Abstract. Notwithstanding the complex cytoarchitecture of the CNS, high sensitivity and metabolic activity of neuronal cells, no specialized anatomical structure has been identified that would facilitate effective «lymphatic» clearance of extracellularly dissolved substances and potentially toxic metabolites. World scientific research has highlighted the concept of a glymphatic system that enables the brain to draine the extracellular harmful substances dissolved in the interstitium. At the same time, aquaporin-4 (AQP4) water channels are an important component of this system, and their dysfunction is associated with a number of neuropathologies. Despite the fact that potential AQP modulators have already been described, there are many concerns over their use as a therapeutic target due to low drug sensitivity.

It is well known that aging is a critical risk factor for neurodegenerative diseases. It has also been experimentally proven that glymphatic activity decreases with aging. Accordingly, this can lead to the accumulation of misfolded and hyperphosphorylated proteins, and thus the brain becomes vulnerable to the development of neurodegenerative pathology. Abnormal expansion of the perivascular space is more commonly observed in Alzheimer's disease in elderly subjects, indicating a possible deformation of the glymphatic pathways and a subsequent decrease in protein clearance.

Current investigations are focused as well on clarifying changes in brain glymphatic drainage in the condition of traumatic brain injury. Modern research has shown that acute brain injury, including traumatic brain injury, subarachnoid hemorrhage, or stroke, dramatically alters glymphatic function and impairs convective fluid flow. It has also been experimentally confirmed that moderate traumatic brain injury is characterized by a prolonged decrease in glymphatic function, which increases the risk of developing chronic traumatic encephalopathy.

Comprehensive analysis of the causes and mechanisms of glymphatic system dysfunction will help to predict and develop methods for diagnosing and treating serious neurodegenerative diseases and traumatic brain injuries.

Key words: glymphatic system, neurodegenerative diseases, aquaporins 4 (AQP-4).

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CORRECTION OF EXOCRINE PANCREATIC INSUFFICIENCY BY PLANT-DERIVED ENZYMES (LITERATURE REVIEW)

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Exocrine pancreatic insufficiency is characterized by the pancreas' inability to secrete enzymes and/or bicarbonates into the intestinal lumen in sufficient quantities, resulting in abnormal food digestion and malabsorption of nutrients. Currently, there are many porcine-derived pancreatin preparations available that replace the patient's pancreatic enzymes deficiency. However, these preparations are not recommended for long-term use, due to a feedback mechanism that suppresses the secretion of the body's own pancreatic enzymes. Therefore, the problem of an alternative choice for temporary exocrine pancreatic insufficiency compensation arises, especially among certain patient groups, with prospects for further development and implementation of a comprehensive plant-derived enzyme preparation.

The most well-known representative of plant-derived enzymes is papain, bromelain, actinidin and zingibain. A comparative analysis of actinidin with bromelain and papain revealed significant differences in protease activity against animal-derived proteins. It was found that actinidin and bromelain are particularly effective for collagen hydrolysis. It was also found that bromelain has better proteolytic properties, demonstrating a higher ability to hydrolyze myofibrillar protein and increase the content of free amino acids in meat, compared to other proteases, especially papain. The zingibain protease preparation is most effective for the hydrolysis of connective tissue proteins, and actinidin proteases – for the hydrolysis of beef myofibril proteins. In general, the use of papain, bromelain, actinidin and zingibain has a favorable effect and improves the digestion of certain food components.

Future research should aim to study the potential role of these plant extracts not only as enzymes, but also for adjuvant therapy or alternative treatment patients for a range of internal organ diseases.

Key words: *exocrine pancreatic insufficiency, plant-derived enzymes, papain, bromelain, actinidin, zingibain.*

Connection of the publication with planned research works.

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Introduction.

Exocrine pancreatic insufficiency (EPI) remains one of the significant issues in modern medicine, due to its high prevalence and adverse impact on patients' quality of life and health. EPI is characterized by the pancreas' inability to secrete enzymes and/or bicarbonates into the intestinal lumen in sufficient quantities, resulting in abnormal food digestion and malabsorption of nutrients [1].

