INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH & DEVELOPMENT

ISSN: 2278 – 0211 (Online)

Application Of Microbes And Enzymes In The Advancement Of Medical Science- Mini Review

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Abstract:

Microbes have made a phenomenal contribution to the health and well-being of people throughout the world. Beneficial microbes can represent the future of medicine with the potential to treat a variety of diseases in humans and animals. Usually microbes can be used to treat a range of clinical conditions that have been linked to pathogens. In addition to producing many primary metabolites, such as amino acids, vitamins and nucleotides, they are capable of making secondary metabolites / enzymes, which constitute half of the pharmaceuticals on the market today. This review centers on these beneficial aspects of microbes and their enzymes.

Key words: *Microbes, Enzyme, Medical Science*

1.Microbial Applications

1.1.Probiotics Microbes

The term probiotic is used to describe microorganisms with antagonistic activity against pathogens in vivo. Gwendolyn & Paul[1] reported that microbes living in the body provide a constant source of irritants and antigens to stimulate the immune system. Probiotics can prevent and treat disease through a number of mechanisms including resistance to colonization, production of antimicrobial substances, inhibition of pathogen adhesion, degradation of toxins, stimulation of local and peripheral immunity, stimulation of brush border enzyme activity, stimulation of secretory-IgA and prevention of microbial translocation. Because of these varied actions, it is unlikely pathogens will develop resistance against probiotic agents. Colonization resistance is achieved by complex interactions between the different resident bacteria of the mucosal microflora which is the ability of the normal flora to protect against unwanted colonization of the gastrointestinal tract by pathogens[2]. Ducluzeau and Bensaada[3] showed that Saccharomyces boulardii has a direct antagonistic effect in vivo in mice against Candida albicans, C. krusei, and C. pseudotropicalis strains; however, it was ineffective against C.tropicalis. Results from experimental animals also showed that S. boulardii inhibit the action of cholera toxin on enterocytes[4]. L. acidophilus was reported to inhibit the adhesion of several enteric pathogens to human intestinal cells in culture[5]. Substances produced by the saccharomyces yeasts have also been shown to compete with red cells for adhesion sites on amoebae, Entamoeba histolytica [6]. Both Lactobacillus acidophilus and L. casei have demonstrated the ability to activate the immune system[7] while L. casei showed to enhance phagocytic activity[8]. Oral administration of S. boulardii activates several cellular and humoral markers of immunity in peripheral blood[9]. Malin et al[10] reported that human L. casei strain GG, administered orally to subjects with Crohn's disease, has also been shown to promote the s-IgA response. Researchers reported that mothers who took milk with a probiotic supplement during and after pregnancy were able to cut the incidence of eczema in their children by almost half [11].

1.2.Microbes In Multiple Medical Applications

Recently researchers have genetically modified a common gut bacterium to respond to a sugar and produce a treatment for Inflammatory Bowel Disease (IBD). They modified Bacteroides ovatus to release human growth factors (called cytokines) that repair the

epithelial cells found in the lining of the gut, reducing the inflammation caused by IBD. There are one or two cytokine therapies in clinical trials, but the problem is that most of the current agents are administered directly into the blood stream. Very little of the drug gets to the damaged tissues in the gut; most stays in the blood where they can have very different effects. These drugs are also very delicate and need to be delivered to the target directly. The technique is currently in preclinical trials [12]. Micro- or nanorobotics, an emerging field involving the miniaturization of devices to micro- or nanometer sizes, is expected to revolutionize the field of medicine. Now, the scientists have invented the smallest created micro-robots, the size of Escherichia coli and similar bacteria, known as artificial bacterial flagella (ABFs) for various medical applications. The scientists suggest the use of ABFs in biomedical applications, such as removal of arterial plaque deposits, delivery of medicines to deep-seated predetermined body targets, and modification of cellular structure that are otherwise too tiny for direct alteration. It was noted by scientists (Martel et al. 2008) that microdevices and nanorobotics can be propelled by flagellated bacteria, specifically MC-1 Magnetotactic Bacteria (MTB), in a medical interventional procedure controlled in situ, to reach remote locations in the body. Through experimental results, researchers demonstrated the potential of MTB-tagged robots in delivering drugs to tumors, even the deep-seated ones.

2.Microbial Enzyme Applications

2.1.Enzymes As Medicine

Enzymes as drugs have two important features that distinguish them from all other types of drugs. First, enzymes often bind and act on their targets with great affinity and specificity. Second, enzymes are catalytic and convert multiple target molecules to the desired products. These two features make enzymes specific and potent drugs that can accomplish therapeutic biochemistry in the body that small molecules cannot. These characteristics have resulted in the development of many enzyme drugs for a wide range of disorders [13]. Development of medical applications for enzymes have been at lease as extensive as those for industrial applications, reflecting the magnitude of the potential rewards: for example, pancreatic enzymes have been in use since the nineteenth century for the treatment of digestive disorders [14]. Microbial enzyme biotechnology has progressed rapidly in the last decade. Microbial enzymes play a major role in the diagnosis, curing, biochemical investigation and monitoring of many dreaded diseases.

