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REVIEW ARTICLE

PROSPECTS AND CHALLENGES OF PHARMACEUTICAL BIOTECHNOLOGY

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Abstract

Biotechnology is a broad area of biology, involving the use of living systems and organisms to develop products. Depending on the tools and applications, it often overlaps with related scientific fields. In the late 20th and early 21st centuries, biotechnology has expanded to include new and diverse sciences, such as genomics, recombinant gene techniques, applied immunology, and development of pharmaceutical therapies and diagnostic tests. Biotechnology has also led to the development of antibiotics. Biotechnology has applications in four major industrial areas, including health care (medical), crop production and agriculture, non-food (industrial) uses of crops and other products and environmental uses. In medicine, modern biotechnology has many applications in areas such as pharmaceutical drug discoveries and production, pharmacogenomics, and genetic testing. Pharmaceutical biotechnology is a relatively new and growing field in which the principles of biotechnology are applied to the development of drugs. A majority of therapeutic drugs in the current market are bio formulations, such as antibodies, nucleic acid products and vaccines. Such bio formulations are developed through several stages that include: understanding the principles underlying health and disease; the fundamental molecular mechanisms governing the function of related biomolecules; synthesis and purification of the molecules; determining the product shelf life, stability, toxicity and immunogenicity; drug delivery systems; patenting; and clinical trials. This review article describes the purpose of biotechnology in pharmaceutical industry, particularly pharmaceutical biotechnology along with its prospects and challenges.

Introduction:-

Biotechnology is "the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services".On a sector level, the largest market potential lies in the production of biopolymers and active pharmaceutical ingredients. Investors have not yet fully identified the area of industrial biotechnology as an attractive investment field but they could become a major capital source as they start to understand more the potential of industrial biotechnology (Gunter*et al.*, 2012).

Biotechnology derived medicines will have an increasing impact not only upon medical practice but also upon the working lives of many pharmaceutical scientists. Whilst such medicines maybe viewed as highly sophisticated to the

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clinician and scientist, the consumer will still rightly demand that they are both efficacious and safe. Impacting as it does upon all phases of drug development and facilitating quantitative relationship between administered dose and systemic drug concentration, pharmacokinetics has an important role to play in the development of all medicines. Bioanalysis is an essentialpreludetoanypharmacokineticinvestigation.Formanybiotechnologyproductsthe immune assayandbioassaymethodologiesemployedareoftenrelativelynonspecificandimpreciseandyieldassaydependentpharmacokineticparameters (Toon, 1996).

Pharmaceutical biotechnology makes animportant contribution, as well as serves as a vast resource of protein therapeutics. By sharing knowledge and developing expertiseamong scientists, pharmacists and other healthcare professionals in the manufacturing ofbiotech products, wehope to help facilitate a widespread, rational, and safe application of pharmaceutical biotechnology (Crommelin*et al.*, 2008).There are many definitions of biotechnology. One of the broadest is the one given at United Nations Conference on biological diversity (also called Earth Summit) held in Rio de Janeiro, Brazil in 1992. Thatconference defined biotechnology as "any technological application that uses biological systems, living organisms, or derivatives thereof to make or modify products or processes for specific use".The use of the microorganism to make the antibiotic penicillin or dairy product, yogurt; the use of microorganism to produce amino acid or enzymes are also the examples of biotechnology (Okafor, 2007).

Pharmaceutical biotechnology is a technology as all technologies needed to produce biopharmaceuticals-other than (non-genetically modified) animal- or human blood-derived medicines. Attention is paid both to these technologies and the products thereof. Biotechnology makes use of findings from various research areas, such as molecular biology, biochemistry, cell biology, genetics, bioinformatics, microbiology, bioprocess engineering, separation technologies etc. Progress in these fields has been and will remain a major driver for the development of new biopharmaceuticals. Biopharmaceuticals form a fast-growing segment in the world of medicines opening new therapeutic options for patients with severe diseases. This success is also reflected by the fast growth in global sales (Ronald, 2019).

Pharmaceutical Biotechnology:

The techniques ofbiotechnology are a driving force of modern drug discovery as well. Due to this rapid growth in the importance of biopharmaceuticals and the techniques of biotechnologies to modern medicine and the life sciences, the field of pharmaceutical biotechnology has become an increasingly important component in the education of today's and tomorrow's pharmacists and pharmaceutical scientists.

Drug products such as epoetin-a(EpogenÒ, EprexÒ, ProcritÒ), abciximab (ReoProÒ), interferon's-a(IntronÒA,RoferonÒA), interferon's –b(AvonexÒ, RebifÒ, BetaseronÒ), anti-TNF-agents (EnbrelÒ,RemicadeÒ, HumiraÒ), andtrastuzumab (HerceptinÒ) are all examples of highly successful biotech drugs that have revolutionized the pharmacotherapy of previously unmet medical needs (Crommelin*et al.*,2008).

Biotech-finished drug products can be broadly classified as-

1. liquids, and
2. lyophilized powders for reconstitution prior to injection.

Relative to small molecules, the fill-finish manufacturing steps for biotech drug products do not involve complex multi-step processes, with lyophilization a notable exception. Due to the complex nature of the molecules, there are significant challenges in consistently manufacturing high-quality biotech drug products (Rathore, 2009).

There are various techniques for the production of biotech drugs, which are used in diseases prevention, diagnosisand/or treatment, are summarized below-

Therapeutic Proteins:

With the advent of genetic modification, however, human proteins have become available in huge quantities. The first "bioengineered" drug, a recombinant form of human insulin, was approved by the U.S. Food and Drug Administration (FDA) in 1982.In the near future, patients with diabetes may be able to inhale insulin, eliminating the need for injections. Recombinant DNA products include, human serum albumin, human insulin, interferon, growth hormone, erythropoietin, etc. (Kim, 2013). Human proteins produced by recombinant DNA have several advantages. They are indistinguishable from their authentic human counterparts but are safer as they are less likely to be contaminated by infectious agents. A case in point is human growth hormone (Figure1), which previously

could only be obtained from human cadavers and carried the risk of Creutzfeldt-Jakob disease (CJD) (Watson and Rogol, 2013).

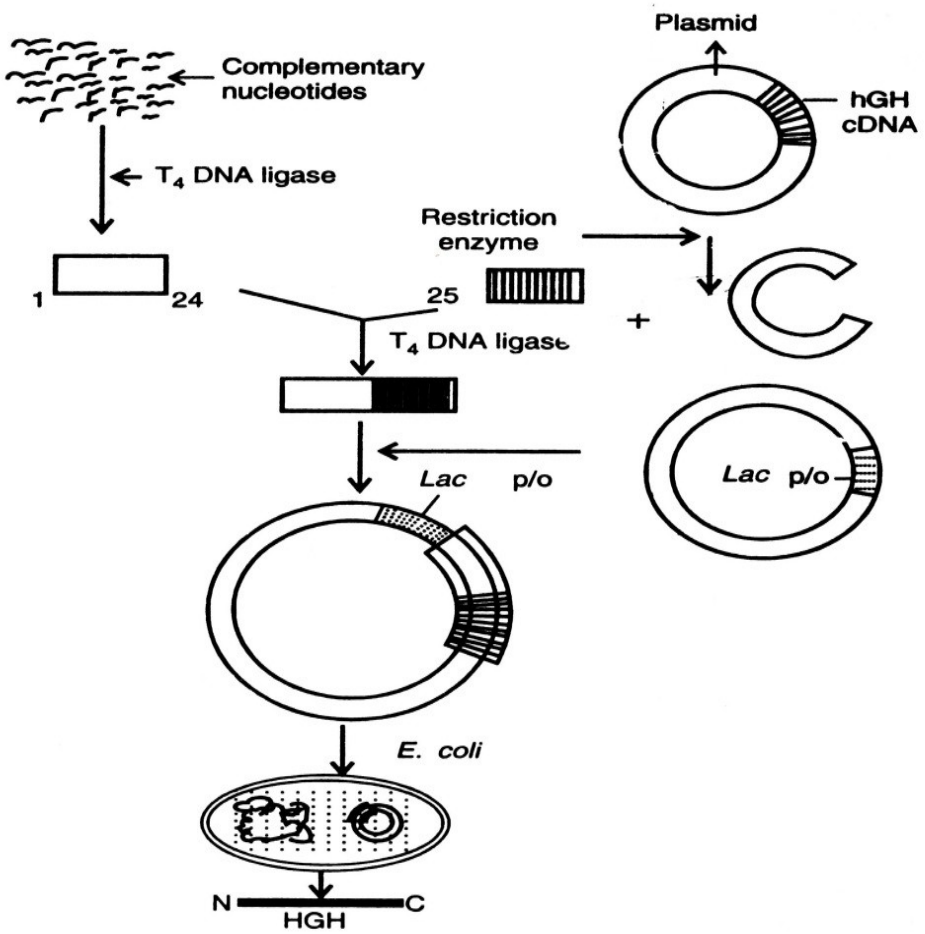

Figure1:- Human growth hormone obtain from therapeutic protein.

Biotech Vaccines:

Fragment of the microbial DNA is used as an alternative vaccine (Figure 2); this will produce the antigenic protein directly in the body and may induce the immune system to produce antibodies. DNA vaccines may be safer than conventional ones. They may also be easier to manufacture and may be stable at room temperature. These traits would greatly facilitate development and distribution of vaccines in the developing world (Anders *et al.*, 2010). The first recombinant vaccine, approved in 1986, was produced by slipping a gene fragment from the hepatitis B virus into yeast. The fragment was translated by the yeast's genetic machinery into an antigen, a protein found on the surface of the virus that stimulates the immune response. This avoided the need to extract the antigen from the serum of people infected with hepatitis B. Because of their efficiency, safety, and relatively low cost, recombinant vaccines may have particular relevance for combating long-standing diseases of developing countries, including leishmaniasis(a tropical infection causing fever and lesions) and malaria (Kniskern and Miller,1992).

