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Gastroprotection without Gastric Acid Suppression Mini Review and Personal Experience

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ABSTRACT

First of all, the protection of gastro mucosa against injury, which can be caused by a variety of noxious agents, and the restitution of mucosal integrity after mucosal damage depends on the interplay of numerous different effectors and mediators. Second. the mucus is the first line of defense against luminal attacks on mucosal integrity. The intact microcirculation which is necessary for tissue protection and repair. Thirdly the process of mucosal restitution and regeneration is controlled by various endogenous components, including growth factors, particularly EGF and TGFα. Fourthly, some agents which can cause mucosal damage like non-steroidal anti-inflammatory drugs, including acetylosalicylic acid, and probably can be protected by natural substances via the mechanism of adaptive gastroprotection. Essential is the presence of a series of exogenous natural substances that have a gastroprotective effect, increasing the gastric mucosa endogenous adaptive cytoprotection potential. Among such exogenous natural substances, we paid attention to the Coniferous Pine Needles Extract (Baltic pine or Pinus sylvestris). The phytochemical substances present in Coniferous Pine Needles Extract are nontoxic at therapeutic levels, with clearly gastroprotective effect.

Keywords: Gastric Mucosal Damage; Gastroprotection; Substances of Natural Origin

Abbreviations: NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; PPI: Proton Pump Inhibitors; EJL: Erosive-Ulcerative Lesions; ATC: Anatomical Therapeutic Chemical; AAN: Australian Approved Name; SGC: State Gastroenteroiogy Ce Dter; SDC: State Diagnostic Center; CGNC: Conifer Green Needle Complex; TGA: Therapeutic Goods Administration; UGI: OTC: Over-The-Counter; UGI: Upper Gastrointestinal; ATC: Anatomical Therapeutic Chemical; IUPAC: International Union of Pure and Applied Chemistry; GI: Gastrointestinal; WIPO: Word Intellectual Property Organization; SCH: State Clinical Stradina Hospitai; SDC: State Diagnostic Center; FTS: Fitesten

Introduction

Gastroprotection Importance

Erosive and ulcerative gastric mucosa lesions remain a significant problem. The potential for non-steroidal anti-inflammatory drugs (NSAID) to cause erosive and ulcerative gastric mucosa lesions is well known. NSAIDs are used by over 30 million people daily across the globe [1]. Studies have shown that NSAIDs are associated with gastropathy (NSAID-induced gastropathy - NIG) irrespective of the duration of use, and the use of NSAIDs has become widespread due to the availability of these agents both as prescription and as over-the-counter (OTC) medicines [2]. Overall, mortality in patients suffering from an upper gastrointestinal (UGI) bleed or perforation related to NSAIDs use is estimated to be about 1 in 5 [3]. It is likely that age is an important independent risk factor for NIG complications. The message for the clinician is that gastroprotection and should mainly be considered in those over the age of 60 years. Moreover, in those over the age of 60, the threshold to offer gastroprotection should decrease as age increases with a particular consideration given to those over the age of 80 years [4].

The same NIG situation at the drug-associated gastric mucosa lesions have been described for: antiplatelet, anticoagulant medication therapy and selective serotonin reuptake inhibitors in addition to the well-known corticosteroids adverse effects. The situation is exacerbated by comorbid conditions such as: malignancy had a 6-fold, those with renal disease a 5-fold, and those with hepatic disease a 4-fold increased risk of mortality from peptic ulcer bleeding [5]. It should be noted the potential for a reactive gastropathy greater prevalence for a whole series of drugs and the wide range of drug related changes seen in gastrointestinal biopsies [6]. Reactive gastropathy represents another distinct type gastric injury that is mainly caused by bile reflux through the pylorus, but also by other noxious agents, such as drugs or ethanol [7].

