INFECTIOUS DISEASES

Editors:

Ferid Murad ***(Nobel Laureate)***

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

Ka Bian

Bentham Books

Herbal Medicine: Back to the Future

(Volume 5)

Infectious Diseases

Edited by

Ferid Murad (*Nobel Laureate*)
Palo Alto Veterans Hospital
California
USA

Atta-ur-Rahman *FRS*
Honorary Life Fellow
Kings College
University of Cambridge
England
UK

&

Ka Bian
George Washington University
School of Medicine
Washington
USA

Herbal Medicine Back to the Future

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Editors: Prof. Ferid Murad, Prof. Atta-ur-Rahman, FRS & Prof. Ka Bian

ISSN (Online): 2542-999X

ISSN (Print): 2542-9981

ISBN (Online): 978-1-68108-922-5

ISBN (Print): 978-1-68108-923-2

ISBN (Paperback): 978-1-68108-924-9

Bentham Science Publishers Ltd.
Executive Suite Y - 2
PO Box 7917, Saif Zone
Sharjah, U.A.E.
Email: subscriptions@benthamscience.net

CONTENTS

PREFACE

Herbal Medicine: Back to the Future presents expert reviews on the applications of herbal medicines (including Ayurveda, Chinese traditional medicines, and alternative therapies). This volume demonstrates the use of sophisticated methods to explore traditional medicine, while providing readers a glimpse into the future of herbal medicine.

The book is a valuable resource for pharmaceutical scientists and postgraduate students seeking updated and critically important information regarding natural product chemistry and pharmacology of natural materials in the treatment of infectious diseases. The chapters are written by authorities in the field. Cundell, in chapter 1, reviews the antimicrobial properties of curcumin and eugenol, with their modes of action. Armutcu and Kucukbayrak, in chapter 2, present various herbal medicines that are effective against respiratory tract infections (RTIs) and their therapeutic mechanisms. Arya *et al*. in chapter 3, provide a comprehensive overview of epidemiological, pathogenesis, diagnostic aspects, and therapeutic interventions to tackle the current outbreak of COVID-19. Severcan *et al*. in chapter 4, discuss the applications of mid-infrared spectroscopy in the investigation of the constituents of herbal medicines used in infectious diseases. Tahri *et al*. in chapter 5, focus on the traditional uses of plants in Algerian pharmacopoeia against infectious diseases. In the last chapter of the book, Wang *et al*. discuss the use of ancient Chinese herbal medicines for treating infectious diseases.

We hope that the readers involved in the study of infectious diseases will find these reviews valuable and thought provoking so that they may trigger further research on herbal medicines and alternative therapies.

We are grateful for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Editorial Director), Mr. Obaid Sadiq (In-charge Books Department), and Ms. Asma Ahmed (Senior Manager Publications), at Bentham Science Publishers for the publication of this book.