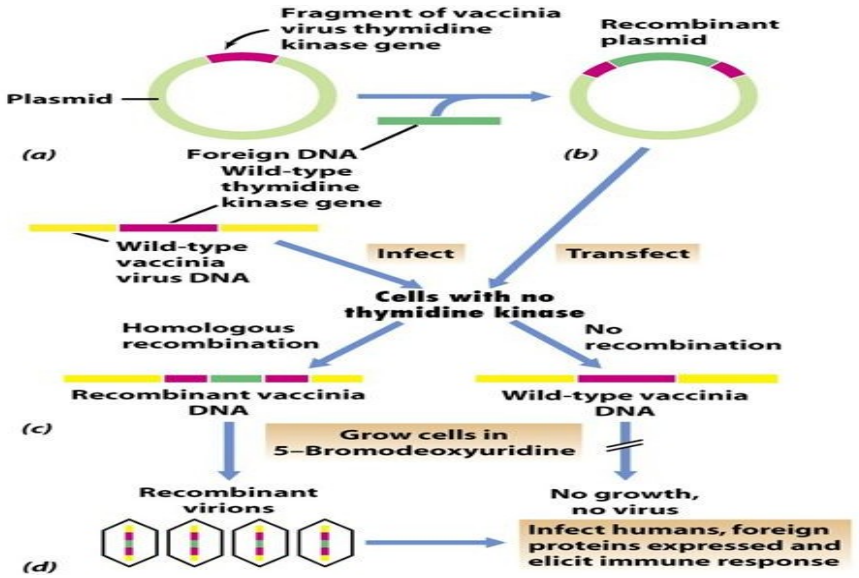

Figure 2:-Fragment of DNA is used as an alternative vaccine by biotech vaccine technology

Plants as Bioreactor:

Plants are being used as bioreactors for the biosynthesis of products with biotechnological interest. Transgenic plants can produce properly folded proteins at low costs and in large amount (Figure 3). Plants also offer greater safety because they do not harbor mammalian pathogens or microbial toxins. Moreover, a handful of candidates are already into human clinical trials, where initial results have shown efficacy and safety (Menkhaus*etal.*, 2004).

In addition to their use as bioreactors, plants can be used as potential delivery systems for oral vaccines. Edible biotherapeutics (edible vaccines), are very intriguing examples. The cost of plant-derived, orally administered hepatitis B vaccine is estimated to be one-sixth of the cost of current hepatitis B vaccines. Moreover, plant tissues provide protection and prevent degradation of the antigen when it passes through the gut (Hayden *et al.*, 2012).

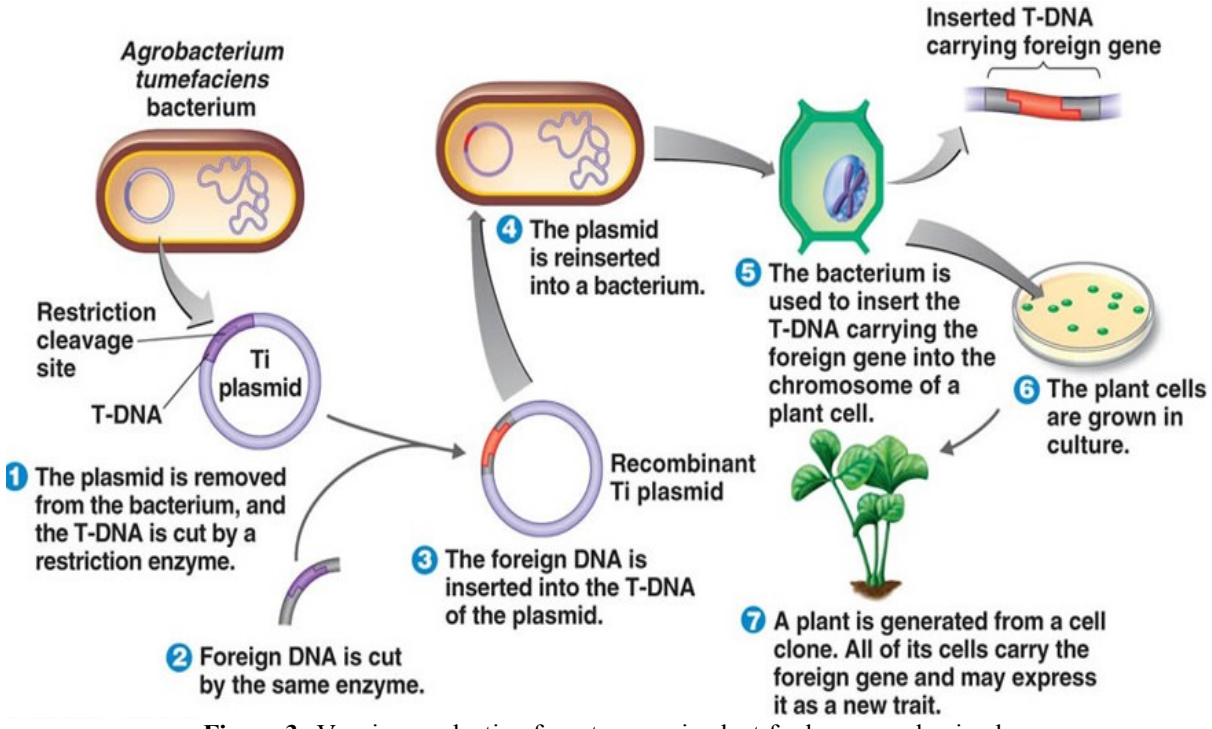

Figure 3:-Vaccine production from transgenic plant for human and animal

Transgenic Animals:

By the early 1980s, scientists were able to insert DNA from humans into mice and other animals.

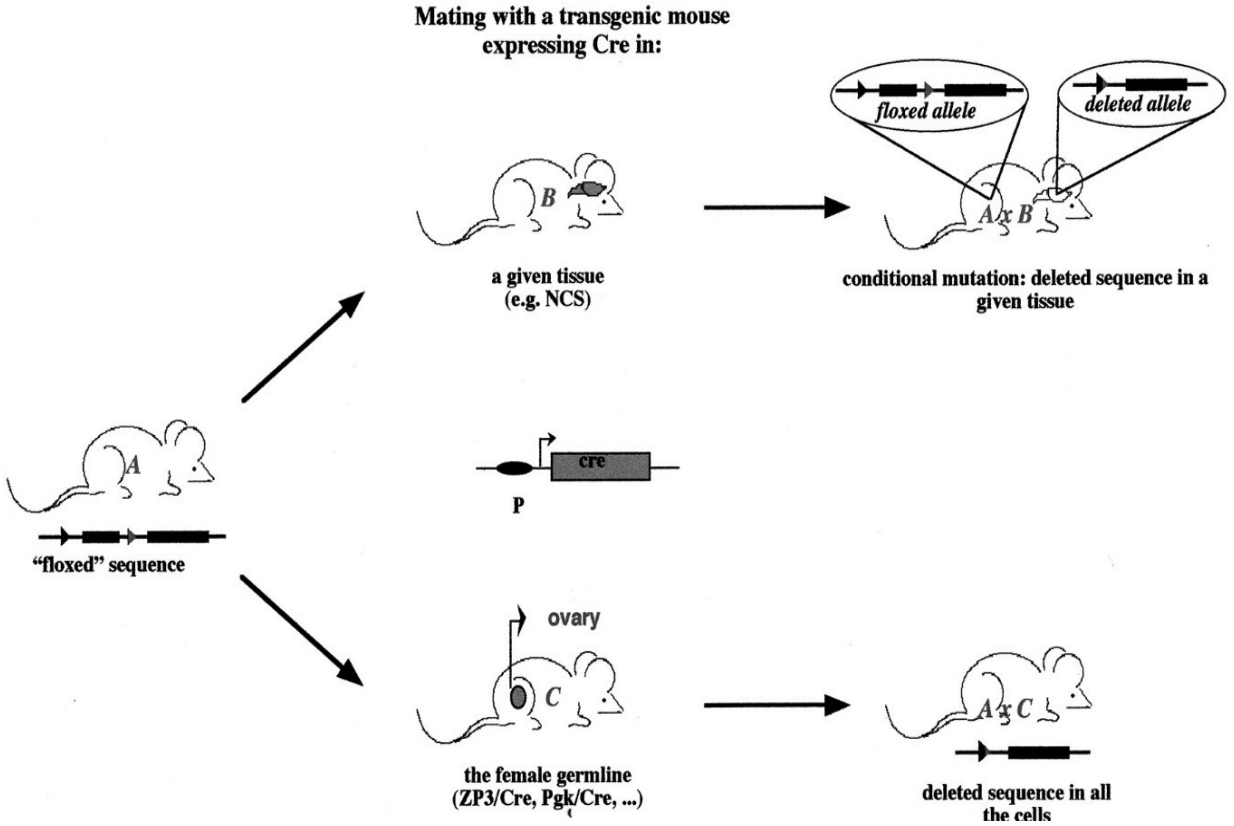

Figure 4:- Transgenic mice.