Currently, there are many porcine-derived pancreatin preparations available that replace the patient's pancreatic enzymes deficiency, which helps eliminate EPI symptoms, optimize digestion, improve nutrient absorption, and enhance overall nutritional status and patients' quality of life [2]. However, these preparations are not recommended for long-term use, due to a feedback mechanism that suppresses the secretion of the body's own pancreatic enzymes. In addition, for a portion of the population, these preparations are not acceptable given vegetarian/vegan lifestyles. Current trends related to mass food production often result in people abstaining from consuming meat and other animal-derived products [3]. For instance, a study examining consumer behavior in British public eating establishments found that doubling the share of vegetarian dishes increased the sale of such food (and decreased the sale of meat) by 41.8–78.8% [4]. Other reasons for refusing animal products, in addition to the need to take the aforementioned enzyme preparations, include religious beliefs, lifestyle, and environmental concerns [3]. Epidemiologic cohort studies (European Prospective Investigation into Cancer and Nutrition-Oxford (EPIC-Oxford) and the Adventist Health Study-2 (AHS-2)) enrolling a large percentage of vegetarians have been highly informative regarding the nutritional adequacy and possible health effects of vegetarian diets [5]. Therefore, the problem of an alternative choice for temporary EPI compensation arises, especially among certain patient groups, with prospects for further development and implementation of a comprehensive plant-derived enzyme preparation.

The aim of the study.

To conduct a review and analysis of scientific literature on enzymes found in plant-derived foods capable of meeting the body's temporary need to supplement the exocrine function of the pancreas in place of animal-derived enzymes.

Object and research methods.

An analytical review of scientific literature from 2011 to 2023, dedicated to the study and analysis of the possibilities, efficacy, and advantages of plant-derived enzymes (papain, bromelain, actinidin, zingibain, avocado lipase, banana α-amylase) for EPI correction. PubMed, Google Scholar, Science Direct, Web of Science, and Scopus internet resources were used to search for information.

Main part.

The most well-known representative of plant-derived enzymes is papain – an enzyme from the class of proteases, which is used in various fields, including the food industry and medicine. This enzyme is found in the fruits, stems, and leaves of the papaya plant (Caricapapaya L.) and has proteolytic activity against proteins, complex acid esters, amide chains, and short-chain peptides with lysine, phenylalanine, and arginine [6]. However, it has been found that the protease activity in papayas of different origins can vary significantly due to its different concentrations, necessitating careful selection of raw materials and papain sources [6]. Enzyme preparations with papain are recommended to improve food digestion, but papain only has proteolytic activity and requires supplementation with other enzymes [7].

Another fairly well-studied plant-derived enzyme is bromelain, which is found in large quantities in the waste (peels, crowns, stems, and cores) of the pineapple processing process. It is from the fruit crowns that bromelain is obtained with the highest activity (20.82 OD/ml) and specific activity of 194.58 OD/mg [8].

Bromelain is a combination of several thiol endopeptidases, protease inhibitors, glucosidase, cellulase, phosphatase, peroxidase, and escharase [9]. Laboratory and animal studies demonstrate bromelain's fibrinolytic, anti-edematous, antithrombotic, and anti-inflammatory effects, outlining the prospects for its use in the treatment of various internal diseases and surgical pathologies [9, 10]. In the food industry, bromelain is widely used as a meat tenderizer and in the production of infant formulas, where it participates as a protease in the hydrolysis of proteins and increases the availability of amino acid absorption for the infant's body [8]. The proteolytic activity of bromelain is also realized against a group of substrates, which include gelatin, chromogenic tripeptides, and casein. The optimal pH range for bro-

melain action is 5.5–8, but the enzyme can exhibit activity in a wider range of pH values [10].

Actinidin (synonym actinidain, EC 3.4.22.14) is a cysteine protease from the papain family, found in kiwi (Actinidia deliciosa) [11]. Research data suggest that the enzyme isolated from the juice of Actinidia arguta fruits has proteolytic functions and promotes the digestion and assimilation of protein, as well as possesses potential antioxidant, anti-inflammatory, anti-allergic, anticancer effects, and α-glucosidase inhibition effect [12, 13]. In vitro and animal studies have shown that actinidin remains active in the conditions of the stomach and ileum environment and affects the rate of food passage from the stomach [14]. The concentration of actinidin at 2.7 OD/ml in gastric contents appears to be effective for hydrolysis, equivalent to the consumption of two kiwis during meals [11, 15]. The results of the study found that a high content of actinidin in the diet improved the digestion of beef protein, gelatin, soy protein isolate, and gluten in the stomach by 40%, 60%, 27% and 29% respectively, but no effect on protein absorption in the ileum was observed [14]. However, data from another animal study showed that actinidin increases the speed of meat protein digestion in the stomach and leads to faster absorption of amino acids in the first half of the small intestine [11]. In studying the activity of enzymes from golden kiwi, it was found that they show a greater ability to break down ovalbumin at higher pH values (5.5 and 7) compared to enzymes from green kiwi. At the same time, there was no increase in the activity of enzymes from golden kiwi under conditions of higher pH regarding three other substrates (soy protein, casein, bovine serum albumin) [6].

