THE HOPE OF ALL NATURAL PLASMID CURING COMPOUNDS

"YOUR BODY'S ABILITY TO HEAL IS GREATER THAN ANYONE HAS PERMITTED YOU TO BELIEVE."

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WHY NATURAL PLASMID CURING COMPOUNDS?

SCIENCE HAS GONE BEYOND NATURE WITH BIOENGINEERED PLASMIDS

"Your scientists were so preoccupied with whether or not they could, they didn't stop to think if they should."

-Jurassic Park

Plasmid DNA Vaccine Vector Design: Impact on Efficacy, Safety and Upstream Production

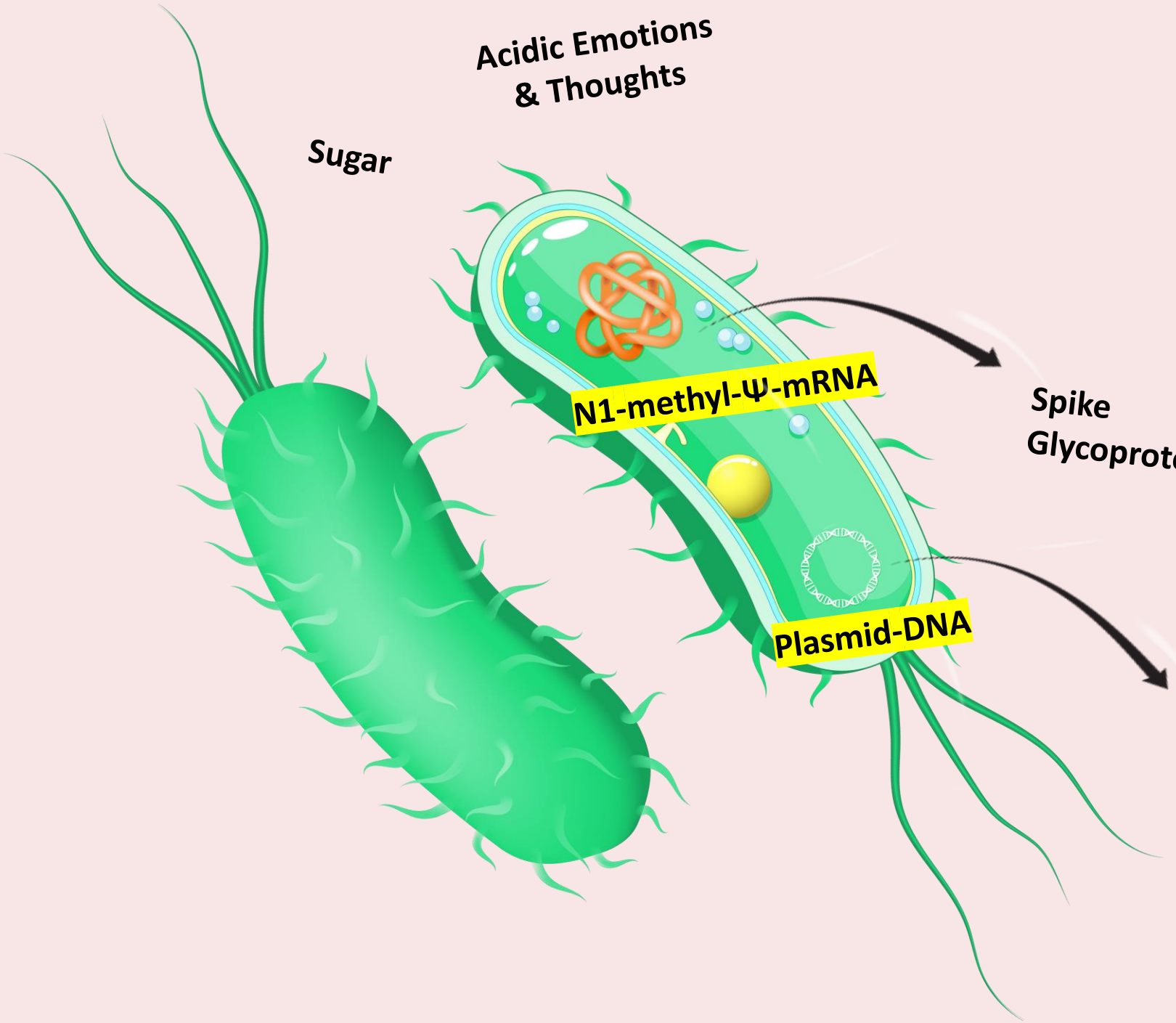
F-factors, the evidence did not support the idea that R-factors could integrate into the chromosome. Thus the term “episome” was eventually dropped and we’ve been using “plasmid” ever since!

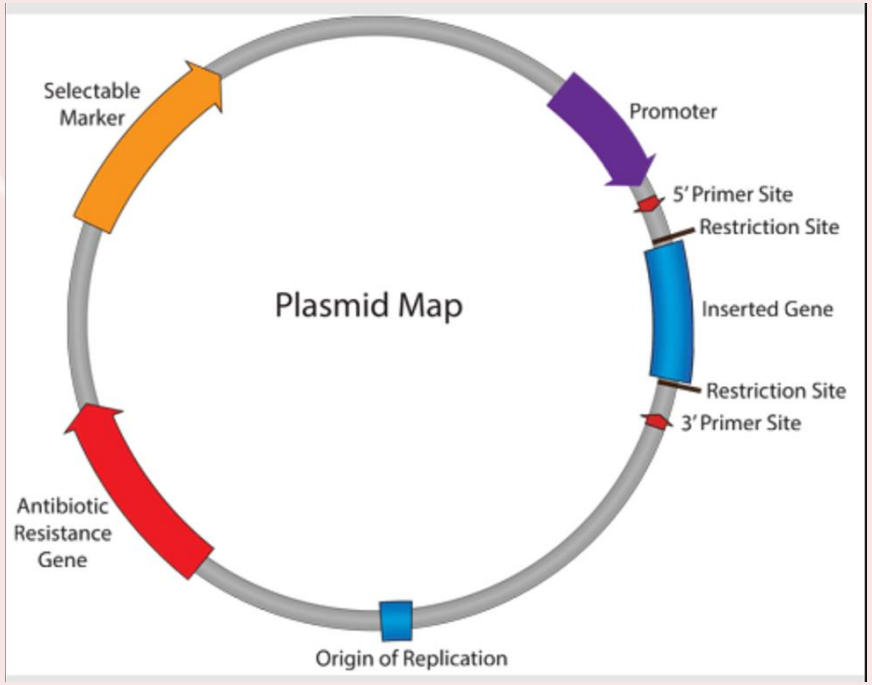
From Napkins to Notebooks

Although discovered in the early 1950s, it took until the 1970s for plasmids to gain prominence in the scientific community. Prior to this, bacteriophage, especially lambda, was the tool of choice for molecular biologists wanting to study bacterial genetics. This all changed thanks, in part, to a collaboration initiated at a Hawaiian deli in 1972. Using a deli napkin for paper, a small group of scientists including Stanley Falkow, Stanley Cohen, Herbert Boyer, and Charles Brinton concocted a wild idea of using the newly discovered EcoRI enzyme (and its predictable cut site) to develop the first plasmid “cloning” experiment. Dr. Cohen and colleagues treated a tetracycline resistant plasmid, pSC101, and a newly developed kanamycin resistant plasmid, pSC102, with EcoRI and selected for *E. coli* transformants that were resistant to both. When this proved successful, pSC101 became the first plasmid cloning vector and molecular biology was never the same.

WEAPONIZED MICROBIOME

- ***Sugar Feeds This Genetic Infection Like Nothing Else***





TARGETED SCREENING OF BIOACTIVE PLANT EXTRACTS & PHYTOCOMPOUNDS AGAINST PROBLEMATIC GROUPS OF MULTIDRUG-RESISTANT BACTERIA

NATURAL PLASMID CURING

TARGETED SCREENING OF BIOACTIVE PLANT EXTRACTS AND PHYTOCOMPOUNDS AGAINST PROBLEMATIC GROUPS OF MULTIDRUG-RESISTANT BACTERIA

[Bioactive Plant Extracts and Phytocompounds Against Groups of Multidrug-Resistant Bacteria]

"Resistance to most commonly used antibiotics… is on the rise. **Bacteria develop resistance through various mechanisms, encoded by chromosomes, plasmids, and transposons.**"

"Considerable work has been done on the antibacterial activity of plant extracts and phytocompounds. In some cases, the mode of action of phytocompounds has been documented. Considering the various mechanisms of drug resistance present in bacteria, the specific activity of plant extracts/compounds may help in combating MDR bacteria. Such novel activity includes (1) **MDR pump inhibition activity**, (2) **inhibition of beta-lactamase production or activity**, (3) **anti-R-plasmid activity (interference with plasmid physiology)**, (4) **synergy of phytocompounds with antibiotics**, (5) **targeting virulence and pathogenicity of bacteria**, and (6) **gene transfer mechanisms**."

PHYTOCHEMICALS AS ANTIMICROBIALS: PROSPECTING HIMALAYAN MEDICINAL PLANTS AS SOURCE OF ALTERNATE MEDICINE TO COMBAT ANTIMICROBIAL RESISTANCE

NATURAL PLASMID CURING

PHYTOCHEMICALS AS ANTIMICROBIALS: PROSPECTING HIMALAYAN MEDICINAL PLANTS AS SOURCE OF ALTERNATE MEDICINE TO COMBAT ANTIMICROBIAL RESISTANCE

Himalayan Medicinal Plants To Combat Antimicrobial Resistance

"Plant phytochemicals have shown multifaceted effects on microbial cells, such as **alkaloids imposing their antimicrobial effects** by inhibiting efflux pumps, nucleic acid synthesis, enzyme activities, ATP synthesis, cell-to-cell communication, cell wall biosynthesis, and jeopardizing the cell division machinery. **Phenols act as antimicrobials by inhibiting** metabolically important enzymes, efflux pumps, and cell wall biosynthesis; inactivating enzymes such as DNA gyrase and penicillinases; and increasing the membrane permeability, eventually leading to cell death. **Organosulfur compounds inhibit** nucleic acid synthesis and act as potent enzyme inhibitors, while terpenes mostly exert their action by compromising the membrane integrity of microbial cells."

"Plant-based antimicrobials have attracted significant attention due to the reduced potency and increasing toxicity of synthetic antimicrobials. Plant-based antimicrobial formulations...are easily available and have almost no side effects. The limited target specificity of existing synthetic antibiotics can be overcome by the broad-spectrum antibacterial action of phytochemicals."

ANTI-ESCHERICHIA COLI ACTIVITY OF HERBAL MEDICINES: A SYSTEMATIC LITERATURE REVIEW

NATURAL PLASMID CURING

ANTI-ESCHERICHIA COLI ACTIVITY OF HERBAL MEDICINES: A SYSTEMATIC LITERATURE REVIEW

Anti-Escherichia coli Activity of Herbal Medicines: A Systematic Literature Review

"E. coli can acquire antimicrobial resistance mechanisms, such as encoding the genes of the enzymes, such as β-lactamases, the genes that alter the bacterial cell wall, which results in no binding site for antimicrobial agent and condensation of outlet pumps, translation, and transduction (12). **Efflux pumps are transportation proteins involved in the extrusion of toxic substrates** (including nearly all types of clinically important antibiotics) (13). Efflux pumps can be discriminated from multidrug efflux pumps, and the extrusion of antimicrobial agents via these efflux pumps is a major factor in antimicrobial resistance (14). Cells can use proton-driven antiporters and/or ATP-driven transporters (ATP-binding cassette) to expel medicines (15). **Efflux pump inhibitors can be utilized to reduce the efflux of antibiotics from bacterial cell.**."

"Several studies have revealed that herbal medicines are good sources of compounds with antioxidant and antimicrobial activity, which are able to protect the body against cellular oxidation and pathogens."

PLASMID CURING COMPOUND CATEGORIES

"YOUR BODY'S ABILITY TO HEAL IS GREATER THAN ANYONE HAS PERMITTED YOU TO BELIEVE."

CATEGORIES

FOR NATURAL PLASMID CURING COMPOUNDS

ANTIBIOTIC RESISTANCE REVERSAL

"The extent of resistance to therapeutic antibiotics can be directly associated with the copy number of the plasmid carrying antibiotic resistance genes (ARGs)."

