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Part 3: The Role of Phytomedicine in the Challenges of Emerging, Re-Emerging Diseases; and Pathogens Resistance to Antibiotics

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Abstract
Reviews literature related to the study. It focuses on the historical use of plants as medicine by human. The approach taken is based on the geographical location of various civilizations in which the plants are/were used as source remedies throughout the five continents of the world. Topical issues and an overview cover on medicinal plants, past and their present uses, use of antibiotics in allopathic medicine and development of antimicrobial and antifungal resistances to the currently used drugs. In addition, issues on the emergence and reemergence of new and old diseases have also been covered.

Keywords: Antibiotics; Re-Emerging Diseases; Pathogens Resistance.

1. Introduction
Reviews literature related to the study. It focuses on the historical use of plants as medicine by human. The approach taken is based on the geographical location of various civilizations in which the plants are/were used as source remedies throughout the five continents of the world. Globally there is a trend of erratic antibiotic use and this has led to challenges of their regimen. This has resulted in the influx of mortalities. There is also an urgent need of patient education on the used such drugs. There is also emergence and reemergence of new maladies. The only answer to such challenges is vested in phytomedicine.

2. Erratic use of antibiotics
Research in Croatia, one of the teaching hospitals, showed that tight control on antibiotics is necessary[1]. Mainly antibacterials were evaluated in two years and it emerged that the antimicrobial utilization was similar in both years. However, the pattern of utilization had changed in contrast to the outpatient setting where the pattern of antimicrobial prescribing remained the same. There was more liberal prescription over the counter sales as compared to the previous years when certain drugs were restricted[1]. Furthermore, it established the fact that when the use of antibiotics is controlled, there is like hood that the bacteria do not develop resistance to the used antibiotics. Common typhoid fever is generally caused by *Salmonella enterica* serovar. *Typhimurium* (common name *S. typhi*) are Gram-negative whose treatments are difficult[2]. The antibiotics used in the management of the diseases include chloramphenicol as the first drug of choice. Other drugs which may be employed are ampicillin, penicillin G, Norfloxacin, Streptomycin and Rifampicin. However, there are cases of resistances to antibiotics which were latertraced to genetic changes within the cell structure[3]. This was noticed while certain strains were subjected to fusidic acid which is a steroid like antibiotic and which establishes EF-G. GDP on the ribosome after translocation has occurred thus blocking protein synthesis. Against this backdrop of genetic modifications, phenotypes of the organism with variable susceptibility to the mentioned antibiotics have emerged. Nosocomial systemic bacterial infections have revealed that there is correlation between nosocomial infections and mortality. Such mortalities have been further complicated by the fact that pathogens so studied have strains that are resistant to treatments by more conventional or the β lactam antibiotics[4].

The research was carried on strains of both Gram-positive and Gram-negative bacteria which included *Staphylococcus, E. coli, Klebsiella* spp, *Enterobacter* spp., *Serratia* spp and other Gram- negative Bacilli. It was evident that Methicillin resistant strains of Staphylococci and penicillin G resistant Streptococci, ampicillin resistant enterococci and cefotaxime resistant enterobacteriaceae *Pseudomonas* spp., were resistant to the drugs that were currently in use in hospital. The above data provided hospital decision makers with pertinent information on the clinical consequences of nosocomial infections caused by antibiotic resistant bacteria. It is important to mention that there are possibilities of bacterial attacks as epidemics universally. In the 21st century, affluent societies lived under the impression that they were free from the attack of pathogenic bacteria and if they by accident suffer, there would be an antibiotic to cure the malady[5]. This is false and it is prognosed that if the conditions of discovering new drugs remain (status quo) the fatalities from such cases may be alarming. The impression that the availability of antibiotics within short notices to combat diseases is a fallacy and such a notion may consequently result into a catastrophic event[6]. This is so because antibiotics have kept human and livestock from many plagues that were the scourges of humanity until the second half of the 20th century. However, ironically antibiotics are weak marketable goods in that patients stop buying them once their health returns, after short courses of treatment before the completion of the stipulated period of treatment[7]. To date a vast majority of infections caused by *Staphylococcus aureus* are penicillin resistant[8]. Hitherto new ones only provide short respite until new resistance emerges which are staphylococcal based. Bovine mastitis induced by *S. aureus* is an example of infection difficult to eradicate by conventional antimicrobial therapies[9]. *In vivo* studies in mice indicated that the pathogens persisted in mice despite being treated with antibiotics. Such studies were carried using several mutants of the bacteria which included isogenic hem mutants that had small colony variant (scv) phenotype. The latter mutant expressed a marked inability to colonise tissues. Although the hem mutant and *S. aureus* were susceptible *in vitro* to cephapirin, it was 100 times more persistent than the parental strains in the mammary glands when the antibiotics were administered at the rate of 1 or 2 mg/ kg[9]. The studies concluded that despite the fact that hem. B mutant has reduced ability to colonise mammary glands, scv phenotype may account for the persistence of *S. aureus* under antibiotic *in vitro*.

