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Review Article

ANTIBIOTIC RESISTANT ORGANISM: AN EMERGING PUBLIC HEALTH PROBLEM AND ROLE OF AYURVEDA (AN OVERVIEW)

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ABSTRACT

Antibiotic resistance is a serious and growing phenomenon in contemporary medicine and has emerged as one of the pre-eminent public health concerns of the 21st century. Antibiotic resistance is a form of drug resistance whereby some (or, less commonly, all) sub-populations of a microorganism, usually a bacterial species, are able to survive after exposure to one or more antibiotics; pathogens resistant to multiple antibiotics are considered multidrug resistant (MDR) or, more colloquially, superbugs. However, the increasing prevalence of antibiotic-resistant bacterial infections seen in clinical practice stems from antibiotic use both within human medicine and veterinary medicine. According to a new report by the U.S. Centers for Disease Control and Prevention (CDC), at least 2 million people in the United States develop serious bacterial infections that are resistant to one or more types of antibiotics each year, and at least 23,000 die from the infections. Ayurveda refers that the *Dosha* get aggravated by exogenous or endogenous causes, which further spread in body by the using improper foods and activities. It vitiates *kosthagni* (Metabolic enzymes) which leads to improper digestion production of *Ama* (toxin) and their minute *Srotas* (body channels) this is called *shrotodushtie* (Disequilibrium in channels). When the *Rasadhatu* (plasma and lymph) containing *Ama* (toxin) and aggravated *Doshas* reaches the place where *Kha Vaigunya* (movement tendency towards empty space) has taken place, it being unable to get into the minute channels, gets obstructed, stagnates/accumulates there and gives rise to such diseases caused by exogenous causes. That is why, Ayurveda advocates enhancing the immunity against the diseases. Several plant extracts have exhibited synergistic activity against microorganisms. The Indian plants possessing significant anti-microbial activity are *Neem* (*Azadirachta indica*), Pippali (*Piper longum*), *Guduchi* stem (*Tinospora cordifolia*) and *Amla* fruit (*Emblica officinalis*), among others. The purpose of this paper is to outline possible ways in which certain concepts of Ayurveda can be used for finding remedy of emerging health problem "The Antibiotic Resistant Organism".

KEY WORDS: *Ama*, *Rasa dhatu*, *Srotas*, MDR, *Kha-vaigunya*, *Sroto-dushti, Sahah bala*, *Yuktikrit bala*.

INTRODUCTION

Ayurveda is well known as the Vedic system of health care of India, practiced effectively for thousands of years by millions of people.[1] The image of life as a river, an endless stream of processes that produce continuous change, yet enable the overall form to remain the same is consistent with the viewpoint of Ayurveda. Every day we breathe, eat and drink, and process large quantities of various kinds of matter, yet we may remain relatively unchanged. By understanding how the different processes involved maintain the bodily system, we may gain insights into its various modes of functioning. The river image is parallel to modern understandings of life based on systems theory[2] and non-equilibrium thermody-

namics,[3] and points to such areas of modern science as possible sources of parallels to Ayurveda. One verse from the major text on Ayurveda, the Charaka Samhita[4] states "*Ayurvedo Amritanaam*," that the purpose of Ayurveda is to gain immortality the longest lifespan of all. Most Western biomedical explanatory models of the body are framed in terms of bio-chemistry, rather than physics. In contrast, most traditional medical systems such as Ayurveda begin with "energy" for their theory of biologic processes, so that in essence they begin with physics, and move on to explaining biochemical and biologic levels on that basis. This may explain the misunderstanding, and, often, dismissal of such models found in modern Western medicine. Ayurveda advocates that a disease emerges by the exogenous or endogenous causes but finally (at biological level) it effects to the natural equilibrium of three body humors '*Tri-dosha*", which are responsible for keeping healthy to a healthy person if they are homogenous. Further Ayurveda refers that Diseases caused by super human / subtle agencies are two types; Humiliated divine/subtle beings and Developing from proximity or contact with another disease person. [5]

Antibiotic resistance Organism

Antibiotic resistance is a serious and growing phenomenon in contemporary medicine and has emerged as one of the pre-eminent public health concerns of the 21st century; particularly as it pertains to pathogenic organisms (the term is especially relevant to organisms which cause disease in humans). It is said by Cesar Arias, M.D., Ph.D., the study's senior author and associate professor in the Division of Infectious Diseases at the UT Health Medical School.[6] According to a new report by the U.S. Centers for Disease Control and Prevention (CDC), at least 2 million people in the United States develop serious bacterial infections that are resistant to one or more types of antibiotics each year, and at least 23,000 die from the infections. [7]

