Significance, Effectiveness and Prospects of Development of Enzyme Preparations in Modern Pharmaceutical Practice

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Abstract

This article presents topical issues devoted to the study and prospects for the development of enzyme preparations in modern pharmaceutical practice in the Republic of Uzbekistan. In the context of existing resources, the rational use of high-quality, effective, safe medicines and the creation of new ones by combining local raw materials with an innovative approach is a priority. The expediency of combinations of drugs useful for medical practice for effort or combination of effects is noted.

In medicine, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat rheumatoid arthritis and other inflammatory diseases. NSAIDs are the basic drugs in the pharmacotherapy of many chronic, acute diseases, normalizing biochemical parameters and the functional state of blood cells. These drugs are taken over-the-counter and for a long time, and therefore resolving issues, related to the safety of their use, the search for a combination is relevant. Currently, domestic developments of NSAIDs (fensulkal, blizketazin) are being carried out by combining enzymes (to enhance the effect) and in justified rectal and transfermal medicinal forms. Many diseases are associated with impaired secondary enzyme deficiency. Clinical studies confirm the high effectiveness of the combination of NSAIDs with enzyme preparations. The classification of proteolytic enzymes, the importance, scale and resources of the prevalence of plant enzymes in the Republic are presented. Of particular interest is the papaya (melon tree). Papain and chymopapain are latex enzymes of the fruits of the melon tree.

Key words: *NSAID's, enzymes, enzyme preparations, pharmacy*

Introduction

Currently, the most topical issues of rational use of drugs is the ability to assess the effectiveness, safety and quality, in circulation of medicines throughout their "life cycle": from the development, quality criterion before registration studies, the procedure of examination before going into wide clinical practice and the period of stay in the pharmaceutical market. In the XXI century medicine came with a powerful arsenal of drugs. Global pharmaceutical industry generates tens of thousands of medical products. [1]

The problem of drug provision, rational and safe pharmacotherapy has now become one of the most urgent tasks of the clinicians and pharmacists. This is due, on the one hand, with the ever-increasing market of medicines (drugs) and the volume of scientific information, on the other - with the need to determine the most popular groups and classes of drugs. [2, 3, 4]

In the context of existing health care resources rational use of high-quality, efficient, safe medicines and the creation of new combination of using local raw materials with an innovative approach is a priority.

This requires the introduction of optimal evidence-based approaches that receive the greatest benefit and cost-effective to carry out, rational, effective and safe therapy combination drugs. [5]

Quality drugs - the basis of the safe treatment of patients. It is known that safety of drugs characterized by the absence of adverse reactions when it is used, and the efficiency – by the level of pharmacotherapeutic effect achieved by using the minimum dose of the active ingredients.

Adverse drug reactions (ADR) are a major problem of pharmacotherapy. The problem of safety conducted drug therapy involves the collection of information about their occurrence. Information about all the side effects of drugs used for more in-depth study of the causes of severe drug complications and their prevention measures. However, in recent years, along with the improvement of the work on timely notification of any cases ADR, remains unresolved the question of creating the conditions for a more complete account of all of these reactions. According to the International Center for the monitoring of adverse reactions to the WHO (Uppsala, September 2006, the Republic of Uzbekistan entered), it is considered that 2-3% of the general population of people suffering from the side reactions of drugs. [5, 6].

The development of modern scientific and practical directions allows individualized drug selection, dosing regimens taking into account features.

The possibilities of modern clinical pharmacology study of drugs open promising directions and have a great future.

These features and methods should be actively used in the expert evaluation of the efficacy and safety of drugs. Questions of the rational, and hence effective, quality and safe pharmacotherapy are gone far beyond the medical community; they rightly belong to the most important strategic tasks of the day, a full program of import substitution drugs.

This is the basis of creating and entering the pharmaceutical market in the broad appeal of highly effective drugs.

In medical practice, often use multiple drugs simultaneously. Thus, they can interact with each other by changing the severity and nature of the main effect, its duration (prolongation), and the effort or weaken side and toxic effects.

Combined differences drugs are often used to enhance or combination of effects, i.e., appropriate combinations useful for medical practice.

