УДК 612.325:615.322]-084

Zayachkivska O. S., Konturek S.J., Drozdowicz D., Brzozowski T., Gzhegotsky M.R.

Influence of plant-originated gastroprotective and antiulcer substances on gastric mucosal repair

(review of literature and own data)

В огляді літератури представлено сучасний погляд на функціональні можливості гастропротекторних і противиразкових речовин рослинного походження. В основі інтересу до цієї групи речовин рослинного походження лежать дані про їхню виражену захисну дію, що реалізується у відновленні слизової оболонки шлунка через експресію різноманітних факторів росту, супресії нейтрофіл/цитокінінового каскаду у травній системі, впливі на скевіндж реакції, проявляючи антиоксидантну, антинуклеолітичну та антиканцерогенну дії, гальмуючи активність цитохрому Р-450. Досліджено цитопротекторні властивості екстрактів софарадину (солон), насіння амаранту та грейпфрутових зерняток за умов експериментального ураження слизової шлунка 100%-м етанолом. Отримані результати свідчать про виражені гастропротекторні властивості досліджуваних речовин і доцільність їхнього застосування у профілактиці та терапії гастроентерологічних хвороб.

INTRODUCTION

All mucosal layers play a role as a barrier that limits exposure of the gastric mucosal cells to numerous injurious luminal agents. Mucosal surface epithelium is a subject of attack by physical, chemical or microbiological agents from the gastric lumen, which are involved in multiple pathologies, such as gastritis, peptic ulcer or gastric cancer. Over the last decade, considerable progress has been made in understanding the cellular and molecular mechanisms involved in mucosal injury and repair in gastrointestinal tract (GIT). These significant findings provide a fundamental basis to identify the etiology and pathogenesis of various gut mucosal injury-related diseases and to develop new therapeutic approaches. Pretreatment with different substances could effectively prevent gastric mucosa from the development of erosions and ulcerations. This action, called gastro- or cytoprotection is not related to the inhibition of gastric acid secretion and known to account for gastroprotection by various irritants and ulcerogens [2, 15, 16, 38].

This article overviews the potential role and also some basic mechanisms of plant-originated gastroprotective substances applied intragastrically (ig). Recent studies found that different substances from plant sources, not only afford gastroprotection, but also facilitate ulcer healing. They may also possess an anti-inflammatory action by suppressing the neutrophil/cytokine cascade in GIT [1, 46], promote tissue repair through expression of various growth factors [22], exhibit antioxidant action [22, 29], scavenging reactive oxygen species (ROS) [28, 34], show antinucleolytic, cytochome P450 2F1 inhibitory acitivity, anti-necrotic and anti-carcinogenic activities [4, 44].

METHODS

Wistar male rats weighing 200-220 g were used in studies with production of acute gast-

ric lesions and measurement of gastric blood flow. All animals were fasted 24 h before the study but had free access to water. They were placed in individual Bollman cages to prevent coprophagy.

Acute gastric lesions were induced by ig administration of 100% ethanol in a volume of 1 ml using special oro-gastric metal tube. One hour after ethanol administration, the animals were lightly anesthetized with ether and after midline incision, the stomach was approached using electrolytic regional H2-gas clearance technique applied by employing Electrolytic Blood Flow Meter (Biomedical Science Co., Tokyo, Japan) with single electrode both for the generation of H2 and measurement of its concentration as described previously [23] . The tested plant-originated preparations were administered at various doses 30 min before ethanol application and in case of L-NNA administration, this agent was injected intravenously (iv) at various doses about 30 min before application of tested plant gastroprotector agent. Then, the animals were killed by blow to the head and the stomach was removed, opened alone the greater curvature and the area of gastric lesions was measured by planimetry (morphomat, Carl Zeiss, Berlin, Germany). The area of lesions in each animal was expressed in mm2. Several groups of animals, each consisting of 6-8 animals were used.

Mean values were calculated for the area of gastric lesions and the gastric blood flow. The results were analyzed by Student's t test, and P values less than 0.05 were considered significant. All results are given as means ± standard error of mean (SEM).

Plant-originated gastroprotective substances, results of their protective action on gastric mucosal lesions and gastric blood flow and discussion of the results

There are various plant-originated "gastroprotectors" with different composition that have been used in practical and folk medicine of many countries due to their beneficial effects on the mucosa of GIT. In China and Japan, polyphenol extracts such as Sopharadin extracts, containing flavonoids and its synthetic flavonoid derivative known as Solon are widely employed in peptic ulcer therapy and also as additives and nutritional supplements, mainly because of their strong inhibition of prostaglandin (PG) metabolism and leukotriene inhibition [26]. According to our experience, Solon (Taisho Pharmaceutical Co, Tokyo, Japan) given ig results in dose-dependent protection against acute gastric lesions produced by 100% ethanol, the corrosive substance for the gastric mucosa (Fig.1). The gastroprotection by Solon is accompanied by dose-dependent increase in gastric mucosal blood flow. Both the gastroprotection and gastric hyperemia can be attenuated by the pretreatment with nonspecific NOS inhibitor such as L-NNA, indicating that local release of NO, possibly due to increased expression and activity of NOS plays a major role in Solon-induced gastroprotection. Our previous studies [23,25] with that agent demonstrated that it enhances the healing of chronic gastric and duodenal ulcers induced by acetic acid and that it acts probably through the increase in mucosal PG content probably due to inhibition of 15-OG-PG dehydrogenase, a PG hydrolyzing enzyme. This agent is of special interest as it is widely used in Japan as gastric protective and anti-ulcer agent in combination with classic antiulcer drugs such as H2-receptor antagonists or proton pump inhibitors. The major factor responsible for the gastroprotection by Sopharadin derivatives are probably flavonoids, the biologically active agents with high pharmacological potency [18].