Gastroprotection Definitions

In the Medical Subject Headings in PubMed publication base, there is a definition of cytoprotection: "Cytoprotection: "The process by which chemical compounds provide protection to cells against harmful agents". Thus, cytoprotection is the process by which chemical compounds protect cells from harmful factors (agents). Since 2000, 10 international symposiums have been held under the general title "International Symposia on Cell/Tissue Injury and Cytoprotection/Organoprotection", in the materials of which the results of numerous studies on cytoprotection have been published. In the context of cytoprotection of the gastric mucosa, attention should be paid to the materials of the 7th Symposium [8], a significant part of which is devoted to the mucous membrane digestive organs, and above gastric mucosa cytoprotection. The proceedings of this international symposium emphasize that the definition of gastroprotection is more complex and is based on the results of multidisciplinary studies in a large number of laboratories around the world. Participants of the 7th International Symposium on Digestive Mucosal Cytoprotection summarized the definition of gastroprotection as follows: preservation of subepithelial endothelial cells and microcirculation, providing surviving foveolar cells of the gastric mucosa, their ability to migrate and proliferate, which together provides adequate repair of epithelial cells of the surface layer of the mucous membrane. The clinically important part is emphasized: "gastric cytoprotection = gastroprotection" is the prevention (by PG, PL, SH, NO, etc.) of chemically induced hemorrhagic erosions of the stomach, by substances other than those that have an inhibitory effect on gastric acid secretion, while preservation of microcirculation is a key element.

Medicines Positioned as Gastroprotectors

Traditionally, many guidelines focus on inhibitors of gastric acid secretion, and designate these drugs as gastroprotectors. The proton pump inhibitors (PPI) has been investigated for their efficacy in preventing NISAND-induced gastrointestinal injuries. However, the choice of these drugs for preventing the gastrointestinal injuries of patients using NISAND (including aspirin) remains controversial. According to the several guidelines [9] PPIs are recommended for patients with high gastrointestinal (GI) risk who could not avoid using nonsteroidal anti-inflammatory drugs (NSAIDs). For patients at low GI risk, PPIs are not recommended, considering its potential adverse effects, high expense, and overuse in clinical settings [10]. Currently, there is paucity in therapeutics investigated for the prevention of NISAND-induced gastrointestinal complications for these low-GI-risk patients who are not recommended to use PPIs. In addition, it should be noted that in accordance with the above definition of gastroprotection, acid-suppressive drugs are not true gastroprotectors. The presented our results of analytical publication on the gastric mucosa cytoprotection showed significant changes in practical ways. Clinically important part of the cytoprotection definition is the prevention chemically induced gastric erosions by substances other than providing an inhibitory action on gastric acid secretion, for the retention of the microcirculation is a key element [11]. There is an increase in research on various aspects of the phenomenon of cytoprotection with the intensification of the search of substances with really cytoprotective effect on gastric mucosa.

These substances have significant characteristics – they have no inhibitory effect on the secretion of acidic gastric mucosa. Such substances allow for effective drug therapy erosions of the gastric mucosa, especially in the medical need for non-steroidal anti-inflammatory agents. The problem of creating effective and safe drugs with a cytoprotective effect, without gastric acid suppression, has a long history. Salts of colloidal bismuth were one of the first such medicines. Medicines based on salts of colloidal bismuth (tri-potassium di-citrato bismuthate) continue to be used in clinical practice. However, a limitation for their use is the presence of a cumulative effect of the accumulation of bismuth in the body, which prevents the use of the drug in case of need for long-term and/or repeated treatment. Drugs based on sucralfate (sulfated polysaccharides), sodium glycyrrhizinate, carbenoxolone (carbenoxolone) and a number of drugs created more than 50 years ago do not even have satisfactory evidence of efficacy, therefore they are not able to compete in their properties with modern drugs, and , despite the fact that some of them are still used in some countries, today they are of no more than historical interest.