The pharmacological interaction related by the fact that one substance alters the pharmacokinetics or pharmacodynamics of other component of the mixture. Furthermore, it is possible chemical and physical-chemical interaction of the substances in their joint application. [7]

In medicine, for the treatment of rheumatic, arthritic and other inflammatory diseases are widely used non-steroidal anti-inflammatory drugs (NSAID). NSAID are the basic drugs in the pharmacotherapy of many chronic, acute illnesses, normalize the biochemical parameters and functional status of the blood cells and connective tissue. More than thirty million people worldwide take NSAID on a daily basis, and 40% of patients older than 60 years and about 20% of hospitalized patients. [8]

However, their long-term use in effective doses is often difficult because of the frequent complications. Strategically important question remains to use the well-known and affordable drugs, adjusting the therapeutic dose, dosage form, or by combining with the possibility of obtaining synergy among them, reducing their toxicity, increasing safety and to introduce in the domestic pharmaceutical practice.

In a variety of publications of domestic and foreign scientists pay attention to the fact that 30% of men and 50% of women taking the recipe less form of NSAID and 60% of patients taking the drug without consulting a doctor.

Among NSAID ibuprofen, due to the relatively low toxicity, has been widely used in pediatric and geriatric medicine. Low toxicity of ibuprofen is proportional to its therapeutic efficacy. Relevance of research on the combination of a rectal and transdermal dosage forms is the need to increase the therapeutic efficacy of ibuprofen and its security application. [9]

The feasibility of using enzymes is associated with their ability to enhance, accelerate the therapeutic effect in various diseases in clinical practice. They act as a catalyst for biochemical processes, stimulate metabolism. Many scientists, as well as Uzbeks, devoted their work to the study and introduction of papaya into domestic practice.

Another important representative of proteases (animal or microbial) is serratiopeptidase, which is called the “silkworm enzyme”, because it is produced from Serration bacteria found in the intestines of silkworms. Serratiopeptidase is a proteolytic enzyme for the treatment of inflammation, and reduces the intensity of inflammation due to the hydrolysis of

biologically active substances. Widely used in Japan, USA, Germany, Italy.

Thus, it is shown that drugs, which are natural physiologically active protein compounds (enzymes) have gained a worthy place among the means of practical medicine. Actual aspects of marketing research of drugs containing enzymes and presented on the pharmaceutical market of the Republic of Uzbekistan (RUz) have been carried out. The data for 2017, 2018 and 2019 were studied on the market of the Republic of Uzbekistan dominated by drugs containing enzymes of imported production (73%), and especially of animal origin (80%). The data presented in the State Register of Medicines by country (foreign, CIS, domestic) as well as by drug companies and pharmacotherapeutic groups are presented. The main types of dosage forms are coated tablets (53.13%). It is noted that the use of local raw materials containing enzymes with an innovative approach by combining drugs in rational dosage forms of quality control is a government priority in the development of the domestic pharmaceutical industry.

Materials and Methods

The search for new classes of chemical compounds that are promising for targeted synthesis of anti-inflammatory, antimicrobial agents will reduce the financial costs of the development of new antimicrobial agents.

In the Uzbek scientific research chemical and pharmaceutical Institute named after A. Sultanov synthesized new biologically active drug-fensulkal, which is a bisulfite derivative of phenylglyoxylic acid, and benzoketazone.

Fensulkal characterized moderate toxicity and has pronounced anti-inflammatory and anti-microbial properties, which in total is very important for pathogenetically oriented treatment of many gynecological diseases. Results patent studies showed that the potassium salt of sodium bisulfite phenylglyoxylic acid derivative is a novel, previously non-synthesized and non-described compound (patent RUz IAP №02245/ 04.10.02). [10]

Today fensulkal used in the form of tablets (0.1g active substance TPA42 Uz- 0663-2003 and ointments (0.5% and 3% PAE 42 Uz-0187-2007).

Also, benzketozon (thiosemicarbazone) NSAID recommended for rheumatic diseases (3%) ointment and combined gel. [11]

Currently under operation of the development combining with enzymes and antiallergic means in reasonable rational medicinal forms.

Many diseases (if not most) are associated with a violation of the qualitative and quantitative composition of enzymes in the body, the occurrence of secondary enzyme deficiency. When conducting pharmacotherapy, special attention must be paid to those drugs that have active metabolites formed during biotransformation. There are drugs that are initially inactive, and only as a result of biotransformation from them is active metabolites formed that determine the pharmacodynamic effects (Fig. 1) [12].

PRODRUGS AND THEIR ACTIVE METABOLITES: THE ROLE OF CYTOCHROME P-450 ISOENZYMES

Spironolactone	CYP 3A4	Canrenone
Clopidogrel	CYP 2C19	2-oxo clopidogrel
Enalapril	Carboxyesterase	Enalaprilate
Azathioprine	Xanthine oxidase	Mercaptopurine
Primidone	CYP 3A4	Phenobarbital
Tamoxifen	CYP 2D6	Endoxifene
Losartan	CYP 2C9	E-3174

Fig. 1. Examples of prodrugs, active metabolites, which are formed with the participation of biotransformation enzymes.

