WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 2, 811-827. Review Article ISSN 2277– 7105

THE PROSPECTS OF USING ENZYME PREPARATIONS IN COMBINATION WITH ANTI-INFLAMMATORY DRUGS IN MODERN PHARMACOTHERAPY

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Article Received on
03 December 2021,

Revised on 24 Dec. 2021,
Accepted on 14 Jan. 2022

DOI: 10.20959/wjpr20222-22941

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ABSTRACT

Annotation: In medical practice, several drugs are often used at the same time. Clinical studies confirm the high efficiency of the combination of enzyme drugs with non-steroidal anti-inflammatory drugs (NSAIDs) with the majority of acute and chronic inflammatory infectious processes. Long-term use of NSAIDs in effective doses is difficult due to frequent complications. In this case, combinations with available enzyme preparations are of particular interest. The sources of production, assortment, identification in accordance with the modern classification and the prospects for the use of enzyme preparations have been studied. A structured content analysis of enzyme drugs was carried out by comparing the quantitative and qualitative characteristics by pharmacotherapeutic groups and origin. It was revealed that there is a relatively large number of imported enzyme preparations on the market. It is important to replace imported drugs with drugs obtained on the basis of substances of local raw materials by combination.

KEYWORDS: effectiveness, prospects, NSAIDs, enzymes, ferment, content analysis.

INTRODUCTION

Currently, the most pressing issues of the rational use of drugs is the possibility of assessing the effectiveness, safety and quality of drugs in circulation throughout their "life cycle": from development, quality criterion for pre-registration studies, examination procedures to entering widespread clinical practice and the period stay in the pharmaceutical market.[1,2,3]

In the context of existing health care resources, the rational use of high-quality, effective, safe drugs and the creation of new ones by combining using local raw materials with an innovative approach is a priority task.

For this, it is necessary to introduce optimal scientifically grounded approaches that receive, with the greatest benefit and the least cost, rational, effective and safe therapy with combined drugs.[4.5]

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

These possibilities and methods should be actively used in the expert assessment of the efficacy and safety of drugs. The issues of rational, and therefore effective, high-quality and safe pharmacotherapy have gone far beyond the medical community, they rightly refer to the most important strategic tasks of today, the full-fledged implementation of the drug import substitution program. This is the basis for the creation and entry into the pharmaceutical market, into the widespread circulation of highly effective drugs.

In medical practice, several drugs are often used simultaneously. At the same time, they can interact with each other, changing the severity and nature of the main effect, its duration, as well as efforts or weakening the side and toxic effects. In this case, there is an appropriate combination of benefits for medical practice. Pharmacological interaction is also associated with the fact that one substance changes the pharmacokinetics or pharmacodynamics of another component of the mixture.[6]

The basic drugs in the pharmacotherapy of many chronic, acute diseases that normalize biochemical parameters are NSAIDs. More than thirty million people in the world take NSAIDs every day, and 40% of these patients are over 60 years old and about 20% of inpatients, and patients also take these drugs without consulting a doctor.[7]

However, their long-term use in effective doses is often difficult due to frequent complications. When conducting pharmacotherapy, special attention should be paid to those drugs that have active metabolites formed in the process of biotransformation (enzymes). The strategically important question remains to use known and available drugs, adjusting the therapeutic dose, dosage form, or combination, taking into account the possibility of

obtaining synergy of their action, reducing their toxicity, increasing safety and introducing them into domestic pharmaceutical practice.

Purpose of the study. To study the classification and effectiveness of the use of enzyme preparations in modern pharmacotherapy by comparing data from a literature review. Also, to study the state of enzyme drugs by comparing the quantitative and qualitative characteristics with the aim of the prospects of using them in the republic independently or by expedient combination.

Materials and research methods. A structured content analysis of enzyme drugs was carried out by comparing the quantitative and qualitative characteristics by pharmacotherapeutic groups and origin using materials from the state register of drugs, Medical Devices (MD) and Medical Equipment (ME).