Because they now express human genes, "transgenic" animals (Figure 4) can be studied as models for the development of diabetes, atherosclerosis, and alzheimer's disease. They also can generate large quantities of potentially therapeutic human proteins. For example, a recombinant "clot-buster," expressed in the milk of transgenic goats, currently is being tested in patients (Roper and Hung, 2012).

Gene Therapy:

To address this issue, nano technological tools in human gene therapy have been tested and nanoparticle-based nonviral vectors in transportation of plasmid DNA (Figure 5)has been described. Therefore, successful introduction of less immunogenic nanosize gene carriers as a substitution of the disputed viral vectors seems beneficial in repairing or replacing impaired genes in human(Gan *etal.*, 2013). Whatever the vector, there are two methods by which gene therapy can be carried out:

1. In vivo gene therapy, in which the vector is injected into the body and has to find its way to the target tissue,
2. Ex vivo in which a sample of tissue is taken from the patient, treated with the vector and then replaced (Hallaj*etal.*, 2013).

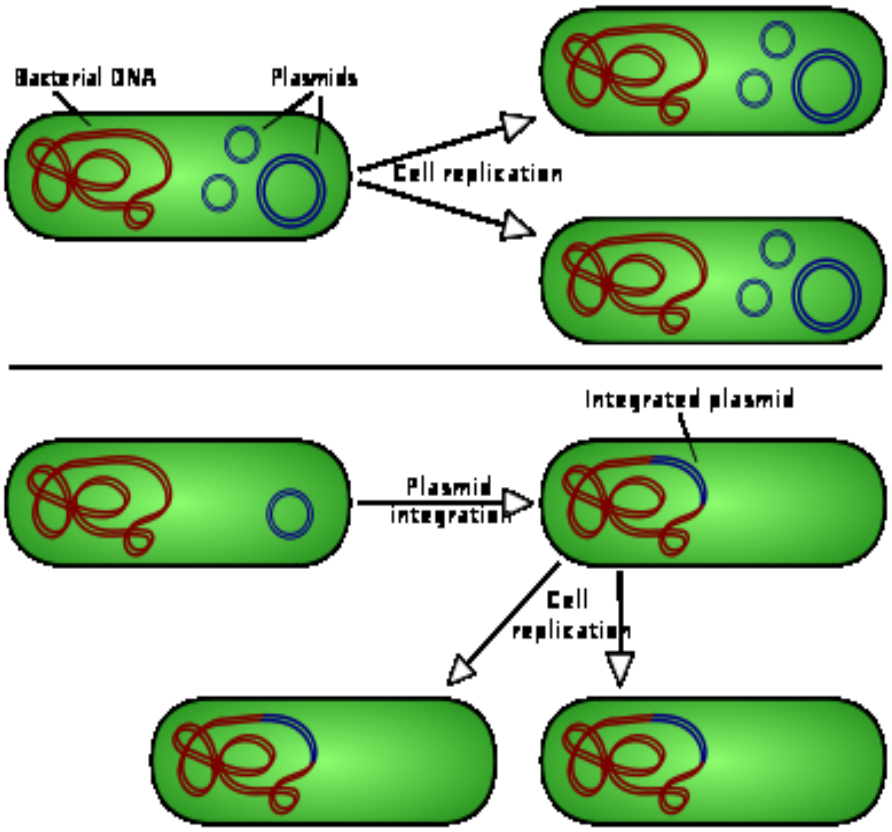

Figure 5:-Transportation of plasmid DNA.

Antisense Technology:

In 1978, Paul Zamecnik of Harvard University demonstrated that the DNA to protein mechanism could be interrupted by the use of small synthetic stretches of DNA called oligonucleotides. He used an oligonucleotide with a sequence complementary to an mRNA molecule needed by a particular virus to reproduce itself. The oligonucleotide bound to the mRNA and stopped it moving onto the ribosome for translation. Early work is in progress to develop antisense technology (Figure 6) as specific DNA drugs against cancer, viral infection and crohn's disease (Morcos, 2007).

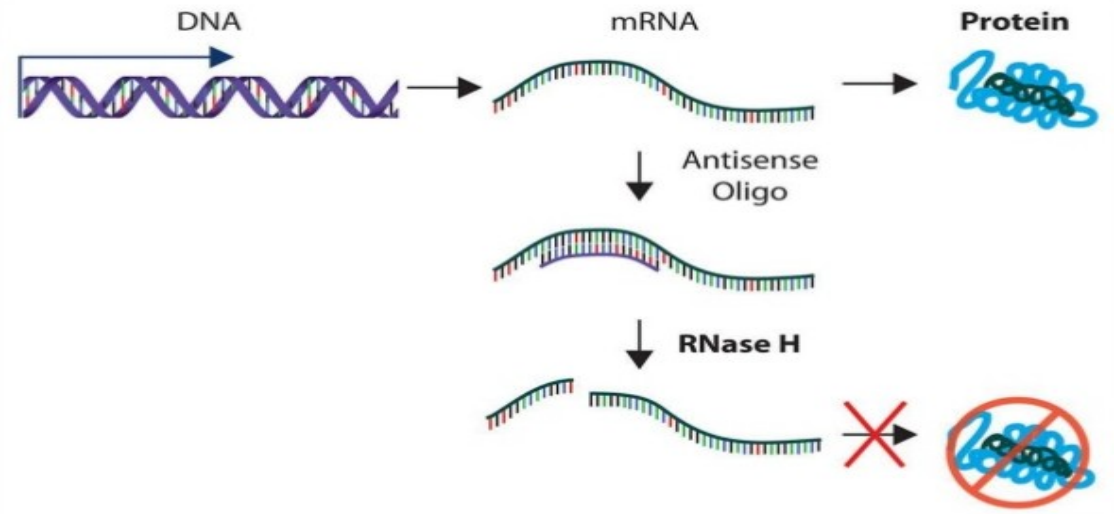

Figure 6:-Mechanism of antisense technology.

Polymerase Chain Reaction (PCR):

The polymerase chain reaction, a method for amplifying tiny bits of DNA (Figure 7) first described in the mid-1980s, a single segment of gene could be identified, copied, and tested within hours. It has been crucial to the development of blood tests that can quickly determine exposure to the human immunodeficiency virus (HIV), for example. Genetic testing currently is available for many rare disorders, such as hemophilia, which is caused by a mutation in a single gene. Little can be done to prevent or slow some of these diseases, however, and the underpinnings of more complex illnesses such as cancer, heart disease, and mental illness are as yet not well understood (Bartlett and Stirling, 2003).

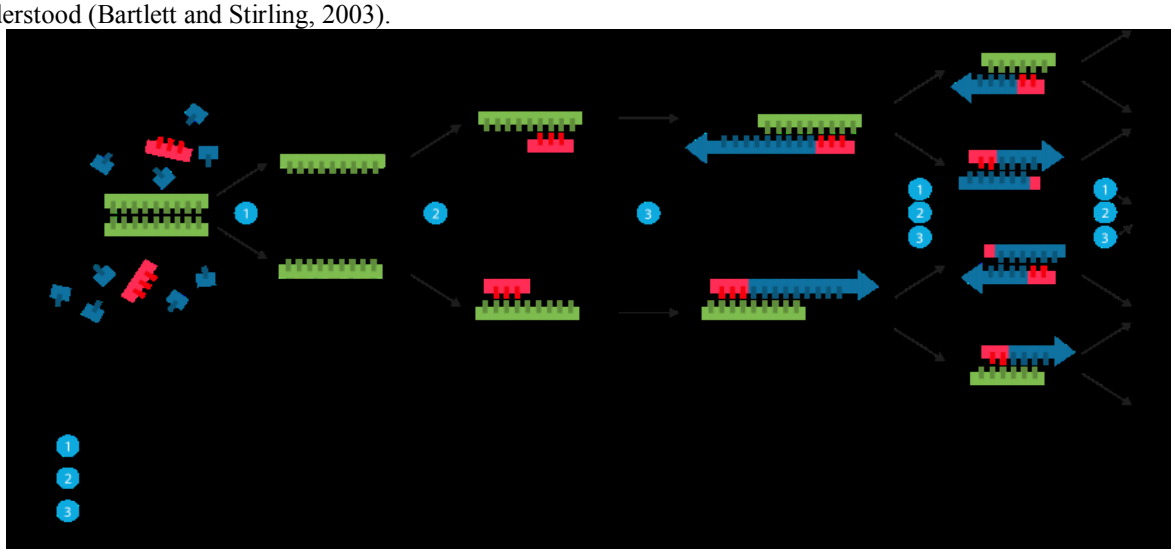

Figure 7:- Polymerase chain reaction, a method for amplifying tiny bits of DNA.

Development of Human Stem Cells:

Stem cells (Figure 8) are the early-stage cells in an organism that have been shown to give rise to different kinds of tissue.