In Ukraine, therapeutic effect of Amaranth, that was found to be related to scavenging of endogenous ROS, was shown to account for the maintenance of integrity and homeostasis of oral and gastric mucous [20].

In accordance with our experience, Amaranth seed extract resulted in gastroprotection against 100% ethanol and its favorable effect could be reversed by the pretreatment with neurotoxic dose of capsaicin that is known to cause functional ablation of sensory afferent nerves and release gastroprotective sensory neuropeptides such as calcitonin-gene related peptide (CGRP) (Fig.2). Based on the results we can speculate that Amaranth acts on gastric mucosa to stimulate afferent nerves and increases gastric microcirculation, but further studies are required to examine the protection by Amaranth in depth.

In India, an important gastroprotective effect was shown in studies on several experimental ulcer models in rats using aqueous extract of Neem (Aradirchta indica) bark [12], ethanol extract of Aqeratum conyzoides [43], Bacopa monniera and Azadirachla indica extract [14]. In Mexico the root bark of Hippocratea excelsa, locally known as "Cancerina"[15] and Azadirachta indica extract [16] are used in gastric disorders. In Spain, the flavonoid fraction (ethyacetate extract) of the plant Erica andevalensis Cabezudo-Rivera [17] of the plant ternatin, tetramethoxyflavone from Eglets viscose are used due to their prostaglandins –independent mechanism of gastroprotection [18].

In Chinese medicine phellodendri cortex (Phellodendron amurense) Ruprecht has been used to treat patients suffering from gastroenteritis, abdominal pain or diarrhea, because the berberine-free fraction of the extract from this plant has anti-inflammatory activity and additive effect on the cytoprotection and reduction of gastric acid secretion [19].

Grape seeds (GSP) and skins are good sources of phytochemicals such as gallic acid, catechin and epicatechin exert scavenging of ROS [20-25]. The data demonstrate that this

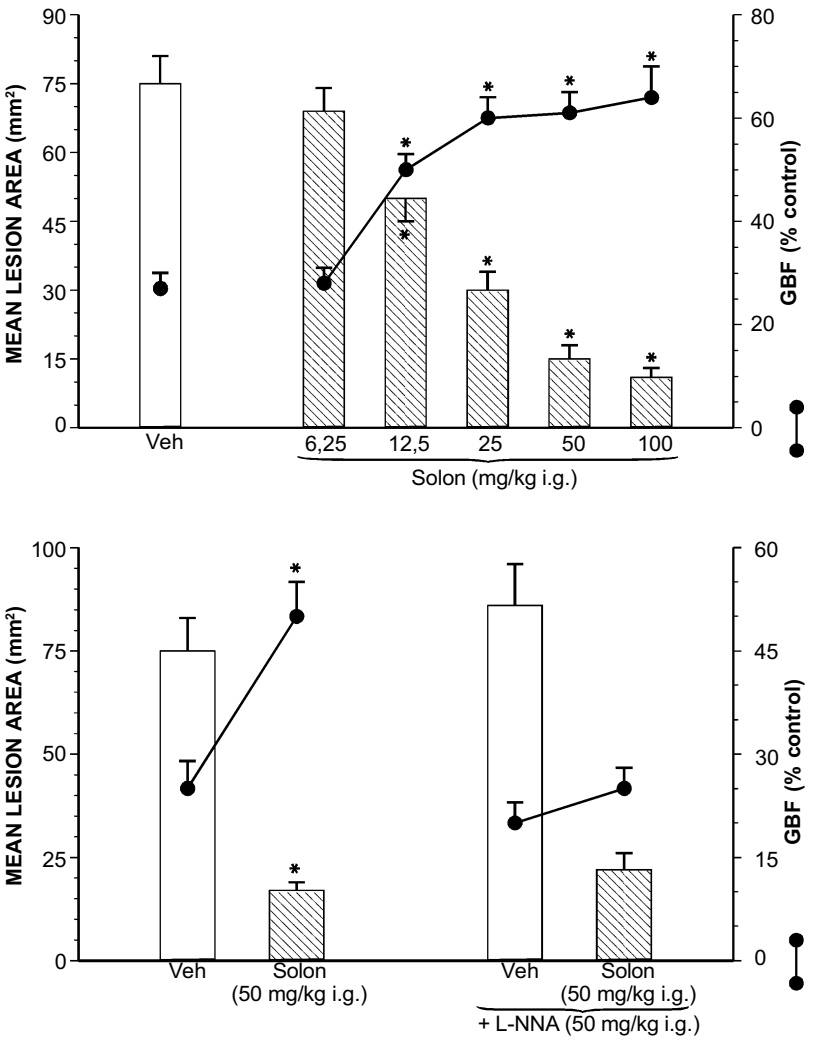

Fig. 1. Mean area of 100% ethanol-induced gastric lesions and the gastric blood flow (expressed as percent of control) in rats without (vehicle only) and with pretreatment with graded doses of Solon. Each column is a mean (± SEM) of 5-8 rats. Asterisk indicates significant ($P < 0.05$) change as compared to the vehicle (control) values.

extract may serve as a potential therapeutic tool in cardioprotection via a number of novel molecular mechanisms [26, 27]. GSP improve insulin sensitivity and/or ameliorate ROS formation and reduce the signs/symptoms of chronic age-related disorders including syndrome X [28]. Identification of these components has been interpreted on molecular basis of "French Paradox" in which good red wine is beneficial for the cardiovascular system [29].

