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Review Article

Recent status in production, biotechnological applications, commercial aspects, and future prospects of microbial enzymes: A comprehensive review

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Abstract

Microbial enzymes can come from bacteria, actinomycetes, fungi, yeast, microalgae, and cyanobacteria. The class of extremophile microorganisms is a source of interesting enzymes that can overcome various technological problems. Globally, these enzymes are industrially produced by fermentation using two techniques: submerged fermentation (SmF) and Solid-State Fermentation (SSF). Currently, microbial enzymes are probably the most important sector in biotechnology. This field finds different applications in various industrial sectors including chemical and pharmaceutical, food and animal feed, textile, agriculture, biodiesel, and so on. The present review surveys the microbial enzymes and their major characteristics, safety, chemical nature and classification, microbial sources of enzymes, production aspects, biotechnological applications, commercial overview, and perspectives and future prospects.

Introduction

In the pursuit of unveiling nature's mysteries over the past decades, science has discovered several hidden natural resources, thereby providing a major market for manufacturing [1]. Among these enzymes are appropriate metabolic catalysts, which require the occurrence of different endogenous biochemical processes along a well-described pathway. Enzymes intensify different bioreactions critical for preserving human survival, reducing the energy of reaction initiation without irreversible alteration [2]. Enzymes are however light spot catchers because of their activity and specificity with regard to their substrate and form of reactions [3]. The word "enzyme" is derived from the sense of the Greek term "ε] ζυμο" in leaven [4]. Wilhelm Friedrich Kuhne first invented it in 1877, although the word enzyme and its use have also been commonly used since a long time ago [5]. On the other hand, microbes are the main source of enzymes since they can be cultivated in high amounts in a limited period of time and due to genetic modifications that may be conducted on bacterial cells to increase their production [6,7]. Microbial enzymes, as biocatalytic molecules, are ecologically efficient and highly specific and can contribute to the improvement, at 105 to 108 rates, of stereo and regio-chemically determined reaction products [5,8]. Diversification in terms of biological, physical, and chemical properties of enzymes has made one type of microbe distinct from other, and also distinct, strains of the same species [3]. Moreover, there are more than 500 industrial products that can be produced with enzymes [9,10]. They are now among the main substances commonly used since the ancestral human civilization. As the population increases, enzymes tend to be one of the most significant substances that have great impacts on all sectors, such as milk, industry, medicine, and agriculture [5]. The present review deals with

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the different aspects related to microbial enzymes, production, commercial aspects, their biotechnological applications, and perspectives and future prospects.

Classification and chemical nature

Chemical nature

The molecular nature of enzymes and their modes of action are two of the most important concerns of biological chemistry [11]. It is conventionally accepted, however, that most enzymes except ribozymes are protein-like in nature [12]. Complex macromolecules composed of protein with or without a non-protein cofactor group (metal ions or **prosthetic** or co-enzyme) are enzymes composing enzymes chemically [3]. Based on differences in chemical nature, enzymes may be grouped into four classes as described in Table 1 [13].

Classification

Based on the reactions they catalyze, the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (Nc-Iubmb) has categorized enzymes into six main groups. In manufacturing techniques, the class of enzymes, the categories of reactions, and the selection of enzymes include Hydrolases; Oxidoreductase; Transferases; Lyases; Ligases, and Isomerases [12]. A special subset grouping is set up within each main class. For instance, the classification of microbial amylases is mainly based on enzyme catalytic properties, like substrate and product particularities. The three EC categories of these enzymes are: transferases (EC 2), hydrolases (EC 3), and isomerases (EC 5), and the majority of these enzymes are a part of the EC 3 category. They comprise: Oligo-1,6-glucosidase; Glucoamylase; Amylo-1,6-glucosidase; Pullulanase; α-Amylase; β-Amylase and many others [14]. Likewise, proteases are enzymes of class 3, the hydrolases, and subclass 3.4, the peptide hydrolases or peptidases. They are classified into two different subcategories, namely endopeptidases and exopeptidases. Further, they are divided into four prominent classes, i.e. cysteine protease, aspartic protease, metalloprotease, and serine proteases according to their site of activity, and dependent on the active site function group [15,16].

Table 1: Chemical nature, classes, and characteristics of enzymes.

Enzyme class	Characteristics
Simple Enzymes	-These enzymes are simplified proteins, i.e., on hydrolysis, they yield amino acids solely
Conjugate Enzymes	-These enzymes consist of two components: a protein component called an apoenzyme and a non-protein component called a cofactor. -In some cases, the cofactor is a basic divalent metallic ion (e.£, Zn, Mg, Co, Ca, and many others), and in some cases an organic non-protein component. -Holoenzyme is the complete conjugate enzyme made up of an apoenzyme and a cofactor.
Metallo-enzymes	-The enzymatic co-factors are monovalent (K^+) and divalent (Cu^{++}, Mg^{++}, Mn^{++}) cations. -Co-factors can be loosely retained by an enzyme, or the molecule itself, as in some examples. - The enzymes are called metalloenzymes if the substance is part of the protein, i.e. iron of hemoglobin or cytochrome.
Isoenzymes (Isozymes)	-A multiple molecular structure is referred to as isoenzymes or isozymes in an enzyme that exists in the same organism and has identical substrate activity.

