Microsphere (2022) 1(1): 22-32
https://doi.org/10.59118/IFJF3014

Review

Employing Food and Industrial Microbiology to Accelerate Sustainable Development Goals

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Received: 11 September 2021 / Accepted: 13 October 2021 / Published online: 18 February 2022

Abstract

Microbes have been employed by humans since ancient times for brewing and fermenting purposes. The knowledge about the potential of microbes has increased tremendously over the past century, wherein it has acted as a savior of human populace by providing antibiotics and vaccines. Microbial biotechnology has expanded ever since and found immense application in the areas of food and industrial processes. Enzymes, vitamins, amino acids, organic acids, alcohols, genetically modified crops and single cell proteins are only few of the vast array of products that have been provided by microbes. Chemical production of these products is not only expensive, but also generates toxic waste by-products which are dumped into the environment. Due to excessive waste generation, pollution and unaccountability towards the environment, we are currently facing a crisis, because of which our renewable resources are endangered, and the environment is deteriorating. To address these issues, microbiologists have been conforming and contributing towards the development of environmentally safe, sustainable and economical production of energy and food alternatives, so that sustainable development goals can be achieved. This review highlights the developments in the field of food and industrial microbiology and their contribution to production of sustainable alternatives.

Keywords: Food microbiology, Industrial microbiology, Sustainable development goals, Green biotechnology

Introduction

In 1837, scientists recognized the role of yeast in an alcoholic fermentation, marking the first recognition that microorganisms play a role in food production processes [1]. Since ancient times, microbes have been used in a wide range of applications, notably in fermentation, curd production, and brewing. Researchers were able to exploit microorganisms for a number of industrial applications owing to the advancements in research related to microbial enzymes, their growth kinetics, and culturing techniques.

The breakthrough in genetic manipulation tools ushered in a revolution in the field of biotechnology, propelling it to new heights. Microbes being ubiquitous are now designated as key players in shaping micro-community structures and community function in diverse ecosystems, including living systems. Many others have been recognized for their beneficial products and services to mankind. Because microbial biotechnology is such a broad field of study, it has been divided into several groups (color-coded) based on its applications [2]. White biotechnology refers to industrial [3], green biotechnology [4] for agricultural and blue denotes marine biotechnology [5]. Others include red for pharmaceutical, brown for desert, purple for patents and inventions, and yellow for applied entomology [6]. Microbiology is thus implicated in problems ranging from immediate concerns demanding urgent answers, such as new and emerging diseases, to long-term issues such as antimicrobial drug resistance, food security, and environmental sustainability.

The fundamental notion of sustainable development is to strike a balance between economic progress and environmental protection in order to meet the demands of current and future generations. Microbial biotechnology holds the potential to contribute to sustainable development by cutting down carbon emissions and replacing carbon consumption with renewable energy sources [7]. Such resources could be used to replace fossil fuels, non-biodegradable plastics, and harmful chemical processes. It has been estimated that if the potential of industrial biotechnology is fully realized, it can reduce carbon dioxide emissions by 50% (SDG 13), energy consumption can be cut down by 20% (SDG 7) and water consumption by 75% (SDG 6) [8]. Towards this end, green biotechnology refers to the advances in the agricultural field which have led to the development of environmentally sustainable means of production and products themselves (SDG 12). Transgenic or genetically modified (GM) organisms, especially plants have been designed, that can withstand harsh environmental conditions, are herbicide resistant, disease resistant, and resistant to predation by insects [9].

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eISSN: 2583-5327

Implementation of GM crops in agricultural systems has reduced dependence on insecticides and thus pushed agricultural practices more towards sustainable development goals (SDG 2). Green biotechnology has also catered to the production of biopolymers to replace synthetic polymers.

Microbes can also be used to provide solutions to challenges like food scarcity, nutritional deficits, waste management, bioremediation of contaminated environments and disease susceptibility [10]. They are continually being engineered to serve as factories (microbial cell factories) for enhanced production of desired products. A number of microbe-derived enzymes have been used to breakdown plant polymers [11]. Microbially generated biopolymers are being used to replace biocompatible plastics [12]. Development of cell free systems has provided a means to produce proteins in expression systems. Yeasts, such as, *Kluyveromyces lactis*, *Yarrowia lipolytica*, *Ogataea polymorpha* and *Ogataea thermomethanolica* have been particularly employed for protein production [13, 14]. Among yeasts, *Pichia pastoris* has been a good source of single cell protein and is now considered as an efficient host for protein production [15]. Lactic acid bacteria (LAB) have been immensely used in the field of biotechnology both as a starter culture and for the production of metabolites [16]. Metabolic engineering has led to the production of soy isoflavones, vitamin B12, amino acids and a number of bioactive compounds [17-19]. Marine microorganisms have been a source of novel foods, bioactive compounds, and biofuels (blue biotechnology) [20]. Cyanobacteria, macroalgae and marine microalgae are considered as important sources of additives and pigments [21]. Nutritional supplements such as glycerol and fatty acids (lipids), carbohydrates, pigments, prebiotics and mineral supplements are being obtained from marine environments.

