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REVIEW PAPER

A comprehensive review on current status and role of microbiology in pharmaceutical and food industry

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ABSTRACT

Microbiology is the study of microorganisms that can't be seen with the naked eyes like protozoa, fungi, bacteria etc. Microbiology has provided advances in Pharmaceutical Industries and other medical industries. The pharmacists and microbiologists are working together to discover new antimicrobial drugs to prevent the spreading communicable diseases. They are working synergistically on the targeted drug delivery mechanisms using microbes ensuring that they don't cause any harm to their hosts. Vaccines are another important contribution of microbiology towards the drug development. A microorganism also provides bio products like steroids which are further used by the pharmaceutical industries. Pharmaceutical industries also use Microbiological techniques like genetic modification to enhance the drugs. Microbiology not only contributes towards the drug development and bio product developments but also contribute towards the Quality Management (Quality control and Assurance) of the Pharmaceutical Industry. Microorganisms have played a major role in food industry and drug production. Some microorganisms which are used in food industries in large scale are bacteria and fungi (yeast and mould).The method of improving quality and quantity of food by the use of microorganisms is known as food engineering. Microbes not only give good taste, texture and smell to the food but also produce some inhibitory compounds that prevent food spoilage. Microbes are generally used in the production of wine, beer, dairy products, bakery products etc. by the process of fermentation. It is a biochemical process which involves the conversion of simple sugars to acid, ethanol and carbon dioxide through metabolic pathways. This paper will be dealing with the importance of microorganisms in food and pharmaceutical industries and also about the status of current techniques used in both the industries.

Keywords: - Microbiology, pharmaceutical, food industry, microbes, quality control

INTRODUCTION

Pharmaceutical Microbiology, it is the combined study of Microbiology along with Pharmacy. Here microbes are studied on the basis of production of antibiotics, enzymes, lipases, vitamins, polysaccharides etc. Particularly in this field microbes are interestingly used in curing communicable

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diseases, producing antimicrobial Drugs, targeted drug delivery systems and many more.

In recent times, Pharmaceutical Industries are willingly using microbes to provide good to mankind. Immeasurable numbers of Microbes are contributing towards the pharmaceutical industries like Synthetic Microbes, Marine Microbes, Gut Microbes those producing steroids etc. This paper will be particularly dealing with the advanced approaches of using microbes in pharmaceutical industries. Few are discussed below.

Synthetic Microbes:

Synthetic cell therapy is a field that has broad potential for future applications in human disease treatment. Next generation therapies will consist of engineered bacterial strains capable of diagnosing disease, producing and delivering therapeutics, and controlling their numbers to meet containment and safety concerns. [1] Bacteriophages, Bacteria, bacteria related lipids and eukaryotic cells are used in targeted drug delivery. Bacteriophage can enhance the killing of antibiotic-resistant bacteria, persister cells, and biofilm cells, reduce the number of antibiotic-resistant bacteria and act as a strong adjuvant for other bactericidal antibiotics like amino glycosides and β-lactams.[2]

Marine Microbes:[3]

Marine Microbes produces high level of polysaccharides which are used in variety of ways by pharmaceutical industries. The earliest product derived from the marine microorganism was a toxin named Holothurin from the organism *Actinopygaagassizi.* Nowadays, Microalgae are widely used because of the easy control on growth, screening and availability of polysaccharides. The unicellular red alga *Porphyridium aerugineum* was shown to be encapsulated by an amorphous, water-soluble, polyanionic polysaccharide of high molecular weight. [4]

Blue Green Algae mostly *Chlamydomonas* Species liberate some polysaccharides into the medium of which 25% of total organic matter producedis constituted by thespecies *Chlamydomonas Mexicana*[5]. Not only microalgae but macroalga like Ulva and exoskeleton of crustaceans are used for the extraction of amylose, cellulose and chitin and chitosan respectively. Also, seaweeds have abundant source of polysaccharides like agar, agarose, alginates and carrageenans which have wide utilities.

Now if we discuss about the roles of these organisms, alginates are used for microencapsulation of drugs in TB patients to improve compliance[6]. Chitosan have antimicrobial properties hence they are used in drug delivery against two pathogens -

Streptococcus mutans and Actinobacillus actinomycetem comitans[7] and as drug delivery devices. More enhancements in this field are yet under processing.