Microorganisms represent an excellent source of many therapeutic enzymes owing to their broad biochemical diversity and their susceptibility to genetic manipulation. Enzymes derived from Aspergillus and other microbial species may prove valuable in a broad range of conditions associated with digestive weaknesses such as pancreatic enzyme insufficiency, maldigestion, malabsorption, steatorrhea, lactose intolerance, celiac disease and food sensitivities. Because of their inherent uniqueness, i.e. their ability to breakdown or hydrolyze physiologically and/or pathologically important substrates over a wide pH range, non-animal enzymes may be particularly well-suited for human use. Although these enzymes are microbially derived, modern filtration technology removes all microbial residue and allows for a clean and pure product [15]. Between 0.5% and 1% of individuals in the United States and Europe are believed to have celiac disease, and their inability to digest gluten protein in wheat and other grains may lead to serious gastrointestinal tract complications Currently, the only treatment for patients with celiac disease is complete exclusion of foods that contain gluten. Doing so is difficult, however, because gluten is ubiquitous and may not be listed as an ingredient in many food products. But recent research suggests that oral formulations of enzymes that are able to break down gluten may be a useful adjunct treatment to dietary restriction or may allow a somewhat less restrictive diet for patients with the disease [16-17]. Scientists had identified bacterial prolyl endopeptidases (PEPs) as enzymes that might be useful in reducing the toxic effects of gluten because they cleave proline structures and can function in the duodenum might be a useful therapy for celiac disease[18]. Leupeptin is produced by more than 17 species of actinomycetes and Streptomyces roseochromogenes[19-20] can be used as powerful tools for inactivating target proteases (casual agent for emphysema,arthritis, pancreatitis, cancer and AIDS). Izumida, et al.[21] reported that the fermentation broth of a marine bacterial strain, Agrobacterium aurantiacum can act as a potent inhibitor of hydroxyakalone by decreasing the uric acid levels, which can be used in the treatment of gout. Borel[22] reported that cyclosporin, a product from the mold Tolypocladium nivenum can act as a narrow-spectrum antifungal peptide, capable of suppressing the immune response and this immunosuppressive activity led to use in heart, liver and kidney transplants and to the overwhelming success of the organ transplant field, as well. Recently, Prehydrolyzed milk, which has been treated with an enzyme derived from the Kluyveromyces lactis yeast, is used with great success by individuals with lactase insufficiency[23]. In addition, lactose maldigestion has been shown to improve in preschool children by the direct addition of lactase derived

from the Aspergillus oryzae to milk at mealtime[24]. Animal studies suggest that an acid-stable lipase derived from Aspergillus may be more effective than conventional pancreatic replacement in helping to improve fat malabsorption in subjects with pancreatic exocrine deficiency. Enzymes administered orally at meals may improve the digestion of dietary protein and, as a result, decrease the quantity of antigenic macromolecules leaking into circulation. Additionally, protease enzymes from Aspergillus oryzae appear to be absorbed intact following oral administration. It has been proposed that once in the bloodstream they may hydrolyze any previously absorbed antigenic dietary proteins they encounter, potentially decreasing an allergic response[25].

2.2.Enzyme Inhibitor

Enzyme inhibitors have been useful tools, not only for the study of enzyme structures and mechanisms but also for other potential uses in medicine and agriculture. Several enzyme inhibitors with various industrial uses have been isolated from microbes. Microbial α-amylase inhibitors can be obtained from culture filtrates of Streptomyces corchorushii[26] and oligosaccharide compounds from Streptomyces calvus TM-521.75[27] which are useful for the control of carbohydrate dependent diseases, such as diabetes, obesity, hyperlipemia, for the treatment weight loss and of rumen acidosis[28]. Weibel et al[29] reported that lipstatin is another pancreatic lipase inhibitor produced by Streptomyces toxytricini which can be used to combat obesity and diabetes. Acarbose is a pseudotetrasaccharide made by Actinoplanes sp. SE50 inhibits intestinal α-glucosidase and sucrase resulting in a decrease in starch breakdown in the intestine, which is useful in combating diabetes in humans[30]. The development of recombinant DNA (rDNA) techniques in recent decades has made clinical enzymology more prominent and more important than ever before. The ability to create enzymes in cell culture has obviated the need to purify them from huge quantities of animal tissues. As a result, it is possible to provide replacement therapy for genetic diseases caused by the inability of the patient's body to make an essential enzyme. The best known example of rDNA replacement therapy is Cerezyme (imiglucerase), an analog of human β-glucocerebrosidase, used for long term treatment of Type I Gaucher disease (Kuehn 2006). Fungal products can also be used as enzyme inhibitors against cancer, diabetes, Alzheimer's disease, etc. The enzymes inhibited include acetylcholinesterase, protein kinase, tyrosine kinase, glycosidases and others[31].