As a result, recent biotechnological advancements have paved the way for a deeper understanding of how microbes could play a major role in achieving sustainable development goals. Translational research in this area has led to major breakthroughs in the field of food and industrial biotechnology. This review focuses on such recent developments which highlight the need for more extensive research, upgradation on the industrial scale and awareness of microbial potential among non-scientific populace.

Food Microbiology

Biotechnological production of organic acids and alcohols

Citric acid is one of the most important organic acids having immense industrial applications in food, beverage, preservatives, pharmaceuticals and cosmetics [22]. Citric acid is produced majorly from *Aspergillus niger* [23] and *Yarrowia lipolytica* [24]. Citric acid, as well as other organic acids such as acetic acid and lactic acid, have been produced through the fermentation of organic waste products [25]. If developed at an industrial scale, such technologies could provide long-term solutions for the disposal of agricultural and other organic wastes. Glutamate, a flavor enhancer, is synthesized from carbohydrates using *Corynebacterium glutamicum* [26, 27]. Glutamate is one of the most commonly used food additives and a flavor enhancer. It enhances the umami flavour and is available in the form of monosodium L-glutamate (MSG). The chemical method of production of MSG is associated with high cost, which has led to the emergence of fermentation as the method of choice for obtaining MSG [28]. Apart from *C. glutamicum*, *Brevibacterium lactofermentum* and *B. flavum* have also been employed for producing L-glutamate [29].

Food industry is facing a huge demand for the production of artificial sweeteners due to increased awareness and rise in the cases of lifestyle diseases such as obesity, diabetes and cardiovascular conditions. Xylitol, Sorbitol, Mannitol, Erythritol, and Aspartame are sweeteners that are in huge demand to replace conventional sugar. They belong to the NNS category (non-calorie or non-nutritive sweeteners), and therefore have a low glycemic index. Aspartame is one of the most popular artificial sweeteners, however, a number of studies have reported its carcinogenic, nephrotoxic and neurotoxic effects [30-34] due to which other sugar alternatives have gained popularity. Xylitol is a rare sugar, produced chemically by the hydrogenation of D-xylose and biotechnologically produced mainly by employing *Saccharomyces cerevisiae* or *Candida* [35]. Xylitol production has also been explored by using glucose as the starting material and its metabolic conversion in a step wise manner by microbes [36]. Sorbitol is another organic alcohol that is high in demand as an artificial sweetener, texturizer, and softener [37]. It is chiefly produced by *Zymomonas mobilis* which uses glucose and fructose as a substrate and produces sorbitol and gluconic acid in the process. *Lactobacillus plantarum* has also been used to produce sorbitol from fructose-6-phosphate through metabolic engineering [38]. Similarly, mannitol is also one of the polyols which can replace conventional sugars in diets. Lactic acid bacteria are used for mannitol production, using fructose as a substrate [39, 40]. Erythritol is another sweet polyol that is produced using lactic acid bacteria. This is considered one of the safest sugars as it is not metabolized by the human body [41]. It is excreted after absorption and is non-fermentative, thus does not produce bloating upon consumption. Although artificial sweeteners do provide an alternative to conventional sugars, a number of studies have reported that they might lead to alterations in gut-brain axis, microbiome and glucose homeostasis, leading even to obesity [42]. Among artificial sweeteners, sugar alcohols have been considered as safe for consumption

[43]. As far as artificial sweeteners are concerned, the consumers must themselves be aware of all the possible effects of what they are consuming before choosing a product off the shelf.