Although it may seem obvious, it is essential to point out that the antibiotics, that were easy to discover have already been found, the search for new ones involves a substantial amount of high quality and laborious research[10]. Currently, there are various antibiotics which can combat most bacterial diseases but several alarms have been raised to develop new antimicrobials which could be used to combat the newly emerging resistant ones[11].

The need has been prompted by several reasons, among them the spread of multi-drug resistant organisms, the spread of emerging and re-emerging pathogens and the consequential high social and economic impacts of infectious diseases. Although vaccinations are a classical way of controlling infections they can only be used for preventive measures and not curative once the diseases is established[12]. Vaccines such as the pneumococcal one may also help in the reduction of antibiotic resistant isolates. However, there have been controversies since studies have failed to establish the role of vaccination in the reduction of resistance but have suggested that reduction of antibiotic pressure may be needed to reduce the resistance frequency[13]. Research may also be slowed down because of the attitude of the clinicians who are satisfied by the fact that what they have is good enough for the time being.

The belief that the need for new antibiotics is not pressing may then appear as justified. However, for cases involving elderly or immunocompromised patients, for whom the prognosis is so dangerously poor, the development of new treatment should be a matter of priority. Patients with diverse medical conditions including those immunocompromised are in one way or the other likely to create another segment with the risk of succumbing to infections in any given human populations. In developed countries, nosocomial infections occur in 5-7% of patients hospitalized for other reasons, thus there is increase in hospital stay for at least an average time of four extra days, increasing the cost of hospitalization by U$500[12, 14]. It is more complicated when the patients are in the intensive care unit in that both the risk and the cost are more than doubled; their additional stay can extend up to nineteen days with a concomitant higher mortality rate, often associated with antibacterial therapeutic failure[15].

3. Mortalities from antimicrobials

The literature hinted that bacterial infectious diseases have impacts with far-reaching effects in terms of morbidity and mortality. In developing countries alone, according to the[16], statistics on bacterial and bacterial related infections are responsible for 60% of the annual mortality. Amongst the dilapidated and elderly, despite existing antibiotic therapies and vaccine, bacteria remain the leading source of morbidity and mortality worldwide[17]. Pathogens also contribute to a third of the deaths and ailments both in Europe and worldwide. Although vaccination contributes substantively towards curbing pneumonia, it does not provide full protection because not all individuals respond equally well to the immunization and because the immunity provided by the available capsular polysaccharide based vaccines do not cover all the possible serotype variants of the pathogen[18]. It would be imperative to look for therapeutic techniques that seek to minimize accelerated development of resistance by micro-organisms to antibiotics; there has been marginal impact of patient education on antibiotics prescribed to children with pharyngitis and adults with acute bronchitis in private practices[19]. Profiling the physician's prescription, records revealed that there was increase in antibiotic prescription for children with pharyngitis in distant control but decrease in local control practices and intervention cases had the highest decrease from 34 to 30%. In adults control through education reduced substantively from 55 to 44% in local control, from 50 to 44% in distant control, and from 60 to 36% at the intervention practices.

