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Review article
Pregledni članak

CURIOUS CASES OF THE ENZYMES

NEOBIČNA ISTORIJA ENZIMA

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Summary: Life as we know it heavily relies on biological catalysis, in fact, in a very nonromantic version of it, life could be considered as a series of chemical reactions, regulated by the guarding principles of thermodynamics. In ancient times, a beating heart was a good sign of vitality, however, to me, it is actually the presence of active enzymes that counts… Though we do not usually pay attention, the history of enzymology is as old as humanity itself, and dates back to the ancient times. This paper is dedicated to these early moments of this remarkable science that touched our lives in the past and will make life a lot more efficient for humanity in the future. There was almost always a delicate, fundamentally essential relationship between mankind and the enzymes. Challenged by a very alien and hostile Nature full of predators, prehistoric men soon discovered the medicinal properties of the plants, through trial and error. In fact, they accidently discovered the enzyme inhibitors and thus, in crude terms, kindled a sparkling area of research. These plant-derivatives that acted as enzyme inhibitors helped prehistoric men in their pursuit of survival and protection from predators; in hunting and fishing… Later in history, while the underlying purposes of survival and increasing the quality of life stayed intact, the ways and means of enzymology experienced a massive transformation, as the 'trial and error' methodology of the ancients is now replaced with rational scientific theories.

Keywords: enzyme, drugs, inhibitors, art, history, industry

Kratak sadržaj: Život oko nas uglavnom se zasniva na biološkoj katalizi, pa bi se čak, u nekakvoj neromantičnoj priči, život mogao opisati kao niz hemijskih reakcija koje regulišu glavni principi termodinamike. U davnoj prošlosti, kucanje srca bilo je znak dobrog zdravlja, međutim, za mene, najvažniju ulogu ima upravo prisustvo enzima... Mada ne obraćamo često pažnju na to, istorija enzimologije stara je koliko i sam ljudski rod i seže daleko u prošlost. Ovaj rad posvećen je baš tim počecima u ovoj veoma zanimljivoj nauci, koja je u prošlosti ostavila traga na našim životima i koja će u budućnosti učiniti da život bude mnogo produktivniji za čovečanstvo. Između čoveka i enzima postojao je oduvek jedan delikatan, suštinski važan odnos. Suočen s nepoznatom i neprijateljski nastrojenom prirodom punom grabljivaca, preistorijski čovek rano je otkrio lekovita svojstva biljaka, i to metodom probe i greške. Štaviše, slučajno su otkriveni inhibitori enzima, čime je, grubo rečeno, još tada otvorena nova oblast istraživanja. Ovi biljni derivati koji su imali ulogu inhibitora enzima pomagali su preistorijskom čoveku u njegovoj borbi da opstane i zaštiti se od grabljivaca; prilikom lova i ribolova... Kasnije kroz istoriju, sa nepromenjenom svrhom opstanka i poboljšanja kvaliteta života, enzimologija je iz korena transformisana, a metodologiju »probe i greške« iz praistorije zamenile su racionalne naučne teorije.

Ključne reči: enzim, lekovi, inhibitori, umetnost, istorija, industrija

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Introduction

Life begins with a catalytic activity. The importance of catalytic activity was annotated by Kleczkowski and Garncarz (1) in a very striking manner, that is, 'the original environment of life on Earth was seawater containing micronutrients with structural, metabolic and catalytic activity'. Today, we know that germination of spores begins with macromolecular synthesis (2).

Historical relevance of clinical enzymology begins with Francis Home in 1780, through his studies on the detection of glucose in urine (3). Catalysis *per se* as a term was first introduced by J.J. Berzelius in 1836 (4). Richard Bright, on the other hand, dedicated his work to the investigation of 'proteinuria' by heating up urine with a candle flame in a tablespoon (1789–1858) (5). After many subsequent works by the 19th century scientists, it became evident that digestion was in fact done by the relevant enzymes (6). Scientific enquiries in clinical enzymology began with rudimental tests, mostly performed haphazardly, and this later paved the way for more sophisticated methods such as nuclear magnetic resonance and mass spectrometry (5). Nowadays, moreover, there are myriads of different, equally fascinating areas of research on enzymes; diseases, metabolic significance, catalytic mechanisms, novel roles and interactions with various chemicals, drugs, agonists, metals are only a few of them… (7–15). Applications of computational protein studies give different points of view for investigation and designing novel catalysts from scratch. Through these delicate, meticulous approaches, clarification of protein-protein interactions and inhibitors of various molecules and large oligomeric assemblies is made possible (16). With the project 'Enzyme Function Initiative', defining sequence-structure interaction/interdependence would provide the prerequisite infrastructure for accurately predicting the *in vitro* functions of previously unknown enzymes and open the door for much more challenging studies (17). Both in the near and distant future, life might require and depend on designing state-of-the-art application areas of enzymes for novel scientific outcomes in daily life in addition to their benefits in medicinal therapies (18–20).