Plant-Assisted Plasmid Curing Strategies for Reversal of Antibiotic Resistance

CONJUGATION INHIBITORS

"Conjugation inhibitors (COINs) are compounds that inhibit plasmid transfer by affecting the conjugative machinery."

Conjugation Inhibitors Effectively Prevent Plasmid Transmission in Natural Environments

COMPETING MICROORGANISMS

"One of the mechanisms by which commensal and probiotic bacteria provide colonization resistance to pathogens is by directly competing for the same niche."

No Vacancy: How Beneficial Microbes Cooperate with Immunity to Provide Colonization Resistance to Pathogens

PLASMID CURING COMPOUNDS

NAPHTHOQUINONES

VITAMIN K

QUERCETIN

PLUMBAGO

CANNABIS

AVOCADO & OLIVE OIL

BENEFICIAL BACTERIA

AND MORE...

PLASMID CURING COMPOUNDS QUICK REFERENCE

"YOUR BODY'S ABILITY TO HEAL IS GREATER THAN ANYONE HAS PERMITTED YOU TO BELIEVE."

NATURAL PLASMID CURING COMPOUNDS QUICK CHART

Natural Plasmid Curing Compounds from plants may be applicable in more categories and include more pathological microorganisms than indicated.

Plant source	Antibiotic Resistance Reversal	Bacterial Conjugation Inhibition	Competing Microorganisms	Pathological Microorganism
Naphthoquinones (Vitamin K, Lawsone, Plumbagin, Juglone , Shikonin, Lapachol)	✓			Unknown
Essential Oils (Peppermint, Eucalyptus, Rosemary)	✓			E. coli & more
Traditional Chinese Medicine (Dandelion, Diplod, Artemisia Leaves, Rhubarb, Scutellaria, Captis Chinensis, Honeysuckle)	✓			S. aureus, E. coli & more (unidentified)
Terminalia Chebula Fruit	✓			Bacillus subtilis, Shigella Sonnei
Barley	✓			E. coli

THE LIST CONTINUES TO GROW AS WE LEARN MORE!

NATURAL PLASMID CURING COMPOUNDS QUICK CHART

Natural Plasmid Curing Compounds from plants may be applicable in more categories and include more pathological microorganisms than indicated.

Plant source	Antibiotic Resistance Reversal	Bacterial Conjugation Inhibition	Competing Microorganisms	Pathological Microorganism
Uvaria Chamae	✓			E. coli, Salmonella
Medicinal Plants from North East India (Garcinia Pedunculata, Phlogacanthus Thyrsiformis, Ziziphus Mauritiana)	✓			E. coli
Piper Nigrum (Black Pepper) (and Zingiber Officinale, Cinnamomum Verum, Nigella Sativa)	✓			Staphylococcus aureus, Salmonella typhi
Piper Longum (Indian Long Pepper)	✓			Enterococcus faecalis, Staphylococcus aureus, Salmonella typhi, E. coli
Akarkara & Nutgrass	✓			Enterococcus faecalis, Staphylococcus aureus, Bacillus sp.

THE LIST CONTINUES TO GROW AS WE LEARN MORE!

NATURAL PLASMID CURING COMPOUNDS QUICK CHART

Natural Plasmid Curing Compounds from plants may be applicable in more categories and include more pathological microorganisms than indicated.

Plant source	Antibiotic Resistance Reversal	Bacterial Conjugation Inhibition	Competing Microorganisms	Pathological Microorganism
Adenopus Breviflorus Benth (Gourd Family)	✓			Staphylococcus aureus & more
Citrus Aurantium (Sour Orange)	✓			S. aureus, E. coli, K. pneumonia, Pr. Vulgaris, Pr. Mirabilis, Ps. Aeruginosa
Hibiscus & Devil's Claw	✓			Pseudomonas aeruginosa
Cuminum Cyminum, Coriandrum Sativum, Myristica Fragrans	✓			Acinetobacter Spp., Pseudomonas Spp., E. coli, Klebsiella pneumonia, Proteus spp.
Dioscorea Bulbifera (Yam Family)	✓			E. Coli
Ascorbic Acid (Vitamin C)	✓			Staphylococcus aureus, Serratia marcescens
Thyme, Cinnamon, Clove	✓			Streptococcus pneumonia, Staphylococcus aureus

THE LIST CONTINUES TO GROW AS WE LEARN MORE!

NATURAL PLASMID CURING COMPOUNDS QUICK CHART

Natural Plasmid Curing Compounds from plants may be applicable in more categories and include more pathological microorganisms than indicated.

Plant source	Antibiotic Resistance Reversal	Bacterial Conjugation Inhibition	Competing Microorganisms	Pathological Microorganism
Nigella Sativa (Black Caraway, Black Cumin)	✓			Staphylococcus aureus
Cardamon	✓			Proteus mirabilis, Staphylococcus aureus
Coccinia grandis L. (Ivy Gourd)	✓			Bacillus cereus, E.coli (ATCC25938)
Tachyspermum ammi (Ajwain, or ajowan caraway)	✓			E.coli, K.pneumoniae, Citrobacter spp., P.aeruginosa and Proteus spp
Helicteres isora L.	✓			Enterococcus faecalis, Escherichia coli, Bacillus cereus and E.coli (RP4)
Richardia brasiliensis (Tropical Mexican Clover)	✓			E.coli, Staphylococcus Aureus, Pseudomonas Aeruginosa, Candida Tropicalis Candida krusei

THE LIST CONTINUES TO GROW AS WE LEARN MORE!

NATURAL PLASMID CURING COMPOUNDS QUICK CHART

Natural Plasmid Curing Compounds from plants may be applicable in more categories and include more pathological microorganisms than indicated.

Plant source	Antibiotic Resistance Reversal	Bacterial Conjugation Inhibition	Competing Microorganisms	Pathological Microorganism
Rhus coriaria (Sicilian Sumac)	✓			S.aureus
Eugenia Jambolana (Black Plum or Jamun)	✓			Enterococci
Alpinia Galangal (in the ginger family)	✓			E.faecalis, S.aureus, S.sonnei, S.typh
Quercus infectoria (Aleppo Oak)	✓			E.coli
Linusm usitatissium (Flax)	✓			E. coli
Cinnamonum zeylanicium	✓			E. Coli
Cannabis		✓		E. Coli
Baicalin (Chinese Skullcap)		✓		E. Coli & Klebsiella

THE LIST CONTINUES TO GROW AS WE LEARN MORE!

NATURAL PLASMID CURING COMPOUNDS QUICK CHART

Natural Plasmid Curing Compounds from plants may be applicable in more categories and include more pathological microorganisms than indicated.

Plant source	Antibiotic Resistance Reversal	Bacterial Conjugation Inhibition	Competing Microorganisms	Pathological Microorganism
Plumbago Zeylanica (Lawsone)	✓	✓		P. aeruginosa, P. vulgaris, E. coli, Klebsiella, Staphylococcus
Myristica Iowiana		✓		E. Coli
Unsaturated Fatty Acids (Oleic & Linoleic)		✓		E. Coli
Melatonin		✓		E. Coli
Mallotus Philippinensis		✓		Various
Evodia		✓		Various
Capsicum		✓		Various
Disaccharides		✓		Various

THE LIST CONTINUES TO GROW AS WE LEARN MORE!

NATURAL PLASMID CURING COMPOUNDS QUICK CHART

Natural Plasmid Curing Compounds may be applicable in more categories and may be indicated for more pathological microorganisms than listed.

Plant source	Antibiotic Resistance Reversal	Bacterial Conjugation Inhibition	Competing Microorganisms	Pathological Microorganism
Rose Hip or Dog Rose		✓		E. Coli
Lactic Acid Bacteria (Lactobacillus Plantarum, Lactobacillus Bulgaricus, Bifidobacterium Longum)			✓	Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella, Shigella sp.

THE LIST CONTINUES TO GROW AS WE LEARN MORE!

Natural PCCs
& The Treatment of Local Tissue Damage Induced By Snake Venoms

"YOUR BODY'S ABILITY TO HEAL IS GREATER THAN ANYONE HAS PERMITTED YOU TO BELIEVE."

NATURAL PCCs THAT ARE USED IN THE TREATMENT OF LOCAL TISSUE DAMAGE INDUCED BY SNAKE VENOMS

List of medicinal plants used against snakebites

Plant name	Countries	Part Used
Allium sativum	Colombia, India, Sri Lanka, Spain	Bulb, inflorescence, leaf
Coriandrum sativum	Sri Lanka	ND (not described)
Cannabis sativa	India, Sri Lanka	ND (not described)
Terminalia chebula	Sri Lanka	ND (not described)
Coccinia grandis	Pakistan, Sri Lanka	Root
Cinnamomum verum	Sri Lanka	ND (not described)
Lawsonia inermis	India	Bark
Helicteres isora	Bangladesh, India	Fruit, root
Piper longum	Bangladesh, Sri Lanka	Flower, fruit, Latex, root
Piper nigrum	Bangladesh, India, Sri Lanka	Floral bud, flower, fruit, root

MEDICINAL PLANTS FOR THE TREATMENT OF LOCAL TISSUE DAMAGE INDUCED BY SNAKE VENOMS: AN OVERVIEW FROM TRADITIONAL USE TO PHARMACOLOGICAL EVIDENCE

NATURAL PCCs THAT ARE USED IN THE TREATMENT OF LOCAL TISSUE DAMAGE INDUCED BY SNAKE VENOMS

List of medicinal plants used against snakebites continued

Plant name	Countries	Part Used
Capsicum annuum (syn. Capsicum frutescens)	Bangladesh, Colombia, India, Sri Lanka	Fruit, root
Alpinia galanga	Sri Lanka	ND (not described)
Zingiber officinale	Ecuador, Nicaragua, Sri Lanka	Rhizome, root
Ziziphus jujuba (syn. Ziziphus mauritiana)	Sri Lanka	ND (not described)
Myristica fragrans	Sri Lanka	ND (not described)
Citrus aurantium	Sri Lanka	ND (not described)
Plumbago zeylanica	Bangladesh, India, Sri Lanka	Root

MEDICINAL PLANTS FOR THE TREATMENT OF LOCAL TISSUE DAMAGE INDUCED BY SNAKE VENOMS: AN OVERVIEW FROM TRADITIONAL USE TO PHARMACOLOGICAL EVIDENCE

ANTIBIOTIC RESISTANCE REVERSAL

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COMPETING MICROORGANISMS

"One of the mechanisms by which commensal and probiotic bacteria provide colonization resistance to pathogens is by directly competing for the same niche."

No Vacancy: How Beneficial Microbes Cooperate with Immunity to Provide Colonization Resistance to Pathogens

WHY PLASMID-MEDIATED ANTIBIOTIC RESISTANCE REVERSAL?