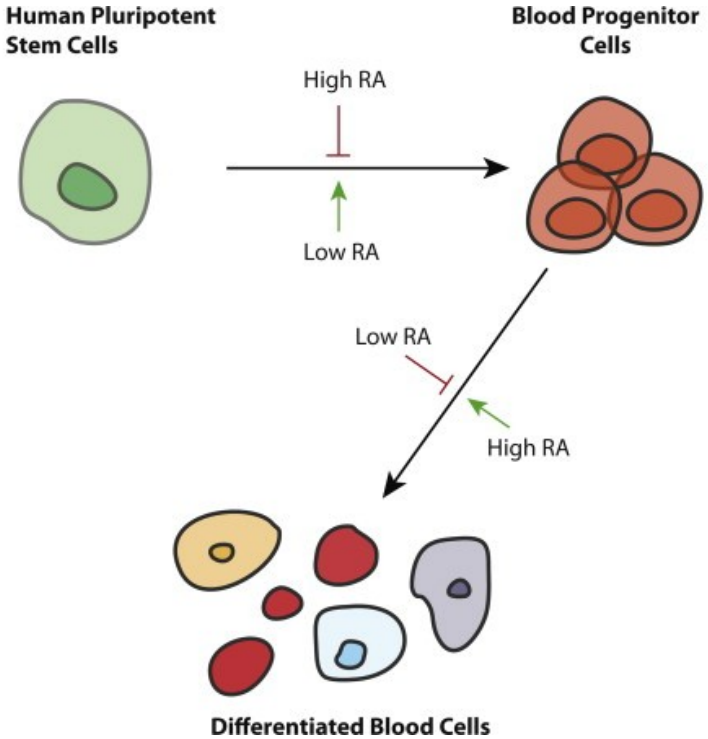

Figure 8:- Development of human stem cell.

They have successfully replaced or repaired damaged tissue in animal models, and they hold great promise for treating various human diseases such as alzheimer's and diabetes. Although the vast majority of people agree that cloning to produce humans (reproductive cloning) is unacceptable, therapeutic cloning, in which the cloning process is used only to harvest stem cells, is vigorously debated. Therapeutic cloning could supply stem cells that exactly match a patient, minimizing the serious risks associated with tissue rejection (William *et al.,* 2011).

Monoclonal Antibodies:

The development of monoclonal antibodies(mAbs) in 1975 led to another pharmaceutical revolution (Figure 9). By fusing antibody-producing cells with myeloma cells, scientists were able to generate antibodies that would, like "magic bullets," sharp in specific targets including unique markers, called antigens, on the surfaces of inflammatory cells. Soon after their invention in 1970's the monoclonal antibodies earned the reputation of 'magic bullet,' in particular against tumor specific antigens and infectious diseases. The molecular biological techniques are augmented both its accuracy and versatility. Antibodies and antibody fragments can be easily modified by molecular biotechnology (Golay and Introna, 2012).

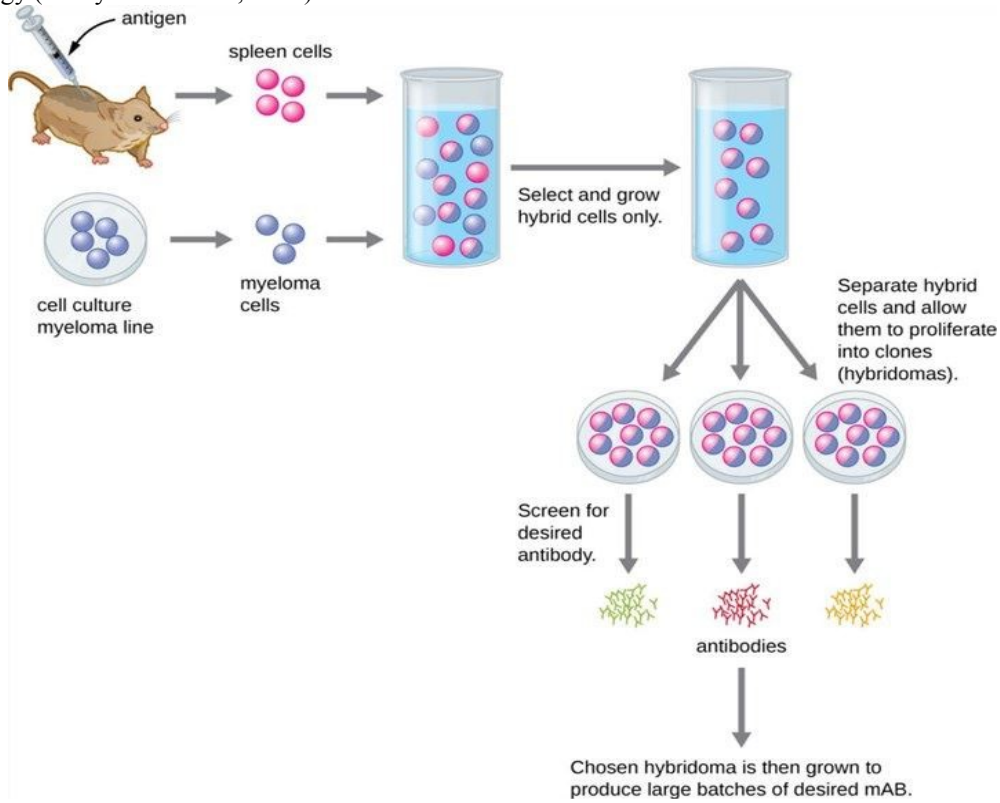

Figure 9:- Development of monoclonal antibodies.

Genomics and Sequencing of Human Genome:

The sequencing of the human genome (Figure 10), also has given scientists an incredibly rich "parts list" with which to better understand why and how disease happens. In the foreseeable future not only will every human gene will be identified, but the factors controlling their expression will also be known. This knowledge will unlock new targets for diagnosis, treatment and prevention of disease. It will change medicine forever, allowing treatments to become increasingly tailored to the specific needs of the individual (Osoegawa*etal.*, 2001).

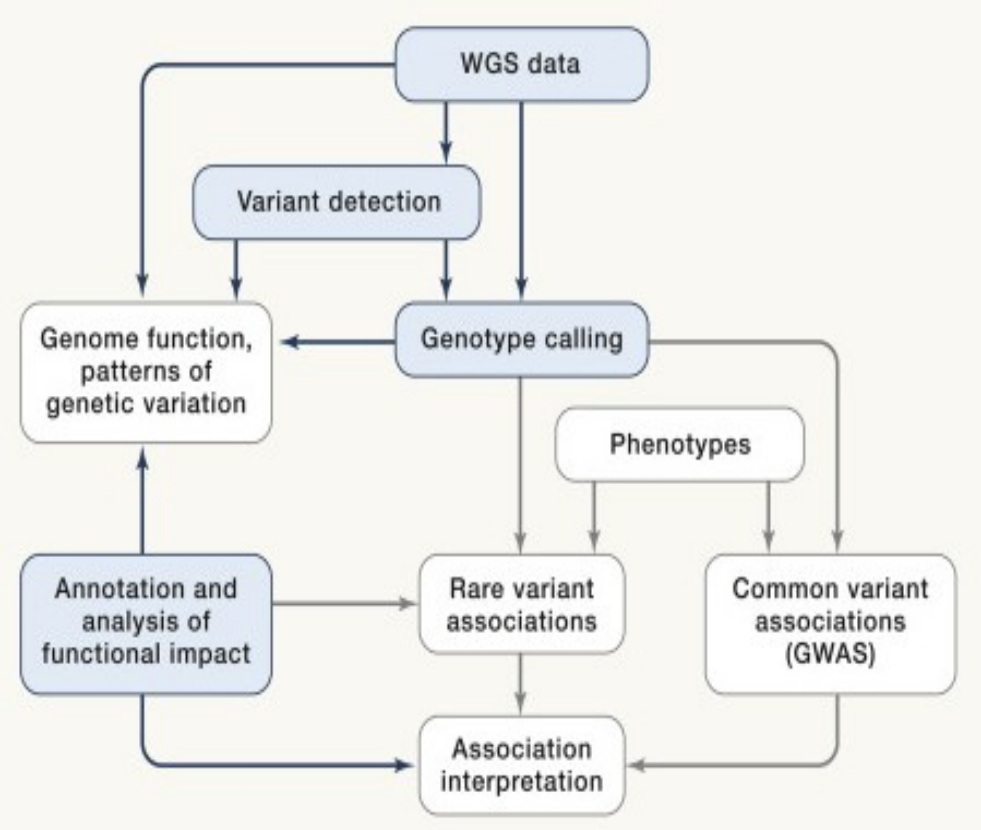

Figure 10:-Genomic analysis in sequencing of the human genome.

Nano-Biotechnology:

Nano-biotechnology or nanomedicine is another rapidly moving field. Nanosensors are being developed from particles that are about 50,000 times smaller than the diameter of human hair to detect protein and gene expression in individual cells in the body, thus allowing the assessment of the health of cells at early stages of disease. Scientists are developing a wide variety of nanoparticles and nanodevices, scarcely a millionth of an inch in diameter, to improve detection of cancer, boost immune responses, repair damaged tissue, and atherosclerosis. Nano-biotechnology can develop powerful diagnostic tools for the isolation and diagnosis of various diseases (Fakruddin*et al.*, 2012).

Drugs can be delivered as nanoparticles to targeted sites (Figure 11), including locations that cannot be easily reached by standard drugs (Guccione*etal.*, 2004). Many agents, which cannot be administered orally due to their poor bioavailability, can be delivered with the help of nanotechnology. Nano-formulations protect drugs from degradation or denaturation and prolong half-life. Nanotechnology can be applied to deliver antigens for vaccination (Diwan *etal.*, 2003).