Lipases: Lipases are the most significant biocatalyst category for biotech technologies [17,18]. They are hydrolytic enzymes that operate to break fatty acids and glycerol on the carboxyl ester bonds of the triacyl glycerols. Lipases function at the interface of aqueous and non-aqueous media leading to low solutions for natural substrates triacylglycerols [19]. Specific lipase (triacylglycerol acyl hydrolase) enzymes catalyzed the reactions of hydrolysis, esterification, and alcoholysis. Moreover, the use of microbial lipases has reached its highest efficiency, thus, they are ideal for several reactions and the aroma of the immobilization processes needs to become better [20]. Lipases are widely distributed in the flora and fauna of the earth. However, in biotechnological processes, more consideration has been devoted to microbial flora including yeast, fungi, and bacteria [19]. Bacteria like *P. fragi*, *Pseudomonas alcaligenes*, *P. fuorescens* BJ-10, *P. aeruginosa*, *B. nealsonii* S2MT, *Bacillus subtilis*, and several fungi species such as *Aspergillus niger*, *Penicillium expansum*, *Penicillium chrysogenum*, and *Trichoderma* produce lipases in elevate amounts [21,22]. Especially, lipase from *Aspergillus niger* is one of the most commonly used lipase types, since it is economically and widely disseminated [23].

Lipases can be used in a number of sectors, namely oil and fat production, dairy manufacturing, detergents, paper and pulp industries, oleochemicals, environmental mitigation, tea processing, diagnostic tools, biosensors, perfume and cosmetics, and medicine [24]. Moreover, emerging features are ester-bonding synthetic plastics, pesticides, insecticides, paraben, and other compound hydrolyses which can be used not only to counter global environmental contamination but also to minimize energy and to produce biological energy [25]. Lipases are part of a variety of other sectors, including medicines, agrochemicals, leather, and several environmental remediation [26]. For instance, flavor development through the synthesis of short-chain acid esters and alcohols which are known flavor and aroma compounds in the food industry has been used extensively to change the flavor [27]. Microbial lipases are frequently used in various areas, including the production of flavors for dairy products (alcoholic beverages, cheese, margarine, milk chocolate, butter, and sweets). Fat removal of fish or meat products is often performed also by lipases [28].

Proteases: In terms of their uses in both physiological and industrial fields, proteases are a single category of enzymes that play an important function. Proteolytic enzymes catalyze the cleavage of peptide bonds in other proteins. They are degrading enzymes that catalyze complete protein hydrolysis [29]. Proteases are categorized as alkaline, acid, and neutral proteases, based on the pH at which they are activated [30]. Mainly, in the biotechnological area, *Bacillus* sp. is the most dynamic and effective extracellular alkaline protease producer. Moreover, strains of *Streptomyces* are also a suitable source among actinomycetes [31,32]. Additionally, yeasts such as *Candida* sp were closely investigated as effective producers of alkaline protease [33].

Proteases are one of the three biggest classes of industrial enzymes and their global demand grows significantly per year [34]. Proteases constitute roughly 60% of the world's overall enzyme sales [15,35]. Particularly, in various corporate industries, such as textiles, leather, feed and others microbial proteases are the most commonly used [34]. Furthermore, these enzymes are utilized for pharmaceutical products, detergent additives, food manufacturing, and silver extraction in the x-ray film industry [36,37]. The pharmaceutical sector uses mainly proteases to prepare medicines, namely ointments [38,39]. One of the main uses of protease is in the laundry detergents and leather industries, where protein-based stains are extracted from garments and dehairing, respectively [40]. Further, the food industry commonly uses microbial proteases in cheese production, baking, soya hydrolyzed preparation and meat tenderizes [41,42]. Another promising area is its use in industrial and household waste management [43,44].

Amylases: Amylase is an extracellular enzyme that is active in the industry of starch production where it transforms starch into basic components of sugar. Starch is an integral part of the human diet and, for many economically important crops, is a significant storage commodity, such as wheat, rice, corn, tapioca, and potato. Microbes establish two main types of amylase, namely alpha-amylase and glucoamylase. In addition, Plant-origin β-amylase has also been recorded from a few microbial strains. These amylases are typically extracellular and are widespread in actinomycetes, fungi, and bacteria [45]. However, Microbial sources are the most common for large-scale manufacturing to meet industrial requirements [46]. For example, *Bacillus licheniformis, Bacillus subtilis*, *Bacillus amyloliquefaciens*, and *Bacillus stearothermophilus* are considered to be effective producers of thermostable amylase and have been commonly used for numerous applications in industrial processing [47]. Moreover, fungi belonging to the *Aspergillus* genus are widely used to produce α-amylase [48,49].

Amylases constitute a group of industrial enzymes that account for about 25% of the global enzyme market and are among the most essential compounds in biotechnology [50,51]. In many manufacturing processes such as dairy, fermentation, and pharmaceutical industry, they have potential applications. For instance, the development of modified starches, maltodextrin, and fructose syrups is based on amylases [52]. Also, amylases are employed to produce glucose/maltose syrups, decrease the viscosity of sugar syrups, clarify and shelf life of fruit juice, solubilize starch in the brewing industry, and prolong the stalling of bread and other baked products [53], and digestibility improvement of animal feeds [54,55]. In addition, amylases are utilized in detergent preparation, production of biofuel and waste management [56], paper making, digestive medicine preparation, textile desizing [57], and fine industry chemicals [58].