4. Patient education on drug abuse

Patient education can help to reduce antibiotic use for adults through physician directed efforts and restrictions. The foregoing statement has more to do with ethical perspective as

opposed to the open happy physicians who prescribe antibiotics at the mention of ailment without carrying out diagnostic survey and investigations[20]. With the unending problems with antibiotics, the studies for alternatives are necessary to evolve potent antibiotics with unending problems with antibiotics, the studies for alternatives are necessary to evolve potent antibiotics with activities against both Gram-positive and Gram-negative bacteria. Antibiotic activities of the extracts from the study of plants were comparable to the standard antibiotics with a zone of inhibition seen to be quite potent[21]. Local communities in Western Kenya claim that there are certain plant extracts, which are known to have antibiotic activities and such plants include: *Chamaecrista absus* against measles, *Emilia coccinea* against syphilis and *Piliostigma thonningii* against gonorrhoea[22]. Some plants like *Kedrostis foetidissima* and *Melia Azadirachta* are used for the treatment of general viral rashes and swellings like measles and mumps. *Aloe* ssp. is used for treatment of herpes zoster.

5. Remedy from plants against viral infections

Currently, tackling "modern" arising infections is crucial[23]. An increasing number of HIV infections and AIDS cannot use the currently approved anti HIV drugs, including the reverse transcriptase and protease inhibitors due to the adverse effects and the emergence of drug resistance[24]. Many of the antivirals presently in use have narrow spectrum activity and restricted therapeutic usefulness[25]. Despite most governments providing free ARVs, it is still not yet 100% coverage among patients in needed for antiretroviral drugs. These drugs are expensive and beyond the reach for most of the victims. For the last two decades, scientists have been forced to address the epidemic, which has drastically, retarded socio-economic development and in turn resulted in a wildfire rate of its spread. There are other plant species, which yield similar compounds with the same activities[26]. Such species are from the Euphorbiaceae family which include plants like *Euphorbia poissonii*; some plants with anticancer principles like *Pedilanthus* ssp. and showed activities against HIV–1 Virus[27]. Oleanolic acid was also identified as an anti HIV principle from several plants, which include *Rosa woodsii*, leaves, *Hyptis capitata* (whole plant) *Syzygium claviflorum* leaves and *Ternstroemia gymnanthera*. There are also other classes of compounds from plants, which have useful effects against the HIV virus[27] which include alkaloids, proteins, polyphenols and polysaccharides. There are also other plant extracts, though unclassified that have been found to have antiviral activities. The plant extracts, however, have been studied *in vivo* and *in vitro* animal experimental models. However, no clinical trials have been conducted yet.

Next to malaria, AIDS is the leading infectious cause of death in the world. Untreated disease caused by HIV has a fatality rate of 100%. Nevertheless, it should be stressed that a number of natural products mainly derived from plants have proved effective in suppressing HIV replication and progress[28]. In regions where herbal medicine could be considered to be at par with the current dominant allopathic medicine, most of the therapeutic plants are from the traditional data bank[23]. Several plants were investigated to establish their scientific potential values in the management of HIV. It emerged that quite a good number had antiretroviral activities and potential drug development that are comparable to the drugs currently in the market[23]. This revelation enhances the use and encourages further studies on the use of plants in tackling modern problems and conservation of indigenous knowledge in Africa. However, only a meagre portion of East African plants has been currently covered in the ongoing work *in vitro* as in the case of[29] on trying to find out new antiplasmodia compounds from the indigenous flora from the East African region.

