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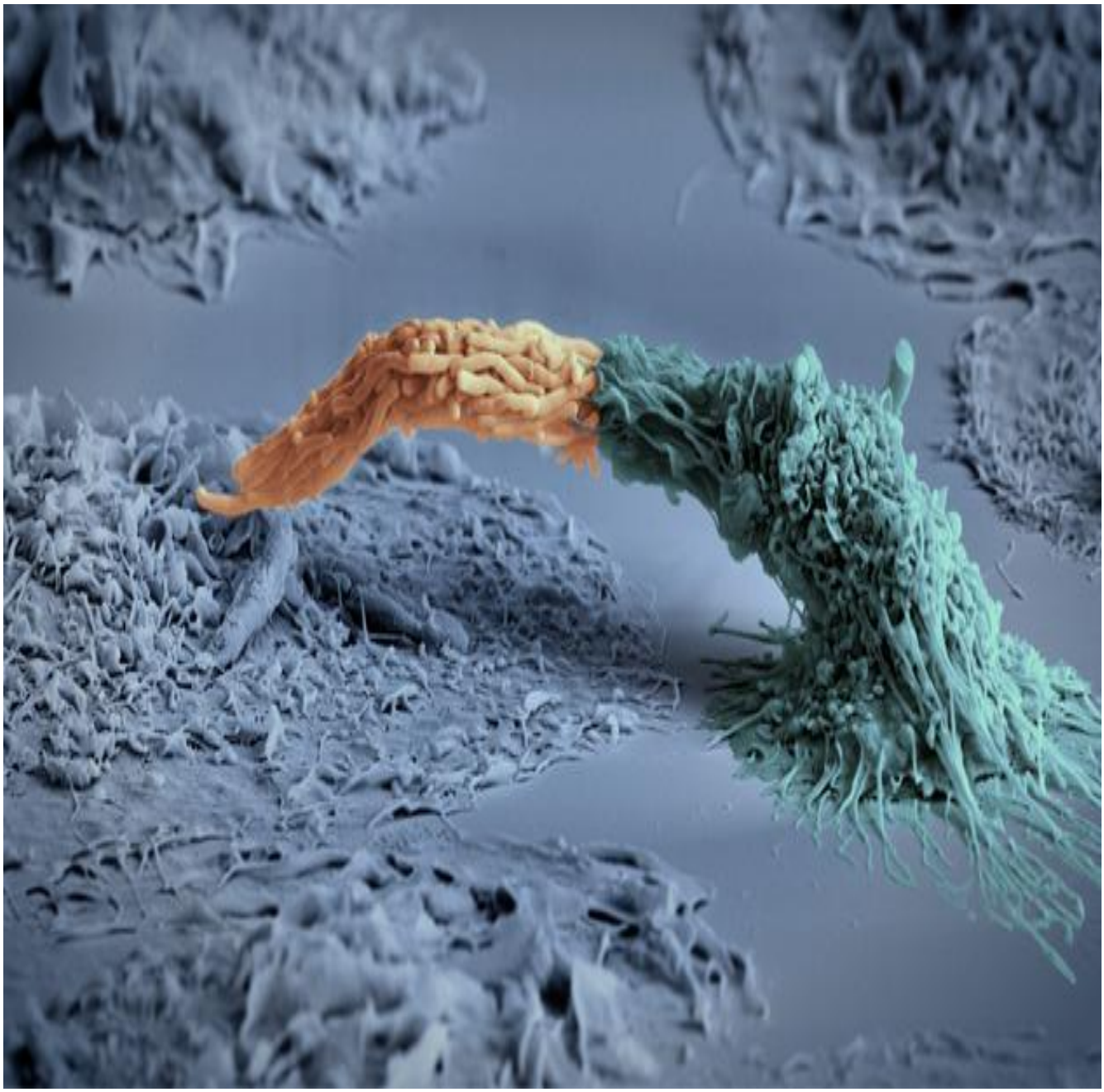

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ENVIS Newsletter on 'Microorganisms and Environment Management', a quarterly publication, brings out original research articles, reviews, reports, research highlights, news-scan etc., related to the thematic area of the ENVIS Centre. In order to disseminate the cutting-edge research findings to user community, ENVIS Centre on Microorganisms and Environment Management invites original research and review articles, notes, research and meeting reports. Details of forthcoming conferences / seminars / symposia / trainings / workshops also will be considered for publication in the newsletter.

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Cover page : MACROPHAGE [on the right] ENGULFS TUBERCULOSIS BACTERIA [left] Pseudo-colored scanning electron micrograph (SEM) of a human macrophage (blue) phagocytizing [devouring, as in eating] a cord of Mycobacterium tuberculosis bacilli (orange)

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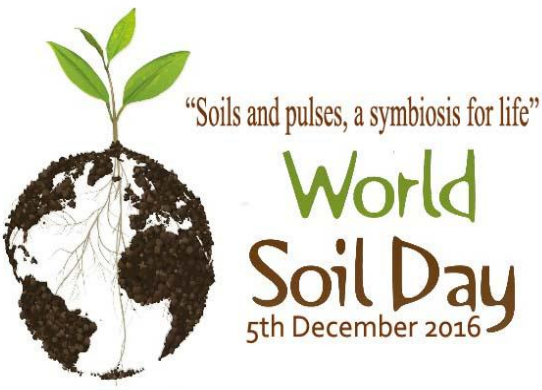

Dear Readers,

Greetings!

