

eISBN: 978-1-68108-369-8  
ISBN: 978-1-68108-370-4

eISSN: 2352-3212  
ISSN: 2452-3208

# Frontiers in Clinical Drug Research

## (Anti Infectives)

Volume 3



**Editor:**  
Atta-ur-Rahman, *FRS*

**Bentham  Books**

# **Frontiers in Clinical Drug Research-Anti Infeetives**

*(Volume 3)*

**Edited by**

**Atta-ur-Rahman, *FRS***

*Honorary Life Fellow Kings College University  
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**Frontiers in Clinical Drug Research – Anti Infeclives**

*Volume # 3*

eISSN (Online): 2352-3212

ISSN: Print: 2452-3208

Editor: Prof. Atta-ur-Rahman

eISBN (Online): 978-1-68108-369-8

ISBN (Print): 978-1-68108-370-4

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First published in 2017.

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## PREFACE

The third volume of *Frontiers in Clinical Drug Research – Anti Infection* comprises five chapters that cover genomic mining for anti-infectives, HIV treatments and photosensitizers for anti-microbial activity.

In the first chapter, Sanchez and colleagues review the research in genomic data mining to predict gene clusters that are responsible for coding for secondary metabolites that exhibit antimicrobial activity. They give information about the tools in metabolomics used for the purpose and also give examples of links established through predictive methods. The authors also provide information about research techniques used in metabolomics adding value to their work for readers.

In the second chapter, Constantin V. Sobol discusses recent developments concerning a new probiotic prophylactic for HIV treatment. This probiotic stimulates the growth of microflora that increase the concentration of antibodies in the mucosa, thereby boosting the immune system. Continuing with the theme of HIV/AIDS treatments, Al-Jabri *et al.*, have contributed a review on the status of HIV medications that are geared towards eliminating the virus from the body. This review is a reminder to readers that the hope for finding a cure for AIDS, while difficult, is still alive. Readers will find the list of drugs covered in this review useful for keeping their knowledge updated on current anti-HIV medicines.

In chapter 4, Sampaio *et al.* provide a review of natural products (essential oils, glycosides, polyphenols and other secondary metabolites) that can be used to treat microbial infections *in vivo*. In the last chapter, Bakthavatchalu and Noel present an interesting review of the use of photosensitizers for treating bacterial infections. Light based treatments (Antimicrobial Photodynamic Therapy, APDT) are a good way to combat drug resistant pathogens.

I would like to acknowledge the efforts of all the contributors for their outstanding contributions. I am also thankful to the team of Bentham Science Publishers, especially Dr. Faryal Sami and Mr. Shehzad Naqvi led by Mr. Mahmood Alam, Director Bentham Science Publishers for their efforts.

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## CHAPTER 1

# Modern Approaches to Genome Mining for the Development of New Anti-infectives: *In Silico* Gene Prediction and Experimental Metabolomics

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**Abstract:** Genome mining consists in assessing the potential encoded in the genome of microorganisms to produce novel secondary metabolites. *Actinobacteria* have been reported to hold unexplored potential for the biosynthesis of secondary metabolites, according to the number of gene clusters predicted from recently published genome sequences. This is of significant interest in the area of anti-infectives, since many of the secondary metabolites produced by *Actinobacteria* have been reported to have antibacterial, antiviral and antitumor properties. The first part of this review offers an overview on *in silico* bioinformatics software and databases for the prediction of gene clusters involved in the production of putative secondary metabolites. The second part of this review encompasses experimental metabolomics techniques, facilitated by mass spectrometry and quantitative proteomics, all of which have the end goal to identify and characterize secondary metabolites. Examples where metabolomics were associated with computational prediction tools to propose the link between genes and metabolites have been highlighted. As an addition, this review also explores the potential of the OSMAC and co-culturing experimental approaches to induce the expression of silent gene clusters under laboratory conditions. Examples are offered of novel secondary metabolites and gene clusters discovered following a genome mining approach.

**Keywords:** *Actinobacteria*, Antibiotics, Anti-infectives, Antimicrobials, Bioinformatics, Biosynthetic pathways, Co-culturing, Cryptic cluster, Gene cluster, Genome mining, Homologous expression, Mass spectrometry, Metabolomics, Natural products, Nonribosomal peptide, OSMAC, Polyketide, Secondary metabolites, Silent cluster.