Among NSAIDs, ibuprofen, due to its relatively low toxicity, has found wide application in pediatric and geriatric medicine.

The relevance of studies to create a combination in soft dosage forms (DF) lies in the need to increase the therapeutic efficacy of ibuprofen and the safety of its use. Synthesized biologically active preparations of phenylglyoxylic acid - fensulcal and benzoketozone, which are characterized by moderate toxicity and have pronounced anti-inflammatory and antimicrobial properties, are registered in the republic.[8]

The data described above indicate that the need to develop and introduce into clinical practice effective and safe anti-inflammatory drugs has not lost its relevance. As an alternative to traditional approaches to the treatment of inflammatory diseases of various etiologies, enzyme therapy, or systemic enzyme therapy, has been widely used in recent decades.

Currently, work is underway to develop a combination of locally produced NSAIDs with enzymes in reasonable rational dosage forms.

Prodrugs and their active metabolites:

Spironolactone	⇨	CYP3A4	⇨	Canrenone
Clopidogrel	⇨	(CH3)2C19	⇨	2-oxo clopidogrel

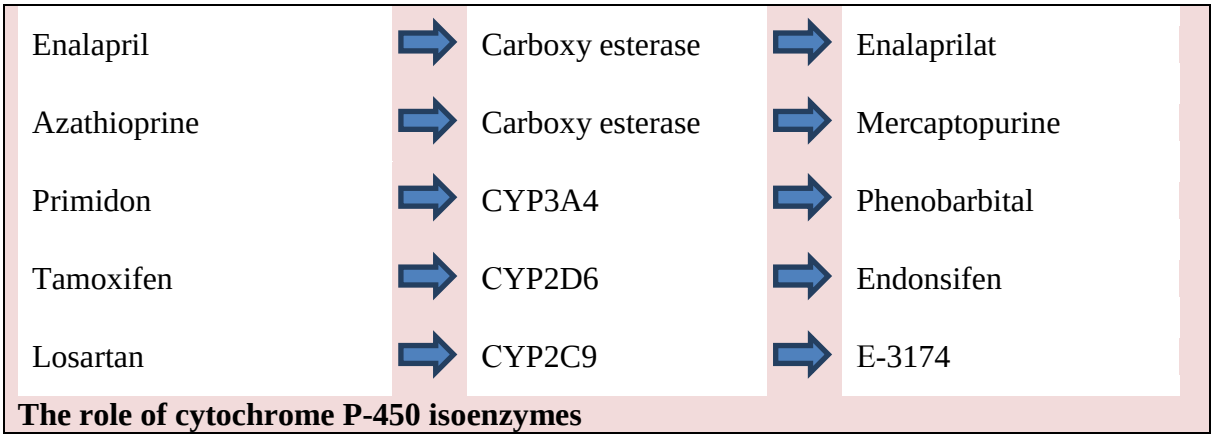

Figure 1: Examples of prodrugs whose active metabolites are formed with the participation of biotransformation enzymes.

There are drugs that are initially inactive, and only as a result biotransformations from them are formed active metabolites that determine the pharmacodynamic effects (fig. 1).[9]

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

This fact and evidence of effectiveness prompted us to think about the need to introduce enzymes into the body from the outside by combining drugs. Enzymes, or ferments, are biological catalysts of a protein nature, which selectively and directionally accelerate the chemical transformations that make up the metabolism in the body. Currently, about 3000 enzymes are known, isolated in pure form, in which the primary structure and spatial organization have been deciphered, and the structure of specific sites in their molecule - active centers directly involved in the biocatalysis process (Veremeenko K.N., Kovalenko V. N. (ed.), 2000).

The study of enzymes - enzymology - has now become a rapidly developing field of science with various branches that have independent significance. Medical enzymology includes the following sections (Veremeenko K.N., Kovalenko V.N. (ed.), 2000): enzymodiagnostics - the study of enzymes in biological fluids and tissues for diagnostic and prognostic purposes;

enzymopathology - the use of enzymes to study the pathogenesis of a number of diseases; enzyme therapy - the therapeutic use of enzymes, their activators and inhibitors.