Results

The most common reason that inflammation does not proceed as necessary for a full and quick recovery is a violation of catabolic processes (destruction) and the release of the focus of inflammation from destroyed tissues, which again is caused by an imbalance in the work of enzymes. If these processes are improved, the damage zone will decrease and will be better prepared for the beginning of the recovery phase of inflammation with high chances of a more favorable outcome.

This fact has led us to the idea of the need to introduce enzymes into the body from the outside by combining drugs.

A lot of importance is the fact that with NSAIDs and antibacterial agents and enzymes (serratiopeptidase) working senergically helps to enhance their positive effects. [12]

Clinical studies confirm the high effectiveness of the combination of antibacterial agents and enzyme preparations in most acute and chronic inflammatory infections. With the simultaneous administration of antibacterial drugs in combination with proteolytic enzymes, the effectiveness of treatment increases, while the side effects of antibacterial agents, as well as the risk of complications, including intestinal dysbiosis, are reduced. Examples are diseases such as sinusitis, bronchitis, cystopyelitis, adnexitis, prostatitis, etc.

In the same way that serratiopeptidase potentiates the action of antibiotics; it potentiates the action of non-steroidal and steroidal anti-inflammatory drugs and therefore is often prescribed in combination with them or as a continuation of treatment after a short course of non-steroidal anti-inflammatory drugs according to all their indications. [13]

The use of enzymes (proteolytic enzymes) in the treatment of various diseases has its own history. Since ancient times, in the treatment of purulent wounds, abscesses and other purulent diseases of soft tissues, they used pumpkin juice, applied the pulp of papaya or green pineapple. Since all these plants contain a large number of enzymes, they contributed to more rapid cleansing and healing of wounds.

Enzymes are substances that are present in the tissues and cells of all living organisms and are able to accelerate the chemical reactions that occur in them many times. Enzymes can be simple proteins, built entirely from polypeptide chains and decomposed by hydrolysis only into amino acids. Simple proteins are hydrolytic enzymes (e.g., proteases, lipases, and ribonuclease) that perform their function in the absence of coenzyme. In most cases, enzymes are complex proteins. Complex proteins (holoenzymes) contain, along with the protein part (apoenzyme), a non-protein component (coenzyme or prosthetic group) (Fig. 2).