The influence of black currant juice on protein and lipid oxidation lowering effect was similar in magnitude to the liver protecting agent kolaviron [30, 31]. The results of investigations of modulatory effects of kolaviron, a bioflavonoid from Gacinia kola, natural antioxidant, on drug-induced kidney toxicity show an interference in the cellular redox status and depression of membrane protein activities that may be relevant to chemoprevention of oxidant-induced genotoxicity and possibly human carcinogenesis [30].

Gingo biloba extract can improve memory, prevents pancreatitis and enhances gastroprotection against necrotizing agents and accelerates healing in rats with duodenal ulcer by cytoprotetive and antioxidant actions [32,33].

Extract from Petasites hybridus with three main compounds oxopetasan esters, petasin and isopetasin inhibit the biosyntesis of the vasoconstrictive peptide leukotrienes, this effect may contribute to gastroprotection and spasmolytic activity [34].

Grapefruit-seed extract (GSE), containing flavonoids, has been shown to possess antibacterial, antiviral and antifungal properties [35, 36]. This beneficial action of GSE was attributed to the antioxidative activity of citrus flavonoids found in grapefruit [37] such as naringenin because this major flavonoid found in the grapefruit juice, exhibited the potent anti-Helicobacter pylori activity in vitro [38] and was also recently implicated in cytoprotection against injury induced by algal toxins in isolated hepatocytes [39]. Moreover, naringenin, the bioactive component of GSE, showed anti-cancer activity against human breast cancers [40]. Therapeutic efficacy of citrus fruits such as red grapes and grapefruits is emphasized by the fact that they contain different classes of polyphenolic flavonoids, that were shown to inhibit platelet aggregation thus decreasing the risk of coronary thrombosis and myocardial infarction [41]. The involvement of flavonoids in the mechanism of gastric mucosal defense has been little studied. Our recent study with GSE (Citrokvapky, HERB-PHARMA, spol s.r.o., Welke Ludince,

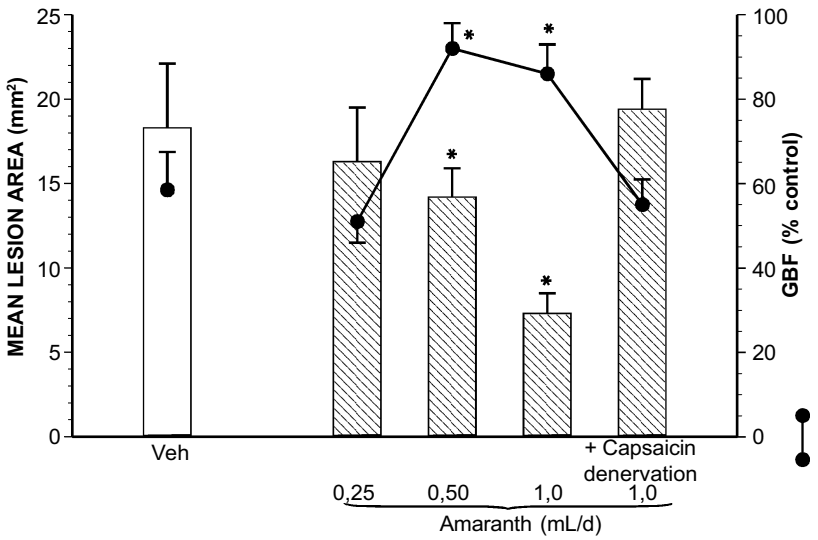

Fig. 2. Mean area of 100% ethanol-induced gastric lesions and the gastric blood flow (expressed as percent of control) in rats without (vehicle only) and with pretreatment with graded doses of Amaranth (extract of Amaranth seeds) without or with sensory denervation by neurotoxic dose of capsaicin (125 mg of capsaicin injected s.c. 2 weeks before experiment). Each column is a mean (± SEM) of 5-8 rats. Asterisk indicates significant ($P < 0.05$) change as compared to the vehicle (control) values.

Slovakia) confirmed that in vitro GSE is a highly antibacterial and antifungal agent. Most important, we found that this extract in minute doses causes dose-dependent diminution of acute gastric lesions induced in rats by 100% ethanol. The mechanism of this protection appears to be dependent on the functional activity of sensory nerves releasing CGRP because a) capsaicin-induced deactivation of these nerves markedly reduced protection and increased gastric circulation provoked by GSE and b) exogenous CGRP, administered in physiological dose to replenish the deficiency of this peptide caused by capsaicin, restored the protective efficacy of GSE. No study so far has been undertaken to examine the gastroprotective or ulcer healing efficacy of GSE but the fact that it is a potent anti-H. pylori substance and exerts profound gastroprotection in laboratory animals suggests that it should be also effective in humans. Citrokvapky is available in Poland and Slovakia without prescription and it does not cause any side effects nor inhibits gastric acid secretion (Fig. 3).

