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MULTI-DRUG RESISTANT PATHOGENS AND FOOD SAFETY

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ABSTRACT

RESULTS: This review has focused on the causes, effect, transmission and prevention of Multi-drug resistant pathogens. Drug resistance strains have developed in most cases through human practices which includes abuse of drugs, use of over dose and self medication. Other methods as been identified in food process through the application of pesticide, herbicides and antibiotics during farming and sometimes for storage. In animal house boundary, antibiotics is usually administered to prevent animals from getting sick in other to reduce loss of live stocks which could affect production; meat and milk. Research have shown that development of resistant strain could be traced to: **1.** *Delayed or inadequate treatment*, **2.** *Wrong diagnostic due to selection of antimicrobials*, **3.** *surviving of resistant strains during treatment of other bacterial illnesses*, **4.** *Formation of Biofilms which increases pathogenicity of resistance genes during treatment of bacteria diseases.* Many pathogenic organism have been found to be resistant to their empirical antibiotics, these includes: Lactic acid bacteria; *Lactobacillus acidophilus, Salmonella spp., Yersinia spp., Escherechia coli, Campylobacta spp., Plasmodium spp., Acinetobacter baumannii, Staphylococcus aureus, Enterococci spp., Clostridium difficile* and some of their empirical drugs that have been resistant to include: *Vancomycin, Floroquinolone, Tetracyclines, Kanamycin, Sulfonamides, Chloramphenicol, Streptomycin, Cephalosporins* and *Penicillins.* These have caused some public health diseases and reduced effective therapy across the world with adverse economic conditions. These have challenged scientist to proffer alternative approach to curb the transmission from farm to fork through: Improved farming practices with reduce use of antibiotics, Food Biosecurity, the use of Green antibiotics like Essential oil, Nanobiotics, other approach like the use of Predatory bacteria, Lactic acid bacteria as an antibiotics and Vaccines. This review has explored different causes of multi-drug resistant pathogens, transmission and prevention and has provided wealth of knowledge that can be of immense benefits for medical practitioners, farmers and the general public to stem the growth and spread of resistant pathogens globally. Multi-Drug resistant pathogens is the new health monster that is causing public health diseases and delay in treatments which is leading to prolong hospital stay, increased cost of therapy and in some cases, the death of people around the world. Further research and serious effort should be channeled into stemming the continuous spread of these menace through public sensitization on self medication and farming practices.

KEYWORDS: Multi-drug resistance, Food Biosecurity, Green Antibiotics; Nanobiotics, Essential oil, Vaccines.

1. INTRODUCTION

In recent times, multi drug resistant pathogens have been on the increase which is the major causes of public health problems globally. There have been increases in mortality rate due to dissemination of resistance infectious pathogens like *Enterococcus (E.) faecium, Staphylococcus (S.) aureus, Klebsiella (K.) pneumoniae, Acinetobacter (A.) baumannii, Pseudomonas (P.) aeruginosa, and Enterobacter species* which can evade biocidal effect of several types or classes of antibiotics both in humans and animals (Rice, 2008; Pendleton *et al.*, 2013; Santajit and Indrawattana, 2016). The occurrence of these pathogens differs based on the bacterial species, the group of the antimicrobial and geographical location in the world. The Centers for Disease Control and Prevention (CDC) reported in 2013 that close to 23,000 people died from about 2 million cases of antibiotic-resistant bacteria each year in the USA and the etiological agents of infections were mostly found to be methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *E. faecium* (VRE), and fluoro-quinolone resistant *P. aeruginosa* (Centers for Disease Control, 2004; 2013).