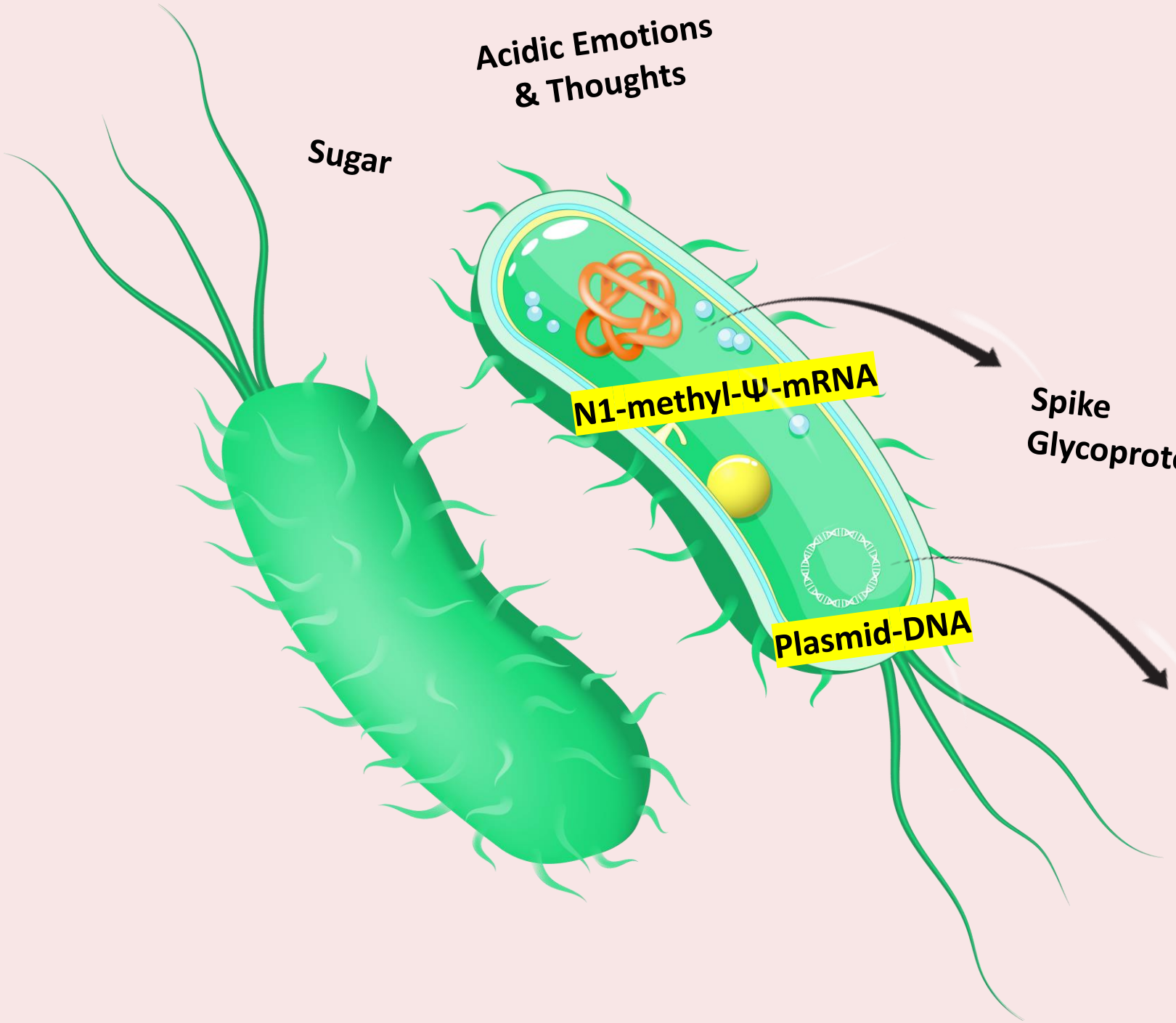
TO INHIBIT ANTIBIOTIC RESISTANCE GENES SO NATURAL ANTIBIOTICS CAN KILL WEAPONIZED BACTERIA. USE IN CONJUNCTION WITH NATURAL ANTIBIOTICS.

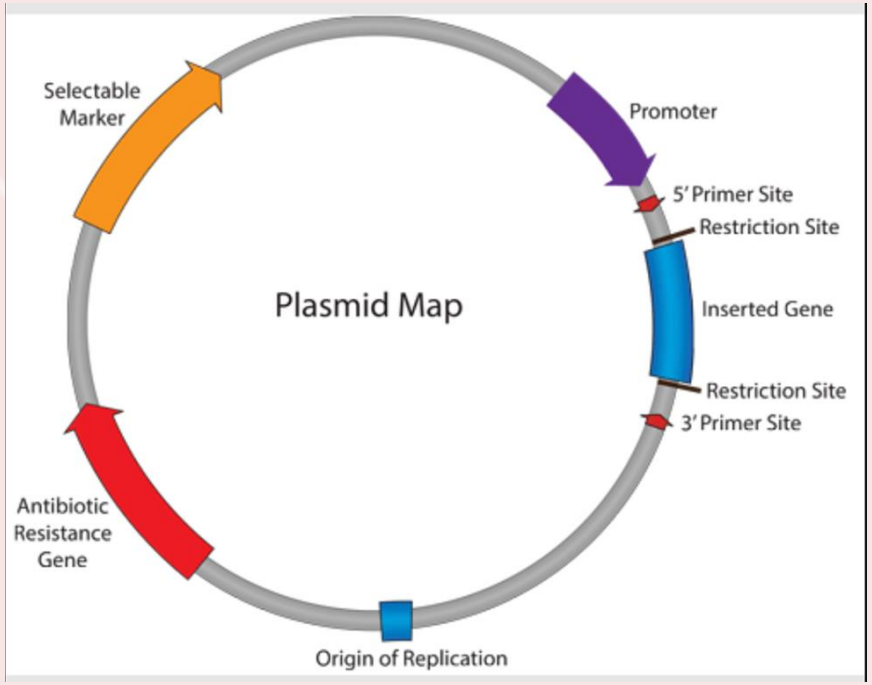
"Antibiotic resistance... has a universal concern in the management of treatment of infectious diseases. The extent of resistance to therapeutic antibiotics can be directly associated with the copy number of the plasmid carrying antibiotic resistance genes (ARGs)."

Plant-Assisted Plasmid Curing Strategies for Reversal of Antibiotic Resistance

WEAPONIZED MICROBIOME

- ***Sugar Feeds This Genetic Infection Like Nothing Else***





PLASMID CURING COMPOUNDS

NAPHTHOQUINONES

VITAMIN K

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PLUMBAGO

CANNABIS

AVOCADO & OLIVE OIL

BENEFICIAL BACTERIA

AND MORE...

NAPHTHOQUINONES (NQ)– PROMISING COMPOUNDS

ANTIBIOTIC RESISTANCE REVERSAL

NAPHTHOQUINONES (NQS) – PROMISING PLASMID CURING COMPOUNDS

"The multiple roles of NQs offer them a promising armory to combat microbial pathogens including MDR (multi-drug resistant pathogens) and ESKAPE (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.) group.

In bacteria, NQs may exhibit their function in the following ways (1) plasmid curing, (2) inhibiting efflux pumps (Eps), (3) generating reactive oxygen species (ROS), (4) the inhibition of topoisomerase activity."

Naphthoquinones and Their Derivatives: Emerging Trends in Combating Microbial Pathogens

Naphthoquinones from Natural Sources and Their Bioactivities

VITAMIN K (NQ)

VITAMIN K: A POTENT NAPHTHOQUINONE

THE GUT CONNECTION

Atherosclerosis is linked to small intestinal bacterial overgrowth *via* vitamin K2-dependent mechanisms

THE IMMUNE SYSTEM & BLOOD

A modulator for the immune system

Vitamin K appears to be both a coagulant & anticoagulant – it's a modulator

THE BRAIN

Cognition & Neurodegeneration

THE NERVES

"Scientists find Vitamin K2 repairs nerve cells."

MITOCHONDRIA

"Vitamin K2 modulates mitochondrial dysfunction."

"Vitamin K: Redox-modulation, prevention of mitochondrial dysfunction and anticancer effect, including role in calcium homeostasis"

VITAMIN K INSUFFICIENCY & CORONAVIRUS

"A Dutch study found a correlation between coronavirus patients and low levels of Vitamin K. That study led Linneberg and colleagues to look at Danish patients. They found a similar link between the severity of Covid-19 symptoms and low levels of the vitamin."

Reduced Vitamin K Status as a Potentially Modifiable Risk Factor of Severe Coronavirus Disease 2019

Dramatic Decrease of Vitamin K2 Subtype Menaquinone-7 in COVID-19 Patients

VITAMIN K & INDUCED VASCULAR DISEASE

"Vitamin K is an essential "switch" in balancing coagulation and anticoagulation process [69]. Indeed, vitamin K acts as a cofactor in the activation of extra-hepatic and hepatic Vitamin K-dependent proteins (VKDPs) including pro-thrombin and clotting factors VII, IX, X, major factors involved in blood coagulation. On the other hand, vitamin K can also trigger key anticoagulants via VKDPs for producing proteins C, S and Z [70, 71, 72]."

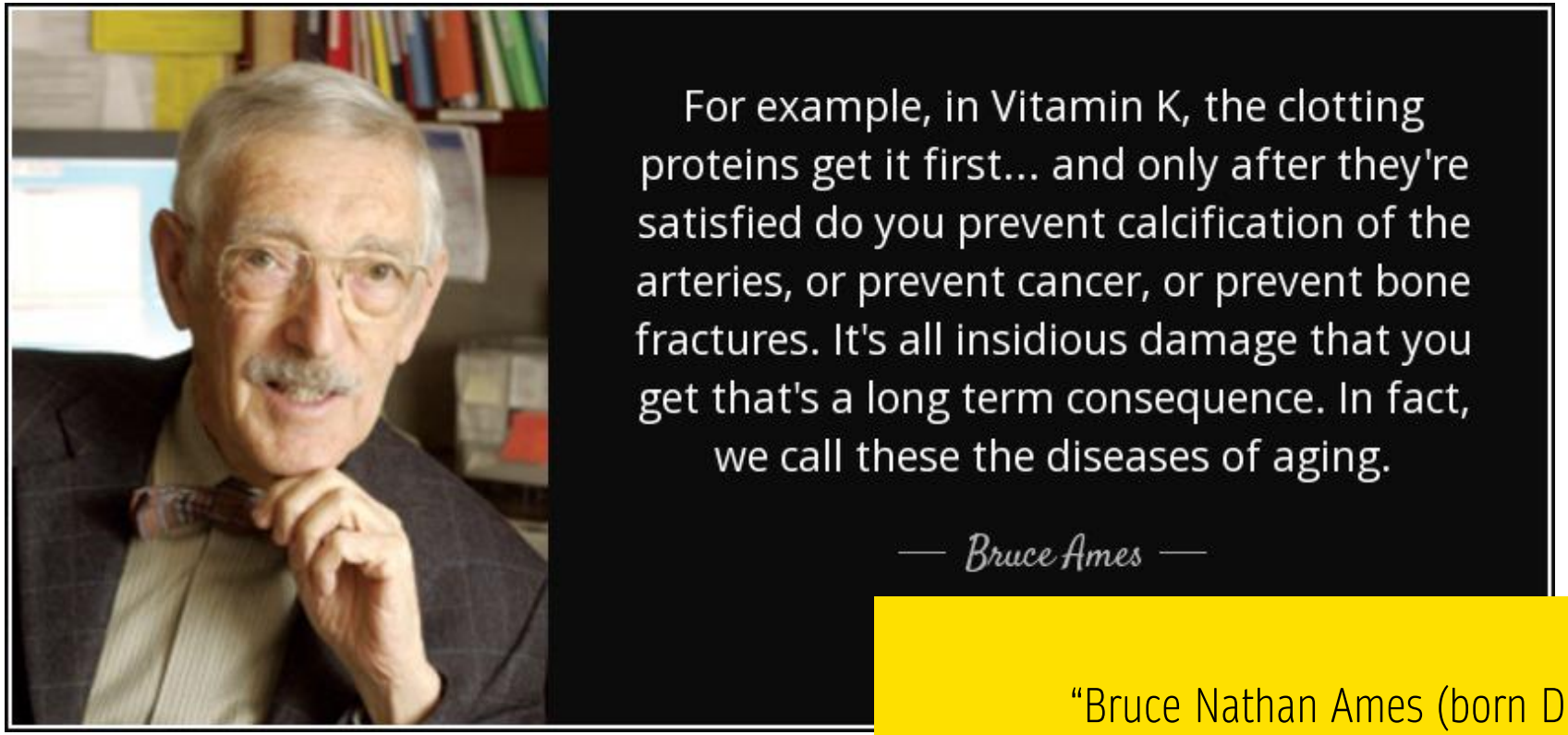
"It is important to note that vitamin K does not start the clotting process, it only enhances the coagulation system to work effectively. While vitamin K involvement in coagulation is well established, it is also a key component of the anticoagulation response. This response is facilitated through the activation of protein C, S and Z. Vitamin K-dependent protein C activation can inhibit clotting factors V and VIII which are responsible for clot generation."

"Beyond its essential role in coagulation, vitamin K is suggested to possess immunomodulatory functions as well as preventing vascular calcification."

"...the imbalance of coagulation system by altering/lysing of endothelial cells after infection can significantly contribute to thrombosis."

"As previously mentioned, vitamin K has also anti-coagulant properties through activation of protein C, S and Z. In contrast to proteins C and Z which are mainly localized in the liver, half of protein S is synthesized in endothelial cells playing thus a fundamental role in local prevention of thrombosis [109, 110, 111]."

Potential Beneficial Effects of Vitamin K in SARS-CoV-2 Induced Vascular Disease?



