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REVIEW ARTICLE

ANTI–ULCER POTENTIAL OF FLAVONOIDS

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The flavonoids are a group of low molecular weight, naturally occurring, plant products widely distributed in the vegetarian kingdom and all are based on the parent compound flavone (2–phenylchromone or 2–phenylbenzopyrone). They occur in fruits, vegetables, nuts, seeds leaves, flowers and barks. The average daily western diet contains about 1 g of mixed flavonoids, an amount that might be sufficient to achieve pharmacologically significant concentration in tissues (1).

A biological function of this group of compounds in man and animals was first suggested in the year 1936 by Szent–Gyorgyi who reported that crude preparations of vitamin C obtained from natural sources, were more effective than the pure vitamin in alleviating the capillary lesions and prolonging the life of scorbutic animals. The unknown substance that protected the capillaries was isolated from lemon and was called citrin. Later on, a variety of naturally occurring substances were found to possess such action and they were eventually identified as flavonoids.

Recently, it has been postulated that human body has a capacity for an environmentally related dietary conditioned resistance to disease (2). This concept is based on the evidence that flavonoids and related compounds synthesized in plants with antiviral, antifungal, bacteriostatic and immunostimulant actions may be absorbed into the body and attached irreversibly to blood cells. In the body, in addition to any potential action against pathogens, certain of these compounds potentiate enzymes which detoxify carcinogenic hydrocarbons, exhibit anti–inflammatory activity, exert anti–adhesive action on blood cells and show antithrombogenic activity (1). A current account on the importance of dietary cosntituents in the prevention of coronary heart disease also highlights the protective effects of flavonoids through their anti–oxidant property (3).

Pathogenesis of peptic ulcer disease :

Peptic ulcers are thought to develop because of an imbalance between aggressive factors (acid, pepsin, bile salts) and defensive factors (mucus, bicarbonate, blood flow, eptithelial cell restoration, prostaglandins).

Most duodenal ulcers occur in the first part of the duodenum. Pathophysiological

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abnormalities producing duodenal ulcers are complex, but are thought to be related to an absolute or relative increase in duodenal acidity. Several theories have been proposed to explain the complex inter-relationship between acid secretion and duodenal ulcer. For example a person with duodenal ulcer may have an abnormally high vagal tone; excessive humoral (gastrin) stimulation of acid; impaired inhibition of gastric acid secretion or a greater capacity to secrete acid. Recently, *Helicobacter pylori* which is known to colonize the antral region of gastric mucosa, has also been implicated in the pathogenesis of peptic ulcer disease.

Most benign gastric ulcers are located in the antrum of the stomach on the lesser curvature, just distal to the acid secreting mucosa. Although the pathophysiology of gastric ulcer has still not been fully elucidated, most studies suggest defect in antral-pylorus-duodenal motility. Abnormal motility patterns permit duodenal contents to reflux into the stomach with resultant damage to gastric mucosa. Delayed gastric emptying can increase exposure of acid, pepsin and refluxed duodenal contents to the gastric mucosa. It appears that the bile salts and pancreatic secretions damage the gastric mucosa and allow back-diffusion of hydrogen ions. This action is thought to result in ulcer formation. The gastric mucosal barrier may also be damaged by drugs such as aspirin and NSAIDs whose mechanism is related to inhibition of cyclo-oxygenases responsible for synthesis of cytoprotective prostaglandins. Thus evidence supports the importance of primary defects in gastric mucosal resistance and/or direct gastric mucosal injury as the most important elements in the pathogenesis of gastric ulcers.

Inspite of the advancements in studies on the pathophysiology of peptic ulcer disease leading to the elucidation of various mediators implicated in its genesis and introduction of highly effective histamine H_2 antagonists and gastric proton pump inhibitors, we have yet to discover an effective anti-ulcer drug which not only heals the peptic ulcers but also prevents their recurrence. This review gives an account of various flavonoids so far studied for their anti-ulcer activity.

The anti-ulcer potential of flavonoids : Early reports : Capillary integrity being vital to normal functioning of mucous membranes, experimental and clinical lesions of the gastric mucosa have been employed by some investigators to study the pharmacological activity of flavonoids. Vogin and Rossi (4) reported that a combination of orange bioflavonoid complex with vitamin C protected against the ulcers induced by histamine in guineapigs and by reserpine in rats. Similarly, vitamin C when combined with rutin could protect against the gastric ulceration induced by phenylbutazone in rabbits (5). Ciaceri and Attaguile (6) reported the protective effect of luteolin and apigenin against histamine induced ulcers in guinea pigs and in pylorus ligated rats.

