Biotechnology of Twenty-First Century

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1 Introduction

Biotechnology can be defined as the "implementation of engineering and biological science theory to produce new products from biologically derived raw materials" or, in other words, it can also be explained as "the manipulation of living organisms or their products to alter or enhance human health and the environment of our planet" (Verma et al., 2011). The word biotechnology was first coined by KarolyEreky in 1919 in a book entitled *Biotechnology of Fat, Meat and Milk Production in Large-Scale Agricultural Farm* (Ereky, 1919).

1.1 Biotechnology: Major Advances Between 2000s and 2020

The following are some of the significant events in the modern era of biotechnology:

2000	Synthesis and amplification of DNA in a test tube by Har gobind Khorana and Kary mullis, respectively (Verma et al., 2011). Completion of rough copy of human genome by Celeria Genomics and

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	Human Genome Project (Verma et al., 2011). Kenya's first biotech crop, a virus-resistant sweet potato, was field-tested (Colwell, 2020). Sir Ian Wilmut cloned an adult sheep and named it "Dolly" (Bhatia & Goli, 2018).
2001	The complete human **DNA** sequence was published in the Science and Nature journals (Bhatia & Goli, 2018). Gleevec® (imatinib), the first drug- gene-targeted for patients with leukaemia chronic myeloid approved by the Food and Drug Administration (FDA) (Colwell, 2020).
2002	The genome of rice is decoded for the first time (Timeline of biotechnology, Wikipedia contributors, 2021). First time cloning of an endangered banteng species (Colwell, 2020). Approval of the first transgenic rootworm-resistant corn by the Environmental Protection Agency (EPA) (Colwell, 2020). Completion of the period of high-throughput shotgun sequencing of major genomes which include rat, chimpanzee, dog and hundreds of animals (Bhatia & Goli, 2018).
2003	Successful completion of the human genome sequencing by Celera and the National Institute of Health (NIH) (Bhatia & Goli, 2018). Gendicine (Shenzhen SiBionoGenTech, China), which expresses the p53 gene as a treatment for squamous cell neck and head cancer, receives the world's first regulatory approval (Colwell, 2020). The first genetically modified pet animal, TK-1 (GloFish), was marketed in Taiwan (Colwell, 2020).
2004	FDA approval of Avastin®, the first antiangiogenic medication for cancer therapy (Colwell, 2020). Approval of DNA microarray analysis device by FDA that aids in the selection of medications for various ailments which is a big move forward in the field of personalised medicine (Bhatia & Goli, 2018). Biotech crops are endorsed by the UN Food and Agriculture Organization which can benefit consumers and poor farmers in developing countries (Colwell, 2020).
2005	The Act called Energy Policy was signed and enacted into law, allowing for multiple bioethanol production incentives (Colwell, 2020).
2006	FDA approval of Gardasil®, first vaccine recombinant developed against papillomavirus (HPV) for human (Colwell, 2020). The 3D structure of the AIDS-causing human immunodeficiency virus (HIV) was deduced (Bhatia & Goli, 2018). Dow Agro Sciences earns the first regulatory approval for a plant-based vaccine from the USDA (Colwell, 2020). Stelarc, an artist, had an ear produced in a lab and transplanted onto his arm (Colwell, 2020). Launch of a 10,000-patient study for 10-year by NIH that employs a DNA test to determine direct care and breast cancer relapse (Colwell, 2020).
2007	Approval of H5N1 vaccine by FDA, making it the first avian flu vaccine to be approved (Colwell, 2020). Researchers have established how to develop embryonic stem cells from human skin cells (Bhatia & Goli, 2018).
2008	Japanese chemists build the first DNA molecule that is almost completely made up of synthetic components which may be useful in the field of gene therapy (Bhatia & Goli, 2018).

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2009	FDA approval of the first genetically modified animal to produce recombinant human antithrombin (Colwell, 2020). Three new genes linked to Alzheimer's disease have been discovered, allowing for new diagnosis and therapy (Bhatia & Goli, 2018). The first FDA-approved clinical trial for involving in embryonic stem cells is launched by Geron (Bhatia & Goli, 2018). Cedars-Sinai Heart Institute produces the first viral pacemaker in guinea pigs, now known as iSANs, using modified Sinoatrial node (SAN) heart genes (Wikipedia contributors, 2021).
2010	Dr. J. C. Venter reveals the finishing of "synthetic life" by incorporating a self-replicating synthetic genome into a recipient bacterial cell (Bhatia & Goli, 2018). Development of "lung on a chip" technology by Harvard researchers (Colwell, 2020). Researchers developed malaria-resistant mosquitos (Colwell, 2020). FDA approval of a personalised new prostate cancer drug that enhances a patient's immune cells' ability to identify and attack cancer cells (Bhatia & Goli, 2018). FDA approval of an osteoporosis drug, first medicine based on genomic research (Bhatia & Goli, 2018). ReNeuron has begun a clinical trial to treat stroke patients with a genetically modified neural stem cell line (Colwell, 2020). Neural stem has begun a clinical trial to treat patients with ALS (Lou Gehrig's disease) employing human embryonic stem cells (Colwell, 2020).
2011	Stem cell-derived trachea was grafted into a human recipient (Bhatia & Goli, 2018). Progressions in 3D printing technologies have enabled "skin-printing" (Bhatia & Goli, 2018). FDA approval for employing first cord blood therapy in the transplantation of hematopoietic stem cells (Bhatia & Goli, 2018).
2012	Synthesis of the polymer, Xeno nucleic acid (XNA) by the molecular biologists Vitor Pinheiro and Philipp Holliger. XNA can be exploited unlike DNA. Complete genome of the foetus was successfully sequenced using only the fragments of DNA present in the mothers blood. Zac Vawter, 31, climbs the Chicago Willis Tower with the help of a bionic leg powered by his nervous system (Wikipedia contributors, 2021).
2013 (Colwell, 2020)	Development of the CRISPR system for editing genes. Generation of functional liver tissue of humans using reprogrammed skin cells.
2014 (Colwell, 2020)	Developments in research discovered that a young mouse blood would restore the muscles and brain of an older mouse. Researchers discovered a way to transform stem cells in human into functioning pancreatic cells. Researchers developed new (deoxy ribonucleic acid) DNA bases testing in lab, extending genetic code for life's and allowing for the development of new types microbes. Woman delivered a baby after undergoing a womb transplant for the first time. Creation of an artificial and highly operational yeast chromosome. The remarkable advance, which took 7 years to achieve, could eventually goes to custom-built species (including humans).

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2015 (Colwell, 2020)	Singapore's Institute of Nanotechnology and Bioengineering developed small strands of peptides which assemble themselves as a fibrous gel in case of water is applied, allowing them to be used like a healing nanogel. CRISPR and 2015: Using the CRISPR gene-editing technology, scientists made a series of breakthroughs. In a controversial move, Chinese developers reported changing the DNA of a nonviable embryo in human. Harvard University scientists introduced DNA a long-extinct into the living cells woolly mammoth for a modern elephant in petri dish. Researchers have also used CRISPR as theoretically alter pig organs into human transplantation to eliminate malaria by mosquitos. Swedish researcher designed a blood test which can diagnose cancer in its early stages using only one blood drop. Researchers discover a new type of antibiotic for the first time in after 30 years, which could shows the way for a next new generation of antibiotics and help in minimise drug resistance. Teixobactin antibiotic that can be used to give treatment in a variety of infections caused by bacteria, including septicaemia and tuberculosis. Stanford University researchers unveiled a mechanism for forcing malignant leukaemia into harmless immune cells to turn known as macrophages.
2016 (Colwell, 2020)	The mosquito-borne disease Zika, which was first detected in 1947 in Uganda country, which blows onto the world wide when it started rapidly spreading around Latin America. Scientists have separated a human antibody which "significantly minimises" Zika virus. CRISPR, ground breaking DNA-editing technology which aims to reduce diseases and fix disasters cause environmentally, took a big forward step in this year when a group of Chinese researchers used it for the first time to treat a human patient. GK-PID, an ancient molecule discovered by scientists, are the reason for organisms single-celled began to involve into organisms multicellular about 8 billion years ago. Bioengineers produced a fully "heart on a chip" 3D-printed for the first time.
2017 (Colwell, 2020)	The first step toward epigenetically enhanced cotton has been taken. The genome sequencing of a green alga offers a model for developing renewable energy and bioproducts. Disease-resistant rice that doesn't sacrifice yield was developed. For the first time stem cells of blood were grown in a lab. Scientists in Sahlgrenska Academy, which is part of the Gothenburg University in Sweden, used a 3D-bioprinter to print cartilage tissue.
2019	16 April 2019—For the first time, scientists described how they used CRISPR technology to alter human genes for treating cancer patients who had failed to respond to standard therapies (Fingas, 2019; Staff, 2019). 21 October 2019—In a new report, researchers define "prime editing," a new method of genetic engineering that outperforms previous methods such as CRISPR (Anzalone et al., 2019; Gallagher, 2019; NPR, 2019).
2020	27 January—Demonstration of designer nanoparticle "Trojan horse" that causes blood cells to eat away at portions of atherosclerotic plaque, which causes heart attacks which is the world's leading cause of death (Michigan State University, 2020; New Atlas, 2020a; Flores et al., 2020; ScienceDaily, WHO). 9 March—Discovery of CRISPR-Cas12b, a promising third CRISPR editing method for plant genome engineering, in addition to Cas9 and Cas12a, phys.org).