Gut Microbes:

The various body surfaces and the gastrointestinal canals of humans maybe colonized by as many as 10^{14} indigenous prokaryotic and eukaryotic microbial cells [8].Generally oral and skin habitats have variable diversity patterns of microbes, while vaginal habitats have consistently the least diverse. The human microbiome Project has provided opportunity to examine these habitats through pyro sequencing-based profiling of 16 S rRNA gene sequences[9].The gut microbiota are able to perform biotransformation on xenobiotics, such as drugs and their metabolites, in ways that can affect absorption and bioavailability[10].

Table-1: Role of microbes in metabolism conventional therapies over the counter Drugs

Drug	**Type**	**Role of gut microbiota in metabolism**	**Clinical Effect**	**References**
Chloramphenicol	Antibiotic	On oral administration of this drug Coliforms present in gut converts Chloramphenicol to toxic form known as p-aminophenyl-2-amin-1,2-propanediol.	Increases toxicity	**[11]**
Diclofenac	Non-steroidal antiinflammatory drug	Initially it is converted to glucuronide metabolite by UDP-glucuronosyl transferase (UGT) enzymes and then in small intestine react with β-glucuronidase enzymes expressed by the symbiotic microbiota and leads to delayed excretion.	Increases toxicity	**[12], [13]**
Acetaminophen	Analgesic and antipyretic	They compete between o-sulfonation and p-cresol produced by gut microbiota and becomes toxic.	Increases toxicity and exaggerate clinical effect.	**[12], [14]**

Those producing steroids:[15]

Steroids are basically biological compound with four rings (Fig1) arranged in specific molecular configuration. They are one of the widely marketed products by pharmaceutical industry. Production of Steroidal Drugs and Hormones using microbes is one of the major contributions of microbiology towards Pharmaceutical industries. The first research was on the endogenous steroids – cortisol (Fig2) and progesterone (Fig 3) with the identification of 11-hydroxylation activity of a Rhizopus species. This led to the invention of using commercial microbes in production of steroids. The manufactured steroid compounds have a wide range of therapeutic purposes, namely as anti-inflammatory, immunosuppressive, progestational, diuretic, anabolic and contraceptive agents.

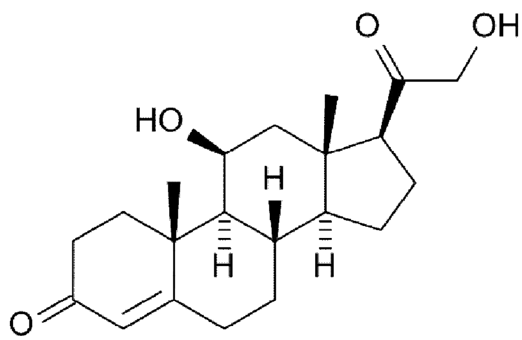

Fig.1: Structure of Steroid

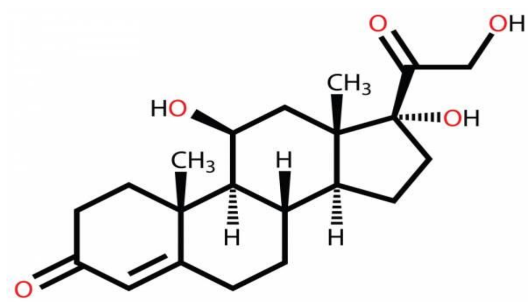

Fig. 2: Structure of cortisol

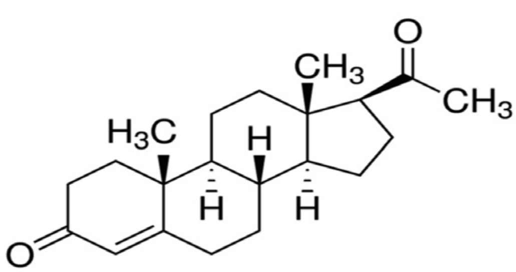

Fig3: Structure of progesterone

Importance of Quality Control in Pharmaceutical Industry:

