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PHARMACEUTICAL WASTE AND THE THREAT OF MICROBIAL RESISTANCE: AN OVERVIEW

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Abstract: The present article provides an overview of the microorganisms present in pharmaceutical waste, which is composed of expired or unused medications, solvents, pharmaceutical dust, sewage water, and other materials generated during the production, distribution, and consumption of medicines. The article highlights the potential risks of bacterial infections and antibiotic resistance associated with pharmaceutical waste, particularly the presence of bacteria, viruses, protozoa, and helminths, which may or may not show multidrug resistance. The objective of the study is to identify useful bacteria and a wide range of medicines that can treat infections caused by these microorganisms, as well as to eliminate dangerous bacteria. The article emphasizes the significance of proper disposal and treatment of pharmaceutical waste to avoid environmental pollution and the emergence of antibiotic resistance. Antibiotic resistance is a major threat to public health, especially when multidrug-resistant (MDR) bacteria are present. These are bacteria that are resistant to one or more drugs from three or more antibiotic categories. Several mechanisms can cause antibiotic resistance, including enzymatic resistance, reducing permeability, altering target sites, and genetic mutation. Understanding these mechanisms is crucial in developing effective strategies to combat antibiotic resistance.

Index Terms **- Pharmaceutical waste, multi drug resistance, antibiotics, dangerous bacteria**

I. INTRODUCTION

Bio-waste, a category of medical waste, encompasses discarded medical and pharmaceutical materials that have the potential to degrade into substances harmful to both human health and the environment.[1, 2] Hospital wastewater (HWW) is particularly problematic due to the presence of emerging contaminants like pharmaceutically active compounds (PhACs), antibiotic-resistant bacteria (ARB), antibiotic-resistant genes (ARG), and persistent viruses.[3] HWW's biodegradability index is lower compared to municipal wastewater, primarily attributed to its elevated biochemical oxygen demand (BOD).[4,5] Unfortunately, in underdeveloped countries or instances of pharmaceutical fraud during production and distribution, waste may be generated despite regulations mandating proper disposal by pharmaceutical industries.

Pharmaceutical waste comprises an array of materials such as waste products, solvents, pharmaceutical residue, and sewage water, often carrying various types of microorganisms.[6] Within this waste, there exists a diverse collection of microorganisms adapted to flourish within a host, potentially posing threats to public health.[7, 8]

The primary objective of this study was threefold:

1. Identification of hazardous microorganisms prevalent in pharmaceutical industry waste, including instances of contamination due to flooding or mismanagement.[9]
2. Discovery of beneficial bacteria with the capacity to eliminate dangerous microorganisms, thereby mitigating their potential harm.[10]
3. Exploration of a wide spectrum of medications employed to counter illnesses or infections caused by harmful pathogens.[11]

The sewage waste originating from pharmaceutical manufacturing processes is complex, incorporating different polymeric components, antibiotic residues, varied solvents, and more. Consequently, numerous microbes have developed resistance, which can profoundly impact public health. While microbes play a pivotal role in producing chemicals across various industries, yielding both beneficial and detrimental products for human well-being, they can also contribute to illnesses. This dichotomy is further complicated by their evolving resistance to antibiotics, transforming them into formidable sources of infections.[11, 12]

The current study offers a comprehensive overview of diverse microorganisms intertwined with the pharmaceutical industry. It delves into the intricate interplay between microbial activities, pharmaceutical waste, and potential implications for human health. By understanding these dynamics, we can better address the challenges posed by hazardous microorganisms, promote the growth of beneficial bacteria, and refine our approach to pharmaceutical waste management.