Enzymes are Vital for Every Part of Life

With the limited evidence, the daily, monotonous life of ancient humans is hard to predict with precision, yet one thing known for sure is that they also required various food sources to sustain life. Based on the preexisting knowledge in addition to newly emerging data, we are putting pieces together and trying to predict and clarify which enzyme-bound products they used.

What was the role of fermentation in the emergence of enzyme products in the ancients' life? In fact, was the first enzyme product a fermented one or not? Which came first? Bread? Wine? Vinegar? Beer? Soy sauce? Kumis? Sake? Koji? Kefir? Sour cream? Pickles? Sauerkraut? Sourdough? Yoghurt? Boza? Kimchi? Miso? Tempeh? Or perhaps a completely distinct, unknown enzyme product was consumed that unfortunately left the scene with no trace for us to follow.

Neanderthal man's food culture began to emerge approximately in 30,000 BC with the introduction of bread (21) and, accordingly, it is very hard to find any documented evidence on this subject. Bakery technology begins with the cultivation of wheat in Göbekli Tepe that is, with its 11,600 years old existence, also the world's oldest temple. Sourdough starters or yeast was used as a food additive in bread baking, however, the exact or approximate date is not clear (22). Dairy products were another important food source in ancient societies. Cheese is an effortless candidate to claim the role of being the first enzymatic product. And the use of milk dates back to 8,000 years ago and it evolved in the 'Fertile Crescent' between the Tigris and Euphrates rivers (23).

Koumiss was an alcoholic beverage (V century BC) of ancient times in central Asia and was used in the treatment of various diseases such as phthisis (24). Yogurt and kefir are also among the ancient traditional dairy products and were used extensively as preventive compounds against diseases, and for curative purposes. The nomads carried fresh milk in bags, probably crudely made from animals' stomach, and the milk, in this relatively perfect condition, fermented into yogurt or kefir (25). The origins of wine and vinegar go back to as far as 2,500 BC. Hammurabi tablets, casted in stone, are perhaps the first documented artifacts on fermentation of grapes. These tablets date back to 2,100 BC and again this was probably the first document on the commercial use of enzymes. The second commercial product of the enzyme origin might have been vinegar, which was widely used in those days both for medicinal purposes as a painkiller, and in disinfection of wounds and finally in food storage (26). However, C. Wang and his colleagues, using five analytical methods to identify the chemical constituents of the potteries originating from China, found out that the emergence of various fermented products dates back to as early as 7,000 BC (27). On the other hand, the origin of sake is an oblique one. Sake may be as old as wine. It goes back as far as 2,500 years when the cultivation of rice became widespread. The most mysterious and acutely necessary component of sake is *koji* which contains alpha-amylase, beta-amylase proteases, peptidases, sulfatases enzymes. Traditionally, koji is also used in soy sauce and in miso. Natto is a traditional, dateless Japanese meal and the enzyme found in natto has been named nattokinase (28).

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Smell or the occurrence of various odors, again an interesting façade of enzyme catalyzed reactions, is another, crucial factor in survival. The first study on enzymatic catalysis and the related occurrence of odors was performed approximately four decades ago. Investigators, for instance, studied the effect of γ-irradiation on cystein sulfoxide lyase and odor of onions (29). Odors originating from the catalytic activities of the enzymes are potent regulators of biological functions. Jasmonic acid, a highly volatile terpene compound, shows its effect on protein kinases or transcription factors (30). Odor evoked behaviors or social interactions show their effect on the enzymes such as flavin containing enzyme monooxygenase-3 (31). In the determination and approximate diagnosis of various health problems, dogs and cats smell some of the diseases such as cancer, epileptic seizures, and hypoglycemia (32, 33).

Meat tenderizer, which contains the enzyme papain, has been recommended for the treatment of bee (34) and fire ant (35) stings. It was also established that these meat tenderizers were safe and effective for patients with a phytobezoar (36).