It is quite important that NSAIDs with enzymes (serratiopeptidase) work senergically to enhance their positive effect. Clinical studies confirm the high efficiency of the combination of antibacterial agents and enzyme preparations in most acute and chronic inflammatory infectious processes. 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, decrease. Examples include diseases such as sinusitis, bronchitis, cystopyelitis, adnexitis, prostatitis, and the like.

Just as serratiopeptidase potentiates the action of antibiotics, it potentiates the action of non-steroidal and steroidal anti-inflammatory drugs and is therefore often prescribed in combination with them or as a continuation of treatment after a short course of NSAIDs for all their inherent indications.[9]

The use of enzymes (proteolytic enzymes, which catalyze the hydrolysis of peptide bonds in molecules of proteins and peptides) in the treatment of various diseases has a history.

For a long time, in the treatment of purulent wounds, abscesses and other purulent diseases of soft tissues, pumpkin juice was used, papaya pulp or green pineapple was applied. Since all of these plants contain a large number of enzymes, they contributed to faster wound cleansing and healing.

Enzymes are substances that are present in the tissues and cells of all living organisms and are capable of accelerating the chemical reactions taking place in them many times. Enzymes can be simple proteins, entirely built from polypeptide chains and degrading upon hydrolysis only into amino acids. Simple proteins are hydrolytic enzymes (for example, proteases, lipases, ribonuclease) that perform their function in the absence of a 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).

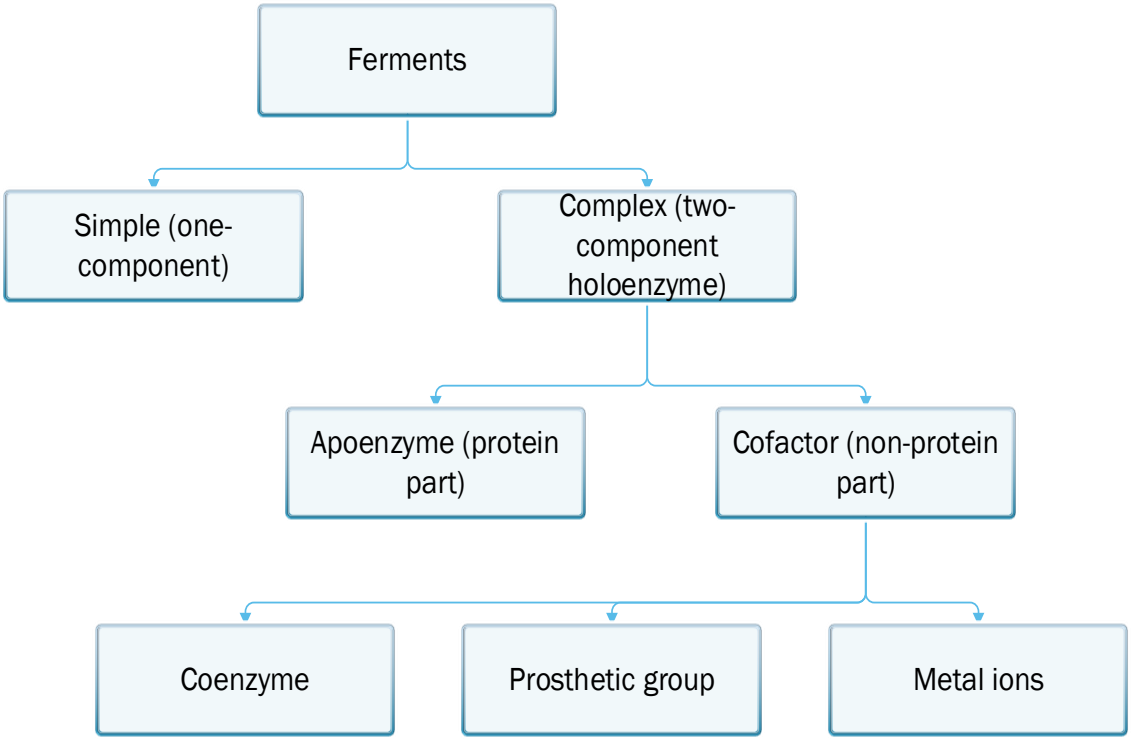

Figure 2: Enzymes' nomenclature.