Cellulases: Cellulose is a fibrous, rigid, crystalline, and water-insoluble, biocarbon source, the primary ubiquitous polysaccharides that are part of the plant cell wall. In order to generate biotechnologically significant monomeric subunits, hydrolysis of b-1,4-cellulose linkages is performed via the synergetic effect of several enzymes, the most prevalent of which are cellulases [59]. However, cellulase does not comprise a single enzyme. It is an enzyme group consisting predominantly of exoglucanases and endoglucanase, comprising β-glucosidase and cellobiohydrolases. A diverse variety of microbes, namely actinomycetes, bacteria, and fungi, synthesize this complicated group of enzymes [60]; living in a wide variety of environments that include soil, ruminant rumen, termite/insect guts, severe habitats, and saline or aquatic environments [61]. Particularly, many of the cellulases used for industrial uses come from fungi like *Humicola*, *Fusarium*, *Trichoderma, Phanerochaete*, *Penicillium*, and many others, in which a significant number of cellulases are described [62,63]. For instance, *Penicillium janthinellum* FS22A and *Trichoderma virens* FS5A were established to be effective in the co-production of laboratory-scale cellulolytic enzymes [64]. Cellulolytic bacteria may be found to contain many distinct physiological classes as seen through the prism of microbial physiology: fermentative anaerobes, usually Gram-positive (*Caldicellulosiruptor, Ruminococcus*, and *Clostridium*) but regrouping a small number of Gram-negative bacteria; aerobic Gram-positive bacteria such as *Thermobifida* and *Cellulomonas*; and aerobic gliding bacteria such as *Sporocytophaga* and *Cytophaga* [65].

The overall demand for cellulase enzymes in 2019 is roughly US$ 1500 million, which is forecast to hit US$ 2320 million in 2024 [66]. For industrial applications, the implementation of the same situation is identified as an emerging field of study. Production of biofuels, polishing and finishing of textiles, the pulp industry and lifestyle farming [60], cotton manufacturing; paper recycling, detergent enzymes, and animal feed additives, in juice extraction are among the main fields in which cellulase enzyme reveals a wider capacity for processing [67], as well as in single-cell protein research and production [68,69], recombinant DNA technology, pharmaceutical industry, and waste treatment [70]. Cellulase was widely regarded as an important solution to the antibiotics available for the treatment of *Pseudomonas*-produced biofilms. The ability of cellulases to combat antibiotic-tolerant bacteria is also a promising trend that will solve healthcare sector concerns [71].

Pectinases: The degradation of pectin compounds is the functional property of microbial enzymes (pectinases) [72]. However, by transforming pectinases into short polysaccharide particles, pectinases digest pectin [73]. They are an enzyme category that hydrolyzes the breakdown of pectic substances by deesterification processes (esterases) and depolymerization (lyases and hydrolases) [74]. Pectinases in higher plants and microbes are broadly spread. Actually, they are one of the industrial sector's upcoming enzymes. Microbes including actinomycetes, bacteria, yeast, and fungi may synthesize microbial pectinases [75]. For example, fungi such as *Trichoderma viride*, *Aspergillus awamori*, *Mucor piriformis* and *Yarrowia lipolytica*, *Aspergillus niger*, and *Penicillium restrictum* [76]. Especially, the most widely used fungal species for the industrial processing of pectinolytic enzymes is *Aspergillus niger* [75]. Several bacteria (*Aeromonascavi*, *Bacillus licheniformis*, *Lactobacillus*, and so on), yeasts such as *Candida*, *Saccharomyces*, and *Actinomycetes* like *Streptomycetes* are also employed [76].

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Microbial pectinases are projected to account for 25% of global sales of food enzymes [75]. Pectinases have been used in many typical manufacturing processes over the years, such as the harvesting of plant fabrics, the handling of industrial wastewater containing pectinous material, and many others [77]. They are used for improved production efficiency in the fruit processing industry to improve clarification/liquidity by reducing viscosity and filtering of juices and enzymatic extraction/ maceration of plant cells to release a flavor, vitamins, carbohydrates, nutrients, and proteins [78-80]. Since the 1960s, pectinases have also been used in the manufacture of wine [81], textile manufacturing and bio-scouring of cotton fabrics, fermentation of coffee and tea, paper and pulp industries, animal feed, plant virus purification, and oil extraction [77]. Other essential applications were pectic enzyme utilization in the hydrolyzed pectin product preparation [82,83] and preservation of wood [84,85].

Other enzymes: Other microbial enzymes of industrial interest include a large variety like lactase (β-galactosidase), esterases, phospholipases, lipoxygenases (LOX), xylanases, glucose oxidase, laccase, catalase, peroxidase, asparaginase, debittering enzymes–naringinase, α-acetolactate decarboxylase [86], pullulanase, limoninase, maltogenic, tyrosinase [35], keratinases and ligninase [87].

Microbial enzyme sources

Many microorganisms, such as actinomycetes, bacteria, yeast, and fungi generate a category of versatile and desirable intracellularly or extracellularly enzymes with a wide range of structures and commercial uses [53]. In addition, cyanobacteria and microalgae are crucial origins of biotechnological enzymes [88,89]. They are also a very important source of enzymes of extreme stability under conditions considered incompatible with biological materials coming from extremophile microbes due to their capacity to survive in environments of ultimate circumstances, whether physical as temperature, pressure, or radiation, and geochemical like pH and salinity [90]. Globally, 50% of industrial enzymes are produced from yeast and fungi, 35% from bacteria, and the remaining 15% from plants [76]. Table 2 illustrates some examples of enzymes, microorganism sources, and their biotechnological applications

Microbial enzyme safety and characteristics

The strong character of microbial enzymes such as thermostability, multifunctionality, and pH stability are potential candidates in varied physiochemical conditions for effective bioprocesses [12]. In their molecular structure, polypeptide chain number, glycosylation degree, and isoelectric point, the enzymes themselves vary. Although the synthetic pattern has been influenced by all the variations, the basic mechanisms for the enzyme synthesis are sufficiently similar to allow global mechanism treatment [91]. Additionally, the wide range of effective uses, niche products, environment friendly, and decreased chemical usage and activity are key factors driving the global hydrolytic enzyme market. Nevertheless, some of the common barriers that impede the enzyme market's increase are several considerations like raw material competitiveness, enzyme protection, handling, lack of stability under severe conditions, and price volatility [66].