Parmar (7) conducted a systematic study on the anti-ulcer activity of various chemical groups of flavonoids like flavones, flavonols, flavans, flavanones and chalcones under an ICMR sponsored research project. His study revealed the anti-ulcer potential of compounds like β-hydroxyethylrutosides, gossypin, naringin, naringenin and (+)–cyanidanol-3 i.e., (+)–catechin. They significantly reduced the severity of

ulceration induced by pylorus ligation, restraint, reserpine, aspirin, phenylbutazone and indomethacin in rats and by histamine in guineapigs. These compounds also exhibited marked antisecretory activity in pylorus ligated rats.

Histidine decarboxylase in ulceration :

Almost simultaneously with these studies, Reimann et al (8) reported the gastric anti-ulcer activity of (+)–cyanidanol-3 in rats immobilized for eight hours. Based on the study of Levine and Senay (9) who had shown that brocresine a histidine decarboxylase inhibitor afforded protection from the ulcerogenic effects of stress and that of Lorenz et al (10) on the histidine decarboxylase inhibitory activity of (+)–cyanidanol-3, we studied the anti-ulcer potential of (+)– cyanidanol-3, using various models of gastric ulceratation in rats and guinea pigs (11). In a preliminary clinical investigation Wendt et al (12) studied the efficacy of (+)–cyanidanol-3 in reducing the gastric tissue histamine content in patients with gastric and duodenal ulcers and acute gastritis. After oral administration of (+)–cyanidanol-3 (5 × 1000 mg daily for 8 days) the biopsies were taken daily from the normal human volunteers and the patients as mentioned above. Similar reduction in histamine could be observed in patients with stomach ulcer disease and gastritis after treatment with (+)–cyanidanol-3. They also showed that the histamine content of gastric mucosa significantly increased in patients with urticaria and food allergy after the local application of the antigen to gastric mucosa. This increase in gastric histamine levels could be significantly decreased by the prior administration of (+)–cyanidanol-3. These studies for the first time established a close link between gastric ulceration and reduction of gastric mucosal histamine levels in man.

These studies further substantiated the work of Ritchie et al (13) who had shown that the level of endogenous tissue histamine could be markedly decreased in rats maintained on a pyridoxine deficient diet for two weeks and these reduced levels provided significant protection against the development of restraint induced ulceration in the glandular portion of the rat stomach and significantly reduced the volume of gastric secretion and free and total acid production in pylorus ligated rats. *Pyridoxine* in all probability acts as a catalyst for histidine decarboxylase, the enzyme responsible for the endogenous formation of histamine.

3–Methoxy–5, 7, 3', 4'–tetrahydroxy flavan (Meciadanol) :

As the studies on (+)–cyanidanol–3 were under progress, the Chemical Laboratories of Zyma SA Nyon, Switzerland developed a congener of (+)–cyanidanol-3, meciadanol which underwent detailed pharmacological and clinical investigations. It appeared to be comparatively more promising compound as far as the pharmacological, pharmacokinetic and preliminary clinical studies were concerned (14). It has been shown by Hackett and Griffiths (15) that meciadanol, unlike (+)–cyanidanol-3 does not undergo microfloral ring fission in the intestine, which has been considered to be the major pathway of flavonoid metabolism (16). This difference may partly account for the increased bioavailability and more pronounced anti-ulcer activity of

this compound as compared to (+)–cyanidanol-3.

Parmar and Ghosh (17) and Parmar and Hennings (18, 19) reported the gastric anti-ulcer activity of meciadanol using various models of experimentally induced ulcers, viz, the pylorus ligated rats, restraint ulcers and gastric mucosal damage induced by aspirin, phenylbutazone, indomethacin, ibuprofen and reserpine in rats. It possessed significant anti-ulcer activity in these models and appeared slightly more potent and better bioavailable as compared to (+)–cyanidanol-3.