Enzyme Inhibition

Medicine is a cumulative pile of interactions from the collective components of science, technology and human values, beginning from the ancient times (37). Poisons, in other words enzyme inhibitors, are widespread in plants and animals and they were used – and are still in use – for hunting as arrow poison, in fishing (38) or in even warfare (39). The history of enzyme inhibitors is as old as humanity (40). However, the very first documented experiment on enzyme inhibition was done on proteolytic enzymes with formaldehyde in 1899 (40).

Enzymes and Art

In his article, Irvine H. Page proclaims that '*Scientific research is, in many ways, related to art*' (41). Enzyme inhibitors have special roles in the production and stimulation of artwork! The whole assumption might seem irrelevant and out of context, but the roads of enzymes and artifacts might effortlessly entangle. One of the known art effector molecules is Thujone, which is widely established as a severely neurotoxic compound. A few liver enzymes are responsible in the metabolism of Thujone; cytochrome P450 (CYP), CYP2A6, CYP3A4, and CYP2B6. Thujone inhibits gamma-aminobutyric acid A (GABA) receptor (42, 43). It was discovered that CYP2A6 is the key enzyme in the metabolism of Thujone in human liver (43). The most interesting and appealing point of Thujone is that it is present in the notoriously famous absinthe drink (42). A number of great artists and writers from the late 1800s used absinthe as a social drink, including Vincent van Gogh and Toulouse-Lautrec (44). There are also implications for the ailments of Vincent van Gogh that involve heavy absinthe consumption (45). Furthermore, another enzymatic product, 'vinegar', is the main subject of a beautiful painting in Rijksmuseum. As a matter of fact, Cleopatra's knowledge of chemistry allowed her to win a bet over Antony (46).

Enzyme Inhibitors and their Effects on Warfare

In the Second World War (WW2), Nazi Germany used acetylcholinesterase inhibitors such as tabun, sarin, and soman as chemical weapons. And following this initial experience in war, widespread weapon development programmes have been initiated in the exploration of various neurophysiological and neurotoxicological chemical compounds (47). These types of studies have opened a new window on enzyme inhibitors such as medical treatment in poisoning with organophosphorus compounds (48) and provided new insights on the reactivation of acetylcholinesterases (49).

Enzyme Inhibitors and Cosmetic Beauty

Sirtuins are associated with cellular energy metabolism and the redox state of the cell through their interactions with multiple signaling and survival pathways. It is accepted that activation of sirtuins is a valuable therapeutic target against aging and age-related diseases, including the renal diseases (50). Aging has now been defined both as a cellular and molecular event. And sirtuin-activating and anti-glycation products are already being marketed by cosmetic and pharmaceutical companies (51). Botulinum toxin, likewise, is an enzyme that enters peripheral cholinergic nerve endings and specifically and selectively cleaves one or more SNARE proteins to induce paralysis (52). Most patients and physicians are using monotherapy by the botulinum toxin for a natural look that softens wrinkles for the upper face profile (53). Recent studies show that botulinum toxin has many other roles in medicine (54).

Enzyme Inhibitors as Therapeutic Compounds

As a rule, most of the drugs derived from food products show their effect on enzyme inhibition (55). Target-based drugs and identifying novel and safe chemotherapy targets with particular emphasis on the inhibition of key reactions in metabolic pathways are many a researcher's dream (56). Understanding the role of enzymes in various diseases and their detailed mechanisms is among the important aims of the enzyme inhibition studies (57). Antibiotics were first

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Table I Analysis of the historiography of enzymes.