The importance of antimicrobials in modern medicine for human, plant and animals cannot be overemphasized. They have been used in agriculture and veterinary for different purposes which include: *to improve feed efficiency, improve growth and almost simultaneously for control, prevention and treatments of infectious diseases* (O'Neill, 2015; WHO, 2015). Antibiotics are chemical substances produced through growth culturing of bacteria and can be natural, synthetic or semi-synthetic which prevent bacteria growth by reducing their metabolic activities and has been adopted in animals and humans to control or treat infection (O'Neill, 2015; WHO, 2015). In meat producing animals, the most common problems due to antibiotics usage include *bovine pneumonia, shipping fever and diarrhea*,(McEwen and Fedorka-Cray, 2002) respiratory diseases, and liver abscesses (USDA, 1999). There have also been reported allergies to using antibiotics which include *anaphylaxis*, *cardiotoxicity*, *nephrotoxicity*, *neurotoxicity* and *hepatotoxicity*, and also documented number of *hematological* and *gastrointestinal* problems (Granowitz and Brown, 2008).

In humans or animals certain consideration should be in place in terms of drug characterization to determine its toxicity before administering antimicrobial in food; for storage, pest control and growth enhancement. Also some important characteristics should be considered, such as the age and immune system of target end user or consumer which would help to determine appropriate drug dose to be administered (Watts *et al.,* 2018). One of the major causes of rise in drug resistance is the use and misuse of antimicrobials which have raised concerns (Cabello, 2006; Heuer *et al.,* 2009).

Antimicrobial resistance occurs when an organism show resistance to a drug that is been administered at lethal dose with the purpose of killing or hinder the growth of such organism. These can occur in two different forms: *Intrinsic resistance*; this occur through evolutionary gene transfer. It is also called *vertical gene transfer.* It is implemented in evolutionary phase and genetic errors accumulated in the plasmid or chromosome of bacterial cells and *acquired resistance* which occurs due to exchange of genetic material between bacteria species. It is also referred to as *Horizontal gene transfer*. This is observed when organisms gain new genes on their mobile genetic elements including plasmids, insertion sequences, phage related elements and integrons transposons (Holmes *et al.,* 2016). Antimicrobial resistance has been found to spread through different means. For example it could be spread in food chain by direct exposure or indirect exposure. The former occurs, through contact of human with animal or its blood, saliva, milk, semen, feaces and urine. While the later occurs, through consumption of contaminated food or food products such as egg, meat and dairy products (Chang *et al.,* 2015; Coetzee *et al.,* 2016; Liu *et al.*, 2016). These have afforded bacteria to be exposed to reservoirs of resistance genes in addition of their pathogenicity to cause various serious public health issues or conditions.

In general, the outcome of dispersing antibiotic-resistant bacteria and infectious diseases could be due to: **1.** *Delayed or inadequate treatment,* ***2.*** *Wrong diagnostic due to selection of antimicrobials,* ***3.*** *surviving of resistant strains during treatment of other bacterial illnesses,*

***4.** Formation of Biofilms which increases pathogenicity of resistance genes during treatment of bacteria diseases* (Fluit, 2005; Gooderham and Hancock, 2009; Guerra *et al*., 2004).

2. SOME COMMON EXAMPLES OF RESISTANT PATHOGENS

Lactic Acid Bacteria (LAB)

Over the years, fermentation of dairy product for yoghurt is at the forefront which is generally acceptable today. Lactic acid bacteria (LAB), is a common microbiota in foods, and widely used as starters culture for specific food products (yoghurt, cheese, dry-cured meat, etc.) which can make a reservoirs of antimicrobial resistance genes similar to those found in clinical pathogens and causing wide spread of resistance genes to food borne pathogenic bacteria (van den Bogaard and Stobberingh, 2000; Smith *et al.,* 2002). As an example, identical tetracycline-, erythromycin-, and vancomycin-resistant genes that were found in clinical bacterial species were also detected in *Lactococcus lactis* and *Lactobacillus species* isolated from fermented meat and milk products (Mathur and Singh, 2005). Besides, some human bacteria revealed the presence of resistance gene determinants within their genomes and therefore they show intrinsic antimicrobial resistance (Cox and Wright, 2013). *Enterococcus spp*. was found to have antibiotic resistance, especially to vancomycin although resistance to chloramphenicol and erythromycin was also observed (Teuber *et al.,* 1999). Therefore, the presence of antimicrobial resistance genes in starter, and/or probiotic cultures that are intentionally added during animal food processing can also pose a substantial risk for increasing food borne diseases that cannot be treated by current antibiotics (Verraes *et al.*, 2013).

