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Industrial biotechnology: An Indian perspective

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ABSTRACT

Advancement in the field of biotechnology has opened a vast global market. The Indian biotechnology arena is promising for advance and pioneering growth with its immense growth potential which could play a significant role toward India's contribution to global industrial biotechnology. Today, India is one of the fastest-growing trillion-dollar economies in the world and the fifth largest overall, with a GDP (gross domestic product) of $2.94 trillion. Biotechnology (BT) and information technology (IT) are the key drivers contributing to this growth which constitutes approximately 5% of the country's total annual GDP. Indian biotechnology growth is fueled by bio-pharmaceutical, bio-industrial, bio-services, bio-agricultural, and bioinformatics, and among them, the bio-industrial area is one of the most promising and advanced. New approaches which Indian industrial biotechnology is exploring, include harnessing microorganisms for the production of value-added bioactive ingredients such as industrial enzymes, organic acids, bulk chemicals, and single-cell proteins, which have played a predominant role in the overall development of biotechnology after bio-pharmaceuticals. The above factors made India one of the world's top 12 destinations for biotechnology. In this article, we review the status of the biotechnological industry and its future perspective in context to the Indian market and its role in global economy.

1. INTRODUCTION

Biotechnology (BT) is a rapidly growing branch of science which deals with the technical application of living systems or organisms to produce products for human welfare such as health care, agriculture, food production and processing, veterinary, and environment. Recent advancements in various streams of biology have paved the way for biotechnology to strengthen its technological capabilities to influence world's economy. Industrial biotechnology helps to utilize the potential of biotechnology by providing a global platform which strengthens the economy in a greater capacity. From recombinant protein production for medical purposes to the waste management at the industrial level, it provides opportunity to the growth of the various sectors aiding to the economy [1,2]. Industrial biotechnology which is also known as white biotechnology started with the intentional use of the fermentation process using microorganisms such as bacteria, fungi, as well as eukaryotic cells to produce products at the industrial level [Figure 1]. Fermentation technology has been existing since the neolithic age where different cultures had developed beverages and medicine without even understanding the scientific mechanism behind it until the 19th century, Louis Pasteur showed that fermentation is initiated by living organisms. Later, the discovery of penicillin by A. Fleming in 1928 shaped the path for the industrial use of fermentation process which then inspired many pharmaceutical companies to launch significant efforts to discover and develop various types of antibiotics. Apart from these, the development of amino acid fermentation by Japan has commercialized the production of enzymes which expanded the possibility of commercialization of the first genetically engineered fermentation product in 1977 [3,4]. Since then, fermentation biotechnology is being widely used at the industrial level in the field of bio-agriculture, probiotics, brewing, biofuel, food, nutraceuticals, and enzyme production to shift the market paradigm from traditional chemical based to more eco-friendly, sustainable, and innovative market. Biotechnology uses minimum resources than the traditional processes to produce high-value industrial goods [5]. Indian industrial biotechnology which has been established decades ago has immense growth potential in many sectors, although the pace has been comparatively slower. This review will provide an overall comprehensive view of Indian Industrial biotechnology in perspective to its global standing.

1.1. Industrial Fermentation Biotechnology

Fermentation biotechnology is a sustainable and rapidly growing field with an expectation to reach $205,465 million by 2023 [6], deals with reduced energy consumption, greenhouse gas emission, and recyclable waste generation for the production of value-added chemicals. Based on the type of production, fermentation biotechnology has vast scopes for various industries [Figure 2] as discussed below.

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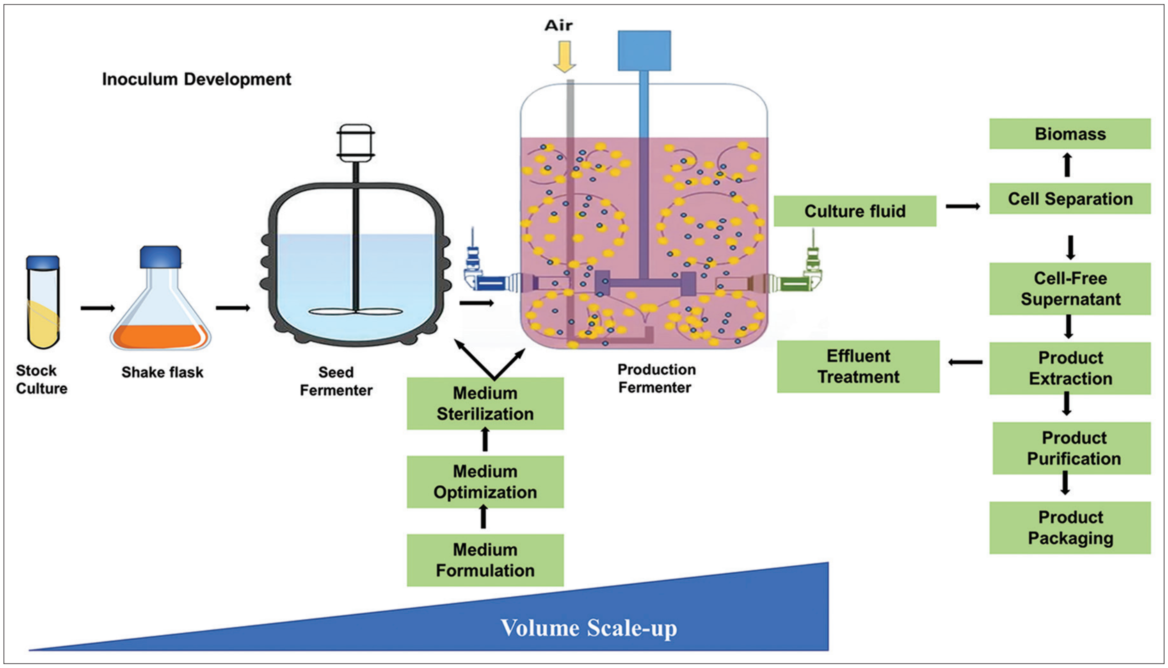

Figure 1: Schematic representation of fermentation process.