Year	Finding	Ref
1683–1757	First biochemical experiment and first enzyme specificity experiment	81
1729–1799	Effect of concentration, temperature, time on enzymes (were unaware of enzymes)	81
1833	Something converts starch into sugar and is named diastase (the suffix 'ase' comes from diastase)	82
1835	Science world gained the word 'catalysis'	83
1836	Theodor Schwann discovered that gastric juice contains a digestive substance and he named this substance pepsin	84
1876	Wilhelm Friedrich Kühne, used a Greek word 'enzymos'	81
1876	Studies on glycolysis were begun in this year by Bernard. Disappearance of sugar from blood upon being left for 24 hours at room temperature	85
1884	Enzymes of the digestive tract of fishe. First publication in PubMed	86
1890	Emil Fischer proposed the 'lock and key' model	81
1897	Bertrand partially purified the enzyme laccase from tree sap	81
1897	The Buchner brothers investigated the first cell-free assay	87
1897	Fermentation explained; homogenisation and filtration of yeast and naming of filtrate as 'zymase'	88
1901	Enzyme theory; for every vital reaction a specific enzyme exists	89
1902	Victor Henri published the first successful mathematical model for describing enzyme kinetics	90
1903	Enzymes are realized in tumour	91
1903	Michaelis-Menten re-derived the enzyme rate equation	92
1910	Beginning of the study of glycolysis	93
1914	Description of the coenzyme and cofactor cozymase zymin respectively	93
1915	First use of a spectrophotometer	94
1915	Effects of acids and salts upon enzyme activity (amylase)	95
1923	Synthesis of urea with urease and understanding of the importance of enzymes	96
1925	Use of digestive enzyme in therapeutics	97
1926	First enzyme purification by James B. Sumner	98
1940s	Completion of the glycolysis pathway	99
1910–1940	Citric acid cycle	99
1943	Biochemists began to speak on enzyme deficiencies	100
1947	Cori cycle was explained	101
1948	Favism was explained	102
1952	The C-terminal residue of lysozyme	103
1953	N-terminal sequence of carboxypeptidase	104
1956	Explanation of the pentose phosphate pathway	105
1959	Koshland explained the induced fit model	106
1960	Became aware of isoenzymes	107
1960	Began to talk about the secondary or tertiary structure of trypsinogen	108
1962	Partial determination of the primary structure of the enzyme	109
1962	Three-dimensional structure of lysozyme	110
1963	Completed the primary structure of bovine pancreatic ribonuclease	111
1965	Allosteric regulation clarified	112
1965	Studies began on immobilized enzymes	113
1972	Synzyme: synthetic enzyme	114
1975	Enzyme replacement therapy was suggested in 1950 and began in 1975	115
1980	Computer programs for use in enzyme kinetic studies	116
1981	Discovery of ribozyme	117
1981	Use of enzymes in biosensors	118
1986	Abzyme, a monoclonal antibody with catalytic activity	119
1990	Telomerase and aging, relationship explained	120
1991	First enzyme replacement therapy	121
1994	Deoxyribozyme, DNA enzymes or catalytic DNA	122
2011	Conformational selection	123
2012	Bio-energetic theory of carcinogenesis and inhibition, Krebs enzymes	124
2014	Ubiquitin signaling explained	125
2014	Artificial photosynthesis in nanobiocatalytic assemblies	126

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Table II Role of enzymes in industry.

Year	Finding	Ref
1917	Enzymes in the fermentation industries	128
1951	Conversion of starch to fermentable sugars, through chill-proofing of beer	131
1957	Pickle industry	132
1972	Enzymes in the detergent industry	133
1976	Role of microbial enzymes in flavor development in foods	134
1984	Enzymes in starch industry	135
2001	Immobilized enzymes applied to peptide synthesis, i.e., sweetener aspartame, enkephalin and other bioactive peptides	136
2004	Diagnostic kits	137
2005	Extracting essential oil (natural perfume) by enzymes	138
2006	Industrial application of β-galactosidase in food technology	139
2007	Making diet foods	140
2010	Food technology (adding enzymes in for example celiac disorders)	141
2011	α-Amylases applications in food, textile, paper, detergent industries	142
2012	Enzymes have been used in cosmetics for more than 20 years	143
2013	Cellulase enzymes in paper, textile, and biofuels industries	144
2013	Pectinase in fruit juice, greater juice extraction	145
2013	Enzymatic treatment of leather technology	146
2013	Biosynthesis of rare hexoses	147
2014	Commercial enzymes are used for producing biofuels	148

defined by Selman Waksman in 1941. He initially described an 'antibiotic agent' as a microbe that antagonizes the growth of other microbes. With the initiation and discovery of many antibiotics of different classes such as penicillin, streptomycin, chloramphenicol, and tetracycline between the years 1945 and 1955, the dawn of antibiotics formally began (58). Likewise, Angiotensin Converting Enzyme Inhibitors are among the most common drugs which are widely prescribed for benign hypertension (60). Furthermore, inhibition of key, regulatory enzymes in lipid metabolism provides medicinal benefits as well. For instance, statins are inhibitors of HMG CoA reductase which have been used for treatment of high cholesterol. Another group of the enzyme inhibitors are used for treatment of obesity (61). Examining and characterizing the mechanism of actions for enzyme inhibition is one of the trending topics in biochemistry (62). From the regulation of respiration, pH balance, gluconeogenesis, ureagenesis, lipogenesis and Na^+ retention; to the prevention of calcification, carcinogenesis, it is clear that enzyme inhibitors can be used for diverse therapeutic purposes (63) and this list could be extendible. Furthermore, enormous clinical success can be achieved with novel enzyme inhibitors in cancer therapy as well and every day, researchers are defining new drug targets for various, equally challenging diseases (65). On the other side of the medallion, pharmaceutical companies spend enormous amounts of money for clinical trials and marketing in novel drug development studies that use enzyme inhibitors (66). It is, thus, not hard to foretell that the current and future researchers will try to investigate novel drugs or modify preexisting drugs in new, alternative therapies for developing novel drug indications such as successfully eliminating seizures with little or no side effects (10–12, 14, 67–72).