Actinidin can enhance the cleavage and digestion of different types of peptides under conditions that mimic gastric digestion. In particular, during the simulation of the gastric system, enhanced digestion of sodium caseinate, beef muscle protein, and to some extent, soy protein isolate was observed [16].

A comparative analysis of actinidin with bromelain and papain revealed significant differences in protease activity against animal-derived proteins, depending on whether connective tissue or muscle protein was used as a substrate [6, 7]. When comparing the activity of cysteine proteases, it was found that actinidin and bromelain are particularly effective for collagen hydrolysis [7]. It was also found that bromelain has better proteolytic properties, demonstrating a higher ability to hydrolyze myofibrillar protein and increase the content of free amino acids in meat, compared to other proteases, especially papain [7].

In vivo studies have shown that both papain and bromelain reduce the immunogenic action of gluten, but in vitro bromelain was less effective in detoxifying wheat gluten compared to papain [11]. A number of studies have proven the effectiveness of papain and bromelain in hydrolyzing gluten. For example, in a study conducted using the ELISA sandwich test (enzyme activity 254 OD/g flour, approximately close to 5.6 OD/mg gliadin), papain, which was included in the composition of wheat flour, led to a reduction in the number of gliadin epitopes by ~ 6 times compared to pepsin. In this study, the use of papain was observed to significantly reduce antigenic peptides (~ 35-fold) compared to pepsin, which can be explained by the higher concentration of papain used in this study (10.2 OD/mg gliadin) [11].

Actinidin increases the rate of proteolysis of both gluten and gliadin, and reduces the number of immunogenic gluten epitopes, which is probably associated with the broad amino acid specificity of actinidin, which allows it to hydrolyze a wide range of peptide bonds that are inaccessible to pepsin [11, 17]. Similar results were observed in an in vivo study where the addition of actinidin to the diet increased the hydrolysis of gluten in the stomachs of rats by 3.2 times, beef muscles and soy protein isolate by 0.6 times [11, 18].

Given a number of data, actinidin may affect the hydrolysis of gluten proteins and peptides in the small intestine, as it is capable of hydrolyzing proteins at a pH from 3 to 10.5 [11, 19].

The results of the studies prove that actinidin in a physiological gastric environment breaks down gluten proteins, as well as the highly resistant 33-mer gliadin peptide and peptides containing QQQ/PFP, present in gluten epitopes, by breaking multiple peptide bonds, including peptide bonds at the N- and C-terminal residues of proline. An actinidin concentration of > 2.7 OD/ml during hydrolysis at gastric pH > 2 is considered ideal for gluten hydrolysis. Actinidin was more effective for the hydrolysis of gliadin than the other two cysteine proteases – papain and bromelain [11].

Thus, the studies have shown that actinidin activity is manifested and maintained over a wide pH range. Actinidin remains active in the stomach for several hours after food intake, unlike some other exogenous enzymes, which can also break down gluten [11].

The enzymes of green kiwi and pineapple have equally potent protease activity with respect to all investigated substrates, while pineapple extract somewhat better preserves its stability and activity in very acidic environments (pH 2.5) [6]. The activity of kiwi protease is destroyed within minutes after exposure to pH ≤ 2.5, while the activity of pineapple protease can recover in the pH range from > 2.0 to 2.5. [6].

Ginger (Zingiber officinale) is well-known for its nutraceutical value, associated with the presence of a large number of bioactive compounds such as gingerol, ingenol, gingerdiol, zingerone, shogaol, and paradol, which make it possible to use it as a spice and for medicinal purposes [20, 21, 22]. Zingerone has quite potent anti-inflammatory, antispasmodic, antidiarrheal, antilipolytic, antidiabetic, and antithrombotic properties [20, 22, 23]. Ginger has a diverse phytochemical composition and contains various minerals, vitamins, as well as the enzyme zingibain [20]. Zingibain, or ginger protease, exhibits relatively high proteolytic activity. Zingibain – a meat tenderizer, is very active against collagen, other connective tissue proteins, and protein substrates as a whole [24].

Zingibain has a hydrolysis profile similar to papain and bromelain. In conducted studies, these enzymes effectively hydrolyzed actomyosin, titin, and nebulin proteins, but this did not apply to other myofibril proteins [25]. The similarity in the catalytic activity of these three enzyme preparations can be explained by homologous amino acid sequences, especially near the active center, leading to similar substrate specificity of zingibain, papain, and bromelain proteases [25].