In another report, naringenin, a major GSE flavonoid, was reported to exhibit gastroprotection against the gastric injury induced by absolute ethanol predominantly due to the increase in the mucus secretion [43]. It is of interest that this gastroprotective effect of naringenin and accompanying increase in the mucus secretion were, in part, attenuated by indomethacin suggesting the involvement of endogenous prostaglandins (PG) in the mechanism of this flavonoid-induced gastroprotection [43].

Our group demonstrated long time ago that

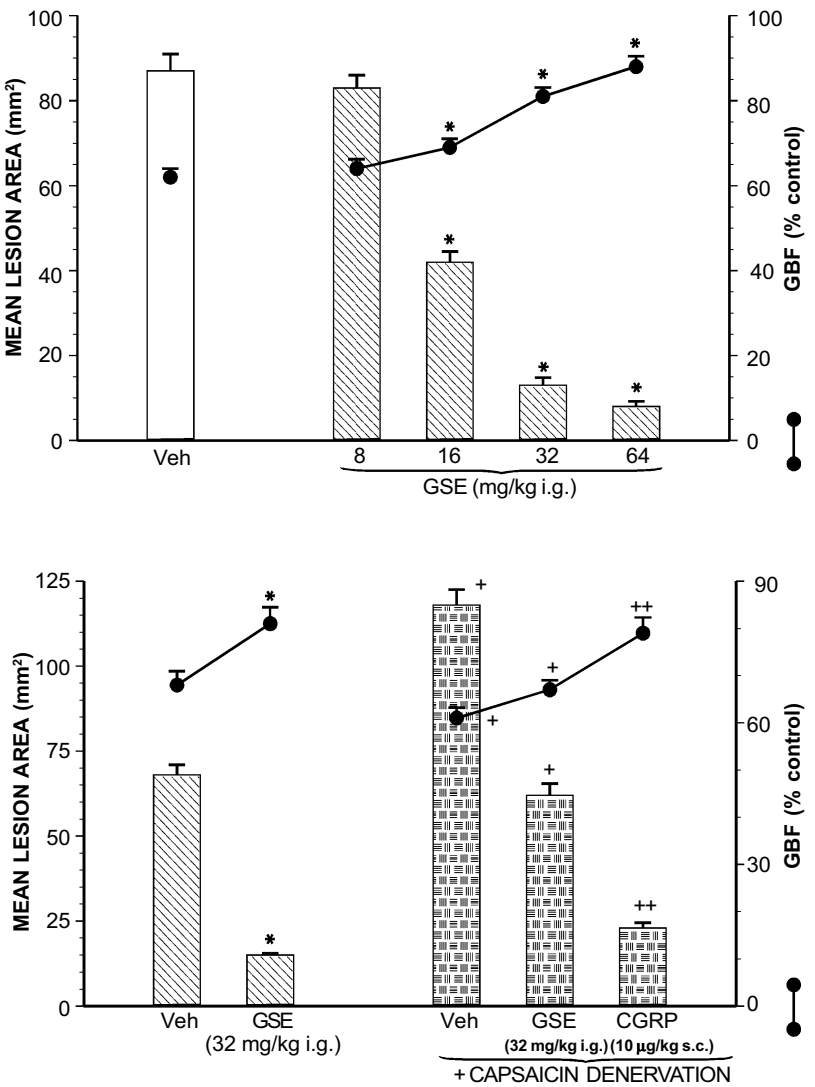

Fig. 3. Mean area of 100% ethanol-induced gastric lesions and the gastric blood flow (expressed as percent of control) in rats without (vehicle only) and with pretreatment with graded doses of grapefruit seed extract (GSE) (upper panel) and effects of capsaicin denervation without or with addition of calcitonin-gene related peptide (CGRP) (lower panel). Each column is a mean (± SEM) of 5-8 rats. Asterisk indicates significant ($P < 0.05$) change as compared to the vehicle (control) values.

meciadanol, a synthetic flavonoid, similar to catechin flavonoid, that inhibits histidine decarboxylase and decreases histamine content in the stomach, attenuated gastric mucosal lesions produced by ethanol and aspirin via mechanism independent of gastric acid secretion and endogenous prostaglandins (PG) [47].

One of the most interesting substances that has been obtained from chilly peppers and is present in spicy plants such as ginger or black pepper is capsaicin [8]. This substance acts on sensory neurons to stimulate their membrane receptors and release various kinins such as CGRP and substance P. When applied in large dose, it destroys selectively C-fiber neurons leading to inactivation of sensory nerves and the loss of all reflexes in which these nerves are involved. In smaller dose, capsaicin is the potent gastroprotective agent and stimulant of gastric microcirculation. According to our experience (Fig 4), capsaicin in dose range from 0.1 to o.5 mg/kg given ig reduced dose-dependently the ethanol-induced acute gastric hemorrhagic lesions and this is accompanied by the dose-dependent increase in gastric microcirculation. These effects can be abolished, also dose-dependently, by the pretreatment with L-NNA that reverses also the gastric hyperemic effects of capsaicin. Capsaicin is ineffective in rats with inactivated sensory nerves by large dose of capsaicin (125 mg sc two weeks before the experiment). Clinical usefulness of capsaicin has not been so far demonstrated but it is an excellent tool to study the implication of sensory nerves in the gastroprotection induced by various gastrorpotective agents including GSE, amaranth and various gastroprotective drugs and substances [48-51].