Misoprastol was created for cytoprotection of the gastric and duodenal mucosa. Clinical trials have shown sufficient efficacy of misoprostol in erosive-ulcerative lesions (EJL) in the gastroduodenal mucosa. Misoprostol proved to be effective in the prevention of NSAID-induced EEP in this area. However, the drug has a number of side effects (on the uterus, intestines), limiting its use. To natural cytoprotectors include donators of sulfhydryl groups, prostaglandins and a number of neuropeptides. Natural cytoprotectors provide a protective effect through effects on the production and composition of mucus mucins or through effects on the epithelial barrier with

the participation of factors (TGF). Natural cytoprotectors include short peptides (di-, tri-, pentapeptides) [12]. It has been shown that such peptides (with a cytoprotective effect) also have antispasmodic properties. However, up to the present no time offered for clinical practice drugs based on short peptides with gastroprotective action. Japanese researchers have proposed a new drug with a protective effect on the mucous membrane of the digestive system – rebamipide (OPC 12759). According to the MeSH classification, PubMed Publication Database rebamipide refers to derivatives of the amino acid alanine.

According to the systematized nomenclature of the International Union of Pure and Applied Chemistry (International Union of Pure and Applied Chemistry (IUPAC) rebamipide has chemical name N-(4-Chlorobenzoyl)-3-(2-oxo-1,2-dihydroquinolin-4-yl) alanine. Moreover, Japan Anatomical Therapeutic Chemical (ATC) classification included position DGROUP: Gastric mucosal protectant, with 19 different components {https://www.genome.jp/entry/DG02008} and in the comments to this section it is written: "This medicine increases secretion of gastric mucus and promotes protection and repair of damaged gastric mucosa. It is usually used in the improvement of acute gastritis and gastric mucosal lesion in acute exacerbation of chronic gastritis (erosion, bleeding, flare, and edema) and treatment of gastric ulcer". The current rationale for drug treatment in gastritis is similar to other gastrointestinal disorders (eg., non-ulcer dyspepsia), and depends mainly on symptomatic relief using gastroprotective agents (e.g., rebamipide, teprenone, ecabet sodium, sofalcone, cetraxate, etc.).

Databases publications (PubMed, ScienceDirect) analysis shows that the development of gastroprotectors based on components from natural plant products is usually carried out in Asian countries, primarily such as Japan, China and Korea. It should be emphasized, gastritis, the "precursor" lesion to mucosal ulceration is both an important clinical entity and an important cause of abdominal pain in children [13]. Inflammation of the gastric mucosa is the end result of an imbalance between mucosal defensive and aggressive factors (i.e., disturbances in gastric acidity and the mucus-bicarbonate barrier), and recently a great deal of attention has been focused on gastric hormones, specifically gastrin, and pepsinogens I and II [14]. For a number of natural gastroprotectors, there are a significant number of publications showing that such gastroprotectors have additional properties, such as: antioxidative, superoxide and hydroxyl radicals scavenger, possesses potent anti-inflammatory activities, regenerates mucosal epithelial cells, and enhances the cytoprotective cytokines. For example, Eupatilin from Artemisia argyi (A. argyi) is a medicinal plant that belongs to the Asteraceae family and Artemisia genus. [15]. Comparative analysis of literature searched through sources available confirmed that the ethnopharmacological use of A. asiatica was recorded in Korea, China, and Japan.

Phytochemical studies revealed the presence of flavonoids, sesquiterpene lactones, monoterpenes, and steroids in A. asiatica. Of these, flavonoids have been shown to exhibit significant pharmacological effects such as gastroprotective, anti-inflammatory, anti-tumor, and anti-microbial actions. Korean authors [16], summing up the effectiveness of Eupatilin, noted the following: Comparative analysis of literature searched through sources available confirmed that the ethnopharmacological use of A. asiatica was recorded in Korea, China, and Japan. Phytochemical studies revealed the presence of flavonoids, sesquiterpene lactones, monoterpenes, and steroids in A. asiatica. Of these, flavonoids have been shown to exhibit significant pharmacological effects such as gastroprotective, anti-inflammatory, anti-tumor, and anti-microbial actions. Authors further noted: "Toxicity studies with A. asiatica have been conducted in order to assess the safety of plant extracts. According to a clinical study on the safety and efficacy of DA-9601(Eupatilin) and DA-5024(Cetraxate) performed with 434 patients having gastric mucosal erosion, it was found that there were no clear toxicological effects on various biochemical markers." This authors statement is true for almost all natural gastroprotectors.