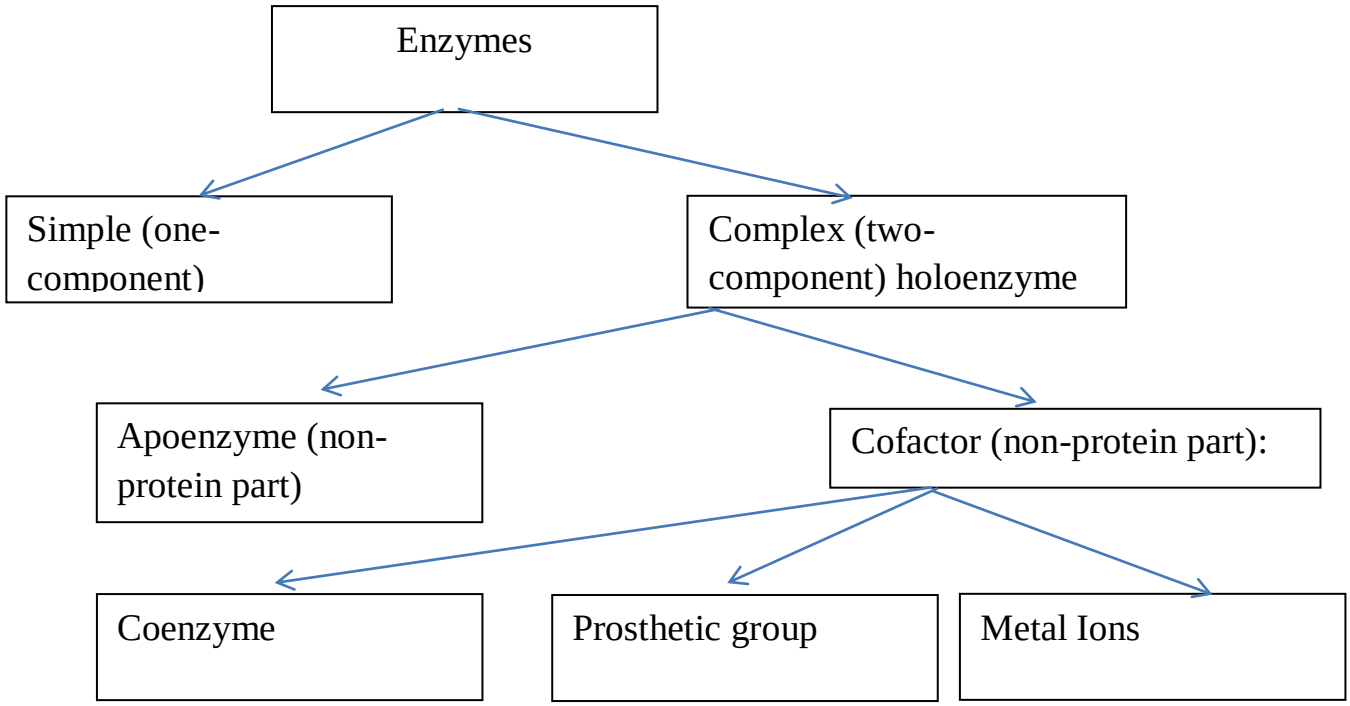

Fig. 2 Nomenclature of enzymes.

A substance whose chemical transformation catalyzes an enzyme is called a substrate.

Classification and nomenclature of enzymes

In 1961, the International Union of Biochemistry and Molecular Biology developed a systematic nomenclature, according to which all enzymes are divided into 6 main classes, depending on the type of catalyzed chemical reaction.

Each enzyme has a common working name, and a systematic one, used to uniquely identify the enzyme. Working names are formed from combining the name of the substrate, the type of reaction and the end of "-ase". For example: lactate + dehydrogenation + ase = lactate dehydrogenase. The systematic name of the enzyme is formed as follows: name of substrates: name of the type of chemical transformation + ase. The same lactate dehydrogenase will have the systematic name “l-lactate: over + oxidoreductase”.

Each of the six classes of enzymes has its own serial number, strictly assigned to it. [14]

In 2009, global sales of enzymes and enzyme preparations amounted to 440 million euros, including enzymes produced using traditional (classic) producer strains of 180 million euros (41% of total sales) homologous to GMM 1-2 safety classes - 132 million euros (30% of total sales). The sales of enzymes from heterologous GMMs of safety class 3 amounted to 128 million euros (29% of total sales in the global food market). [15]

Discussion

The production of enzyme preparations is one of the most large-scale and dynamically developing branches of biotechnology. Large volumes of production and a wide range of enzyme preparations are due to their demand in various industries, medicine, and scientific research.

According to the current classification, about 2,000 enzymes have been identified. The industry produces about 250 types of enzyme preparations. At the same time, about 99% are accounted for by 18 enzyme preparations. [16, 17]

Sources of enzyme preparations.

Of all the existing natural sources of enzymes, microorganisms, some plants or individual organs of plants and animals that can accumulate significant amounts of enzymes are of practical interest for large-scale production of enzyme preparations.

Plant raw materials. The source of enzymes can be sprouted cereal grain, which can be used directly as a technical enzyme preparation or feedstock to obtain purified preparations. As a raw material for proteinases use the latex of melon tree and ficus, green juice of pineapple, papain, bromelain, ficin papaya, pineapple, figs.

The technology for the production of enzyme preparations from plant and animal raw materials includes two main stages: collecting enzyme-containing raw materials; isolation and purification of the target product. [18]

Proteolytic enzyme. These enzymes catalyze the hydrolysis of the peptide bond in the molecules of proteins and peptides.

Previously, proteolytic enzymes were classified into proteinases that break down proteins into polypeptides, and peptidases that hydrolyze polypeptides to amino acids. According to modern classification, proteases are divided into endo- and exopeptidases. The former can hydrolyze deep peptide bonds and break down proteins. In turn, endopeptidases, depending on the structure of the active center, are divided into serine, thiol, acid (carboxyl) and metalloproteinases. Exopeptidases can cleave terminal amino acids. In this regard, exopeptidases are divided into: [18, 19]

- aminopeptidases catalyzing the cleavage of N-terminal amino acids;
- carboxypeptidases catalyzing the cleavage of C-terminal amino acids;
- dipeptidases exhibiting specificity for dipeptide substrates.

Proteases are widely used in agriculture, food industry, and medicine.

Proteases of technological importance are divided into plant, animal and microbial.

Plant proteases. Papain and chymopapain are latex enzymes of the fruits of the melon tree. They belong to the group of thiol proteinases, activated by reduced glutathione and cysteine.