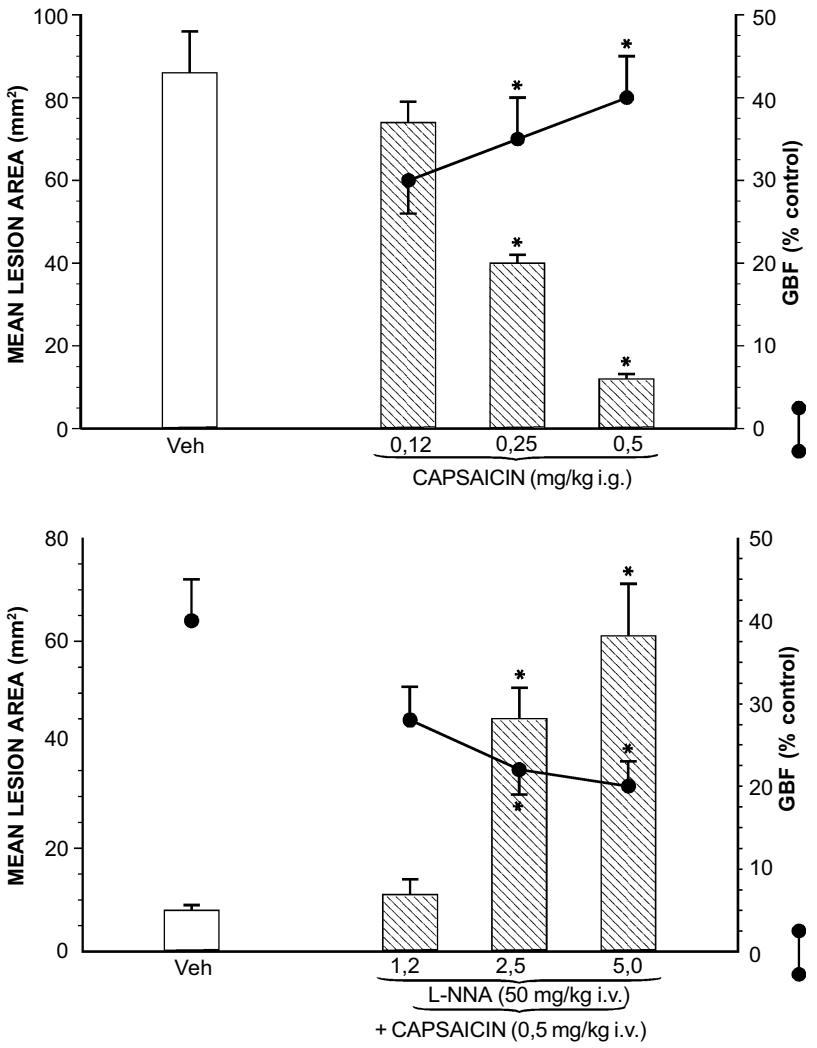

Fig. 4. Mean area of 100% ethanol-induced gastric lesions and the gastric blood flow (expressed as percent of control) in rats without (vehicle only) and with pretreatment with graded doses of capsaicin (upper panel) without and with addition of L-NNA, a NO synthase inhibitor (lower panel). Each column is a mean (± SEM) of 5-8 rats. Asterisk indicates significant ($P<0.05$) change as compared to the vehicle (control) values.

Table 1 summarizes the sources of plant cytoprotection and their known physiological actions on GIT. Data on the composition of these sources include different chemical compounds with different molecular structures. They are represented in Table 2.

Table 1. Pharmacological actions and plant-originated cytoprotectors

Physiological actions	Origins
Gastroprotective and antiulcer	Grapefruit (Citrus paradisi) seeds Panax ginseng
Induced changes in amount and glycoprotein content of gastric mucus	Erica andevalensis Cabe zudo-Rivera UL-409, herbal formulation
Preventive and curative effects	Sea buckthorn (Hippophae rhammoides L.)
Inhibition the basal and histamine-induced gastric acid secretion	Azadirachta indica Chinese cinnamon Phellodendron amurense Ruprecht
NO-induced rise in mucosal blood flow	Gingi biloba Silybum marianum Grapefruit seeds Bacopa monniera Grape seeds
Mucus and alkaline secretion	Tasmannia lanceolata Bacopa monniera Azadirachta indica Mikania cordata Solon (Sophoradin)
Prostaglandin release	Tamannia lanceolata Petasites hybridus Ruta chalepensis L. (Rutaceae)
Hepatoprotective	Tinospora bakis (Menisoermaceae) Premma tomentosa (L. Verbanacae)
Anticancerogenic	Grapefruit seeds Garsinia kola Grape seeds