6. Emerging and remerging diseases a burning issue

Problems of emerging and reemerging resistant micro-organisms and their strains are common phenomena[30]. The continuous development of antimicrobial resistance to the currently used drugs has called for an urgent attention for development of novel drugs. Some of the organisms that were previously easily managed to commonly used antibiotics have become a challenge in patients' management. For instance *E. coli,* under virulent conditions causes extra intestinal infections a wide diverse spectrum of diseases including: urinary tract infections (UTI), new born meningitis, abdominal sepsis and septicemia[30]. All these infectious diseases have posted a challenge on their management due to high incidence rates of drug resistance being transmitted by plasmids[19, 31]. Studies have shown that antibiotics can start to lose their efficacy at the beginning of their clinical use through the development of antibiotic resistance by bacterial pathogens[32]. The emergence of antimicrobial resistance is primarily due to excessive and often unnecessary use of antibiotics in humans and animals[33, 34]. Use of counterfeit drugs and suboptimal management of drugs due to lack of education are some of the factors associated to development of antibiotic resistance. Challenges in antimicrobial resistance are more real due to emerging and reemerging diseases. The advent of HIV/AIDS epidemics have also led to over use of drugs like Trimethoprim-Sulfisoxazole for the prevention of opportunistic infections. This overuse propagates antibiotic resistance. In In additionally, HIV infection is associated with primary multi-drug resistant-tuberculosis[34, 35]. Challenges in antimicrobial resistance are more real due to emerging and reemerging diseases. It is, therefore, empirical that further studies on antibiotic discovery is vital considering the threat posed by the emergence of drug resistance[35]. The best example is the frequent upsurge of Legionella an organism which becomes a threat due to change of lifestyle of using air conditioning systems more frequently. Such a condition enhances quick multiplication of the organism and its delivery to human respiratory system. Based on metagenomics in microbiology it is possible to identify the gene pool which is either cultivable or not cultivable which may be used in future identification of unexpected potential pathogens following the identification of all the virulence related genes–"resistone" present in the environment[37]. The ecological impact of human activity is well-illustrated by the changes seen in antibiotic resistance through the years[38]. Bacteria quickly develop resistance to antibiotics usually within a few years of their commercial manufacture and marketing. For example in 1943 when penicillin was first prescribed, virtually all Gram-positive infections were susceptible to its effects on cell wall synthesis[38]. However, the bacteria now developed resistances to the drug and by 1946 resistant strains were already well-recognized. Mycobacteria require special attention, but lightly, because it causes infections of a killer disease, tuberculosis

(TB). Currently, the disease is the leading cause of deaths worldwide from a single human pathogen. The disease claims more adult lives and children than diseases like AIDS, malaria, diarrhoea, leprosy and all the other tropical diseases combined (3S, 4R). It is estimated that a third of the world's population is currently infected with *M. tuberculosis*, where 10% of those infected will develop clinical diseases, more so those that are immunosuppressed or immunocompromised as a result of HIV (3S, 4R). Although there are several broad spectrum antibiotics, there has been an upsurge in the mortality rate due to the emergence of multi drug resistant strains of *M. tuberculosis*[39]. By the year 2000 the mortality due to the disease had reached over 3.5 million[40, 41]. The upsurge in the incidences of TB mortality is further attributed to poor physical infrastructure in the rural areas where majority of the developing world live, lack of diagnosis and drug supply. There is also poor supervision and medical care and as a result of drug resistance development[10]. This means that there is need for broad effective spectrum to curb this malady. Tuberculosis was considered as a conquered malady that was disappearing, but has made a comeback in the recent past[41]. This new scenario is only due to the associated of *Mycobacterium* with AIDS but due to evolution of strains of the pathogens that are resistant to several drugs which are currently in use[41]. It seems clear that besides biomedical research, additional social measurements are urgently required to deal with the problem of infectious diseases in a global scenario.

7. Conclusion

With all the above surveyed and discussed scenarios, it would be logical to do a documentation of the local medicinal flora for future references. It is also imperative that a thorough pharmacological profiling be done if a scientific selection and discovery of the new products is to be achieved. Finally, it is important that; the Pharmacognosy of such drugs is carried out to assist in the selection of the new products for commercial development. Such are the compounds that may be used to intercede for the rapidly mutating pathogens.

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