Quality Control is one of the important practices that should be followed by every industry to ensure their final products are safe, consistent and effective. It is also done to avoid the loss and recall at the end due to poor quality or any microbial contamination to Drug or any other pharmaceutical related Products. Antimicrobial substances are compounds used in livestock production with the objectives of inhibiting the growth of microorganisms and treatment or prevention of diseases. It is well recognized that the issues of antimicrobial use in food animals are of global concern about its impact on food safety. [34]

One of the recent examples is the January 2011 recall of Alcohol Prep Pads, Alcohol Swabs and Alcohol Swabsticks, manufactured by the Triad Group. This recall was initiated due to potential contamination of *Bacillus cereus*.[16]

To provide a good quality product an industry should understand the followings:

Pharmacopoeias:

Three major Pharmacopoeias throughout the world include: the United States Pharmacopeia (USP), the European Pharmacopoeia (Ph. Eur.) and the Japanese Pharmacopoeia (JP). Each of these organizations has their own set of standards to ensure the quality of end products for human welfare. In India Indian Pharmacopeia is necessarily followed by every pharmaceutical industry and testing labs.

The growth promotion test:

The Growth Promotion Test is a very important Quality Control function in the Pharmaceutical industry. [17] It is imperative for establishing the nutritive properties of the microbiological culture medium that will be used in a pharmacopoeial procedure, such as a test for specified microorganisms. As per the Good Laboratory Practices the microbial growth can be measured by using the HPLC assay development of pharmaceutical drugs. [32]

Application of microbes in food

Microorganisms play an important role in assessment and maintenance of food quality and safety and also in food production, processing, preservation and storage. Microbes such as bacteria, yeast and moulds are used as food ingredients to enhance the flavors in food and also in production of food. It is very important in food microbiology that the microorganisms chosen should not produce any toxins or toxic metabolites and should be thermo tolerant and osmo-tolerant. [24]

Conventional approaches of microbes in food

Microorganisms help in fermentation processes e.g. the conversion of lactose to lactic acid by *Lactobacillus bulgaricus and Strep. thermophilus*in yogurt production, ripening processes – making a particular product ready to eat e.g. cheese, cream, fruits etc. and for aroma and flavor development in food.

Moulds are multicellular, filamentous fungi. These are used in ripening of various food products like cheese (Roquefort) and oriental food. A specie of *Bothrytiscinerea* is used in rotting of grapes for production of wine. These are also used in production of enzyme amylase and citric acid which are used as ingredients in bread and soft drinks respectively.

Yeast is most commonly used microorganism in food industry. It can convert sugars to ethanol and carbon dioxide. Baker's yeast is most commonly used yeast.

*Saccharomyces carlsbergenesis*is commonly used in fermentation of beer.[19]

Some microorganisms like algae, yeast and bacteria can be grown in large quantities to yield a cell crop which is rich in protein and is known as singe cell protein. It can be used as both human and animal feed.

Acetobacter are used for the oxidation of ethanol to acetic acid. They oxidize acetate and lactate to CO_2 AND H_2O. They are found on fruits and vegetables and are involved in souring of fruit juices and alcoholic beverages (beer and wine).

South African sorghum beer is an alcoholic, effervescent, pinkish-brown beverage with a sour flavor. The malt was traditionally made by soaking sorghum grains in water for 8–24 h, draining, and then, allowing the grains to sprout for 5–7days. Then the malt was grinded in fine powder and then made into thin slurry and boiled. But now in new microbiological approach it undergoes lactic fermentation by adding selected lactic acid bacteria (LAB) and *Saccharomyces cerevisiae* which leads to better fermentation and better quality of beer.[24]

Advanced approaches of use of microbes in food

Xanthan gum – it is a naturally fermented product derived from pure culture of improved strain of *Xanthomonas campestris*. It exhibits high velocity in low concentration. This microorganism ferments aerobically in a primarily carbohydrate medium which contains micronutrients. It is used as food additive in many industries, used to add smoothness to cream cheese, control ice crystal growth and freeze/ thaw properties of frozen food. [18]