The antisecretory activity of meciadanol was further studied in conscious gastric fistula cats using pentagastrin, insulin and food as secretory stimulants whereas pentagastrin stimulated gastric secretion was inhibited only by a high i.v. dose of 200 mg/kg of meciadanol, food and insulin induced gastric secretion was inhibited with a dose of 25 mg/kg given intravenously (20). It was found to possess similar antisecretory activity in rats subjected to pylorus ligation for 6 hours and it was as effective as the H_2– antagonist cimetidine in these experiments (21). Further studies showed that meciadanol promotes the healing of gastric ulcers induced by restraint in rats (22). The healing took place significantly faster in the rats receiving meciadanol than in control rats. It also produced a significant synergistic action when used in combination with cimetidine in different models of experimental ulceration in rats.

Meciadanol had undergone detailed preclinical toxicity studies. The acute, subacute and chronic toxicity studies in rats, administration by intravenous dose in dogs and the local tolerance studies in rabbits showed that the compound was safe for conducting the clinical investigations by oral route in human beings. It has been found to be devoid of any teratogenic potential in rats and rabbits. It did not produce any mutagenic effect in the Ames test and in the cytogenic test done on bone marrow cells of mouse. It was also found inactive in the carcinogenicity test on BALP 3T3 mouse cells in culture (14).

Pharmacokinetic studies on meciadanol show that the orally administered drug is well absorbed and gradually excreted in urine and faeces during a period of 72 hours in rats, mice and marmosets. It is metabolized by methylation of the hyroxyphenol groups of the B nucleus in 3, 3' dimethoxy 5, 7, 4'-trihydorxy flavan. This metabolite is then conjugated and excreted in the urine and bile (15).

No breakdown products of meciadanol or its principal metabolite by the intestinal tract microflora due to ring fission have been observed in any of the species tested because the substitution in position 3 probably stabilises the molecule. There was also no evidence of the demethylation of the compound at any stage of the metabolism. The fact that it is not demethylated *in vivo* means that its action is not due to its conversion to (+)–cyanidanol-3 in the body. This stability of ether link in position 3 is also likely to persist in man (15, 16).

The results of preliminary clinical trials showed a significant potential for developing it into a promising anti-ulcer drug. It

showed protective effect against aspirin induced irritation of the human gastric mucosa as demonstrated by measuring the gastric potential difference (23) according to the method of Laule et al (24). Oral pretreatment with 250–1000 mg of meciadanol reduced the degree of irritation of gastric mucosa in a dose dependent manner. In volunteers treated with meciadanol, the histamine content was significantly reduced in the fundus, corpus and antrum of the stomach (12). In another study on the effect of meciadanol on gastric secretion and aspirin induced gastric mucosal injury in humans, Konturek et al (25) found that meciadanol did not affect either basal or pentagastrin stimulated gastric acid secretion or pepsin secretion and did not produce any endoscopic or histological changes in the stomach or duodenum. Nevertheless, it prevented aspirin-induced microbleeding and aspirin-induced DNA loss suggesting that gastric mucosal histamine is involved in the mucosal injury caused by aspirin. Subsequently, Konturek et al (26) have established a true cytoprotective effect of meciadanol on ethanol and aspirin induced gastric mucosal damage in rats which was comparable to that of 16, 16-dimethyl PGE_2. It was neither mediated by the reduction of gastric or pepsin activity nor by enhancing the endogenous muscosal PGI_2 levels.

Inspite of its highly effective anti-ulcer profile and unique mode of action, this compound could not be introduced in therapeutics as an useful anit-ulcer drug. As catechins were shown to produce hemolytic anemias, further attempts to develop meciadanol and other potential compounds as anti-ulcer drugs were given up.

However, these studies point towards a strong possibility of finding out a safe and effective flavonoid possessing histidine decarboxylase inhibitory and anti-ulcer activity in future (22). Recent publications of Murakami et al (27) and Alarcon de la Lastra et al (28) reveal the property of gastric H^+, K^+–ATPase inhibition in catechins and that of lipoxygenase inhibition in silymarin respectively. These findings also support the above contention and provide impetus for further indepth studies on anti-ulcer profiles of flavonoids. Another recent publication reveals the dose dependent reduction in gastric mucosal damage and the mucosal content of platelet activating factor by flavonols like rutin, quercetin and kaempferol (29).