Infectious diseases are caused by pathogenic microorganisms such as bacteria, viruses, parasites or fungi. With the emergence of antimicrobial resistance (AMR) among these organisms the effective prevention and treatment of these diseases are difficult. Further, an ever-increasing range of infections are caused by these microorganisms which are difficult to treat with the presently antibiotics. One such disease is Tuberculosis (TB) caused by bacteria (*Mycobacterium tuberculosis*) that most often affects the lungs. Tuberculosis is curable and preventable but the emergence of Multidrug-resistant TB (MDR-TB) is a formidable obstacle to effective TB care and prevention globally. In 2015, WHO estimated 480000 people worldwide developed MDR-TB and an additional 100000 people with rifampicin-resistant TB. India, China and the Russian Federation accounted for 45% of the 580000 cases. It was estimated that about 9.5% of these cases were extensively drug-resistant TB (XDR-TB). Natural medicine such as the use of herbs and plants had offered solutions to most of the diseases for the mankind. WHO intends to integrate traditional medicine into National Health Systems (NHS) globally.

This issue themed on TB contains a scientific review article on the therapeutic potentials of plants against *Mycobacterium tuberculosis* infections with comparison to the merits and demerits of conventional medicine. Also we have included reports on the advances in treatment of TB, drugs available in nature, related abstracts and many more. Hope this issue would trigger awareness among the readers in this regard.

Dr. C. Arulvasu

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SCIENTIFIC ARTICLE

Therapeutic Potentials of Medicinal plants against *Mycobacterium tuberculosis* (MTB) infections

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Mycobacterium tuberculosis,
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MDR and XDR-TB,
Anti-tubercular, Natural,
Ayurveda.

A B S T R A C T

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB) is an infectious dreadful disease to mankind. The treatment and management of TB remains to be a constant challenge to the scientific community world-wide. TB is the cause for the second largest number of deaths globally and the death tolls remain all time high with co-infections with HIV. MTB-H37Rv is the typical MTB organism studied in many labs and in 1998 its complete genome was published. In general H37Rv are susceptible to all the first line of drugs. But emergence of Multi Drug Resistant (MDR) and Extensively Drug Resistant (XDR) strains of MTB is not uncommon and management of such clinical isolates are extremely difficult. Asian countries are known for their cultural richness in usage of several folk medicines. The use of herbal medicine is becoming popular due to less toxicity and side effects compared with allopathic medicines. Medicinal plants from Ayurveda (Indian traditional medicine system) and from foreign origin have been employed to treat TB. In this review we have addressed the merits and demerits of conventional (Allopathcic) medicine system in comparison to traditional (Ayurvedic) medicine system.

Introduction

Tuberculosis is a highly infectious disease with about one third of the world's population including 40% from India estimated to be infected[1]. However, this problem has become serious as MTB developed resistance against both the first line as also the second line of drugs. Due to this, there is an emergence of multi-drug resistant (MDR) and extensively-drug resistant (XDR) strains of MTB all over the world including India[2].The WHO intends to integrate traditional medicine into National Health systems (NHS) globally. This is an opportunity for building safe, affordable and effective NHS especially for Third world countries, rich in both medicinal plant resources and traditional medicine knowledge. It is the time for Governments to found research into holistic health models as an alternative of squandering more billions on 'health genomics', which will increase intervention and iatrogenic damages to health. The recent increase of TB is associated with the emergence of the human immunodeficiency virus (HIV) and the rapid spreads of MDR-TB strains degenerate the situation. Second-line drugs have many more adverse effects than the first-line anti-TB drugs. Medicinal plants offer a great hope to fulfill these needs and have been used for curing diseases for many centuries. These have been used extensively as pure compounds or as a crude material. Only a few plant species have been thoroughly investigated for their medicinal properties[3]. India is one of the few countries in the world which has unique wealth of medicinal plants and vast traditional knowledge of use of herbal medicine for cure of various diseases. Most healthy individuals are able to control the infection with a strong immune response, halting the progression of the disease, but not necessarily eradicating the organism[4].

Conventional anti MTB drugs

Drugs such as Isoniazid (INH or H), Rifampicin (RMP or R), Streptomycin (STM or S), Ethambutol (EMB or E) and Pyrazinamide (PZA or Z) are all considered first line of drugs to control MTB. Besides that second line and third line of drugs are being administered when drug resistance surfaced. Multi drug resistant tuberculosis (MDR-TB) or Vank's disease show resistance to isoniazid and rifampicin[5] and Extensively drug-resistant TB (XDR-TB) is a rare type of multidrug-resistant tuberculosis (MDR-TB) that is resistant to isoniazid, rifampin, plus any fluoroquinolones and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)[6]. Though these drugs are in clinical use they are known for their adverse side-effects.

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Side-effects caused by conventional anti MTB drugs

Besides developing drug resistance long term administering of isoniazid can cause side effects such as nausea, vomiting, epi-gastric pain and in some cases cutaneous pruritus[7]. Similarly administering of rifampicin can cause fatigue, dizziness, headache, dyspnea, and ataxia in patient's treated. Pyrazinamide administration for longer period can develop dermatitis. Another effective anti MTB drugs is ethambutol and chronic administering can lead to Retrobulbar neuritis, nausea, vomiting, abdominal pain and hepatotoxicity, hematological symptoms (eosinophilia, neutropenia, and thrombocytopenia), cardiovascular symptoms (myocarditis and pericarditis), neurological symptoms (headache, dizziness, and mental confusion), hyperuricemia/ gout (due to a reduction in the excretion of uric acid by the kidney), hypersensitivity (skin rash, arthralgia, and fever) and (occasionally) pulmonary infiltrates.Treatment with streptomycin reported to cause vestibular and auditory nerve damage and occasionally renal damage[8].

Use of medicinal plants

The use of plants as the source of remedies for the treatment of many diseases dates back to prehistory period and people of all continents have practiced this old tradition. Plants contribute to be the major source of medicines throughout the human history. The World Health Organization (WHO) estimated that about 80% of world's population rely on traditional medicinal plants for their primary health care. The uses of herbs and herbal products have also been broadly accepted in our modern way of life[9]. Plant species serve as a rich source of many novel biologically active compounds; although very few have been thoroughly investigated for their medicinal properties. About 30-40% of plants are used in today's conventional drugs and rest are used as herbal supplements, botanicals and beverages[10].