II. MICROORGANISM

A microbe, also referred to as a microorganism, is a minute life form that exists as either a single cell (unicellular) or a cell cluster. In contrast, organisms composed of multiple cells tend to exhibit more intricate and beneficial complexities.[13]

Tragically, it is estimated that approximately 700,000 individuals across the globe succumb annually to infections caused by drug-resistant strains of common bacteria, tuberculosis, and malaria. The grim projection suggests that the cumulative global deaths attributed to antibiotic-resistant infections could escalate to 10 million annually by the year 2050. This alarming trend is anticipated to result in economic losses exceeding a staggering US$100 trillion.[14, 15]

The discovery of antibiotic-resistant bacteria in pharmaceutical manufacturing sites in Hyderabad, New Delhi, and Chennai is troubling. Among 34 sites investigated, 16 had antibiotic-resistant bacteria, with four sites showing resistance to crucial antibiotics, including carbapenems.[15]

This unsettling discovery underscores the pressing need for robust measures to address the emergence and proliferation of drug-resistant bacteria. The implications extend beyond the realms of public health, impacting sectors like pharmaceutical production and beyond. Swift and effective actions are imperative to curb the propagation of antibiotic resistance, safeguard human lives, and protect economic well-being.

Bacteria found in waste

Pharmaceutical waste consists of various materials produced during the manufacture, distribution, and consumption of medicines. These materials may comprise expired or unused drugs, empty containers, packaging materials, and other related items. However, pharmaceutical waste may also harbor dangerous bacteria that can endanger human health and the environment.[16, 17] The most frequently found types of harmful bacteria in pharmaceutical waste are those responsible for human infections, are given as following table 1.

Table 1: list of harmful bacteria in pharmaceutical waste

Strain of resistant bacteria	Major Diseases
Campylobacter jejuni	Gastroenteritis.
Esherichia coli	Gastroenteritis.
Salmonella spp.	Salmonellosis, Typhoid, Paratyphoid.
Shigella spp.	Bacillary dysentery.
Vibrio Spp	Cholera.
Hepatitis A	Jaundice, Fever, Fatigue.
Giardia Lamblia	Diarrhea.
Legionella pneumophila	Fever, Muscle ache.
Yersinia spp	Gastroenteritis.
Cryptosporidium	Diarrhea
Klebsiella spp.	
Proteus spp	
Citrobacter spp.	
Bacillus Spp.	
Pseudomonas Spp.	

Bacteria with the potential for causing harm can be present within expired or unused medications, especially those intended for injection or invasive administration. Beyond the immediate concern of bacterial infections, the improper disposal of pharmaceutical waste introduces a significant risk in the development of antibiotic resistance. When antibiotics are inadequately discarded, they can contaminate the environment and exert selective pressure, ultimately prompting bacteria to evolve resistance against these drugs. This phenomenon poses a formidable challenge to the effective treatment of bacterial infections, both in humans and animals, thereby compounding the complexities of healthcare.[18, 19]

Among the bacteria mentioned earlier, including Pseudomonas spp., Bacillus spp., E. coli, Staphylococcus spp., Klebsiella spp., and Vibrio spp., a concerning trait emerges: their ability to develop resistance against multiple drugs. This phenomenon of multi-drug resistance underscores the adaptability and tenacity of these microorganisms, which can diminish the efficacy of various therapeutic interventions.[20] Addressing this challenge necessitates comprehensive strategies that span healthcare practices, pharmaceutical waste management, and environmental conservation, aiming to mitigate the progression of antibiotic resistance and preserve the efficacy of these critical drugs.

Viruses found in waste

Pharmaceutical waste constitutes a reservoir for a diverse array of viruses, encompassing those originating from human and animal sources. The presence of these viruses within such waste stems from several origins, spanning individuals or animals who have consumed the medications, as well as potential contamination during the manufacturing processes.[21]

Among the spectrum of viruses that can be encountered within pharmaceutical waste, the human immunodeficiency virus (HIV) stands out as one of the most frequently identified. Particularly, antiretroviral drugs employed in the treatment of HIV/AIDS can harbor traces of this virus. Furthermore, pharmaceutical waste has been found to harbor other viruses, including but not limited to hepatitis A, B, and C viruses, influenza viruses, and respiratory syncytial virus (RSV).[22] The assortment of viruses discovered within pharmaceutical waste raises concerns regarding possible disease implications.