Antibiotic resistance is a form of drug resistance whereby some (or, less commonly, all) sub-populations of a microorganism, usually a bacterial species, are able to survive after exposure to one or more antibiotics; pathogens resistant to multiple antibiotics are considered multidrug resistant (MDR) or, more colloquially, superbugs. Microbes, rather than people, develop resistance to antibiotics. [8]

Antibiotic resistant organism may take the form of a spontaneous or induced genetic mutation or the acquisition of resistance genes from other bacterial species by horizontal gene transfer via conjugation, transduction, or transformation. Many antibiotic resistance genes reside on transmissible plasmids, facilitating their transfer. Exposure to an antibiotic naturally selects for the survival of the organisms with the genes for resistance. In this way, a gene for antibiotic resistance may readily spread through an ecosystem of bacteria. Antibiotic-resistance plasmids frequently contain genes conferring resistance to several different antibiotics. This is not the case for *Mycobacterium tuberculosis*, the bacteria that causes Tuberculosis, since evidence is lacking for whether these bacteria have plasmids. [9]

Historical Review of Antibiotic Resistance

There is evidence that naturally occurring antibiotic resistance is common.

In 1945, in his Nobel Lecture, "Penicillin," Alexander Fleming warned against the use of sub-therapeutic doses of antibiotics – "bought by anyone in the shops" without a prescription*:* "The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose he and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death?"[10] While experimenting at the University of Wisconsin-Madison, Joshua Lederberg and his graduate student Norton Zinder also demonstrated preexistent bacterial resistance to streptomycin. [11]

In 1962, the presence of penicillinase was detected in dormant *Bacillus licheniformis* endospores, revived from dried soil on the roots of plants, preserved since 1689 in the British Museum. [12] (a,b) Six strains of Clostridium, found in the bowels of William Braine and John Hartnell (members of the Franklin Expedition)

showed resistance to cefoxitin and clindamycin. [13] It was suggested that penicillinase may have emerged as a defense mechanism for bacteria in their habitats, such as the case of penicillinase-rich *Staphylococcus aureus*, living with penicillin-producing Trichophyton, however this was deemed circumstantial. Search for a penicillinase ancestor has focused on the class of proteins that must be a priori capable of specific combination with penicillin. [14]

Causes: In medicine, the major problem of the emergence of resistant bacteria is due to misuse and overuse of antibiotics. [15] In some countries, antibiotics are sold over the counter without a prescription, (India is one of them), which also leads to the creation of resistant strains. Other practices contributing towards resistance include antibiotic use in livestock feed. [16]

Household use of anti-bacterial in soaps and other products, although not clearly contributing to resistance, is also discouraged (as not being effective at infection control). [17] (a,b) Unsound practices in the pharmaceutical manufacturing industry can also contribute towards the likelihood of creating antibiotic-resistant strains. The procedures and clinical practice during the period of drug treatment are frequently flawed - usually no steps are taken to isolate the patient to prevent re-infection or infection by a new pathogen, negating the goal of complete destruction by the end of the course. [18]

Antibiotic resistance increasing with duration of treatment

Antibiotic resistance has been shown to increase with duration of treatment; therefore, as long as a clinically effective lower limit is observed (that depends upon the organism and antibiotic in question), the use by the medical community of shorter courses of antibiotics is likely to decrease rates of resistance, reduce cost, and have better outcomes due to fewer complications such as C. *difficile* infection and diarrhea. [19] In some situations a short course is inferior to a long course.[20] One study found that with one antibiotic a short course was more effective, but with a different antibiotic, a longer course was more effective.[21] Advised to complete a course of antibiotics is not always based on strong evidence, and some researchers discourage the use of the prescription label "Finish all this medication unless otherwise directed by prescriber." Often, antibiotics can be safely stopped 72 hours after symptoms resolve.[22] However, some infections require treatments long after symptoms are gone, and in all cases, an insufficient course of antibiotics may lead to relapse (with an infection that is now more antibiotic resistant).[23]

As we aware that the Patients taking less than the required dosage or failing to take their doses within the prescribed timing results in decreased concentration of antibiotics in the bloodstream and tissues, and, in turn, exposure of bacteria to suboptimal antibiotic concentrations increases the frequency of antibiotic resistant organisms.[24] A large number of people do not finish a course of antibiotics primarily because they feel better (varying from 10% to 44%, depending on the country).[25] There is a bdlief that compliance with once-daily antibiotics is better than with twice-daily antibiotics.[26] Hence, it is required that the Doctors must provide instructions to patients so they know when it is safe to stop taking a prescription since patients may feel better before the infection is eradicated. Some researchers advocate doctors' using a very short course of antibiotics, reevaluating the patient after a few days, and stopping treatment if there are no longer clinical signs of infection.[27]