Mapping the active sites of the enzymes began in the middle of the 1960s but designing drugs that

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interact with the active site is an important field in drug development (73). Kinetic or modelling studies provide us with the information on differentiating the active site and binding site of the enzymes, respectively. Enzyme research, or in other words biochemical research, today focuses on the molecular basis of biological processes and it applies especially to human health and diseases (80). Self-evidently, enzyme inhibitors will always be one of the dominating trends in drug development (74–79).

Enzymes in Industry

In the beginning of the current century, more than 3000 different enzymes from different organisms have been identified and many have found their respective applications in biotechnology as well as in the pharmaceutical, chemical and food industries (127). In fact, enzymes effectively changed the applications and methods in industries (128). Half a century ago, studies that involved various microorganisms began on clots formed in spoiling milk. By the year 1933, on the other hand, enzymes in bread and bakery industries started to mature with the observations of Blagoveschenski and Sossiedov on wheat flour (129). And even today, one of the most important study subjects is designing novel biocatalysts for the relevant industries (130) (*Table II)*.

Applications that eventually ended up being used for commercial purposes initially started with the study of enzymes in daily, routine life. An effortless example, vinegar, practically had many applications in the past such as pickling of various food products both for preservation as well as for culinary purposes; carpet cleaning or removing of stains from fabrics, and as a brightening agent in dishwashing or antipyretic in villages, in Turkey. However, vinegar is still in use for similar or almost the same purposes in modern life.

Today, enzymes and the related enzyme products have many roles in industries including but not limited to pharmaceutical and food industries; perhaps most importantly, though, in medicine, enzymes can be used as valuable biomarkers in the diagnosis and management of various diseases such as heart, lung, liver, muscle, bone, pancreas, hematology, genetic diseases and malignancies as well as applications in toxicology and forensic medicine. Besides their roles as biomarkers in medicine, there are also various other applications in medicine such as; medicinal digestive enzymes that are used for therapeutic reasons, determination of parental lineage (149), and in plastic surgery (150). Examples of the industrial applications (wine, beer, cheese, bread, cosmetics, detergents, textile) are given in *Table II*. Advances in the science and technology of enzymes will give birth to revolutionary progress in many distinct areas.

Conclusion

Enzymes braced their roles in pharmaceutical industry as diagnostic markers or therapeutic molecules, still a very vivid area of research in the field. Commercial, mass production of many consumer goods such as cheese is made possible by some enzymes. Similar to his prehistoric cousin who made cheese from the stomach of slaughtered animals, the modern man also uses the same enzymes to make this widely consumed, delicious dairy product, only in immobilized forms suitable for commercial use. Moreover, the food industry today relies on enzymes as well. Biological detergents containing specialized enzymes such as proteases, lipases and isomerases are widely used in consumer products. Mighty enzymes have accompanied us on our journey through history and clearly they will be with us in the future with myriads of novel and preexisting benefits.

Both from a macro and micro perspective, needless to say, enzymes played key roles in humanity as well as in the preservation of life quality for ordinary men in everyday life. Enzymes have sparkling roles in every part of our life, from an apoptotic cell on the verge of dying to the sustaining of delicate balances in metabolic pathways. In fact, enzymes solidly marked their footprints in diverse, sometimes interrelated, mostly distinct fields; medicinal therapeutics, warfare, art and food industry are among some of these fields... These small machines that have the potency to make enormous chemical reactions possible in sometimes less than milliseconds constitute the magnificent and marvelous building blocks of our cells. An insight into the history of enzymology enhances our knowledge and understanding of biochemistry. Research on enzymes has had a central indispensable role in the past, present and future of biochemistry in almost every aspect of life. Enzymes are cardinal contents of life and, therefore, exploration of the functions of enzymes and various biochemically uncharacterized proteins with undisclosed functions will continue in the experimental designs of future research. Both current and future scientists working in biochemistry will always resort to enzymes and the methods in enzymology in their pursuit of reliable, scientific remedies and solutions.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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