VITAMIN K

[Growing Evidence of a Proven Mechanism Shows Vitamin K2 Can Impact Health Conditions Beyond Bone and Cardiovascular (Including Peripheral Neuropathy)]

"Bruce Nathan Ames (born December 16, 1928) is an American biochemist. He is a professor of Biochemistry and Molecular Biology Emeritus at the University of California, Berkeley, and was a senior scientist at Children's Hospital Oakland Research Institute (CHORI). He is the inventor of the Ames test, a system for easily and cheaply testing the mutagenicity of compounds." -Wikipedia

OTHER NQ DERIVATIVES: JUGLONE (*BLACK WALNUT*)

"Juglone occurs naturally in the leaves, roots, husks, fruit…and bark of plants in the Juglandaceae family, particularly the **black walnut** (Juglans nigra)…"

Discovery of Juglone and Its Derivatives as Potent SARS-CoV-2 Main Proteinase Inhibitors

Juglone in Oxidative Stress and Cell Signaling

OTHER NQ DERIVATIVES: LAPACHOL (*PAU D'ARCO*)

Lapachol is a naphthoquinone from the Bignoniaceae family (ie. isolated from the bark of the Tabebuia Avellaneda; Pau D'Arco).

Lapachol: An Overview

OTHER NQ DERIVATIVES: PLUMBAGIN (*PLUMBAGO*)

"Plumbagin was originally found in the plant genus **Plumbago** but is also present in Artisea, Aldrovanda, Dionasea, Drosera, Nepenthes, Drosophyllum, Dioncophyllum, Triphophyllum, Ancistrocaldus, Ceratostigma, Diospryros, Juglans and other belonging to families like Iridaceae, Juglandaceae, Droseraceae. Nepenthaceae, Drosophyllaceae, Diocophyllaceae, Anicistrocladaceae, Anicistrocladaceae, Plumbaginaceae and Ebenaceae."

"...it is remarkable that any single agent could cause efficient plasmid loss since detailed analysis of F and other plasmids has revealed multiple plasmid strategies for survival. "

Phytoconstituent plumbagin: Chemical, biotechnological and pharmaceutical aspects

Curing of F-like plasmid TP181 by plumbagin is due to interference with both replication and maintenance functions

OTHER NQ DERIVATIVES:
LAWSONE (*HENNA, PLUMBAGO*)

"Lawsone, also known as hennotannic acid, is a red-orange dye present in the leaves of the **henna plant** (Lawsonia inermis), for which it is named.."

Ayurvedic Medicinal Plant Lawsonia Inermis Linn.: A Complete Review

Lawsone Produces Mitochondrial Dysfunctions and Triggers Mitophagy in Saccharomyces Cerevisiae

Purification and Characterization of an Active Principle, Lawsone, Responsible for the Plasmid Curing Activity of *Plumbago zeylanica* Root Extracts

Lawsone from Lawsonia Inermis: Isolation and Pharmacological Activities

Some of Phytochemical, Pharmacological and Toxicological Properties of Henna (Lawsonia inermis L.): A Review of Recent Researches

Curing Plasmid-Mediated Vancomycin Resistance in Staphylococcus Aureus using Herbal Naphthoquinones

OTHER NQ DERIVATIVES: SHIKONIN (*ZICAO*)

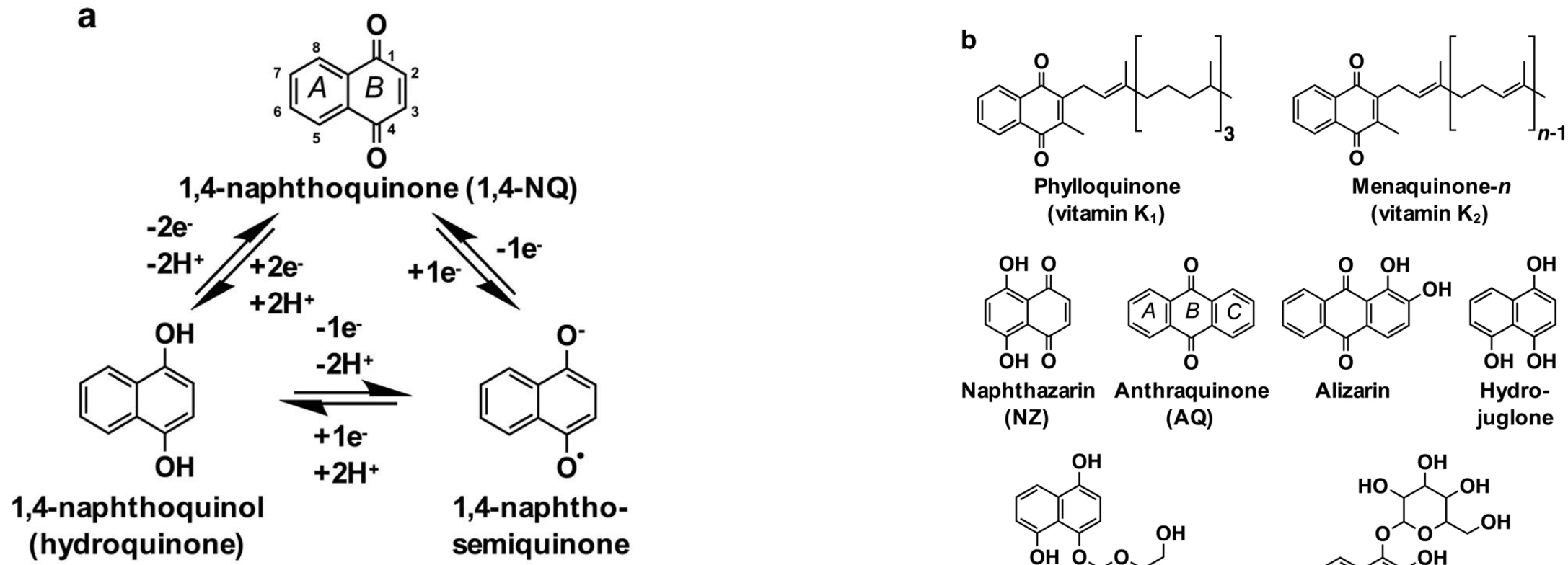
"Shikonin is the major bioactive component extracted from the roots of Lithospermum erythrorhizon which is also known as **"Zicao" in Traditional Chinese Medicine (TCM)**."

Pharmacological properties and derivatives of shikonin-A review in recent years

MAJOR 1,4-NQ NATURAL PRODUCTS PRODUCED BY HORTICULTURAL SPECIES

Common name	Scientific name	Major 1,4-NQ natural product(s) present
Medicinal or ethnobotanical		
Henna	Lawsonia inermis	Lawsone
Pau d'arco tree	Tabebuia impetiginosa	Lapachol
Madder	Rubia tinctorum	Alizarin
Purple gromwell (Zi cao) Arnebia	Lithospermum erythrorhizon Arnebia euchroma	Shikonins
Alkanet Arizona popcorn flower	Alkanna tinctoria Plagiobothrys arizonicus	Alkannins
Pipsissewa One-flowered wintergreen	Chimaphila umbellate Moneses uniflora	Chimaphilins
Indian leadwort	Plumbago indica	Plumbagin
Nuts and seeds		
Black walnut English walnut	Juglans nigra Juglans regia	Juglone
Pecan	Carya illinoensis	Juglone
Sesame	Sesamum indicum	Anthrasesamones

Biosynthesis and Molecular Actions of Specialized 1, 4-naphthoquinone Natural Products Produced By Horticultural Plants



(**A**) BASIC STRUCTURE AND REDOX FORMS OF 1,4-NQS AND

(**B**) EXAMPLES OF 1,4-NQ NATURAL PRODUCTS REFERENCED IN THE TEXT.

QUERCETIN

ANTIBIOTIC RESISTANCE REVERSAL

QUERCETIN

"The present study was to investigate the plasmid curing activities of natural compounds over multidrug resistant bacteria. An E. coli strain known to have pUC19 plasmid was selected for assessing the plasmid curing efficacy of the compounds. Eliminating the plasmid using the natural compound makes the compound vulnerable to any antibiotic without its drug resistance."

PLASMID CURING ACTIVITY OF NATURAL COMPOUNDS AGAINST DRUG RESISTANT BACTERIA

PROJECT REPORT

Submitted in partial fulfillment of the requirements for the award of the degree of

MASTER OF TECHNOLOGY

in

BIOTECHNOLOGY

by

PRAVEEN RAJ R. [1640910057]

Under the guidance of

Dr. WAHEETA HOPPER
Professor and HOD
Department of Bioinformatics

DEPARTMENT OF BIOTECHNOLOGY
SCHOOL OF BIOENGINEERING
FACULTY OF ENGINEERING AND TECHNOLOGY
SRM UNIVERSITY
KATTANKULATHUR 603 203

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5.3 Percentage curing of the compounds by replica plate method:

Table 12: Percentage curing of natural compounds calculated from the results of replica plate method,

Compound µg/ml	Percentage curing
DMSO(512)	0
Quercetin(512)	93
Quercetin(1024)	87
Epicatechin(512)	0
Morin hydrate(512)	0
Shikimic acid(512)	0
Umbelliferone(512)	27
Ursolic acid(512)	27

QUERCETIN

MICROORGANISM

E.COLI

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

PLASMID CURING ACTIVITY OF NATURAL COMPOUNDS AGAINST DRUG RESISTANT BACTERIA

PLUMBAGO

ANTIBIOTIC RESISTANCE REVERSAL

PLUMBAGO

"Multiple drug resistance (MDR) is a serious and emerging problem in treatment of diseases caused by nosocomial pathogens. Most of the bacteria harbour plasmids and show resistance to multiple antibiotics. Plasmid elimination can be one of the ways to make the antibiotic resistant clinical strains sensitive. In the present investigation 23 nosocomial pathogens like Pseudomonas aeruginosa, Proteus vulgaris, Escherichia coli, Klebsiella pneumoniae were isolated..."

"Root extracts of Plumbago auriculata were used to cure plasmid mediated antibiotic resistance."

ANTIBIOTIC RESISTANCE REVERSAL

PLUMBAGO

MICROORGANISM

E.COLI, P. AERUGINOSA, P. VULGARIS, K. PNEUMONIA

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Reversal of Plasmid Encoded Antibiotic Resistance from Nosocomial Pathogens by Using Plumbago auriculata Root Extracts

TRADITIONAL CHINESE MEDICINE PCCs

ANTIBIOTIC RESISTANCE REVERSAL

TRADITIONAL CHINESE MEDICINE (TCM) PCCs

"TCM-induced reversal of bacterial drug resistance is discussed, particularly in terms of the elimination of resistant (R) plasmids..."

"...several studies have confirmed that TCM can eliminate drug-resistant plasmids..."

ANTIBIOTIC RESISTANCE REVERSAL

TRADITIONAL CHINESE MEDICINE (TCM)

DANDELION

DIPLOD

ARTEMISIA LEAVES

RHUBARB

SCUTELLARIA

CAPTIS CHINENSIS

HONEYSUCKLE

[Antimicrobial Mechanisms of Traditional Chinese Medicine and Reversal of Drug Resistance: A Narrative Review]

MICROORGANISM

Staphylococcus aureus, E. Coli, Other (non-identified) antibiotic-resistant plasmids

MECHANISM OF ACTION

Antibiotic Resistance Reversal

A POINT OF INTEREST...

"Antibacterial drugs face increasing challenges due to drug resistance and adverse reactions...Herbs have played an important role in the treatment of infectious diseases. This review aims to summarize, analyze and evaluate the antibacterial activities and mechanisms of components from popular herbs in East Asia. In this review, we have searched and summarized the scientific papers published during the past twenty-year period from electronic databases such as PubMed, ScienceDirect, and Web of Science."

Antimicrobial Activities and Mechanisms of Extract and Components of Herbs in East Asia with Microorganisms

ANOTHER POINT OF INTEREST...

"The formation, transfer and transmission of resistant plasmids are important mechanisms that cause extensive antibiotic resistance, which play a major role in the dissemination of resistance genes (Laurent et al., 2018; Lerminiaux and Cameron, 2019). One of the effective mechanisms of TCM on decreasing antibiotic resistance may be to inhibit the transfer of resistant plasmids or eliminate those plasmids."

Novel Opportunity to Reverse Antibiotic Resistance: To Explore Traditional Chinese Medicine With Potential Activity Against Antibiotics-Resistance Bacteria

ESSENTIAL OILS

ANTIBIOTIC RESISTANCE REVERSAL

ESSENTIAL OILS

"The antimicrobial and antiplasmid activities of essential oils (orange oil, eucalyptus oil, fennel oil, geranium oil, juniper oil, peppermint oil, rosemary oil, purified turpentine oil, thyme oil, Australian tea tree oil) and of menthol, the main component of peppermint oil, were investigated…Each of the oils exhibited antimicrobial activity and three of them antiplasmid action."