General Assessment of the Health Properties of Pine Components

In according to EU Novel food catalogue (https://webgate.ec.europa.eu/fip/novel_food_catalogue) Pinus sylvestris classified as food. In the description section marked: "The request concerns the needle extract of Pinus sylvestris. In addition the use of cones, needles, bud, bark and young shoots are authorized only in food supplements (Belgian list of plants that are considered to be not novel for the use in food supplements)". Differences in the composition of various groups of lipophilic extractives, low-molecular carbohydrates, cyclitols, phenolic glycosides, polysaccharides, lignin, ash and crude protein in green needles and brown needle litter from the same stand of Scots pine (Pinus sylvestris) were studied. There was a great drop of sugars, steryl esters and triglycerides going from green to brown needles on the tree. Some isoprenoid alcohols, sterols and some acids as well as lignin belong to the components that changed least. Moreover, there are over one hundred species of pine worldwide, and most have recorded medicinal uses. Cultures around the globe have used the needles, inner bark, and resin for similar ailments [17]. Internally, pine is a traditional remedy for coughs, colds, allergies, and urinary tract and sinus infections. Topically, pine is used to address skin infections and to lessen joint inflammation in arthritic conditions. Pine needles have been used in Chinese traditional medicine to treat diseases, such as wind-cold-dampness arthralgia, traumatic injury, sleeplessness, eczema and oedema. Previous literature suggested that the medicinal properties of pine needles may be related to their several bioactive substances. The bioactive substances in pine needles may provide protection against oxidative DNA damage in non-cellular and cellular systems [18,19].

Database by Word Intellectual property organization (WIPO/ Patentscoper) search revealed the following: in A61P - subclass covers therapeutic activity of chemical compounds or medicinal preparations already classified as such in subclasses A61K or C12N, and from 2353 results (pinus AND health)- 503(21%) fine for A61P, predominantly from China, Republic of Korea and Japan - 2234(95%). The overall assessment of found patents can be represented by the following characteristic. Pinus sylvestris preparations are widely used for infectious and inflammatory diseases of the respiratory tract (laryngitis, pharyngitis), including those accompanied by cough with sputum difficult to separate (tracheitis, chronic bronchitis), bronchopneumonia - as part of complex therapy. It is a valuable vitamin remedy. Often included in breast fees and dietary supplements. Scotch pine has expectorant, diuretic, diaphoretic and disinfectant properties. In folk medicine, Scots pine is used for bronchitis, pneumonia, rheumatism and arthritis, cholecystitis, cholangitis, pyelonephritis and cystitis. The needles have antiscorbutic, biostimulating and antimicrobial effects. Kidneys - have an emollient, expectorant, antimicrobial, disinfectant, diuretic, weak choleretic, antiscorbutic and blood-purifying effect. Pollen in rheumatism, gout, after serious illnesses.

There are patents with a positive gastroprotective effect of extracts from pine needles including H.pylori IgG antibody reduced, a treatment rate is high as a result of converting a treatment rate through CLO test in a gastric mucosal tissues, and a result reduced concentration of TNF- alpha; and IL-1 beta or cytokine changes in the gastric mucosa. Pine needle oil, pine resin-derived turpentine oil, and pine sprouts are approved by the German Commission E for treating coughs, chronic bronchitis, and other irritations or infections of the respiratory tract. [20]. Moreover, there is a product on the market based on pine needle extract with the name Bioeffectives®. Bioeffective® is so easily assimilated, has such high efficacy and extremely low toxicity. It is also why it has such a wide range of applications in the prevention and treatment of illnesses and in the promotion of health. Bioeffective® A is approved by the TGA for use in listed oral and topical products. It is the active component in TAIGA PROFESSIONAL A 320 capsules, approved as an antioxidant complex, and registered and sold in Australia. It is also commercialised in the UAE, and in Malaysia as NuvaPine® capsules. In Australia Bioeffective® Gel (with Bioeffective® A), a product designed to be a potent antioxidant and to aid in the healing of minor skin irritations such as minor burns and wounds is also marketed.