Herbal medicine is a major component in all indigenous people traditional medicine and is a common element in ayurvedic, homeopathic, naturopathic, traditional, oriental and Native American Indian medicines. WHO notes that of the 119 plant-derived pharmaceutical medicines, about 74% are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines by native's culture[11]. The uses of some medicinal plants vary a lot according to regional and cultural aspects. Their use is often associated with witchcraft and superstition because the practitioners do not have the scientific insight to explain or predict the curative action of the plants. One example of such an irrational concept is the Doctrine of Signatures (elements of which are found in many of the healing cultures of the world) based on the assumption that the appearance of plants may give clues to their medicinal properties[12].

The forest in India is the principal repository of large number of medicinal and aromatic plants, which are largely collected as raw materials for manufacture of drugs and perfumery products. About 8,000 herbal remedies have been codified in AYUSH systems in INDIA. Ayurveda, Unani, Siddha and Folk (tribal) medicines are the major systems of indigenous medicines. Among these systems, Ayurveda and Unani Medicines are most developed and widely practiced in India[13]. According to WHO, around 21,000 plant species have the potential for being used as medicinal plants[14].

It has been estimated, that in developed countries such as United States, plant drugs constitute as much as 25% of the total drugs, while in fast developing countries such as India and China, the contribution is as much as 80%. These countries provide two third of the plants used in modern system of medicine and the health care system of rural population depend on indigenous systems of medicine[15].

Treatment with medicinal plants is considered very safe as there is no or only minimal side effects. These remedies are in sync with nature which is the biggest advantage. The golden fact is that use of herbal treatments is independent of any age groups and the sexes. Medicinal plants such as Aloe, Tulsi, Neem, Turmeric and Ginger cure several common ailments. These are considered as home remedies in many parts of the country. It is a known fact that lots of consumers are using Basil (Tulsi) for making medicines, black tea, in pooja and other activities in their day to day life[16]. Now, after finding the role of herbs in medicine, lots of consumers started the plantation of tulsi and other medicinal plants in their home gardens.

Medicinal plants are considered as rich resources of ingredients which can be used in drug development pharmacopoeial, non- pharmacopoeial or synthetic drugs and play a critical role in the development of human cultures

around the whole world. Moreover, some plants are considered as important source of nutrition and as a result of that they are recommended for their therapeutic values. Some of these plants include ginger, green tea, walnuts, aloe, pepper and turmeric etc. Some plants and their derivatives are considered as important source for active ingredients which are used in aspirin and toothpaste etc.[17]. Apart from the medicinal uses, herbs are also used in natural dye, pest control, food, perfume, tea and so on. In many countries different kinds of medicinal plants/ herbs are used to keep ants, flies, mice and flee away from homes and offices. Now a day's medicinal herbs are important sources for pharmaceutical manufacturing[18].

Over the past two decades, there has been a tremendous increase in the use of herbal medicine; however, there is still a significant lack of research data in this field. Medicinal plants are also important for pharmacological research and drug development, not only when plant constituents are used directlypeutic agents, but also as starting materials for the synthesis of drugs or as models for pharmacologically active compounds[19]. Major pharmaceutical companies are currently conducting extensive research on plant materials, gathered from forests and other habitats, for their potential medicinal value[20].

Anti MTB agents derived from the ayurvedic literature

Ayurveda, means the science of life (Ayur = Life, Veda = Science), is an ancient medical knowledge which was developed in India thousands of years ago and describes numerous plants to treat several diseases. When we particularly talk about TB, more than 250 medicinal plants from India have been reported[17]. The comprehensive safety, toxicity and clinical studies are needed for these plants before using them effectively as curative and/or preventive medications against TB. List of plants in India used in Ayurvedic treatment has been discussed in Table 1.

Table 1: Plants used for ayurvedic treatment in India[3,21-32]