Antibiotic resistance Mechanisms

Antibiotic resistance can be a result of horizontal gene transfer,[28] and also of unlinked point mutations in the pathogen genome at a rate of about 1 in 108 per chromosomal replication. The antibiotic action against the pathogen can be seen as an environmental pressure. Those bacteria with a mutation, allows them to survive live to reproduce. They then pass this trait to their offspring, which leads to the evolution of a fully resistant colony.

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

- ✓ Drug inactivation or modification: for example, enzymatic deactivation of penicillin G in some penicillin-resistant bacteria through the production of β-lactamases
- ✓ Alteration of target site: for example, alteration of PBP the binding target site of penicillins-in MRSA and other penicillin-resistant bacteria.
- ✓ Alteration of metabolic pathway: for example, some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by

sulfonamides, instead, like mammalian cells, they turn to using preformed folic acid.

- ✓ Reduced drug accumulation: by decreasing drug permeability and/or increasing active efflux (pumping out) of the drugs across the cell surface. [29]

Antibiotic resistance can also be introduced artificially into a microorganism through laboratory protocols, sometimes used as a selectable marker to examine the mechanisms of gene transfer or to identify individuals that absorbed a piece of DNA that included the resistance gene and another gene of interest. A recent study demonstrated that the extent of horizontal gene transfer among Staphylococcus is much greater than previously expected and encompasses genes with functions beyond antibiotic resistance and virulence, and beyond genes residing within the mobile genetic elements. [30] For a long time it has been thought that for a microorganism to become resistant to an antibiotic, it must be in a large population.

However, recent findings show that there is no necessity of large populations of bacteria for the appearance of antibiotic resistance. We know now, that small populations of E.coli in an antibiotic gradient can become resistant. Any heterogeneous environment with respect to nutrient and antibiotic gradients may facilitate the development of antibiotic resistance in small bacterial populations and this is also true for the human body. Researchers hypothesize that the mechanism of resistance development is based on four SNP mutations in the genome of E.coli produced by the gradient of antibiotic. These mutations confer the bacteria emergence of antibiotic resistance. A common misconception is that a person can become resistant to certain antibiotics. It is a strain of microorganism that can become resistant, not a person's body. [31]

Antibiotic-tolerant states

Antibiotic-tolerant states may depend on physiological adaptations without direct connections to antibiotic target activity or to drug uptake, efflux, or inactivation. Identifying these adaptations, and targeting them to enhance the activity of existing drugs, is a promising approach to mitigate the public health crisis caused by the scarcity of new antibiotics. Poor hand hygiene by hospital staff has been associated with the spread of resistant organisms, [32] and an increase in hand washing compliance results in decreased rates of these organisms. [33]

What is a "superbug"?

The term "superbug" is a nonspecific word that is used to describe any microorganism that is resistant to at least one or more commonly used antibiotics. Some authors restrict its use to microorganisms resistant to two or more antibiotics. Unfortunately, the term superbug is used in the medical and popular press to describe several different types of organisms which can lead readers to be confused about specific diseases and the infectious agents that cause them. Depending on the type of bacteria, "Superbugs," just by coexisting in the same environment (manure piles, contaminated water, in the throats or colons of infected patients, or hospital staff carriers) have the ability to share antibiotic resistant genes by the transmission of plasmids, sometimes referred to as "gene jumping." Certain antibiotic classes are highly associated with colonization with "superbugs" compared to other antibiotic classes. A superbug, also called multi-resistant, is a bacterium that carries several resistance genes. [34]

The most common bacteria described as superbugs are the following:

1. The growing prevalence and incidence of infections due to MDR (Multi Drug Resistant) pathogens is epitomized by the increasing number of familiar acronyms used to describe the causative agent and sometimes the infection generally; of these, MRSA (Methicillin-resistant Staphylococcus aureus) is probably the most well-known.
2. But others including VISA (vancomycin-intermediate S. aureus)
3. VRSA (vancomycin-resistant S. aureus)
4. ESBL (Extended spectrum beta-lactamase)
5. VRE (Vancomycin-resistant Enterococcus)
6. MRAB (Multidrug-resistant A. baumannii) are prominent examples.