Notably, the viruses found within pharmaceutical waste can potentially pose health risks to both individuals and the environment. Proper management and disposal of pharmaceutical waste are paramount not only for preventing inadvertent transmission of these viruses but also for curbing their potential impact on public health and ecosystem integrity. Some of the examples of viruses found in bio waste with possible diseases are as table 2[23]:

Table 2: List of pathogens and major viral disease

Name of Pathogen	Major Diseases
Adenovirus	Uppaer respiratory infection.
Astrovirus	Gastroenteritis.
Coxsackie virus	Meningitis, Fever,Pneumonia.
Echovirus	Meningitis, Paralysis,.Enciphilatitis.
Hepatitis A virus	Infectious hepatitis.
Hepatitis E virus	Infectious hepatitis, miscarriage and death.
Human calicivirus	Epidemic gastroenteritis with severe diarrhea.
Polio virus	Poliomyelitis.
Rotavirus	Acute gastroenteritis.
TT hepatitis	Hepatitis.

The presence of these viruses in pharmaceutical waste can pose a risk to human health and the environment. If pharmaceutical waste is not disposed of properly, it can contaminate water sources and soil, leading to potential exposure to these viruses.

Protozoa found in waste

Protozoa are unicellular organisms widely distributed in diverse environments, encompassing water bodies and soil. When considering pharmaceutical waste, the presence of protozoa can emerge in medications derived from natural origins or through manufacturing process contamination.[24] Among the protozoa that could potentially inhabit pharmaceutical waste, instances include Giardia lamblia, Entamoeba histolytica, and Cryptosporidium parvum.[25] It's important to note that certain protozoa have the capability to induce infections in humans, often transmitted through consumption of contaminated water or food. The following table 3 lists some of these disease-causing protozoa along with their associated infections. When pharmaceutical waste is not disposed of properly, it can contaminate water sources and soil, leading to potential exposure to protozoa. This can occur if medications are flushed down the toilet or discarded in the trash.

Helminth found in waste

It is known as parasitic worms are large macro parasites, generally be seen by the naked eye. Some of these are present in following table 3 with major causing diseases.[26]

Table 3: List of pathogens and major disease

Name of Pathogen	**Major Diseases**
Balantidium coli	Balantidiasis
Cryptosporidium	Cryptosporidiosis
Entamoeba histolytica	Acute amoebic dysentery
Giardia duodenalis	Giardiasis
Toxoplasma	Toxoplasmosis
Name of helminthes	**Diseases**
Ascaris lumbricoides.	Ascariosis.
Ascaris suum.	Coughing and chest pain.
Hymenolepis nana.	Hymenolepiasis.
Necator americans.	Hookworm disease.
Taenia saginata.	Insomnia,Anorexia.
Toxocara canis.	Fever,abdominal pain,muscle ache.
Taenia solium.	Insomnia,Anorexia.
Trichuris trichura.	Diarrhea,Anemia,weight loss.

Useful Bacteria

Probiotics are a category of microorganisms that closely resemble the beneficial bacteria inherent in the human body. Their significance lies in their potential to positively impact human health and their therapeutic application in managing certain medical conditions.

Often termed as "probiotics," these microorganisms bear a striking resemblance to the bacteria naturally occurring within the human body. Demonstrating their value in bolstering human well-being and addressing specific medical ailments, probiotics have gained significant recognition.[27] Some of the species with sources are in table given below

Table 5: List of evaluated pharmaceutical contaminants with sources

Genus/Species	**Evaluated Pharmaceutical Contaminant**	**Source of Contaminant**
Actinobacteria *Chryseobacterium* *Flavobacterium* *Pseudoxanthomonas*	Alprenolol Bisoprolol Metoprolol Propranolol Venlafaxine Salbutamol Fluoxetine Norfluxatine	Biorector
Bacillus thuringiensis	Ibuprofen Naproxen	Chemical factory floor
Microbacterium sp.	Sulfamethazine Benzenesulfonamide	Soil
Pseudomonas Flavobacterium	Carbamazepine Gemfibrozil Phenazone	Sand Filter
Pseudomonas sp.	Cefalexin Sulfamethoxazole	Activated Sludge