Production of Amino acids and Vitamins

Valine, leucine, lysine, isoleucine, methionine, threonine, histidine, phenylalanine, tryptophan are some amino acids that are produced biotechnologically to be used in food additives, pharmaceuticals, cosmetics, antibiotics, biofuels and polymers. Main producers of amino acids are *C. glutamicum* and *E. coli* because they produce a broad spectrum of amino acids and have undergone metabolic engineering optimizing the yield under industrial settings [44]. A number of mutations and screening steps are performed to select for the overexpression of particular amino acids by metabolic engineering [45]. Several aromatic compounds such as L-phenylalanine, L-tyrosine and L-tryptophan are being produced from aromatic amino acids [46]. Earlier produced chemically by petrochemical process, the focus has now shifted to more eco-friendly ways of production using microbial cell factories [47]. Aromatic compounds have applications in pharmaceuticals, cosmetics, nutritional supplements, chemicals, solvents, plastics and food additives [48]. Aromatic compounds can be produced in an eco-friendly way using renewable sugar feedstock. They are produced by microbes by the shikimate pathway, especially from *E. coli* and *S. cerevisiae* [47].

Vitamin production is an expensive chemical process as the synthesis of vitamins requires numerous steps because most vitamins are produced by complex biochemical cycles. Bacterial strains that have been screened for the production of vitamins have to be engineered to overproduce these vitamins as vitamins are micronutrients and are synthesized by bacteria in trace amounts. Riboflavin (vitamin B2) has been produced from different strains of lactic acid bacterium *Lactobacillus plantarum* [49]. Along with riboflavin, the cofactors flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) are also in huge demand in the food and pharmaceutical industries [50]. These cofactors are a part of many proteins and enzymes that carry out essential functions in the body such as protein folding, DNA repair and many other cellular functions. Cyanocobalamin or vitamin B12 is an essential vitamin that is only synthesised by microbial organisms. It protects an animal body against development of pernicious anaemia and is marketed as a nutritional supplement. Mass production of this vitamin is possible using *Pseudomonas denitrificans*, *Propionibacterium shermanii*, or *Sinorhizobium meliloti* strains [51]. Recent gene engineering tool CRISPR-Cas (Clustered Regularly Interspaced Palindromic Repeats) has been instrumental in modulating the biosynthetic pathway of cobalamin production [51].

Transgenic plants or Genetically Modified (GM) crops

Because the current agricultural system is not designed to support the ever-increasing population, the human race is always confronting a food deficit. Even with great efforts to boost agricultural yields, unforeseen events such as drought, illnesses, pest population surges, and soil quality degradation owing to high reliance on chemical fertilizers, insecticides, and herbicides always create deficits in agricultural yield. These factors are responsible for major setbacks in predicted crop yields. Emergence of green biotechnology has been viewed as a probable solution for feeding nutritionally rich food to billions of people without discrimination [52] (SDG 2: zero hunger; SDG 3: good health and well-being; SDG 10: reduced inequality). Nutritionally fortified rice, oilseeds and potatoes have been produced with the aim of combating malnutrition, especially among the economically weaker section of the society [53]. Green biotechnology deals with the genetic manipulation of plant species (with microbes as major players) to deliver desirable traits such as insecticide tolerance, herbicide tolerance, drought and salinity tolerance, disease tolerance, and improvement in crop yield [9]. Apart from these, nutrient enrichment or enhancements for edible parts are also being carried out, which will lead to better human health in the long run.

Flavr savr tomato, which has the special attribute of delayed ripening, was the first transgenic plant to be commercialized in the United States in 1994 [54]. In 1996, Roundup Ready Soybean (RR Soybean) was introduced. RR Soybean is herbicide tolerant as it harbors glyphosate resistance gene from *Agrobacterium tumefaciens* [4]. Corn, soy, cotton and canola are the most frequently grown GM crops. Bt cotton and Bt maize are transgenic varieties having genes from *Bacillus thuringiensis* which makes them insect resistant. In developing countries like India, pest-resistant Bt cotton has boosted harvests [55]. The development of Genetically Modified (GM) crops is targeted towards achieving drought and salinity tolerance, improving yield and efficiency of nitrogen utilization and resistance to pests and diseases.

Crop varieties are also being improved for the production of ethanol. Similarly, some modifications have been made to sugarcane varieties for increasing the productivity, sucrose content, drought tolerance, high content of cellular fibers and easily breakable walls. Some varieties of soy and castor are also being engineered for utilization in biodiesel production. Vegetables and fruits with extra nutrients are being cultivated. Recent surge in the use of CRISPR-Cas technology has led to its application in the development of GM crops as well. Recently, enhanced β-carotene production has been achieved in bananas by using CRISPR-Cas gene editing technology [56].