Table 2. Active constituents in plant gastroprotectors

Active substances	Sources
Polysacchrides	Opunta ficus indica cladodes
Flavonoids	Erica andevalensis Cabezudo-Rivera Garcinia kola seeds (kolaviron) Achyrocline satureioides Silydum marianum Scutellaria baicalensis
Proanthocyanidins	Grape seeds extract Grape skin extract
Polyphenolic natural compound	Neem (Azadiracta indica) Curcumin
Diterpnes	Tasmannia Lanceolata Egletes viscosa
Sesquiterpenes	Petasites hybridus Emblica officinalis
Saponins	Hippocrata excelsa
Scvalen	Amaranth
Sitosterol	Egletes viscosaless
Ternatin	Horse chestnuts
Escins	Cinnamonum cassia
Berberine	Phellodendron amureuse Ruprecht

CONCLUSIONS

1. We demonstrated that plant-originated substances such as Solon – Sophoradin root originated flavonoid, seed extract of Amaranth, extract of grapefruit seeds - Citro kvapky, and capsaicin present in chilly pepper, all exerted beneficial and dose-dependent reduction in acute gastric lesions induced by corrosive concentration (100%) of ethanol and this reduction was accompanied by dose-dependent rise in gastric blood flow;

2. The mechanism of this protection is closely related to the increase in gastric microcirculation probably caused by stimulation of afferent nerves and release of NO in the mucosa because the protection and gastric hyperemia could be significantly attenuated following the inactivation of neurotoxic dose of capsaicin and the application of NOS inhibitor, L-NNA;

3. This study provides evidence that extracts originating from the plants used in ancient herbal medicine appear to contain highly effective, but unfortunately little studied in humans substances, most likely flavonoids, that are capable of protecting gastric mucosa from necrotizing substances and possibly are useful in the therapy of acute and chronic gastric ulcerations. Only Solon is now widely used in gastritis and

peptic ulcer therapy in certain countries.
Acknowledgement: To Prof. W. Pawlik for invaluable assistance with research in Jagiellonian University.
Source of support: Department resources/

O.S. Zayachkivska, S.J. Konturek, D. Drozdowicz, T. Brzozowski, M.R. Gzhegotsky

INFLUENCE OF PLANT-ORIGINATED GASTROPROTECTIVE AND ANTIULCER SUBSTANCES ON GASTRIC MUCOSAL REPAIR

Fundamental basis of cellular and molecular mechanisms involved in mucosal injury and repair in gastrointestinal tract helps to develop new therapeutic approaches to various gut mucosal injury- related diseases. The study was aimed to assess the relations between plant-originated substances and their bioactivity measured in terms of antioxidant, cytoprotective and antiulceric activities and to determinate if these effects are capable of affecting the gastric mucosal lesions induced by absolute ethanol applied intragastrically. The following plant-originated substances were considered: Solon, capsaicin, grapefruit-seed extract and amaranth. The area of gastric mucosa lesions and gastric blood flow were measured in rats with ethanol-induced lesions without (control) and with one of the tested substances without and with capsaicin denervation of afferent nerves or administration of L-nitro-arginine (L-NNA), an inhibitor of nitric oxide synthase (NOS).
Material/Methods: male Wistar rats, weighing 180-220 g fasted for 24 h before the study, 100% ethanol was applied ig to induced gastric lesions, whose area was determined by planimetry. Gastric blood flow was assessed using electrolytic regional blood flowmeter.
Results: All tested plant-originated substances afforded gastroprotection against ethanol-induced damage and this was accompanied by an increase in gastric microcirculation, both changes being reversed by pretreatment with neurotoxic dose of capsaicin or by pretreatment with L-NNA.
Conclusions: Plant-originated substances are highly gastroprotective probably due to enhancement of the expression of NOS I, NO release and an increase in gastric microcirculation.