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	16 March—Development of a new type of CRISPR-Cas13d screening platform for designing successful guide RNA for target RNA. This technology was made accessible through an interactive website and free and open source software, along with a guide on how to create guide RNAs to target particular genes such as SARS-CoV2 RNA genome (Wessels et al., 2020, phys.org). 10 April—Wireless regulation of secretion of adrenal hormone in genetically unmodified rats using injectable magnetic nanoparticles (MNPs) (Rosenfeld et al., 2020, phys.org 16 May 2020). 8 May—Scientists claim to have created artificial chloroplasts (Barras, 2020b, phys.org 12 June 2020; Miller et al., 2020; New Atlas, 2020b). 10 November—Microorganisms could be used to mine useful elements from basalt rocks through bioleaching in space, according to scientists who conducted an experiment on the International Space Station with different gravity environments (Cockell et al., 2020; Crane, 2020). 18 November—For the first time, researchers announce that CRISPR/Cas9 was successfully used to treat cancer in a living animal using a lipid nanoparticle delivery system (Rosenblum et al., 2020; Tel Aviv University, 2020). 25 November—Development of symbiotic algal-bacterial multicellular spheroid microbial reactors that can produce oxygen and hydrogen through photosynthesis (Xu et al., 2020, phys.org 9 December 2020). 30 November—In tests of the biennial CASP evaluation with AlphaFold2, an artificial intelligence company shows how an AI algorithm-based method for protein folding, one of biology's most difficult problems, achieves a 90% precision in protein structure prediction (BBC News, 2020; DeepMind, 2020). 2 December—The Government of Singapore grants the world's first regulatory approval for a cultivated meat product (Shanker, 2019). 11 December—Scientists announce that they have used stem cells and a bioengineered scaffold to reconstruct a human thymus (Francis Crick Institute, 2020; Campinoti et al., 2020).
2021	12 January—CRISPR/Cas9 genome editing has resulted in a tenfold rise in superbugs that target formicamycin antibiotics, according to researchers (Devine et al., 2021; EurekAlert, 2021).

1.2 Benefits Due to Advances of Biotechnology

There are a huge number of benefits attributed to the innovative advances made in the field of biotechnology. Complete human DNA sequence published enabled researchers all over the world to begin researching new therapies for diseases with genetic roots, such as heart disease, Alzheimer's disease, cancer, etc. (Bhatia & Goli, 2018). Sequencing of genomes of crops like rice can guide in the development of resistant crops on the other hand sequencing of genomes of hundreds of animals can help in bringing back the endangered species to life like in the case of banteng. Discovery of genes related to different diseases may aid in the complete cure of the diseases. Another major achievement is the creation of functional trachea, liver, pancreas using stem cells. Now-a-days, stem cell banks are maintained just like blood banks which can be used in future in case of incidents where new organs or skin are needed to be created. Discovery of CRISPR-cas system can be considered as a boon to cancer patients as it can alter human genes. Not only human genes, this technology can also be employed in plant genome engineering.

1.3 Global Research in Biotechnology/Biotechnology in Private/Public Sector

From the above discoveries/advances made in the start of twenty-first century, it can be understood that global research in biotechnology focussed majorly in the medical science field in order to develop treatments for various diseases which humans are suffering and also in the agricultural field to develop genetically modified crops. In the growth of the biotechnology industry, public-private collaboration is crucial. In India, there are several government agencies, including the Science and Technology Department (DST), the Scientific and Industrial Research Department (DSIR), the Scientific and Industrial Research Council (CSIR), the Agricultural Research Indian Council (ICAR), the Medical Research Indian Council (ICMR), the Atomic Energy Department (DAE) and the Grant Commission University (UGC) which are focused on the development of biotechnology in India. In addition, there are research institutions such as Immunology National Institute (NII), New Delhi; Centre for DNA Diagnostics and Fingerprinting (CDFD), Hyderabad, etc. which work under the supervision of Department of Biotechnology (DBT) (Konde, 2008). In the private sector, industries, colleges and other institutes play a major role in developing biotechnology.

Biotechnology is being used in a wide range of fields, including bioremediation, forensics and agriculture, where fingerprinting DNA is widely used. Similarly techniques like PCR, immunoassays, and recombinant DNA are commonly used in both industry and medicine. The first reason that biology is known now as a potential science and biotechnology as a leading industry is because of genetic manipulation (Colwell, 2020). Biotechnology has applications in a number of fields, ranging from agriculture to medicine. Based on applications, biotechnology is divided into several branches, each of which is referred to by a different name, which is highlighted by different colours to distinguish the biotechnological area in which it is used (Fig. 1). Four major branches of biotechnology are Industrial biotechnology (White biotechnology), Medical biotechnology (also called Red biotechnology), Environmental biotechnology (Grey biotechnology) and Agricultural biotechnology (Green biotechnology). This chapter gives a brief introduction to the four major branches of biotechnology.

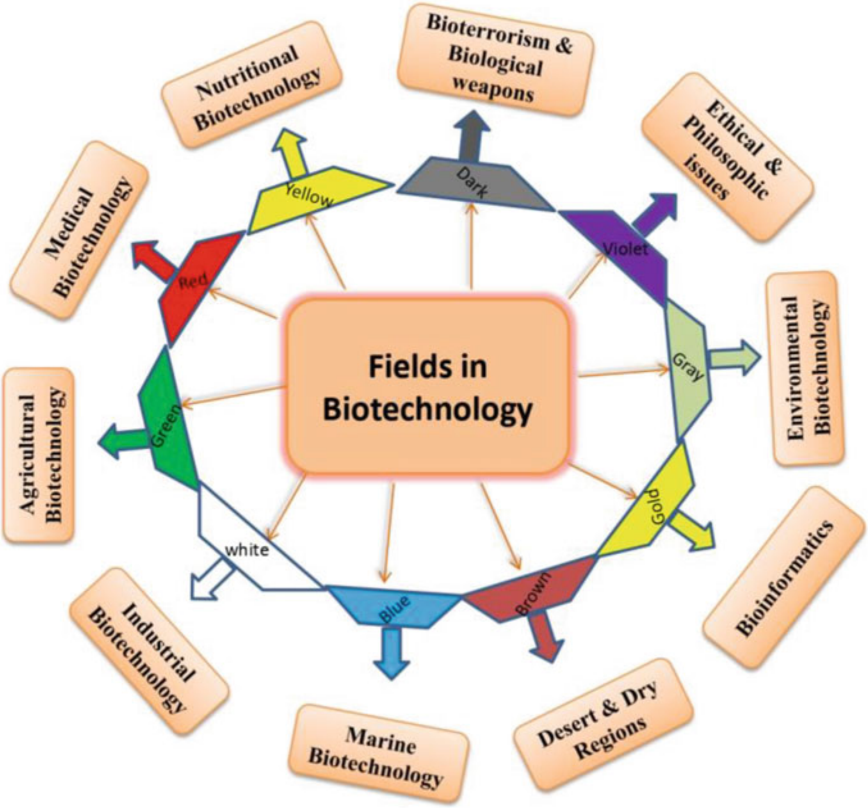

Fig. 1 Biotechnology classification. (Modified after Indira Padhy et al., 2020)

2 Environmental Biotechnology

Environmental biotechnology can be defined as the body of science and engineering expertise combined together which is concerned with the use of microbes and their products in the surveillance, treatment and prevention of environmental contamination (Ivanov & Hung, 2010).

2.1 Components and Importance of Environmental Biotechnology

Environmental monitoring/Biomonitoring of environment (employs biosensors to diagnose environmental issues) and treatment process, biotreatment of solid, liquid, and gaseous wastes, bioremediation/biodegradation of contaminated environment (degradation of organic molecules or contaminants in the environment by employing microbes) and pollution prevention (includes the use of renewable resources, biodegradable goods, and alternative energy sources) are the major concerns/components of environmental biotechnology (Bhatia & Goli, 2018). Bacteria and Archaea, Fungi, Algae, and Protozoa are examples of microbial biotechnological agents employed in environmental biotechnology (Ivanov & Hung, 2010; Maddela et al., 2016).Some microorganisms consume materials that are harmful to others whereas certain bacteria feed on chemical compounds of waste products. Using such living organisms particularly microorganisms, environmental biotechnology study is developing successful methods for minimising, preventing and reversing environmental harm. Such an approach is called bioremediation.