A substance whose chemical transformation is catalyzed by an enzymes is called a substrate. Back 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 enzymes. Working names are formed by combining the name of the substrate, the type of reaction and the ending "-ase". For example: lactate + dehydrogenation + ase = lactate dehydrogenase. The systematic name of the enzyme is formed as follows: the name of the substrates: the 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, which is strictly assigned to it.[10]

In 2009, the global sales of enzymes and enzyme preparations amounted to 440 million euros, including enzymes produced using traditional (classical) producer strains.[11]

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

According to the modern classification, about 3000 enzymes have been identified. The industry produces about 250 types of enzyme preparations. At the same time, about 99% is accounted for by preparations of 18 enzymes.[12,13]

The sources of obtaining enzyme preparations have been studied. Of all the existing natural sources of enzymes, of practical interest for the production of enzyme preparations are microorganisms, some plants or individual organs of plants and animals capable of accumulating significant amounts of enzymes.

From plant raw materials, the source of enzymes can be sprouted cereal grains, which can be used directly as a technical enzyme preparation or as a raw material for obtaining purified preparations. Melon and ficus latex, pineapple green mass juice, papain, bromelain, ficin papaya, pineapple, figs are used as raw materials for obtaining proteinases.

The technology for the production of enzyme preparations from plant and animal raw materials includes two main stages: collection of enzyme-containing raw materials; isolation and purification of the target product.[14]

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

In this regard, exopeptidases are subdivided into.[14,15] -aminopeptidases that catalyze the cleavage of N-terminal amino acids; carboxypeptidases that catalyze the cleavage of C-terminal amino acids; dipeptidases showing 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 - latex enzymes of the fruit of the melon tree. They belong to the group of thiol proteinases and are activated by reduced glutathione and cysteine.

Ficin and bromelain: the first is obtained from figs, the second from pineapple juice. These enzymes are classified as thiol proteases. Both enzymes share similar properties and uses with papain. They are also used to remove protein haze in beer and to soften meat.

Proteases of animal origin: they play a huge role in the digestion processes. Trypsin is secreted by the pancreas as an inactive precursor of trypsinogen and is activated by another enzyme. Chymotrypsin is secreted by the pancreas into the small intestine as inactive chymotrypsinogen. Activated by trypsin; in this case, two dipeptides are cleaved off.[16]

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 expediency of using proteolytic enzymes is systemically related to their ability in clinical practice to enhance and accelerate the therapeutic effect in various diseases, influencing their introduction on the general patterns of their development, the activity of inflammation in patients with rheumatoid arthritis, ulcerative colitis, etc. Currently, proteolytic enzymes are effectively used to reduce the inflammatory process.[16]

Proteolytic enzymes are not direct anti-inflammatory drugs. They act as a catalyst for biochemical processes, triggering or accelerating biochemical reactions in the inflammation zone, where a local deficiency of own proteolytic enzymes has arisen, in which the duration of inflammation increases and recovery is delayed. al., 1976.

Proteolytic enzymes provide reliable relief of inflammation as a result of pronounced fibrinolytic activity and exert an effect through anti-inflammatory, immunomodulatory, antiplatelet, fibrinolytic, decongestant and analgesic effects (Klein G. et al., 1999). One of the properties of these drugs is the ability to potentiate and alleviate 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, facilitate their penetration into tissues and thereby increase the effectiveness of therapy is well known (Koyama A. et al., 1986; Selan L. et al., 1993).