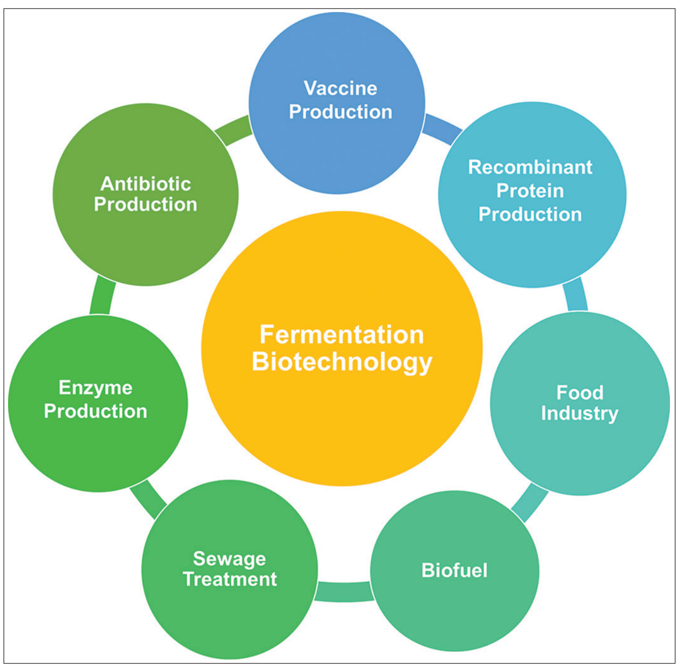

Figure 2: Scope of fermentation biotechnology.

1.1.1. Food industry

Fermentation has been used in food preservation and for increasing nutrient value since ancient times. It has been used for producing cheese, bread, wine, curd, syrups, etc., which has been utilized by various industries and large-scale production of these has come into practice in the food industry. The probiotic enzymes and lactic acid in fermented food increase the Vitamins B and C and enhance folic acid, riboflavin, niacin, thiamin and biotin, etc., making them more accessible for absorption [1,7]. Table 1 lists the metabolites produced by microbes during fermentation process which are used exclusively in food industry. Due to the rapidly growing population, food technology could develop as a really important aspect in India both in terms of economy and also for national food security. It can empower small-scale industrial sectors by creating job opportunities and strengthening the economy which will fuel up the basic need of self-reliant India.

1.1.2. Biofuel industry

Fermentation technology has changed the fate of biofuel industry making it more efficient and economical. Bioethanol is one of the major producers of biofuel industry. The fact that it is originated from sustainable sources such as grass and feedstock makes it an affordable and effective renewable resource that can cut both cost and pollution, making it a cleaner and greener alternative. The United States, Brazil, and some of the European countries have used this technique to become the more efficient producer of low price ethanol fuel (biofuel) by fermenting corn and sweetgrass [8]. Fermentation can also produce hydrogen gas using *Clostridium pasteurianum* which converts glucose to butyrate, acetate, carbon dioxide, and hydrogen gas [9,10]. Hence, there is an immense scope to develop new technologies to produce biofuel using biotechnological processes which can be highly beneficial both to environment and economy of India. Since India has a vast area of agricultural land, the by-product produced from harvesting of the crops could be used for their conservation into biofuel by fermentation technology. Furthermore, substantial research and advancements in metabolic engineering have the potential to switch from fossil fuel to biofuel and lead the way to next-generation biofuels which would foster this industry in creating annual employment and job opportunities as well as making the planet greener. This could revolutionize the energy sector of India too and make it less dependent on non-renewable resources as well as acknowledge the challenges of air pollution due to emission making the life headlines which, in turn, will cut the health expenses.

1.1.3. Sewage treatment

The process of sewage non-toxic products and treatment by fermentation include digestion of solid organic matter by enzymes into harmless soluble substances and gases where the digested solids (sludge) can be used as fertilizer and the gaseous byproduct such as methane can be used as biogas (biofuel) [11]. This self-sustainable model can spear a

Table 1: Application of primary metabolites of microbes in food industry.

Primary metabolite	Micro-organism	Industrial Application	References
Ethanol	*Saccharomyces cerevisiae, Lactobacillus acidophilus, Wickerhamomyces anomalus* (CDBT7).	Active ingredient in alcoholic beverages	[55,56]
Organic acid	*Bacillus licheniformis, A. aceti, Lactococcus* sp.	Used in antioxidant, flavoring agent, fruit juice, beverages making products	[57]
Amino acids	*E. coli*, *C.glutamicum.*	Flavor enhancer, Nutraceutical, Food technology.	[58]
Nucleotide	*Corynebactrium, Bacillus, E. coli*	Flavor enhancer and production of riboflavin	[59]
Vitamins	*Streptomyces* sp., *Rhizosphere.*	Food supplement	[60]

revolutionary role in waste management as it can be turned into a profit-making system and could be developed for commercial purposes as well. Various bioremediation methods could also be applied for the treatment and management of waste. Hence, this avenue of biotechnology has immense potential for research and development.

1.1.4. Enzyme production

By the help of various microorganisms such as yeast and bacteria, fermentation can produce several enzymes which can be further used in many enzyme-dependent industries such as wine brewing, cheese making, and baking. The two main methods to produce enzymes are submerged fermentation and solid-state fermentation. In submerged fermentation, the product is produced in a liquid medium and in solid-state medium, the product is produced on a solid substrate by immobilizing microorganisms on various scaffolds [12]. With time, advanced biotechnological techniques and more sophisticated fermenters have brought enzymes with novel properties on the table such as enzymes from thermo-tolerant organisms and marine organisms various sensitive enzymes utilizing genetic engineering tools. Due to the increasing demand for enzymes in the near future, many more research and production systems would be required to meet up the needs which will create more opportunities in the field. Therefore, further research and innovation can strengthen this field toward more efficient market.

1.1.5. Antibiotic production

Since the discovery of penicillin by Alexander Fleming, production of antibiotics has been improved tremendously and scaled up to an industrial level and improved by several pharmaceutical companies. Antibiotics can be produced either by natural fermentation process as secondary metabolites by growing large batches of microorganisms in fermenters or by a semi-synthetic method where the modifications are done in naturally produced antibiotics, for example, ampicillin, dihydrostreptomycin, tetracylin, etc. [13]. Biocon Limited is India's largest antibiotic-producing pharmaceutical company which has generated a revenue of 920 million USD in the year 2020 [14]. Use of advanced biotechnological tools has been instrumental in achieving these goals.