Nosocomial infections overwhelmingly dominate cases where MDR pathogens are implicated, but multidrug-resistant infections are also becoming increasingly common in the community. [35] Although there were low levels of preexisting antibiotic-resistant bacteria before the widespread use of antibiotics,[36](a,b) evolutionary pressure from their use has played a role in the development of multidrug

resistance varieties and the spread of resistance between bacterial species. [37]

Alternatives

(A) Prevention: Rational use of antibiotics may reduce the chances of development of opportunistic infection by antibiotic-resistant bacteria due to dysbacteriosis. Our immune systems will cure minor bacterial infections on their own. If we give it the chance without relying on antibiotics to cure a small infection, we will be less likely to become immune or resistant to the antibiotic. It is also important to note that antibiotics will not cure viral infections. These are the preventive approaches which might help in this regard:

i. **Vaccines:** Vaccines do not have the problem of resistance because a vaccine enhances the body's natural defenses, while an antibiotic operates separately from the body's normal defenses. Nevertheless, new strains may evolve that escape immunity induced by vaccines; for example an updated influenza vaccine is needed each year. While theoretically promising, anti-staphylococcal vaccines have shown limited efficacy, because of immunological variation between Staphylococcus species, and the limited duration of effectiveness of the antibodies produced. Development and testing of more effective vaccines is under way. [38]

ii. **Others:** The Australian Commonwealth Scientific and Industrial Research Organization (CSIRO), realizing the need for the reduction of antibiotic use, have been working on two alternatives. One alternative is to prevent diseases by adding cytokines instead of antibiotics to animal feed. [39] These proteins are made in the animal body "naturally" after a disease and are not antibiotics, so they do not contribute to the antibiotic resistance problem. Furthermore, studies on using cytokines have shown they also enhance the growth of animals like the antibiotics now used, but without the drawbacks of non therapeutic antibiotic use. Cytokines have the potential to achieve the animal growth rates traditionally sought by the use of antibiotics without the contribution of antibiotic resistance associated with the widespread nontherapeutic uses of antibiotics currently used in the food animal production industries. Additionally, CSIRO is working on vaccines for diseases. [40]

iii. **(B). Phage therapy:** Phage therapy, an approach that has been extensively researched and used as a therapeutic agent for over 60 years, especially in the Soviet Union, represents a potentially significant but currently underdeveloped approach to the treatment of bacterial disease. [41] Phage therapy was widely used in the United States until the discovery of antibiotics, in the early 1940s. Bacteriophages or "phages" are viruses that invade bacterial cells and, in the case of lytic phages, disrupt bacterial metabolism and cause the bacterium to lyse. Phage therapy is the therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections.[42] *Bacteriophage therapy is an important alternative to antibiotics in the current era of multidrug resistant pathogens*. A review of studies that dealt with the therapeutic use of phages from 1966–1996 and few latest ongoing phage therapy projects via internet showed: phages were used topically, orally or systemically in Polish and Soviet studies. The success rate found in these studies was 80–95% with few gastrointestinal or allergic side effects. British studies also demonstrated significant efficacy of phages against Escherichia coli, Acinetobacter spp., Pseudomonas spp. and Staphylococcus aureus. US studies dealt with improving the bioavailability of phage. Phage therapy may prove as an important alternative to antibiotics for treating multidrug resistant pathogens.[43] Discovery of the structure of the viral protein PlyC is allowing researchers to understand the way it kills a significant range of pathogenic bacteria. [44]

Nonetheless there is evidence that heavy metals and some pollutants may select for antibiotic-resistant bacteria, generating a constant source of them in small numbers. [45]

Constraints in Medicinal Approach

Inappropriate prescribing of antibiotics has been attributed to a number of causes, including people who insist on antibiotics, physicians who simply prescribe them as they feel they do not have time to explain why they are not necessary, and physicians who do not know when to prescribe antibiotics or else are overly cautious for medical legal reasons.[46] For example, a third of people believe that antibiotics are effective for the common cold,[47] and the

common cold is the most common reasons antibiotics are prescribed[48] even though antibiotics are completely useless against viruses. The number of persons inappropriately prescribed antibiotics is a greater factor in the increasing rates of bacterial resistance rather than non-compliance with antibiotic protocol among those prescribed the drugs. However, the non-compliance rate is high. [49] A single dose of antibiotics leads to a greater risk of resistant organisms to that antibiotic in the person for up to a year. [50]

Ayurveda view on the Exogenous Diseases: Ayurveda classifies the diseases, as followed:

- ***Adhyatmika Vyadhi-*** diseases of one's own body It further sub-divided into

1. ***Adibala Pravratta Vyadhi*** (Genetic Diseases)

Adibala Pravratta diseases are those produced by the abnormalities of *Shukra* (sperm) and *Shonita* (ova) such as leprosy, piles etc.