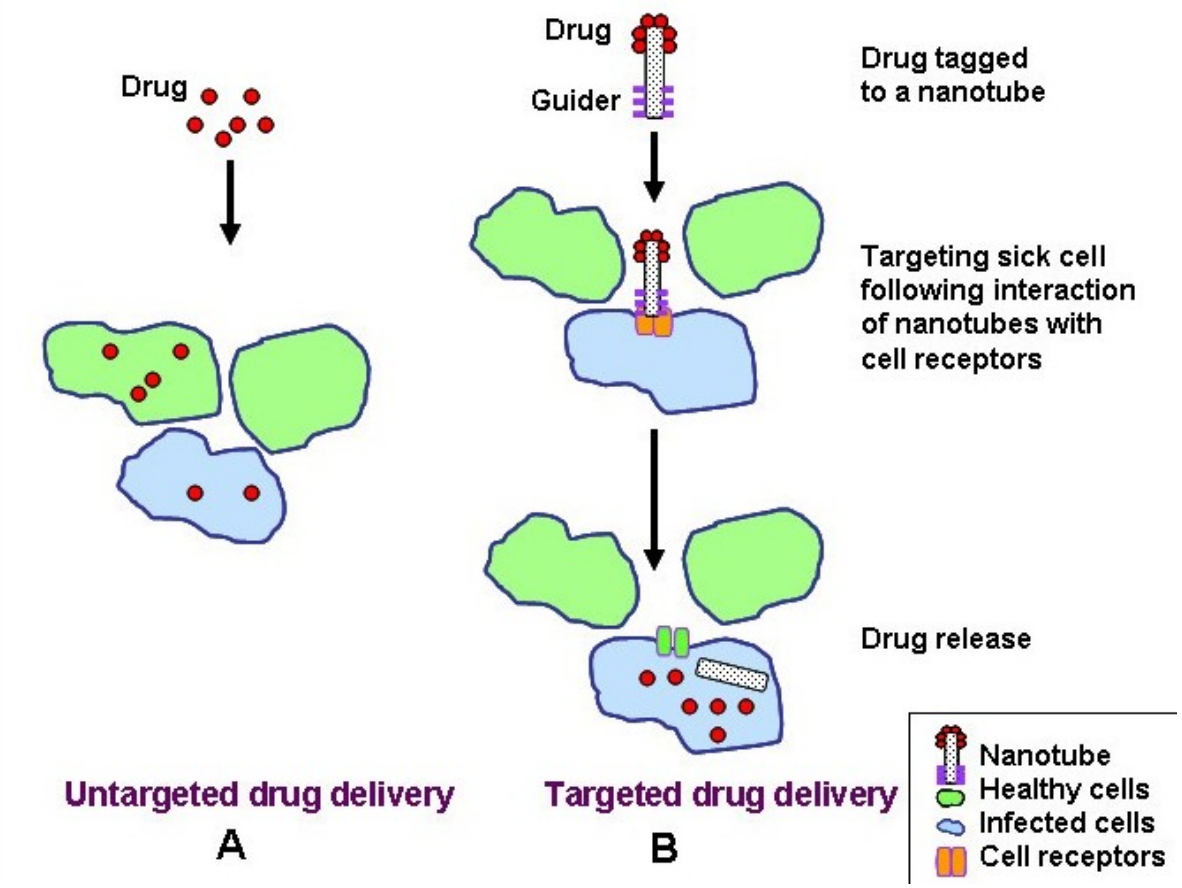

Figure 11:- Nanoparticle drug delivery to the targeted site.

Proteomics:

Proteomics is about analyzing the complete set of expressed proteins in a given cell (Wilkins *etal.*, 1996);the path was open to understand emergent properties that result from the complex interactions of metabolic and regulatory networks. The technical cornerstone of proteomics is the high throughput mass-spectrometry-basedidentification and quantification of proteins (Figure 12) (Han *etal.*, 2008). Proteomics is being used to unravel protein constellation of the cell, virulence factors, deranged host proteins, host-pathogen interactions, identification of microorganisms, characteristics of genes and genomes, and also for designing drugs against diseases including cancer, cardiovascular and infectious diseases (Clewley, 2000).

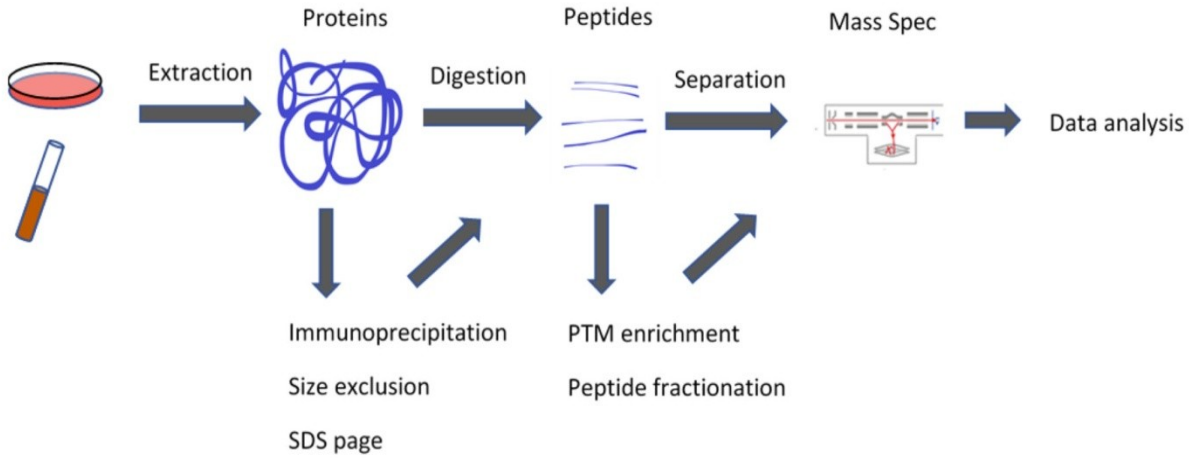

Figure 12:-Proteomics through mass spectroscopy.

Microarray Technology:
The automation of biochemical binding assays in small chips called microarrays enables scientists to screen thousands of chemical compounds for their effectiveness against disease-causing proteins in a very short time.

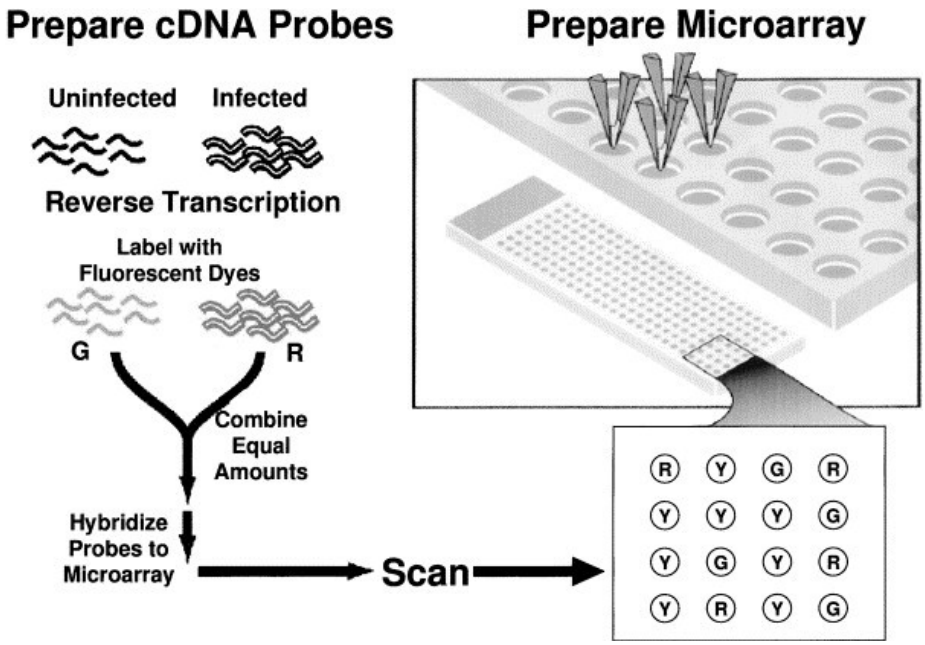

Figure 13:-cDNA for preparation of microarray technology.

This high-throughput screening, as it is called, would not have been possible without years of serious investment in basic biotechnology research. A microarray is a two-dimensional arrangement of specific biological probes deposited in an addressable fashion on a glass slide or other substrates. The size of the glass slide is usually one by three inches, with thousands of isolated biological probes ranging from 50 to 300µm in diameter arrayed on the surface. DNA, protein, cell and tissue microarrays also called biochip microarrays, have helped understanding gene and protein functions (Figure 13). Microarrays can also be used for disease diagnosis, prediction, prevention, and drug discovery (Choudhuri, 2004).

Computer Aided Drug Design:
Computer aided drug design is the use of computational techniques to find out the characteristics of an appropriate drug molecule (Figure 14).