1.1.6. Vaccine production

Vaccines play an important role in keeping the global health safe from many diseases even before the onset. Vaccines are manufactured by pharmaceutical industries in a series of steps out of which fermentation is one of them. For example, Gardasil – a vaccine against human papillomavirus (HPV) was derived in a series of steps which included the insertion of genetic information from HPV outer coat into the yeast and then multiplying these modified yeasts in a fermenter to make virus-like particles (VLPs). These VLPs look like the real virus but lack the genetic material inside. After growing them in fermenters, the yeast cells are collected and ruptured to release the VLPs, which are purified and then used as a vaccine. The immunogenic properties of these VLPs are sufficient to produce antibodies in human cells on injection to impart immunity from high-risk HPV infections [15]. In India, where millions of women develop cervical cancer due to HPV infection, this type of vaccine could be a crucial factor in cutting down health-care cost of the population.

Recent outbreaks of COVID-19 infection have affected the world population considerably. Governments and agencies across the world are seeking novel ways to contain the infection, among which the development of vaccine is one of the dire needs of the time to stop further transmission. Hence, one can understand the importance of vaccines and its impact on both global health and economy toward being self-reliant. Serum Institute of India, Bharat Serums and Vaccine Limited, and Indian Immunological Limited are among the top 10 biotech companies (based on revenue) of India involved in vaccine production. The Indian vaccine and recombinant protein market are one of the largest producers in the world. Now with the slogan of "self-sufficient and self-reliant," India must invest in research towards developing more advanced and sophisticated vaccine and recombinant protein production systems. It has immense market potential worldwide, as shown in Table 2, and can strengthen Indian economy too in the coming times.

1.2. Biotechnology of Antibiotics Production

The discovery of antibiotics has crucially changed the health-care management from simple wound management to post-surgical care. Since, the first antibiotic penicillin was discovered by Alexander Fleming in 1928, they have been the reason for saving lives of billions. If it was not for the availability of antibiotics, the mortality rate after World War II would have unimaginably been many folds higher [16], because before its discovery, even small wounds resulted in amputation or life-threatening conditions. Since then, many natural and artificial novel antibiotics have come to existence due to which, millions of lives could be saved because most of the bacterial diseases can be cured which earlier were considered deadly such as tuberculosis, cholera, and plague. Hence, it could be stated without exaggeration that the discovery and evolution of antibiotics is one of the most important discoveries of the 20th century toward managing both human and animal health care. Because of its extensive use, the revenue generated by this industry is nearly $50,000 million worldwide, hence, one can understand the impact this industry brings in contributing to the GDP of a nation. Globally, the use of antimicrobial agents save almost 3 million lives annually and this might still be under-represented data. Even in developed and hygienically more advanced countries such as the USA, use of antibiotics saves 200,000 lives every year [17,18].

India, with time emerged as the antibiotic capital of the world [Figure 3] [19,20], fastly growing not only as the top antibiotic producer but also as the largest consumer of antibiotics. India's Daily Defined Dose (DDD) is 6.3 billion, which means every day in India, 6.3 billion

Table 2: Major groups of recombinant proteins developed and application.

Group	Recombinant protein	Production system	Application	References
Blood factors	Factor VIII *8.5 billion	Mammalian cells	Anemia treatment	[1,61]
Thrombolytics	Tissue plasminogen activator *2.4 billion	Mammalian cells, *E. coli*	Clot lysis	[1,62]
Anticoagulants	Hirudin *3.8 billion	*S. cerevisiae*	Anticoagulant	[1,63]
Hormones	• Insulin *34.8 billion • Human growth hormone *3.8 billion • Follicular-stimulating hormone *1.4 billion • Glucagon *524 million	*S. cerevisiae, E. coli* *S. cerevisiae, E. coli* Mammalian cells *S. cerevisiae, E. coli*	-Diabetes treatment -Hypopituitary dwarfism treatment -Infertility treatment -Type 2 diabetes treatment	[1,64-67]
Growth factors	• Erythropoietin • macrophage colony-stimulating factor • Granulocyte colony-stimulating factor *42.6 billion	Mammalian cells *E. coli* Mammalian cells, *E. coli*	-Anemia treatment -Bone marrow transplantation -Cancer treatment	[1,68]
Cytokines	• Interferon-alpha • Interferon-beta *1.6 billion	*E. coli* *E. coli*	Cancer, hepatitis B treatment cancer, genital warts, amyotrophic lateral sclerosis treatment	[1,69]
Antibodies	Monoclonal and polyclonal antibodies *3.6 billion	*S. cerevisiae, E. coli, P. pastoris*	Detection and diagnosis	[70,71]

*Global market share/value (in USD) for the financial year 2019–2020

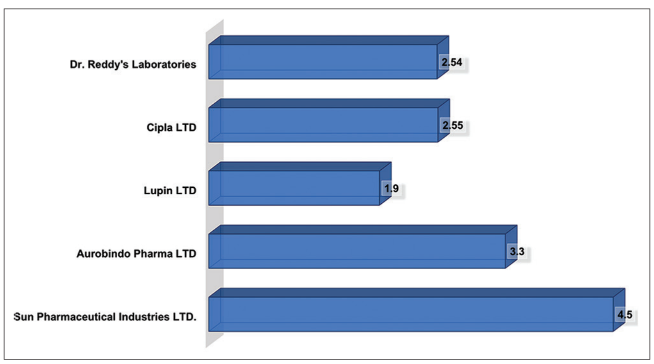

Figure 3: Revenue generated by Indian pharma companies in 2020–2021 (in USD billion).

antibiotics doses are consumed, which is almost double the amount consumed in China (DDD is 3.6 billion) which stands second and the US stands third with 2.9 billion DDD [21]. India's need for such huge consumption could be because of climate, hygiene, and health awareness. In light of new development, India could evolve as a global player by venturing into the field of innovation and redesigning with more potency and less environmental toxicity. This industry could play an instrumental role toward projecting and building a more self-reliant and stronger economy that can accommodate a large workforce, which in turn can strengthen both the economy and employment in the country. Due to vast natural resources and workforce, India has all the potential to become a new-generation antibiotic research and production hub of the world.

