature. We have noted that powdered seeds of Nirmali (*Strychnos potatorum* Linn.) in the oral dose of 1 g /kg/day for three consecutive days along with the said dose of hydrocortisone could prevent gastric ulcer induced by hydrocortisone(Table – 5). Ulcer index was 25. After Nirmali (*Strychnos potatorum* Linn.) treatment ulcer index came down to 14. This anti-ulcer effect of Nirmali (*Strychnos potatorum* Linn.) was not related with gastric secretion, gastric acidity and peptic activity (Table – 13) but had relation with mucus secretion, lipid peroxidation and DNA content of the stomach. We had seen that Nirmali (*Strychnos potatorum* Linn.) could increase the amount of gastric mucus (Tables – 21, 29), decrease lipid peroxides and increase DNA content of gastric mucosa (Table – 37) and thus exerted its anti – ulcer effect. All changes were found statistically significant ($p < 0.025$ to $p < 0.001$) when compared to that of hydrocortisone group.

Prednisolone induced ulcers : Role of Nirmali (*Strychnos potatorum* Linn).

Several reports (46 – 49) are available in the literature showing the

ulcerogenic potency of prednisolone in experimental animals. Researchers have noted that prednisolone induces gastric ulcer in rats. We also observed the presence of ulcers at glandular part of the stomach of albino rats when the animals received prednisolone (30 mg/kg/day intraperioneally) for three consecutive days. 4 rats out of 33 died during experiment showed the extension and perforation of ulcers. This findings were in agreement with the earlier reported observation of Khan *et al.* (45).

When studied the effect of prednisolone on acid-peptic as well as mucus factor, we found that this drug with the said dose had no effect on the rate of gastric secretion, gastric acidity and peptic activity (Table – 14). But the mucus factor represented by the levels of dissolved gastric mucin and gastric mucosal mucus was found significantly ($p<0.025$ to $p < 0.001$) decreased in comparison to that of control values (Table – 22, 30). Earlier, this was observed by Seyle (48) who stressed on the fact that diminution of tissue resistance is related to the anti-inflammatory action of corticosteroids in the genesis of ulceration.

Ulcerogenic property of prednisolone has not been explained earlier in terms of lipid peroxidation. We had noted that prednisolone in the said dose could increase the level of lipid peroxides and decrease the amount of DNA of gastric mucosa in albino rats (Table – 38). Results were statistically significant ($p < 0.001$) when compared to that of control values.

Effect of Nirmali (*Strychnos potatorum* Linn.) on prednisolone induced gastric ulcers in albino rats was not reported in the available literature. We found that powdered seeds of Nirmali (*Strychnos potatorum* Linn.) in the oral dose of 1 g /kg/day for three consecutive days along with the said dose of prednisolone could prevent gastric ulcer induced by prednisolone (Table – 6). Ulcer index was 25. After Nirmali (*Strychnos potatorum* Linn.) treatment ulcer index came down to 10.2. This anti-ulcer effect of Nirmali (*Strychnos potatorum* Linn.) was not related with gastric secretion, gastric acidity and peptic activity (Table – 14) but had relation with mucus secretion, lipid peroxidation and DNA content of the stomach. We had seen that Nirmali (*Strychnos potatorum* Linn.) could increase the amount of gastric mucus (Tables – 22, 30), decrease lipid peroxides and increase DNA content of gastric mucosa (Table – 38) and thus exerted its anti – ulcer effect. All changes were found statistically significant ($p < 0.025$ to $p < 0.001$) when compared to that of prednisolone group.

Phenylbutazone induced ulcers : Role of Nirmali (*Strychnos potatorum* Linn).

Ulcerogenic property of phenylbutazone in man as well as in experimental animals had been studied by various workers (25 - 37). We also observed that phenylbutazone in the dose of 100 mg/kg/day when given to guinea pigs orally for three consecutive days produced massive ulcers of different sizes at the glandular region of stomach (Table – 7). Almost all ulcers were accompanied by haemorrhage. We found that this ulcerogenic dose of phenylbutazone had no effect on the rate of gastric secretion, gastric acidity and peptic activity (Table – 15) but decreased the levels of dissolved gastric mucin and gastric mucosal mucus (Tables – 23, 31). All carbohydrate components of mucus like total hexoses, hesosamine, methyl pentose and sialic acid were found decreased significantly($p < 0.025$ to $p < 0.001$) in gastric juice and gastric mucosa after the administration of phenylbutazone in comparison to the control values. Zaidi *et al.* (117) observed a steady decrease in mucus secretion in gastric juice after phenylbutazone administration in guinea pigs.