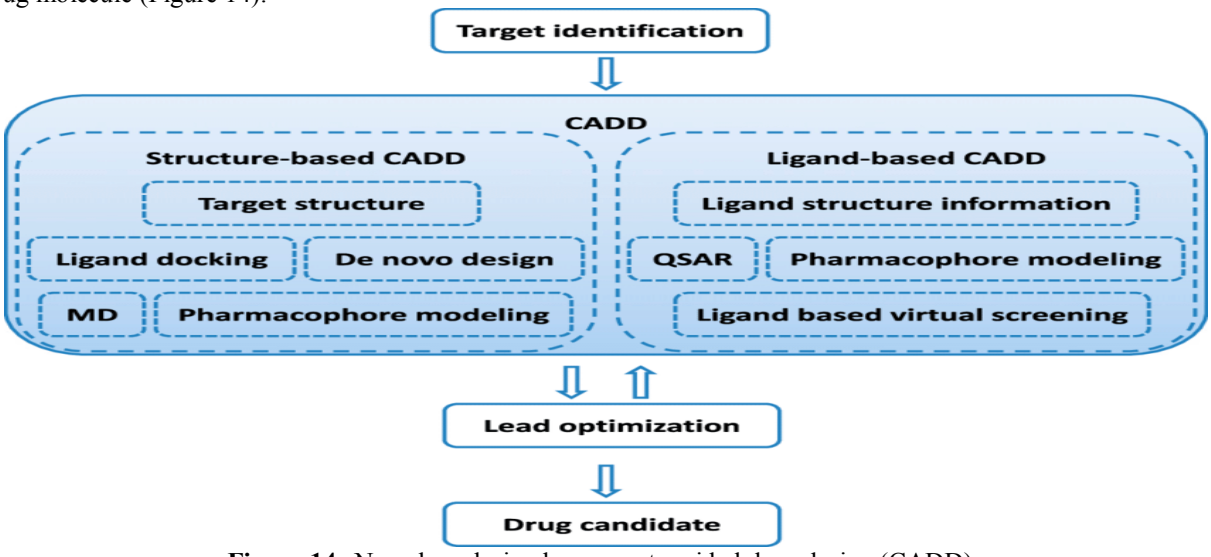

Figure 14:-New drug design by computer aided drug design (CADD).

Often a single molecule, for example, a protein from a pathogen creates the whole range of disease features. In such cases the strategy to combat the disease is to introduce a new molecule that binds and inactivates the causative molecule. Computer aided drug design or rational drug design has cut the cost and time of drug search by several orders of magnitude. Today it is possible to select candidate drug molecules from huge available databases and check whether it can bind to the active site of the troublesome molecule using computational docking procedures (Basak, 2012).

Bioinformatics:
With the help of bioinformatics powerful computer programs are capable of analyzing billions of bits of genomic sequence data then scientists are cracking the genetic codes to use the information for achieving various medical goals. For example, by analyzing the codes of bacteria and discovering "weak spots" vulnerable to attack by compounds identified via high-throughput screening. This kind of work led in 2000 to the approval of Zyvox, the first entirely new antibiotic to reach the market in 35 years (Leach *etal.*, 2011).

Industrial Biotechnology And Drug Development:
The primary objective of the biotechnology and pharmaceutical value chain relates to the discovery, development and distribution of therapeutics and drug delivery mechanisms. Significant biotechnology industry participants target non-drug-based activities, such as medical instruments and diagnostics (Nightingale and Mahdi, 2006).

The majority of the analysis will address publicly traded firms, due to significantly greater access to information compared to privately held firms. The biotechnology and pharmaceutical industries present a complex network of technology-focused firms. Analysts and industry participants define the pharmaceutical industry as firms involved in the discovery, development, manufacture, distribution and marketing of pharmaceutical therapeutics. The biotechnology industry is more difficult to delineate. In general, analysts and industry participants define the biotechnology industry as including firms that apply technologies to the life sciences(Gottingerand Umali, 2008).

Aims of Industrial Biotechnology:
The goal of biotechnological product development is to design and establish a formulation composition and robust manufacturing process to consistently and reliably meet all the quality standards intended for its therapeutic purpose. Traditionally, products are released onto the market only after successful 'end product testing', however, with the introduction of 'Quality by Design' for pharmaceuticals, quality standards need to be built into the product by design and cannot be met merely at the end-product-testing stage(Bhalani and Tirgar, 2015).

Economic and Technological Challenges in Industrial Biotechnology:
Except labor cost, the production cost of a bio product consists of upstream and downstreamparts:theup-streampartcontainssubstrates,includingsubstratepre-treatments,processenergyincludingsterilization agitation,aeration,coolingandheating.Althoughthedownstreampartrequires equipmentandenergytoseparatetinymicrobialcellsfromtheirgrowthmedium,extractandpurifyintracellularorextracellular products.Anyattempttoreduceenergyconsumptionisbeneficialforproductioncostreduction.Inaddition,mostmicrobialfermentationprocessesarepronetobecontaminated over a longperiodofculturetime,prohibitingthemoreefficientcontinuousprocessesfrombeingwidelyused.Arobustandcontamination resistant microorganismisthusimportanttoreduceproductioncost.Thisformsthebasisforthenext generation industrial biotechnology (NGIB)toreducebiotechnological productioncost (Dumorne*etal.*, 2017).

The Adoption Of Pharmaceutical Biotechnology In The Pharmaceutical Industry Of Bangladesh:
With the patent expiration of most first-generation biological internationally in 2004, and new biologics having a patent period of just twenty years, prospects for developing biotechnological products are brighter than ever. Taking advantage of the biotechnological movement Bangladesh keep up with other growing Southeast Asian pharmaceutical industries (such as those of India, Vietnam and Thailand) seek the clinical and economic benefits of biotechnological products (Azevedo *etal.*, 2014).

However, there is currently a large gap in documented literature of the country's biotechnological need, usage, regulatory policy and post marketing surveillance strategies which we aim to fill through this study. Although in its initial stages, the pharmaceutical industry of Bangladesh has steadily begun to employ biotechnology in the field of medicine. The industry aims to meet global pharma trends and reduce the local demand for biotechnology developed products. As a result, pharmaceutical companies are investing huge capital behind the development of anti-cancer,

anti-HIV/AIDS, vaccines, insulin and several other biotechnological drugs to meet local demand (Farhat *etal.*, 2017).

Opportunities of Biotechnology in Pharmaceutical Industry:
For the lasttwenty years, academic research has been the major, and often only, driving force behind the spectacular development of gene transfer technology for the therapy of rare genetic diseases. Investors and industry became eventuallyinterested in gene and cell therapy, due to the successof a series of pioneering clinical trials that proved efficacy and safety of current technology,and to favorableorphan drug legislationin both Europe and the United States. Developing this form of therapy is however complex and requires skills and knowledge, not necessarily available tothe industry, which is better placed to develop processes and products and put them on the market. Cooperation between academia and industry is an opportunityto de-risk innovative approaches and ensure a faster and more economical development of therapiesfor diseases with high unmet medical needs and low profit expectations (Mavilio, 2017).

To expand the market for biopharmaceutics, the opinions of professionals toward biotechnological products are highly valuable for the industry personnel, government policy-makers, and others for taking appropriate decision. Bangladesh is considered as a highly potential country for marketing biotechnological products. It is indispensable to know the present status and future potentiality of biotechnological products to develop a demand-driven market in Bangladesh (Abdullah *etal.*, 2018).

Application of Pharmaceutical Biotechnology:
There are various applications of pharmaceutical biotechnology; some of their examples are given below here-

Potential Applications of Plant Biotechnology against SARS-CoV-2:
An outbreak of potentially lethal coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, in December 2019, has created a pandemic (COVID-19) that has provoked governments acrossthe world to introduce emergency containment and control measures. The aim of these measures is to delay the spread of infection, thus reducing the acute pressure on hospital beds, front-line medical staff, and resources. Researchers working on the applications of plants can have a key role during this critical time by using their knowledge and infrastructure as a means to develop and produce new diagnostics and therapeutics. Indeed, plants may offer the only platform that can be used to manufacture such reagents at scale in a timeframe of weeks, compared with months or even years for cell-based systems (Figure 15). Here, we look at three areas where plants could make major contributions: diagnostic reagents to identify infected and recovered individuals, vaccines to prevent infection, and antivirals to treat symptoms (Sabalza*etal.*, 2013).

Plants have been used as a platform for the production of diagnostic reagents and pharmaceuticalproteins for more than 30 years, an approach often described as molecular farming(Schillberg*etal.*, 2019). Several molecular farming companies specialize in the development of plant-derived proteins as di-agnostic reagents, for example Agrenvec (Madrid, Spain), Diamante (Verona, Italy), ORF Genetics(Kópavogur, Iceland), and Ventria Bioscience/Invitria (Fort Collins, CO, USA). Furthermore, multipleproducts have been tested in clinical trials, with a small number reaching the market as medical de-vices and, more recently, pharmaceuticals.For example, a chimeric secretory IgA/G produced in transgenic tobacco plants was marketed as a medical device (CaroRX) for topical useto prevent dental caries whereas a recombinant form of the human enzyme glucocerbrosidase produced in plant cell suspension cultures is marketed as a pharmaceutical (Taliglucerase alfa,Elelyso) for patients with gaucher'sdisease (Ma *etal.*, 2003).