Ferid Murad (Nobel Laureate)
Palo Alto Veterans Hospital
California
Usa

Atta-ur-Rahman, *FRS*
University of Cambridge
Cambridge
UK

Ka Bian
George Washington University
School of Medicine
Washington
USA

List of Contributors

Abdulkadir Kucukbayrak	Department of Infectious Diseases and Clinical Microbiology, Izzet Baysal Medical Faculty, Bolu, Turkey
Acharya Balkrishna	Patanjali Herbal Research Department, Patanajli Research Institute, Haridwar, India Department of Applied and Allied Sciences, University of Patanjali, Patanjali Yogpeeth, Haridwar, Uttarakhand, India
Bin Qu	Biophysics, Center for Integrative Physiology and Molecular Medicine (CIPMM), School of Medicine, Saarland University, Homburg, Germany
Diana R. Cundell	College of Life Sciences, Thomas Jefferson University, 4201 Henry Avenue, Philadelphia, PA 19128, USA
Djilali Tahri	Laboratoire de Recherche des Sciences Fondamentales, Université Amar TELIDJI, Route de Ghardaïa, BP 37G, 03000 Laghouat, Algérie
Fatiha Elhouiti	Laboratoire de Recherche des Sciences Fondamentales, Université Amar TELIDJI, Route de Ghardaïa, BP 37G, 03000 Laghouat, Algérie
Ferah Armutcu	Department of Biochemistry, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey
Feride Severcan	Department of Biophysics, Faculty of Medicine, Altinbas University, Istanbul, Turkey
Gulkizilca Yurur	Department of History of Medicine and Medical Ethics, Faculty of Medicine, Altinbas University, Istanbul, Turkey
Han Zhang	State Key Laboratory of Component-based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China
Mete Severcan	Department of Electrical and Electronics Engineering, Faculty of Engineering and Natural Sciences, Altinbas University, Istanbul, Turkey
Mohamed Ouinten	Laboratoire de Recherche des Sciences Fondamentales, Université Amar TELIDJI, Route de Ghardaïa, BP 37G, 03000 Laghouat, Algérie
Mohammed Seba	Institut de Biologie Intégrative de la Cellule, CEA, CNRS, Univ. Paris-Sud, Université Paris-Saclay, Gif-sur-Yvette cedex, France
Mohamed Yousfi	Laboratoire de Recherche des Sciences Fondamentales, Université Amar TELIDJI, Route de Ghardaïa, BP 37G, 03000 Laghouat, Algérie
Nazli Ezer Ozer	Department of Biophysics, Faculty of Medicine, Altinbas University, Istanbul, Turkey Biomedical Sciences Graduate Program, Altinbas University, Istanbul, Turkey
Rashmi Mittal	Patanjali Herbal Research Department, Patanajli Research Institute, Haridwar, India
Tugce N. Gedik Kapancık	Department of Microbiology, Faculty of Medicine, Altinbas University, Istanbul, Turkey Department of Basic Sciences, Microbiology, Faculty of Dentistry, Burdur Mehmet Akif Ersoy University, Burdur, Turkey

Vedpriya Arya Patanjali Herbal Research Department, Patanajli Research Institute, Haridwar, India

Yi Wang Pharmaceutical Informatics Institute, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, China
Innovation Institute for Artificial Intelligence in Medicine of Zhejiang University, Hangzhou, China

Yu Wang State Key Laboratory of Component-based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China

Yunru Yu Pharmaceutical Informatics Institute, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, China

Zehua Jin State Key Laboratory of Component-based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China
Pharmaceutical Informatics Institute, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, China

CHAPTER 1

Improving Curcumin and Eugenol Through Computational Chemistry and Nanotechnology

Diana R. Cundell[*,1]

[1] *College of Life Sciences, Thomas Jefferson University, 4201 Henry Avenue, Philadelphia, PA 19128, USA*

Abstract: Curcumin and eugenol have been appreciated as broad-spectrum antimicrobial agents since the early 20th century, and their parent plants of turmeric and clove have been used in Ayurvedic and traditional Chinese medicines for thousands of years. Although extensive research has identified several antimicrobial mechanisms of action, it is the only eugenol that has become established for dental uses. Curcumin and eugenol have been hard to purify and stabilize and, in their native states, show poor bioavailability. New antimicrobial agents are now needed due to the growth in resistant strains, and this means natural agents are back in vogue. Nanoparticle and antimicrobial-coated surfaces are popular strategies to maximize the consistent delivery of mainstream pharmaceuticals. Computational chemistry and docking analyses are the primary methods used to identify and design novel variants of natural molecules to improve bioavailability and stability. Both curcumin and eugenol have benefitted from the expansion of these fields, and reports of stabilized forms with superior activity are now rapidly appearing in the literature. This chapter will review the antimicrobial spectrum of curcumin and eugenol, explaining their antimicrobial modes of action. Finally, potential and currently available delivery systems will be explored using the semi-synthetic analogs and bioengineered structures that have been created.

Keywords: Bioengineering, Curcumin, Eugenol, Nanoparticles, Natural molecules, Semi-synthetic analogs.