Antibiotics are produced by three major ways:

1.2.1. Fermentation

Industrial microbiology could be used to produce a large amount of antibiotics using microbial sources. Microbes are grown in large fermentation vessels designed with appropriate automation. The microbes produce the antibiotic either as a secondary metabolite or in the form of secretion. Genetically engineered microbes could be used for better production with minimum cost input [1]. The scope of research toward producing more efficient microbes and also toward designing high throughput and more advanced fermenters is enormous. Use of genetic engineering can result in more better microbes and can explore new feasible ways to make the antibiotic more sensitive and least resistive. For achieving this, research institutions can work hand in hand with industries to design more efficient fermenting technologies and equipment. Because of its dynamic research workforce, India could easily achieve this goal where interdisciplinary research projects could be practiced.

1.2.2. Semi-synthetic

This is the most common and applicable form of the second-generation antibiotics where both microbial fermentation method and synthetic chemistry are applied. One of the best examples is ampicillin which was developed by adding an amino (NH_2) group to the R group of penicillin. Similarly, by adding two methoxy groups to the phenyl group of penicillin, methicillin is produced which is potent against penicillin-resistant bacteria [22]. This method of antibiotic production [Figure 4] has tremendous room for innovation and research, where new synthetic groups could be designed, tested, and screened for better potency, less toxicity, and more environment friendly.

1.2.3. Synthetic

Some of the antibiotics, especially that of the third generation, are produced entirely synthetically such as quinolones (nalidixic acid), carbapenems, and oxazolidinones [23]. There is a greater scope for designing and producing this class of antibiotics in India. It could require multidisciplinary collaboration for designing, formulating, synthesizing, screening, and testing the antibiotics. Further, it could

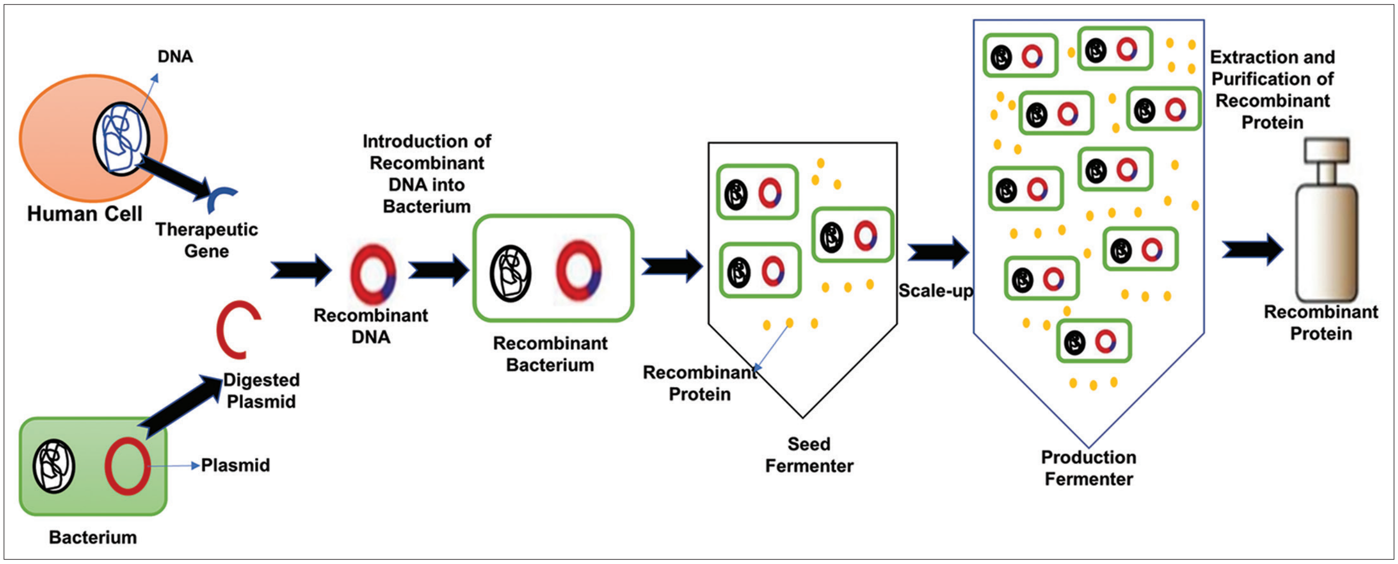

Figure 4: Schematic representation of recombinant protein production.

be scaled up for industrial grade production in collaboration with industries.

Although antibiotics have emerged as life saviors, such an enormous amount of antibiotics pushed into the environment has seriously led to the development of antimicrobial resistance (AMR) which is now responsible for almost 700,000 deaths worldwide and this number is increasing every day. The emergence of superbugs in India, for example, a common *Klebsiella pneumoniae* strain became resistant to almost dozens of antibiotics because it laterally acquired a gene called NMD-1 from other bacteria. This AMR strain also has the ability to transfer the trait to sensitive bacteria and makes them resistant [24,25]. Several antibiotic-resistant strains of tuberculosis bacteria have been reported till date and many more awaiting to be. AMR can seriously jeopardize global health because many of the curable diseases might become lethal due to resistant varieties of bacteria evolving at much faster pace than expected [26]. Recent studies have identified several genes which are responsible for making the microbes resistant to a wide variety of antimicrobial agents. Several possible strategies which target efflux pumps, β-lactamases, outer membrane, and virulence factors are already being used to overcome AMR [27]. Apart from this, other strategies could also be developed to address the issue of neutralizing microbial genes responsible for resistance while designing a new generation of antibiotics. Hence, strict regulations and practices of antibiotic stewardship are must in a densely populated country like India.