Ficin and bromelain. The first is obtained from figs, the second - from pineapple juice. These enzymes belong to thiol proteases. Both enzymes have similarities in properties and use with papain. They are also used to remove protein turbidity in beer and to soften meat.

Proteases of animal origin. They have a huge role in digestion processes.

Trypsin is a serine proteinase secreted by the pancreas, which is used as a crude pancreatin in the food industry for the production of hydrolysates.

It hydrolyzes peptide bonds formed by arginine and lysine. Trypsin is secreted by the pancreas as an inactive trypsinogen precursor and is activated by another enzyme.

Chymotrypsin - is secreted by the pancreas into the small intestine in the form of inactive chymotrypsinogen. It is activated by trypsin; wherein two dipeptides are cleaved off.

Hydrolyzes peptide bonds formed by tyrosine, tryptophan, phenylalanine. [20]

Pepsin - is produced by the gastric mucosa in the form of pepsinogen, which turns into active pepsin under the influence of HCl or by cleavage of one peptide bond.

Pepsin is part of the drug, tonic agents, chewing gum.

Microbial proteases. Fungal and bacterial proteases exhibit trypsin-like, pepsin-like, thiol-like, and other actions. There are enzymes with optimum in acidic, neutral and alkaline environments.

The feasibility of using proteolytic enzymes is systematically associated with their ability in clinical practice to enhance, accelerate the therapeutic effect in various diseases, affecting their introduction to the general patterns of their development, inflammation activity in patients with rheumatoid arthritis, ulcerative colitis, etc. Currently, proteolytic enzymes are effectively used to reduce the inflammatory process. [20]

Proteolytic enzymes do not belong to anti-inflammatory drugs of direct action. They act as a catalyst for biochemical processes, triggering or accelerating biochemical reactions in the inflammation zone, where there is a local deficiency of their own proteolytic enzymes, in which the duration of inflammation increases and recovery is delayed. Visher T.L et. al., 1976

Proteolytic enzymes (PE - catalyze the hydrolysis of the peptide bond in the molecules of proteins and peptides) provide reliable relief of inflammation as a result of pronounced fibrinolytic activity and exert an effect through anti-inflammatory, immunomodulating, antiaggregant, fibrinolytic, decongestant, and analgesic effects (Klein G. et al. 1999). .

Depending on the purpose of the application, certain requirements are imposed on the enzyme preparations with respect to the composition of the enzymes, the optimal conditions for their action, the degree of their purification, which is especially important for microbial preparations that require chemical, microbiological and toxicological control, the use of excipients, cost, etc. [14]

The search and implementation in medical practice of new highly effective enzyme preparations of plant origin is of certain interest. [21]

One of the properties of enzyme preparations is the ability to potentiate and facilitate the action of other drugs, as well as reduce their side effects.

The ability of enzymes to increase the concentration of antibacterial agents in the blood, to facilitate their penetration into the tissues and thereby increase the effectiveness of therapy is well known (Koyama A. et al., 1986; Selan L. et al., 1993).

World medicine limits the use of antibiotics. Scientists believe that in the future, antibiotics can be replaced by super-antibodies, for which the cell wall will not be an obstacle, will be able to penetrate into the cells and destroy pathogenic bacteria, viruses and toxins. They are testing antibody modification technology that allows them to freely enter cells and leave them [22, 23].

In the modern world, much attention is paid to the use of biologically active herbal preparations in medical practice.

A typical representative of plant proteases is papain and chymopapain, and belongs to the group of thiol proteases.

Papain is a monothiol cysteine endoprotease. By the nature of the enzymatic action, it is called "plant pepsin." But, unlike pepsin, papain is active not only in acidic, but also in neutral and alkaline media (pH range 3–12, optimum pH 5). It retains activity over a wide temperature range. [22]

The papain catalytic center contains a dithioacyl group. [15, 16]

Papain also has anti-inflammatory properties. Without acting directly on the focus of inflammation, papain stimulates metabolism, which affects the acceleration of the regeneration of inflamed tissues. Papain increases blood flow and destroys toxic substances in the focus of inflammation. In addition, papain destroys toxins released by many pathogens, participates in the synthesis of arginine, an amino acid that stimulates growth hormone, which in turn is very important for the regeneration of liver cells. Papain also accelerates the healing of wounds, trophic ulcers and pressure sores. [18, 24, 25, 26, 27]

Exopeptidases having the ability to cleave terminal amino acids have already been indicated that proteolytic enzymes catalyze the hydrolysis of the peptide bond of proteins and peptides.