A rigorous successful implementation of microbial enzymes is usually appropriate before market entry with European and other global regulators, even needing toxicological assessment for microbial enzyme certification [92]. In addition, the attributes and safety reports of each of the donor species adding genetic material to the production strain are tested when it includes recombinant DNA [5]. Except for the possible irritating consequences of such proteases on the skin and eyes and the well-documented potential for pulmonary sensitization in the

Table 2: Examples of enzymes, microorganism sources, and their biotechnological applications.

Microorganisms	Enzymes	Industrial applications	References
Streptomyces hyalurolyticus	Hyaluronidase	Pharmaceutical (ophthalmic treatments)	Schuler and Schuler 2005 [193]
Populus canescens	Pectin lyase	Food industry (production of cranberry juice and clarification of apple)	Semenova, et al. 2006 [81]
Bacillus spp	Alpha amylase	Food waste biodegradation	Msarah, et al. 2020 [194]
Bacillus licheniformis	Keratinase	Feed (increase body weight, feed conversion, and breast yield of broiler Chickens)	Wang, et al. 2006 [195]
Bacillus subtilis 168 E6-5	Protease	Textile (improvements in the physical properties of wool fabric)	Demirkan, et al. 2020 [196]
Streptomyces phaeochromogenes, Streptomyces setonii, Nocardia corynebacterioides, Nocardia asteroides and Arthrobacter oxydans	Phosphotriesterases	Bioremediation of water and soils, decontamination of particular foods, and as poisoning antidote Degradation of organophosphorus compounds employed as pesticides, plasticizers, and petroleum additives	Santillan, et al. 2020 [197]
Trichoderma reesei, Aspergillus niger	Cellulase	Biofuel (hydrolysis process of corncobs for producing bioethanol)	Winarsih and Siskawardani 2020 [198]
Bacillus megaterium	Xylanase	Pulp (improve bleaching)	Sindhu, et al. 2006 [163]
Candida antarctica	Lipase A, Lipase B	Chemical (asymmetric synthesis of amino acids/amino esters)	Dominguez de Maria, et al. 2005 [199]
Bacillus sp, Bacillus halodurans	Laccase, Xylanase	Paper (deinking of waste paper)	Gupta, et al. 2015 [200]
Bacillus subtilis NZYM-CK	L-asparagine amidohydrolase	Food enzyme preparation	EFSA CEP Panel, et al. 2023 [201]
Penicillium roqueforti		Food industry (milk clotting)	Nogueira, et al. 2022 [202]

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situation of exposition to the workplace, enzymes usually do not cause acute toxicity, cutaneous sensitization, genotoxicity or repetitive oral dose toxic effect. For enzymes carcinogenicity, reproduction, chronic toxicity, and acute inhalation are not also relevant [92]. The safety assessment criteria are focused on the potential involvement of harmful substances in the formulation of commercial enzymes [93]. Given the general availability of scientific evidence supporting enzyme safety and the widely accepted (peer-reviewed) methods and decision trees for determining the safety of microbial enzymes used in food production and in animal feed, respectively, the Generally Recognized as Safe (GRAS) process is well adapted for enzymes [94].

Production of microbial enzymes

Microbial enzymes are the preferable source of industrial enzymes as they can be obtained in huge amounts in a short time duration and have lesser generation times [6]. The processing of microbe enzymes effectively brings numerous benefits, like simple handling, fast multiplication under regulated conditions, easy genetic modification, high yields, and so on. In addition, due to their catalytic action, specificity, stability, non-toxicity, environmentally friendly design, economic efficiency, ease of processing, and many others, the industrial use of microbial enzymes often receives more attention [2]. The advances in biotechnology, such as controlled evolution and protein engineering, further revolutionized the commercial production of industrial essential enzymes. This progress in biotechnology is offering various kinds of enzymes showing new activities, and adaptability to new environments contributing to their increased usage for industrial purposes [5].

Fermentation methods

Since ancient times, microbes have been used in food fermentation, and fermentation methods are still used in the processing of several food items [95]. Due to their environmental and economic benefits, fermentation techniques have gained immense significance over the years. In order to maximize productivity, ancient techniques have been further refined and modified. The innovation of new machinery and procedures was also involved. As a consequence of this rapid growth, two broad fermentation methods have emerged: Solid State Fermentation (SSF) and Submerged Fermentation (SmF) [96]. Microbial enzymes can also be produced with less time and space required cost-effectively through those fermentation methods, and process modification, and optimization may be done very easily due to their high consistency [5].

Solid-state fermentation (SSF): Solid-state fermentation is a technology for cultivating microbes on a solid and low moisture substrate. Solid substrates are substances that typically contain agro-industrial by-products such as rice bran, sugar cane bagasse, wheat bran, fruit and plant waste, and many others [97]. Other mediums may be used for the processing of enzymes through SSF. These comprise rice bran, corn flour, and sugar beet pulp. Substrate choice depends on numerous parameters, primarily related to the cost of the substrate material and its availability. Particulate size and moisture levels are further considerations [98]. The only organism that may be used for SSF is generally fungi rather than bacterial species, provided that fungi are more likely to accept a low abundance of water [99]. It provides many benefits over submerged fermentation such as high-end product levels, fewer effluent production and convenient process equipment [100], easy and economical substrates, removal of the need for nutrient solubilization from solid substrates, elimination of the need for stringent monitoring of many fermentation parameters, higher product yields, lower energy needs, less wastewater processing, no foam emission and relatively easy recovery of end products [101].