1.2.4. Biotechnology of industrial enzymes

Enzymes are one of the most proficient biocatalysts which catalyze specific biochemical reactions resulting in environment-friendly products, which are more efficient and cost effective. Throughout the last decades, enzyme processes have increasingly replaced conventional chemical processes in many fields, including the fine chemical and pharmaceutical industries. With about 3% of the world's biotechnology industry which primarily includes enzyme technology, Indian enzyme market is rising at 7% annually and has reached 370.5 million USD in the year 2018–2019 [28,29]. There is immense scope for research and innovation in this area, and India could play a very important role in answering many questions related to developing new technologies and ways to make this sector more empowered.

1.2.5. Biotechnological process of enzyme production

At present, the process of enzyme production [Figure 5] is employed for the production of novel and sustainable products with higher yields which includes modification of enzyme structure and catalytic function to make them novel and efficient [30]. The industrial enzyme technology includes:

1. Screening or selection of appropriate microorganisms for the desired enzyme.
2. Possible modification using genetic engineering to improve the selected microbial strain.
3. Laboratory scale production to determine the optimum conditions required for microbial growth.
4. Small-scale fermentation to test optimum operating conditions (pilot plant).
5. Large-scale or industrial-scale fermentation.

Enzymes are used in a wide range of many commercial processes [Table 3] [31]. They are classified into different categories depending on their usages such as technical enzymes, feed enzymes, and food and beverage enzymes. The Indian bio-industrial sector is majorly composed of enzyme manufacturing firms which contribute nearly 6% of the revenues of the total biotechnology industry and the increase in enzyme consumption is attributed to the rise in demand from the food, pharmaceutical, detergent, and energy sectors. Of these, the pharmaceutical enzymes segment is the newest and only a few specialized manufacturers are present. On the other hand, textile and leather enzyme firms have been exploring this technology for hundreds of years. This market is dominated by multinational manufacturers who account for 65% of the market while the rest is contributed by local players. However, the local companies in India have now realized the huge potential of enzymes utilized in the food and beverage industry and are investing in their research and development facilities, manufacturing units, and distribution network. In addition to importing enzymes, India also exports enzymes to several countries. According to the Directorate General of Commercial Intelligence and Statistics (DGCI&S), India has exported enzymes worth 45.05 million USD in 2018–2019 and worth 12.3 million USD in first quarter of 2019–2020 [32,33]. Market of enzyme industry in India was relatively very small in comparison to other sectors but slowly it has reached an influential state [Figure 6] [34]. There are nearly 25 major industrial

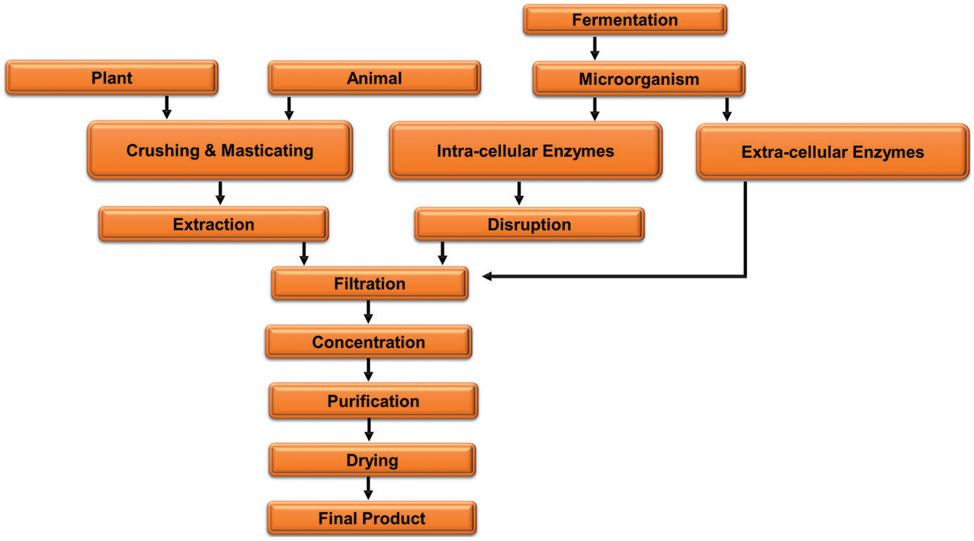

Figure 5: Process of enzyme production and isolation.

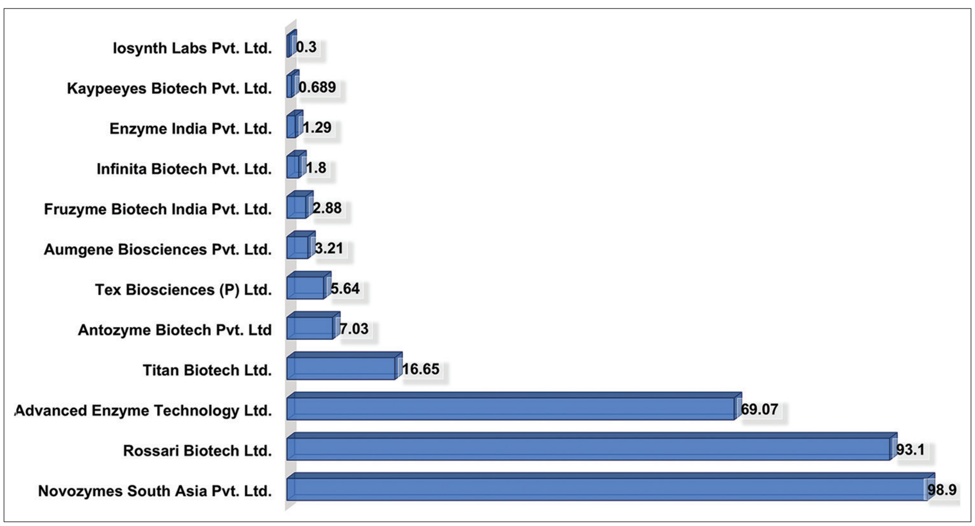

Figure 6: Revenue generated by Indian industrial enzyme companies in 2020–2021 (in USD million).

enzyme manufacturers in the market and most of them are involved in marketing and formulation, and among them, only few Indian companies rank as multinationals that locally produce enzymes and several other eco-friendly bioproducts which are used in other different industries such as food, pharmaceuticals, paper, pulp, and textiles.