Depending on the purpose of application, certain requirements are imposed on enzyme preparations with respect to the composition of enzymes, the optimal conditions for their action, the degree of their purification, which is especially important for microbial preparations requiring chemical, microbiological and toxicological control, used fillers, cost, etc.[10]

The search and introduction into medical practice of new highly effective enzyme preparations of herbal origin is of particular interest.

The prospects for the use of enzymes are undoubtedly high, since world medicine begins to limit 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 cells and destroy pathogenic bacteria, viruses and toxins. Experiencing technology for modifying antibodies, which allows them to freely enter and leave cells.[17,18]

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 remains active over a wide temperature range.[17]

Papain also has anti-inflammatory properties. Without acting directly on the site of inflammation, papain stimulates metabolism, which has an effect on accelerating the regeneration of inflamed tissues. Papain increases blood flow and destroys toxic substances at the site of inflammation by stimulating growth hormone, which in turn is very important for the regeneration of liver cells. Also, papain accelerates the healing of wounds, trophic ulcers and pressure sores.[13.19- 21]

Exopeptidases having the ability to cleave off terminal amino acids, as it was already 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.

Homeland of the melon tree Central and South America. Cultivated in all tropical countries of the world as a fruit tree.

In Uzbekistan, there are all natural and climatic conditions to cultivate a melon tree (papaya), the fruits of which can be used as raw materials for obtaining enzyme preparations, and the aerial part for obtaining effective drugs. Many works have been devoted to the phytochemical and proteolytic study of papaya growing in Uzbekistan (Rakhimov M.R., Musaeva N.A. 2000).[20,21] As a result of the study, useful amino acids were identified and the anti-inflammatory effect of the papaya substance, as well as the anti-inflammatory and immunostimulating activity of the tincture of the aerial part of the domestic papaya, was revealed. As a result, the substance and injectable DF were approved for medical use in Uzbekistan. (2000)

The leaves contain free and bound phenolic compounds, tannins, organic acids, steroidal and triterpene saponins, flavonoids, lipids, coumarins, glucose, alkaloids used in the treatment of tuberculosis and possessing bile and diuretic properties. In the republic, work is underway on the use of extracts of the aerial part in a combination of NSAIDs in the form of a gel for external use and have encouraging results on its action.[22]

In Peru, papaya leaves are renowned as an indispensable remedy for wound healing. Recently, papaya made a splash in the medical world: Indian scientists discovered that the bark of the 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 now underway (the bark has never been used in medicine before), if contraindications are not identified, papaya will give the world an effective remedy for this terrible disease.[18]

Papain is used in medicine: ophthalmology, neurosurgery, neuropathology, gastroenterology, urology. It has proteolytic, anti-inflammatory, anticoagulant, analgesic, bactericidal, hemolytic, and is able to destroy proteins of polypeptides and amino acids, dissolve dead cells.[23]

Another important representative of proteases (animal or microbial) is serratiopeptidase. Serratiopeptidase is a enzyme for the treatment of inflammation and is one of the most widely

used proteolytic enzymes in the treatment of inflammatory diseases in Japan, Germany, Italy, and the USA. Serratiopeptidase has been for more than 40 years. It is present in all living systems, but was first discovered in the body of the silkworm, which uses it to dissolve the cocoon when the butterfly appears. Serratiopeptidase is a proteolytic enzyme (that is, it is used by the body to break down proteins into amino acids) and is sometimes referred to as the "silkworm enzyme" because it is produced from the serration bacteria found in the intestines of the silkworm. This enzyme is responsible for breaking down the silkworm cocoon.[24]

Doctors have long appreciated the anti-inflammatory and analgesic properties of this natural substance and are successfully using it as an alternative to anti-inflammatory drugs.