Ulcerogenic property of phenylbutazone has not been explained earlier in terms of lipid peroxidation. We, however, noted that phenylbutazone in the said dose could increase the level of lipid peroxides and decrease the amount of DNA of gastric mucosa in guinea pigs (Table – 39). Results were statistically significant ($p < 0.001$) when compared to that of control values.

Effect of Nirmali (*Strychnos potatorum* Linn.) on phenylbutazone induced gastric ulcers in guinea pigs was not reported in the available literature. We found that powdered seeds of Nirmali (*Strychnos potatorum* Linn.) in the oral dose of 1 g /kg/day for three consecutive days along with the said dose of phenylbutazone could prevent gastric ulcer induced by phenylbutazone (Table – 7). Ulcer index was 25. After Nirmali (*Strychnos potatorum* Linn.) treatment ulcer index came down to 14. This anti-ulcer effect of Nirmali (*Strychnos potatorum* Linn.) was not related with gastric secretion, gastric acidity and peptic activity (Table – 15) but had relation with mucus secretion, lipid peroxidation and DNA content of the stomach. We had seen that Nirmali (*Strychnos potatorum* Linn.) could increase the amount of gastric mucus (Tables – 23, 31), decrease lipid peroxides and increase DNA content of gastric mucosa (Table – 39) and thus exerted its anti – ulcer effect. All changes were found statistically significant ($p < 0.025$ to $p < 0.001$) when compared to that of phenylbutazone group.

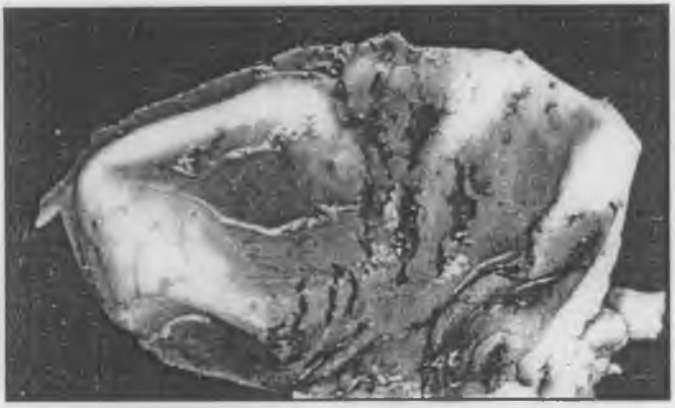


Figure-1 : Showing phenylbutazone induced ulcers in the stomach of guinea pig.

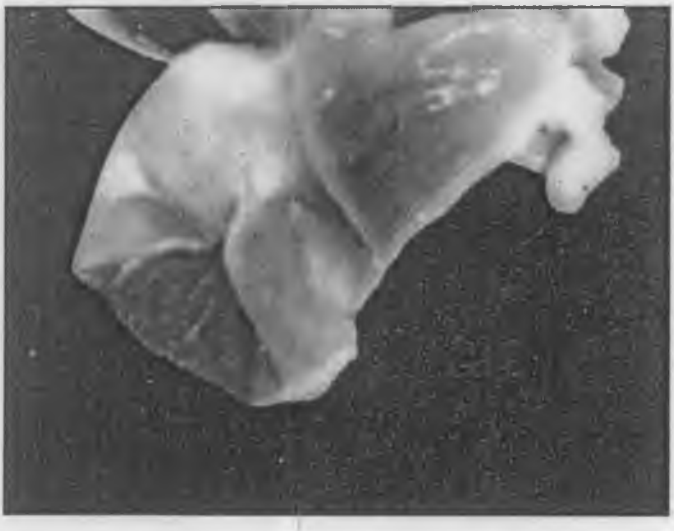


Figure-2 : Showing the effect of Nirmali (*Strychnos potatorum* Linn.) on phenylbutazone induced ulcers in the stomach of guinea pig.

Histamine induced ulcers : Role of Nirmali (*Strychnos potatorum* Linn).