Campylobacter spp.: Disease related to *Campylobacter* has been found to be short lived with low mortality rate and public health problem. Examples of some drug *Campylobacter spp*. are resistant to includes: *macrolides*, *quinolones*, *chloramphenicol*, *ampicillin*, *tetracycline, lincosamides*, *aminoglycosides* and other *tylosin, β-lactams* and *cotrimoxazole* (Alfredson and Korolik, 2007; Koluman and Dikici, 2013).

Salmonella spp.**:** This is a major food borne pathogens which has high risk factor to human health and it is widely distributed. *Salmonella spp*. Have shown resistance mostly to beta-lactan antibiotics drugs which includes: *tetracyclines, kanamycin, sulfonamides, chloramphenicol*, *streptomycin*, *cephalosporins* and *penicillins* (Olsen *et al.*, 2004)

Staphylococcus aureus is also a common pathogen for animals and human which has shown resistance to *penicillins* as early as 1948 (Huttner *et al*., 2013). These resistant pathogens are important common causes of spoilage in dairy product.

Enterococci spp. These are common bacteria in the gastro intestinal tract of birds and mammals and are indicators for determination of enteric contamination of foods. These pathogens are resilient and can endure adverse conditions such as low or high pH, temperature and hypertonic salt solution (Werner *et al.*, 2013). *Enterococci* can transfer resistance gene to human-adapted strains and have adverse effect, indirectly (Werner *et al.*, 2013). These pathogens with their unique resistance abilities can be responsible for municipal transmission of diseases related to them.

Yersinia spp.: There are different species including *Y. pestis*, *Y. enterocolitica* and *Y. pseudotuberculosis*, which are pathogenic strains in this genus (Carniel, 2002). *Y. enteroco*litica has been found to be the causes of various diseases including: *septicemia*, *septic arthritis*, *pneumonia*, *cellulitis*, *meningitis*, *empyema*, *osteomyelitis and panophthalmitis*. Genus *Yersinia* has indicated resistance to *carbenicillin, cephalothin and ticarcillin, cefoxitin* and *amoxicillin/clavulanic* acid (Preston *et al*., 1990; Pham *et al*., 1991).

Plasmodium spp.: *Chloroquine* was the empirical antimalarial agent used for treating malaria for years. It is the first hand therapy for malaria. During the past few years, *Plasmodium falciparum* and *Plasmodium vivax* have grown increasingly resistant to this empirical drug; *chloroquine* (Boland *et al.*, 1997). This has challenged the scientist to produce another drug that would be of effective dose against this disease which leads to the production of Artemita and Lufemantrin; a non-itching anti malaria drug (White, 1998). And recent studies have shown that it is getting less effective as well.

Acinetobacter baumannii: This is common causes of nosocomial infections, such as *bloodstream infection*, *ventilator-associated pneumonia*, *urinary tract infection*, and *wound infection* (Urban *et al*., 2003). *A. baumannii* has generated concerns with its resistance to commonly prescribed antimicrobial agents and thereby making it very difficult to treat any disease related to it (Bergogne-Berezin and Towner**,** 1996; Cisneros and Rodriguez-Bano, 2002).

Escherichia coli: This one of the common microbial flora in gastrointestinal tract of poultry and human being which has the capacity to become pathogenic to both due to its ability to form biofilm (Jawetz *et al.*, 1984; Levine 1987). *E. coli* are nonpathogenic yet opportunistic pathogens that are widely used as indicator of faecal contamination in food (Barnes and Gross 1997). Example of diseases caused by *E.coli* and other gastrointestinal coliforms are: *meningitis, endocarditis, urinary tract infection, septicemia, epidemic diarrhea* in adults and children (Daini *et al.*, 2005) and also yolk sac infection, *omphalitis, cellulitis*, swollen head syndrome, *coligranuloma, and colibacillosis* (Gross, 1994). The extensive use of antibiotics as growth promoters in poultry production or to control infectious disease has led to the resistance of these pathogens today (Moreno *et al.*, 2000; Okeke *et al.*, 1999).