These are again two kinds viz –

1. *Matraja*- derived from the mother

2. Pitraja- derived from the father.

2. ***Janmabala Pravratta Vyadhi*** (Diseases are those produced by improver conduct of the mother)

Janmabala Pravratta diseases are those produced by improver conduct of the mother, such as lameness, deafness, muteness, nasal speech, dwarfness etc. all by birth. Even these are of two kinds, viz.

1. *Rasakrata* – produced by rasa

2. *Dauhridapachaara krita* (produced by non-fulfilling of longing of the mother during pregnancy).

3. ***Doshabala Pravratta Vyadhi*** (Diseases are those diseases arising from improper food and activities)

Doshabala Pravratta diseases are of two kinds-

1. *Amashya samuttha*- (produced/born in the stomach and small intestine)

2. *Pakvashaya Samuttha* – (produced/born in large intestine)

Again these are two kinds, viz

1. *Sharira*- Somatic

2. *Manasa*- Psychic

All the above are *Adhyatmika* diseases concerning ones own self.

- ***Adhibhautika Vyadhi*- (Diseases occurs due to external objects)**

The diseases occurs with the close connection to external objects.

1. ***Sanghata bala Pravratta Vyadhi*** (Diseases which are external /accidental, caused by assault)

Those diseases which are external /accidental, caused by assault by the strong on the weak. These also are two kinds-viz

1. *Shastrakratta*- caused weapons

2. *Vyalakratta*- caused by wild animals

- ***Adhidaivika Vyadhi*- (Diseases caused by super human agencies):** Furthermore, Ayurveda categorizes the types of diseases are as bellowed;-

1. ***Kalabala Pravratta Vyadhi*** (Seasonal Diseases)

Those diseases produced by *kala* (season) such as cold, heat, wind, rain, sunlight etc. Even these are of two kind viz-

1. *Vyapanakratta* – produced from abnormal seasons

2. *Avyapannakratta*- produced by normal seasons.

2. ***Davibala Pravratta Vyadhi*** (Diseases humiliated by divine or subtle beings)

Those diseases caused by humiliated divine/subtle beings, by *Atharvana* rites (sorcery, witchcraft etc.) and by *Upsarga* (infections) – developing from proximity or contact with another disease person. These are also of two kinds. Viz.

1. *Vidyudarshanikratta*- produced by lightning, thunderbolt etc.

2. *Pishachadikratta*-produced by demons like *pishacha* (microbes) etc.

3. ***Svabhava Bala Pravratta Vyadhi*** (Natural Disease)

Those diseases such as hunger thirst, old-age, death, sleep and such other; these are also of two kinds. Viz.

1. *Kalaja*- appearing at the proper/usual time

2. *Akalaja*- appearing at improper time

Among these *kalaja* is those which appear even after protection and *Akalaja* are those which appear without any protection.

Cause of All Diseases – the *Dosha* – *Sarvavyadhi Karana* and *Doshas* : For all disease, *Vata, Pitta* and *Kapha* only are the causes, because of exhibiting their features, result being actually seen / observed and because of being exhorted in the scriptures. Just as the myriads of substances of the universe are not beyond of *Satva, rajas* and *Tamas*, similarly the multitude of diseases cannot be beyond *Tridosha*, which are present all over the body.; their differentiation is done on the basis of their combination, association with tissues (*Dhatus*) and (excreta) *Malas* of their seats and of their causes; these are named after the particular Dhatu, which is vitiated greatly, such as *Rasaja, Shonitaja, Mansaja, Medaja, Asthija, Majjaja* and *Shukraja*.

Vyadhi Utpatti Sthana- place of origin of disease; Diseases manifest at the place where the aggravated *Dosha* (by exogenous or endogenous causes) circulating all over the body become obstructed, due to abnormality of the channels. In summary, an important doctrine of diseases manifestation in Ayurveda; the *Dosha* get aggravated by use of improper foods and activities first and vitiate the *kosthagni* (Metabolic enzymes) leading to improper digestion production of *ama* (toxin) and their minute *srotas* (body channels) this is called *shrotodushtie* (Disequilibrium in channels). When the *rasadhatu* (plasma and lymph) containing *ama* (toxin) and aggravated *doshas* reaches the place where *Kha Vaigunya* (movement tendency towards empty space) has taken place, it being unable to get into the minute channels, gets obstructed, stagnates/accumulates there and gives rise to diseases.