INTRODUCTION

Ethnomedicine practices existed at least 60,000 years ago when man sought to alleviate pain and infection using the plant species that grew in his local environment [1 - 3]. Spices especially provided both flavorings to food and helped to naturally preserve it from spoilage, *i.e.*, they were antibacterial and antifungal [4]. These plants became both food and medicine in countries, like Ancient India

[*] **Corresponding author Diana R. Cundell:** College of Life Sciences, Thomas Jefferson University, 4201 Henry Avenue, Philadelphia, PA 19128, USA; E-mail: Diana.Cundell@jefferson.edu

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and China, and this concept was preserved even in the Ancient Greek Hippocrates' medicinal treatises [5, 6]. Two plants emerged as important in these cultures, turmeric (*Curcuma longa* L.) [7] and the clove tree *Syzgium aromaticum* [8]. Easy to cultivate in both tropical and semi-tropical climates, turmeric is still used today as a nutraceutical in India and China to treat infections, tumors, gastrointestinal issues, and arthritic conditions [9, 10]. Since the 1st century AD, cloves have been traded from Indonesia around the world to be used as flavoring and medicinal agents [11]. Traditional Chinese Medicine (TCM) practices have established clove essential oils (EO) in the treatment of toothache and as a broad-spectrum antimicrobial, for alleviating gastrointestinal disorders [8]. Extracts of both turmeric and cloves have been successfully and continuously used in an anti-microbial capacity for thousands of years but to evaluate their abilities further, an understanding of their individual phytochemical activities is required.

At the beginning of the early 1900s, chemists began to identify the agents responsible for plant-derived antimicrobials [12] and it soon became apparent that there were numerous groups of secondary metabolites responsible for this activity [13]. It was revealed that plant extracts contain many complex antimicrobial molecules, including flavonoids, alkaloids, phenolics, and terpenoids [13]. Interestingly, the most prominent groups in this respect have been the terpenes and terpenoids, which have demonstrated the most broad-spectrum and potent activities [13]. Terpenoids are branched, lipid-based cyclic molecules found in most plants that are easily able to penetrate and disrupt phospholipid cell membranes [13]. As a result, they have been reported to inhibit the activities of at least 60% of bacterial species investigated and approximately one-third of all fungi [13]. As the individual terpenes from this group were identified, several molecules emerged [13]. Some compounds, such as artemisinin from sweet wormwood, eugenol from cloves, and capsaicin from chili peppers, were subsequently developed into pharmaceutical agents [13]. Others, including curcumin from turmeric, remain primarily nutraceuticals [13], however, it can be seen from this chapter, that situation may be changing.

Antimicrobial Activities of Turmeric and Clove

Sometimes referred to as "the Golden Spice," turmeric tubers contain a diverse series of compounds, but the most powerful and prevalent antimicrobial is curcumin (5.0-6.6%) [7, 14]. Curcumin constitutes three-quarters of the curcuminoids present in turmeric [15]. Demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) together constitute another 20% of the curcuminoids but are without antimicrobial activity [15]. Vogel and Pelletier named curcumin in 1815 for the yellow discoloration they observed on the surface of turmeric tubers [16]. After several attempts to chemically analyze curcumin, in 1881, Jackson and Menke were able to create the first salts of curcumin, identify its poor solubility in water, and also theorize that it contained a vanillin group [17]. Purified curcumin was finally reported by the Polish scientists Milobedzka and Lampe in 1910 [18], who identified its structure as being a phenolic diaryl heptanoid, diferuloylmethane or (1*E*,6*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione).

Curcumin's antibacterial and antifungal activity was identified in 1949 by Schraufstätter and Bernt [19]. The gram-positive bacteria *Staphylococcus aureus* and *Mycobacterium tuberculosis*, gram-negative bacterium *Salmonella paratyphi,* and the fungus *Trychophyton gypseum* were found to be effectively killed by curcumin *in vitro* [19]. Schraufstätter and Bernt [19] were the first to identify that a dibenzalacetone analog of curcumin (4,4'-dihydroxy-3,3'-dimethoxydi benzalacetone) possessed similar antibacterial and antifungal activity. Since then curcumin has been shown to possess potent antibacterial, antifungal, and antiviral activity [12]. Several reports of anti-protozoal [20, 21] and anti-helminthic [21 - 24] activity have also appeared in the literature.