Despite the fact that researchers are striving hard to develop GM crops, they are yet to reach the farms. Lack of understanding among the general public and farmers in particular is a major contributor. Therefore, both farmers and consumers must be educated on the basics of GM crop development, with special emphasis on their cost effectivity. The benefits of GM crops must be made known to the general people, and certain false information about GM groups that are spread in society with political goals must be debunked. Green biotechnology's long-term development goals can only be met if scientists and the general public work together.

Single cell proteins

Protein malnutrition is prevalent in developing and under-developed countries. To fill this nutritional gap, non-conventional methods for large scale production of protein sources were adopted. The concept of microbes expressing high level of proteins was introduced as a potential solution. Single cell proteins are dried microorganism cells that are highly proteinaceous and widely used as a protein supplement by humans and as animal feed. Single cell protein production requires biomass over which bacterial, algal and fungal cells are cultured. Some requirements must be met for it to be suitable for human consumption. Microbes should not produce carcinogenic by-products, and protein content and quality, as well as digestive abilities, should be tested [57]. Some of the common microbial cells used as single cell proteins, are mentioned in table 1.

Table 1: Candidate bacteria, algae, fungi and yeast employed for the production of single cell proteins.

Microbial group	**Candidates for single cell protein production**
Bacteria	*Pseudomonas fluroscens, Lactobacillus, Bacillus megaterium*
Algae	*Spirulina* spp., *Chlorella pyrenoidosa*
Fungi	*Aspergillus fumigatus, Asperigillus niger, Rhizopus cyclopium*
Yeast	*Saccharomyces cerevisae, Candida tropicalis*

Industrial Microbiology

Microbes have been used for production of fermented foods and beverages for centuries. Later, with the widespread production of antibiotics, the outlook for industrial microbiology was completely altered. Since then, microbes are being employed for the production of vaccines, pharmaceutical biomolecules, organic acids, vitamins, healthcare products, biopolymers, biofuel, pigments and various other products (figure 1) [58]. The advent of biotechnological tools has broadened the range for the types of microorganisms which might be employed in industrial microbiology and the unique products that can be produced. The recent genome editing tool, i.e., CRISPR-Cas system has led to a revolution in the engineering of industrial microbes. It has proved beneficial in modulating the microbial metabolic pathways to yield desired biomolecules, metabolites and proteins [59]. It is a multiplexed system, wherein different sites can be edited in one event. Knock outs and knock ins of genes are possible with the Cas endonuclease and a guiding RNA [60]. Introduction of new genes can cause alteration in the existing metabolic pathways to either improve or produce novel by-products, thereby increasing the number of strains used in industrial biotechnology.

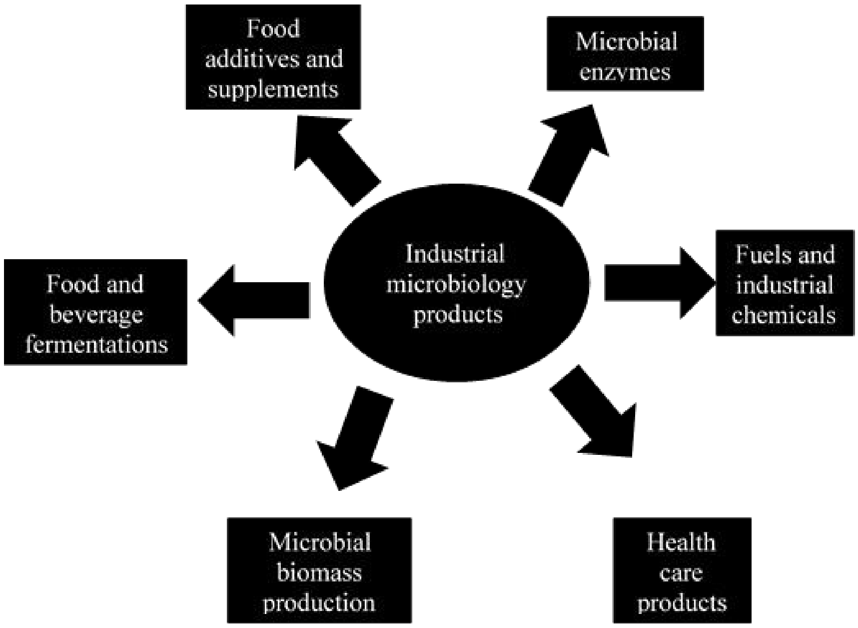

Figure 1: The flow-diagram highlights some of the major applications of industrial microbiology in various sectors.