Shroto dushti is of four kinds

1. *Atipravratti*- increase of structure and function of thatu vis-à-vis-organ or organ.

2. *Sanga*- obstruction leading to stagnation and increase of size of the Dhatu or organ.

3. *Siragranthi*- formation of tumour, thickening of the channels (Dhatus).

4. *Vimarga Gamana*- action or movements of materials etc. inside the Dhatus happening in the wrong manner. This kind of movement may be seen in the exogenous (infectious) diseases. [51]

Are there any 'Antibiotics' in 'Ayurveda'?: It is quite natural that Ayurveda, the oldest health care system in the world (about 5000 years old), will not have the word 'Antibiotics'. But a curious search in its literature will definitely yield number of references stating that certain diseases are produced due to micro-organisms and one has to destroy them to preserve the health. Various types of these organisms are also described in Veda and Ayurveda. Ex. – *Arati, Arjun*, *Alinsh*, *kravyad* etc. One interesting thing can be noted in these references. Ayurveda has not only advised on destroying these disease producing organisms but has also stressed that one should also increase the resisting power-immunity against these organisms to prevent the relapses of the disease. Almost all the herbs and medicines suggested by Ayurveda for killing these germs also have the property of increasing the immunity. This is called 'Rasayana' in Ayurveda. '*Sushruta*', the father of Surgery, has written in detail about various surgical procedures and has also described number of techniques to prevent the infection of these surgical wounds. He has described various means for doing post operative surgical dressings. Disease specific recommendations of Ayurveda drugs for some common infectious diseases are as bellowed:

A. **Gold** is considered as excellent antiseptic and has got *'Rasayana'* properties also. *Suvarna Bhasma* (Gold Calx) is effectively used in cases of pulmonary tuberculosis.
B. ***'Mahasudarshan Kwath'*** has been found very effective in cases of Malaria and other P.U.O. cases without any unwanted side effects.
C. ***Triphala guggulu*** is also seen to be effective in surgical prophylaxis.

An Ayurvedic approach to antibiotic resistant microbial infections

The methods of treatment prescribed by Ayurveda are meant both for the healthy and for the sick person. [52] Ayurveda categories the infectious diseases are under the *Agantuj* - "Exogenous – diseases", which are caused by Close physical contacts, nail cut, teeth infections, fall, spell, and natural calamities. Further it says that these may caused of disturbance in equilibrium of *Vata, Pitta* and *Kapha*. Exogenous diseases are again two-type viz., caused by these three *doshas* and caused by vitiation of three *doshas*. [53] "Exogenous – diseases" while based on vitiated *dosha* then the each *dosha* share of symptoms with each other[54]. When an

individual effected once with "Exogenous – diseases" and ignores the proper treatment then these diseases may turn into *Nij Vyadhi* - "Endogenous chronic diseases" and effect to the immune system. Thus once natural immunity becomes weak then smaller disease may manifest as a life-threatening disease. The Ayurvedic approach to the prevention and treatment of microbial infection recognizes the emergency use of modern drugs, but recommends traditional herbal combinations and extracts known to balance the individual and improve health, as well as herbs that help to combat or prevent microbial infections.

Ojas – An Overview

Ojas or *Bala* is defined in Ayurveda to the natural immunity of a human body. There are the three clinical conditions viz., *Ojo Visramsa*, *Ojo-Vyapat* and *Ojokshaya*, which result due to mild, moderate and severe impairment in the availability of *Ojas* to the tissues. These conditions arise out of injury to or diseases of the channels of distribution of this vital substance, its altered composition and deficiency respectively. The aetiological factors which bring about these conditions or the causes for reduced immune capability, according to Ayurveda, range from trauma (both physical and microbial), severe degenerative and wasting diseases, malnutrition, starvation to psychological stresses - anger, anxiety and grief etc. These factors depending upon their extent, degree and intensity of operation may result in the production of one of the above mentioned conditions. [55]

Practice of Immunomodulation in Ayurveda

It is now being recognized that modulation of immunological response could provide an alternative to conventional chemotherapy for a variety of diseased conditions of impaired immune responsiveness or when a selective immunosuppression has to be induced in situations like autoimmune disorders and organ transplantations. The basic concept of immunomodulation not only existed in Ayurveda but is being really practiced by the Ayurvedists for centuries. *Vyadhi-ksamatwa*, as it is understood in Ayurveda has much wider implications than the term "Immunity" used in modern medicine. In fact, one of the therapeutic strategies in Ayurvedic medicines is to enhance the body's overall natural resistance to the disease causing agent rather than directly neutralizing the agent itself.