Clostridium difficile: *C. difficile* is a serious nosocomial infection, with transmission been through faecal-oral (CDC, 2013). The symptoms exhibited by infected patients includes: fever, abdominal pain, diarrhea, and in severe cases, development of pseudo-membranous colitis. *C. difficile* has been discovered to be resistant to *fluoroquinolones* which have been observed in patients that the drug was administered to (CDC, 2013; He *et al.*, 2013). Transmission of *C.difficile* may be associated with food production and animal husbandry.

3. THE ROLE OF FOOD IN MULTI DRUG RESISTANCE

Food as been shown to be the major causes of the raise in resistant pathogens due to the abuse of antimicrobial in food processing; planting, processing and storage. As such, it has helped in harboring antimicrobial residual traits which the pathogens eventually acquire and become resistant.

There are several routes of transmission of these resistant strains to infectious pathogens along the food chain. However, the direct impact of foods to infections caused by multi-drug resistant pathogens have not been estimated yet (Likotrafiti *et al.*, 2018). The use of antibiotics for prevention of disease or to improve growth has been largely found in Animal farming and Aqua culture (Verraes *et al.*, 2013). The use of overdose or misappropriation of antimicrobial drugs for therapy and prophylaxis of bacterial infections in Animal farming or with their use in feeds as growth promoters in food producing animals are the leading causes of multi-drug resistant pathogens in livestock production (Barber *et al.*, 2003; Aarestrup, 2005; Normanno *et al.*, 2007; Verraes *et al.*, 2013; Schrijver *et al.*, 2018). Van Boeckel *et al.* (2015) estimated the antibiotic consumption rate in livestock and predicted its global importance in the future. Examples include: the use of 3rd and 4th generation *cephalosporins* to treat *E. coli* infections in livestock is related to presence of resistances *E. coli* found in humans. Also, *ciprofloxacin-resistant Salmonella*, and *macrolides* and *fluoroquinolones-resistant Campylobacter* strains are on the rise in food producing animal (Kumar *et al.*, 2012; Mukherjee *et al.*, 2013).

3.1 FOOD FROM ANIMAL ORIGIN

Food from animal products or Aqua culture can indeed act as the resistance booster due to their exposure to the antimicrobial used during their cultivation. Farmers apply antimicrobial to prevent the animals from diseases related to bacteria and vaccines to prevent viral infection to reduce mortality rate in animals. Multi-drug resistance transmission is not exclusive to animal house boundary or Aqua culture as green plants or vegetables can also contribute to Multi-drug resistant microorganisms due to their exposure to effluents from industries, erosion from neighboring farm, or contaminated water with fecal material from effluent of surrounding farms. It is not generally common to find pathogens in food but the risk factor is from non-pathogenic microorganisms or probiotics that could harbor resistance gene and transfer such trait when its forms Biofilms with a virulent organism to cause public health disease is the major concern (i.e., transformation, conjugation, and transduction) (Aarestrup, 2005; Appelbaum, 2006; Hammerum *et al.*, 2010; Verraes *et al.*, 2013). In food producing animals, *Enterocccus spp.* was isolated and was found to contain resistance gene of *gentamicin* (Donabedian *et al.*, 2003). Studies have also shown that, antimicrobial resistance gene can be transferred in inactivated cells, including pathogens, or microbiota in general and, after ingestion, it mobilizes into guts in humans and interact with probiotics in guts to form Biofilms in which genetic materials are transferred by quorum sensing to and fro (Verraes *et al.*, 2013). In general, causes of Multi-drug resistance genes should not be limited to transfers of traits from animals to humans or vice versa with the later been caused by effluent or improper sewer system, but also in overall agricultural practices which include the application of biocides; disinfectant, preservatives during food production could be the leading causes of Multi-drug resistance in the world today (Capita and Alonso-Calleja, 2013; Händel *et al.*, 2013).

3.2 FOOD FROM PLANT ORIGIN

Common Agriculture practices include the application of biocides; Preservatives, Pesticides, Fertilizers during planting season for fear of invasion of insects; locust and microbial contamination etc.