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## INTRODUCTION

More than half of the known natural products that have antimicrobial, antiviral or antitumor activity originate from only five cultivated bacterial groups: filamentous *Actinomycetes*, *Myxobacteria*, *Cyanobacteria*, as well as members of the genera *Pseudomonas* and *Bacillus* [1]. *Actinomycetes* are Gram-positive mycelial bacteria found mainly in the soil, but are also present in symbiotic association with terrestrial and aquatic invertebrates [2]. *Actinomycetes* produce metabolites as they undergo the morphological and physiological differentiation processes that are part of their life cycle [2].

The secondary metabolites that bacteria produce include aminoglycosides, polyketides, as well as small proteinaceous and peptide structures such as bacteriocins, oligopeptides and lipopeptides. These secondary metabolites may have bactericidal, immune suppression and tumor suppression properties and can be useful for human and veterinary medicine. Lipopeptides and polyketides have linear, cyclic or branched structures. Lipopeptides are generated by non-ribosomal peptide synthases (NRPSs) whilst polyketides are generated by polyketide synthases (PKSs) [3, 4].

The function that these metabolites have in their natural environment is not always known, but they are thought to provide a competitive advantage to the producing organism since many of these possess potent antibiotic activity [2]. It has also been suggested that antibiotics act as signaling molecules facilitating intra- or interspecies interactions within microbial communities [5].

Most of the antibiotics clinically used are microbial natural products or their derivatives [6]. In fact, of the 18,000 currently known bioactive compounds, 10,000 were described from the genus *Streptomyces* (*Actinobacteria*) [7]. *Actinobacteria* still are one of the most important producers of natural products that are currently applied as antibiotics, immunosuppressants, anticancer drugs, anthelmintics and antifungals [8, 9].

The threat of multi-drug resistant pathogens puts at grave risk the advances of modern medicine [6, 10, 11] and yet, new antibiotics emerging in the markets are few. Drug discovery is expensive and the return on investment is difficult to predict. New products in the market are poorly sold because they are not prescribed in the hope to slow down development of resistance [6, 8].

### Silent Biosynthetic Gene Clusters

With the onset of the genomic era, it became evident that *Actinomycetes* contain a

largely untapped and unexplored potential for the production of secondary metabolites [2, 12]. Analyses of genome sequences have been revealing that each genome contains clusters to synthesize 20 or more secondary metabolites [13], which increases the chances of discovering novel bioactive natural products. Genome mining bioinformatics software detects biosynthetic gene clusters encoded in the genome, but bioinformatics programs alone will not lead to the discovery of new metabolites, since many of the secondary metabolism gene clusters are silent under laboratory conditions [14].

Secondary metabolite biosynthetic gene clusters remain silent until the required signals occur, which may be environmental or physiological [15]. However, it has been proposed that the majority of secondary metabolism gene clusters in *Streptomyces* are not silent, but are expressed at very low levels under laboratory conditions, so the transcription of these gene clusters is not sufficient to produce detectable amounts of novel secondary metabolites [16].

### **What is Genome Mining?**

Genome mining consists on using genetic information to assess the potential of microorganisms to produce novel compounds [17]. Such analysis has to be followed by extensive experimental research [2] involving proteomics and metabolomics to confirm that the predicted gene cluster produces the target secondary metabolite [7]. Genome mining as a natural product discovery strategy is based on connecting an unknown structure of a natural product with its corresponding biosynthetic genes by applied biosynthetic knowledge. As proposed by Nett [18] genome mining involves “basic *in silico* analyses” to aid in the proposal of putative genes and putative products, as well as “the emerging chemical or genetic methods that are applied to trace the metabolic products of the (putative genes)”. New methods are necessary that allow linking conclusively a gene cluster and a natural product [19]. Several *in silico* and experiment-guided approaches have been developed for this purpose.

The first step in a genome mining approach is to identify the putative biosynthetic gene clusters in the genome sequence [17]. In the second step, once putative clusters have been identified, it is necessary to predict the biosynthetic products resulting from the enzymes encoded in the cluster [17].