One of the new techniques evolved is the use of ozone forfood surface hygiene, for sanitation of food plant equipment andtreatment and lowering biological oxygen demand (BOD) and chemical oxygen demand (COD) of food plant waste. Treating fruits and vegetables with ozone has been found to increase shelf-life of the products.[20] Lactic acid bacteria other than yogurt production produce antimicrobial substances, sugar polymers, sweeteners, aromatic compounds, vitamins. Lactic acid bacteria can be used as starter culture to initiate rapid acidification of raw materials.[23]

The human microbiota consists of the aggregate of microorganisms that resides in or within the tissues or body fluids of human body including the skin, mammary glands, placenta, conjunctiva, gastrointestinal tracts etc. [26]

Microbes in gut are either harmless or benefits the host. Majorly *Escherichia coli* can be isolated from gut of most people. In adults, Bacteroidetes and Firmicutes usually dominate the microbiota, whereas *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia*, although found in many people, are generally minor constituents.[25]

The food supplements: prebiotics, probiotics and synbiotics termed as functional foods have been verified to alter, transform and reinstate the pre-existing intestinal flora. [27]

Probiotics, Prebiotics and synbiotics

Probiotics are live microorganisms which when consumed promote health benefits and also contributes to intestine's microbial balance. Numerous probiotic microorganisms (e.g. *Lactobacillu srhamnosus* GG, *L. reuteri*, bifidobacteria and certain strains of *L.casei* or the *L. acidophilus*-group) are used in probiotic food, particularly fermented milk products e.g.-Yakult. [28]Non-dairy products like sauerkraut, fermented cereals, other plant-based foods, and salami contain essential probiotics. [29]

A **prebiotic** is a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon. E.g.-oligosaccharides. Fructose oligosaccharides are able to modify the gut flora composition in favour of bifidobacteria.[30] Oligosaccharides, including N-acetylglucosamine [28], glucose, galactose, and fructose oligomers or certain glycoprotein's which form a significant proportion of human breast milk, may be specific growth factors for bifidobacteria.[31]

Synergistic combinations of pro- and prebiotics are called **synbiotics**. The live microbial additions (probiotics) may be used in conjunction with specific substrates (prebiotics) for growth (e.g.: fructooligosaccharide in conjunction with a bifidobacterial strain or lactitol in conjunction with a lactobacillus organism). [31]

Control of food spoiled by microorganisms

The no. of microorganisms in food is determined by its Aerobic Plate Count (APC).The APC of food may vary from 10 to 100,000,000 microorganisms per gram. The microbial count is used to predict the shelf life of the food product. By determining the shelf life of food product, we can calculate that for how much time a food product can be stored. [21]

Orange peel was spoiled by gram negative bacteria like *Enterobacter agglomerans*, and *Pseudomonas* and yeast like *Rhodotorulaglutinis*, and *Saccharomyces cerevisiae*. Infusion of 0.5% w/v citric acid extended shelf life of both peeled whole and chunked fruits.Maximal shelf life extension was attained with 0.5% w/v citric acid for 4°C storage or 1.0% w/v citric acid for 8 and 21°C storage. [22]

Bacteriocins also play very good roles as food preservatives. Bacteriocins are ribosomally synthesized extracellular bioactive peptides, known for its antimicrobial activity, has no side effect on human health.[33]

Discussion and Conclusion

In this paper the roles of microorganisms in both pharmaceutical and food industries have been discussed. The discussion has been made on the conventional and the advanced approaches of use of microorganisms in both the industries.

The conventional or primitive methods are yet used in pharmaceutical industries, but this paper has enlightened the new approaches like utilization of Marine Microbes, Gut microbes, Synthetic Microbes, and their products like enzymes, Steroids to enhance the products made by Pharmaceutical Industry.

The importance of Quality Control also has been discussed to provide Hassle free products which will bring goodness to Mankind.

If we discuss about food, the use of microorganisms in food was initiated by Louis Pasteur through fermentation techniques.

The application of Conventional Methods is still being utilized and will always be applicable in future like to produce Wine, Beer, Yogurt, Cheese etc. Also, with the invention of advanced technologies for Production of Prebiotics, Probiotics, Synbiotics, use of Xantham gum as Food additives, use of Ozone for Food surface sterilization purposes, and use of microorganisms as SCP have provided benefit and betterment to mankind.

The Pharmaceutical and Food are fast growing industries which are working to provide the best products for goodness and betterment of upcoming generations.

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