2.2 *Role of Biotechnology in Bioremediation and Phytoremediation*

Bioremediation is the process of using microorganisms to eliminate or detoxify toxins from polluted sites of soils, water, or sediments that would otherwise be harmful to human health. Bioremediation is also known by the terms biodegradation, biotreatment, bioreclamation and biorestoration (Maddela et al., 2017a, b, 2019). Bioremediation isn't a brand-new concept. For several years, microorganisms have been used to extract organic matter and hazardous chemicals from domestic and industrial waste (Godani, 2021; Kaur & Maddela, 2021). Toxic compounds like organics, metals, oil and hydrocarbons, dyes, detergents, etc. are broken down into less toxic and less complex metabolites such as inorganic minerals, H_2O, CO_2 (aerobic) or CH_4 (anaerobic) (Alexander, 1999). Bioremediation is a more effective and budget friendly cleaning method than other cleaning techniques such as chemical or physical techniques (Kamaludeen et al., 2003). For bioremediation, natural microorganisms are used; these natural microorganisms may be indigenous or non-indigenous (introduced). The chemical structure of the pollutant is taken into account when selecting microorganisms for bioremediation (Prescott et al., 2002). Occasionally, naturally occurring microbial species are insufficiently active or suitable for bioremediation of pollutants resistant to microbial assault (Dejonghe et al., 2000). Here comes the role of environmental biotechnology in developing Genetically Modified Microorganisms. Genetic engineering, a branch of molecular biology, builds novel strains with desired traits where the properties of naturally occurring microbes are modified in order to construct novel pathways, alter the existing regulatory mechanisms, alter and assemble various degradative enzymes extracted from different microorganisms into a single microorganism for degradation of pollutants and enhance the genetic stability of catabolic activities of microbes (Timmis & Pieper, 1999; Chen et al., 1999).

On the other hand, phytoremediation employs plants in place of microbes. The use of fast-growing, high-biomass plants capable of absorption and accumulation of large quantities of toxic metals in their aboveground harvestable sections is the most significant prerequisite for phytoremediation. Bioengineering of non-accumulators with high biomass is important for successful phytoremediation because many metal hyper accumulators are slow growing and have low biomass (Buhari et al., 2016). Biotechnology allows for the transfer of hyper accumulator phenotypes into fast-growing, high-biomass plants, which could be very useful in Phytoremediation (Rupali & Dibyengi, 2004). Biotechnology/Genetic engineering develops methods to boost plants' ability to withstand various contaminants and the efficacy of phytoremediation.

2.3 Pollution Control: Air, Water and Soil

The introduction of hazardous and toxic substances called pollutants into the environment is referred to as pollution. Volcanic ash, for example, is a natural pollutant. Human activity, such as garbage or industry runoff also causes pollution. Pollutants have a negative impact on the quality of the air, water, and land. Air, water, and land/soil pollution are the three primary kinds of pollution. There has been a substantial rise in the levels of environmental pollution over the last two decades as a result of direct or indirect human activities (because all kinds of human activity produce wastes). Industries, anthropogenic sources (man-made activities primarily in urban areas), biogenic sources, and other sources of emissions are currently the primary sources of environmental pollution (Saranya et al., 2020). Environmental pollution is often linked to the global industrial explosion, which is designed to meet the needs of the world's growing population (Okpokwasili, 2007). Therefore, it can be concluded human activities are the major reason for the massive environmental pollution during these days which can be resolved using environmental biotechnology. Environmental biotechnology is primarily used in wastewater treatment (water pollution) (Maddela et al., 2019), soil treatment to eliminate contaminants (land/soil pollution) (Maddela et al. 2015a, b; 2017a, b), and gaseous pollutant (air pollution) removal using microbiological catabolic operation.

Environmental, or outdoor, air quality has been the primary subject of air pollution control in developed countries. This entails the regulation of a limited number of unique "criteria" pollutants linked to urban smog and chronic public health issues. Fine particulates and gases (carbon monoxide, sulphur dioxide, nitrogen dioxide, ozone) and lead are among the criteria pollutants (Nathanson, 2019). The major air pollution control technologies are incinerators, gravitational settling chambers, electrostatic precipitators, cyclone separators, selective catalytic reduction systems, cloth filters, biofilters, biotrickling filters, bioscrubbers and membrane bioreactors (Kalender, 2019). Biofilters, biotrickling filters, bioscrubbers and membrane reactors come under the biological waste gas purification technologies which employ microbial communities to remove the criteria pollutants from the air. There are different approaches to treat water pollution which include aerobic, anaerobic and physicochemical processes in fixed-bed filters and in bioreactors. In all these

Table 1 List of microbes responsible for chemical compound degradation (Godani, 2021)

Compound	Organisms
Petroleum hydrocarbons	*Acinetobacter, Mycobacter, Pseudomonas, yeasts, Cladosporium, Scolecobasidium*
Pesticides (Aldrin, Dieldrin, parathion, malathion)	*Xylaria xylestrix*
Hydrocarbons, phenols, organophosphates, polychlorinated biphenyls and polycyclic aromatics.	*Pseudomonas*
Nitrate, nitrite, phosphate and heavy metals	*Phormidium laminosum*
Paraquat	*Lipomyces* sp.
Formaldehyde	*Candida* sp.
Benzaldehyde to benzyl alcohol	*Rhodotorula* sp.
Tannins	*Aspergillus Niger, Chaetomium cupreum*
Recalcitrant, pentachlorophenol	*Phanerochaete chrysosporium*
Volatile organic chemicals (VOCs)	*Nocardia* sp., *Xanthomonas* sp.

methods, the waste water containing industrial effluents and other contaminants and microbes are held in suspension (Godani, 2021). In order to treat soil pollution, a mixture of either naturally occurring or GEM'S (Genetically Engineered microbes) are added to the contaminated sites. The microbes responsible for degrading chemical compounds are given the below Table 1 (Godani, 2021).

3 Agricultural Biotechnology

Agricultural biotechnology, or agritech, is the application of modern scientific techniques based on our knowledge of DNA to boost crops and livestock in ways that traditional breeding alone cannot. Modern molecular plant breeding techniques including marker-assisted selection (MAS) can help with this.

3.1 Plant Growth and Yield

The world's growing population has posed a serious threat to food security. By 2050, population growth, especially in developing economies, would necessitate a 70% increase in food production, making substantial increases in agricultural productivity a priority over the next several decades. In this regard, biotechnology has focused its attention on developing technologies that can boost crop yields (Freddy et al., 2020).

The potential role of developmental features in growing crop yield was demonstrated in the "green revolution," where semi-dwarf rice and wheat varieties were bred to achieve unparalleled yield increases.

Reduction in plant height, an example is, by altering signalling and biosynthesis of gibberellic acid (GA) (Spielmeyer et al., 2002; Peng et al., 1999), reduced lodging and increased the tillers number. Given that the primary site of photosynthesis is a leaf, it's reasonable for assuming that plants may be genetically modified for the production of leaves in ideal size and shape for more effective harvesting, which results in faster higher yield and growth (Horton, 2000).

Another function that controls a plant's overall output is its vasculature, which not only provides strength but also gives as a conduit for the transport of minerals, water, and photosynthesis (Sack & Scoffoni, 2013; Brodribb et al., 2007). As a result, manipulations in genetics is that they change this developmental traits in favourable manner may be a large step forward in terms of crop yield (Jazayeri et al., 2020). Domestication impact on crop plant and also architecture of leaf adds to the argument that manipulating these developmental traits will boost crop production (Meyer & Purugganan, 2013).

Developmental traits are engineered with the goal of increasing efficient photosynthesis and therefore yield necessitates a detailed understanding of genetic basis. The molecular basis and genetics of the developmental procedure regulating these traits has made significant progress, especially in the model plant thaliana Arabidopsis. Anyhow, only a few crop plant examples that have grasped this concept exist. Despite this, it can be concluded that basic knowledge gained from the entire plant developmental studies can be applied to increase crop yield.

3.2 Agricultural Engineering (Breeding Techniques/Genetic Engineering/Organic Farming)

Techniques of breeding plant are methods allowing the development of new plant varieties with desired traits, by modifying the DNA of the seeds and plant cells. There are three major procedures for manipulating plant chromosome combination in general. To begin, plants from a given population can be selected for desired traits and used for further breeding and cultivation, a process known as pure line selection. Second, desired traits from different plant lines may be combined to create plants that display both traits at the same time, a process known as hybridisation. Third, crop improvement can be aided by polyploidy (an increase in the number of chromosome sets). Finally, natural or artificially induced mutations may introduce new genetic variability (Pandey et al., 2011).