Microbes can be developed as chemical factories for producing a single product with high yield. The key features of microbes include easy maintenance, cultivation, genetic stability, high metabolic activity and varied repertoire of enzymes. The entire industrial microbiology revolves around microbes and therefore the choice of strain used becomes a vital step in any microbial process. During the initial stages of biotechnology, microbial strains were selected from the natural wild environment. However, with the development of genetic manipulation tools and techniques, the focus on developing pure and improved microbial strains has shifted towards bioengineering of already available strains to make them suited to current requirements. Different approaches have been implemented for isolating microbial strains either by randomly screening the natural habitats or selecting particular habitat where the desired microbe is expected to be present. Genome sequencing of industrially important microorganisms and use of functional genomics has helped to scale-up expression systems of industrial organisms such as *E. coli, B. subtilis, S. cerevisiae, Pichia pastoris, Hansenula polymorpha,* and species of *Aspergillus* and *Trichoderma* [61].

Microbial Fermentation

Mass culturing of microorganisms under anaerobic conditions using specific substrates and enzymes has been termed as fermentation. The microbes are cultured on a low-cost crude biomass such as plant wastes, cheese processing by-products, whiskey processing by-products, etc [62]. Soil, water or spoilt fruits have been a major source of these microbes.

Fermentation systems can be liquid (submerged) or solid (surface). The submerged liquid system, in which microbes are submerged in a liquid growth media, is mostly utilized for enzyme production. With sterilized raw materials such as corn and sugars, both batch and continuous fermentation are successful. In case of solid or surface type of fermentation, the microbes grow over a solid growth medium. It is less common than submerged fermentation and used in specific cases such as for the growth of *Aspergillus niger* used for citric acid production. The fungal mycelia grow on solid trays which are stacked in fermentation rooms. Liquid type of fermentation always scores over the soil system in being cost effective, better control of process and less fermentation time required [63]. The process of fermentation majorly involves two processes: upstream and downstream processing (figure 2). Upstream processing includes initial steps, that is, selection of desired microbial strain, sterilization of the growth medium and microbial growth leading to fermentation process. Prerequisites of microbial growth are genetic stability of the microbial strain, maintenance of culture, and growth regulation. Downstream processing involves harvesting and processing of the desired metabolite. It follows the fermentation process where recovery of the product with minimal changes is achieved. If the fermented product is intracellular, it is much more problematic. The cell in that case must be lysed and may require straining.

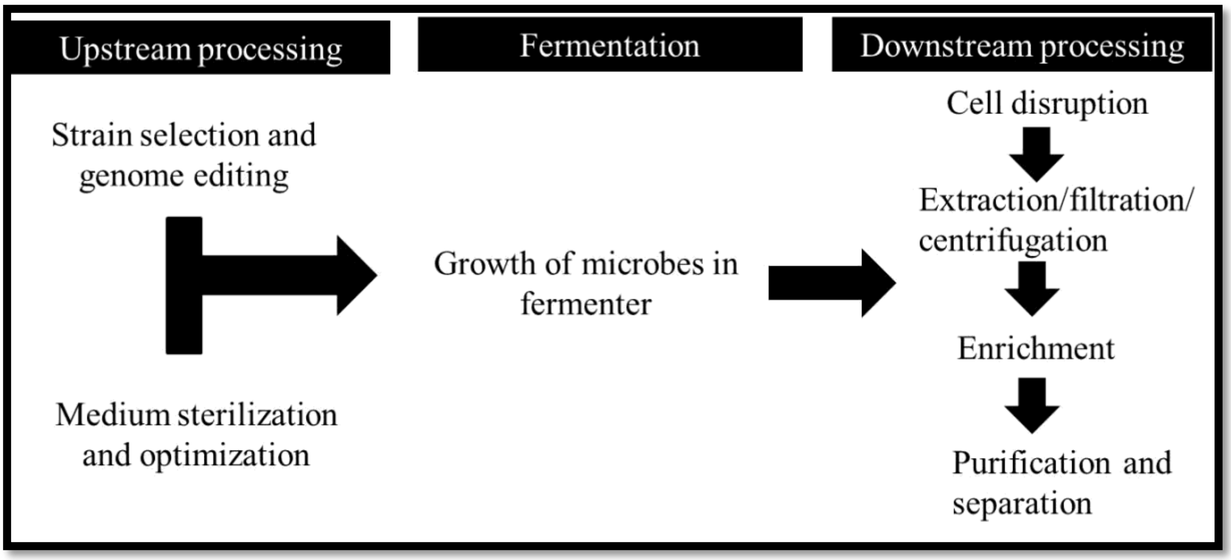

Figure 2: Overview of major steps involved in the process of fermentation.