The 'TGA assessed' claim (symbol and/or statement) shows that the Therapeutic Goods Administration (TGA) has assessed the medicine's indications (conditions the medicine says it will treat) and found they are supported by scientific evidence. and is known by the TGA Australian Approved Name (AAN) Conifer Green Needle Complex (CGNC) and Bioeffective A. This is also called an 'efficacy' assessment. Ongoing development and research worldwide of Bioeffectives® for medical, cosmetic, agricultural and veterinary applications. Approximately 90 clinical and preclinical trials completed in a number of areas, including: Liver Disease, Alzheimers, Antiviral, Detoxification, Helicobacter Pylori, Alcoholism, Hormone regulation, Immune system, Oncology support. Let's pay attention to one study [21], the authors of which showed the following: A tablet form of CGNC (extracted from Pinus sylvestris and Picea abies (L) Karst) was prescribed to 26 patients with precancerous gastric lesions (twotablets, 100mg τCGNC/tablet, three times per day for six months). Another 24 patients received no treatment. Results. Compared with control patients, CGNC-treated patients showed total or partial regression (using the quantitative Rome III diagnostic criteria) of dyspeptic symptoms (92.3%, $p < 0.0001$), eradication of H. pylori infection (57.1%, $p < 0.03$), a reduction in endoscopic signs of gastritis (92.3%, $p < 0.001$), an increase of pepsinogen-pepsin in the gastric juice (57.7%, $p < 0.05$), and total regression or reduction in the degree of intestinal metaplasia (46.2%, $p < 0.05$) and lymphoplasmacytic infiltration (53.8%, $p < 0.05$).

Results of Own Research

We chose Pinus sylvestris as the raw materials for the developed product - Dense Conifer Needle Extract/DCNE (Fitesten®) Pre-clinical results of Dense Conifer Needle Extract (Fitesten®) Preventive Effect of DCNE on the Acute Indomethacin Model of Ulcerogenesis. The animals(rats) were divided into groups:

1. Group - control with indomethacin - 20 mg/kg;
2. Group- experiment - allantoin 20 mg/kg + indomethacin;
3. Group – experiment with sea buckthorn oil 1 ml/kg + indomethacin;
4. Group - experiment DCNE 40.0 mg/kg + indomethacin.

To achieve the preventive aim studied substances were inserted into the stomach with a help of a probe during three days and one hour before indomethacin. A probe without the preparation was inserted into the stomach to control animals. In 24 hours after the administration of indomethacin all animals were slain by the method of cranio-cervical dislocation under light ether narcosis. The stomach was extracted, the incision was made along a big curvature and washed by cold saline solution. The stomachs were pinned on corks plates. The examination of the stomachs was conducted with the help of a loupe with the increasing l x7. Destructive changes were assessed in points:

1. No apparent changes;
2. The presence of edema, blood or 1-3 ulcers;
3. More than 3 small ulcers or 1 big one;
4. One ulcer up to 4 mm;
5. Some small ulcers;
6. Perforated ulcer.

An average number of ulcerations per one animal in the group and the percentage of animals with ulcers were calculated. Then, index of ulcerations (index of Pauls IP) (Table 1). High PA index for DCNE can be explained by the absence of stomach ulcers in this experimental group. Microscopically: in group with indomethacin all the animals have a pronounced gastritis with acute erosions. One animal has acute ulcer.

Table 1: Macroscopic Picture of Anti-Ulcer Activity of the Studied Substances.