No	Botanical/ family name	Ayurvedic name	Part used	Chemical constituents	Other biological activities
1	**Acalypha indica, Euphorbiaceae**	Kuppi	Leaves	Kaempferol, acalyphamide and other amides, quinone, sterols, cyanogenic glycoside	Antibacterial, used in bronchitis, asthma
2	**Adhatoda vasica. Acanthaceae**	Vaasaa	Leaves	Quinazoline alkaloid	Expectorant (used in bronchial asthma)
3	**Allium cepa, Liliaceae**	Palaandu	Bulbs	Volatile oil with sulphurous constituents, including allylpropyl disulphide, sulphur containing compounds, including allicin, alliin, flavonoids; phenolic acids and sterols	Antibiotic, antibacterial, antisclerotic, anticoagulant
4	**Allium sativum, Liliaceae**	Lashuna	Bulbs	Sulphurcontaining amino acids known as alliin	Antibiotic, bacteriostatic, fungicide, anthelmintic, antithrombic, hypotensive, hypoglycaemic, hypocholesterolaemic
5	**Aloe vera, Liliaceae**	Ghritkumaarika	Leaves, gel from leaves	Anthraquinone glycosides, known as aloin	Purgative
6	**Vitex negundo, Verbenaceae**	Nirgundi	Leaves, seeds	Iridoid glycosides, isomeric flavanones and flavonoids	Anti-inflammatory, analgesic
7	**Trichosanthes dioica, Cucurbitaceae**	Patola	Roots, fruits	Free amino acids, nicotinic acid, riboflavin, vitamin C, thiamine, 5-hydroxytryptamine	Cathartic, febrifuge
8	**Tinospora cordifolia, Menispermaceae**	Guduuchi	Stem, leaves	Alkaloidal constituents, including berberine; bitter principles, including columbin, chasmanthin, palmarin and tinosporon, tinosporic acid and tinosporol	Antipyretic, antiperiodic, anti-inflammatory
9	**Caesalpinia pulcherrima, Caesalpiniaceae**	Padangam	Leaves, flowers	Flavonoid, myricitroside	Laxative, antipyretic
10	**Prunus armeniaca, Rosaceae**	Peetaalu	Kernels	Salicylic acid,organic acids tannins and potassium salts. Protocatechuic, pcoumaric, ferulic and diferculic acids	Antitussive, antiasthmatic
11	**Ocimum sanctum, Labiatae**	Tulasi	Leaves, flowers, Seeds	Ursolic acid, apigenin, orientin luteolin, apigenin -7-Oglucuronide, luteolin-7-Oglucuronide	Carminative, stomachic, antispasmodic, antiasthmatic, antirheumatic, expectorant, hepatoprotective, antiperiodic
12	**Morinda citrifolia, Rubiaceae**	Ashyuka	Leaves, roots, fruits	Anthraquinonesalizarin and its glycosides, nordamnacanthol. Ursolic acid and β- sitosterol. asperuloside and caproic acid	Antileucorrhoeic, antidysenteric emmenagogue
13	**Myrtus communis, Myrtaceae**	Muuraddaan	Fruits	Tannins (pyrogallol derivative), flavonoids (including myricetin, kaempferol, quercetin glycosides; volatile oil containing α-pinene, cineole, myrtenol, nerol, geraniol and dipentene	Antimicrobial, antiparasitic, antiseptic
14	**Canscora decussate, Gentianaceae**	Daakuni	Roots	β-amyrin, friedelin,genianine mangiferin, Xanthones	Anticonvulsant, CNS depressant, antiinflammatory, hepatoprotective.
15	**Piper species, Piperaceae**	Pippali	Fruits	Aristolactams, dioxoaporphines long chain isobutyl amide, lignans, longamide, pluviatilol, methyl pluviatilol (fargesin), sesamin, asarinine, piperine	Digestive, appetizer and carminative
16	**Vitex trifolia, Verbenaceae**	Sinduvaara	Leaves, roots, fruits	Flavonoids-artemetin, luteolin, orientin, casticin; and iridoid glycosides, aucubin and agnuside. alkaloid, vitricin	Febrifuge, antibacterial, anthelmintic, cytotoxic
17	**Mallotus philippensis, Euphorbiaceae**	Kampillaka	Gland and hair of fruit	Phloroglucinol derivatives; rottlerin, isorottlerin, iso allorottlerin	Purgative, anthelmintic, styptic
18	**Colebrookea oppositifolia, Lamiaceae**	Binda	Leaves, fruits, roots	Flavonoids	Antiinflammatory
19	**Rumex hastatus, Polygonaceae**	Katambal	Root and bark	Tannins	Astringent
20	**Mimosa pudica, Mimosaceae**	Laajavanti	Leaves, roots	Mimosine and turgorin	Mimosine and turgorin

Anti-tubercular plants from foreign origin

Anti-tubercular plants are not only in India but are found in places all over the world such as South Africa, New Zealand, Malaysia, Nigeria, Tibet etc. A list of anti-tubercular plants from foreign origin are shown in Table 2.

Conclusion

Natural products as crude materials with efficacy against various diseases have been selected by humans over many generations of practical experience. However many effective medicines such as morphine, aspirin, atropine, ephedrine, reserpine and digitoxin were developed from natural products. Medicinal plants, since times immemorial have been used in virtually all cultures as a source of medicine. The widespread use of herbal remedies and health care preparations described in ancient texts such as the Vedas and the Bible are obtained from commonly used traditional herbs and medicinal plants, traced to the occurrence of natural products with medicinal properties.

Conventional (allopathic) medicines are indeed effective until the emergence of MDR and XDR isolates but are known to cause side-effects. In contrast ayurvedic and other traditional medicines appear to be promising by inhibition of MTB and XDR isolates but are known to cause side-effects. In contrast ayurvedic and other traditional medicine appear to be promising by inhibition of MTB and XDR strains *in-vitro*. However their overall *in-vivo* efficacy, toxicity and Maximum tolerated dose reveal to be extensively studied before it enters in to human usage.

Table 2: List of some plants anti-tubercular plants of foreign origin[16,33-47]

S. no	Botanical name	Family	Extract	Chemical constituents
1	*Clavija procera*	Theophrastaceae	Ethanolic	Oleanane triterpenoid (aegicerin)
2	*Rhodomyrtus tomentosa*	Myrtaceae	Alcoholic	Rhodomyrtone
3	*Aristolochia taliscana*	Aristolochiaceae	Hexane	Neolignans
4	*Astraeus pteridis*	Astraeaceae	Ethanolic	Lanostane triterpenes and phenylalanine
5	*Byrsonima crassa*	Malpighiaceae	Chloroform	Triterpenes:α-amyrin, β-amyrin and their acetates, lupeol, oleanolic acid, ursolic acid and α-amyrinone
6	*Galenia africana*	Asteraceae	Ethanolic	Flavonoids
7	*Gentianopsis paludosa*	Gentianaceae	Ethanolic	1,7,8-Trihydroxy-3-methoxyxanthone, luteolin-7-O-glucoside
8	*Cryptocarya latifolia*	Lauraceae	Acetone, water	Coumarins
9	*Euclea natalensis*	Ebenaceae	Acetone, water	Naphthoquinones
10	*Helichrysum melanacme*	Asteraceae	Acetone, water	Essential oils
11	*Nidorella anomala*	Asteraceae	Acetone, water	Naphthoquinones
12	*Thymus vulgaris*	Lamiaceae	Acetone, water	Flavonoids, essential oils
13	*Buddleja saligna*	Scrophulariaceae	Alcoholic	Non-cytotoxic triterpenoids oleanolic
14	*Leysera gnaphalodes*	Asteraceae	Alcoholic	Non-cytotoxic triterpenoids oleanolic
15	*Laggera pterodonta*	Asteraceae	Methanolic	Flavonoids
16	*Laggera aurita*	Asteraceae	Methanolic	Flavonoids
17	*Salvia hypargeia*	Lamiaceae	Alcoholic	Diterpene
18	*Salvia sclarea*	Lamiaceae	Alcoholic	Diterpene
19	*Angiopteris evecta*	Marattiaceae	-	Lactones, coumarins
20	*Costus speciosus*	Costaceae	-	Flavonoids
21	*Pluchea indica*	Asteraceae	-	Phenolics
22	*Tabernaemontana coronaria*	Apocynaceae	-	Alkaloids
23	*Pelargonium reniforme*	Geraniaceae	Ethanolic, acetone	Phenolics
24	*Pelargonium sidoides*	Geraniaceae	Ethanolic, acetone	Phenolics
25	*Quinchamalium majus*	Santalaceae	Methanolic	Triterpenes
26	*Senecio chionophilus*	Asteraceae	Hexane, dichloromethane	Sesquiterpenoids
27	*Evodia elleryana*	Rutaceae	Hexane, ethyl acetate, methanol	Alkaloid, quinoline