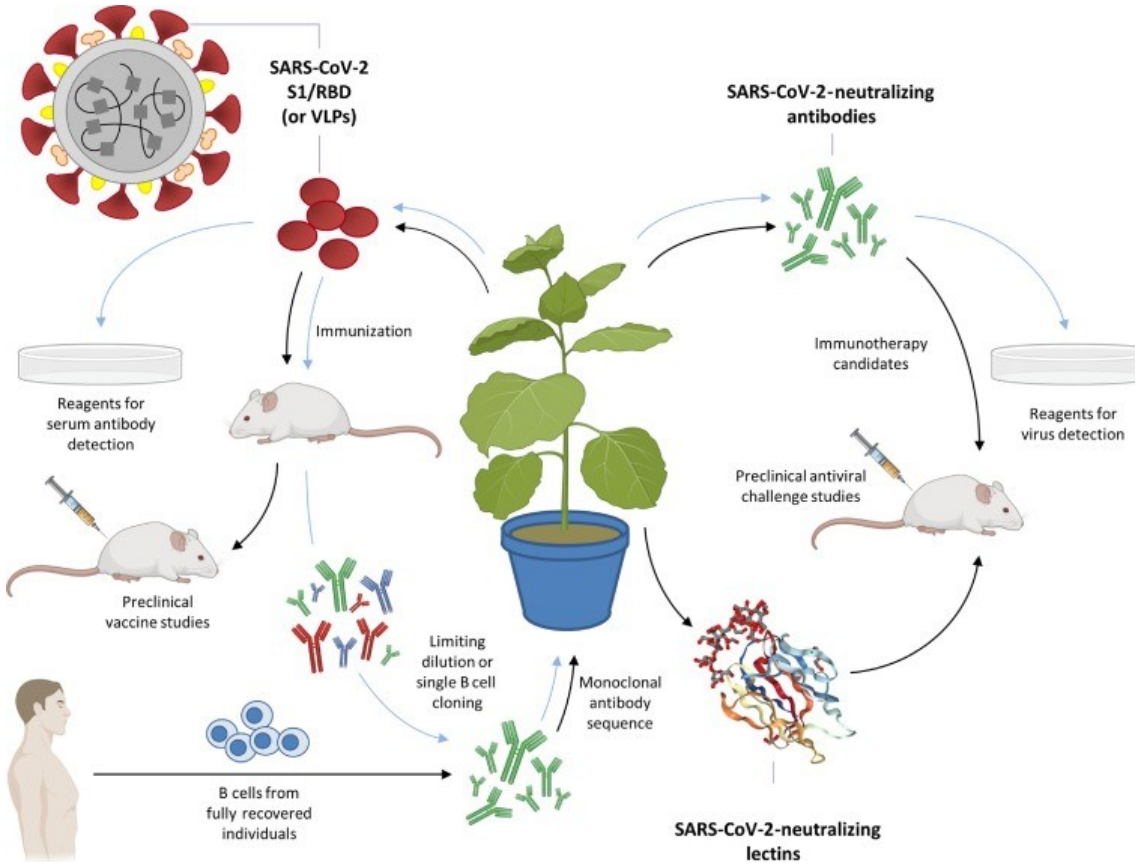

Figure 15:- The applications of plants for the production of diagnostic reagents, vaccine candidates, and antiviral proteins to address the COVID-19 pandemic.

The pioneers of molecular farming originally considered the main advantages of plants to be economy, scalability, and safety, because plants can be cultivated inexpensively on a large scale and do not support the growth of human pathogens (Fischer and Buyel, 2020). However, these advantages have generally not been persuasive enough to displace the major production platforms used in the biologics manufacturing industry. These established platforms utilize the bacterium *Escherichia coli* and a few other microbes, and various mammalian cell lines, mainly due to the robust regulatory framework that exists for these systems and the historic industry investment in corresponding production technologies. However, plants have carved a niche in a small number of cases because they can produce biologics with favorable glycan configurations(such as taliglucerase alfa) they allow production on a massive scale (as required for HIV microbicides) (Vamvaka*et al.*, 2014) and, most relevant to the current situation, when transient expression systems are used, they can be scaled up rapidly to meet sudden and unforeseen demand .This is ideal for the production of diagnostic reagents, vaccine candidates, and antiviral drugs in the face of a rapidly spreading pandemic disease (Whaley *et al.*, 2010).

Nanobody-Derived NanoBiotechnology Tool Kits for Diverse Biomedical and Biotechnology Applications:
Within the new vista of nanobiotechnological applications, different nanosized biotools, nanoscaled biomacromolecules, and engineered bacteriophages have been employed as promising approaches to meet the unmet needs of biomedicine and biotechnology development for human health (Zielonka*etal.*, 2015). Owing to the desired properties of nanobody, including nanoscaled size, stable and soluble behavior in aqueous solution, reversible refolding, humanizable sequences, and specific and high affinity for only one cognate target, as well as a sustainable source, nanobody has been an ideal research tool for the development of sophisticated nanobiotechnologies(Flajnik and Kasahara, 2010). Currently, the nanobody has been evolved into versatile research and application tool kits for diverse nanobiotechnology applications (Meyer *etal*., 2014).

A variety of nanobody-derived formats, including the nanobody itself, the radionuclide or fluorescent dye-labeled nanobodies, fluorescent protein or chromogenic enzyme fusion nanobodies, bivalent nanobodies, self-assembly

motif-mediated nanobody homo-or heteromultimers, nanobody-coated nanoparticles, and nanobody-displayed bacteriophages, have been successfully demonstrated as powerful nanobiotechnological tool kits for diverse biomedical applications, including targeting drug delivery and therapy, disease diagnosis,bioimaging, and agricultural and plant protection(Harmsen and De-Haard, 2007). These applications indicate a special advantage of these nanobody-derived technologies, already surpassing the "me-too" products of other equivalent binders, such as the full-length antibodies, scFvs, Fabs, targeting peptides, and DNA-based aptamers (Muyldermans*etal.*, 2009).

Versatile Applications of Nanobody-Derived Nanobiotechnologies:

There are various biomedical applications using the nanobody-derived nanobiotechnologies, which has been extensively covered recently elsewhere (Helma*etal.*, 2015). Here, we focus on a number of examples, wherein nanobodies provide special advantages over other equivalent binders (Desmyter*etal.*, 2001).These applications demonstrated a promising future of the use of nanobodies in versatile environments, including basic research, bioimaging, clinical diagnosis, therapeutics, and agricultural and plant protection. Compared to the conventional single-domain antibodies (sdAbs), these diverse applications indicate the versatile and novel properties of nanobodies as promising sdAbs (De Marco, 2011).

Biotechnology Applications of Plant Callus Cultures:

The field of bioengineering focuses on the application of biological principles to generate economically useful products. Bioengineering is needed for medical devices, diagnostic tools, biocompatiblematerials, recyclable bioenergy, agricultural engineering, and more (Figure 16).The aim of bioengineering is to rebuild or modify biologic systemsin order to generate marketable products in the fields of biotechnology, microbiology, biocatalysis, and others. Tissue engineering is notonly related to human (or animal) tissue replacement, but also toplant tissues. Furthermore, the pharmaceutical sciences includeengineering technologies to produce chemical drugs and recombinant proteins (i.e.,therapeutic antibodies).

Plants adapt to abiotic and biotic stresses using their astonishing plasticity to remodel themselvesand by the generation ofsecondary metabolites that are activated by elicitors and releasedas defense responses (Zhao *etal.*, 2005).

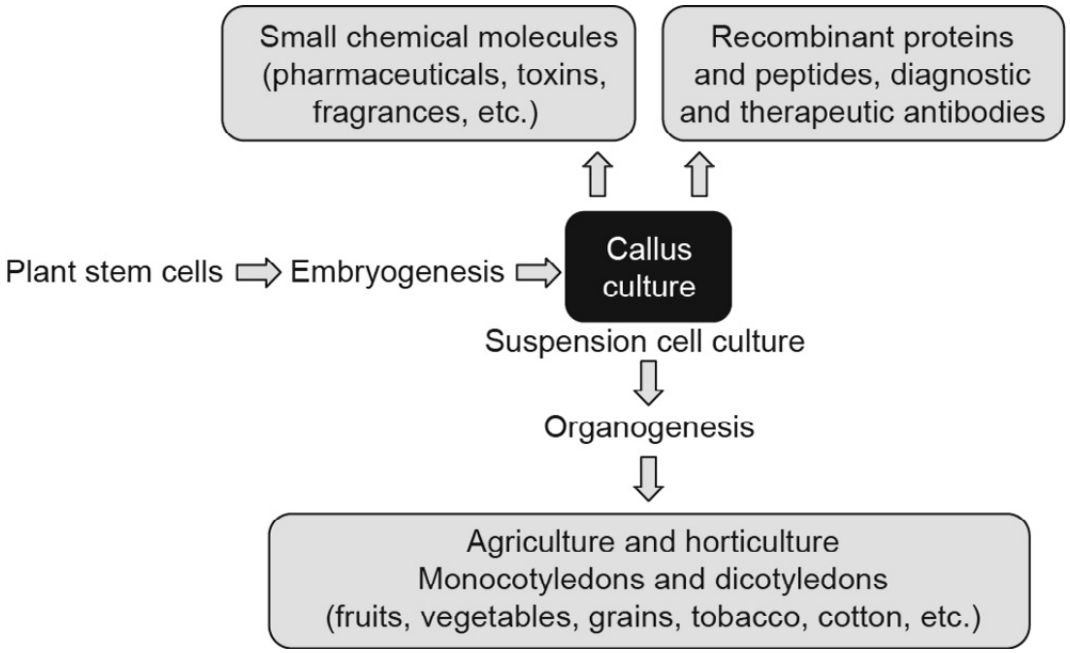

Figure 16:-A synopsis of biotechnological applications for callus cultures.

The generation of chemical compounds from secondary metabolism can be induced by external stress signals (e.g., pathogen elicitors, oxidative stress, wounding, etc.), which are internally mediated by jasmonate, salicylic acid, and their derivatives as signal transducers (Nascimento and Fett-Neto, 2010). These elicitor molecules stimulate defense or stress-induced responses in plants. These can be derived from the pathogens themselves (exogenous elicitors;e.g.,

chitin, chitosan, and glucans) or are released by plants by the action of the pathogen (endogenous elicitors; e.g., pectin, pecticacid, cellulose, and other polysaccharides) (Radman*et al.*, 2004).