Genome mining consists not only of the *in silico* determination of a gene cluster, but also in the activation of a cryptic gene cluster [20]. In fact, genome mining is typically accompanied by proteome and/or metabolome analyses to accurately link a metabolite to its biosynthetic gene cluster [17, 21]. Such a connection may

**CHAPTER 2**

# A Novel Complementary Approach Using New Probiotic Product for the Improvement of HIV Therapy

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**Abstract:** AIDS is a challenge to mankind. Widespread use of cART changed HIV from a progressive illness with a lethal prognosis into a chronic controlled disease with some side-effects. There is a problem of latent infection or viral reservoir(s), which is unaffected by ART and is not recognized by the immune system. Many researches have concentrated on reducing/disrupting the latent viral reservoir(s) to get rid of HIV. Mucosal surfaces are the entry point and the major regions of HIV-replication. HIV is associated with dramatic loss of gastrointestinal Th17 cells, high mucosal permeability, and chronic inflammation. Effective treatments or prophylaxis at the mucosal level are much needed. Understanding the interplay between microbiota and HIV is important for development successful strategies for HIV/AIDS prevention, treatment and care. Increasing evidence indicate that microbiota can play an important role in HIV transmission and pathogenesis. A new powerful probiotic product (PP) was developed. PP stimulates growth of symbiotic microflora and has a very broad spectrum of antimicrobial activity. PP boosts the immune system. The strongest stimulation of mucosal immune system occurred when PP was administered directly at a mucosal surface. Various routes of PP administration are discussed. PP can improve function of cardiovascular system and cognitive function in HIV/AIDS patients. PP provided relief from opportunistic infections and improved immunological status in HIV/AIDS individuals. It is expected that PP can be used as supplemental therapy to cART.

**Keywords:** AIDS, Antiretroviral therapy, Cytotoxic T lymphocytes, Gut permeability, HIV, HIV-1, HIV-associated neurocognitive disorders, Human immunodeficiency virus, Inflammation, Latency, Latency reversing agent, LRA, MALT, Microbiota, Mucosal immunology, Mucus-associated lymphoid tissue, Neurotrophic factors, Non-toxicity, Opportunistic infection, Probiotics, Th17,

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Viral reactivation, Viral reservoirs.

## INTRODUCTION

HIV/AIDS is still a global health problem [1]. According UNAIDS report about 36.9 million people are infected with HIV; most of them are in sub-Saharan Africa [2]. Around 17 millions are taking antiretroviral (ARV) drugs to treat HIV [2]. The significant success in the treatment of HIV results in an increase the amount of HIV-infected individuals. Effective combination antiretroviral therapy (cART), suppressing virus replication, allows HIV-infected persons to keep infection under control for long period. AIDS deaths reduced by 1.7 times between 2004 and 2014 [2]. Widespread use of cART changed HIV from a progressive illness with a lethal prognosis into a chronic controlled disease [1]. Therapy is likely to be permanent. cART may not be working or can be associated with severe adverse effects that may leads to switch ARV drugs or even to discontinuation of cART due to toxicity [3]. Moreover, many HIV-infected persons have limited or no access to proper treatment.

During the course of HIV infection the number of T cell is depleted and their function is progressively impaired. For example, cytotoxicity and CD8+ T-cell polyfunctionality, secretion of cytokines and proliferative capacity of T cells are depressed [4 - 6] and they are virtually not recovered by cART [6]. Therefore, with suppression and eradication of virus, it had better to boost immune system of HIV patients and/or reverse exhaustion of the immune system.

There is a problem of latent infection or viral reservoirs, which are unaffected by cART and are not recognized by the immune system [7 - 10]. These latent reservoirs are established early during acute viral infection [7]. Currently, researchers are focusing on various strategies to reactivate latent viral infection in the continued presence of cART [9, 11 - 15]. An understanding of HIV reservoir dynamics in tissue is critical to HIV eradication and cure efforts.

HIV and its ancestor SIV are primarily mucosal infection [16]. The vast majority of HIV infection around the world (about 85%) is through mucosal surfaces, genital, oral, or rectal [16, 17]. Initial HIV replication and amplification occur in mucosa causing rapid loss of CD4+ T cells, especially in the gastrointestinal (GI) tract, thereby worsening mucosal defense mechanisms [18 - 20]. Therefore, effective treatments or prophylaxis at the mucosal level are much needed. Th17 cells play an important role in mucosal immunology and the depletion of Th17 cells is a key moment in the progression to AIDS [17, 21, 22]. Mucus layers becomes more permeable to bacteria that leads to translocation of bacteria, or

bacterial products, into the bloodstream where they are a major contributor to the immune hyperactivation seen in HIV infection and contributing to the pathology [17, 20, 23 - 26]. Microbial translocation and inflammation are becoming inextricably linked [27, 28].