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RESEARCH REPORTS

Researchers find advanced treatment of tuberculosis by targeting new enzyme

Researchers at Johns Hopkins hospitals reported that they have laid the foundation to develop novel antibiotics that work against incurable, antibiotic-resistant bacteria like tuberculosis by targeting an enzyme essential to the production and integrity of bacterial cell walls.

Their findings suggested that antibiotic drugs specifically targeting the recently discovered LD-transpeptidase enzyme, which is needed to build bacterial cell walls in some bacteria, could potentially cure many antibiotic-resistant infections.

An additional implication of their research is that drugs targeting the enzyme could offer quicker, cheaper and more easily accessible treatment against tuberculosis, a disease that still kills more people worldwide than any other infection, according to the Centers for Disease Control and Prevention.

Dr. Gyanu Lamichhane, an associate professor of medicine at the Johns Hopkins University School of Medicine said that the complexity of TB treatment and growing prevalence of antibiotic resistance is a serious threat to public health. His team joined with the research team of Dr. Craig Townsend, the Alsoph H. Corwin Professor of Chemistry at The Johns Hopkins University's Krieger School of Arts and Sciences, to tackle this complex issue. Townsend said that their research offers steps toward the design of new antibiotics that attack a previously untargeted bacterial enzyme.

At the root of their investigation, Lamichhane said that more than half of antibiotics prescribed today are of a class called beta-lactams, which work by interrupting the function of the DD-transpeptidase enzyme that creates bacterial cell walls. Without it, bacteria quickly die. However, in 2005, a team of researchers found a second wall-building enzyme, LD-transpeptidase, that allows bacteria like the ones that cause TB to survive antibiotic treatments. Hence they looked at the structure of LD-transpeptidase, thought about how it works and started making new compounds that could be used against it.

Dr. Pankaj Kumar, a postdoctoral fellow in infectious diseases at the Johns Hopkins University School of Medicine, began the research in the new study by extracting LD-transpeptidase from many species of bacteria and examining its detailed molecular structure with a sophisticated imaging system known as X-ray protein crystallography using the Advanced Photon Source at the Argonne National Laboratory in Chicago.

By analyzing the enzyme's structure, Johns Hopkins researchers were able to design new compounds in the carbapenem group, a subclass of the beta-lactam antibiotics that bind to the LD-transpeptidase wall-building enzyme and stop its function.

In live bacterial cultures, the carbapenems were shown by Lamichhane's and Townsend's groups to stop the enzyme's wall-building activity. The new compounds were even effective against the ESKAPE pathogens, a group of six bacterial species that the Centers for Disease Control and Prevention had identified as a threat because of their propensity for developing antibiotic resistance.

Following these successes, Dr. Amit Kaushik, a postdoctoral fellow in infectious diseases at the Johns Hopkins University School of Medicine, tested two carbapenems in vivo against TB in mice infected with TB.

Researchers infected mice with tuberculosis bacteria and separated them into different treatment groups. The rodent's lungs were sampled periodically over a period of three weeks, and the results showed that even without use of classic TB antibiotic treatments, the new carbapenems, specifically biapenem, cured TB infection in mice.

Townsend and Lamichhane said that the focus of their research is now on creating variations of their original compound those are designed to target specific bacteria. Many commonly prescribed antibiotics today work on a broad spectrum of bacterial species, meaning that in addition to killing off bad bacteria, they also destroy the friendly bacteria of our bodies that are needed to function normally and whose destruction can cause dangerous side effects. Lamichhane believes that the future of antibiotic treatments relies on good antimicrobial stewards and treats specific bacteria without affecting our body's natural microbiome. Not only will this cut down on antibiotic side effects, but it will also slow the development of antibiotic resistance in the bacterial species not being targeted.

The researchers are now in the process of initiating clinical trials to test the safety and efficacy of some of these new compounds.

Antibiotic resistance has been an ever-present threat since the discovery of penicillin in 1928. Scientists and physicians have historically kept up with resistant bacteria through the frequent introduction of new antibiotic treatments. However, the research and development of antibiotics plummeted in the 1980s as other drugs became more profitable to produce. Because of the decreased incentive to invest in new antibiotics and the liberal use of antibiotics we already have, many bacterial species have quickly outpaced our ability to treat them. The Centers for Disease Control and Prevention estimates that annually, 2 million illnesses and 23,000 deaths are caused by antibiotic-resistant bacteria in the United States alone, and that 70 percent of hospital-acquired infections are now antibiotic-resistant.

Source: www.sciencedaily.com

Engineers design a new weapon against bacteria Antimicrobial peptides can kill strains resistant to existing antibiotics

Over the past few decades, many bacteria have become resistant to existing antibiotics, and few new drugs have emerged. A recent study from a U.K. commission on antimicrobial resistance estimated that by the year 2050, antibiotic-resistant bacterial infections will kill 10 million people per year, if no new drugs are developed. To help rebuild the arsenal against infectious diseases, many scientists are turning toward naturally occurring proteins known as antimicrobial peptides, which can kill not only bacteria but other microbes such as viruses and fungi.