Papaya breaks down proteins into polypeptides and amino acids, and hydrolyzes any peptide bonds.

The homeland of the melon tree is Central and South America. It is cultivated in all tropical countries of the world as a fruit tree.

Uzbekistan has all the climatic conditions to cultivate a melon tree (papaya), the fruits of which can be used as raw materials for enzyme preparations, and the aerial part for obtaining effective medicines. A lot of works have been devoted to the phytochemical and proteolytic study of papaya growing in Uzbekistan (Aziizov I.K., Rakhimov M.R., Musaeva N.A. 2000) [26, 27]

As a result, the substance and injection drug were approved for medical use in Uzbekistan. (2000) As a result of the study, useful amino acids were identified and the anti-inflammatory effect of the papaya substance was revealed, as well as the anti-inflammatory and immunostimulating activity of the tincture of the aboveground part of the domestic papaya.

The leaves contain free and bound phenolic compounds, tannins, organic acids, steroid and triterpene saponins, flavonoids, lipids, coumarins, glucose, alkaloids used in the treatment of tuberculosis and having choleretic and diuretic properties.

In Peru, papaya leaves are famous as an indispensable tool for healing wounds. Recently, papaya made a sensation in the medical world: Indian scientists have discovered that the cortex of a melon tree contains a substance that is 250 times more effective in inhibiting the growth of cancer cells than the most modern and advanced drugs. Research is underway (bark has never been used in medicine before), if contraindications are not identified, papaya will give the world an effective cure for a terrible disease. [23, 24]

Papain is used in medicine: ophthalmology, neurosurgery, neuropathology, gastroenterology, urology.

Properties:

It is capable of breaking down proteins of polypeptides and amino acids, acting on any peptide bonds (except for bonds of preline, glutamic acid of a dislocated carboxyl group), breaking down proteins deeper than most enzymes of animal and bacterial origin, and dissolving dead cells.

It has: proteolytic, anti-inflammatory, anticoagulant, dehydration, analgesic, bactericidal, hemolytic properties. Another important representative of proteases (animal or microbial) is serratiopeptidase. Serratiopeptidase is an enzyme for the treatment of inflammation. Serratiopeptidase is a proteolytic enzyme (that is, it is used by the body to break down proteins to amino acids), which is sometimes called the "silkworm enzyme" because it is produced from Serration bacteria found in the intestines of the silkworm. This enzyme is responsible for the splitting of the silkworm cocoon. [28]

One of the most widely used proteolytic enzymes in the treatment of inflammatory diseases in Japan, Germany, Italy, the USA for more than 40 years is serratiopeptidase. It is present in all living systems, but was first discovered in the body of a silkworm, which uses it to dissolve a cocoon when a butterfly appears. Doctors have long appreciated the anti-inflammatory and analgesic properties of this natural substance and have successfully used it as an alternative to anti-inflammatory drugs. Serratiopeptidase has proven itself in the treatment of post-traumatic and postoperative edema, as well as the relief of pain and inflammation in rheumatic diseases (Esch P.M. et al., 1989; Panagariya A. et al., 1999). [20, 28, 29]

Over the years, serratiopeptidase (an enzyme of animal origin) has been shown to be effective in sports injuries, sprains and ruptures of the ligaments, fractures and dislocations, postoperative edema, the risk of transplant rejection, and cavity surgery, not only to improve healing processes, but also to prevent postoperative adhesions, for the treatment of ENT pathology and inflammatory lung diseases - not only with the aim of resolving inflammation as soon as possible, but also giving dynamic properties to the mucociliary system of transport thanks to the action thins mucus. Also, it increases the effectiveness of the treatment of acute inflammatory dermatoses. The drug reduces breast edema and is indispensable for mastitis in breast-feeding thanks to not only high efficiency, but also safety.

Serrata has a direct effect on the pathogenetic mechanisms of these diseases and contributes to their cure due to the fact that:

• reduces the intensity of inflammation due to the hydrolysis of biologically active substances - inflammatory mediators (bradykinin, histamine, serotonin, etc.), a decrease in the dilatation of capillaries and the regulation of their permeability;

• working synergistically with non-steroidal anti-inflammatory drugs and antibacterial agents, enhances their positive effect. [15, 29]

The authors of [17] studied the interaction of local and general reactions of the body in patients with traumatic osteomyelitis of the lower jaw of the fermentative drug "Serrata".