The microbiome and immune response coevolve in response to infection during HIV/SIV pathogenesis that may determine the disease progression [22]. Understanding the interplay between microbiome and HIV is vital for development effective approaches for prevention and treatment of HIV infection [22]. Alteration of vaginal and rectal microbiome may influence HIV acquisition and mother-to-child transmission [22]. The abnormal change of microbiota occurs after HIV infection [29]. Levels of beneficial bacteria (*Bifidobacteria* and *Lactobacillus* species) are reduced in HIV patients; potential pathogens begin to prevail [21 - 23, 30, 31]. The gut microbiota plays a crucial role in the evolution and maturation of adaptive and innate arms of the host's intestinal mucosal immune system [31 - 35]. Recent evidence suggests gut microbiota may determine the fate of Th17 cells [22] and can induce Th17 cell differentiation [21, 33].

The fact, that host microbiota plays important role in maturation and balancing of the mammalian immune system, can give us possibility to use bacterial ingredients with immunoregulatory peculiarities for the prevention and treatment of human diseases [33, 36 - 39]. We have created a powerful new probiotic product (PP) that has far wider medical potential than traditional probiotic products [36]. Application of this agent does not disturb highly organized relationship between immunity and host's symbiotic microflora. Mucosal tissue compartments are the best locations for the application of PP to stimulate the innate and the adaptive immune systems. PP boosts the immune system: stimulates phagocytes, normalizes the number and functions of blood cells, especially lymphocytes (for the most part, cell-mediated immunity) [36, 38, 40]. Methods of administration of PP depend on the specific condition and the particular needs. For general application, oral administration is useful and enough. The strongest mucosal immune responses would be expected when PP is administered directly at a mucosal surface. PP can improve function of cardiovascular system and stimulate contraction of heart and blood vessels [36, 41 - 43], thereby reducing risk factors associated with cardiovascular diseases (CVDs) in HIV-infected individuals for whom "CVDs are a major cause of morbidity and mortality" [3]. HIV-1 can cause severe neurologic disease, including neurodegeneration [44 - 49]. Moreover, cART may contribute to cognitive decline [50], lead to neurotoxicity [51, 52] and promotes amyloidosis



## Anti-HIV Agents: The Way Forward for the Complete Eradication of the Virus

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**Abstract:** With effective antiretroviral treatment available for patients, acquired immunodeficiency syndrome (AIDS) is currently considered as a chronic disease. The life expectancy for HIV/AIDS patients on combined antiretroviral treatment (cART) is close to hundred percent with less pain. Such achievement was a dream for scientists and patients during the past twenty five years. The subsequent stage is the complete eradication of the human immunodeficiency virus (HIV) and a cure for AIDS. However, due to the HIV strategic ability of being able to hide in silence as a “provirus” inside its target cells for years, its high rate of mutations and its ability to change its outer envelope with the advantage of staying one step ahead of the immune responses, scientists used to believe that it is almost impossible to eradicate HIV from the human body. The hope for a “sterilizing cure” so that all traces of HIV are eliminated from the body, and/or a “functional cure” so that HIV is controlled by the function of the immune system, is not a dream anymore. Recently, with the discovery of cancer drugs, such as vorinostat, scientists believe that a cure for AIDS is possible with the complete eradication of HIV from the human body. With the advanced knowledge about HIV and the immune responses to it, hopes and optimism for an HIV/AIDS-cure is a hot topic now and we can dream that soon we will be living in an HIV/AIDS free world. There are currently more than 25 anti-HIV drugs used for the treatment of HIV/AIDS patients. This chapter briefly describes our knowledge of the anti-HIV agents currently available and the future plans for designing more effective agents against HIV in its state as a hidden provirus and as a released virus. The chapter will also discuss the way forward for the complete eradication of HIV.

**Keywords:** Acquired, Agents, AIDS, Anti-HIV, Anti-retroviral, cART, Cure, Eradication, Functional, Gene, HIV, Immune, Immunodeficiency, Post-exposure, Pre-exposure, Prophylaxis, Provirus, Response, Sterilizing, Therapy, Vaccine, Virucides.