However, Multi-drug Resistant pathogens entry cannot be limited to a specific food processing point alone, they can be seen to be present in both raw materials and also in finished foods (Lee, 2003; Verraes *et al.*, 2013). Although, the complete elimination of pathogens by lethal treatments is not a precursor to Antimicrobial Resistance transmission, because DNA released from lysed cells can still be transferred to living microorganisms through foods consumption or in human digestive system. Also, adverse environmental conditions can drive pathogens to adapt thereby causing the expression of the resistance genes, and as a result, increase the resistance capacity and changes in virulence to the populations (Horn and Bhunia, 2018). Examples of such stress include: *thermal*, *acidic*, and *saline* conditions in which the pathogen adapt to and increase their infectivity (Verraes *et al.*, 2013).

3.3 DAIRY PRODUCT

The fermentation of dairy products to improve its taste and quality in food technology has contributed immensely to the transmission of resistance gene and adaptation of virulent pathogens to adverse condition; heat.

Lactic acid bacteria (LAB), one of the most commonly used starters in food products such as: yoghurt, cheese, dry-cured meat, etc. can act as reservoirs of resistance genes and thus cause the spread of resistance genes to food borne pathogenic bacteria (van den Bogaard and Stobberingh, 2000; Smith *et al.*, 2002). For example, *tetracycline*-, *erythromycin*-, and *vancomycin-resistant* genes that has been indentified in clinical bacterial species were also detected in *Lactococcus lactis* and *Lactobacillus* species isolated from fermented meat and milk products (Mathur and Singh, 2005). In humans, some probiotics have shown the presence of antimicrobial resistance within their genomes (Cox and Wright, 2013). For example, *Enterococcus spp.* was found to have antibiotic resistance, especially to *vancomycin* although resistance to *chloramphenicol* and *erythromycin* was also observed (Teuber *et al.*, 1999). Therefore, the presence of antimicrobial resistance genes in starter or probiotic cultures that are intentionally added to improve the quality of food during animal food processing can also pose risk for increasing resistance of food borne diseases that cannot be treated by their empirical antibiotics (Verraes *et al.*, 2013).

4 HEALTH IMPLICATION OF MULTI DRUG RESISTANT PATHOGENS

Delay in therapy

Multi-drug resistance has reduced the ability to administer effective therapy to patients in time (Ibrahim *et al.*, 2000; Kollef *et al.*, 1999; Lautenbach *et al.*, 2001). Lautenbach et al., (2001) matched control subjects infected with non extended spectrum β-Lactamase (ESBL) producing strains of *K.pneumoniae* and *E.coli* against its empirical antibiotics. After 11.5 h, there was reduction in its lethal efficiency and infection was still detected. Infections caused by antimicrobial-resistant organisms has enforced more drastic approach which could have some adverse effect on the subject. For instance, the use of colistin for highly resistant *Pseudomonas* or *Acinetobacter* infections is also associated with a high susceptible risk of renal dysfunction (Levin *et al.*, 1999). In addition, the use of vancomycin for the treatment of deep-seated *methicillin-resistant Staphylococcus aureus* (MRSA) infections has shown little success recently (Levine *et al.*, 1991). Finally, multi-drug resistant pathogens have increased surgical procedures for patients with such infection to remove the nidus of infection (Harris *et al.*, 1999).

Economic Importance

Multi-drug resistant pathogens have increased the cost of diagnosis, therapy and treatments across the world. The reason been that the empirical antibiotics that have lethal effects on each pathogens has little effect now when administered to patients due to the resistance that these pathogens have acquired from consistent usage or overdose, from food; Animals and Diary products due to prolonged exposure to antibiotics or plant treatments.

Increased Mortality rate

Multi-drug resistance has increased the death rate amongst patients across the world, many of which have been traced to resistance of pathogens to their empirical drugs.