Sofalcone

In Chinese medicine, a crude drug called Kohzukon (*Sophora subprostrata* Chun et T. Chen) has been used in the treatment of digestive diseases. It has been reported that sophoradin, a compound isolated from the root of this ancient Chinese plant exhibits anti-ulcer activity in experimental models. One of the sophoradin derivatives, an isoprenyl flavonoid known as sofalcone (2'–carboxy–methoxy–4–4'–bis (3–methyl–2–butenyloxy) – chalcone has been extensively studied for its anti-ulcer potential. Sofalcone prevents acute gastric ulceration induced by acidified aspirin, water immersion and restraint ulcers (30) and has a cytoprotective effect against 0.6 N HCl and aboslute ethanol induced mucosal lesions in rat stomach (30, 31, 32) and taurocholate induced gastritis in rats (33). Prostaglandins have been shown to be involved in its anti-ulcer and cytoprotective effects (30). It

TABLE I : Naturally occurring and semisynthetic flavonoids with significant anti-ulcer activity.

Plants	*Effective compounds*	*Models studied*	*References*
Sophora Subprostata	Sophoradin	Experimental gestric ulcers in rats and guinea pigs, Pylorus ligated rats	39
	Sofalcone (Semisynthetic)	Now in clinical use	37
Glycyrrhiza glabra	Hydroxychalcones	HCl-ethanol, water–immersion and acetic acid induced gastric ulcers in rats	38
Silybim marianum	Silymarin	Ethanol, cold-restraint, pylorus ligration in rats	28
Rhamnus procubens	Kaempferol	Pylorus ligation and restraint in rats, histamine in guineapigs	40
Anacardium occidentale Linn and other sources	Catechins	Pylorus ligation, NSAIDs in rats. Histamine in guinea pigs	11, 16, 17, 20, 21, 22, 23, 24, 25, 26
	(+)–Cyandidanol-3 Catechins	Gastric H^+, K+ ATPase inhibition	27
	Meciadanol (Semisynthetic)	Undergone clinical trials	24, 25
Erica andevalensis	Flavonoid Extract	Cold stress, Pylorus ligation, Ethanol in rats	41
	Amentoflavone	Pylorus ligation, restraint in rats : histamine in guineapigs	42, 43
Genista rumelica	Genistine (Total flavonoid mixture)	Experimental gastric ulcers in rats	44
Sideritis leucantha	Hypolaetin–8–O–beta–D–glucoside	Ethanol and aspirin in rats	45
Eucalyptus maculata Hook; Citrus paradisi Macfad	Quercetin, Naringenin	Cold + restraint and pylorus ligation in rats	46, 47
Aurantii frustus immaturus	Nobiletin and Marmin	Ethanol and aspirin in rats	48
Dittrichia Viscosa	Flavonoid fraction	Ethanol, HCl, Hypertonic saline and indomethacin in rats	49
Cistus incanus	Flavonoid extract	HCl, ethanol indomethacin, reserpine and serotonin in rats.	50

inhibits the activity of PG metabolizing enzyme 15-hydroxy-PG-dehydrogenase and elevates the PGE_2 content of the gastric mucosa in rats subjected to absolute ethanol induced gastric mucosal damage and taurocholate induced gastritis (30, 33).

Sofalcone has been clinically tried in Japan for the treatement of gastroduodenal ulcers by a number of workers (34–37). It has been found particularly useful in accelerating the healing of gastric ulcers which were shown to be accompanied by a deficiency of PG biosynthesis in gastric mucosa.

Hydroxychalones

Taking a lead from the studies of sofalcone, Yamaoto et al (38) studied the gastroprotective effect of a number of hydroxychalcones obtained from various plants against necrotizing agents – induced gastric ulcers in rats viz. HCl–ethanol and NaOH and those induced by water immersion stress and acetic acid. Amongst the nine hydroxychalcones tested by them, 2', 4' – dihydroxychalcone appears to be most promising compound for further development as an anti–ulcer agent.

A number of publications have appeared during the last two decades describing the anti-ulcer potential of flavonoids or flavonoidal extracts from plants. Some important reports have been summarized in Table I.

CONCLUSION

During the recent years flavonoids have been the most widely studied natural compounds for their anti-ulcer potential. Both meciadanol and sofalcone have been studied for their clinical effectiveness and were found effective in the clinical trials. Though these compounds could not be developed and marketed as effective anti-ulcer agents, they have opened new vistas in ulcer research and pharmacologists are still working to find out an effective and safe anti-ulcer drug from this class of naturally occurring compounds.

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