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## INTRODUCTION

Over twenty five years ago when people got infected with the human immunodeficiency virus (HIV), it was more like being hit with a death sentence, with patients going through incredible pain as the acquired immunodeficiency syndrome (AIDS) had no effective treatment. Nowadays, HIV/AIDS treatment is so effective that many people with HIV/AIDS can live a virtually normal life. HIV/AIDS patients, especially in their early stages after infection, who have access to combined anti-retroviral therapy (cART) have almost a hundred percent life expectancy and live with less pain. The eradication of HIV completely or the word “cure” for AIDS was not even thought of until most recently and now evidence is accumulating for the possibility of a complete eradication of HIV and a possible cure for AIDS [1 - 3].

In 2009, it was reported that a man infected with HIV named Timothy Ray Brown, also known as the “Berlin Patient”, received a bone-marrow stem-cell transplant as a treatment for his leukemia and was shown to be cleared from HIV infection. He was given a double stem cell transplant from a donor with *CCR5Δ32* mutation [4]. The Berlin Patient lived for six years without any signs of the HIV and he no longer needed antiretroviral therapy. His case is the closest representation of an HIV cure [5, 6]. Moreover, in 2013, another case known as the “Mississippi Baby” was made public. This case represents a newborn who became infected with HIV while he was in its mother's womb. The Mississippi Baby was treated with anti-HIV medications, from as early as the second day of its life. When his mother stopped giving him the anti-HIV medications after one year and six months, the child was still capable to keep HIV under control [7].

These case reports demonstrated that it is possible to eradicate HIV from someone who has previously been infected with the virus. In addition, evidence has accumulated for a possible cure with the right combination of drugs during AIDS treatment. This may lead to “remission” or “functional cure” *i.e.* complete control of HIV without the need for lifelong antiretroviral treatment or “sterilizing cure” whereby all HIV traces are no longer present in the body. However, the evidence mentioned above is based on very specific cases with specific circumstances and therefore it may not be possible or predictable to reproduce these observed cases to result in a complete eradication of HIV in the infected patient or a cure for AIDS.

Antiretroviral therapy is currently used to prevent the transmission of HIV from the mother to her child [8] and now the same strategy may potentially be used for eradicating HIV. New born babies who were treated early after birth and within a

few days of their birth were shown to have a unique combination of a small pool of integrated HIVs, a high proportion of HIV resistant naive T cells, and a capacity to regenerate an effective immune response [9]. These characteristics make this group of babies an excellent model for the investigation of the potential efficacy of therapies based on the responses of the immune system [9].

In general, infectious diseases are cured due to the immune system's ability to control the replication of the pathogen and to eradicate it, with or without the use of anti-microbial agents. Despite the help of the anti-microbial agents, it is actually the immune system that leads to the cure of a disease. Elements of the immune responses, both innate and adaptive, are essential and many immune cells take part in and each plays an important role. Memory CD4<sup>+</sup> T helper cells, have the most important role, as they are involved in organizing immune actions against the invading pathogen [10]. The memory CD4<sup>+</sup> T helper cells represent the foundation of the adaptive immune responses and these cells perform an important function in the protection against infection.

For the complete eradication of HIV and curing AIDS multiple obstacles and factors must be overcome [11]. These include the fact that HIV is able to mutate its outer envelope and this enables it to evade elements of the adaptive immune responses such as neutralizing antibodies. During the life cycle of HIV, the genetic materials of the virus is integrated into its host cellular genome and stay there for a period of time known as the "latency period", and this allows the virus to escape the immune responses of the host. In this latency period, HIV can survive for many years as a latent virus [12]. In order to achieve the "cure for AIDS", a full understanding of HIV itself and how the immune system responds to it is required. Complete elimination of HIV from the human body is known to involve both viral factors as well as human factors affecting the immune response to the virus [11, 13].

In this chapter, we will briefly discuss the current antiviral agents in use to tackle HIV infection as well as other ways of targeting the HIV and preventing infection and the way forward for the complete eradication of HIV.