Chloroquine: Malaria is a common infectious disease and very particular to Africa due to its favorable weather conditions, poor drainage systems and poor human hygiene practices. In recent times, *Plasmodium falciparum* and *Plasmodium vivax* have grown increasingly resistant to chloroquine factors which could be responsible have been highlighted above (Boland *et al.*, 1997). These have challenged scientist to provide a more efficient drugs that could cure malaria if a patient gets infected. This led to the discovery of *Artemita* and *Lufematrin*; an effective dose that has no itching effect when taken. Today, *Artemita* and *Lufemantrin* is seemly less effective due to over use, under use; not completing the dose required by the patient and these have enabled *plasmodium*, once again to develop or developing resistance to the drug with more cost implications.

Empirical Antibiotics: In Africa, the abuse of drug is no news as its common amongst citizens. It is an arbitral practice to self medicate in Africa especially in Nigeria without consulting a medical practitioner for proper diagnosis and administration of drugs. Some of the abused antibiotics include: *Tetracycline, Chloramphenicol, Ciproflaxin, Flagyl,* e.t.c. which are not effective except in combination.

Due to the abuse of usage or self medication, the cost of running a complete diagnosis and also cost of research to produce effective drug(s) that would be lethal have increased considerable. Infact many patients have had to spend longer time in hospital, difficulty in determining the actual therapy to diagnose or drug to administer due to resistance that have been developed by these pathogens to their empirical drugs. It has increased human-human transmission rate and in some cases death of the patients.

1. TRANSMISSION OF MULTI DRUG RESISTANT PATHOGENS

Some part of Africa is still struggling to cope with the rise in their population and human activities that could be potent drivers of antibiotic resistance. Example include: poor sanitation, infection control standards, poor water hygiene systems, low drug quality, diagnostics and therapeutics, and travel or migration quarantine. These are precursors to the mutation in various genes residing on the chromosome of the microorganism, as well as exchange of genetic material between organisms plays a vital role in the distribution of antibiotic resistance (Holmes *et al.*, 2014). Local transmission from human to human is usually through faeco–oral route which is the most important route especially for resistant pathogens of the family *Enterobacteriaceae*, and these is linked to poor sanitation practices. Another example is *Methylene Resistant Staphylococcus aureus* (MRSA) which is usually transmitted from human to human due to prolonged hospital stay or poor hygienic hospital. The most common mode of transmission of resistant strains is through sexual intercourse example include *N. gonorrhoeae* (Wellington *et al.*, 2013; Lewis, 2013; Chamchod and Ruan, 2012).

Indiscriminate use of antimicrobial growth promoters in farm animals, poultry or on plants is associated with the transmission of resistance to humans through dairy products or meat consumption or food. Another issue to consider is the environmental factor which has enhanced antibiotic resistance due to prolonged exposure to unfavorable conditions like heat, herbicides, pesticides and antimicrobial due food processing as contributed to resistance and transmission with organisms and to humans. Poor sewage systems, waste pollution from pharmaceutical industry effluents, and inadequate waste management procedures have enhanced environment transmission to resistant strains (Lewis, 2013; Kristiansson *et al.,* 2011).

2. PREVENTION AND CONTROL OF MULTI DRUG RESISTANT PATHOGENS

Improved farming procedures

Improved agricultural practices have significant role to play in reducing transmission of antimicrobial resistance pathogens from farm to gut. Food security/Biosecurity is essential in other to achieve healthy living. Biosecurity can be defined as the measures in place to reduce or eliminate the potential threat of the emergence or spreading of diseases at region or country-levels (FAO, 2011; 2003). It can be broken down into; HACCP (Hazard Analysis and Critical Control Points), good agricultural practices, good hygiene practices focus on health and management and Microbial assessments, risk assessments.

Therefore, biosecurity can play economical role in public health especially in agricultural production; reduction in use of chemical preservatives for crops during production and reduction in the use of antibiotics in treating animals (Nahar *et al.*, 2014; Postma *et al*., 2016; Sivapuram *et al.,* 2010). Early diagnostics of resistant bacteria and their genes will aid agricultural practitioners to early detect and separate the infectious plants and animals to stem the spread of disease (O'Neill, 2015). Today, there are a lot of modern methods which is used to determine and diagnoses of resistance bacteria in food process chain including, Polymerase Chain Reaction (PCR), Fourier Transform Infrared Spectroscopy (FTIR) (Lechowicz *et al.,* 2013), Nanoparticles whose indicator is based on bacterial metabolic activity and also antibiotic susceptibility in blood or milk is also a means to early detect and determine proper diagnosis (Huh, 2011).