"A new mechanism of plasmid curing was established for one of the oil components."

ESSENTIAL OILS

MICROORGANISM

E.COLI & MORE

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

(INCLUDING ANTIMICROBIAL ACTIVITIES)

Antimicrobial and Antiplasmid Activities of Essential Oils

Recent advances in research of antimicrobial effects of essential oils and plant derived compounds on bacteria

THE ANTIPLASMID ACTION OF 3 ESSENTIAL OILS

PEPPERMINT

"Peppermint oil inhibited replication of the F'lac metabolic plasmid of E. coli to an extent of 37.5%..."

EUCALYPTUS

"Eucalyptus...caused slight (plasmid) elimination... Eucalyptus oil: 0.2 – 0.5%"

ROSEMARY

"Rosemary...caused slight (plasmid) elimination... Rosemary oil: 3.1%"

ASCORBIC ACID (VITAMIN C)

ANTIBIOTIC RESISTANCE REVERSAL

ASCORBIC ACID (VITAMIN C)

"The effect of ascorbic acid on plasmid-coded antibiotic resistance in *Staphylococcus aureus* was investigated... The presence of ascorbate induced a 50–75% decrease in minimal inhibitory concentrations of different antibiotics for resistant strains... These results suggest that ascorbate can induce the loss of several plasmids of *S. aureus*, and that the levels of antibiotic resistance are also affected by the presence of this compound."

"This result refer to the fact that ascorbic acid – treated cells have lost the plasmid coding for resistance of antibiotics. "

ASCORBIC ACID (VITAMIN C)

MICROORGANISM

STAPHYLOCOCCUS AUREUS, SERRATIA MARCESCENS

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Decreased resistance to antibiotics and plasmid loss in plasmid-carrying strains of *Staphylococcus aureus* treated with ascorbic acid

Ascorbic acid induced loss of an antibiotic resistance plasmid in Serratia marcescens

MORE ANTIBIOTIC RESISTANCE REVERSAL

"YOUR BODY'S ABILITY TO HEAL IS GREATER THAN ANYONE HAS PERMITTED YOU TO BELIEVE."

MORE NATURAL PLASMID CURING COMPOUNDS

"Why plasmid curing is essential in drug resistance pattern... Phytochemicals have a novel anti-bacterial actions like inhibition of MDR efflux pump, anti-antibiotic resistance properties, R plasmid elimination. So, elimination of R plasmid containing genes are responsible for MDR is useful method.[34] Genes responsible for resistance to antibiotics are present in plasmid DNA."

"Plasmid curing is a process of completely removing plasmids from bacteria by means of chemical agents or now a days by means of herbal extracts or phytocompounds...But herbal extracts are more effective in use, as they do not have toxicity and mutagenic effects.[39]"

ANTIBIOTIC RESISTANCE REVERSAL

MORE NATURAL PLASMID CURING COMPOUNDS

MICROORGANISM

NIGELLA SATIVA, STAPHYLOCOCCUS AUREUS, PROTEUS SPP., BACILLUS CEREUS, E. COLI, KLEBSIELLA, CITROBACTER SPP., PSEUDOMONAS AERUGINOSA, EN, SHIGELLA SONNEI, ENTEROCOCCUS FAECALIS, E.COLI, CANDIDA TROPICALIS, CANDIDA KRUSEI, SALMONELLA TYPHI, STREPTOCOCCUS PNEUMONIA

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Herbal Extraction and Plasmid Curing (Curing of Multiple Drug Resistance in Bacteria Using Herbal Extracts)

MORE NATURAL PLASMID CURING COMPOUNDS

HERBAL EXTRACTION AND PLASMID CURING (CURING OF MULTIPLE DRUG RESISTANCE IN BACTERIA USING HERBAL EXTRACTS)

NIGELLA SATIVA

Also known as:
Black Caraway, Black Cumin

Plant Part Used in Study:
Leaves, flowers, fruits, seeds

Microorganism:
Staphylococcus aureus

CARDAMON

Also known as:
Cardamon (Elettaria cardamon)

Plant Part Used in Study:
Seeds

Microorganism:
Proteus mirabilis, Staphylococcus aureus

COCCINIA GRANDIS L.

Also known as:
Ivy Gourd

Plant Part Used in Study:
Leaves

Microorganism:
Bacillus cereus, E.coli (ATCC25938)

TACHYSPE-RMUM AMMI

Also known as:
Ajwain, or ajowan caraway

Plant Part Used in Study:
Seeds

Microorganism:
E.coli, K.pneumoniae, Citrobacter spp., P.aeruginosa and Proteus spp

HELICTERES ISORA L.*

Also known as:
Avartani, sometimes called the Indian screw tree

Plant Part Used in Study:
Fruits

Microorganism:
Enterococcus faecalis, Escherichia coli, Bacillus cereus and E.coli (RP4)

**Helicteres isora L (Avartani) is used as a folk medicine to treat snake bites*

MORE NATURAL PLASMID CURING COMPOUNDS

HERBAL EXTRACTION AND PLASMID CURING (CURING OF MULTIPLE DRUG RESISTANCE IN BACTERIA USING HERBAL EXTRACTS)

RICHARDIA BRASILIENSIS

Also known as:
Tropical Mexican Clover

Plant Part Used in Study:
Leaves

Microorganism:
E.coli, Staphylococcus Aureus, Pseudomonas Aeruginosa, Candida Tropicalis Candida krusei

RHUS CORIARIA

Also known as:
Sicilian Sumac

Plant Part Used in Study:
Dried plant

Microorganism:
S.aureus

EUGENIA JAMBOLANA

Also known as:
Black Plum or Jamun

Plant Part Used in Study:
Seeds

Microorganism:
Enterococci

PIPER LONGUM

Also known as:
Long Pepper

Plant Part Used in Study:
Fruit Pulp

Microorganism:
Shigella sonnei, Enterococcus faecalis, Staphylococcus aureus, Salmonella typhi

ALPINIA GALANGAL

Also known as:
A plant in the ginger family

Plant Part Used in Study:
Rhizome

Microorganism:
E.faecalis, S.aureus, S.sonnei, S.typh

MORE NATURAL PLASMID CURING COMPOUNDS

HERBAL EXTRACTION AND PLASMID CURING (CURING OF MULTIPLE DRUG RESISTANCE IN BACTERIA USING HERBAL EXTRACTS)

QUERCUS INFECTORIA

Also known as:
Aleppo Oak

Plant Part Used in Study:
Bark

Microorganism:
E.coli

LINUSM USITATISSIUM

Also known as:
Flax

Plant Part Used in Study:
Seeds

Microorganism:
E.coli

CINNAMONUM ZEYLANICIUM

Also known as:
Ceylon Cinnamon

Plant Part Used in Study:
Bark

Microorganism:
E.coli

THYME

Also known as:
Thyme

Plant Part Used in Study:
Dried Plant

Microorganism:
Streptococcus pneumonia, Staphylococcus aureus

CINNAMON

Also known as:
Cinnamon

Plant Part Used in Study:
Dried Plant

Microorganism:
Streptococcus pneumonia, Staphylococcus aureus

MORE NATURAL PLASMID CURING COMPOUNDS

HERBAL EXTRACTION AND PLASMID CURING (CURING OF MULTIPLE DRUG RESISTANCE IN BACTERIA USING HERBAL EXTRACTS)

CLOVE

Also known as:
Clove

Plant Part Used in Study:
Dried Plant

Microorganism:
Streptococcus pneumonia, Staphylococcus aureus

"Everyone has a doctor in him or her;
we just have to help it in its work.

The natural healing force within each one of us is the greatest force in getting well."

-Hippocrates

TERMINALIA CHEBULA FRUIT

ANTIBIOTIC RESISTANCE REVERSAL

TERMINALIA CHEBULA FRUIT

COMMONLY KNOWN AS BLACK- OR CHEBULIC MYROBALAN

“”...the extract cured plasmids pUB110 and pARI-815 at curing efficiency of 100% and 44% respectively. Most of the plasmid curing agents such as ethidium bromide, acridine orange, acriflavine, etc. has been reported to be mutagenic and carcinogenic in nature. Mutagenic activity of a compound can be harmful, especially in therapeutic applications. It was, therefore, of interest to confirm that reversal of antibiotic resistance in cured derivatives was indeed due to loss of plasmid and not due to mutations.”

ANTIBIOTIC RESISTANCE REVERSAL

TERMINALIA CHEBULA FRUIT

MICROORGANISM

BACILLUS SUBTILIS, SHIGELLA SONNEI

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

In Vitro Plasmid Curing Activity of Aqueous Extract of Terminalia Chebula Fruit Against Plasmids of Bacillus Subtilis and Shigella Sonnei

Study of *In vitro* antioxidant and DNA damage protection activity of a novel luteolin derivative isolated from *Terminalia Chebula*

BARLEY

ANTIBIOTIC RESISTANCE REVERSAL

BARLEY & OTHER PCCS

"Could the increasing problem of plasmid mediated antibiotic resistance in humans and animals be addressed by employing plant defense systems?"

"We have determined that a leaf extract of a certain barley cultivar (MSU 121) elicit curing of E. coli plasmids.."

ANTIBIOTIC RESISTANCE REVERSAL

BARLEY

MICROORGANISM

E.COLI

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Harnessing Plant Plasmid Curing Activity as an Alternative

Award Granted by the Gates Foundation

BARLEY & OTHER PCCS FOR VARIOUS PLASMIDS

HARNESSING PLANT PLASMID CURING ACTIVITY AS AN ALTERNATIVE APPROACH TO THE ANTIBIOTIC RESISTANCE PROBLEM

ALPINIA GALANGAL

A plant from the ginger family

PLUMBAGO

CHITRAK

(Plumbago Zeylanica)

FERMENTED OLIVE LEAVES

CHINESE GINGER

UVARIA CHAMAE

ANTIBIOTIC RESISTANCE REVERSAL

UVARIA CHAMAE

"This study confirms that the U. chamae plant possesses some antimicrobial substances...

The study further portrays the resistance patterns of these test organisms were reverted by the removal of plasmid-mediated genes. Therefore, resistance profiling and rapid detection of the presence of plasmids are essential for the proper treatment of bacterial infections...

There are reports that extracts of U. chamae can neutralize snake venom in rats...

Additionally, U. chamae should be greatly exploited for discoveries that might not have been considered in this study."

ANTIBIOTIC RESISTANCE REVERSAL

UVARIA CHAMAE

MICROORGANISM

E.COLI & SALMONELLA

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Resistance Patterns and Plasmid Profile of Isolates from Diarrhoeic Stool Samples Subjected to Susceptibility Testing on Crude Root Extracts of Uvaria chamae (P. Beauv)

INDIAN MEDICINAL PLANTS

GARCINIA PEDUNCULATA
PHYLOGACANTHUS THYRSIFORMIS
ZIZIPHUS MAURITIANA

ANTIBIOTIC RESISTANCE REVERSAL

MEDICINAL PLANTS FROM NORTH EAST INDIA:

GARCINIA PEDUNCULATA, PHLOGACANTHUS THYRSIFORMIS, ZIZIPHUS MAURITIANA

"In the present study, plasmid curing by plant extracts of Garcinia pedunculata, Phylogacanthus thyrsiformis, and Ziziphus mauritiana is at much higher frequency (9-62%), Hence they can be authentic plasmid curing agents. Sub-inhibitory concentrations of curing agents were used in the present research. It means that to these concentrations of compounds, the bacteria were already resistant. Therefore, it is projected that bacteria may not ever develop any way to counter the plasmid curing ability of the compounds present in the plant extracts of Garcinia pedunculata, Phlogacanthus thyrsiformis and Ziziphus mauritiana. The ability of these plant extracts to cure plasmid encoded antibiotic resistance in standard E. coli plasmid containing strains is significant particularly since the E. coli strains are known to act as a reservoir of antibiotic resistance genes."