	Caffeine Salicylic acid Chloramphenicol	
Chryseobacterium taeanense *Rhizobium daejeonense* *Diaphorobacter nitroreducens* *Achrmobacter Mucicolens* *Pseudomonas veronii* *Pseudomonas lini*	Carbamazepine	In vitro
Paucibacter *Filomicrobium*	Sulfamethoxazole	Bioreactor
Novosphingobium sp. *Sphingomonas sp.* *Sphingopyxis sp.* *Sphingobium sp.* *Isoptericola sp.* *Nubsella sp.* *Rhodococcus sp.* *Bacillus sp.*	Triclosan Bisphenol Ibuprofen 17β-estradiol Gemfibrozil	Sewage treatment plant
Delftia tsuruhatensis *Pseudomonas aeruginosa*	Paracetamol	Bioreactor
Nitrosomonas europaea	17α-ethynylestradiol	Bioreactor
Acinetobacter sp. *Phyllobacterium Myrsinacearum* *Ralstonia pickettii* *Pseudomonas aeruginosa* *Pseudomonas sp.* *Acinetobacter sp.*	17α-ethynylestradiol	Wastewater
Paracoccus sp. *Arthrobacter sp.*	Methylamine Trimethylamine Dimethylamine	Biofilter
Psudomonas flurescens	Salicyclic acid	In vitro
Saccharomyces Cerevisiae	Trimethylmethane dyes	In vitro
Sphingomonas sp.	Ibuprofen	In vitro
Halophilic bactorial strains	Trimethylamine	In vitro
Psudomonas putida TriRY *Alcaligenes xylosoxidans*	Triclosan	In vitro
Paracoccus sp.	Trimethylamine Dimethylamine Methylamine	In vitro

III. ANTIBITICS

A Medicine which is used for destroying bacteria & curing infections. It is the most important type of antibacterial agent for fighting. Bacterial infections & antibiotic medications are widely used in the treatment & prevention of such infections. They may either kill or inhibit the growth of bacteria few antibiotics names which helps in killing bacteria namely[28],

1. Penicillins Such as penicillin & a moxicillin.
2. Cephalosporins such as cephalexin (keflex).
3. Macrolides Such as erythromycin (fmycin), Clarithromycin (Biaxin) and azithromycin (zithromax).
4. Fluoroquinolones such as ciprofol xacin (cipso), levofloxacin (Levaquin), I of boxacin (floxin).

5. Sulfonamides such as co-trimoxazale (Bacteristm) & trimethoprim (Proloprim) Tetracyclines such as tetracyline (Sumycin, panmycin) I doxycyline (vibramycin) Aminoglycosides such as gentamicin.

Antibiotic resistance

Process of bacteria to resist the mechanism of antibiotics is called as antibiotic resistant bacteria. If bacteria resists one or more drugs from three or more antibiotic category is called as multidrug resistant bacteria. The loss of susceptibility of bacteria to the bactericidal or bacteriostatic properties of antibiotics can lead to antibiotic resistance. In cases where a resistant strain of bacteria is the dominant strain in an infection, the infection can become life-threatening and difficult to treat. This could be due to variation in genetic setup or due to spontaneous mutation.[29, 30] Various mechanisms of multidrug resistance is as follows[31]:

a) Enzymatic
b) Reducing permeability
c) Altering target site
d) Increasing mutation