Recent Trends in Plant origin Immunomodulatory Drug Research and *Ayurveda Rasayan Dravya*

The recent trend in evaluation of the herbal immunodulators is towards assessing the activity profile of the isolated principles in a battery of experiments with a view to identify the components responsible for the activity profile of the isolated principles in a battery of experiments with a view to identify the components responsible for the activity as also to understand the mechanism of their action. Amongst diverse class of compounds, it was observed the flavonol series possess the most potent anticomplementary activity. The potent antiphlogistic and antiallergic activity of the flavonoid wedelolactone from *Rasayana* drug *Bhringraj* (*Eclipta alba* and *Wedelia calandulacea*) was found to be due to its 5-lipoxygenase inhibitory activity, suggesting that it act by free oxygen radical scavenger mechanism. [56]

The active principles of *Guduchi* (*Tinospora cordifolia*), an important *Rasayana* drug, have been found to possess anticomplementary and immunostimulating activities. Previous studies on the extracts of Guduchi reported antidiabetic, anti-inflammatory and hepatoprotective activities. Syringin (TC-4) inhibited the invitro immunohaemolysis of antibody coated erythrocytes. The reduced immunohaemolysis was found to be due to inhibition of the C3-convertase of the classical complement pathway. The commounds gave rise to significant increase in IgG antibodies in the serum. Humoral and cell mediated immunity were also dose dependently enhanced. Macrophase activation was reported for cordioside (TC-2), cardiofolioside – A (TC-5) and Cordiol (TC- 7). These compounds induced significant increase in phagocytic activity by activation of the peritoneal macrophases. [57]

Yastimadhu (*Glycirrhiza glabra*), another important *Rasayana* drug has been found to be immunostimulative, which accelerates lymphocytic transformation activation of macrophage and increases the leucocyte count. [58]

Review of Recent Studies carried out for MDR

1. A study reveals that some plants of importance in the Ayurvedic system of traditional medicine used in India to treat enteric diseases. Fifty four plant extracts (methanol and aqueous) were assayed for their activity against multi-drug resistant **Salmonella typhi**. Strong antibacterial activity was shown by the methanol extracts of **Bilva-** *Aegle marmelos*, **Shalmali** - *Salmalia malabarica*, **Dadim-** *Punica granatum*, **Kutaj -** *Holarrhena antidysenterica*, **Arjun** - *Terminalia arjuna* and ***Triphala*** (mixture of (Amla) *Emblica officinalis*, (Haritaki or Harad) *Terminalia chebula* and (Vibhitak or Baheda) *Terminalia belerica*. Moderate antimicrobial activity was shown by **Kutki -** *Picorhiza kurroa*, **Khadir -** *Acacia catechu*, **Babbul -** *Acacia nilotica*, **Vidang -***Embelia ribes*, **Makoya -** *Solanum nigrum*, **Tulsi -** *Ocimum sanctum*, and **Palash -** *Butea monosperma*. [59]
2. Another study advocates using the silver for the treatment to M D R (Multi Drug Resistant) organism and refers that in the present scenario, pharmaceutical and biomedical sectors are facing the challenges of continuous increase in the multidrug-resistant (MDR) human pathogenic microbes. Re-emergence of MDR microbes is facilitated by drug and/or antibiotic resistance, which is acquired way of microbes for their survival and multiplication in uncomfortable environments. MDR bacterial infections lead to significant increase in mortality, morbidity and cost of prolonged treatments. Therefore, development, modification or searching the antimicrobial compounds having bactericidal potential against MDR bacteria is a priority area of research. Silver in the form of various compounds and bhasmas have been used in Ayurveda to treat several bacterial infections since time immemorial. As several pathogenic bacteria are developing antibiotic resistance, silver nanoparticles are the new hope to treat them. This review discusses the bactericidal potential of silver nanoparticles against the MDR bacteria. This multiactional nanoweapon can be used for the treatment and prevention of drug-resistant microbes. [60]
3. A study has found that Manuka honey could help in clearing chronically infected wounds, and even in reversing bacterial resistance to antibiotics. Professor Rose Cooper from the University of Wales Institute Cardiff is looking at how Dry grapes and honey interacts with three types of bacteria that commonly infest wounds: *Pseudomonas aeruginosa*, Group A Streptococci and Meticillin-resistant *Staphylococcus aureus* (MRSA). Her group has found that honey can interfere with the growth of these bacteria in a variety of ways and suggests that honey is an attractive option for the treatment of drug-resistant wound infections. Honey has long been acknowledged for its antimicrobial properties. Traditional remedies containing honey were used in the topical treatment of wounds by diverse ancient civilizations. *Manuka honey is derived from nectar collected by honeybees foraging on the manuka tree in New Zealand and is included in modern licensed wound-care products around the world*. However, the antimicrobial properties of honey have not been fully exploited by modern medicine, as its mechanisms of action are not yet known. Cooper`s group is helping to solve this problem by investigating at a molecular level the ways in which manuka honey inhibits wound-infecting bacteria. [61]
4. A study was conducted in Sri Lanka to determine antimicrobial activity of selected Ayurvedic preparations against bacteria and fungi and it refers that: "increasing antimicrobial resistance exhibited by microorganisms causing superficial skin infections has led to extensive research on the therapeutic potential of Ayurvedic preparations. Medicinal plants contain many types of naturally occurring and side effects-free anti microbial compounds that can be effectively used against microbial infections. Antimicrobial activity of twenty-eight Ayurvedic preparations used to treat superficial infections in a local Ayurvedic healthcare institution were tested against *Trichophyton rubrum, Microsporum gypseum, Candida albicans*, *Malassezia furfur, Staphylococcus aureus* and *Streptococcus pyogenes*. Twelve preparations showed significant antimicrobial activity and gave inhibition zones >10 mm. Two Ayurvedic preparations (Mixture *containing Terminella chebula, Terminella bellerica* and *Emblica officinalis* and one of *Terminella chebula* only) showed antimicrobial activity against all the microorganisms tested."
5. One more Ayurveda herb "*Rason*" or *Lahasun* (A. *sativum*) *was* studied and concluded that the it was tested against gram-positive and gram-negative bacterial isolates from Urinary Tract of Indian patients, which were