A team of researchers at MIT, the University of Brasilia, and the University of British Columbia has now engineered an antimicrobial peptide that can destroy many types of bacteria, including some that are resistant to most antibiotics.

One of their main goals was to provide solutions to combat antibiotic resistance said MIT postdoc Cesar de la Fuente who is the corresponding author of the study, and one of its lead authors along with Osmar Silva, a postdoc at the University of Brasilia, and Evan Haney, a postdoc at the University of British Columbia. Timothy Lu, an MIT associate professor of electrical engineering and computer science and of biological engineering, is also an author of the paper, which appears in the Nov. 2 issue of Scientific Reports.

Improving on nature

Antimicrobial peptides produced by all living organisms as part of their immune defenses kill microbes in several different ways. First, they create holes in the invaders cell membranes. Once inside they can disrupt several cellular targets including DNA, RNA, and proteins.

These peptides also have another critical ability that sets them apart from traditional antibiotics: They can recruit the host's immune system, summoning cells called leukocytes that secrete chemicals that help kill the invading microbes.

Scientists have been working for several years to adapt these peptides as alternatives to antibiotics, as bacteria become resistant to existing drugs. Naturally occurring peptides can be composed of 20 different amino acids, so there is a great deal of possible variation in their sequences.

de la Fuente said that their sequences could be tailored and tuned in such a way that could be used for specific functions. With the computational power they try to generate therapeutics that can make it to the clinic and have an impact on society.

In this study, the researchers began with a naturally occurring antimicrobial peptide called clavanin-A, which was originally isolated from a marine animal known as a tunicate. The original form of the peptide kills many types of bacteria, but the researchers decided to try to engineer it to make it even more effective.

Antimicrobial peptides have a positively charged region that allows them to poke through bacterial cell membranes and a hydrophobic stretch that enables interaction with and translocation into membranes. The researchers decided to add a sequence of five amino acids that would make the peptides even more hydrophobic in hopes that it would improve their killing ability.

This new peptide, which they called clavanin-MO, was very potent against many bacterial strains. While tested in mice, the researchers found that it could kill strains of Escherichia coli and Staphylococcus aureus that are resistant to most antibiotics.

Suppressing sepsis

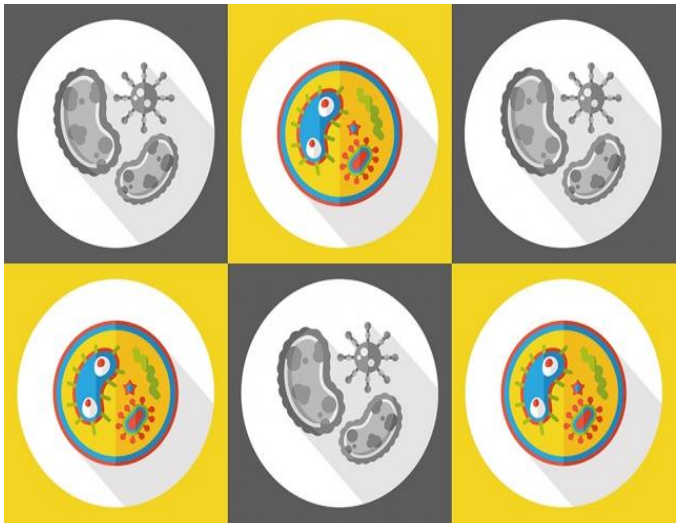
Another key advantage of these peptides is that while they recruit immune cells to combat the infection, they also suppress the overactive inflammatory response that can cause sepsis, a life threatening condition.

de la Fuente added that in this single molecule, there is a synthetic peptide that can kill microbes both susceptible and drug-resistant and also at the same time can act as an anti-inflammatory mediator and enhance protective immunity.

The researchers also found that these peptides can destroy certain biofilms, which are thin layers of bacterial cells that form on surfaces. That raises the possibility of using them to treat infections caused by biofilms, such as the Pseudomonas aeruginosa infections that often affect the lungs of cystic fibrosis patients. Or, they could be embedded into surfaces such as tabletops to make them resistant to microbial growth.

Other possible applications for these peptides include antimicrobial coatings for catheters, or ointments that could be used to treat skin infections caused by Staphylococcus aureus or other bacteria.

If these peptides are developed for therapeutic use, the researchers anticipate that they could be used either in stand-alone therapy or in combination with traditional antibiotics, which would make it more difficult for bacteria to evolve drug resistance. The researchers are now investigating what makes the engineered peptides more effective than the naturally occurring ones, with hopes of making them even better.



(Image: MIT News; Source: www.news.mit.edu)

KNOW A SCIENTIST

Dr. Susumu Tonegawa

Most notably, she received the Nobel Prize for Physiology or Medicine in 1983, the first woman to win that prize credited by the Nobel Foundation for discovering "mobile genetic elements"; it was more than 30 years after she initially described the phenomenon of controlling elements. She was compared to Gregor Mendel in terms of her scientific career by the Swedish Academy of Sciences when she was awarded the Prize.

ONLINE REPORT

Drugs from nature: Big effects of multiple compounds in small amounts

A research group led by Professor Helge Bode from Goethe University, Frankfurt, Germany has discovered a whole class of new peptides with which bacteria are able to kill insect larvae.

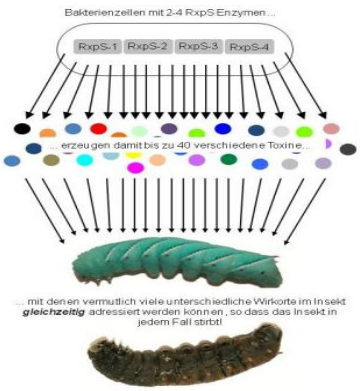
Nature often produces whole weaponry of active ingredients to ensure it is well prepared for any scenario that might occur. Pharmacists and medical experts have meanwhile learnt from this, since pathogens develop resistance more easily to single active drugs than to a combination therapy. The research group led by Professor Helge Bode has now discovered a whole class of new peptides with which bacteria are able to kill insect larvae.