Clove oil was first studied by Carl Jacob Ettling who, in 1834, identified its major constituent as eugenol (4-Allyl-2-methoxyphenol) [8, 25]. Eugenol occurs naturally in plant species, including turmeric, cinnamon, and nutmeg (~ 3 mg/kg) but the major commercial source remains clove flowers and buds (180 mg/kg) [26]. Clove EO consists primarily of eugenol (40-50%) and α-selinene (40%), with lesser amounts of monoterpenes [11]. Selinenes are known to be microbial defense molecules of plants [27] and possess anti-tumor activity [28]. Although less thoroughly investigated than eugenol, it is likely that these entities might be additive to eugenol's activities.

Since the 1800s, eugenol has been shown to possess potent broad-spectrum antimicrobial activity [29, 30]. Interestingly, the early use of cloves for dentistry led to the incorporation of eugenol into a root canal zinc oxide paste (ZOE) by Chisholm in 1876 [30, 31]. By 1930, Charles Sweet established the use of ZOE for primary teeth, with this same compound still in use today [32]. Studies have shown that eugenol's phenol group assists with the setting of ZOE and that eugenol gradually dissociates without weakening the complex [30, 31]. Eugenol's anti-inflammatory and antimicrobial activities persist in the root canal area for at least a month and assist in the healing process [31]. Additionally, eugenol acts on the γ-aminobutyric acid type A ($GABA_A$) receptor, providing pain-relieving and anesthetic properties [33].

CHAPTER 2

Herbal Remedies for Respiratory Tract Infections

Ferah Armutcu[1,*] and **Abdulkadir Kucukbayrak**[2]

[1] *Department of Biochemistry, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey*

[2] *Department of Infectious Diseases and Clinical Microbiology, Izzet Baysal Medical Faculty, Bolu, Turkey*

Abstract: Herbal medicine is simply the science of using plants to treat or prevent medical conditions. It is one of the main modalities in traditional as well as contemporary medicine and is increasingly acknowledged due to the extensive use of herbal remedies in public and societies. As respiratory tract infections (RTI) are highly prevalent and variable, especially lower respiratory infections are a leading cause of sickness and mortality both in children and adults. There is a growing need for new treatments for such infections, particularly in the setting of worsening antibacterial resistance. Since ancient times, people who have tried herbs to treat diseases have also used them to treat infectious respiratory diseases. Many plants and herbal medicine-derived natural products could be used as an alternative therapeutic potential for RTI since they have antibacterial, antiviral, and anti-inflammatory effects. Although there are some doubts about safety and efficacy, Chinese Herbal medicines may help treat symptoms of viral respiratory disease, including COVID-19. Natural products such as plant extracts and their active compounds, directly target the processes involved in RTI and could be suitable therapeutic options with fewer adverse effects. In the meantime, it should be kept in mind that there are many factors that affect the therapeutic potential of medicinal herbs and related products, including the collection and development processing. This section aims to highlight the examples of herbal medicines that are effective against RTI and their properties and therapeutic mechanisms.

Keywords: Antibacterial, Antiviral, COVID- 19, Essential oil, Inflammation, Medicinal plants, Respiratory tract infections.

INTRODUCTION

Herbal medicines, which have formed the basis of health care throughout the world since the beginning of humankind, are still widely used and play an economically important role in human society. Despite the use of herbal or botani-

* **Corresponding author Ferah Armutcu:** Department of Biochemistry, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey, and School of Natural Medicine Berkeley Square, London, UK; Tel:07404461213; E-mail: drferah@gmail.com.

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cal medicines for many centuries, only a relatively small number of plant species have been studied for possible medical applications [1]. For two decades, the interest in medicinal plants and their international market value has been increasing. Herbal medicine may be used in lieu of or in addition to pharmaceutical treatments. Many countries and some health organizations classify herbal alternatives as a dietary supplement [2].