The process of transferring individual genes between species or altering genes in an organism to eliminate or add a desired trait or feature is known as genetic engineering. Genetically modified crops or species are created by genetic engineering. GMOs or genetically modified crops are used to make biotech foods. Figure 2 shown global area distribution of the genetically modified crops (Beck et al., 2016). Restriction Fragment Length Polymorphism is the most effective and commonly used process of this kind in plant breeding (RFLP). Restriction endonucleases are

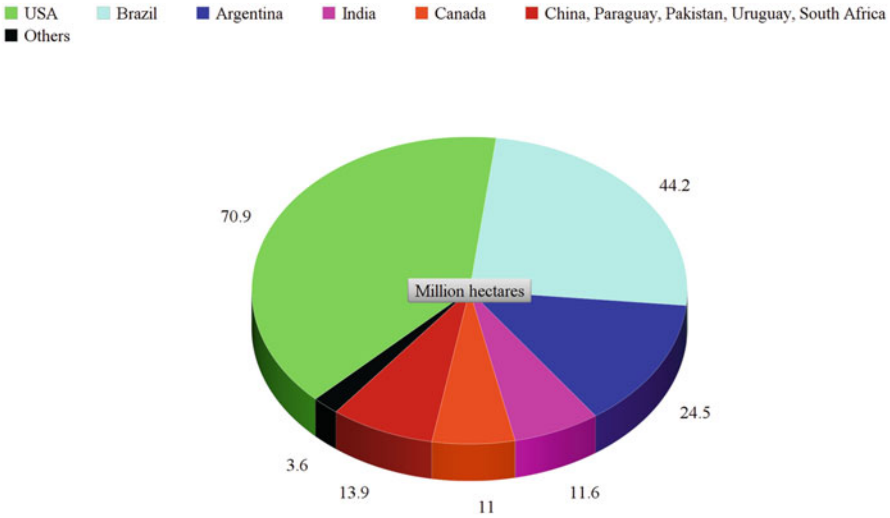

Fig. 2 Global area of genetically modified crops. (Modified after Beck et al., 2016

used in RFLP. Enzymes that identify and cut unique nucleotide sequences in DNA are known as restriction enzymes. Gene transfer allows any organism (other plants, bacteria, fungi, animals, viruses) to introduce useful traits coded for by unique genes into the genome of any plant. Transgenes are normally incorporated into a plant cell's nuclear genome (Ghosh et al., 2011).

Northbourne coined the word "organic" in his book *Look to the Land*, published in 1940. Organic farming is a form of farming that prevents or limits the use of synthetic fertilisers, pesticides, growth regulators, and feed additives in livestock (Ramakrishnan et al., 2020). Organic farming's fundamental goals are natural, social, and economic sustainability (Stockdale et al., 2001). Protecting long-term soil fertility by maintaining organic matter levels, fostering soil biological activity, careful mechanical intervention, biological nitrogen fixation, nitrogen self-sufficiency through the use of legumes and effective recycling of organic materials such as livestock wastes, weed and crop residues are the significant characteristics for organic farming. To reduce the distance between (Nitrogen, Phosphorous, Potassium) NPK removal from the soil and NPK addition, a strong focus is put on maintaining soil fertility by returning all wastes to soil primarily through compost (Chhonkar, 2002). Many countries are now forced to use pesticides and fertilisers to increase farm productivity in order to meet their ever-increasing food demands as a result of rising population pressure. Long-term and excessive chemical use, on the other hand, has resulted in human and soil health risks, as well as environmental contamination. As a result, farmers in developing countries are encouraged to turn their current farms to organic farms.

3.3 Global Food Security

The background of agriculture food security is expected to feed a growing population globally, which is expected to exceed 7500 million people by 2020, with 6300 million of them living in developing countries. There is a high-level concern over food insecurity due to trophic transfer of environmental pollutants (Maddela et al., 2020). Despite the fact that the population growth rate is slowing, the rise in people absolute numbers to feed could soon exceed the carrying capacity of agricultural lands, given current technology (FAO, 1999). Biotechnologies, for example, offer a responsible way to boost agricultural productivity now and in the future if properly oriented.

The issues of poverty reduction, food security and environmental protection in the developing world are all very important to the biotechnology revolution. However, for many, it poses serious ethical, intellectual property, and biosafety concerns (Johnson, 1999). Protests against the spread of agrobiotechnology have been widespread. Scientists are concerned that "novel" products would obliterate transforming agricultural trends, agricultural diversity into unrecognisable and uncontrollable types. Civil society organisations have staged several marches based on ethical or environmental concerns.

Fears of a new period of competitive disadvantage and increased dependency in the developing world have been posed by the domination of a highly concentrated private sector (British Medical Association, 1999). Patenting and intellectual property rights are also hot topics. Supporters of patenting argue that in order for the private sector to mobilise and spend substantial amounts of money in agrobiotechnology research and development, it must be able to protect and recoup its investment (Biotechnology Industry Organization, 2021).On the other hand, there is concern that patenting could lead to knowledge monopolisation, limited access to germplasm, research process restrictions, research focus selectivity, and increased marginalisation of the major world's population (Rural Advancement Foundation International, 2021). These issues can't and shouldn't be overlooked. To ensure that the effect of agrobiotechnology is both benign and positive, effective regulatory frameworks and protections must be implemented globally. In order to promote food security and assist the vulnerable, every tool of agricultural transformation should be used.

In the past last decade, cereals harvested per person were 370 kg, up from 275 kg in the 1950s; an increase of more than 33% per capita (FAO, 1995). Despite the fact that there are twice as many people on the planet today as there were 40 years ago, and there are 1.5 billion hungry people. Despite this remarkable increase in crop productivity, still more progress is needed to feed 2 billion people additionally by the early twenty-first century (Anderson, 1996), to generate income, combat food insecurity and jobs.

However, it is unclear if any of the current benefits agricultural biotechnology development would reach consumers and poorer farmers without significant public sector involvement. Farmers with limited financial resources are unlikely to get easy passage to agricultural inputs like improved pesticides, seeds, fertilisers and irrigation. Given that women are over 70% of those living in poverty in the developing countries, with the many of them are staying in rural areas (IDRC-UNCTAD, 1998), science alone is unlikely to provide a "scientific remedy" for eradicating poverty. Lack of access to land, low buying power and other productive resources, fragile ecosystems, political powerlessness and isolation from markets are just some of the systems, causes and socioeconomic structures that contribute to rural people's poverty. Biotechnology must be integrated as a supplement to agricultural technology, resulting in better and more widely available seeds and more sustainable production methods.

4 Industrial Biotechnology

Industrial biotechnology is the industrial application of biotechnology for the manufacture and processing of chemical products, materials, and fuels in a sustainable manner.

4.1 Industrial Products

Biotechnological processing employs enzymes and microorganisms to create goods for a variety of industries, including pharmaceutical, chemical, human, pulp and paper, energy, fabrics, textiles, and polymers, all of which rely on renewable raw materials.

Many of these sectors are more effective and environmentally sustainable as a result of the use of biotechnology to replace conventional technologies, leading to industrial sustainability in a number of ways. This paradigm shift affects a variety of fields, including the most well known, such as pharmaceuticals and agriculture, as well as the manufacture of biopolymers and bioplastics (Wikipedia, 2018).

The following are the seven most popular biotechnology applications in industry:

1. Fermentation Product Improvement.
2. Synthetic Fuels Generated by Microbes.
3. Bioleaching or Microbial Mining.
4. Single Cell Protein Production and Microbial Biomass.
5. Enzyme and Human Protein Production.
6. Secondary Metabolites Produced by Cultured Plant Cells.
7. Molecular Farming for Healthcare Products.

Modern biotechnology has the ability to provide a wide range of useful products to help us avoid diseases, diagnose and treat illnesses, and improve our overall health. Medicine, pharmacology, bioremediation, nutrition, food processing, energy production and forensics are all fields where biotech products are used. Biological medicines such as antibodies, vaccinations, recombinant proteins, antibiotics (e.g. enzymes, hormones, blood products, growth factors etc.), packages, diagnostic tests, cell therapy products, and gene therapy are several of the biotech-based health products. Haemophilia, diabetes, other illnesses and cancer are currently treated or diagnosed with biotech-based health products. In addition, genetic modification techniques have resulted in the development of many improved crops in terms of improved nutritional quality and material, disease and insect resistance, and crops that can produce antibodies, edible vaccines, pharmaceutically essential compounds. Food biotechnology is a relatively new branch of molecular biology that is rapidly expanding. Biotechnology is widely used in the food industry. It aids in the recovery of texture, food edibility and storage; it helps to prevent the attack of virus-like bacteriophage on food, especially dairy; it aids in the destruction of unwanted microorganisms in food that cause toxicity; and it aids in the prevention of mycotoxins and other toxins and anti-nutritional elements present in food. It also has the potential to play a significant role in protein engineering. Pathogens, toxins, and anti-nutritional elements in food can all be classified using this technology.