The peptides, known as rhabdopeptide/xenortide peptides (RXPs), are produced exclusively by the bacterial genera Photorhabdus and Xenorhabdus. They live in symbiosis with nematodes, together with which they infect and kill insect larvae. Since many RXPs are toxic for eukaryotic cells (including insect cells) and are produced by many different strains of Xenorhabdus and Photorhabdus, they presumably play a very important role during infection.

One single strain of bacteria can produce upto 40 RXP derivates. As the research group, which is led by Professor Helge B. Bode, Merck Endowed Professor of Molecular Biotechnology at Goethe University, Frankfurt reported in the latest issue of *Nature Chemistry* that it was surprising to know that only a maximum of four enzymes was required for their production. Bode compares them with classic chemical catalysts for the formation of polymer chains. His group has successfully solved the mechanisms responsible for the production of the unusually high diversity of RXPs.

Why do the bacteria produce a whole library of RXPs instead of a single compound? The researchers explain that the bacteria cannot control into which insect larvae they are delivered by their nematode host. However, in order to survive they must be able to kill any insect quickly and efficiently and direct the mixture of substances at perhaps completely different target sites in the insect cells at the same time. "Imagine shooting with a shotgun," explains Bode, "even if you're a poor marksman, there's a good chance that the spray of bullets will ensure that at least one hits the target!"

Future work will focus on detecting the exact mode of action of the RXPs and identifying, by means of structure-activity analysis, particularly potent derivates, which can then be produced biotechnologically or chemically and perhaps used as insecticides.



The peptides, known as rhabdopeptide/xenortide peptides (RXPs), are produced exclusively by the bacterial genera Photorhabdus and Xenorhabdus. They live in symbiosis with nematodes, together with which they infect and kill insect larvae.

Credit: Image courtesy of Goethe-Universität Frankfurt am Main

Source: www.sciencedaily.com

New class of drugs holds promise for combating antibiotic resistance

A new class of drugs that combat antibiotic resistance has been discovered by a University of Oklahoma researcher and his team. In the study supported by the National Institutes of Health, laboratory experiments were combined with supercomputing modeling to identify molecules that boost the effect of antibiotics on disease-causing bacteria.

Helen Zgurskaya, professor of chemistry and biochemistry in the OU College of Arts and Sciences, and OU team members Narges Abdali, Julie Chaney, David Wolloscheck and Valentin Rybenkov, collaborated with Jeremy Smith, Jerry Parks and Jerome Baudry, the University of Tennessee-Oak Ridge National Laboratory Center for Molecular Biophysics; Adam Green, UT; and Keith Haynes and John Walker, Saint Louis University School of Medicine. They collectively identified four new chemicals that seek out and disrupt bacterial proteins called "efflux pumps," a major cause of antibiotic resistance in bacteria.

The supercomputing power of ORNL's Titan supercomputer had allowed them to perform large-scale simulations of the drug targets and to screen many potential compounds quickly said Zgurskaya, head of the OU Antibiotic Discovery and Resistance Group at the Stephenson Life Sciences Research Center. She added that the information received by stimulations was combined with their experiments to select molecules that were found to work well and that drastically reduced the time needed to move from the experimental phase to clinical trials.

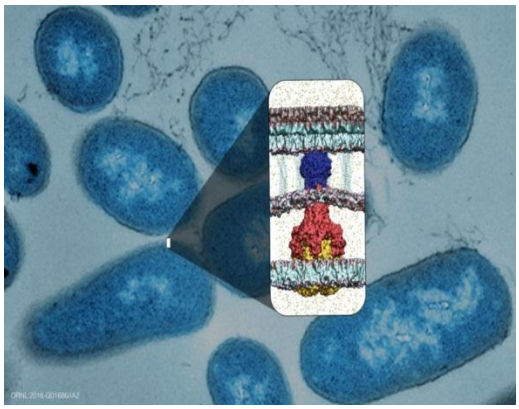
The team focused on one efflux pump protein, known as AcrA, which connects two other proteins in a tunnel shape through the bacterial cell envelope. Disrupting this protein could essentially break the efflux pump, an approach unlike other drug design strategies that try to inhibit the biochemical processes.

"In contrast to previous approaches, our new mechanism uses mechanics to revive an existing antibiotic's ability to fight infection," said Smith, UT-ORNL Governor's Chair and director of the UT-ORNL Center for Molecular Biophysics.

Using computational models produced by the Titan supercomputer, researchers screened various combinations of molecules and proteins to determine which would be the most effective in preventing AcrA proteins from assembling properly.

"The first screening took only 20 minutes using 42,000 processors and yielded several promising results," said Parks, ORNL. "After more extensive analysis, we narrowed down our list to predict which molecules were most likely to disrupt the function of the efflux pump." he added.

OU researchers then conducted laboratory experiments to confirm the disruption of the efflux pump and the antibiotic-reviving capability of four of the molecules selected. The SLU School of Medicine research team synthesized structural analogs of the discovered efflux pump inhibitors and identified properties essential for their activities.



(Image Credit: Oak Ridge National Laboratory**)**

Once antibiotics have entered the cell by crossing the outer membrane (inset, top), they enter the efflux pump protein shown in yellow near the inner membrane (bottom) only to be pumped back out of the cell (upward). The Titan supercomputer identifies molecules that target the "red" proteins and potentially disable the efflux pump by preventing it from assembling properly.

Source: www.sciencedaily.com

Abstract of Recent Publications

01. International Journal of Mycobacteriology, 2016, Vol. 5 (1), Pages: 108-109

Antimycobacterial activity assessment of three ethnobotanical plants against *Mycobacterium Tuberculosis:* An *In Vitro* study.

Emami, Ghasem Habibi, Ali Asghar Farazi, Manijeh Kahbazi, Hossein Sarmadian, Mansooreh Jabbari, Hossein Hosseini, Mona Ramezani.