At present, enzyme engineering is focused on the production of more evolved enzymes with higher substrate specificity and stability using computational methods. The development of software like ProSAR which uses sequence data to predict the changes to be made in the gene for better evolved enzyme with much higher activity [35,36]. This kind of technology could make enzyme production more efficient and cost effective at the industrial level. In the global market, India holds a marginal share in industrial enzymes. Hence, India needs to invest in research and development to explore and develop tools toward finding more cost-effective and eco-friendly ways to produce enzymes at the industrial level.

1.3. Biotechnology of Bioremediation

The term bioremediation technology stands for the technology which uses microbes and biological products for neutralizing, detoxifying, and degrading environmental waste. The waste could be either natural or human generated. The very first commercial use of bioremediation was in control of the sun oil pipeline spill in Pennsylvania, USA. The growing population worldwide is creating a huge burden of waste in nature. Bioremediation is a cost-effective sustainable process that works using certain microorganisms which utilize the contaminants such as oil, pesticide, and solvents as the source of food and energy and converts them into water and harmless gases like CO_2. Bioremediation involves oxidoreductase reactions, where either an electron acceptor adds to oxidize reduced pollutants or an electron donor is added to reduce oxidized pollutants. The extent of biodegradation by the microorganisms depends on several factors such as (i) system selected specific treatment, (ii) initial concentration and toxicity of contaminant, and (iii) biodegradable property of soil. [37].

There are two main types of bioremediations: *In situ* and *ex situ*. The *in situ* bioremediation process treats the contaminated groundwater or soil in the location where it is found. Phytoremediation, bioventing, bioleaching, bio-slurping, biostimulation, and bioaugmentation are *in*

Table 3: Major industrial enzymes and their applications.

Enzyme	Applications	References
Alkaline proteases *20.89 billion	In laundry, dishwashing, textile washing, food and dairy industries, glass lens cleaning, etc.,	[32,72]
Alpha amylases *279.8 million	In food industries, detergent industries, paper industries, and pharmaceuticals	[32,73]
Glucose isomerases	Isomerize glucose to the sweetener molecule and high fructose, Starch liquefaction, glucose-fructose sugar syrup making and ethanol making industries	[32,74]
Penicillin acylases	In beta-lactam semi-synthetic antibiotics intermediates production and racemic mixture isolation	[32,75]
Cellulases *1.6 billion	In food, feed and beverages, pulp and paper industries, detergent industries and bioethanol production	[32,76,77]
Xylanases	In pulp and paper industries, food and feed industries, textile and bioethanol production	[32]
Pectinases *30.04 million	In food and feed production, fruit juice purification and stabilization, textile industries, retting and degumming of fiber crops and quality paper production	[32,78,79]
Lipases *585.56 million	In dairy and other food processes, detergents, pharmaceuticals, cosmetics, leather processing, and production of aliphatic acids	[32,80]
Tannases	In hydrolyzing of tannins, leather processing, wine making by reducing the haze, preparation of cold water-soluble instant tea, coffee, etc.,	[32,81]
Phytases *473.8 million	In reducing phosphorus excretion of monogastric animals by replacing inorganic phosphates, animal nutrition, processing of human food, and environmental protection	[32,82,83]
Laccases *3 million	Delignification of pulp and paper, fine paper making, fruit juice clarification and stabilization, bioremediation, xenobiotic substrate removal, detoxification of plant cell wall-derived sugar syrups.	[32,84]

*Global market share/value (in USD) for the financial year 2019–2020

situ types of bioremediation methods. Whereas, the *ex situ* process requires pumping of groundwater or the excavation of contaminated soil before it can be treated. Composting, controlled solid-phase treatment, and slurry-phase biological treatment are examples of *ex situ* bioremediation. Other criteria for the categorization of bioremediation are on the basis of application and technology [Table 4] [38,39].

The ever-increasing use of bioremediation techniques for treating sewage, lakes, rivers and streams, ponds, and aquaculture is anticipated to create a large number of growth opportunities for the market in the coming years. In recent years, however, the rise in the agriculture industries has largely contributed to pesticides, herbicides, and other highly toxic organometallo pollutants in the environment.

Table 4: Common bioremediation technologies.

Bioremediation technology	Properties	References
Bioaugmentation	Addition of bacterial cultures to a contaminated medium. It is frequently used in bioreactors and *ex situ* systems	[85-87]
Biofilters	Use of microbial striping columns to treat air emissions or odors for volatile compounds	[85,88]
Biosparging	The injection of air under pressure can enhance biological degradation. It usually performed in in *situ*. It's noninvasive technique.	[85,89,90]
Biostimulation	Stimulation of indigenous microbial populations in soil or groundwater which can be performed either *in situ* or *ex situ*	[85,87]
Bioreactors	Biodegradation in a container or reactor. It is used to treat several liquid wastes or slurries, rapid degradation kinetics but relatively high capital and operational cost.	[85,90]
Bioventing	Method of treating contaminated soils by drawing oxygen through the soil to stimulate microbial growth and activity	[85,89,90]
Composting	Aerobic, thermophilic treatment process; can be performed using static piles, aerated piles, or continuously fed reactors; low cost but extended treatment time	[85]
Land farming	Solid-phase treatment system for contaminated soils; may be performed *in situ* or in a constructed soil treatment cell; cost efficient	[85,89,90]

Serious threats to the environment and public health are also created due to industrial effluents and city sewage wastes. Because of this, human-generated pollution, health-care problems such as cancer, respiratory diseases, diabetes, abnormal growth, and many other ailments are increasing at an alarming rate. Bioremediation can provide a much safer and sustainable solution for managing these toxic wastes. Scope of innovation, research, and application are tremendous, and hence, there is a huge market lying in front of bioremediation technology. There are many important advantageous aspects of using bioremediation technology over chemical or physical remediation, like low cost of treatment per unit volume of soil or groundwater compared to other remediation technologies. Less energy consumption and its eco-friendly and efficient nature make it the technology of coming era. The biggest advantage of using this technology is that toxic chemicals are destroyed or removed from the environment and not just merely separated. The above qualities make bioremediation, a technology of the future which could answer the challenging questions brought as a side effect of industrialization and urbanization.