Microbial enzymes

Microbial enzymes have always been the preferred choice over the plant and animal enzymes because of the ease of production, manipulation and extraction. The fermentation of wine, bread and vinegar has been carried out since ancient times using microbial cocktails even when the constitution and function of enzymes was not well understood. Microbial enzymes produced in the industry are stable, non-toxic and can be easily produced in large quantities. The extensive variety of enzymes produced are used in dairy for milk coagulation, cheese production (figure 3), processing and ripening; in baking for enhancing the softness of bread and dough conditioning; beverage production (using pectinase and amylase) and many other applications. Animal feed, pulp and paper production, polymer stabilisation and detergent industry are few of the beneficial sectors that employ microbial enzymes. With the advancement in recombinant DNA technology, the quality of the microbial enzymes has improved immensely [64].

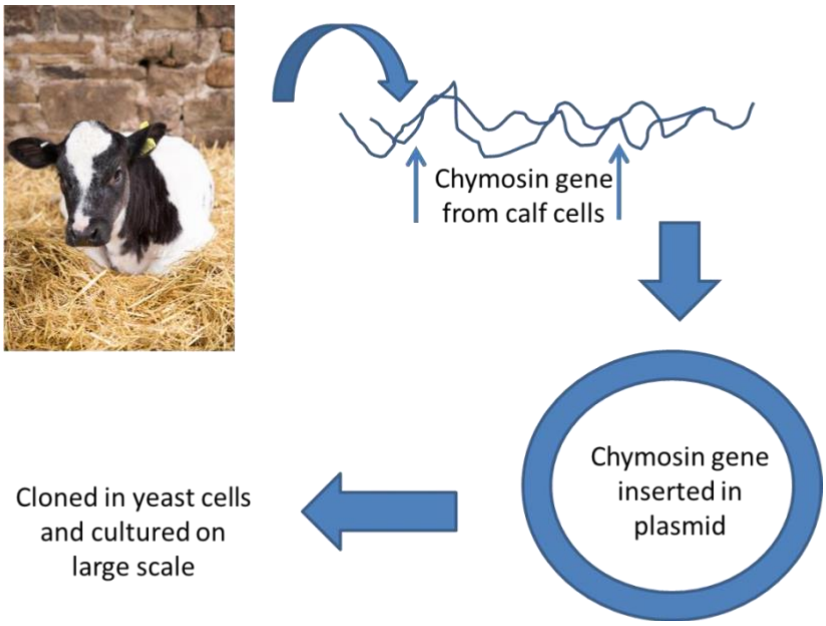

Figure 3: Schematic representation of the engineering of Chymosin cloned in yeast cells. Chymosin is the enzyme used for manufacture of cheese. The calf chymosin gene is inserted in the yeast cells (*Aspergillus niger*) and cultured in fermenter, following which the enzyme is harvested.

Enzymes are widely used in the industry. Some enzymes produced biotechnologically are amylases, proteases, oxidases, xylanases and lipases. Xylanases are enzymes that breakdown xylan present in plant lignocellulosic material into xylose and xylobiose [65]. Bacteria such as *Cellulomonas, Bacillus* and *Micrococcus* are employed for the industrial production of xylanase [66, 67]. Xylanases are enzymes of industrial importance, being utilized in the processes of brewing, baking, food processing, starch production, animal feed, paper, pulp and textiles production. Xylanases are also used for management of agricultural, municipal and food waste. They also have applications in the production of bioethanol. Galactosidase production from various microbes is being explored due to its huge application spectrum in prebiotics, dairy, food and pharmaceuticals [68].

Industrial microbiology in healthcare products: therapeutic steroids, vaccines

To bypass the extraction of steroids from animal tissue, a novel method of combining microbial transformation with chemical processing has been gaining popularity. This method of biotransformation uses sterols as the growth medium and filamentous microorganisms like *Fusarium* and *Aspergillus* as the microbial source. They convert the basic chemical structure of sterols by ring expansion, hydroxylation and side chain cleavages into the desired steroid compound [69].