Serratiopeptidase has positively proven itself in the treatment of post-traumatic and postoperative edema, as well as relief of pain and inflammation in rheumatic diseases (Esch P.M. et al., 1989; Panagariya A. et al., 1999).[16, 24]

Over the years of use, serratiopeptidase (an enzyme of animal origin) has shown its effectiveness in sports injuries, sprains and ruptures of the ligamentous apparatus, fractures and dislocations, postoperative edema, in abdominal surgery, not only to improve healing processes, but also to prevent postoperative adhesions, therapy of ENT pathology and inflammatory diseases of the lungs - not only for the speedy resolution of inflammation, but also for imparting dynamic properties to the mucociliary transport system due to the diluting effect on sputum. The drug reduces edema of the mammary glands and is indispensable for mastitis in breastfeeding due 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: it reduces the intensity of inflammation due to the hydrolysis of biologically active substances - inflammatory mediators (bradykinin, histamine, serotonin, etc.), a decrease in capillary dilation and regulation of their permeability; working synergistically with NSAIDs and antibacterial agents, it enhances their positive effect.[11, 24]

The authors[14] studied the interaction on local and general reactions of the body in patients with traumatic osteomilitis of the lower jaw of the enzymatic preparation "Serrata". It should also be noted that many are taken for chronic inflammatory pathologies, which means for a long period (key enzyme No. 41 of October 20, 2008. Weekly "Pharmacy").[16-18]

According to the 2017 BioMed Research International magazine, serratiopeptidase reduces swelling by reducing the amount of fluid in the tissues, thinning it and facilitating drainage. 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 breast tightening. A "moderate to significant" improvement was seen in 85.7% of the supplemented patients, compared with 60% of the placebo group. A "noticeable" improvement was seen in 22.9% of the treated patients, compared with 2.9% in the placebo group.[24] Helps relieve symptoms of superficial thrombophlebitis.[14]

Italian researchers compared the efficacy of serratiopeptidase and seaprose S in the treatment of inflammatory venous disease. Both treatments have been found to be effective in relieving pain and relieving thrombophlebitis symptoms.

In most studies, serratiopeptidase has been used at a dosage of 10 to 60 mg. However, more research is still needed to determine the optimal dose.

Also, based on the available research data, this enzyme is effective in reducing swelling after surgery and can be an alternative to conservative measures such as ice.[25.26]

In the republic, the drug Seramig SD (10 mg) is registered, coated tablets containing the enzyme serratiopeptidase as a proteolytic enzyme produced by the manufacturer Sharq Darmon, the substance for which is supplied from India. Although the silkworm cocoon is grown and silkworming is established in the republic. Those. we can get the domestic substance of serratiopeptidase.

Most enzyme preparations are available in the form of pills or tablets in enteric coatings, which protects the enzymes from release in the stomach and destruction of gastric juice by hydrochloric acid. Most tablets or dragees are 10 mm or more in size. Nevertheless, it is known that solid particles can be evacuated from the stomach simultaneously with food, the diameter of which is no more than 2 mm with an optimal size of 1.4 mm.[18]

If a tablet or dragee is in the stomach for a long time, the enteric membrane is destroyed, and the enzymes inside are inactivated. However, in gynecology, proteoastic enzymes are used in suppositories. (Longidaza). Also, suppositories are used according to the recipe of the Ruhr University G. Bohuli, Germany.

Thus, we see those drugs, which are natural physiologically active protein compounds (enzymes, their inhibitors and activators, hormones), have found a worthy place among the means of practical medicine. Unfortunately, the daily clinical use of enzymes is limited both by economic factors - their high cost and low availability, and by their rapid inactivation under the conditions of the body and by various side reactions caused by or as foreign proteins (antigenicity, allergenicity, toxicity, etc.). To a certain extent, these obstacles can be eliminated through the use of enzymes in a stabilized, immobilized form, especially since by the efforts of engineering enzymology, a significant number of methods for covalent and non-covalent fixation of enzymes on insoluble and soluble carriers of a very different nature have been developed.[27]

We have presented the relevant aspects of marketing research of medicines containing enzymes presented on the pharmaceutical market of the Republic of Uzbekistan. The results obtained indicate the advisability of further marketing research of the range of drugs to assess the prospects for the creation and introduction of new domestic drugs containing enzymes.[28]