ANTIBIOTIC RESISTANCE REVERSAL

MEDICINAL PLANTS FROM NORTH EAST INDIA:

GARCINIA PEDUNCULATA, PHLOGACANTHUS THYRSIFORMIS, ZIZIPHUS MAURITIANA

MICROORGANISM

E.COLI

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Plasmid-Curing, Antimicrobial, Antioxidant Properties and Phytochemical Analysis of Medicinal Plants from North East India

PIPER NIGRUM
(BLACK PEPPER)

ANTIBIOTIC RESISTANCE REVERSAL

PIPER NIGRUM
(BLACK PEPPER)
-*AND*-
ZINGIBER OFFICINALE, CINNAMOMUM VERUM, NIGELLA SATIVA, PLUMBAGO ZEYLENICA

"Plant extracts can be used to reverse antibiotic resistance... compounds, like quinones (consisting of bioactive compounds major class), that are derived from plants show activity against resistance and have the ability to eliminate plasmids [16]. Herbal extracts of *Piper nigrum*, *Zingiber officinale*, *Cinnamomum verum*, *Nigella sativa, Plumbago zeylenica,* etc. contain phenol (eugenol), saponin, naphthoquinones, flavonoids, tannins, and alkaloids, which can be used as the plasmid curing agent [17]."

ANTIBIOTIC RESISTANCE REVERSAL

PIPER NIGRUM (BLACK PEPPER)

-AND-
ZINGIBER OFFICINALE,
CINNAMOMUM VERUM,
NIGELLA SATIVA,
PLUMBAGO ZEYLENICA

MICROORGANISM

STAPHYLOCOCCUS AUREUS,
SALMONELLA TYPHI

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Piper nigrum Fruit Extract as an Antibiotic Resistance Reversal Agent in MDR Bacteria

PIPER LONGUM
(INDIAN LONG PEPPER)

ANTIBIOTIC RESISTANCE REVERSAL

PIPER LONGUM
(INDIAN LONG PEPPER)

"...showed strong antibiotic resistance reversal activities against R-plasmid harboring strains of clinical origin- Enterococcus faecalis, Staphylococcus aureus, Salmonella typhi with curing efficiencies of 64%, 50% and 32% respectively. This antibiotic resistance reversal may be attributed to the elimination of R-plasmids as the multiple antibiotic resistance genes are usually located on R-plasmids..."

"From the above experiment, it can be concluded that...Piper longum and Syzygium aromaticum successfully reversed the Multiple Drug Resistance in the plasmid cured E. coli which made them susceptible to antibiotics/Drugs. Drug resistance reversal was only possible due to curing of plasmid from MDR harbored bacterial strains.

PIPER LONGUM
(INDIAN LONG PEPPER)

MICROORGANISM

ENTEROCOCCUS FAECALIS, STAPHYLOCOCCUS AUREUS, SALMONELLA TYPHI, E.COLI

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Antibiotic resistance reversal of multiple drug resistant bacteria using Piper longum fruit extract

Piper Longum, Syzygium Aromaticum Microbiology Extract as Supplementary Drug for Reversal of Plasmid Generated Multiple Drug Resistance

ANACYCLUS PYRETHRUM ROOT & CYPERUS ROTUNDUS RHIZOME (AKARKARA & NUTGRASS)

ANTIBIOTIC RESISTANCE REVERSAL

ANACYCLUS PYRETHRUM ROOT & CYPERUS ROTUNDUS RHIZOME
(AKARKARA & NUTGRASS)

"...and extracts of Anacyclus pyrethrum root and Cyperus rotundus rhizome were evaluated against plasmid mediated multidrug resistance of Enterococcus faecalis, Staphylococcus aureus and Bacillus sp. isolated from unstimulated saliva of chronic periodontitis. The main aim of the current study centres the reduction of antibiotic consumption and the development of natural compounds to combat multidrug resistance..."

"To our knowledge, this is the first study to investigate... extracts... against plasmid mediated resistance of opportunistic E. faecalis, S. aureus and common bacillus sp. in chronic periodontal conditions... (they had) a greater potential in eliminating plasmid mediated resistance acquired by periodontal pathogens, thus addressing this crisis in dentistry."

ANACYCLUS PYRETHRUM ROOT & CYPERUS ROTUNDUS RHIZOME
(AKARKARA & NUTGRASS)

MICROORGANISM

ENTEROCOCCUS FAECALIS,
STAPHYLOCOCCUS AUREUS,
BACILLUS SP.

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Effect of Chitosan, Chitosan Nanoparticle, Anacyclus pyrethrum and Cyperus rotundus in combating Plasmid Mediated Resistance in Periodontitis

ADENOPUS BREVIFLORUS BENTH
(GOURD FAMILY)

ANTIBIOTIC RESISTANCE REVERSAL

ADENOPUS BREVIFLORUS BENTH

(GOURD FAMILY)

"Adenopus breviflorus (Benth) extract showing plasmid curing properties is a needful medicinal plant for this purpose of removing the so-call multiple resistance saga in infectious diseases"

ANTIBIOTIC RESISTANCE REVERSAL

ADENOPUS BREVIFLORUS BENTH

(GOURD FAMILY)

MICROORGANISM

STAPHYLOCOCCUS AUREUS

OTHERS INCLUDED IN STUDY:

BACILLUS AREUS, KLEBSIELLA PNEUMONIA, STAPHYLOCOCCUS TYPII, PSEUDOMONAS AERUGINOSA, STAPHYLOCOCCUS EPIDERMYDIS, SALMONELLA TYPHI, E.COLI, PROTEUS VULGARIS, SALMONELLA GALLIMARIUM

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Pre/Post-Plasmid Profile Analysis, Killing- Kinetics and Secondary Metabolites Screening Of Adenopus breviflorus (Benth) Fruit Extract Against Multiple Drug Resistant Isolates Using Staphylococcus aureus (MDRSA) as a Case Study

CITRUS AURANTIUM
(SOUR ORANGE)

ANTIBIOTIC RESISTANCE REVERSAL

CITRUS AURANTIUM
(SOUR ORANGE)

"The apparent contrast between the bacterial species after curing in terms of their resistance to antibiotics is due to the fact that the plasmid that carries antibiotic resistance is of the R-plasmid, as it is in the form of two molecules and each molecule carries genes responsible for resistance. From the above results of curing, we find that the rates of curing efficiency of plant extracts on the bacteria under study showed a variation in the rates of curing and loss of resistance to antibiotics. The plasmid DNA of the parent cell and the distribution of these plasmids during the process of cell division leads to the production of nuclear cells with few plasmids and at other times lacking plasmids. Consequently, the bacteria missing the plasmids are transformed from resistance to antibiotics to sensitive [46]."

ANTIBIOTIC RESISTANCE REVERSAL

CITRUS AURANTIUM (SOUR ORANGE)

MICROORGANISM

S.AUREUS, E. COLI, K. PNEUMONIA, PR. VULGARIS, PR. MIRABILIS, PS. AERUGINOSA

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Evaluation of inhibitory and plasmid curing activity of Citrus aurantium L fruit extracts against some bacteria isolated from urinary tract infections

HIBISCUS SABDARIFFA & HARPAGOPHYTUM PROCUMBENS

ANTIBIOTIC RESISTANCE REVERSAL

HIBISCUS SABDARIFFA & HARPAGOPHYTUM PROCUMBENS

"In folk medicine, the herbs Hibiscus sabdariffa and Harpagophytum procumbens were investigated for their photochemical and antimicrobial activity (Auddy et al., 2003) Hibiscus sabdariffa was used in the treatment of diseases like abscesses, bilious conditions, and it was suggested for use as antibacterial and anticancer agents (Auddy et al., 2003). While Harpagophytum procumbens (also mentioned as devils claw) was used in the treatment of a wide range of conditions including fever, malaria and indigestion (Gagnier et al., 2007). Currently, the major uses of devil's claw are as an anti -inflammatory and pain reliever for joint diseases, back pain, and headache. There is currently wide spread use of standardized devil's claw for mild joint pain in Europe (Loots, 2005). Recently, extracts of medicinal plants were used in enhancement of plasmid curing (Rose et al., 2008)".

ANTIBIOTIC RESISTANCE REVERSAL

HIBISCUS SABDARIFFA & HARPAGOPHYTUM PROCUMBENS

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MICROORGANISM

E.COLI, PSEUDOMONAS AERUGINOSA

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Evaluation The Effect of Some Plant Active Compounds on Bacterial Plasmid

CUMINUM CYMINUM, CORIANDRUM SATIVUM, MYRISTICA FRAGRANS

ANTIBIOTIC RESISTANCE REVERSAL

CUMINUM CYMINUM, CORIANDRUM SATIVUM, MYRISTICA FRAGRANS

"Curing percentage for Cuminum cyminum was 33.33-50%, for Coriandrum sativum was 10-75% while for Myristica fragrans Houtt. was 20-72%."

ANTIBIOTIC RESISTANCE REVERSAL

CUMINUM CYMINUM, CORIANDRUM SATIVUM, MYRISTICA FRAGRANS

MICROORGANISM

ACINETOBACTER SPP., PSEUDOMONAS SPP., E.COLI, KLEBSIELLA PNEUMONIA, PROTEUS SPP.

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Plasmid Curing Activity by Seed Extracts of Cuminum cyminum, Coriandrum sativum and Myristica fragrans...

DIOSCOREA BULBIFERA

(WILD YAM)

ANTIBIOTIC RESISTANCE REVERSAL

DIOSCOREA BULBIFERA
(WILD YAM)

"The present study affirmed the fact that plant extracts D. bulbifera, represent a novel source for bioactive compounds employable as new antibacterial agents and safe plasmid curing agent. More so, it is conclusive that D. bulbifera is a rich source of relevant bioactive agents that do not only enhances the antibacterial properties of the tubers but also ascertain its health promoting qualities..."

"The present piece of work may prove to be beneficial for searching novel potential phytotherapeutic plasmid curing agents against multiple drug resistant bacterial strains and reversal of their plasmid-mediated-resistance."

ANTIBIOTIC RESISTANCE REVERSAL

DIOSCOREA BULBIFERA
(WILD YAM)

MICROORGANISM

E.COLI

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Pre/Post Plasmid Curing and Killing Kinetic Reactivity of Dioscorea Bulbifera Linn Against Multiple Antibiotics Resistant Clinical Isolates, Using Escherichia Coli as A Case Study

NATURAL VETERINARY USE IN CHICKENS

CHINESE PULSATILLA

ANTIBIOTIC RESISTANCE REVERSAL

NATURAL VETERINARY USE IN CHICKENS

CHINESE PULSATILLA

"Multiple drug resistance (MDR) is a serious and emerging problem in treatment of diseases caused by nosocomial pathogens. Most of the bacteria harbour plasmids and show resistance to multiple antibiotics. Plasmid elimination can be one of the ways to make the antibiotic resistant clinical strains sensitive. In the present investigation 23 nosocomial pathogens like Pseudomonas aeruginosa, Proteus vulgaris, Escherichia coli, Klebsiella pneumoniae were isolated..."

"Root extracts of Plumbago auriculata were used to cure plasmid mediated antibiotic resistance."

ANTIBIOTIC RESISTANCE REVERSAL

NATURAL VETERINARY USE IN CHICKENS

CHINESE PULSATILLA

MICROORGANISM

E.COLI

MECHANISM OF ACTION

ANTIBIOTIC RESISTANCE REVERSAL

Chinese pulsatilla extracts eliminate resistance of Escherichia coli to streptomycin

BACTERIAL CONJUGATION INHIBITORS

"YOUR BODY'S ABILITY TO HEAL IS GREATER THAN ANYONE HAS PERMITTED YOU TO BELIEVE."

CATEGORIES

FOR NATURAL PLASMID CURING COMPOUNDS

ANTIBIOTIC RESISTANCE REVERSAL

"The extent of resistance to therapeutic antibiotics can be directly associated with the copy number of the plasmid carrying antibiotic resistance genes (ARGs)."

Plant-Assisted Plasmid Curing Strategies for Reversal of Antibiotic Resistance

CONJUGATION INHIBITORS

"Conjugation inhibitors (COINs) are compounds that inhibit plasmid transfer by affecting the conjugative machinery."

Conjugation Inhibitors Effectively Prevent Plasmid Transmission in Natural Environments

COMPETING MICROORGANISMS

"One of the mechanisms by which commensal and probiotic bacteria provide colonization resistance to pathogens is by directly competing for the same niche."