2.3.Enzymes For The Treatment Of Cancer

The field of cancer research has some good examples of the use of therapeutic enzymes. Actinomycin D is the oldest microbial metabolite used in cancer therapy. Its relative, actinomycin A, was the first antibiotic isolated from actinomycetes. The latter was obtained from Actinomyces antibioticus (now Streptomyces antibioticus). Bleomycin, an anticancer agent, is a non-ribosomal glycopeptide microbial metabolite produced by the bacterium Streptomyces verticillus [20]. Mitosanes are formed during the cultivation of Streptomyces caespitosus, are composed of several mitomycins that show the activity against several types of cancer (lung, breast, bladder, anal, colorectal, head and neck), including melanomas and gastric or pancreatic neoplasms. Although the mitosanes are excellent antitumor agents, they have limited utility owing to their toxicity. On the other hand, Mithramycin (plicamycin) is an antitumor aromatic polyketide are produced by Streptomyces argillaceous shows antibacterial and antitumor activity. Streptozotocin (a glucosamine-nitroso-urea compound) is a microbial metabolite with antitumor properties, produced by Streptomyces achromogenes which can be used for the treatment of pancreatic islet cell cancer[32]. Scientists invented a new approach for targeting gene therapy to hypoxic regions of tumors sites, which employs an attenuated strain of the non-pathogenic bacterium, Salmonella typhimurium, carrying an exogenous gene under the regulation of a new, highly hypoxia-inducible promoter. This bacterial vector was seen to rapidly migrate into, and thrive in, hypoxic areas of both mammary tumor spheroids grown in vitro and orthotopic mammary tumors after systemic injection. The researcher also found that bacterial expression of high levels of β-galactosidase occurred only in hypoxic/necrotic sites of spheroids and tumors which represents a promising new strategy for delivering gene therapy to poorly vascularized regions of tumors and the efficacy as an anti-tumor agent. Showalter[33] stated that pentostatin (deoxycoformycin) can be used as an anticancer chemotherapeutic drug produced by S. antibioticus and can commonly be used to treat hairy cell leukemia, acute lymphocytic leukemia, prolymphocytic leukemia (B- and T-cell origin), T-cell leukemia and lymphoma. It was found that calicheamicins, a highly potent antitumor microbial metabolites produced by Micromonospora echinospora, can be use in patients over the age of 60 years (who are not considered candidates for standard chemotherapy) with relapsed acute myelogenous leukemia[34]. It was also found that the endophytic fungi Taxomyces andreanae and Nodulisporium sylviforme produced paclitaxel which can inhibit rapidly dividing mammalian cancer cells by promoting tubulin polymerization and interfering with

normal microtubule breakdown during cell division and can be used as anti-cancer treatment[35]. Recent studies have shown that PEGylated arginine deaminase, an arginine-degrading enzyme, can inhibit human melanoma and hepatocellular carcinomas, which are auxotrophic for arginine owing to a lack of arginosuccinate synthetase activity[36]. Recently, another PEGylated enzyme, Oncaspar1 (pegaspargase), already in clinical use, has shown better results for the treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia than the native, bacterial asparaginase[37]. Antibody-directed enzyme prodrug therapy (ADEPT) illustrates a further application of therapeutic enzymes in cancer. A monoclonal antibody carries an enzyme specifically to cancer cells where the enzyme activates a prodrug, destroying cancer cells but not normal cells[38-39]. This approach is being utilized to discover and develop a class of cancer therapeutics based on tumor-targeted enzymes that activate prodrugs. The targeted enzyme prodrug therapy (TEPT) platform, involving enzymes with antibody-like targeting domains, will also be used in this effort. Bischoff et al[40] found in their research that when the mutant adenovirus was injected into p53-deficient (cellular tumor suppressor protein) human cervical carcinomas grown in nude mice caused a significant reduction in tumor size and caused complete regression of 60% of the tumors and these data raised the possibility that mutant adenoviruses can be used to treat certain human tumors.

3.Conclusion

Microbes occur elsewhere. During their metabolism, microbes produce chemicals, some of which have been in use by human beings since ages. Microbes can also be modified genetically to produce any type of chemical. Genetic engineering involves synthesis of artificial genes, repair of genes through fusion, deletion, inversion, shifting of genes, production of recombinant DNA and manipulating them for improvement in human beings. In agriculture, crop plants are being altered through insertion of genes from microbes to enhance their productivity and usefulness. The transgenic gene is transferred from another organism artificially by technique of genetic engineering. Therefore, the advancement in microbes and their enzymes can be potential tools to the improvement of human health.

4.Reference

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