Studied substance	Pathological changes in the mucous membrane of the stomach in points	A number of animals with erosions %	Index of Paul's IP	Anti-ulcer activity AA
Indomethacin	14.0	100.0	14.0	00
Sea buckthorn oil	6.0	100.0	6.0	2.3
Allantoin	4.0	70.0	2.8	7.0
DCNE	4.0	50	2.0	7.0

All the animals have a pronounced inflammatory process; in group with indomethacin+DCNE only one animal has gastritis but less pronounced in comparison with the previous groups. More than weekly hyperemia in indomethacin group - 4/0, in DCNE+indomethacin – 0/4 and a similar situation in terms of the severity of gastritis (indomethacin group - 4/0, in DCNE+indomethacin – 0/4) The frequencies analysis for the 2 x 2 table shows a significant difference: Chi-square (df=1)-8,00, p= 0,0047; V-square (df=1)-7,00, p=0 ,0082 and Yates corrected Chi-square - 4,50, p= 0,0339; Fisher exact p, one-tailed p= 0,0143, two-tailed p= 0,0286.Anti-Ulcerogenic Action of DCNE at Chronic Acetate exposure. The animals(rats) were divided into groups per 27 individuals in each group:

1. Group - control - only operation(acetate);
2. Group - experiment - operation + sea-buckthorn oil I ml/kg;
3. Group- experiment - operation+ DCNE - 20.0 mg/kg;
4. Group - experiment - operation+ DCNE - 40.0 mg/kg (Figure 1).

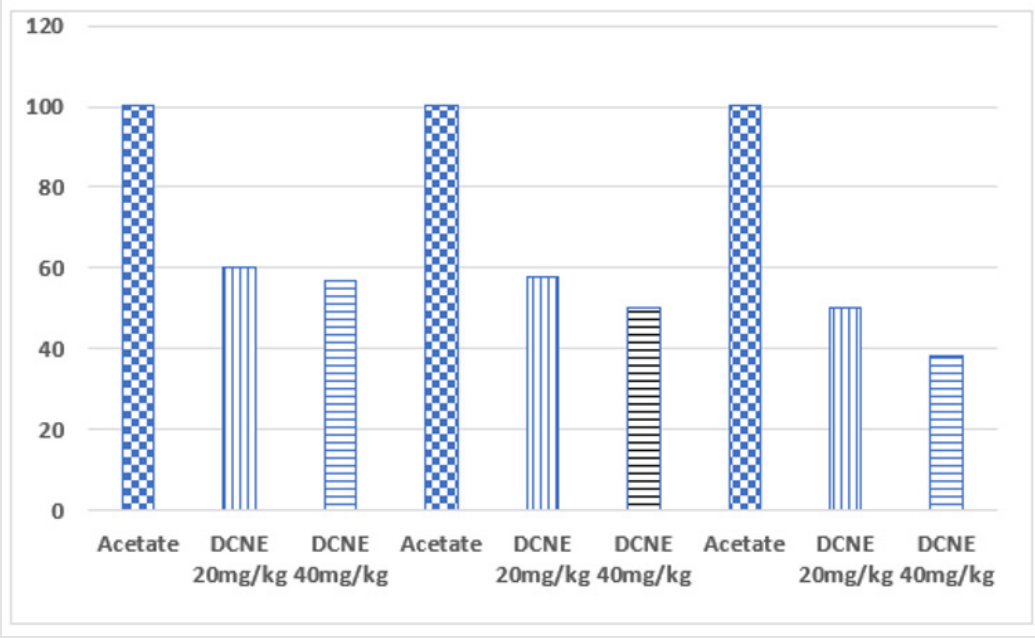

Figure 1: The Change of the area of Acetate Ulcer under the Influence of Studied Preparations. 100% is taken as the Area of the Ulcer after the Exposure by Acetic Acid.