4.2 Food/Dairy Industry

Dairy products are widely regarded as natural, organic foods (Ramchandran & Shah, 2009) Biotechnology has the potential to play a huge role in improving the country's food and nutritional welfare. Biotechnology has been used in the processing of dairy products for centuries (cultured milk products, cheeses, and refined milk byproducts) by using starter cultures or enzymes for milk clotting, cheese ripening acceleration, fat, protein, or lactose hydrolyzate production, and antimicrobial purposes.

Modern biotechnology advances have opened up new and exciting possibilities in dairying, putting milk and milk products within reach of the poor and catering to the needs of a wide segment of the population. The dairy industry, in particular, will benefit greatly from biotechnological interventions that boost not only the overall quality and protection of processed dairy foods, but also their commercial value for both domestic and international consumption. Because the dairy industry's primary responsibility is to provide customers with high-quality, nutritious, and affordable dairy foods, biotechnological activity at various stages of milk production and processing has become anticipated. Biotechnology has previously significant offerings in dairy industry.

Possible applications are

Dairy Production

- Recombinant vaccines.
- Recombinant bovine.

DNA fingerprinting

- Animal cloning.
- Gene forming and transgenic.
- Embryo transmit technology.

Dairy Processing

- Dairy enzymes/proteins.
- Food grade bio-preservatives.
- Probiotics.
- Dairy waste organisation and pollution control.
- Functional foods and nutraceuticals.

5 Medical Biotechnology

Medical biotechnology is a branch of medicine that studies and then manufactures pharmaceutical and diagnostic products using living cells and cell materials. These items aid in the treatment and prevention of diseases. Medical biotechnology is a relatively new and rapidly growing area in which biotechnology concepts are applied to drug production (Maddela et al., 2021a). Biotechnology has a variety of effects on the medical industry and has the potential to alter its characteristics (Shan et al., 2018).

5.1 Pharmaceutical and Vaccinology

Biotechnology concepts such as recombinant DNA technology are used by pharmaceutical firms who have marketed bioformulations to design more successful protein-based drugs.

For treating the symptoms of an illness or disease, traditional pharmaceutical formulations are relatively simple molecules produced primarily by trial and error. Biopharmaceuticals, on the other hand, are complex biological molecules, widely known as proteins, that are used to cure diseases by removing the underlying mechanisms (Tables 2 and 3).

Table 2 Disease and examples of biopharmaceuticals used in treatment (Almeida et al., 2011)

Disease	Active substance
Multiple sclerosis	Interferon β
Hepatitis	Interferon α
Haemophilia	C factor VIII and factor IX
Renal cancer	Interleukin
Anaemia	Erythropoietin
Diabetes	Human insulin

Table 3 Marketed biotechnology products by different pharma and biotech companies (Evens & Kaitin, 2015)

Company	Name of the product	Uses
Sanofi	Gardasil	Prevention of certain strains of human papillomavirus (HPV)
Roche	Actemra	Moderate to severe treatment for active rheumatoid arthritis (RA)
Novartis	Eyelea	Treatment of patients with wet age-related macular degeneration (AMD)
Pfizer	Enbrel	Treatment of the symptoms of rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis and psoriatic arthritis
Merck KGaA	Erbitux	Treatment for people with neck and head cancers and certain advanced colorectal
Novo Nordisk	Procrit, Remicade	Treatment for anaemia (low red blood cell count) for people with long-term kidney disease
GlaxoSmithKline	Pediarix	A vaccine used to immunise children against diphtheria, pertussis and tetanus
AbbVie	Humira	Treatment of rheumatoid arthritis
Eli Lilly	Erbitux, Forteo	Treatment of cancer of the colon
Astra Zeneca	Synagis	Treatment for respiratory syncytial virus (RSV) in children; disease prevention of serious lung caused

However, in some cases, such as type 1 diabetes mellitus, where insulin is used to treat only the symptoms of the condition rather than the underlying causes, this is not the case. Pharmaceutical biotechnology is basically the use of living cells to create complex larger molecules like those found in the human body. Living cells such as yeast cells, animal or plant cells and bacteria cells are being used. The large molecules are normally injected into the patient's body, unlike the smaller molecules that are given to them through tablets (Nehal et al., 2011).

The majority of medication therapies, such as nucleic acid products, antibodies and vaccines, that are commonly used for molecular diagnostics today are the result of biotechnology formulations. The first biotechnologically produced drug is Insulin, which is one of the most popular examples. Aside from that, biotechnology offers specialised medical facilities and equipment for both prevention and diagnosis (Vijayakuma & Sasikala, 2012).

A vaccine is a biological preparation that is used to develop artificial active immunity to a specific disease. The main goal is to boost immunity; the antigen is referred to as a vaccine (Afzal et al., 2016).

Vaccination is a medical procedure that involves eliciting an immune response that decreases the risk of developing a specific disease. Vaccines are one of the most active achievements against a variety of infectious diseases and mortality in the twenty-first century, outperforming any other medical advance (Plotkin, 2001). Recent advances in molecular biology have resulted in two vaccine approaches:

DNA vaccines and therapeutic vaccines (Poland et al., 2002). Cancer, allergic disorders, and autoimmunity may all be treated or prevented with DNA vaccines (Wahren & Liu, 2014).For example therapeutic vaccine against HIV that will induce virus specific cytotoxic T lymphocytes against HIV and activate T cells to destroy latently infected cells.

The United States Food and Drug Administration has licensed more than 170 biotechnology-related drugs and vaccines, with 113 currently on the market. Another 350 biotechnology medicines are in the final stages of growth, with a combined goal of over 200 diseases. Medicines to treat pneumococcal diseases in children, diabetes, cancer and haemophilia were among those approved in 2000 (BIO). In the future, DNA technology is expected to revolutionise vaccine production. DNA vaccines have only recently begun to be tested, but they are expected to potentially replace other vaccine manufacturing methods (Human Genome Project Information, 2021).

5.2 Novel Methodologies

The rapid growth of both agricultural and medical biotechnology may have recently provided the perception of technological separation due to specialisation. Microencapsulation, immobilised bacterial cells and enzymes, genetic modification of microorganisms, liposome processing, creation of novel vaccines from plants, biocomputational methods and epigenomics of mammalian cells and organisms for disease modelling and bioinformatics are some of the novel techniques used in Medical Biotechnology. In the treatment of thrombosis, immobilised enzymes (Plasmin and Heparin) are used to achieve a balance between coagulation and degradation of coagulated blood (fibrinolysis) (Baianu et al., 2004). In the recent past, there is a much emphasis on the quorum quenching mechanism, which is a sustainable tool for the control of bacterial biofilms in the field of medicine and industry (Maddela & Meng, 2020).

6 Challenges in Biotechnology

6.1 Challenges/Gaps for Further Developments

1. Setting biotechnology goals: National officials are often forced to make decisions about priorities, user feedback, with limited financial resources and scientific knowledge.
2. Developing suitable and affordable technologies: Technologies that complement current farming systems and native crops, are affordable, and are healthy for humans and the environment must be developed.
3. Involving citizens: To assess needs and resolve issues, public participatory processes are needed.

4. Investing in science and local capacity: In developing countries, investment is needed to establish and improve national scientific expertise.
5. Creating long-term alliances: Partnerships may help to stimulate research in resource-poor countries, but it's crucial to understand each partner's priorities.
6. Participating in global discussions and negotiations about biosafety, biodiversity, trade and intellectual property rights: Scientists and lawyers from developed countries must engage in negotiations and discussions about biodiversity, biosafety, trade and intellectual property rights to ensure that agreements can be enforced in ways that help their countries achieve their objectives.
7. Anticipating directions and future needs: Researchers and policymakers must predict shifts in agricultural production and market demand.

Given how quickly the future unfolds, current biotechnology research has a greater potential to serve as the foundation for future innovation to address society's major challenges, such as ensuring food security for an ever-increasing population, providing sustainable healthcare, resource conservation, precision agriculture, climate change, and meeting energy shortages.

6.2 Future Directions of Research/Suggestions

Major areas Biotechnology with tremendous future opportunities which can impact all include:

(a) Drug and pharmaceutical development;
(b) Medical device and diagnostics;
(c) Noninvasive sensor in agriculture;
(d) Rapid testing of pathological conditions;
(e) Fast testing for food adulteration;
(f) Precision Agriculture and Biofortification;
(g) Machine learning and Artificial Intelligence in Biotechnology.

Over the last two decades, rapid advances in biotechnology and information technology have occurred in lockstep. Several biotechnology studies that would have taken years to complete are now simpler and cheaper thanks to the vast amount of data available and modern testing technologies developed in recent years (Maddela et al., 2021b). The large amounts of data produced and stored in biotechnology research, mostly extracted via omics-technologies, open up a slew of new possibilities for researchers and companies that provide products and services in this field.