In contrast to these biotic elicitors, there are also abiotic elicitors that act as physicalagents (i.e., cold, heat, UV light, and osmotic pressure) and chemical agents (i.e., ethylene, fungicides, antibiotics, salts, and heavymetals). Elicitors modulate gene expression in response to chemical and physiologic stimuli (Fritz *et al.*, 2010). They also induce enzyme synthesis, and thereby promote the formation of numerous secondary metabolites such as flavonoids, alkaloids, terpenoids, thionins, phenyl propanoid, and polypeptides.

Plant cell cultures represent an effective means for the bioreactor-based large-scale production of therapeutically relevant secondary metabolites (e.g., anticancer drugs) (Basu*et al.*, 2010).

The major advantages of cell culture systems, as compared with conventional whole-plant cultivation, include the following:

1. The plant compounds of choice can be generated independentlyof external factors (e.g., soil composition or climate),
2. Culturedcells are not threatened by the attacks of microorganisms orinsects,
3. Cells of any plant even rare or endangered ones can easily be maintained in order to produce their secondarymetabolites, and
4. Roboticdriven regulation of secondarymetabolite production decreases costs and improvesproductivity.

Engineering Mammalian Cells for Human Therapy:

Cellular therapeutics can be administered in various formats, including direct infusion of cell suspensions, engraftment of structured tissues, and implantation of cells encased in biomaterials. The adoptive transfer of autologous T cells that have been engineered to express synthetic, tumor-targeting chimeric antigen receptors (CARs) (Chang and Chen, 2017) became the first genetically modified cell therapy to be approved for human use by the US Food and Drug Administration (FDA) in August 2017.

In addition to immunotherapy, pluripotent stem cells with the ability to self-renew and differentiate into diverse cell types hold obvious potential as cellular therapeutics. The most mature form of stem-cell therapy is hematopoietic stem-cell transplantation (HSCT), a well-established treatment for hematological malignancies such as multiple myeloma and leukemia as well as non-cancerous conditions ranging from anemia to severe combined immunodeficiency (Gwiazda *etal.*, 2016).

Cellular engineering requires the ability to introduce or edit genetic material, and retroviral vectors have been the tool of choice due to their high gene-delivery efficiency and stable gene-expression capability. However, retroviral vectors also have a well-established preference for integration at transcription start sites (TSSs) (Wright *et al.*, 2006), leading to insertional mutagenesis and oncogene activations that have resulted in unanticipated clinical outcomes in multiple gene therapy trials (Halter and Zahn, 2018).

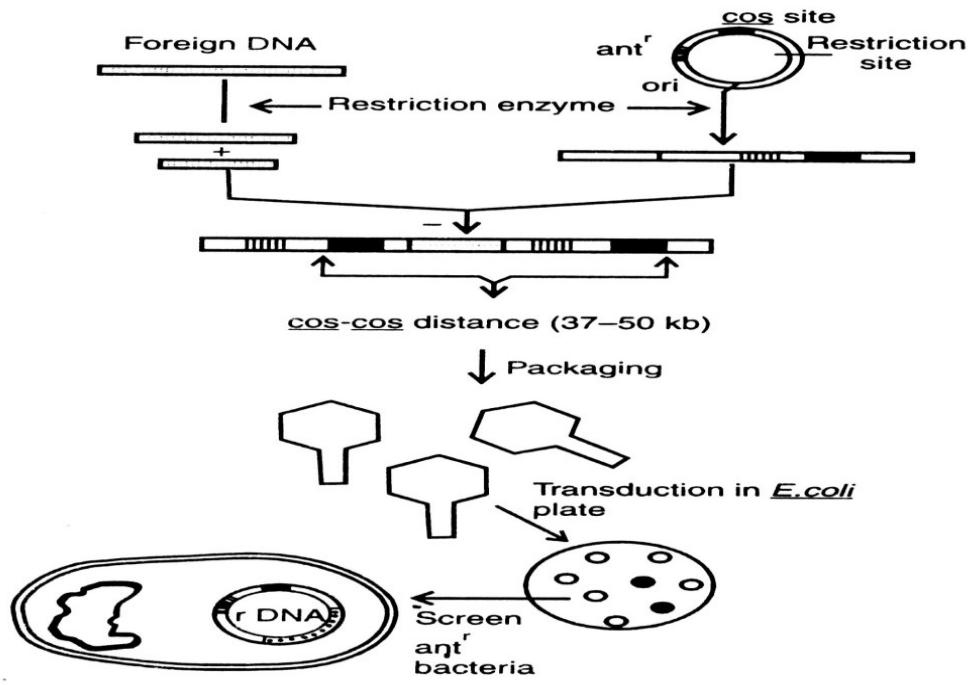

Figure 17:-Mammalian cell engineering.

To retain the high-delivery efficiency of retroviral vectors while reducing the probability of insertional mutagenesis, researchers have employed high-throughput protein engineering techniques to generate new vector systems that incorporate engineered zinc-finger DNA-binding domains (DBD) into the Gag-Pol regions of viral vectors, thus enabling the specification of target integration sites (Lim *et al.*, 2010).

Although the target-site selectivity is imperfect, the engineered vectors effectively overcome the preference for genomic integration at TSSs and shift integration patterns toward safer regions in the human genome (Figure 17). In addition to viral vectors, recent developments in genome-editing tools have generated exciting alternatives with improved safety profiles. Zinc fingers (ZFs) and transcription activator-like effectors (TALEs) have been coupled to nucleases to enable site-specific gene insertion, deletion, and disruption. In both systems, well-defined ZF or TALE subunits are modularly combined to target specific DNA sequences. To edit a specific genome site, pairs of ZF or TALE DBDs that flank the target site are generated, with a FokI endonuclease domain tethered to the C terminus of each DBD. Upon binding to the target DNA sequence, the FokI endonuclease domains dimerize and execute double-stranded DNA breaks, which enable sequence disruption or the introduction of exogenous DNA through non-homologous end joining or homology-directed repair (Mussolino and Cathomen, 2010).

In a landmark study for adoptive T-cell therapy, researchers treated two infants suffering from relapsed refractory CD19+ B-cell acute lymphoblastic leukemia with “off-the-shelf” T cells, whose endogenous T-cell receptor (TCR) α chain had been knocked out using TALE nucleases (TALENs) (Qasim*etal.*, 2017). These T cells were also virally integrated with an anti-CD19 CAR that recognizes CD19+ malignant B cells, and both patients achieved remission within 28 days of T-cell infusion. The removal of endogenous TCRα significantly reduced the risk of graft-versus-host disease (GVHD), thus enabling the infusion of donor-derived T cells into allogeneic hosts. However, both patients eventually presented with symptoms of skin GVHD attributed to incomplete TCR knockout (Porteus and Carroll, 2017). Therefore, truly “universal” cell products will require improved gene-editing efficiency coupled with cell-enrichment protocols that can precisely remove unedited cell populations.

Future Prospects of Pharmaceutical Biotechnology:

It is noteworthy that the birth of the biotechnology industry was initiated with the chemical synthesis of genes encoding human insulin A and B chains, cloning and expression in *E. coli*, followed by industrial scale up, clinical development, and commercialization (Goeddel *etal.*, 2013). The cost of chemical synthesis of genes was very expensive in the 1970s, but the need to develop a renewable supply of insulin independent of the unpredictable and

diminishing supply of bovine and porcine pancreas glands was compelling (Johnson, 1982). Since the early visionary projections on the development of the field of synthetic biology in the early 2000s (Voigt and Keasling,2005), the costs of DNA synthesis and sequencing have declined dramatically, and many new methods have been added to the toolbox for precise genome engineering of bacteria, yeast, and mammalian cells.

From the perspective of the biotechnology industry, synthetic biology has already been applied to engineer the efficient production of small organic molecules for the chemical industry, and is making important contributions to the engineering of mammalian cells for human therapy. Synthetic biology is also in the early stages of contributing to the discovery of novel secondary metabolites of bacteria and fungi directed at human medicine, animal health, and plant-crop protection by providing robust methods to activate otherwise cryptic pathways identified by genome mining. Furthermore, synthetic biology methods, including machine learning from multiple related NRPS and type I PKS BGCs, will undoubtedly accelerate the successful application of combinatorial biosynthesis of novel chemicalscaffolds by these complex mechanisms. The future applications of synthetic biology in the biotechnology industry to address issues of human medicine, robust food supplies, fine chemicals, and renewable energy will undoubtedly accelerate in the coming years. The biotechnology industry has over three decades of experience in serving the public good responsibly. As synthetic biology progresses, it will be important to continue serving the public good in a safe and secure manner (Ho and Chen, 2017).

Conclusion:-

Biotech dramatically has improved the success of product development in the pharmaceutical industry and has become a cornerstone in new and novel product development. FDA approval rates for biotech products exceed drugs. Biotech product sales now lead sales in the biopharma industry. Partnerships between pharmaceutical and biotechnology companies are yet another success factor in novel and new product development. It implies that biotechnological products have high potentials to be introduced in Bangladesh. It assumes that attitudes toward biotechnological products strongly influenced by age, education, length of service, information source and knowledge about biotechnology. Different types of biotechnological products are introduced or to be introduced for development of a prominent in global market as well as Bangladesh.

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Author Contributions:

Mahonaz Tabassum Samantaand Sadia Noor conducted the literature searches and reviews. Mahonaz Tabassum Samantadrafted the manuscript. Sadia Noor edited and revised the draft manuscript. All authors approved the final version for publication.

Conflicts Of Interest:

There is no conflict of interest regarding the publication of this manuscript.

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