Green Antibiotics

As earlier stated, the abuse of antibiotics has led to the increase in resistance genes and thus increased infectious diseases that cannot be treated with today's antibiotics which is why the use of natural and effective antimicrobial agents as alternative therapeutic approach (Calo *et al.,* 2015)**.** A typical example is essential oils which are biological and active substances produced by plants and has been traced to have antibacterial, antifungal, sedative, antioxidant, digestive, anticancer, anti-inflammatory and antiviral activities (Aumeeruddy-Elalfi and Gurib-Fakim, 2015; Sharifi-Rad *et al.*, 2015; Pilevar and Hosseini, 2013). The efficiency of essential oils produced by plants depends on their genotypes, chemical composition, agronomic and environmental conditions (Mohamed *et al.*, 2014).

Essential oils

These are biological and active substances which are produced by plants that have some therapeutic advantages such as: *antibacterial, antifungal, sedative, antioxidant, digestive, anticancer, anti-inflammatory* and *antiviral activities* (Aumeeruddy-Elalfi and Gurib-Fakim, 2015; Sharifi-Rad *et al.*, 2015; Pilevar and Hosseini, 2013) in which the effectiveness is dependent on their genotypes, chemical composition, agronomic and environmental conditions (Mohamed *et al.*, 2014). Recently, essential oils have been shown to have preservative characteristics which can be adopted in food industry to preserve food and also to prevent developing multidrug-resistance in bacteria (Aumeeruddy-Elalfi and Gurib-Fakim, 2015; Sharifi-Rad *et al.*, 2015; Pilevar *et al.*, 2017). Essential oil also has some synergistic effect against microbial activities when used with thyme and this could have some economic importance (Yap *et al.*, 2014)73. Duarte *et al.*, (2011) has studied on antimicrobial effect of essential oil and antibiotics against *A. baumannii* and the result shows that essential oil can improve antimicrobial effect of *ciprofloxacin*, *gentamicin* and *tetracycline.*

Nanobiotics

Nanobiotics are nano-sized materials that can be bio-augmented with antibiotics to have antimicrobial activity with no adverse health effect (Huh and Kwon, 2011). Example of such process is Nano-encapsulation to improve efficacy of antibiotics (Hajipour *et al.*, 2012; Jamil and Syed, 2017). Also, nano-carriers have been discovered to improve drug absorption by enhancing solubility which helps in cellular absorption (Thorley *et al.*, 2014). Examples of a nano-carrier is *liposomes* and *chitosan* have been used as drug carrier because of their characteristics which includes: *biodegradability, biocompatibility*, with minimal side effects (Kumari *et al.*, 2010). Other functional advantages of nanobiotics are (i) production of different antibiotics by the same nanoparticles, (ii) using different mechanisms to prevent bacteria growth, (iii) improving drug efflux, (iv) releasing high amount of antibiotics at the infection site ((Huh and Kwon, 2011; Pelgrift *et al.*, 2013).

Lactic acid bacteria as an antibiotic

Lactic acid bacteria as a probiotics can serve as an alternative approach due its unique characteristics (Woolhouse *et al.,* 2015). Some of these unique qualities include: reduction of pH, production of lactic acids, diacyls, bacteriocins, hydrogen peroxide, etc., which prevents mycotoxins, growth and activity of food spoilage microorganisms (Mokoena, 2017). For example, *Lactobacillus plantarum,* has high antifungal activity and also antiviral activity in a controlled experiment in vitro (Kwak et al., 2013; 2014). One major concern is the bacteria ecosystem within the gut due to the ability to form Biofilms and therefore becomes virulent (Gaggia *et al.,* 2010; Callaway *et al.,* 2008). Probiotics serves different functions in the gut which includes: protecting the guts microbial flora, improving immune system and preventing antigen colonization (Allen *et al.,* 2014). Using Lactic acid bacteria as an antibiotic could of immense benefits to improve strains that have more antimicrobial properties in other prevent drug resistance in the body.