Submerged fermentation (SmF): Commercially, submerged fermentation is used as an efficient enzyme synthesis processing technology. This method involves the growth of microorganisms in a closed liquid medium composed of different nutrients dissolved either for the suspension of particulate solids or in most cases inside a shake flask containing a commercial medium [102]. The fermenting medium sterilizes renewable nutrients including soya, sugar, and corn. In order to optimize the fermentation process parameters including pH, temperature, carbon dioxide formation, and oxygen consumption are measured and regulated [98]. Both molds and various bacterial species are part of the variety of organisms that can be used in SMF [99]. For instance, a strain of *Bacillus subtilis* was isolated and used for the development of protease under ordinary sources and LED lights by submerged fermentation with various agro-wastes as substrates [103]. The benefits of SMF comprise strong environmental criteria monitoring, decreased work costs, lower space, and low scale-up demands compared to SSF [104]. The submerged liquid conditions are often favored in industrial enzyme processing relative to solid-substrate fermentation because the yields are better in the submerged culture methods and the risks of contamination are fewer [98].

Recovery and formulation

Purification techniques are implemented to ensure enzymes with sufficient ability, economy, and purity. Enzymes may be intracellular and involve various methodologies of cell destruction. In fermented broth, extracellular hormones are released and exposed to centrifugation or filtration processes. There can be no implementation of a single purification procedure as enzymes are heterogeneous [100]. The recovery of products is based on solvent extraction using Dimethylsulfoxide (DMSO), methanol, ethanol, and water in the case of Solid-State Fermentation (SSF) [105]. Enzymes are purified with various chromatographic methods in case of submerged fermentation (SmF). This approach includes UFPLC, HPLC, and column chromatography, supplemented by gel electrophoresis for the purpose of studying the enzyme homogeneity and purity [99]. The procedure is primarily influenced by the low concentration of the finished product in broth contributing to further purification steps and cost increases [100].

Commercial enzyme supplies typically come from aqueous solutions that are sold as liquids or converted into dry

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products, called microgranulates or granules. With the final implementation in mind, liquid and dry formulations are formulated [5]. Many commercial enzymes are very stable in their dry state, but others need stabilizers and stimulators to be available to achieve optimum performance and stability [106]. Some applications require solid enzyme products to make the basic powder enzyme granules more suitable for use. Often liquid formulas are chosen because, unlike other liquid ingredients, they can be conveniently treated and dosed [107].

Boosting microbial enzyme production

Natural enzymes have deficiencies such as poor catalytic potency, operation, and stability, in particular in industrial environments [108]. Thus, the production of resistance enzymes is of vital importance for improved industrial efficiency due to harsh environmental conditions such as high temperatures, moderate/low pH, elevated pressure, oxidative conditions, high shears, or short delays [109,110]. Thus, customized biotechnological enzyme catalysts should have special characteristics including thermostability, high stereo and chemo specificity, multifunctionality, stability pH, and other characteristics [12]. A significant number of microbes and their enzymes with a special function are now widely identified by intensive screening. In combination with existing biotechnologies, such as genetic engineering, protein engineering (including guided and spontaneous mutagenesis), metabolic engineering, and so on, the selection of such enzymes would bring more exciting prospects for the commercial use of microbial enzymes [111]. Triggered by current revelations in the use of additives and immobilization, all these approaches can facilitate improved development of enzymes with better yields [112]. Furthermore, in a post-translational method, innovative strategies such as genetic fusion of coding open reading frames or protein connection are utilized to generate the fused industrialized enzymes with the combined characteristics of their parental substances [113].

Genetic engineering strategies

Genetic engineering is the method of transferring or changing genes into an entity to delete or incorporate a desired function or feature of particular genes between organisms [114]. This method ultimately involves taking the related gene of the microbe generating a specific enzyme (donor) naturally into a separate microbe that more effectively synthesizes the enzyme (host) [5]. Genetic changes are very significant and the development of recombinant DNA technologies has increased 100-fold [67]. Many bacteria and fungi used for the processing of industrial enzymes were genetically engineered to greatly overproduce them [115,116]. For instance, changes at different stages, like genetic sequences (site-directed mutagenesis), transcriptional factors, promoters, number of gene copies, leader peptides, chaperones, codons, and at structural levels, like glycosylation and enzyme folding, have led to the production of vigorous strains generating cellulose [117,118].

High-level expression

Metabolic engineering methods can be utilized through genetic manipulation approaches such as gene destruction and over expression [119,120]. If the gene has been detected, one of the techniques introduced to maximize the output of the enzyme is to induce over-expression of this gene in the initial producer or another microbial host [121]. Over expression of the genes of Fatty Acid Synthase (FAS) resulted in a maximum rise in the amount of fatty acids that was 2.8 times greater than that of the wild strain [122]. On the other hand, enzyme contribution in recombinant output pathways in elevated gene expression is a beneficial characteristic of cell factories in the kingdom of life. The use of powerful promoters to improve gene transcription and mRNA levels is usually targeted at high levels of enzymes [123]. For example, in *Pichia pastoris*, a GAP promoter-regulated gene XynA from *Thermomyces lanuginosus* has been established. On the medium without zeocine, after 56 hours of fermentation, *Pichia pastoris* expressed higher xylanase levels (160 IU/ml). The efficiency of this enzyme was proven in bagasse pulp bio-bleaching [124]. If the genes concerned are identified, the metabolic engineering technique often improves their expression [125,126]. If the genes required for the synthesis of an enzyme of concern are unidentified, the production improvement is increased by adding random mutations through ultraviolet (UV) irradiation or treatment with mutagens into the chromosomes of the synthesizing microorganism [127]. In addition, cultural conditions have been optimized to further improve development [128].