Machine learning (ML) and Artificial intelligence (AI) technologies to explore, process and analyse broad data sets are new emerging fields in biotechnology at the moment, and thus AI and ML are exciting areas essential in advancing biotechnology's benefits. Biotechnology will be able to address complex social problems with its own systemic testing by adapting AI and ML. For example, in the health sector, electronic health record systems are increasingly integrating so that health-related data can be accessed internationally, allowing for a comprehensive approach.

In the field of biotechnology, rapid technological innovation has resulted in remarkable discoveries and innovations over the last three decades. The Human DNA Project, for e.g. provided a comprehensive map of human genome. From the fertilised egg cell to death, the human being's growth is driven by inherited instructions encoded in DNA. As a consequence, decoding the human DNA sequence possesses tremendous strength. DNA sequencing technology has advanced so quickly that in 2014, a single human genome that cost $100 million to sequence in 2001 cost just $5000 (National Human Genome Research Institute, 2015).

Parallel to this, assembling artificial DNA and technology for synthesising has improved to the point that whole genomes and genes of bacteria and viruses can now be recreated (Andrew, 2002, Eckard et al., 2009, Gibson et al., 2010; Monya, 2011). Recent advances in DNA engineering technology have made modifications in genetics of bacteria, plants, insects and animals, more feasible including human gene therapy (Jennifer and Emmanuelle, 2014; Cossins, 2013). Herbicide-resistant soybeans, corn and cotton are examples that have lowered prices, increase national yield, enhanced personal protection and reduced the amount of pesticides used (National Academies of Sciences, 2010).

"Pharmacogenomics or Personalised medicine," is the field in which the genetics for individual patient suggest the possible reaction of the disease to the biologic treatment, would be a key initiative in the future. Prescribers would be able to customise individual care regimens to include medications with a high probability of providing a beneficial clinical outcome while eliminating therapies that can cause severe side effects. Trastuzumab's effectiveness in aggressive metastatic breast cancer, for example, is dependent on the presence of the HER2/neuoncogene, which is found in approximately 1/4% of patients and is the only breast cancer patients group that can respond to trastuzumab. According to a report involving nearly 30 firms, personalised medicine was present in 12–50% of product pipelines, with a median of about 25% expected for 2015 (Tufts Center for the Study of Drug Development, 2010).

In the coming decade, product production will continue to grow. According to a recent study, 88 fully human monoclonal antibodies, as well as a comparable number of chimeric and humanised molecules, were in clinical development in 2010. The two most common disease types were cancer and immune disorders (Nelson et al., 2010). Novel formulations are being tested to improve product delivery by increasing effectiveness while reducing toxicity.

Over 900 biotech-related molecules are currently being studied in clinical trials around the world (PhRMA, 2013). With 431 and 276 molecules, monoclonal antibodies and vaccines were the two most common product categories. Even if we assume a 10% clinical success rate for biologic candidates, we can expect 100 new molecules to hit the market in the next 5–10 years.

The regulatory landscape will continue to change. Biosimilar regulations were recently finalised by the FDA, and the first biosimilar products have hit the market in early 2015. Ten of the top-selling biotech drugs have already lost their patents, and several more will lose their patents in the next 5–6 years, presenting huge opportunities for biosimilar developers. However, because of the biotechnology expertise needed, the complex and sophisticated biologic testing required, and the extremely high cost and complexity of development, obtaining FDA approval for bio-similars is likely to be difficult.

7 Conclusions

Biotechnology research has made a significant contribution and will continue to do so in the future to fulfil human needs.

An everchanging biological and economic climate, technical and scientific growth, and need-of-the-moment biotechnology advances have characterised the last few years. This is especially true in light of the recent COVID-19 pandemic and other emerging threats, as biotechnology is at the heart of finding solutions to current and future problems.

Identifying the most important biological, social, economic, and technical patterns will aid scientists in determining future biotechnology research directions.

The study of recent progress in the field's long-term effects will open up new research areas that will serve as a springboard for new innovation addressing future needs. It necessitates ongoing cooperation with stakeholders and the identification of both routine and new emerging problems in order to improve biotechnology innovation production.

Furthermore, many ethical and regulatory questions about biotechnology-based products, such as patents on living organisms, have been raised. Biotechnology is currently used to manufacture antibiotics, carbohydrates, hormones, monoclonal antibodies and vaccines, among other medicinal products. These items are used to treat and prevent a variety of diseases that affect a large number of people.

Many promising biotechnology-based approaches are currently being established for the advancement of medicine and the treatment of various diseases. Biotechnology-based treatments such as gene therapy, pharmacogenomics, and stem cell therapy, for example, have the ability to significantly improve the treatment process in a variety of ways.

Biotechnology has had a huge effect on health care over the last few years. If our understanding of the pathophysiology of many currently incurable diseases improves, this trend will continue in the near future governments all over the world are advancing policies to encourage biotech innovation, and market strategies are evolving to handle the costly, time-consuming, and dangerous phase of product growth. As a result, a steady stream of new drugs will be created, leading to major advances in patient care.

References

Afzal, H., Zahid, K., Ali, Q., Sarwar, K., Shakoor, S., Nasir, U., & Nasir, I. A. (2016). Role of biotechnology in improving human health. *Journal of Molecular Biomarkers & Diagnosis, 8* (309), 2.

Alexander, M. (1999). *Biodegradation and bioremediation* (2nd ed.). Academic Press.

Almeida, H., Amaral, M. H., & Lobão, P. (2011). Drugs obtained by biotechnology processing. *Brazilian Journal of Pharmaceutical Sciences, 47*(2), 199–207.

Anderson, J. (1996). Feeding a hungrier world. *Phytopathology News, 30*(6), 90–91.

Andrew P., "Traces of terror: the science; scientists create a live polio virus."(New York Times, July 12, 2002). https://www.nytimes.com/2002/07/12/us/traces-of-terror-the-science-scientists-create-a-live-polio-virus.html. Accessed 3 Feb 2021

Anzalone, A. V., Randolph, P. B., Davis, J. R., Sousa, A. A., Koblan, L. W., Levy, J. M., et al. (2019). Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature, 576*(7785), 149–157.

Baianu, I. C., Lozano, P. R., Prisecaru, V. I., & Lin, H. C. (2004). Applications of novel techniques to health foods, medical and agricultural biotechnology. *Other Quantitative Biology (q-bio.OT)*. https://arxiv.org/abs/q-bio/0406047

Barras, C. (2020a, May 7). Cyber-spinach turns sunlight into sugar. *Nature*. https://doi.org/10.1038/d41586-020-01396-4. PMID: 32393873

Barras. (2020b). *Researchers develop an artificial chloroplast*. phys.org

BBC News. (2020, November 30). *One of biology's biggest mysteries 'largely solved' by AI.*

Beck, A., Haerlin, B., & Richter, L. (2016). *Agriculture at a crossroads: Finding and recommendations for future farming*. The Foundation on Future Farming.

Bhatia, S., & Goli, D. (2018). *Introduction to pharmaceutical biotechnology, Volume 1: Basic techniques and concepts*. IOP Science.

Biotechnology Industry Organization. (2021). http://www.bio.org

British Medical Association. (1999, May 17). Press release. Action Network–Asia Pacific (www.poptel.org.uk/panap) and Union of Concerned Scientists (www.ucsusa.org).

Brodribb, T. J., Feild, T. S., & Jordan, G. J. (2007). Leaf maximum photosynthetic rate and venation are linked by hydraulics. *Plant Physiology, 144*, 1890–1898. https://doi.org/10.1104/pp.107.101352

Buhari, M., Sulaiman, B., Vyas, N. L., Badaru, S., & Harisu, U. (2016). Role of biotechnology in phytoremediation. *Journal of Bioremediation & Biodegradation, 7*(2), 330.

Campinoti, S., Gjinovci, A., Ragazzini, R., Zanieri, L., Ariza-McNaughton, L., Catucci, M., & Bonfanti, P. (2020). Reconstitution of a functional human thymus by postnatal stromal progenitor cells and natural whole-organ scaffolds. *Nature Communications, 11*(1), 1–16.

Chen, W., Brühlmann, F., Richins, R. D., & Mulchandani, A. (1999). Engineering of improved microbes and enzymes for bioremediation. *Current Opinion in Biotechnology, 10*(2), 137–141.

Chhonkar, P. K. (2002, December). Organic farming myth and reality. In *Proceedings of the FAI Seminar on Fertilizer and Agriculture Meeting the Challenges*, New Delhi, India.

Cockell, C. S., Santomartino, R., Finster, K., Waajen, A. C., Eades, L. J., Moeller, R., et al. (2020). Space station biomining experiment demonstrates rare earth element extraction in microgravity and Mars gravity. *Nature Communications, 11*(1), 1–11.