Infectious diseases have posed a threat to human life since the dawn of human existence and continuous efforts are required to develop effective treatments. The respiratory tract involves the nose, sinuses, pharynx, larynx, and bronchial tubes, finally extending to the smallest bronchi branch and into very small tubules called bronchioles in the lungs. A variety of bacteria, viruses, and fungi can cause respiratory tract infections. Respiratory tract infections are a group of common infectious lung diseases, including bronchitis, bronchiolitis, common cold, epiglottitis, laryngotracheitis, pharyngitis, tuberculosis, pneumonia, and respiratory distress syndromes. Many of these diseases cause serious and even life-threatening health problems [3 - 5]. More than 50 million deaths worldwide are due to respiratory infections, which are the main cause of clinical visits and antibiotic prescriptions. Malnutrition and poor immunity are the main causes of the high incidence of respiratory infections [6].

Although the discovery of antibiotics and antiviral agents has made the treatment of many infectious diseases possible, it has been observed that the emerging antibiotic-resistant strains and mutant microorganisms are stronger than existing ones. It is also known that microbial biofilms that cannot be treated with antibiotics can cause chronic infections [7, 8]. As infectious diseases continue to pose a threat to human health and antibiotic-resistant bacteria remain a challenging public health problem worldwide, continuous efforts are required to develop effective treatments. Natural products derived from many herbs and herbal remedies have been used as an alternative therapy for infectious respiratory diseases. For example, standardized Myrtol essentially consists of three mono-terpenes, namely (+)-alpha-pinene, d-limonene, and 1,8-cineole, which are used as a distilled phytotherapeutic extract [9]. The aim of this section is to draw attention to the herbal medicines used in the treatment of respiratory tract infections and to evaluate their efficacy by discussing their therapeutic effects. The antibacterial, antiviral, and anti-inflammatory effects of medicinal plants and other related natural compounds and brief mechanism of action will also be discussed.

FREQUENTLY USED HERBAL REMEDIES FOR TREATMENT OF RESPIRATORY INFECTIONS

Respiratory ailments are generally classified into two broad categories: upper and lower respiratory tract problems. Upper respiratory tract infections (URTI) usually manifest as cold, runny nose, sinusitis, laryngitis, and sore throat. These problems are typically bothersome but easier to treat. Lower respiratory tract infection (LRTI) is often synonymous with pneumonia but can also embrace other diseases, including lung abscess and tuberculosis, as well as infections affecting the airways such as bronchitis, influenza, and whooping cough [4]. It will be appropriate to start this discussion by giving examples of the effects of medicinal plants on the oral mucosa and upper respiratory tract rather than their effects on LRTI. In an early study, it was reported that 15% *Salvia officinalis* (sage) spray provided appropriate and safe treatment for patients with acute pharyngitis. In addition, the same study suggested that symptomatic relief occurred within the first two hours and was statistically significantly superior to the placebo effect [10]. Chamomile is one of the most ancient medicinal herbs; it is a member of the *Asteraceae*/*Compositae* family and represented by two common species, *Chamomilla recutita* (German Chamomile) and *Chamaemelum nobile* (Roman Chamomile). Chamomile is widely used to treat inflammations of the mucous membranes and various bacterial infections of the skin, oral cavity, and respiratory tract [11]. Due to their healing effect on the mucous membranes, some herbs such as *Salvia officinalis* and *Thymus serpyllum* are recommended to be re-evaluated for oral mucositis treatment. These plants contain essential oils that have been shown to have antimicrobial activity against multidrug-resistant S. aureus [12, 13]. Lower respiratory disorders usually affect the lungs and the bronchi. Acute bronchitis and pneumonia are conditions commonly diagnosed in inpatient and outpatient settings. Chronic respiratory problems can increase a person's chances of developing more serious conditions such as bronchitis and pneumonia. Most patients that suffer from bronchitis or pneumonia wheeze and have chest pain, have difficulty breathing, and cough [4, 7].