## **ANTIRETROVIRAL AGENTS**

The AIDS clinical course was drastically changed during the nineties of the last century with the use of highly active antiretroviral treatment (HAART) or combined antiretroviral treatments (cART). In most of the HIV/AIDS patients, HAART or cART causes reductions in the HIV load, increase in CD4<sup>+</sup> T helper cells, and therefore better immune responses against the virus, resulting in

## CHAPTER 4

## Essential Oils, Polyphenols and Glycosides: Secondary Plant Metabolites against Human Pathogenic Microbes

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**Abstract:** Higher plants produce secondary metabolites involved in defense mechanisms against herbivores, pests and pathogens. These phytochemicals have also potential healthy properties on human organism, including antioxidant, anti-inflammatory and anti-microbial. The pressure to discover and develop new and effective anti-infectious substances has grown due to the intensification of new and re-emerging infectious diseases as well as the increasing resistance to the antibiotics in current clinical use. There are several approaches to control diseases caused by microorganisms, and one of them is the use of natural bioactive chemicals that can combat the infection. The essential oils, polyphenols and glycosidic glucosinolates extracted from various species (*e.g.* medicinal and aromatic plants) have shown promising anti-microbial activity against several pathogens responsible for human diseases. Some of these diseases include mouth diseases as periodontitis, urinary infections, acne, stomach cancer and ulcers associated with *Helicobacter pylori*, wound infections and gastric infections. Beyond the *in vitro* and *in vivo* studies, several compounds from the plant secondary metabolites have been subjected to clinical trials in order to validate their efficacy as anti-infectives (*e.g.* proanthocyanidins, a polyphenol, that have been tested against periodontitis or tea tree oil 4% against methicillin-resistant *Staphylococcus aureus* – MRSA) for future prescription. As most of these compounds have poor water solubility and are easily oxidized a chemical transformation which may alter their anti-infective properties, new strategies are being

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considered both to protect these phytochemicals against oxidation and to enhance their bioavailability and delivery to the desired organs. This chapter summarizes and discuss the most promising phytochemicals that are being used to treat human diseases, anti-microbial mechanisms, the results of clinical trials and the new approaches based on nanoencapsulation strategies to deliver and target these compounds *in vivo*.

**Keywords:** Anti-infective properties, Bioavailability, Clinical trials, Essential oils, Glucosinolates, *In vivo* anti-microbial activity, Nanoencapsulation, Phenolic acids, Polyphenols, Proanthocyanidins.

## ESSENTIAL OILS

EOs are a mixture of compounds derived from natural sources, usually plants, obtained by hydrodistillation and having the characteristic odor of the plant, or other source from which they are extracted, and used either for its healing properties or as a perfume. The term “essential oil” is a contraction of the original “quintessential oil”, based on the Aristotelian view of the four elements (water, fire, earth and air) and the fifth element, the spirit of life, release during the distillation process [1]. In order to be distillate, EO's components need to have molecular weights below 300 Daltons [1].

The ability to accumulate EOs is not a property of all plants and often this characteristic is scattered throughout the Plant kingdom. However, the production and accumulation of EOs is frequently shared by certain plant families. EOs from the same plant family have in general identical inhibitory abilities, probably due to the similarity of their chemical composition [2]. Nevertheless, their chemical composition can vary greatly (even within the same species), depending of several factors including variety, cultivar, geographic origin, climate, soil composition, and environmental conditions, which are the main reasons to have numerous chemotypes [2 - 5].

Chemically, the majority of EOs constituents are hydrocarbons and oxygenated compounds. The first group, one of the most important in EOs, is almost exclusively composed of terpenes, lipophilic and highly volatile secondary plant metabolites (monoterpenes, sesquiterpenes, and diterpenes), and the second group are mainly composed by esters, aldehydes, ketones, alcohols, phenols, and oxides [6], substances derived from primary metabolism, or degradation products from primary and secondary metabolites [1]. Other substances that have been identified in EOs, are coumarins and anthraquinones [4, 7].

The applications of EOs are diverse and date back to ancient times. Some of them were used for their aroma, preservative properties and as holy balms. For instance, cinnamon EO, an ingredient of a holy oil used by the Egyptians as embalmer, was also used to reduce inflammations of the intestines and the kidneys, and as a diuretic [8]. Nowadays, EOs are widely used in cosmetics and perfumes, applied in medicine due to their therapeutic properties, as well as in agro-food industries because of their anti-microbial and antioxidant effects. Many EOs are extracted from plant species that are also used as spices, are also used for their antiseptic and disinfectant properties [9].