1.3.1. Scope of bioremediation

1.3.1.1. Petroleum spillage management

Bioremediation is a highly cost-effective and less hazardous technology for managing petroleum spillage. Many genetically engineered microorganisms have been successfully produced which can effectively degrade petroleum hydrocarbons under aerobic conditions [39]. Further research could add on to this list and produce more efficient oil-eating microbes. Research contributions from interdisciplinary institutions could also play a critical role in developing these superbugs.

1.3.1.2. Solid waste management

In India, approximately 150,000 metric tonnes of solid waste are produced daily which is likely to increase rapidly in the coming few years because of improper use of land, unplanned waste management plans, and lack of awareness. The management of solid waste apart from cleaning the environment could also serve multiple purposes such as revenue generation and employment [40,41].

Below are some of the ways to manage solid wastes:

- Heavy metal contamination from tanneries by leaching toxifies both soil and ground water. To avoid the entry of heavy metals into the food chain, it is important to remove them from soil and water for which microorganisms such as *Pseudomonas aeruginosa* and *Aspergillus niger* are being currently used and could be further engineered to make them more efficient and cost effective in the cleaning process [42-44].
- Rubber waste is 12% of total solid waste and can neither be degraded easily nor recycled due to its physical property. Since incineration of rubber produces toxic gases, removal of toxic components from the same would be the method of choice. Regarding this, use of fungi like *Recinicium bicolor* followed by devulcanization using bacteria such as *Pyrococcus furiosus* and *Thiobacillus ferrooxidans* could be greener solution. Research should be encouraged to produce chimera for cost effective and more efficient ways to detoxify rubber wastes [45].
- Agricultural waste is a nutrient-rich organic waste and use of microorganisms (*Methanobrevibacter ruminantium, M. bryantic,* etc.) [46] for the degradation of these kind of waste can also produce by-products like methane gas which can be used as biogas and organic fertilizers for the crops. Approximately 350 million tons of agricultural waste is produced every year in India [47], and this large quantity of waste can be efficiently converted to biofertilizer by vermicomposting. Furthermore, by the process of fermentation, these wastes could be converted into biofuels to power various agricultural, industrial, or automotive sectors creating a sustainable and greener model.

1.3.1.3. Sewage treatment

The process of sewage treatment includes digestion of solid organic matter into harmless soluble substances and gases by microbes, where the digested solids (sludge) can be used as fertilizer and the gaseous by-product (such as methane) can be used as biogas [11]. Rising population and rapid urbanization have left India with water bodies contaminated with toxins such as arsenic, chlorine, fluorine, other heavy metals, and organic effluents and to meet the increasing demand for water, treatment of sewage water is necessary. Industrial set-up utilizing biotechnological solutions could not only provide eco-friendly solutions but also revenue generation [42].

Apart from these, bioremediation has other applications such as onsite sanitation systems, mine site tailing, and clearing of accidental chemical spills.

1.3.2. The current market scenario of bioremediation technology

The Global Bioremediation Technology and Services market accounted for $9.13 billion in 2019 and is expected to reach $17.53 billion by 2027 growing at a CAGR of 8.5% during the mentioned forecast period [Figure 7] [48]. Some of the key factors propelling the market growth are the usage of fungus for treatment of soil, use of bacteria for bioleaching, phytoremediation, and oil spill management and cleaning.

North America was valued at $27.4 billion in 2017, and it is anticipated to reach $62.4 billion by 2023, growing at a compound annual growth rate (CAGR) of 15.0% [49]. North America dominated the bioremediation market and accounted for 36.22% in 2018 and 32.40% during the upcoming year 2028 [50]. Indian global contribution [Figure 8] [51-53] is negligible despite the fact that it contributes to a high amount of industrial and agricultural pollutants. Hence, India has a long way to go in this direction, and the scope of improvement is tremendous, small and big players could be invited, new entrepreneurs should be encouraged to establish this market, which can benefit the country both ways, by cleaning the environment as well as empowering the economy and creating a job market.

From 2018 to 2023, *in situ* and *ex situ* bioremediation is expected to grow at a compound annual growth rate (CAGR) of 15% and 16.7%, respectively. The Asia-Pacific region is expected to be the fastest-growing market for bioremediation, growing at a CAGR of 16.7% from 2018 to 2023. Asia-Pacific holds the second largest contributor to

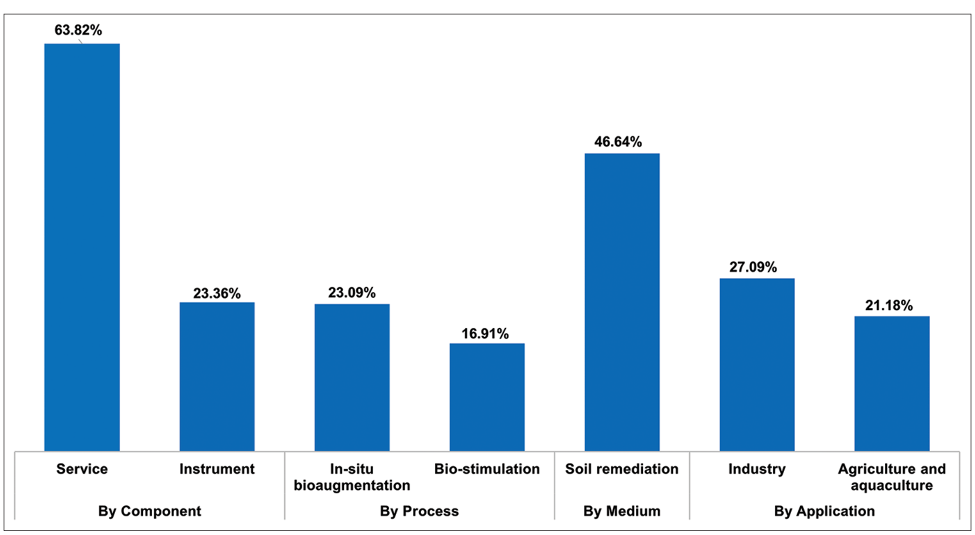

Figure 7: Market share on global level in percentage (2018–2019).