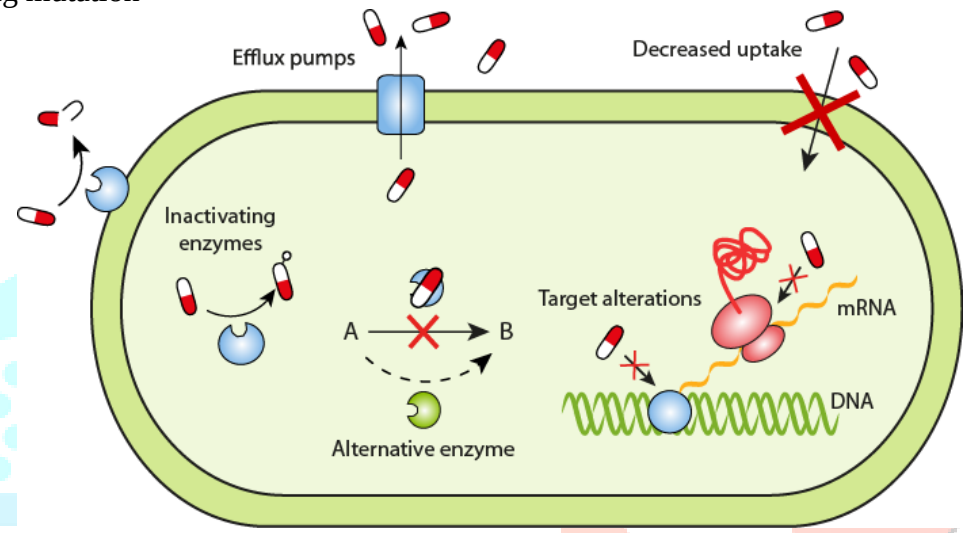

Figure 1: mechanisms of antibiotic drug resistance

a) Enzymatic MDR:

It occurs when cells produce enzymes that chemically modify drugs, making them less effective or entirely inactive. The enzymes that mediate this resistance are known as drug-metabolizing enzymes, which include cytochrome P450 enzymes and glutathione S-transferases (GSTs). These enzymes play an essential role in the detoxification of drugs and other xenobiotics in the body, but their upregulation in cancer cells and infectious agents can lead to drug resistance. Cytochrome P450 enzymes are a superfamily of heme-containing enzymes involved in the oxidative metabolism of drugs, steroids, and other xenobiotics. They are essential for the metabolism of approximately 75% of all clinically used drugs. In some cases, cytochrome P450 enzymes can convert drugs into toxic metabolites, leading to adverse drug reactions. However, in other cases, they can modify drugs in a way that enhances their excretion or inactivation, leading to drug resistance. GSTs are another group of drug-metabolizing enzymes that play a vital role in the detoxification of drugs and other xenobiotics. They catalyze the conjugation of reduced glutathione to drugs and other electrophilic compounds, facilitating their elimination from the body. However, overexpression of GSTs can lead to drug resistance by increasing the rate of drug conjugation, resulting in the inactivation and reduced efficacy of the drug.[32]

b) MDR with reducing permeability:

This mechanism is also known as the efflux pump mechanism or the pump-mediated multidrug resistance mechanism. It involves the expulsion of drugs from the cell through specialized membrane transporters, known as efflux pumps, which act as molecular pumps to actively extrude drugs from the cell. Efflux pumps belong to the ATP-binding cassette (ABC) transporter superfamily and the major facilitator superfamily (MFS). These transporters are expressed in various tissues, including the gut, liver, and kidney, and they play a critical role in the absorption, distribution, metabolism, and excretion of drugs and other xenobiotics. However, in cancer cells and infectious agents, the upregulation of these transporters can lead to drug resistance.[33]