Biotechnological applications of microbial enzymes

In designing industrial bioprocesses, microbial enzymes are of considerable significance. Present applications rely on a wide variety of sectors, including leather, detergents and textiles, chemicals, pulp and paper, food and drinks, pharmaceuticals, animal feed and personal care, and biofuels, among others [90]. Biotechnological applications of microbial enzymes are summarized in Figure 1.

Microbial enzymes as detergent additives

The detergent industry needs more enzymes and accounts for nearly 60% of global manufacturing [129]. The most important area of use for enzymes (such as cellulose, protease, cutinase, amylase, and lipase) is the incorporation in detergents, primarily used for washing up, laundry, and industrial and organizational cleaning purposes [12]. In the manufacturing of detergents after proteases, amylases take 2nd position and makeup approximately 30% of the overall sales of enzymes [130]. All of these enzymes are hydrolases that are applied to detergents in order to improve the efficacy of washing. Proteases, lipases, and amylases were then used to extract protein, oily, and starchy color from the cloth substrates, respectively [131]. For instance, the enzyme protease synthesized from alkaliphilic *Bacillus* sp. strain KSMKP43, *Bacillus clausii* KP-43, and strain KSM-K16 have been integrated into laundry detergents. Subtilisin-like serine proteases affiliated to subtilase super family A have been used for cleaning and washing up in detergent additives [132]. The preference for alkaline yeasts is that they can be used at lower temperatures than bacterial and fungal lipases [133,134].

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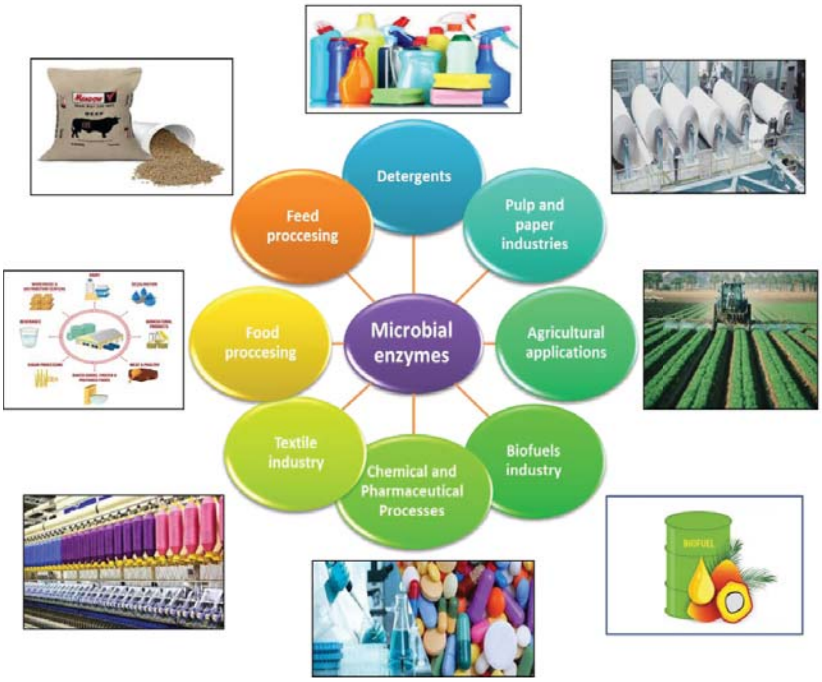

Figure 1: Biotechnological applications of microbial enzymes.

Textile industry

Textiles use costly and corrosive chemicals which constitute a major threat to public health and environmental quality. Thus, enzymes represent a sustainable solution to the already harsh harmful chemicals in textile production [135]. Oxidoreductases and hydrolases in the textile industry are used mostly for different applications. These microbial enzymes are helpful in terms of their origins more often than plants or animals [136,137]. Likewise, other enzymes are mainly used in a number of utilizations such as amylases, lipases, proteases, and cellulases [138]. Most textile enzyme uses are limited to the production of cotton: elimination of contaminants (bleaching, scouring, desizing); bio-finishing to enhance the appearance and eliminate fabric fuzz from the surface; bio-stoning or 'stonewashing' of denim to achieve the trendy aged look; bleaching cleaning to eliminate excess H_2O_2 before dyeing [139]. Significant microbes which produce textile enzymes importance include fungi such as *Aspergillus niger*, *Trichoderma*, *Rhizopus*, and bacteria like *Bacillus coagulans*, *Bacilllus subtilis*, and many others [140].

Feed and food processing

An age-old technology is the use of enzymes or microbes in food preparations. New enzymes with a wide variety of uses and specificities have been introduced with the development of science and new use fields are also being investigated. In different food preparations, microbes such as fungi and yeast, bacteria, and their enzymes are commonly used to enhance flavor and texture and give tremendous economic advantages to industries [86]. The implementation of enzymes (esterases, proteases, lipases, catalase, and lactase) is well-known in milk technology. Rennet (rennin) is used in the first step of cheese manufacture for the coagulation of milk. Proteases of different forms shall be used to speed up cheese maturement, adjust the functional characteristics, and alter milk proteins to decrease the allergic characteristics of cow milk infant formula. Lipases are utilized specifically for the development of lipolytic flavors in cheese maturation. Lactase is employed as a digestive aid for hydrolyzing lactose to galactose and glucose and to increase sweetness and solubility in different processed foods [53]. Enzymes and microbes have also been used in the process of making bread, cheese, and wine for decades [141]. Exogenous enzymes are used in the fish and meat industries for a number of purposes [142], and procedures of starch transformation [143,144]. Moreover, enzymes may play a major role in the preparation and processing of numerous fruit and vegetable juices, like carrots, apples, pineapples, bananas, grapefruit, lemons, and many others [53].