It should also be noted that many takes with chronic inflammatory pathologies, which means for a long period (key enzyme No. 41 of October 20, 2008. Weekly "Drugstore"). [20-23]

However, many studies of this substance were poorly structured and did not include control groups. Further research will shed light on the ability of serratiopeptidases to treat these and other conditions.

A prospective study of the effects of serratiopeptidase (Aniflazim) on postoperative edema and pain was carried out with the participation of three randomized groups of patients. Sixty-six patients participating in this study received surgical treatment due to rupture of the lateral ligament of the knee joint.

In addition to reducing swelling, subjects also noted a decrease in pain.

According to BioMed Research International, for 2017, serratiopeptidase reduces swelling by reducing the amount of fluid in the tissues, thinning it and facilitating outflow. In addition, the enzymatic activity of this drug dissolves the dead tissue surrounding the damaged area, which helps to speed up the healing process.

Serratiopeptidase was noted to be superior to placebo in reducing pain, swelling, and chest tightening. A moderate to noticeable improvement was observed in 85.7% of patients receiving the supplement, while among the placebo group; only 60% of the subjects experienced a similar improvement. A "noticeable" improvement was found in 22.9% of patients receiving treatment, compared with 2.9% of the placebo group. [30]

It helps relieve symptoms of superficial vein thrombophlebitis. [21]

Italian researchers have compared the efficacy of serratiopeptidase and seaprose S in the treatment of inflammatory vein disease. Both treatments have been found to effectively reduce pain and alleviate the symptoms of thrombophlebitis.

In most studies, serratiopeptidase was used in a dosage of 10 to 60 mg. However, additional studies are still required to determine the optimal dose.

Also, judging by the available research data, this enzyme is an effective tool to reduce swelling after surgery and can be an alternative to conservative measures, such as the use of ice. [31, 32]

One of the properties of enzyme preparations is the ability to potentiate and facilitate the action of other drugs, as well as reduce their side effects. The ability of enzymes to increase the concentration of antibacterial agents in the blood, to facilitate their penetration into tissues and thereby increase the effectiveness of therapy. (Koyama A. ct al, 1986, Senan L.et al., 1993)

Most enzyme preparations are available in the form of dragees or tablets in enteric coatings, which protects the enzymes from being released in the stomach and destroyed by hydrochloric acid of gastric juice. The size of most tablets or dragees is 10 mm or more. Nevertheless, it is known that solid particles with a diameter of not more than 2 mm with an optimal size of 1.4 mm can be evacuated from the stomach at the same time as food [21].

If the tablet or dragee is in the stomach for a long time, the enteric coating is destroyed, and the enzymes inside are inactivated. However, proteoastic enzymes are used in suppositories in gynecology. (Longidase).

Suppositories are also used for the registration of the Ruhr University G. Bohuli, Germany.

Thus, we see that drugs, which are natural physiologically active protein compounds (enzymes, their inhibitors and activators, hormones), have found their rightful place among the means of practical medicine. Unfortunately, the daily clinical use of enzymes is limited by both economic factors - their high cost and low availability, and their rapid inactivation under the conditions of the body, and various adverse reactions caused by or as foreign proteins (antigenicity, allergenicity, toxicity, etc.). Significant number of these obstacles can be eliminated through the use of enzymes in a stable, immobilized form, especially since the efforts of engineering enzymes today operated by a significant number of methods of covalent and non-covalent fixation of enzymes on insoluble and soluble carriers of diverse nature.

Modern medicine is increasingly using highly purified preparations of physiological active substances (PAS) of a protein nature in various fields of clinical medicine as promising drugs for medical treatment due to their extremely high activity and specificity. [33, 34]

We have given relevant aspects of the marketing research of drugs containing enzymes on the pharmaceutical market of the Republic of Uzbekistan. The results obtained indicate the feasibility of further marketing research of the nomenclature of drugs to assess the prospects of creating and introducing new domestic drugs containing enzymes. [35]

A content analysis of drugs containing enzymes presented on the pharmaceutical market of the Republic of Uzbekistan and included in the State Register of Medicines of the Republic of Uzbekistan was carried out.

In the process of conducting a content analysis, as an object of study, we studied the data on the registration of drugs of enzyme origin based on the materials of the "State Register of Medicines and Medical Devices" for the period 2017, 2018 through the first half of 2019, and a list of essential drugs. [36, 37]

Content analysis is a formalized method for studying textual graphic information, which consists in translating the studied information into quantitative indicators and its static processing. In our studies, we developed and used a scheme for conducting content analysis. [35]

Currently, 63 trade names of pharmaceutical preparations containing enzymes are registered in the Republic of Uzbekistan, taking into account various forms, dosages and packaging. The pharmaceutical market of the Republic of Uzbekistan is mainly dominated by drugs containing imported enzymes (73%).