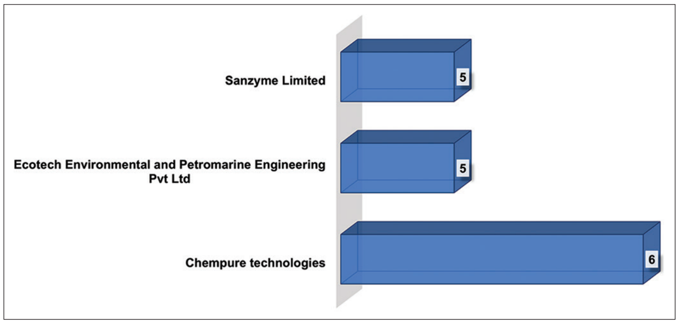

Figure 8: Revenue generated by Indian bioremediation companies in 2020–2021 (in USD million).

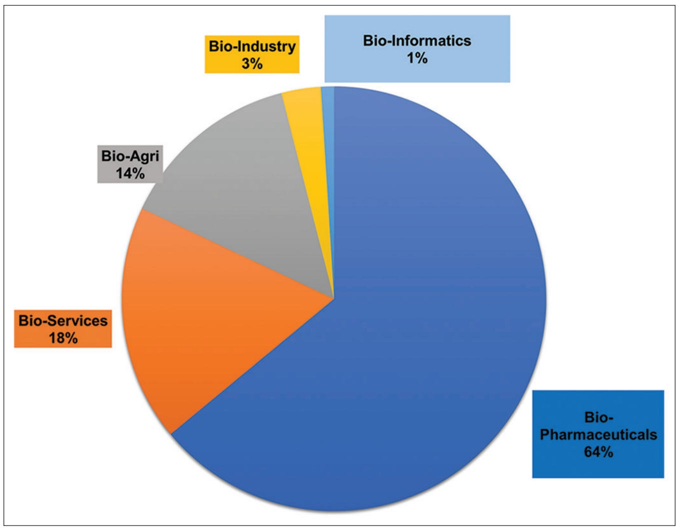

Figure 9: Market share of different sectors of biotechnology industries.

the bioremediation market, due to its increasing industrialization and urbanization, which has also resulted in serious environmental pollution problems [54]. India has to call for serious steps to be taken towards managing pollution and waste management, as India is growing as one of the fastest industrial hubs in the world which will create more and more environmental toxicity and pose serious challenges to animals, plants, and human health. Keeping the current and future developments in mind, the participation of institutions, industries, and independent players is need of the time. Investment to promote research to find new solutions has to be done and interdisciplinary collaborations must be promoted where various streams (such as chemistry, physics, engineering, biology, and medical sciences) could come together to create sustainable and cost-effective ways to handle the crisis. This will not only solve one of the most challenging problems which are ahead of us but also create enormous potential in terms of the economy which will result in creating a large job market, giving opportunities for innovations and research.

2. CONCLUSION AND FUTURE PERSPECTIVES

Industrial biotechnology is an emerging area in biotechnology which is related to the production of different biological products for numerous valuable purposes in different aspects of human welfare. The high demand for various biotech products has also opened up the scope for foreign investments in India. India has emerged as a leading destination for clinical trials, contract research, and manufacturing activities due to the growth in the bio-services sector. The biotechnology industry in India comprises 2700+ biotech start-ups and is expected to grow up to 10,000 by the year 2024, and currently, there are more than 2500+ biotech companies in India. The maximum number of the US FDA approved plants (665) outside of the US, as well as 44% of global abbreviated new drug applications (ANDA), are produced by India. Furthermore, 1400 manufacturing plants are compliant with the WHO standards [29]. The global market size for fermentation products was valued at 149.5 billion USD in 2016 and is forecast to be worth over 205.5 billion USD by 2023 [54]. This represents the vast market for fermentation products in the near future and India should exploit it to its advantage. At present, the biotechnology industry is growing at a respectable pace and contributing to India's growth and needs. India is among the top 12 biotech destinations and ranks 3rd in the Asia-Pacific region and holds a 2% share of the global biotech industry in the world. India has the second-highest number of the US Food and Drug Administration-approved plants after the USA and is the largest producer of recombinant hepatitis B vaccine. The biotechnology industry in India comprises around 800 companies of value 64 billion USD in the year 2019 and targets a turnover of 150 billion USD by 2025. The biopharmaceutical industry is the largest sector contributing to 62–64% of the total revenue followed by bio-services (18%), bio-agri (15%), bio-industry (4%), and bio-informatics (1%) [Figure 9] [29,54]. The proposed investment value in the Indian fermentation industry for the fiscal year 2019 amounted to about 126.9 million USD [6].

With a vision to become major contributor to global biotech industry and to empower the future of bio-innovation in India, the GoI's (Government of India's) department of biotechnology (DBT) through its BIRAC scheme has established so far 60 successful bio-incubation centers such as InCeNSE-IISc, AIC-CCMB, NCL-Pune, and BioNEST-BHU which have developed more than 200 products that have already been commercialized. Moving at this pace India's contribution in biotech innovation will be significantly visible in coming years. Like the US, Australia, China, etc., India needs to attract more private and foreign investment to catch up with the pace it needs to grow in future. Furthermore, India has large number of institutions and universities which are engaged in basic biotechnological research and they need to be encouraged to participate toward developing innovation and entrepreneurial skills to fuel up future human resource requirements for meeting the needs. With the above achievements, challenges, and goals, India is poised to be a major contributor to the global biotechnological industry in coming years.

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4. AUTHORS' CONTRIBUTIONS

Samarendra K Singh conceived the idea; Samarendra K Singh, Kumud Tiwari, Garima Singh, Gajender Singh, and Sonika K Sharma wrote the manuscript.

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6. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

7. ETHICAL APPROVALS

This research does not involve experiments on animals or human subjects.

8. DATA AVAILABILITY

The authors confirm that all datasets gathered and analyzed during this research are included within published article.

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