A worldwide enzyme sales report attributed 6% to feed enzymes [145]. Natural feed additives like enzymes are becoming more important in helping animals sustain proper digestion of feed [146]. Carbohydrases and proteases are among the numerous items in the animal feed industry [147]. Mainly, xylanase is a prime illustration of an industrial enzyme that must be stable and active at elevated pH and temperatures, when used as an ingredient for feed products [148]. Furthermore, B-glucanase and phytase from *Aspergillus niger* are employed in hydrolyzing phytic acid in animal feed for the release of phosphorus and digestive improvement [35]. Thus, feed enzymes can improve nutrient digestibility, contributing to greater productivity in the use of feed. Also, they could decompose undesirable feed components that are either toxic or of little or no benefit [149].

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Pharmaceutical and chemical processes

In the pharmaceutical and diagnostic industry, enzymes play several essential functions. These are commonly used in health conditions relating to enzymatic dysfunction and digestive diseases as preventive medications and in medical procedures such as ELISA and diabetes monitoring kits [150]. Enzymes are used for the prevention of enzyme dysfunction and metabolic diseases and the replacement of dead skin as medicinal drugs [12]. Also, these chemicals and medications are used to cure common human diseases. That includes obesity, prion diseases, malaria, diabetes, acne, ulcers, and even alumina in patients with kidney dialysis (but not limited to) [151]. For the development of water-soluble intermediates, intermediates for aspartame, semi-synthetic antibiotics, and biosynthetic human insulin, microbial enzymes such as glutaric acid acylase, nitrile hydratase, D-amino acid oxidase, penicillin G acylase, penicillin acylase, humulin, and ammonia lyase may be used [152]. For example, in the pharmaceutical and chemical sectors, lipases ensure a significant function [6,153]. Also, proteases might be used for drug use, like digestive medications, and anti-inflammatory medicines [154,155]. In addition, microbial enzymes may be used as biodegradable polymers for synthetic chemistry. *In vitro,* polymer-catalyzed enzyme synthesis is an environmentally friendly procedure with many benefits over traditional chemical processes [156,157]. For instance, 130 g/L of L-tyrosin was produced with continuously substration feeding in 30 h at the end of the enzyme transformation of pyruvate, phenol, ammonium chloride, and pyridox phosphate to L-tyrosine using a thermostable and chemostable tyrosine lyase. The enzyme was released by *Symbiobacterium toebiii* [158].

Pulp and paper industries

Initially, the use of pulp and paper enzymes was not theoretically and commercially practical since these biocatalysts were not readily available [159]. Whereas, later the utilization of enzymes in the paper and pulp industry was eventually adopted in 1986. The most important enzymes that may be used in paper and pulp operations are lipase, laccase, xylanase, and cellulose [160]. Microbial enzymes are allowing new technology for manufacturing fibers and pulps. Xylanases decrease the number of chemicals needed for bleaching, lipases decrease pitch, improve drainage cellulases smooth fibers, and stimulate the extraction of ink enzymes that degrade and remove lignin from pulps [161]. Although the formation of xylanase is described by different microbes, *Cellulosimicrobium* sp has rarely been recorded. *C. Cellulans* CKMX1 isolated from mushroom compost develops xylanase with marginal cellulase and has properties ideal for biobleaching of pulp [162]. Also, the *Bacillus megaterium* xylanase producer demonstrated an 8.12% and 1.16% increase in brightness and viscosity, a 13.67% reduction in KN, and a 31% decline in chlorine intake [163].

Researchers discovered many decades ago that microbial enzymes and microbes may be helpful in paper manufacturing because it is made of natural polymers like lignin, hemicellulose, and cellulose [161]. For example, the Nippon paper industry uses *Candida rugosa* lipase to extract up to 90% of these contaminants [164]. On the other hand, Fillat, et al. [165] in printed paper on the recycling of enzyme laccases formed in the presence of synthetic mediators by the three main fungi belonging to the basidiomycetes group (*Pycnoporus coccineus*, *Coriolopsis rigida*, *Trametes villosa*) and other fungi belonging to the ascomycetes group (*Myceliopthora thermophila*) the deinking mechanism has been demonstrated.

Biofuels industry

Because of the dependence on petrochemical products, increasing oil prices, and emissions from use, the world expects alternative renewable energy supplies from multiple sources [166]. Biofuels are an effective alternative and are primarily composed of live material called "biomass". Biofuels are divided generally into four groups (designed generations) related to the substrate used for biofuel processing. These comprise the first, second, third, and fourth generations [167]. Microbial and enzymatic fuel cells are among the primary groups of biofuels. Microbial fuel cells are systems in which organic matter microbes develop and produce electrical currents. However, to accomplish the same function, enzymatic fuel cells use cell-free enzymes as electrodes [168]. A critical component of bioprocessing configurations designed to turn lignocellulosic biomass into biofuels is enzyme cocktails that hydrolyze plant cell wall polysaccharides [169]. Bio-oil, cellulosic ethanol, biomass-based diesel, biobutanol, renewable gasoline, and bio-based jet fuel are now getting closer and nearer to the era of advanced biofuels [166]. A great deal has been researched for alcohol-based biofuel development with the usefulness of amylases and now monooxygenases, xyllanasas, and cellulases [170].