The most important plant sources of EOs are the Magnoliophyta Division (formerly angiosperms), in Dicotyledoneae, mainly in the families Apiaceae (*e.g.*, fennel, coriander), Asteraceae or Compositae (chamomile, wormwood, tarragon), Geraniaceae (geranium), Illiciaceae (star anise), Lamiaceae (mint, patchouli, lavender, oregano, and many others), Lauraceae (litsea, camphor, cinnamon, sassafras), Myristicaceae (nutmeg and mace), Myrtaceae (cloves, myrtle and allspice), Oleaceae (jasmine), Rosaceae (rose), and Santalaceae (sandalwood). In Monocotyledoneae, EOs are substantially restricted to Zingiberaceae (*e.g.*, ginger and cardamom) and Cyperaceae. In Pinopsida, one of the groups of the formerly gymnosperms division, the Pinaceae family constitute the main source (Table 1).

**Table 1. Plant sources of EOs with anti-microbial activity and their respective main constituents. The data were retrieved from the references cited along the chapter.**

Family	Species	EO Main Constituent(s)
Apiaceae	<i>Cuminum cyminum</i>	Limonene
	<i>Angelica archangelica</i>	$\alpha$ -pinene, limonene, $\delta$ -3-carene
	<i>Coriandrum sativum</i>	Linalool, <i>p</i> -cymene
Asteraceae (Compositae)	<i>Achillea biebersteinii</i>	<i>cis</i> -ascaridol, <i>p</i> -cymene, camphor, 1,8-cineole
	<i>Achillea fragrantissima</i>	<i>cis</i> -thujone, 2,5-dimethyl-3-vinyl-4-hexen-2-ol, 3, 3,6-trimethyl-1,5-heptadien-4-one, <i>trans</i> -thujone
	<i>Achillea millefolium</i>	Chamazulene, $\beta$ -pinene, sabinene, germacrene D, $\beta$ -caryophyllene, 2,5-Dimethyl-3-vinyl-4-hexen-2-ol
	<i>Achillea santolina</i>	Fragranyl acetate, 1,6-dimethyl-1,5-cyclooctadiene, <i>cis</i> -thujone, fragranol, 1,8-cineole, camphor
	<i>Artemisia absinthium</i>	Myrcene, <i>trans</i> -thujone, <i>trans</i> -sabinyl acetate,
	<i>Artemisia biennis</i>	( <i>Z</i> )- $\beta$ -ocimene, ( <i>E</i> )- $\beta$ -farnesene, acetylenes
	<i>Artemisia vulgaris</i>	$\alpha$ -thujone, $\beta$ -thujone, 1,8-cineole, <i>trans</i> -carveol, sabinene
	<i>Helichrysum italicum</i>	Nerol, neryl acetate, neryl propanoate, limonene, $\alpha$ -pinene, $\gamma$ -curcumene, linalool

## Photosensitizers: An Effective Alternative Approach to Microbial Pathogen

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**Abstract:** Increasing antibiotic resistant pathogens incidence brings to an end of “the antibiotic era” which extended over the past 50 years, and necessitates exploration of alternative approaches to combat emerging infections. Increase global spread of drug resistance pathogens has prompted researchers to search for new strategies for microbial eradication. The efficient and often selective inactivation of microbial pathogens by means of photosensitized processes (Photodynamic therapy) has opened favourable avenues to treat numerable infectious diseases. Antimicrobial Photodynamic therapy (APDT) is a light-based antimicrobial therapy capable of efficiently eradicating wide microorganisms. It is an oxygen-dependent photochemical reaction that occurs upon light mediated activation of a photosensitizing compound leading to the generation of reactive oxygen species. Antimicrobial photodynamic therapy is a topical, non-invasive approach suitable for treating local infections. This chapter focus on introduction to antimicrobial photodynamic therapy with an emphasis on the use of photodynamic therapy for the treatment of resistant microbial strains.

**Keywords:** Aminolevulinic acid, Antibiotic resistance, Antimicrobial chemotherapy, Fungicidal, Laser, Methylene blue, Photodynamic therapy, Photosensitizer, Porphyrin, Singlet oxygen.

### INTRODUCTION

Antibiotics are one of the most common forms of therapy to treat infectious agents. Conventional antimicrobial strategies against multidrug resistance strains have been ineffective [1]. Antibiotic resistance results in elevated morbidity and mortality rates as well as increased treatment costs, which is considered to be one

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of the major global public health threats [2].

The rising issues of antibiotic resistance and their spread in the environment due to the inappropriate and unnecessary use of antibiotics, brings the need for the development of novel, convenient and inexpensive methods for combating infection caused by resistant pathogens [3].