No Vacancy: How Beneficial Microbes Cooperate with Immunity to Provide Colonization Resistance to Pathogens

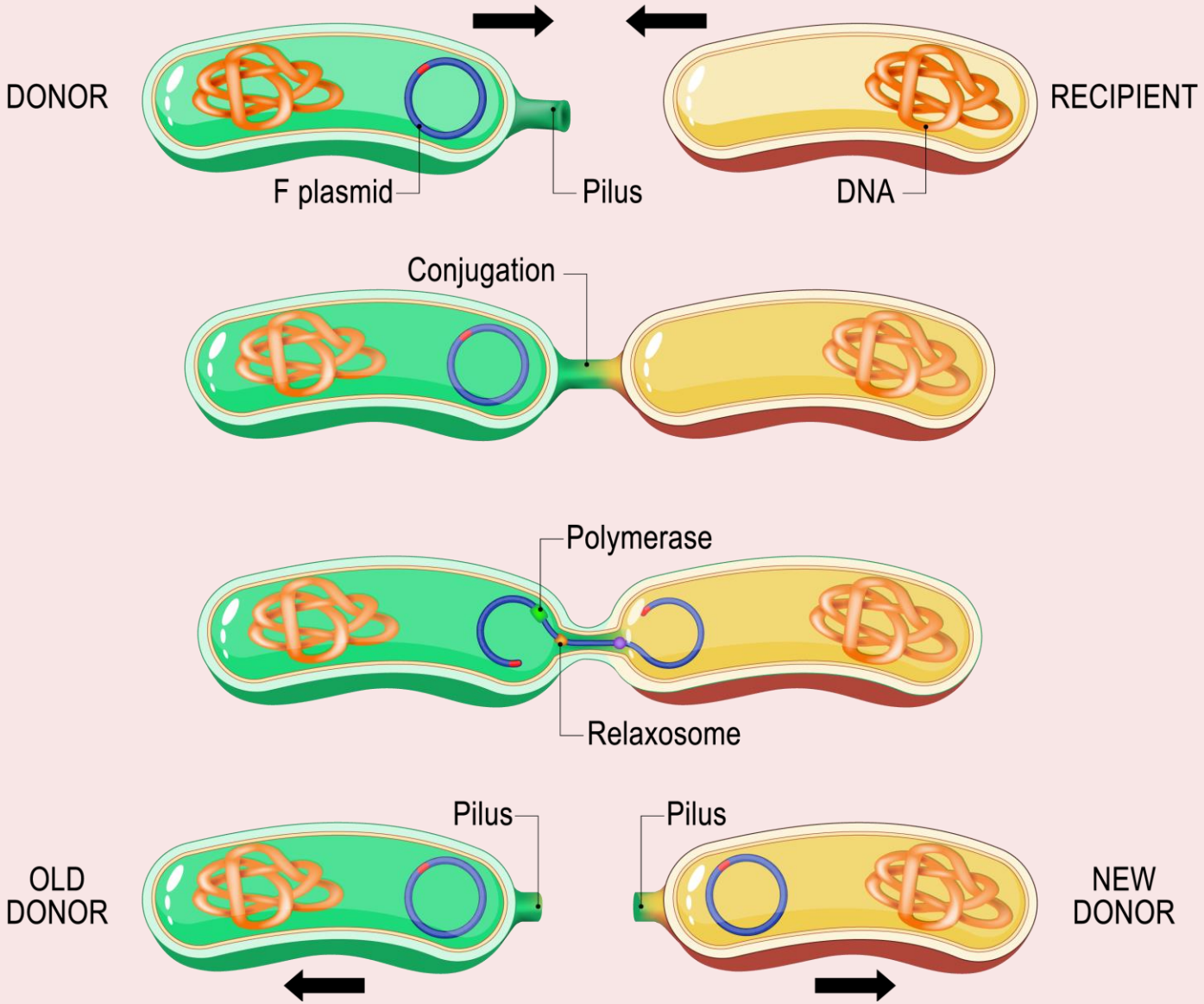
WHY BACTERIAL CONJUGATION INHIBITORS?

INHIBITING CONJUGATION INHIBITS WEAPONIZED PLASMID TRANSFER

"Conjugation inhibitors (COINs) are compounds that inhibit plasmid transfer by affecting the conjugative machinery."

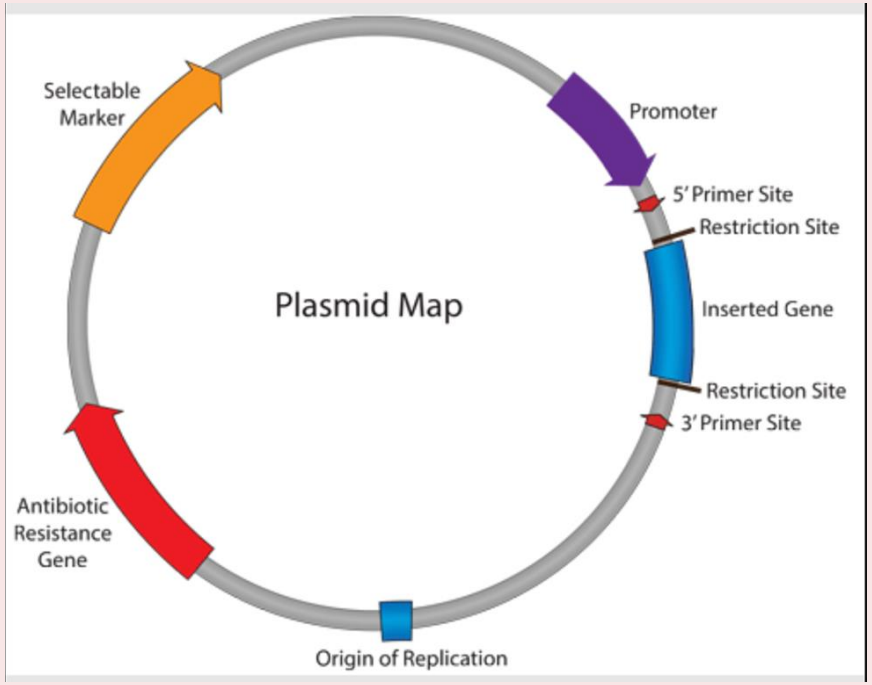
Conjugation Inhibitors Effectively Prevent Plasmid Transmission in Natural Environments

BACTERIAL CONJUGATION



WEAPONIZED MICROBIOME

- ***Sugar Feeds This Genetic Infection Like Nothing Else***



PLASMID CURING COMPOUNDS

NAPHTHOQUINONES

VITAMIN K

QUERCETIN

PLUMBAGO

CANNABIS

AVOCADO & OLIVE OIL

BENEFICIAL BACTERIA

AND MORE...

CANNABIS & MORE

BACTERIAL CONJUGATION INHIBITORS

CANNABIS – BACTERIAL CONJUGATION INHIBITION

‘”The antibacterial activities and plasmid curing efficiency curing efficiency of active constituents of Cannabis and its phenathryl derivatives have been reported (Spengler et al., 2006)… F’lac plasmid in E. Coli K12 was sensitive to tetrahydracannabidiolic acid caused 30% loss of the plasmid…”

"The mechanism by which cannabinoids interfere with the bacterial plasmid system is yet to be elucidated but could be associated with binding to the transconjugal DNA, intercellular inhibition of the mating pair formation, replication or plasmid partition processes (Weisser and Weidemann 1985).”

Interesting Point:

E.coli K12 “was among the first microorganisms targeted for genome sequencing.” It also seems to be used in CRISPR, “the majority of all common, commercial lab strains of E.coli used today descended from two individual isolates, the K12 strain and the B strain…”

CANNABIS

STUDIED MICROORGANISM

E.COLI

MECHANISM OF ACTION

BACTERIAL CONJUGATION INHIBITION

Antiplasmid and Antimicrobial Activities of Synthetic and Natural Products from Selected Medicinal Plants

The Mechanism of Plasmid Curing in Bacteria (Including Cannabis & Phenanthryl Derivatives)

CANNABIS & OTHER PCCS FOR VARIOUS PLASMIDS

ANTIPLASMID & ANTIMICROBIAL ACTIVITIES OF SYNTHETIC AND NATURAL PRODUCTS FROM SELECTED MEDICINAL PLANTS

PLUMBAGIN

Inhibitory activities against the conjugal transfer of five plasmid strains

Plumbagin: Plumbago

Purification and Characterization Responsible for the Plasmid Curing Activity of *Plumbago zeylanica* Root Extracts

ROTTLERIN

Inhibitory activities against conjugal transfer of resistant R-plasmids

Rottlerin: Polyphenol in Mallotus philippinensis

Novel R-plasmid conjugal transfer inhibitory and antibacterial activities of phenolic compounds from *Mallotus philippensis* (Lam.) Mull. Arg.

EVODIA

Inhibitory activities of plasmid conjugal transfer

Evodia: The fruit is commonly used in Traditional Chinese Medicine

Topoisomerase I Inhibitor Evodiamine *(compound in Evodia)* Acts As an Antibacterial Agent against Drug-Resistant Klebsiella pneumoniae

CAPSICUM

Inhibitory activities against conjugal transfer of resistant R-plasmids

Capsicum: Peppers

Capsaicin *(compound in Peppers)* and gingerol *(Ginger)* analogues inhibit the growth of efflux-multidrug resistant bacteria and R-plasmids conjugal transfer

DISACCHARIDES

Mild inhibitory activities of plasmid conjugal transfer

Disaccharide: Cellulobiose

3.3.7 The anti-plasmid activities of various disaccharides against PKM 101, TP114 and PUB 307 (page 141)

CANNABIS & OTHER PCCS FOR VARIOUS PLASMIDS

ANTIPLASMID & ANTIMICROBIAL ACTIVITIES OF SYNTHETIC AND NATURAL PRODUCTS FROM SELECTED MEDICINAL PLANTS

MALLOTUS PHILIPPENSIS

Inhibitory activities against the conjugal transfer of plasmids

Mallotus philippensis: Kamala Tree

Novel R-plasmid conjugal transfer inhibitory and antibacterial activities of phenolic compounds from *Mallotus philippensis* (Lam.) Mull. Arg.

"We must turn to nature itself,
to the observations of the body in health
and in disease to learn the truth."

-Hippocrates

BAICALIN
(CHINESE SKULLCAP)

BACTERIAL CONJUGATION INHIBITORS

BAICALIN
(CHINESE SKULLCAP)

"The dissemination of carbapenem resistance in E. coli has major implications for the management of common infections. Baicalein may be used in clinical practice to prevent or contain outbreaks of carbapenem-resistant infections by inhibiting the horizontal transfer of genes... across bacteria.."

"We speculated that baicalein may also inhibit the horizontal transfer of other resistant genes..."

BACTERIAL CONJUGATION INHIBITION

BAICALIN

(CHINESE SKULLCAP)

MICROORGANISM

E.COLI & KLEBSIELLA

MECHANISM OF ACTION

BACTERIAL CONJUGATION INHIBITION

Baicalein Inhibits Plasmid-Mediated Horizontal Transmission of the blaKPC Multidrug Resistance Gene from Klebsiella pneumoniae to Escherichia coli

UNSATURATED FATTY ACIDS
(AVOCADO & OLIVE OIL)

BACTERIAL CONJUGATION INHIBITORS

UNSATURATED FATTY ACIDS

"We found that unsaturated fatty acids, a common component of those extracts, are inhibitors of plasmid conjugation…It is known that unsaturated fatty acids can affect the function of some proteins associated with the bacterial membrane…Our results have shown that unsaturated fatty acids inhibit conjugation mediated by plasmids F and R388…"

"Bacterial conjugation is a key mechanism by which bacteria acquire antibiotic resistance. Therefore, conjugation inhibitors (COINs) are promising compounds in the fight against the spread of antibiotic resistance genes among bacteria. Unsaturated fatty acids (uFAs)… (oleic and linoleic acids)… have been reported previously as being effective COINs…"

UNSATURATED FATTY ACIDS

(AVOCADO & OLIVE OIL)

MICROORGANISM

E.COLI

MECHANISM OF ACTION

BACTERIAL CONJUGATION INHIBITION

Unsaturated fatty acids are inhibitors of bacterial conjugation

Conjugation inhibitors compete with palmitic acid for binding to the conjugative traffic ATPase TrwD, providing a mechanism to inhibit bacterial conjugation

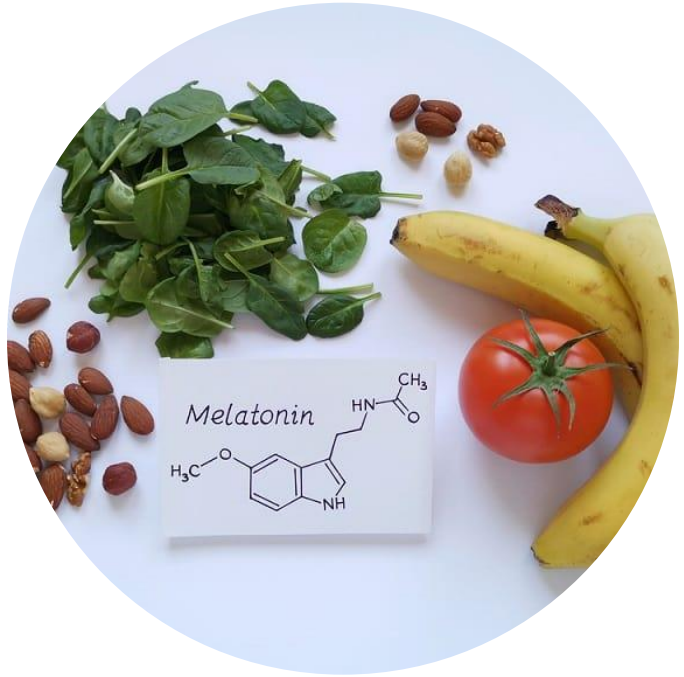
MELATONIN

BACTERIAL CONJUGATION INHIBITORS

MELATONIN

"Most importantly, we uncovered that melatonin disrupted bacterial proton motive force (PMF), which is an essential bacterial energy metabolism substance and is important for conjugative process. Collectively, these results provide implications that some non-antibiotics such as melatonin are effective inhibitors of transmission of ARGs and raise a promising strategy to confront the increasing resistant infections."