Agricultural applications

Enzymes, especially since produced, accumulated, inactivated, and decomposed in soil constantly, ensure a vital function in agriculture and nutrient cycling [171]. Soil enzymes may help facilitate many biological processes that result in organic matter degradation and inorganic nutrient release for nutrient cycling and plant development [172]. Likewise, the utilization of enzymes in several developed countries has the ability to improve production, reliability, and quality of manufacturing in agro-industrial processing operations [173]. Endophytes obtained from Brazilian mangrove plants displayed strong enzymatic activity; *Bacillus* sp (MCR2.56) showed especially high amylase and esterase activity among these isolates; six *Bacillus* isolates (MBR2.4, MCA2.42, MCR2.51, MBA2.4, MCA2.51 and MBA2.33) demonstrated greater endocellulolytic activity, while the actinobacteria *Microbacterium* sp. (MCA2.54) and *Curtobacterium* sp. (MBR2.20) demonstrated elevated activity of endoglucanase and protease, respectively [174]. Additionally, the use of microbial enzymes in nanofertilizer biosynthesis is gaining quick traction in nano-biological formulas due to its high performance and economic efficiency [175]. Further, certain kinds of enzymes are capable of helping to suppress crop pests and can contribute to cell wall destruction of pathogens [176,177]. In the synthesis of these enzymes, numerous microbes are implicated, namely chitinase, pectinase, β-1,3-glucanase, lipase, protease, and many others [178].

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Commercial aspects

Global enzyme market scenarios

Approximately 12 main manufacturers and 400 small suppliers serve the world's enzyme market. Three top enzyme firms, namely Denmark-based Novozymes, US-based DuPont (through the purchase of Denmark-based Danisco in May 2011), and Switzerland-based Roche, manufacture almost 75 % of the total enzymes. The industry is intensely competitive, with limited margins for profit and high technology [179]. In 2015, the global demand for industrial enzymes was valued at around $4.6 billion, expanding by $6.3 billion in 2021 at a compound annual growth rate of 4.7% for 2016 - 2021 [180]. Currently, more than 500 commercial products for a wide variety of biotechnological uses have been synthesized using enzymes [10,181]. Europe and North America are the world's main users of industrial enzymes, but the developing nations of the regions of the Asia Pacific, the Middle East, and Africa, among others, are beginning to emerge as the most promising industrial enzyme markets, representing the scale and power of the economies of these nations. High use in developing regions was associated with knowledge of green technology solving environmental problems, increased competitiveness, and improved product value, leading to an increase in the Innovation field and in enzyme-using industries [182]. For instance, the lipase industry scope approached $590.5 million during 2015 and 2020 worldwide, at a CAGR of 6.5 % by 2020. The Asia-Pacific market in 2014 was the main lipase consumer [183,184].

Market progress and evolution

The worldwide demand for industrial enzymes is growing from year to year, representing the largest commodity category in the worldwide sales of industrial enzymes in different industries such as detergent, leather, clothing, diagnostics, pharmaceutical, silver recovery, and waste management [40]. A Compound Annual Growth Rate (CAGR) of 7.1% from 2020 to 2027 is projected to rise in the global enzyme market [185]. The key reason for the steady growth in microbial enzyme sales is the growth in demand for consumer products and biofuels [186]. Particularly, proteases are the largest product group in the industry with a market share of approximately 60 % [187]. Lipases, phytases, and carbohydrases are another fast-growing field, with proteases covering about 70 % of the industry [182]. Enzymes are being used more and more to improve cleaner technologies in textile and paper and manufacturing and increasing the use of raw materials and waste generation [188]. A pectate lyase has recently been used as an alternative enzymatic method in the processing of cotton [189]. These market forecasts have been largely driven by process developments in the production of enzymatic biofuels which provide good opportunities for immobilized biocatalysts to scale up [190,191].

Perspectives and future prospects

The factories are also in search of new microbial strains to generate various enzymes to satisfy enzyme needs [6]. Substrates are often artificial compounds in industrial processes, and enzymes that are established to catalyze the necessary reactions for such procedures remain unknown. Therefore, screening is continually needed for novel enzymes that may catalyze new reactions [111,192]. Sometimes, because of either lower enzyme yield or other primary catalytic properties, microbial enzymes are not appropriate for biocatalytic operations. Thus, to satisfy these criteria tailoring or designing the enzyme is therefore necessary. The advancement of microbial enzymes and the discovery of new microbial enzymes have been encouraged by recent developments in metagenomics, genomics, proteomics, successful expression mechanisms, and rDNA technology [2]. Additionally, the development of novel microbial enzymes has resulted in many new and easy routes for synthetic processes by comprehensive and continuous screening [111]. In order to establish modern, sustainable, and economically viable production methods, more new, enhanced, and/or more flexible enzymes are required today. The discovery of new microbial enzymes whose catalytic characteristics could be modified/enhanced by various strategies focused on semi-rational, rational, and randomly guided evolution is based on microbial diversity and current molecular methods such as metagenomics and genomics [90].

Conclusion

The field of microbial enzymes utilization in biotechnology seems to be still relevant given their importance in various industries and the ever-increasing needs of the global market. On the other hand, technological and environmental constraints, environmental pollution and the current trend towards the use of green energy, the great diversity of unexploited microbial species, and the need for new enzymes, as well as innovative techniques (metagenomic, genetic engineering, and many others) leave this field of research in constant evolution. Also, the use of immobilized enzymes emerges as a very promising strategy in terms of basic and first-rate techniques for improving enzyme yield. Other aspects such as optimization of technological processes, reduction of production costs, and application of microbial enzymes in new technologies remain to be exploited.

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