confirmed for resistant against commonly used antibiotics for urinary tract infections. In this study, only five quantities (10, 20, 30, 40 and 50µg) of aqueous allicin from A. sativum cloves and leaves were used, which has antibacterial activity against test isolates by disc diffusion method. The maximum inhibitory activity of allicin against all test isolates was observed at 40µg and the quantity was found statistically significant (P< 0.01) for antibacterial activity of allicin extracted from A. sativum cloves and leaves against UT bacterial isolates. [62]

6. **Several Ayurveda plants extracts have exhibited synergistic activity against microorganisms**. The Ayurveda plants possessing significant anti-microbial activity are **neem** (*Azadirachta indica*), **Krishna-marich** (*Piper longum*), **Guduchi** stem (*Tinospora cordifolia*) and **amla** fruit (*Emblica officinalis*). Thus it can be said that the Ayurveda herbs may play a vital role to the treatment of antibiotic resistant microbial infections. [63]

CONCLUSION

It can be concluded that there is evidence that naturally occurring antibiotic resistance is common. A single dose of antibiotics leads to a greater risk of resistant organisms to that antibiotic in the person. Antibiotic resistance has been shown to increase with duration of treatment. The term "superbug" is a nonspecific word that is used to describe any microorganism that is resistant to at least one or more commonly used antibiotics.

In medicine, the major problem of the emergence of resistant bacteria is due to misuse and overuse of antibiotics. WHO has declared the “Superbug” as a threat which may be major cause of human death? Role of alternative therapies is being explored. Prevention and phag-therapy are in focus yet now. The Ayurvedic approach to the prevention and treatment of microbial infection recognizes the emergency use of modern drugs, but recommends traditional herbal combinations and extracts known to balance the individual and improve health, as well as herbs that help to combat or prevent microbial infections. Several plant extracts have exhibited synergistic activity against microorganisms. In nut and shell it can be said that the Ayurveda’s emphasis on the role of *Doshas* and their imbalance as the main causative factor of the diseases assumes importance in the light of the fact that mere presence of causative organisms in the environment does not necessarily results in the manifestation of the disease. The concepts of Ojas and *Bala,* of the inherent immunological capabilities including innate immunity and acquired immunity in terms of *Sahajabala* and *Yuktikritabala e*tc., playing key role in the health and disease have to be understood and appreciated by the modern immunolgists. There is urgent need of time to switchover on this serious issue for finding an effective and safe remedy. Ayurveda may play a vital role in this regard.

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