Reduced permeability can also be caused by changes in the cell membrane composition, such as an increase in the level of cholesterol or the expression of membrane proteins that decrease drug permeability. These changes can result in a reduced rate of drug uptake and an increase in the efflux of drugs from the cell, leading to drug resistance. To reduce the permeability multidrug resistance mechanism, several

strategies have been proposed, including the use of efflux pump inhibitors, the modulation of membrane fluidity, and the targeting of specific membrane transporters. Efflux pump inhibitors are compounds that can block the activity of efflux pumps, thereby preventing the extrusion of drugs from the cell. Modulating membrane fluidity can also reduce the rate of drug efflux by altering the composition of the cell membrane. Moreover, specific membrane transporters can be targeted to reduce drug resistance. For example, the development of selective inhibitors of specific ABC transporters, such as P-glycoprotein, can reduce drug resistance in cancer cells. Similarly, the targeting of specific MFS transporters, such as the MexAB-OprM system in Pseudomonas aeruginosa, can improve the efficacy of antibiotics against these bacteria.

c) MDR with altering target sites

Drugs are designed to target specific proteins or enzymes in the cancer cells or bacteria to inhibit their growth or replication. However, cancer cells or bacteria can alter the structure or expression of the target proteins or enzymes to prevent the drugs from binding and functioning effectively. This results in decreased drug efficacy and increased resistance. In cancer cells, the most common mechanism of target alteration is through mutations in the genes that code for the target proteins. These mutations can lead to changes in the protein structure or expression, making it difficult for drugs to bind and inhibit their function. For example, mutations in the epidermal growth factor receptor (EGFR) gene can lead to resistance to targeted therapies used in the treatment of non-small cell lung cancer. In bacteria, the alteration of target site can occur through various mechanisms, such as mutations in the genes that code for the target proteins, decreased expression of the target proteins, or acquisition of new target proteins that are not affected by the drugs. For instance, resistance to fluoroquinolone antibiotics in bacteria can be due to mutations in the genes that code for the target enzymes, DNA gyrase and topoisomerase IV, which are involved in DNA replication and repair.[34]

d) MDR with genetic mutation:

Multidrug resistance (MDR) is a phenomenon where certain cells, such as cancer cells or bacteria, become resistant to multiple drugs that would otherwise be effective against them. This resistance is often caused by genetic mutations that impact drug transport or metabolism within the cells. For example, in cancer cells, mutations in genes like ABCB1 (also known as MDR1) or ABCC1 (also known as MRP1) can result in the overproduction of transport proteins. These proteins then remove chemotherapy drugs from the cancer cells, reducing the efficacy of treatment. Similarly, in bacteria, mutations in genes that encode efflux pumps, which remove antibiotics from the bacterial cell, can lead to MDR. These mutations can increase the production of efflux pumps or alter their structure, making them more effective at removing drugs from the cell. Overall, mutations in these genes can result in reduced drug efficacy, making it challenging to treat certain diseases and infections. Researchers are currently developing new drugs and treatment strategies to overcome these mechanisms of resistance.[35]

IV. CONCLUSION:

This study underscores the intricate relationship between pharmaceutical waste, hazardous microorganisms, and their potential impact on human health and the environment. The presence of harmful microorganisms such as bacteria, viruses, protozoa, and helminths in pharmaceutical waste poses significant health risks if not managed properly. The emergence of antibiotic-resistant bacteria in pharmaceutical manufacturing sites adds urgency to the need for effective intervention. The ability of microorganisms to develop multidrug resistance and genetic mutations that alter target sites further complicates the challenge of combating infections.

Effective strategies must be developed to identify, manage, and mitigate the proliferation of hazardous microorganisms in pharmaceutical waste. Beneficial bacteria like probiotics hold promise for restoring microbial balance. While antibiotics are essential for treating bacterial infections, the growing concern of antibiotic resistance demands judicious usage.

This study's implications extend beyond health, influencing pharmaceutical practices, environmental preservation, and economic stability. Collaborative efforts across industries, regulations, healthcare, and waste management are vital. Understanding the complex interplay between microorganisms and pharmaceutical waste is key to devising strategies that combat antibiotic resistance, safeguard the environment, and elevate healthcare quality. Continued research and collaboration are pivotal to establish sustainable solutions for this intricate challenge.

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