REFERENCES

1. Alarcon de la Lastra A.C., Martin M.J., MotilvaV. et al. Gastroprotection induced by silymarin, the hepatoprotective principle of Silybum marianum in ishemia-reperfusion mucosal injury: role of neutrophils// Planta Med. – 1995. – **61** (20). – P.116–119.
2. Bae E A , Han M J , Kim D H. In vitro anti-Helicobacter pylori activity of some flavonoids and their metabolites. – Planta Med. – 1999. – **65**. – P. 441–443.
3. Bagchi D. , Bagchi M. , Stohs S. et al. Cellular protection with proanthocyanidins derived from grape seeds // Ann N. Y. Acad. Sci. – 2002. – **957**. – P. 260–270.
4. Bagchi D., Ray S.D., Bagchi M., Preuss H.G., Stohs S.J. Mechanistic pathways of antioxidant cytoprotection by a novel IH636 grape seed proanthocyanidin extract // Indian J. Exp. Biol. – 2002.– **40**(6). – P. 717–726.
5. Bagchi D., Sen C.K., Ray S.D. et al. Molecular mechanisms of cardioprotection by novel grape seed proanthoceanidin extract // Mutat Res. – 2003. – **523–524**. – P. 87–97.92.
6. Bandyopadhyay U., Biswas K., Chatterjee R. et al. Gastroprotective effects of Neem (Azadirachta indica) bark extract: possible involment of H(+)–K(+)–ATPase inhibition and scavenging of hydroxyl radical // Life Sci.– 2002.– **71**(24).–P. 2845–2865.
7. Bickel D., Roder T., Bestman H.J., Brune K. Identification and characterization of inhibitiors of peptidoleukotrienes syntesis from Petasites hybridus// Planta Med. – 1994. – **60**(4). – P. 318–322.
8. Blankson H., Grotterod E.M., Seglen P.O. Prevention of toxin-induced cytoskeletal disruption and apoptotic liver cell death by the grapefruit flavonoid, naringin // Cell Death Differ. – 2000. – **7**. – P. 739–746.
9. Brzozowski T., Konturek P.C., Iliwowski Z. et al. Importance of nitric oxide and capsaicin-sensitive afferent nerves in healing of stress lesions induced by epidermal growth factor // J. Clin Gastroenterol. – 1997. – **25** (1). – P. 28–38.
10. Chao J.C., Hung H.C., Chen S.H., Fang C.L. Effects of Ginkgo biloba extract on cytoprotective factors in rats with duodenal ulcer // World J. Gastroenterol. – 2004. – **10**(4). – P. 560–566.
11. Dorababu M., Prabha T., Priyambada S., Agrawal V.K., Aryya N.C., Goel R.K. Effect of Bacopa monniera and Azadirachta indica on gastric ulceration and healing in experimental NIDDM rats // Indian J. Exp. Biol. – 2004. – **42**(4). – P.389–397.
12. Farombi E.O., Alabi M.C., Akuru T.O. Kolaviron modulates cellular redox status and impairment of membrane protein activities induced by potassium bromate (KbrO(3)) in rats // Pharmacol Res. – 2002. – **45**(1). – P. 63–68.
13. Farombi E.O., Hansen M., Ravn-Haren G. et al. Commonly consumed and naturally occurring dietary substances affect biomarkers of oxidative stress and DNA damage in healthy rats // Food Chem. Toxicol. – 2004. – **42**(8). – P. 1315–1322.
14. Farombi E.O., Moller P., Dragsted L.O. Ex vivo and in vitro protective effects of kolaviron against oxygen derived radical induced DNA damage and oxidative stress in human lymphocytes and rat liver cells // Cell Biol Toxicol. – 2004. – **20**(2). – P. 71–82.
15. Fitzpatrick D.F., Bing B., Maggi D.A. et al. Vasodilating procyanidins derived from grape seeds // Ann N. Y.