In the process of carrying out content analysis - translation of the studied information into quantitative indicators and its static processing as an object of research, data on registration of drugs of enzyme origin were studied according to the materials of the State Register of Medicines and Medical Products for the period of 2018, 2019 through the first half of 2020 biennium, list of essential drugs.[29,30] In our studies, we have developed and used an analysis scheme.[31]

Currently, 63 trade names of medicines 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%), of which drugs imported from CIS countries account for (24%), from non-CIS countries (49%), and domestic (25%) and (27 %) for the period 2018-2021

In accordance with the State Register of Medicines, medical devices and MT conducted an analysis of the nomenclature of medicines containing enzymes by origin. Currently, enzymes of animal origin prevail (74%) (tab. 1).

Table 1: Analysis of the range of medicinal products containing enzymes by origin.

№	By origin	2018 y.		2019 y.		2020 y.	
		Quantity	%	Quantity	%	Quantity	%
1.	Vegetable	5	7,94%	7	10,94%	8	12,12%
2.	Microbial synthesis	5	7,94%	6	9,37%	6	9,09%
3.	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 agents, immunomodulatory agents, enzyme agents (systemic action), multivitamins and other drugs. The largest number of trade names of medicines containing enzymes is noted in the pharmacotherapeutic group "enzyme agents" (54.5%), Fig. 3.

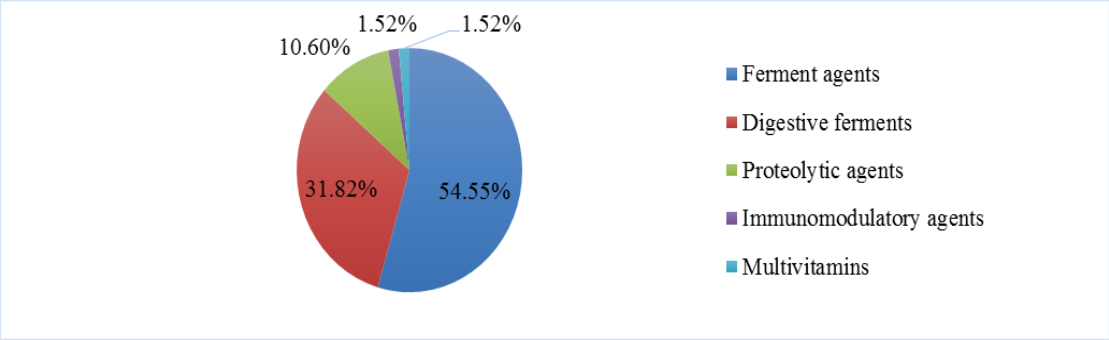

Figure 3: Distribution of trade names of medicinal products containing enzymes by pharmacotherapeutic groups.

Also, a content analysis of enzyme drugs was carried out by the type of dosage forms. During the analysis of the market for medicinal products containing enzymes, it was revealed that the main type of DF for this group are coated tablets (53.13%).

CONCLUSIONS

The sources of production, assortment, identification in accordance with the modern classification and the prospects for the use of enzymes preparations, due to their demand in various industries, medicine, and scientific research, have been studied.

A structured content analysis of enzymes drugs was carried out by comparing the quantitative and qualitative characteristics according to the criteria: pharmacotherapeutic group, origin of the range of non-CIS countries, neighboring countries and domestic production.

A relatively large number of imported enzyme preparations (73%) was revealed, 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 obtaining enzymes of plant and animal origin. Also relevant is the issue of obtaining drugs using local raw materials with an innovative approach.

The strategically important question remains, the use of known and available drugs, in various combinations and dosage forms, taking into account the possibility of obtaining a synergistic effect of their action, thereby reducing toxicity, increasing safety and their introduction 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 funds, and will reduce the consumption in their imports in the future. The use of local raw materials (enzymes and NSAIDs) with an innovative approach to combining drugs in rational formulations for quality control and standardization is an urgent and priority task of the government in the development of the domestic pharmaceutical industry.

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