There are reports that histamine in specific dose when administered through specific route caused gastric and duodenal ulcers in man and animals (52 – 55). Ulcerogenic potency of the drug was related to gastric hyper secretion. In our experiment when histamine in the dose of 33 micro gram/mouse/day when given to mice intraperitoneally for three consecutive days produced massive ulcers at the glandular region of stomach (Table – 8). Ulcers were accompanied by haemorrhage and other pathologies like adhesion and acute dilatation of the blood vessels. We found that this ulcerogenic dose of histamine had no effect on the rate of gastric secretion, gastric acidity and peptic activity (Table – 16) but decreased the levels of dissolved gastric mucin and gastric mucosal mucus (Tables – 24, 32). All carbohydrate components of mucus like total hexoses, hexosamine, methyl pentose and sialic acid were found decreased significantly($p < 0.025$ to $p < 0.001$) in gastric juice and gastric mucosa after the administration of histamine in comparison to the control values.

Effect of ulcerogenic dose of histamine on lipid peroxidation was not reported elsewhere. We, had noted that histamine in the said dose could increase the level of lipid peroxides and decrease the amount of DNA of gastric mucosa in mice(Table – 40). Results were statistically significant ($p < 0.001$) when compared to that of control values.

Effect of Nirmali (*Strychnos potatorum* Linn.) on histamine induced gastric ulcers in mice was not reported in the available literature. We found that powdered seeds of Nirmali (*Strychnos potatorum* Linn.) in the oral dose of 1 g /kg/day for three consecutive days along with the said dose of histamine could prevent gastric ulcer induced by histamine (Table – 8). Ulcer index was 28. After Nirmali (*Strychnos potatorum* Linn.) treatment ulcer index came down to 10.1. This anti-ulcer effect of Nirmali (*Strychnos potatorum* Linn.) was not related with gastric secretion, gastric acidity and peptic activity (Table – 16) but had relation with mucus secretion, lipid peroxidation and DNA content of the stomach. We had seen that Nirmali (*Strychnos potatorum* Linn.) could increase the amount of gastric mucus (Tables – 24, 32), decrease lipid peroxides and increase DNA content of gastric mucosa (Table – 40) and thus exerted its anti – ulcer effect. All changes were found statistically significant ($p < 0.025$ to $p < 0.001$) when compared to that of histamine group. ##

Concept of antiulcerogenic property of indigenous plants and fruits was not new. Several reports are now available in literature (70 – 86). In the present study we confirmed anti–ulcer property of Nirmali (*Strychnos potatorum* Linn.) and explored the possible mechanism behind this anti–ulcer property. Our observations were :

1. Nirmali (*Strychnos potatorum* Linn.) could decrease the incidence and severity of gastric ulcers in experimental ulcer models induced by the drugs like salicylic acid, aspirin, paracetamol, indomethacin, hydrocortisone, prednisolone, phenylbutazone and histamine.

2. Nirmali (*Strychnos potatorum* Linn.) had no effect on rate of gastric secretion, gastric acidity and peptic activity during ulceration.

3. Nirmali (*Strychnos potatorum* Linn.) increased the levels of gastric dissolved mucin and gastric mucosal mucus which were found decreased during ulceration.

4. Nirmali (*Strychnos potatorum* Linn.) decreased the level of gastric lipid peroxides which was found increased during ulceration.

5. Nirmali (*Strychnos potatorum* Linn.) increased the amount of DNA of gastric mucosa which was found decreased during ulceration.

Thus, we conclude ;

* **Nirmali (*Strychnos potatorum* Linn.) has anti–ulcer effect against drug induced experimental ulcers.**

{Nirmali (*Strychnos potatorum* Linn.) could prevent the incidence and severity of ulcers as induced by different ulcerogenic drugs to the extent of 60 – 90%}

**** Anti-ulcer effect of Nirmali (*Strychnos potatorum* Linn.) is through inhibition of gastric lipid peroxidation.**

{ Ulcerogenic drugs could increase gastric lipid peroxidation thereby generate reactive oxygen metabolites. This could damage gastric cells as observed by various workers (118 – 123). This was reflected by decreased amount of DNA in gastric mucosa which, in turn, was responsible for decreased synthesis of gastric mucosubstances. In absence of proper protective layer of mucosubstances, ulcer developed in the stomach.

Nirmali (*Strychnos potatorum* Linn.), on the other hand , could inhibit gastric lipid peroxidation thereby inhibit generation of reactive oxygen metabolites. This could protect the gastric cell from damage. DNA of gastric mucosa was, thus, found increased with a concomitant increase in the level of gastric mucosubstances. These mucosubstances gave a proper protection in the stomach for which ulcers could not develop.

Anti-ulcer property of Nirmali (*Strychnos potatorum* Linn.) was thus explained by its anti-oxidative activity. } ##