The animals after the administration of the acetic acid were given DCNE at doses 20 mg/kg and 40 mg/kg. Morphological evaluation of the material has shown that zone of the necrosis narrowed by the tenth day after the simulation of the pathology. On the edges of the ulcer the epithelization took place with the formation of mucous glands. Complete epithelization of the ulcer surface was observed by the 21st day in 25% of cases. A significant decrease of absolute number of perforations, large multilocular cysts and purulent abscesses were observed. The Assessment of the Activity of Dense Conifer Needle Extract in Chronic Experiment at the Ulcer of the Mucous Membrane of the Stomach Caused by Indomethacin. The studied substances were inserted into the rats' stomach with a help of a probe during 20 days: indomethacin at dose 5 mg/kg, DCNE - 20 mg/kg and 40 mg/kg. The animals were divided into groups: 8 individuals in each group:

1. Group - control — indomethacin 5 mg/kg every day;
2. Group - experiment with sea buckthorn 1 ml/kg + indomethacin;
3. Group - experiment witth DCNE 20.0 mg/log + indomethacin;
4. Group - experiment with DCNE 40.0 mg/kg + indomethacin.

The mean number of lesions of the mucous membrane of the stomach per one animal in the group was calculated. Histological preparations of the stomachs fixed in 10% buffered formalin from four animals from each group according to the standard methods were prepared. The therapeutic action of DCNE on this model reduced the number of destructions by the 5th day of the treatment till 2.8 ±0.4 mg/kg (dose 20mg/kg) and 2.5±0.3 at dose 40 mg/kg, on 21st day 1,2+0,2 and 1,1+0,1, what significantly differs from the group only indomethacin(5th day – 8,2+0,9, on 21st day -6,9+0,7). Morphological evaluation of the material has shown that the destructive changes were characterized by the formation of ulcerations and hemorrhages that were on the tops of the folds in the form of strips of 2- 3 mm long and located in the upper part of the stomach at indomethacin. In most cases the characteristic phenomenon of destruction was found: glandular tubes parted by the accumulation of red blood cells, leukocytic infiltrates capturing the muscular layer. On the 10t' day with DCNE the edema and hyperemia of the mucous membrane decreased; the symptoms of the desquamation gastritis disappeared. The animals taking DCNE had small erosions in ½ of the thickness of the mucousmembrane, the edema of muscular layer, lymphatic infiltrates. By the end of experiment (with DCNE) these changes disappeared, the edema and hyperemia of the mucous membrane decreased. Thus, the conducted investigations of anti-ulcerogenic action of DCNE on different experimental models in the conditions of acute and chronical influence of ulcerogenic agents have shown that DCNE in the examined doses reduces the process of ulcer formation and makes morphological indices better, that is DCEN has a gastroprotective effect.

The Study of the Influence of Dense Conifer Needle Extract on the gastric juice secretion and its acidity. The investigations were conducted on eight dogs of both sexes of the age of 3 to 6 years, their mass was 10-12 kg. The dogs were kept in the standard conditions. Every day in the morning for a month the experimental animals were given DCNE at dose 150 mg/kg. with food. The control animals were given only food. The influence of DCNE on the acid formation, ferment formation have been studied. The volume of the gastric juice vas measured; pH was measured with the help of pH-meter. The amount of gastric juice of dogs before the use of the preparations ranged from 10 ml to 60 ml and after the administration of DCNE -from 1.5 ml to 52 ml. The significant increase or decrease of the amount of gastric juice under the influence of the preparation was not detected. The lowest value of pH (1,5) was noted in dogs and the same low value of pH was noted alter the DCNE use. The amount of pepsin in investigated dogs ranged from 1 mg/100 ml till 2.0 mg/ 100 ml, and DCNE had no effect on pepsin content.