Colwell, B. (2020). Biotechnology timeline: Humans have manipulated genes since the 'dawn of civilization'. *Genetic Literacy Project*. https://geneticliteracyproject.org/2020/09/08/biotechnology-timeline-humans-manipulating-genes-since-dawn-civilization/

Cossins, D. (2013). Gene therapy coming of age? *The Scientist.*

Crane, L. (2020). Asteroid-munching microbes could mine materials from space rocks. *New Scientist.*

DeepMind. (2020, November 30). AI cracks 50-year-old problem of protein folding. *The Guardian 30 November 2020. Retrieved 30 November 2020.*

Dejonghe, W., Goris, J., El Fantroussi, S., Höfte, M., De Vos, P., Verstraete, W., & Top, E. M. (2000). Effect of dissemination of 2,4-dichlorophenoxyacetic acid (2,4-D) degradation plasmids on 2,4-D degradation and on bacterial community structure in two different soil horizons. *Applied and Environmental Microbiology, 66*(8), 3297–3304.

Devine, R., McDonald, H. P., Qin, Z., Arnold, C. J., Noble, K., Chandra, G., & Hutchings, M. I. (2021). Re-wiring the regulation of the formicamycin biosynthetic gene cluster to enable the development of promising antibacterial compounds. *Cell Chemical Biology, 28*(4), 515–523.e5.

Eckard, W., Steffen, M., Terrence, M. T., & Jeffery, K. T. (2009). Synthetic viruses: a new opportunity to understand and prevent viral disease. *Nature Biotechnology, 27*(12), 1163–1172.

Ereky, K. (1919). *Biotechnologie der Fleisch-, Fett-, und Milcherzeugung im landwirtschaftlichen Grossbetriebe: für naturwissenschaftlich gebildete Landwirte verfasst*. P. Parey.

EurekAlert. (2021, January 12). Gene-editing produces tenfold increase in superbug slaying antibiotics. *EurekAlert*!

Evens, R., & Kaitin, K. (2015). The evolution of biotechnology and its impact on health care. *Health Affairs, 34*(2), 210–219.

FAO. (1999, January 25–29) *Committee on Agriculture: Biotechnology*. COAG. http://www.fao.org/3/X1551e/X1551e.htm

FAO (Food and Agriculture Organisation of the United Nations). (1995). *Dimensions of need: An atlas of food and agriculture*. FAO, Rome, Italy. http://www.fao.org/3/u8480e/U8480E00.htm. Accessed 6 Feb 2021.

Fingas, J. (2019, April 16). CRISPR gene editing has been used on humans in the US. *Engadget*.

Flores, A. M., Hosseini-Nassab, N., Jarr, K. U., Ye, J., Zhu, X., Wirka, R., et al. (2020). Pro-efferocytic nanoparticles are specifically taken up by lesional macrophages and prevent atherosclerosis. *Nature Nanotechnology, 15*(2), 154–161.

Francis Crick Institute. (2020, December 11). *Scientists build whole functioning thymus from human cells*.

Freddy, Z. G., Diva, S. A., Claudemir, Z., Eduardo, H. H., João, S. Y., Andre, P. B., Luiz, A. R. A., Luz, G. C., Maddela, N. R., & Maria, F. G. (2020). Co-inoculation of cyanobacteria with Azospirillum brasilense on the development of maize hybrids. *Rhizosphere, 15*, 100224.

Gallagher, J (2019, October 21). Prime editing: DNA tool could correct 89% of genetic defects. *BBC News*.

Ghosh, S., Ghosh, P., Basu, K., Das, S. K., & Daefler, S. (2011). A discrete event based stochastic simulation platform for ‘in silico’ study of molecular-level cellular dynamics. *Journal of Biotechnology & Biomaterials, S6*, 001.

Gibson, D. G., Glass, J. I., Lartigue, C., Noskov, V. N., Chuang, R. Y., Algire, M. A., et al. (2010). Creation of a bacterial cell controlled by a chemically synthesized genome. *Science, 329*(5987), 52–56.

Godani, K. (2021). Environmental Biotechnology: Meaning, Applications and Other Details. Biology Discussion. https://www.biologydiscussion.com/biotechnology/environmental-biotechnology/environmental-biotechnology-meaning-applications-and-other-details/8528. Accessed 3 Feb 2021.

Horton, P. (2000). Prospects for crop improvement through the genetic manipulation of photosynthesis: Morphological and biochemical aspects of light capture. *Journal of Experimental Botany, 51*, 475–485.

Human Genome Project Information. (2021). http://www.ornl.gov/hgmis. Accessed 6 Feb 2021

IDRC-UNCTAD. (1998). *Technology for small scale economic activities to address the basic needs of low income populations* (pp. 248–258). FAO. https://www.idrc.ca/sites/default/files/openebooks/800-7/index

Ivanov, V., & Hung, Y. T. (2010). Applications of environmental biotechnology. In *Environmental biotechnology* (pp. 1–17). Humana Press.

Jazayeri, S. M., Villamar-Torres, R. O., Zambrano-Vega, C., Cruzatty, L. C. G., Oviedo-Bayas, B., Santos, M. A., Maddela, N. R., Ghafoor, A. M. H. A. S., & Viot, C. (2020). Transcription factors and molecular markers revealed asymmetric contributions between allotetraploid upland cotton Gossypium hirsutum and its two diploid ancestors. *Bragantia, 76*, 1.

Jennifer, A. D., & Emmanuelle, C. (2014). The new frontier of genome engineering with CRISPR-Cas9. *Science, 346*(6213), 1258096.

Johnson, B. (1999, March 26). Personal communication (from a presentation at BioVision, Lyon, France). http://www.bibalex.org/cssp/publications/BioVision2006.pdf

Kalender, S. S. (2019). Air pollution prevention technologies. In C. Hussain (Ed.), *Handbook of environmental materials management*. Springer. https://doi.org/10.1007/978-3-319-73645-7_109

Kamaludeen, S. P. B., Arunkumar, K. R., & Ramasamy, K. (2003). Bioremediation of chromium contaminated environments. *Indian Journal of Experimental Biology, 41*(9), 972–985.

Kaur, J., & Maddela, N. R. (2021). Microbial bioremediation: A cutting-edge technology for xenobiotic removal. In N. R. Maddela, L. C. García Cruzatty, & S. Chakraborty (Eds.), *Advances in the domain of environmental biotechnology. Environmental and microbial biotechnology*. Springer. https://doi.org/10.1007/978-981-15-8999-7_16

Konde, V. (2008). Biotechnology in India: Public–private partnerships. *Journal of Commercial Biotechnology, 14*(1), 43–55.

Maddela, N. R., & Meng, F. (2020). Discrepant roles of a quorum quenching bacterium (Rhodococcus sp. BH4) in growing dual-species biofilms. *Science of the Total Environment, 713*, 136402.

Maddela, N. R., Scalvenzi, L., Pérez, M., Montero, C., & Gooty, J. M. (2015a). Efficiency of indigenous filamentous fungi for biodegradation of petroleum hydrocarbons in medium and soil: Laboratory study from Ecuador. *Bulletin of Environmental Contamination and Toxicology, 95*(3), 385–394.

Maddela, N. R., Reyes, J. J. M., Viafara, D., & Gooty, J. M. (2015b). Biosorption of copper (II) by microorganisms isolated from crude oil contaminated soil. *Soil and Sediment Contamination: An International Journal, 24*(8), 898–908.

Maddela, N. R., Burgos, R., Kadiyala, V., Banganegiri, M., & Carrión, A. R. (2016). Removal of crude oil from soil by using novel microorganisms of Ecuador soils: Solid and slurry phase methods. *International Biodeterioration and Biodegradation, 108*, 85–90.

Maddela, N. R., Rodriguez, L., Sanaguano, S. H., Morán, R. E. B., Venkateswarlu, K., & Scalvenzi, L. (2017a). Biodegradation of diesel, crude oil and spent lubricating oil by soil isolates of Bacillus spp. *Bulletin of Environmental Contamination and Toxicology, 98*, 698–705.

Maddela, N. R., Scalvenzi, L., & Venkateswarlu, K. (2017b). Microbial degradation of total petroleum hydrocarbons in crude oil: A field-scale study at the low-land rainforest of Ecuador. *Environmental Technology, 38*, 2543–2550.

Maddela, N. R., Sheng, B., Shasha, Y., Zhou, Z., Villamar-Torres, R., & Fangang, M. (2019). Roles of quorum sensing in biological wastewater treatment: A critical review. *Chemosphere, 221*, 616–629.

Maddela, N. R., Kakarla, D., Garcia, L. C., Chakraborty, S., Venkateswarlu, K., & Megharaj, M. (2020). Cocoa-laden cadmium threatens human health and cacao economy: A critical view. *Science of the Total Environment, 720*, 137645.

Maddela, N. R., Chakraborty, S., & Prasad, R. (Eds.). (2021a). *Nanotechnology for the advances in medical microbiology*. Springer Nature Singapore Pte Ltd. https://doi.org/10.1007/978-981-15-9916-3; ISBN: 978-981-15-9916-3, (pp X, 467).