Researches on novel non-antibiotic approaches, which can prevent and protect against infectious diseases are looked upon with high priority for research and development projects [4]. Prominent among novel non-antibiotic approaches are a group of light based technologies such as, ultraviolet C (UVC) irradiation therapy, photodynamic therapy (PDT), blue light therapy and other light based therapies [5]. The most attractive advantages of light based antimicrobial therapies lie in their ability to eradicate microbes regardless of antibiotic resistance and improbability of the microbes themselves in developing resistance to these light based therapies due to the non-specific nature of the targets [6, 7].

Antimicrobial photodynamic therapy (APDT) is a localized and non-invasive method to decrease bacterial load [8]. Photosensitization of bacteria has not shown induction of resistance to APDT even after multiple treatments. Further, microbial selectivity is observed with APDT which can be due to differences in pharmacokinetics of mammalian and bacterial cells [9]. APDT is also known as lethal photosensitization (LPS), photodynamic inactivation (PDI), photodynamic antimicrobial chemotherapy (PACT) and photo activated disinfection (PAD).

The targets for antibacterial and antiviral photodynamic activity are the external microbial structures such as cell walls, cell membranes, capsid, lipid envelopes, and nucleic acids, which causes cellular contents leakage and/or membrane transport systems and enzymes inactivation. Antifungal photodynamic activity induces functional alternations of the cytoplasmic membrane [10].

### **Antimicrobial Photodynamic Therapy**

Photodynamic therapy involves three major components: light source, a photosensitizer and tissue oxygen. When these components are combined together, they become toxic to the targeted cells [11]. Light source with appropriate wavelength is required for exciting the photosensitizer (PS) to produce reactive oxygen species (ROS) such as singlet oxygen, hydrogen peroxide and hydroxyl radical, which are able to irreversibly oxidize micro-organism's vital constituents resulting in lethal damage.



ROS generated during APDT is by two types of reactions, Type I reaction involves direct transfer of electron/hydrogen from photosensitizer producing ions or electron/ hydrogen abstraction from a substrate molecule to free radicals. Type II reaction produces electronically excited and highly reaction state of oxygen known as singlet oxygen [12]. APDT is advantageous because of non-target specificity and lack of resistance development [13].

Further APDT is advantages over traditional antibiotics: (i) APDT has a broad spectrum of action; (ii) APDT shows low mutagenic potential and greater phototoxicity; (iii) There is a low chance of any possibility of developing photo-resistant species even after multiple treatments [14]; and (iv) APDT kills microbial cells rapidly (minutes) while antibiotics can take days to work.

APDT reported to be potential towards local microbial infections [15]. Photodynamic antimicrobial chemotherapy represents an alternate antibacterial, antifungal, and antiviral treatment against drug resistant organisms [16].

### **History of Photodynamic Therapy**

Use of light as a therapy in medicine and surgery has been traced from ancient times [17]. Dr. Niels Finsen demonstrated the beneficial effects of various wavelengths in the treatment of tuberculosis for which he was awarded Nobel Prize in 1903 [18]. Von Tappeiner in 1904 coined the term *Photodynamic* to describe oxygen-dependent chemical reactions induced by photosensitization and this therapy was approved by the Food and Drug Administration in 1999 to treat pre-cancerous skin lesions of the face or scalp.

### **Components of Photosensitization**

#### ***Light Source***

Development in fiber optic technology has led to the increase use of laser light in health care and management industry [19]. Due to strong thermal component, poly-chromaticity characteristics and incoherency conventional bulb are used initially in ADPT, but they did not yield good results. The most commonly used light source now is Light Emitting Diode (LED) and Light Amplification by Stimulated Emission of Radiation (LASER) [20 - 22].

When compared to blue light red and infrared radiations penetrate more deeply through tissue. Region between 600 and 1200 nm is often called the optical (therapeutic) window of tissue. Light up to  $\approx 800$  nm can generate  $^1\text{O}_2$ , beyond this wavelengths have insufficient energy to initiate a photodynamic reaction [23]

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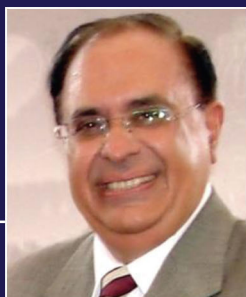
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