Infectious Diseases Research Center (IDRC), Arak University of Medical Sciences, Arak, Iran.

Objective/Background

Resistances to herbal medicines are still not defined and finding natural remedies against drug resistant *Mycobacterium tuberculosis* (MTB) has research priority. The antimycobacterial susceptibility method for herbal extracts is unclearly defined and there is no standard method for assessment of the materials against bacteria. In the present study, time kill of three medicinal plants was determined against MTB.

Methods

The clinical isolate of MTB from a patient who harbored confirmed tuberculosis was used in the study. Aqueous extracts of *Aloe vera* leaves, mint, and *Hypericum perforatum* were prepared using reflux distillation. Disk diffusion methods were conducted in Petri dishes and McCartney bottles containing Löwenstein–Jensen medium to measure the sensitivity of plant extracts in serial concentrations of 0.25–8 mg/mL. A pour plate method was performed by mixing 0.7 mL of each concentration of extract in 5 mL Löwenstein–Jensen medium followed by surface culturing of MTB fresh cells. The time kill method was conducted by bacterial suspension in equal amounts of the extract and viable evaluation in fresh culture at the beginning, and at 24-h, 48-h, 72-h, and 1-week intervals. All cultures were incubated at 37 °C for 4 weeks. Inoculum concentrations were considered as a variable.

Results

The zones of inhibition of *A. vera*, *H. perforatum*, and mint extracts in the disk diffusion method in McCartney bottles were 60 mm, 41 mm and zero respectively, but Petri dishes did not have repeatable results. In the pour plate method, an extract concentration up to 1 mg/mL could inhibit cell growth. In mint extract, colony forming was four times more than the others at 0.5 mg/mL. Time kill of 95% of cells occurred when exposed to extracts of *A. vera* and *H. perforatum* separately, but was 50% in 24 h and 20% in 10 min. The time kill for mint was 95% in 1 week.

Conclusion

The results give some scientific basis to the use of plant extracts for growth control of MTB cells. Clinical trials are recommended for assessment of the extract as complementary medicine, as well as for antisepsis.

Keywords: *Aloe vera; Extracts; Hypericum perforatum; Mint; Mycobacterium tuberculosis*

11th December, 2016

E - Resources on Microorganisms

NATIONAL

Central Institute of Freshwater Aquaculture
http://cifa.nic.in

Institute of Microbial Technology
http://www.imtech.res.in

Indian Institute of Soil Science
http://www.iiss.nic.in/index.html

National Institute for Interdisciplinary Science and Technology
http://www.niist.res.in/english/

INTERNATIONAL

American Society for Microbiology
http://www.asm.org

British Society for Plant Pathology
http://www.bspp.org.uk

Biotechnology Industry Organisation
http://www.efb-central.org

Fungal Genetics Stock Center
http://www.fgsc.net

EVENTS
Conferences / Seminars / Meetings 2017

Plant microbiota. March 26 – April 07, 2017. **Venue:** Cologne, **Germany. Website:** http://events.embo.org/17-plant-microbiota/

ASM Conference on Tuberculosis: Past, Present and Future. April 01 - 04, 2017. **Venue:** New York, **USA. Website:** http://conferences.asm.org/index.php/upcoming-conferences/asm-conference-on-tuberculosis

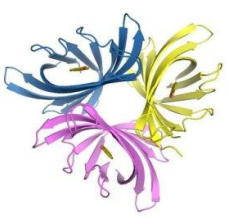
Fourth International Conference on Next Generation Computing and Communication Technologies 2017. April 19 - 20, 2017. **Venue:** Dubai, **UAE**. **Website:** http://www.icngcct.com

ASBMB Annual Meeting. April 22 - 26, 2017. **Venue:** Chicago, **USA**. **Website:** http://www.asbmb.org/meeting2017/

Malaria Experimental Genetics (Accra, Ghana). April 30 – May 06, 2017. **Venue:** Accra, **Ghana. Website:** https://coursesandconferences.wellcomegenomecampus.org/events/item.aspx?e=634

Protein disrupts infectious biofilms

Many infectious pathogens are difficult to treat because they develop into biofilms, layers of metabolically active but slowly growing bacteria embedded in a protective layer of slime, which are inherently more resistant to antibiotics. Now, a group of researchers at Caltech and the University of Oxford have made progress in the fight against biofilms. Led by Dianne Newman, the Gordon M. Binder/Amgen Professor of Biology and Geobiology, the group identified a protein that degrades and inhibits biofilms of *Pseudomonas aeruginosa*, the primary pathogen in cystic fibrosis (CF) infections.



Crystal structure of the PodA protein complex with three molecules of 1-hydroxyphenazine, the reaction product, bound in the active sites.
(Image Credit: Kyle Costa/Caltech**)**

Pseudomonas aeruginosa causes chronic infections that are difficult to treat, such as those that inhabit burn wounds, diabetic ulcers, and the lungs of individuals living with cystic fibrosis. Newman says. "In part, the reason these infections are hard to treat is because *P. aeruginosa* enters a biofilm mode of growth in these contexts; biofilms tolerate conventional antibiotics much better than other modes of bacterial growth. Our research suggests a new approach to inhibiting *P. aeruginosa* biofilms."

The group targeted pyocyanin, a small molecule produced by *P. aeruginosa* that produces a blue pigment. Pyocyanin has been used in the clinical identification of this strain for over a century, but several years ago the Newman group demonstrated that the molecule also supports biofilm growth, raising the possibility that its degradation might offer a new route to inhibit biofilm development.

To identify a factor that would selectively degrade pyocyanin, Kyle Costa, a postdoctoral scholar in biology and biological engineering, turned to a milligram of soil collected in the courtyard of the Beckman Institute on the Caltech campus. From the soil, he isolated another bacterium, Mycobacterium fortuitum, which produces a previously uncharacterized small protein called pyocyanin demethylase (PodA).

Source: www.sciencedaily.com

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