Clinical Study Data

The first form of Dense Conifer Needle Extract (paste for internal use) was registered in the Latvian State Medicines Agency from 1995 to 2005 for indications - stomach ulcers, erosions and gastritis by name Fitesten®. Now Fitesten®(FTS) is used in capsules by many patients with speaks very well about the product. FTS clinical study was performed at the Latvian Medical Academy (Rector J. Vetra) on the clinical basis of the Department of Intemal Diseases #3 at the State Clinical Stradina Hospitai (SCH, Physician-in-Chief Dr. H. Runds), the State Gastroenteroiogy CeDter (SGC, Head Prol N. Skuja) and the State Diagnostic Center (SDC, Physiciar-in-Chief Dr. J Ducmanis) [22]. For the clinical study a two-week FTS treatment course was selected - 1.5 g by 0,5g three times per day taken half an hour before meal washing down with warm water or tea without sugar. Before proceeding, patients were supplied with instruction for FTS use and were told about the preparation, its activity, the approbation procedure and possible discomforts. The selection of patients and the clinical study were performed in full accordance with The Helsinki Declaration statements and after approval by the local ethics committee.

Main Results

F'TS Effect on Gastric Hydrochloric Acid Secretion: The intragastric pH measurement was performed, and FTS effect on gastric hydrochloric acid secretion was tested in 20 patients. The clinical findings provided evidence that FTS does not stimulate H-ions secretion and does not decrease this secretion. pH test lists did not show any duodenogastric reflux signs.

Determination Secretory Immunoglobulin A(Siga) Level Performed By Radial Imunodiffrsion Method: Of the 23 cases, slgA above the upper reference value was found in saliva in 19 patients

(82,6% (95% C.I. (Fisher's) = 61,2 - 95,0), in gastric juice in 13 patients 56,5% (95% C.I. (Fisher's) = 34,5 - 76,8). There is a credible ($p<0.05$) proof of increased sIgA level in saliva in patients receiving FTS compared with patients without. This might be connected with the increase of mucosa protective qualities in the presence of FTS.

When Fts Treatment Course was Completed Gastric Mucosa Mucine Increased Excretion Was Observed in Dynamics and Goblet Cells In Duodenal Mucosa Growth In Absolute Number: It is well known that, goblet cells are abundant constituents of the intestinal surface epithelium in both small and large intestine, and goblet cells are considered to play a role in mucosal protection. [23]. The presented results of preclinical and clinical studies clearly show the presence of gastroprotective properties in the of Dense Conifer Needle Extract from Pinus sylvestris without affecting the acid function of the stomach [24].

Conclusion

The presented mini review of gastric mucosa protection showed significant changes in practical significant ways. Clinically important part of the cytoprotection definition is the prevention chemically induced gastric erosions by substances other than providing an inhibitory action on gastric acid secretion, at the same time, the usefulness of the gastric mucosa barrier is primary importance and its compounds is a key element. Methods for assessing the state of the components of the gastric mucosa of direct relevance to the cytoprotection developed and widely used on the one hand, and the manifestations of cytoprotection disorders on the other. «The mucosal barrier is the name given to the barrier in the stomach that resists the back-diffusion of hydrogen ions. The barrier is a layer of thick mucus secreted together with an alkaline fluid. Since the mucus is a gel, it entraps the alkaline fluid so that the stomach is coated» [24 Britannica, The Editors of Encyclopaedia. "mucosal protective agent". Encyclopedia Britannica, 17 May. 2016, https://www.britannica.com/science/mucosal-protective-agent. Accessed 13 February 2023]. We have demonstrated that, there is an increase in research on various aspects of the phenomenon of gastict cytoprotection with the intensification of the search of substances with cytoprotective effect. Such substances allow for effective drug therapy erosions of the gastric mucosa, especially in the medical need for non-steroidal anti-inflammatory agents. A discussion of such substances presented with a focus on a series of natural substances, including our own experience with preclinical and clinical evaluation of pine needle extract.

Authors' Contribution

- Marakhouski Yury (ORCID 0000-0001-7327-7762) – general management of the study; analysis of the available preliminary results of studies on gastroprotection identification and formulation of the conflict of current statements in publication and presented results, in comparison with those assumed in this review, with an assessment of their novelty.
- Rubens Juris - development of an original research for Coniferous Pine Needles Extract with the most effective testing; evaluation of the fidelity of the preliminary hypothesis, new facts and prospects for further research.

Conflict of Interest

Nothing to declare.

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