In the early era of vaccine development, there were two types of vaccines; live vaccines (attenuated or weakened live forms) and inactivated vaccines (inactivated bacterial cells or component of a cell, surface antigens or metabolic product). Live vaccines are widely used for prevention against anthrax, typhoid and shigellosis. With advancement in medical sciences, the use of microbial protein toxins such as toxoids was used as an inactivated vaccine that is highly effective against diseases caused by *Clostridium* sp. like diptheria and tetanus [70]. Recombinant DNA technology has paved the way for vaccines against bacterial, viral and protozoan infections like influenza, poliomyelitis, rabies and hepatitis B. Recombinant viral vaccines are synthesised by cloning viral antigen in a microbial host cell. The virulence factors of Hepatitis B and viral protein of foot and mouth diseases have been successfully cloned in *E. coli*. Recently manufactured Covishield and Covaxin against the dreaded SARS-CoV2 virus are designed on the lines of recombinant viral protein vaccines [71, 72].

Biofuel production

Several processes are being developed for the production of liquid and gaseous biofuels from organic waste substrates that have the potential to replace fossil fuels. The development of both liquid and gaseous biofuels has the potential to reduce the burden of the world's energy consumption reliance on fossil fuels [73-77] (SDG 7: Affordable and Clean energy). Application of biofuels has been shown to contribute to sustainable development by a study in which sustainable development indicators were used to access the effect of utilizing biofuels in 17 countries [78]. Other studies have also substantiated that reliance on biofuels can accelerate our achievement of sustainable development goals [79, 80]. Liquid biofuels include bioethanol, biodiesel, biobutanol and biokerosene. These can be obtained from the fermentation of starch and lignocellulosic biomass such as xylan, cellulose and hemicellulose. A number of cellulases and xylanases have been mined from microbes. Bacteria having lignocellulosic enzymes such as *Caldicellulosiruptor*, *Caldanaerobius*, *Clostridium* spp. have the potential to be used for biofuel production [73, 81, 82]. Biobutanol production has been explored from the genus *Thermoanaerobacterium thermosaccharolyticum* [83]. Gaseous biofuels such as methane and hydrogen on the other hand can be obtained from anaerobic fermentation of feedstock and waste products [84]. Biohydrogen is one of the most appealing gaseous biofuels since it produces no waste or toxic gases. Microbes, particularly cyanobacteria, can make it photosynthetically by converting sunlight and water. Anaerobic dark fermentation of organic materials also generates hydrogen [84-86]. Methanotrophs which utilize the greenhouse gas methane are being employed for producing methanol which can be used not only as a biofuel but also for various other industrial applications [77].

Conclusion

Global warming, the depletion of oil, overcrowding, excessive use of fossil fuels, lack of food (or more appropriately, nutritional) resources, waste management, emergence of diseases, and land use are some of the existential issues that the world is currently battling with. Mitigation of challenges like these is achievable with innovative approaches, which are being provided by technology. Microbiologists have been instrumental in providing some solutions with the use of microbes for a number of sectors in which chemical production can lead to the generation of polluting and toxic by-products. Green biotechnology is constantly in perusal of solutions for nutritional and physical food deficiencies, for feeding nutritionally rich food to billions of people. Microbiologists are constantly working to produce single cell proteins, organic acids, artificial sweeteners, flavour additives and probiotics for improving the quality of food. Metabolic engineers are working on scaling up the production so that cost effectiveness can be achieved.

With this, we can aim to achieve SDG 2 (zero hunger), SDG 3 (good health and well being), SDG 10 (reduced inequalities) and SDG 12 (responsible consumption and production). Industrial microbiologists are searching for sustainable biofuels, waste management techniques, microbial production of enzymes, vaccines and a number of other sustainable alternatives for bioremediation leading to acceleration of sustainable development goals such as SDG 6 (clean water and sanitation), SDG 7 (affordable and clean energy), SDG 9 (industry, innovation and infrastructure) and SDG 12 (responsible consumption and production). With such developments in the fields of food and industrial microbiology, we can be hopeful that some, if not all, of the sustainable development goals can be met in the future by spreading microbial literacy and reliance on translational microbiology research.

Acknowledgement

CT gratefully acknowledges UGC for providing research funding under UGC-BSR project F. 30-461/2019(BSR).

Declarations

The authors declare that there is no conflict of interest.

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