In accordance with the State Register of Medicines, we conducted an analysis of the nomenclature of drugs containing enzymes of origin. Currently, enzymes of animal origin prevail (80%), (tab. 1).

Table 1. Analysis nomenclature medicaments containing enzymes origin.

№	By origin	2017 y.		2018 y.		2019 y.	
		Amount	**%**	**Amount**	**%**	**Amount**	**%**
1.	Plant	5	7.94%	7	10.94%	8	12.12%
3.	Microbial synthesis	5	7.94%	6	9.37%	6	9.09%
2.	Animal	53	84.12%	51	79.69%	52	78.78%

Also, all drugs containing enzymes can be divided into pharmacotherapeutic groups: proteolytic agents (for external and internal use), digestive enzyme preparations, immunomodulating agents, enzyme preparations (systemic effects), multivitamin preparations and other drugs. The largest number of trade names of drugs containing enzymes is noted in the pharmacotherapeutic group "enzyme preparations" (54.5%), Fig. 3.

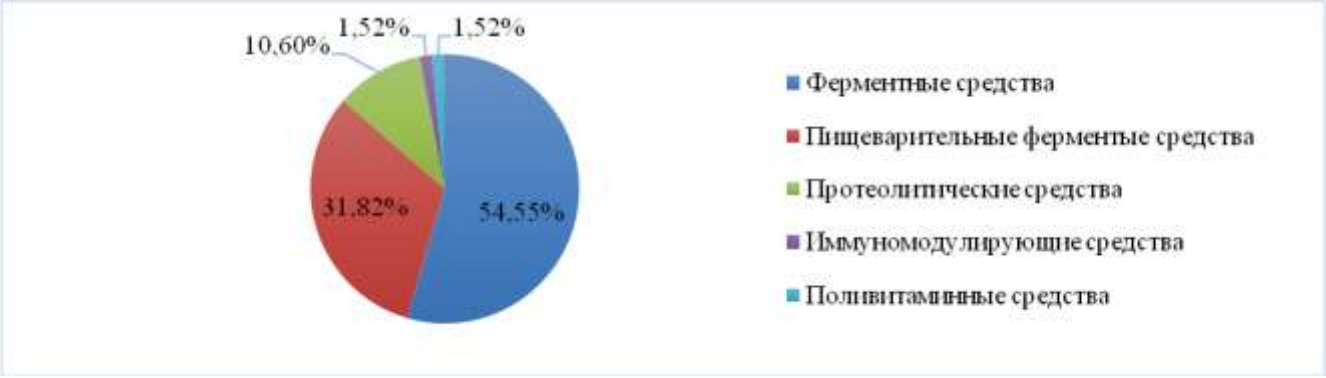

Figure 3. Distribution of trade names of drugs containing enzymes by pharmacotherapeutic groups.

A content analysis of enzyme drugs by type of dosage form was also carried out. In the course of the analysis of the market for drugs containing enzymes, it was found that the main form of the dosage form for this group are coated tablets (53.13%).

It can be concluded that a structured content analysis of enzyme drugs was carried out by comparing quantitative and qualitative characteristics according to the criteria: pharmacotherapeutic group, origin of the assortment of non-CIS countries, CIS countries and the Republic of Uzbekistan.

A relatively large number of enzyme preparations of foreign production were identified (73%), of which drugs imported from the CIS countries (24%), from foreign countries (49%), and domestic (25%) and (27%) for the period 2017- 2019, which suggests the relevance of replacing imported drugs with drugs of local origin obtained on the basis of substances of local raw materials. Moreover, Uzbekistan is rich in raw materials for the production of enzymes of plant and animal origin. Also relevant is the issue of obtaining drugs using local raw materials with an innovative approach, combining PAS to improve absorption and obtain a synergistic effect and reasonable selection of a rational dosage form.

Conclusion

The issue of strategic importance remains the use of well-known and affordable drugs in various combinations in various dosage forms, taking into account the possibility of obtaining the synergistic effect of their action, thereby reducing toxicity, increasing safety and introducing them into domestic pharmaceutical practice.

Moreover, the main emphasis is on those types of products, the introduction of which into production does not require large expenditures, time and money, and will reduce future consumption in their imports. The use of local raw materials with an innovative approach by combining drugs in rational dosage forms of quality control, standardization is an urgent and priority task of the government in the development of the domestic pharmaceutical industry.

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