"...melatonin is well recognized as a key player of regulating circadian rhythm. Recent studies, however, have highlighted the pleiotropic nature of melatonin, which is widely related to the normal functioning of different systems, including the CNS. Due to its diverse effects, the melatonin signaling system could be a possible treatment target of disorders of the CNS....melatonin is pro-neurogenic... may be used for treating neurogenesis-related disorders, such as mood disorders, neurotrauma, and neurodegenerative disorders."



MELATONIN

MICROORGANISM

E.COLI

MECHANISM OF ACTION

BACTERIAL CONJUGATION INHIBITION

Melatonin prevents conjugative transfer of plasmid-mediated antibiotic resistance genes by disrupting proton motive force

Protective Effects of Melatonin on Neurogenesis Impairment in Neurological Disorders and Its Relevant Molecular Mechanisms

ROSA CANINA

(ROSE HIP OR DOG ROSE)

BACTERIAL CONJUGATION INHIBITORS

ROSA CANINA L
(ROSE HIP OR DOG ROSE)

"Unfortunately, synthetic plasmid-curing agents… are unsuitable for therapeutic application owing to their toxic nature. There is therefore a need to develop new antibiotics with alternative mechanisms to overcome bacterial resistance, particularly as resistance modifying efflux inhibitors or plasmid curing compounds [8, 9]. In this context, plant-derived products have been proposed as a new source of drug leads to combat bacterial resistance mechanisms [10].."

"We have shown that while the RC extract had mild to poor antibacterial activity, the sample was able to potentiate tetracycline activity…possessing a multidrug efflux mechanism and had a moderate inhibitory effect on plasmid conjugation…"

ROSA CANINA

(ROSE HIP OR DOG ROSE)

MICROORGANISM

E.COLI

MECHANISM OF ACTION

BACTERIAL CONJUGATION INHIBITION

In vitro assessment of antibiotic-resistance reversal of a methanol extract from Rosa canina L

PLUMBAGO

BACTERIAL CONJUGATION INHIBITORS

PLUMBAGO

"Ability of lawsone (plumbago zeylenica) to interfere with interspecies plasmid transfer by conjugation and transformation and thus contain the spread of multi-resistance to antibiotics was investigated in the present study. It was observed that Lawsone not only cured plasmids but also inhibited the transfer of plasmid by both conjugation as well as by transformation."

"Thus, in conclusion, this investigation has revealed a compound with an ability to eliminate antibiotic resistance and cure plasmids from pathogenic strains that are resistant to multiple antibiotics without any ill effect on mammalian cells at lower concentrations."

PLUMBAGO

MICROORGANISM

ACINETOBACTER SPECIES

MECHANISM OF ACTION

BACTERIAL CONJUGATION INHIBITION & TRANSFORMATION

Purification and Characterization of an Active Principle, Lawsone, Responsible for the Plasmid Curing Activity of *Plumbago zeylanica* Root Extracts

MYRISTICA IOWIANA
(NUTMEG FAMILY)

BACTERIAL CONJUGATION INHIBITORS

MYRISTICA IOWIANA

MYRISTICACEAE - SOMETIMES CALLED THE 'NUTMEG FAMILY'

"*Myristica lowiana* specifically and significantly inhibited the conjugal transfer of the IncW plasmid R7K, a plasmid which harbors ampicillin-, streptomycin-, and spectinomycin-resistant genes. The transfer of this plasmid via the conjugative pilli of *Escherichia coli* was reduced..."

BACTERIAL CONJUGATION INHIBITION

MYRISTICA IOWIANA

MYRISTICACEAE -SOMETIMES CALLED THE 'NUTMEG FAMILY'

MICROORGANISM

E.COLI

MECHANISM OF ACTION

BACTERIAL CONJUGATION INHIBITION

Myristica lowiana Phytochemicals as Inhibitor of Plasmid Conjugation in Escherichia coli

BACTERIAL CONJUCATION INHIBITORS (Continued)

PLANT-ASSISTED PLASMID CURING/CONJUGAL INHIBITION

(a) Plant-derived compounds as plasmid curing agents			
Plant source	**Part of the plant used**	**Bioactive compound**	**References**
Dioscorea bulbifera	Bulbs	8-Epidiosbulbin E acetate	Shriram et al. (2008)
Alpinia galanga	Rhizome/root	1'-Acetoxychavicol acetate	Latha et al. (2009)
Tropical/subtropical Plumbago species	Root	Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone)	Lakshmi et al. (1987), Patwardhan et al. (2015b), Patwardhan (2020)
Plumbago zeylanica	Root	Lawsone	Patwardhan et al. (2018)
(b) Plant extracts in plasmid curing/conjugal inhibition			
Name of plant	**Part of the plant used**	**Name of microorganisms**	**References**
Allium sativum, Myrtus communis	Dry plant powder	Proteus mirabilis	Khder (2008)
Dioscorea bulbifera	Bulb	Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Shigella sonnei, and Enterococcus faecalis	Shriram et al. (2008), Osuntokun et al. (2019)
Quercus infectoria, Linusmus itatissium, Cinnamonum zeylanicium	Seeds, plant bark	Escherichia coli	Khider and Muhammed (2010)

Table 18.1 Plant-assisted Plasmid curing/conjugal inhibition

PLANT-ASSISTED PLASMID CURING/CONJUGAL INHIBITION

(b) Plant extracts in plasmid curing/conjugal inhibition continued...

Name of plant	Part of the plant used	Name of microorganisms	References
Helicteres isora	Fruits	Escherichia coli (RP4), Escherichia coli, Bacillus cereus, and Enterococcus faecalis	Shriram et al. (2010)
Eugenia jambolana and Elephantopus scaber	Seed, whole plant	VR enterococci	Jasmine and Selvakumar (2011)
Cardamom (Elettaria cardamom)	Seed	Proteus mirabilis, Staphylococcus aureus	Akrayi (2012)
Rhus coriaria	Dried plant	S. aureus	Akrayi and Abdullrahman (2013)
Piper longum	Fruits (Aq)	Enterococcus faecalis, Staphylococcus aureus, Salmonella typhi, Shigella sonnei	Kumar et al. (2013)
Alpinia galanga	Rhizome (Aq)	Enterococcus faecalis, Staphylococcus aureus, Salmonella typhi, Shigella sonnei	Shriram et al. (2013)
Cuminum cyminum, Coriandrum sativum, Myristica fragrans	Seeds (methanolic extract)	Acinetobacter spp., E. coli and Proteus spp., Klebsiella pneumonia, and Pseudomonas spp.	Soman et al. (2015)

Table 18.1 Plant-assisted Plasmid curing/conjugal inhibition

PLANT-ASSISTED PLASMID CURING/CONJUGAL INHIBITION

(b) Plant extracts in plasmid curing/conjugal inhibition continued...

Name of plant	Part of the plant used	Name of microorganisms	References
Terminalia chebula	Fruits	Bacillus subtilis (pUB110) and Shigella sonnei (pARI-815)	Srivastava et al. (2015)
Rosa canina	Fruit	Escherichia coli (conjugal inhibition)	Oyedemi et al. (2016)
Zingiber officinale, Ocimum gratissimum, Xylopia aethiopica	Rhizome, leaves, seeds	Citrate-negative motile Salmonella species	Iheukwumere et al. (2020)

Table 18.1 Plant-assisted Plasmid curing/conjugal inhibition

COMPETING MICROORGANISMS

"YOUR BODY'S ABILITY TO HEAL IS GREATER THAN ANYONE HAS PERMITTED YOU TO BELIEVE."

CATEGORIES

FOR NATURAL PLASMID CURING COMPOUNDS

ANTIBIOTIC RESISTANCE REVERSAL

"The extent of resistance to therapeutic antibiotics can be directly associated with the copy number of the plasmid carrying antibiotic resistance genes (ARGs)."

Plant-Assisted Plasmid Curing Strategies for Reversal of Antibiotic Resistance

CONJUGATION INHIBITORS

"Conjugation inhibitors (COINs) are compounds that inhibit plasmid transfer by affecting the conjugative machinery."

Conjugation Inhibitors Effectively Prevent Plasmid Transmission in Natural Environments

COMPETING MICROORGANISMS

"One of the mechanisms by which commensal and probiotic bacteria provide colonization resistance to pathogens is by directly competing for the same niche."

No Vacancy: How Beneficial Microbes Cooperate with Immunity to Provide Colonization Resistance to Pathogens

WHY COMPETING MICROORGANISMS?

TO KILL WEAPONIZED BACTERIA & REPOPULATE MICROBIOME WITH WHAT GOD INTENDED

"One of the mechanisms by which commensal and probiotic bacteria provide colonization resistance to pathogens is by directly competing for the same niche."

No Vacancy: How Beneficial Microbes Cooperate with Immunity to Provide Colonization Resistance to Pathogens

PLASMID CURING COMPOUNDS

NAPHTHOQUINONES

VITAMIN K

QUERCETIN

PLUMBAGO

CANNABIS

AVOCADO & OLIVE OIL

BENEFICIAL BACTERIA

AND MORE...

LACTIC ACID BACTERIA

COMPETING MICROORGANISMS

LACTIC ACID BACTERIA (FERMENTED FOODS)

FERMENTI LEMONS

https://fermenti.biz/product

LACTIC ACID BACTERIA (PROBIOTICS)

"The (Lactic Acid Bacteria) LAB extracts were tested for their effect on plasmids of the ten antibiotic resistant bacteria mentioned above. After plasmid profile screening it was observed that the extracts were able to stop 100% plasmid replication (Fig. 9) which means that they reversed antibiotic resistance of the pathogens. Thus, these extracts offer a natural safe therapy if combined with antibiotic treatment."

COMPETING MICROORGANISMS

LACTIC ACID BACTERIA (PROBIOTICS)

LACTOBACILLUS PLANTARUM

LACTOBACILLUS BULGARICUS

BIFIDOBACTERIUM LONGUM

MICROORGANISM

Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella and Shigella sp.

MECHANISM OF ACTION

Share Wild-Type Toxic Plasmids Capable Of Killing Weakened Weaponized Bacteria

Antibacterial and Plasmid Curing Activity of Lactic Acid Bacteria Against Multidrug Resistant Bacteria

CHASE HOPE AND DARE TO HEAL WITH LOVE

“WHEREVER THE ART OF MEDICINE IS LOVED, THERE IS ALSO A LOVE OF HUMANITY.”

-HIPPOCRATES

THE HOPE OF ALL NATURAL PLASMID CURING COMPOUNDS

"YOUR BODY'S ABILITY TO HEAL IS GREATER THAN ANYONE HAS PERMITTED YOU TO BELIEVE."