Acad. Sci. – 2002. – **957**. – P. 78–89.
16. Gastointestinal mucosal repair and experimental therapeutics (Cho C.-H., Wang J.-Y.,eds). Frontiers of Gastrointestinal Res – Basel. Karger – 2002, **25**. – 251 p.
17. Giamperi L., Fraternale D., Bucchini A., Rocco D. Antioxidant activity of Citrus paradisi seeds glyceric extract // Fitoterapia. – 2004. – **75**(20). – P. 221–224.
18. Havsteen B. Flavonoids with, a class of natural products of high pharmacological potency // Biochem. Pharmacol. – 1983. – **32**. – P. 1141–1149.
19. Heggers J.P., Cottingham J., Gusman J. et al. The effectiveness of processed grapefruit-seed extract as an antibacterial agent: II. Mechanism of action and in vitro toxicity // J. Altern Complement Med. – 2002. – **8**. –P. 333–340.
20. Horoz L.M., Zubachyk W.M., Lukavetsky O.V. et al. Influence of thyroid gland hypofunction on apoptosis in oral mucous and salivatory glands// AML. – 2001. – **1**. – P.70–78.
21. Ito M., Suzuki Y., Ishihara M., Suzuki Y. Anti-ulcer effects of antioxidants: effect of probucol // Eur J. Pharmacol. – 1998. – **354**(2–3). – P.189–196.
22. Kim S.C., Byun S.H., Yang C.H. et al. Cytoprotective effects of Glycyrrhizae radix extract and its active component liquiritigenin against cadmium-induced toxicity (effects on bad translocation and cytochrome c-mediated PARP cleavage)// Toxicology. – 2004. – **197**(3). – P. 239–251.
23. Konturek S.J., Brzozowski T., Drozdowicz D. et al. Gastroprotective and ulcer healing effects of solon, a synthetic flavonoid derivative of Sophoradin // Hepato-Gastroenterol.– 1987.– **34**.– P.164–170.
24. Konturek S.J., Kitler M.E., Brzozowski T., Radecki T. Gastric protection by meciadanol. A new synthetic flavonoid inhibiting histidine decarboxylase // Dig. Dis. Sci. – 1986. – **31**. – P.847–852.
25. Konturek S.J., Radecki T., Piastucki I. et al. Antiulcer and gastroprotective effect of Solon, a synthetic flavonoids derivative of sophoradin. Role of endogenous prostaglandins // Eur. J. Pharmacol. – 1986. – **21**. – P. 6–10.
26. Kyogoku K., Hatayma K., Yokomori S. et al. Anti-ulcer effect of isoprenyl flavonoids. Synthesis and anti-ulcer activity of a nea chalone related to sophoradin // Chem. Pharm. Bull. – 1979. – **27**. – P. 2943–2952.
27. Laurent C., Besancon P., Anger C. et al. Grape-seed extract affects proliferation and differentiation of 37 human intestinal Caco-2 cells // J. Agric. Food. Chem. – 2004. – **52**(11). – P. 3301–3308.
28. Liu C.F., Lin C.C., Lin M.H. et al. Cytoprotection by propolis ethanol extract of acute absolute ethanol-induced gastric mucosal lesions// Amer. J. Chin. Med. – 2002. – **30**(2–3). – P. 35–254.
29. Llopiz N., Puiggros F., Cespedes E. et al. Antigenotoxic effects of grape seed procyanidin extract in Fao cells submitted to oxidative stress // J. Agric. Food. Chem. – 2004. – **52**(5). – P. 1083–1087.
30. Moreno D.A., Ilic M., Poulev A. et al. Inhibitory effects of grape seed extract on lipases. – Nutrition. – 2003. – **19**(10). – P. 876–879.
31. Motilva V., Alarcon de la Lastra C., Martin M.J. Ulcer-protecting effects of naringenin on gastric lesions induced by ethanol in rat: role of endogenous prostaglandins // J. Pharm. Pharmacol. – 1994. – **46**. – P. 91–94.
32. Natella F., Belelli F., Gentili V., Ursini F., Scaccini C. Grape seed proanthocyanidins prevent plasma postprandial oxidative stress in humans // J. Agric. Food. Chem. – 2002. – **50**(26). – P. 7720–7725.
33. Navarrete A., Trejo-Miranda J.L., Reyaes-Trjo L. Principles of root bark of Hippocratea excelasa (Hippocrataceae) with gastroprotective activity// J. Ethnopharmacol. – 2002. – **79**(3). – P. 383–388.
34. Pastrada-Bonilla E., Akoh C.C., Sellappan S., Krewer G. Phenolic content and antioxidant capacity of muscadine grapes // J. Agric. Food. Chem. – 2003. – **51**(18). –P. 5497–5503.
35. Preuss H.G, Bagchi D., Bagchi M. Protective effects of a novel niacin-bound chromium complex and a grape seed proanthocyanidin extract on advancing age and various aspects of syndrome X.-Ann N. Y. Acad. Sci. – 2002. – **957**. – P. 250–259.
36. Raji Y., Ogunwande I.A., Osadebe C.A., John G. Effects of Azadirachta indica extract on gastric ulceration and acid secretion in rats // J. Ethnopharmacol. – 2004. – **90**(1). – P. 167–170.
37. Rang H.P., Dale M.M., Ritter J.M. Pharmacology. – Churchill Livingstone, 1995. – P. 615.
38. Rao V.S., Santos F.A., Solreira T.T., Souza M.F., Melo C.L. et al. Investigations on the gastroprotective and antidiarrhocal properties of ternatin, a tetramethoxyflavone from Egletes viscose //Planta Med. – 1997. – **63** (20). – P. 146–149.
39. Reagor L., Gusman J., McCoy L., Carino E., Heggers J.P. The effectiveness of processed grapefruit-seed extract as an antibacterial agent: I. An in vitro agar assay // J. Altern. Complement Med. – 2002. – **8**. – P. 325–332.
40. Reyes M., Martin C., Alarcon de la Lastra C., Trujillo J., Toro M.V. et al. Antiulcerogenicity of the flavonoid fraction from Erica andevalensis Cabezudo-Rivera// Z. Naturforsch. – 1996. – **51** (7–8). – P. 563–569.
41. Saeki T/, Ohno T/, Boku K/ et al. Mechanism of prevention by capsaicin of ethanol–induced gastric mucosal injury – a study in the rat using intravital microscopy // Aliment Pharmacol Ther. – 2000. –**143**. – P. 135–144.
42. Sano A., Ymakoshi J., Tokutake S., Tobe K. et al. Procyanidin B1 is detected in human serum after intake of proanthocyanidin-rich grape seed extract // Biosci Biotechnol Biochem. – 2003. – **67**(5). – P. 1140–1143.
43. Shirwaikar A., Bhilegaonkar P.M., Malini S., Kumar J.S. The gastroprotection activity of the ethanol ex-

tract of Ageratum conyzoides // J. Ethonopharmacol. – 2003. – **86**(1). – P.117–121.
44. So F.V., Guthrie N., Chambers A.F., Moussa M., Carroll K.K. Inhibition of human breast cancer cell proliferation and delay of mammary tumorogenesis by flavonoids and citrus juices // Nutr. Cancer. – 1996. – **26**. – P.167–181.
45. Szocsanyi J., Bartho L. Capsaicin-sensitive afferents and their role in gastroprotection: an update. – J. Physiol. Pharmacol. – 2001. – **95**. – P. 181–188.
46. Tsybina T., Dunaevsky Y., Musolyamov A., Egorov T. et al. New protease inhibitors from buckwheat seeds: properties, partial aminoacid sequences and possible biological role // Biol. Chem. – 2004. – **385**(5). – P. 429–434.
47. Uchiyama T., Kamikawa H., Ogita Z., Yakugaku Zasshi. Anti-ulcer effect of extract from phellodendri cortex// Eur J. Pharmacol. – 1989. – **109**(9). – P. 672–676.
48. Yimaz Y., Toledo R.T. Major flavonoids in grape seeds and skins: antioxidant capacity of catechin, epicatechin, and gallic acid // J. Agric. Food. Chem. – 2004. – **52**(2). – P. 255–260.

DepartmLviv National Medical University, Ukraine;
Jagiellonian University College of Medicine, Cracow, Poland

Paper vas submited 21.10.2004