The results of one of the studies indicate that the zingibain protease preparation is most effective for the hydrolysis of connective tissue proteins, and actinidin proteases – for the hydrolysis of beef myofibril proteins [25].

It should be noted that the bioactive compounds of ginger extract can exert their physiological actions both in the intestinal lumen and when absorbed from the intestine into the bloodstream. Therefore, modifications in the process of gastrointestinal digestion, transport mechanisms through the intestinal epithelium, and enzymatic modifications should be considered [21].

Banana is the common name for the edible fruits of several species of large herbaceous flowering plants of the genus Musa spp. The high levels of antioxidant activity, phenolic compounds, biogenic amines, carotenoids, dietary fibres and starch in banana pulp and peel have made this tropical fruit an outstanding source of nutritive ingredients. Green banana starch contains approximately 21% amylase. Waste from banana fruit peduncles can be used for the production of α-amylase using Bacillus subtilis by solid-state fermentation [26, 27].

Animal studies have shown that the advantages of microbial-derived enzymes are a less effective dose, the ability to maintain their stability in conditions of heating and inactivation by stomach acid, and a wider range of pH activity compared to digestive enzymes of animal origin [2]. However, it has been found that condensed tannins of banana origin suppress the digestion of lipids (fats and cholesterol) when interacting with components of gastric juice due to interaction with lipase, cholesterol esterase, bile acids, and cholesterol [28]. Accordingly, not every component of the banana can be chosen to improve the digestion of food, which requires careful separation of necessary factors.

Previous attempts to create a non-animal-derived enzyme preparation (liprotamase – a biotechnological substitute therapy containing three purified and stable enzymes) were not approved by the Food and Drug Administration in the United States. The presence of preparations containing pepsin or amylase of bacterial origin does not fully meet the body's need for comprehensive replacement of EPI (Exocrine Pancreatic Insufficiency) [2].

Regarding animal-derived enzymes, their activity and concentration are determined by various factors, including animal species, age and sex, as well as methods of rearing. For instance, the level of enzymatic activity of enzymes from pig sources is approximately 30–50% higher than from bovine sources [2], but they are not acceptable to part of the population, especially in cases of overeating when the body lacks its own enzymes.

At the same time, plant-derived enzymes have other beneficial properties that positively affect both the state of the gastrointestinal tract and other organs and systems of the body [9, 10, 13, 14, 20, 29]. For example, bromelain has anti-inflammatory, antitumor, antithrombotic, fibrinolytic and immunomodulating effects [9, 10, 30, 31]. Furthermore, its use led to a reduction in severe consequences of SARS-CoV-2 [31]. Actinidin has antioxidant, anticancer, antiallergic effects, and is also able to reduce the severity of dyspeptic manifestations and bloating [13, 14].

Ginger has anti-inflammatory, analgesic, antioxidant, antitumor, anti-ulcer, antimicrobial, and immunomodulating effects [24, 29]. Ginger components increase muscle tone and stomach peristalsis, have an antispasmodic effect, enhance gastrointestinal tract motility and spontaneous peristalsis, and reduce symptoms of bloating [23].

It is important to note that there is a large interindividual difference in response to enzyme preparations [32], which requires a more detailed study in the future of the optimal response to enzyme replacement therapy among different population categories. In particular, there is potential for the use of actinidin as a beneficial factor to improve and accelerate the protein digestion process among certain groups of people – athletes, the elderly, and people with digestive organ pathology [33].

In general, the use of papain, bromelain, actinidin, and zingibain has a favorable effect and improves the digestion of certain food components, but their activity and effectiveness largely depend on the characteristics of the initial substrate for cleavage, its level of heat treatment, and the properties of the enzymes themselves [7].

Conclusions.

Analysis and systematization of literature sources have allowed the authors to determine the effectiveness and a number of advantages of enzymes for temporary supplementation of exogenous pancreatic enzymes (EPE), depending on their origin. Plant-based enzymes have a sufficiently high activity with respect to certain food components and under favorable conditions of the gastrointestinal tract, they are able to effectively break them down and improve assimilation. In addition, plant enzymes have other beneficial properties that have a positive effect on patients with digestive organ pathology and other internal diseases.

Prospects for further research.

Future research should aim to study the potential role of these plant extracts not only as enzymes, but also for adjuvant therapy or alternative treatment patients for a range of internal organ diseases.

Currently, the combination of plant, bacterial, and fungal enzymes with innovative delivery forms is the most promising direction for further scientific development. Therefore, it is interesting and promising to create a plant-based enzyme complex that would meet the needs of certain population groups. This issue requires further study, research, and approval of a combined enzyme preparation, the potential components of which collectively possess proteolytic, amylolytic, and lipolytic activity.