Maddela, N. R., Garcia, L. C., & Chakraborty, S. (Eds.). (2021b). *Advances in the domain of environmental biotechnology*. Springer Nature Singapore Pte Ltd. https://doi.org/10.1007/978-981-15-8999-7; ISBN: 978-981-15-8999-7, (pp XVIII, 717).

Meyer, R. S., & Purugganan, M. D. (2013). Evolution of crop species: Genetics of domestication and diversification. *Nature Reviews. Genetics, 14*, 840–852. https://doi.org/10.1038/nrg3605

Michigan State University. (2020, January 27). *Nanoparticle chomps away plaques that cause heart attacks.*

Miller, T. E., Beneyton, T., Schwander, T., Diehl, C., Girault, M., McLean, R., & Erb, T. J. (2020). Light-powered CO2 fixation in a chloroplast mimic with natural and synthetic parts. *Science, 368*(6491), 649–654.

Ming, M., Ren, Q., Pan, C., He, Y., Zhang, Y., Liu, S., & Qi, Y. (2020). CRISPR–Cas12b enables efficient plant genome engineering. *Nature Plants, 6*(3), 202–208.

Monya, B. (2011). The next step for the synthetic genome. *Nature, 473*(7347), 403–408.

Nathanson, J. A. (2019, December 24). Air pollution control. *Encyclopedia Britannica*. https://www.britannica.com/technology/air-pollution-control

National Academies of Sciences. (2010). The impact of genetically engineered crops on farm sustainability in the United States. In *The National Research Council Committee on the impact of biotechnology on farm-level economics and sustainability*. The National Academies Press. https://www.nap.edu/catalog/12804/the-impact-of-genetically-engineered-crops-on-farm-sustainability-in-the-united-states

National Human Genome Research Institute. (2015). https://www.nih.gov/about-nih/what-we-do/nih-almanac/national-human-genome-research-institute-nhgri

Nehal, M. M., Patel, P. M., & Patel, N. M. (2011). A review on regulatory aspects of biotechnology derived product. *International Journal of Research in Ayurveda and Pharmacy, 2*(5), 1495–1500.

Nelson, A. L., Dhimolea, E., & Reichert, J. M. (2010). Development trends for human monoclonal antibody therapeutics. *Nature Reviews. Drug Discovery, 9*(10), 767–774.

New Atlas. (2020a, January 28). *Nanoparticle helps eat away deadly arterial plaque.*

New Atlas. (2020b, May 11). New technique makes thousands of semi-synthetic photosynthesis cells. *New Atlas*.

NPR. (2019). *Scientists create new, more powerful technique to edit gene.s*

Okpokwasili, G. C. (2007, November). Biotechnology and clean environment. In *Proceedings of the 20th Annual Conference of the Biotechnology Society of Nigeria (BSN), 14th–17th.*

Padhy, I., et al. (2020). Role of biotechnology in pharmaceutical research: A comprehensive review. *Indo American Journal of Pharmaceutical Sciences, 7*(5), 472–486.

Pandey, S., Negi, Y. K., Marla, S. S., & Arora, S. (2011). Comparative *insilico* analysis of ascorbate peroxidase protein sequences from different plant species. *Journal of Bioengineering and Biomedical Sciences, 1*, 103.

Peng, J., Richards, D. E., Hartley, N. M., Murphy, G. P., Devos, K. M., Flintham, J. E., Beales, J., Fish, L. J., Worland, A. J., Pelica, F., et al. (1999). 'Green revolution' genes encode mutant gibberellin response modulators. *Nature, 400*, 256–261. https://doi.org/10.1038/22307

Pharmaceutical Research and Manufacturers of America. (2013). *Medicines in development: Biologics*. PhRMA.

Plotkin, S. A. (2001). Vaccines in the 21st century. *Infectious Disease Clinics of North America, 15*, 30727.

Poland, G. A., Murray, D., & Bonilla-Guerrero, R. (2002). New vaccine development. *British Medical Journal, 324*(7349), 1315–1319.

Prescott, L. M., Harley, J. P., & Klein, D. A. (2002). *Microbiology* (5th ed.). McGraw-Hill.

Ramakrishnan, B., Maddela, N. R., Venkateswarlu, K., & Megharaj, M. (2020). Organic farming: Does it contribute to contaminant-free produce and ensure food safety? *The Science of the Total Environment, 769*, 145079.

Ramchandran, L., & Shah, N. P. (2009). Effect of EPS on the proteolytic and ACE inhibitor activities and textural and rheological properties of low-fat yogurt during refrigerated storage. *Journal of Dairy Science, 92*, 895–906.

Rosenblum, D., Gutkin, A., Kedmi, R., Ramishetti, S., Veiga, N., Jacobi, A. M., et al. (2020). CRISPR-Cas9 genome editing using targeted lipid nanoparticles for cancer therapy. *Science Advances, 6*(47), eabc9450.

Rosenfeld, D., Senko, A. W., Moon, J., Yick, I., Varnavides, G., Gregureć, D., et al. (2020). Transgene-free remote magnetothermal regulation of adrenal hormones. *Science Advances, 6*(15), eaaz3734.

Rupali, D., & Dibyengi, S. (2004). Biotechnology in phytoremediation of metal-contaminated soils. *Proceedings of the Indian National Science Academy, B701*, 99–108.

Rural Advancement Foundation International. (2021). https://www.rafiusa.org/. Accessed 10 Feb 2021.

Sack, L., & Scoffoni, C. (2013). Leaf venation: Structure, function, development, evolution, ecology and applications in the past, present and future. *The New Phytologist, 198*, 983–1000. https://doi.org/10.1111/nph.12253

Saranya, K., Maddela, N. R., Mallavarapu, M., & Kadiyala, V. (2020). *Total petroleum hydrocarbons—Environmental fate, toxicity, and remediation*. Springer International Publishing AG. https://doi.org/10.1007/978-3-030-24035-6, ISBN 978-3-030-24035-6. (pp. VIII 262).

Shan, M., Khan, Y. A., & Nazar, H. (2018). Application of biotechnology in medicinal field. *Single Cell Biol, 7*, 174.

Shanker, D. (October 22, 2019). *These $50 Chicken Nuggets Were Grown in a Lab*. Bloomberg. Retrieved February 27, 2020

Spielmeyer, W., Ellis, M. H., & Chandler, P. M. (2002). Semidwarf (sd-1), "green revolution" rice, contains a defective gibberellin 20-oxidase gene. *Proceedings of the National Academy of Sciences of the United States of America, 99*, 9043–9048. https://doi.org/10.1073/pnas.132266399

Staff. (2019, April 17). CRISPR has been used to treat US cancer patients for the first time. *MIT Technology Review*.

Stockdale, E. A., Lampkin, N. H., Hovi, M., et al. (2001). Agronomic and environmental implications of organic farming systems. *Advances in Agronomy, 70*, 261–327.

Tel Aviv University. (2020, November 18). *TAU breakthrough may increase life expectancy in brain and ovarian cancers*.

Timmis, K. N., & Pieper, D. H. (1999). Bacteria designed for bioremediation. *Trends in Biotechnology, 17*(5), 201–204.

Tufts Center for the Study of Drug Development. (2010). *Personalized medicine is playing a growing role in development pipelines*. The Center. https://www.policymed.com/2010/12/tufts-study-shows-drug-development-for-personalize-medicine-on-the-rise.html

Verma, A. S., Agrahari, S., Rastogi, S., & Singh, A. (2011). Biotechnology in the realm of history. *Journal of Pharmacy & Bioallied Sciences, 3*(3), 321.

Vijayakuma, S., & Sasikala, M. (2012). Application of biotechnology: A current review. *International Journal of Pharmacy, 2*, 59–66.

Wahren, B., & Liu, M. A. (2014). DNA vaccines: Recent developments and the future. *Vaccine, 2* (4), 785–796.

Wessels, H. H., Méndez-Mancilla, A., Guo, X., Legut, M., Daniloski, Z., & Sanjana, N. E. (2020). Massively parallel Cas13 screens reveal principles for guide RNA design. *Nature Biotechnology, 38*(6), 722–727.

Wikipedia. (2018). *Biotechnology*. Wikimedia Foundation. https://en.wikipedia.org/wiki/Biotechnology

Wikipedia contributors. (2021). Timeline of biotechnology. *Wikipedia, The Free Encyclopedia*. https://en.wikipedia.org/w/index.php?title=Timeline_of_biotechnology&oldid=1009136337

Xu, Z., Wang, S., Zhao, C., Li, S., Liu, X., Wang, L., & Mann, S. (2020). Photosynthetic hydrogen production by droplet-based microbial micro-reactors under aerobic conditions. *Nature Communications, 11*(1), 1–10.