Predatory bacteria

Some bacteria have the ability to feed on other bacteria. Such bacteria are referred to as *predatory bacteria*. They are usually gram-negative which contains an enzyme DNases and Proteases that have proven effective against pathogenic bacteria e.g *Micavibrio aeruginosavorus, Bdellovibrio bacteriovorus* and belong to two subgroup of proteobacteria (Davidov et al., 2009; Davidov and Jurkevitch, 2004; Borthwick, 2012; Bragg *et al.*, 2014). They have proven effective against biofilms and multidrug-resistant pathogens including *E. coli, P. aeruginosa, A. baumannii, Pseudomonas putida and Klebsiella pneumonia* (Allen *et al.,* 2014; Kadouri *et al.*, 2013; Lambert and Sockett, 2013)**.** These bacteria could serve both beneficial functions as probiotic and protective functions as antibiotic (Economou and Gousia, 2015). These bacteria are effective in treatment of ocular diseases caused by *Shigella flexneri and Moraxella bovis* in animals which includes rabbits and cows, respectively (Dwidar *et al.,* 2012). With the development of antibacterial resistant bacteria and inadequately treatment by conventional antibiotics, predatory bacteria as live anti-bacterial can have effective role in human health and treatment of diseases (Dwidar *et al.*, 2012; Sockett and Lambert, 2004). In spite of useful properties of these bacteria, they have some limitations in their application. Predatory bacteria can have negative effect on the natural microbiota of the body. Furthermore, existence of Gram-positive bacteria can reduce their predation efficacy (Kadouri *et al.,* 2013; Schoeffield *et al.*, 1996).

Vaccines

Vaccination is one of the primitive preventive measures against infectious diseases. It interact with the immune system to activate response against an antigen and master the method of exterminating the antigen to incase of future occurrence (Sanghi and Twilu, 2014). Vaccines are inactivated or attenuated pathogens in which the body triggers immune response to protect the body and invariable prevent future occurrence (Atkins and Flasche, 2018; Ginsburg and Klugman, 2017). Today, modern medicine has adopted the combine therapy approach using antibiotics and vaccines for treatments and prevention of diseases. Vaccines have prevalence role on resistant bacteria by reducing the use of antibiotics and prevent intrinsic transmission of infectious pathogens. There are many immunization programs set up to stem the growth of certain infection diseases. These are preventive measures to reduce the spread of diseases in animals and can significantly increase the productivity by lowing the use of antibiotics and with appropriated novel vaccines program will be able to lessen the worldwide spread of infective diseases also the cost of treating farm animals, poultry and plants which would have a ripple effect in reducing the exposure of humans to resistance pathogen and diseases (Atkins and Flasche, 2018; Lipsitch and Siber, 2016).

3. CONCLUSION

Multi-drug resistant Pathogen is a global concern that has caused several public health issues and adverse effect on the world's economy today. It is incumbent to note that the assurance of public food safety is to be taken with seriousness because it has the ability to stem the growth and spread of resistant pathogens and reduce public health diagnosis, unnecessary delay in hospital and cost of treatments. The common practice of self medication and abuse of drug should be stopped by sensitization of the populace to adopted proper use of antibiotics and reach out professionals before taken any drugs. The transmission of these resistant pathogens to human and animals have been traced to farm practices; use of pesticides, herbicides, fungicides and antibiotics which have helped the pathogens to acquire resistant strains. In other to curb these, biosecurity procedures to ensure food safety in agriculture and food production process are really beneficial practices that can play a significant role in reducing the development of resistant strains and transmission of drug resistant pathogens to humans. Recently, scientist have been in search for alternative measures to combat the rise in resistant pathogens through good farm practices, the use of essential oil; a substance produced by plant that have antimicrobial properties, in combination with empirical antibiotics which have shown success and have proven to be more cost effective. Although further research is encourage to ascertain the level of potency and efficiency of these alternative measures in dealing with drug resistant pathogens and human treatment.

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