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КОРЕКЦІЯ ЕКЗОКРИННОЇ НЕДОСТАТНОСТІ ПІДШЛУНКОВОЇ ЗАЛОЗИ ФЕРМЕНТАМИ РОСЛИННОГО ПОХОДЖЕННЯ (ОГЛЯД ЛІТЕРАТУРИ)

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Резюме. Екзокринна недостатність підшлункової залози та шляхи її корекції залишаються актуальними проблемами сучасної медицини. Ферменти тваринного походження, які широко використовуються при недостатності зовнішньосекреторної функції підшлункової залози, не рекомендовано вживати протягом тривалого проміжку часу, а також вони не є прийнятними для окремих категорій пацієнтів, що потребує пошуку альтернативних джерел ферментів з визначенням перспектив їх подальшого застосування.

Мета: провести огляд і аналіз даних наукових досліджень щодо можливостей і ефективності ферментів продуктів харчування рослинного походження, екстракти яких потенційно здатні задовольнити потреби у тимчасовому доповненні зовнішньосекреторної функції підшлункової залози замість ферментів тваринного походження. Об'єкт і методи дослідження: аналітичний огляд наукової літератури за період 2011–2023 років, присвячений вивченню та аналізу активності ферментів рослинного походження з папаї, ананасу, ківі, імбиря та банану щодо певних субстратів та їх ефективності в цілому. Для пошуку інформації використовували інтернет-ресурси PubMed, Google Scholar, Science Direct, Web of Science та Scopus.

Вивчено і проаналізовано дані наукових літературних джерел відносно найбільш відомих ферментів рослинного походження (папаїн, бромелаїн, актинідин, зингібаїн, α-амілаза банана). Узагальнено дані щодо ферментативних особливостей, активності, ефективності і переваг зазначених ензимів та визначено перспективні напрямки їх застосування.

Ферменти рослинного походження мають достатньо високу активність відносно певних харчових компонентів та за сприятливих умов середовища шлунково-кишкового тракту здатні ефективно розщеплювати їх і покращувати засвоєння. Одним із перспективних і цікавих напрямків подальших досліджень вбачається створення ферментного комплексу рослинного походження для корекції зовнішньосекреторної недостатності підшлункової залози, що задовольнятиме потреби окремих категорій пацієнтів. Дане питання потребує подальшого вивчення та дослідження з наступною розробкою і апробацією комбінованого ферментного препарату, потенційні компоненти якого сукупно володітимуть протео-, аміло-, та ліполітичною активністю.

Ключові слова: екзокринна недостатність підшлункової залози, ферменти рослинного походження, папаїн, бромелаїн, актинідин, зингібаїн.

CORRECTION OF EXOCRINE PANCREATIC INSUFFICIENCY BY PLANT-DERIVED ENZYMES (LITERATURE REVIEW)

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Abstract. Exocrine pancreatic insufficiency and its correction methods remain pressing issues in modern medicine. Animal-derived enzymes, widely used in treating exocrine pancreatic insufficiency, are not recommended for long-term use and are not acceptable for certain patient groups, necessitating the search for alternative sources of enzymes with the potential for future use.

Purpose: to review and analyze scientific research data on the possibilities and effectiveness of food-derived plant enzymes, the extracts of which can potentially meet the need for temporary supplementation of the exocrine function of the pancreas instead of animal-derived enzymes. Object and research methods: an analytical review of scientific literature from 2011 to 2023, dedicated to the study and analysis of the activity of plant enzymes derived from papaya, pineapple, kiwi, ginger, and banana, and their overall effectiveness. Information was sought through internet resources such as PubMed, Google Scholar, Science Direct, Web of Science, and Scopus.

Scientific literature data on the most well-known plant enzymes (papain, bromelain, actinidin, zingibain, α-amylase of banana) were studied and analyzed. Information regarding the enzymatic characteristics, activity, effectiveness, and advantages of these enzymes was summarized, and potential areas of their application were identified.

Plant-derived enzymes have sufficiently high activity against certain food components and under favorable conditions of the gastrointestinal tract can effectively break them down and improve absorption. One of the promising and interesting directions of future research is the creation of a plant-derived enzyme complex to correct exocrine pancreatic insufficiency, which will satisfy the needs of specific patient categories. This issue requires further study and research, followed by the development and approval of a combined enzyme preparation, the potential components of which will have proteolytic, amylolytic, and lipolytic activity.

Key words: exocrine pancreatic insufficiency, plant-derived enzymes, papain, bromelain, actinidin, zingibain.

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