In a review article analysing eight studies, the authors reported that *Pelargonium sidoides* alleviates the symptoms of acute rhinosinusitis and cold in young people and maybe effective in relieving the symptoms of acute bronchitis in children and adults and of sinusitis in only adults [14]. According to one double-blinded study, the proprietary root extract of *Pelargonium sidoides* (known as EPs 7630) is a well-tolerated and effective treatment for acute bronchitis in adults, except for very restricted indications for antibiotic therapy [15]. Indeed, in some cases, URTI and LRTI are intertwined. Based on the results of 7 studies performed by Coon and Ernst with 896 participants, 6 of which were randomized, double-blind, and placebo controlled, *Andrographis paniculata* was found to have a preventive

CHAPTER 3

COVID-19 Pandemic: A Comprehensive Overview of Epidemiological, Pathogenesis, Diagnostic Aspects and Therapeutic Interventions to Tackle Current Outbreak

Acharya Balkrishna[1, 2], **Rashmi Mittal**[1] and **Vedpriya Arya**[1,*]

[1] *Patanjali Herbal Research Department, Patanajli Research Institute, Haridwar, India*

[2] *Department of Applied and Allied Sciences, University of Patanjali, Patanjali Yogpeeth, Haridwar, Uttarakhand, India*

Abstract: Coronavirus disease 2019 has been declared a pandemic globally by WHO after its first emergence in Wuhan city of China. The disease was observed to be caused by SARS-CoV-2 infection. Although a complete spectrum of clinical manifestations linked with COVID-19 is yet to be determined, on the basis of virus evolution and genomic recombination; SARS-CoV-2 is believed to be belonging to the Coronaviridae family with the zoonotic origin, exhibiting several symptoms in human patients ranging from being asymptomatic to severe illness, ultimately leading to high mortality rate. Different molecular, serological, and radiological techniques have been employed to detect SARS-CoV-2 infection. Epidemiological insights have revealed that the infection has threatened the health and economy of all the nations worldwide. Diverse pharmacological interventions are already under place to fight against the current pandemic, and a few of them have already been approved by FDA. Natural products and herbal medicine could also play a prominent role as an alternative therapeutic approach to fight against the current pandemic, and few of their clinical trials have already been registered. The purpose of this chapter is to provide a comprehensive overview of the origin, genomic diversity & evolution, epidemiology, pathogenesis, transmission, diagnosis, possible therapeutic approaches of COVID-19, and experiential learning to enhance our preparedness for upcoming but unknown outbreaks.

Keywords: Cathepsin, Chloroquine, COVID-19, Epidemiology, Favipiravir, HCoV, Helicase, Herbal Medicine, Interspecies Transmission, Methyl Transferase, mTOR, Pathogenesis, Phyto-Constituents, Plasma Therapy, PLpro, Radiology, RdRp, Remdesivir, RT-PCR, SARS-CoV-2, Serology, TMPRSS2, Zoonotic Origin.

* **Corresponding author Vedpriya Arya:** Patanjali Herbal Research Department, Patanajli Research Institute, Haridwar, India; Tel:+91 7060472471; E-mail: vedpriya.arya@prft.co.in

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) first emerged from Wuhan City of China and has been declared a global pandemic by World Health Organization (WHO). In December 2019, when the Chinese Health Authority reported several cases of pneumonia with unknown etiology to WHO, different clinical investigations were carried out globally, and ultimately, it was observed to be caused by a novel coronavirus strain, abbreviated as 2019-nCOV upon isolation from the throat swab sample of a patient. Later on, the coronavirus study group named the virus "Severe Acute Respiratory Syndrome Corona Virus 2", now popularly known as SARS-CoV-2, and the disease was called "Corona Virus Disease 2019" (COVID-19). Because of the rapidly increasing number of cases, it was announced as Public Health Emergency of International Concern (PHEIC). Upon investigation, SARS-CoV-2 was noticed to be belonging to the members of the Coronaviridae family comprising of positive-sense single-stranded enveloped ribonucleic acid (RNA) viruses. The genome size of the virus lies in the range of 27-34 kilobases, which is comparatively larger than other RNA viruses (Fig. **1**). The name "corona" virus originated from the Latin word "corona," which means 'crown' or 'halo' on the virtue of its characteristic features visualized under the 2-dimensional transmission electron microscope. Club-shaped spikes were also observed on its surface [1 - 3]. Alpha-coronaviruses and Beta-coronaviruses belonging to the subfamily Orthocoronavirinae, family Coronaviridae are generally transmissible to humans and are known to originate from bat species named *Rousettusleschenaultii*. Clinical symptoms of viral infection may vary from a mild cold, sneezing, coughing, shortness of breath to severe respiratory disorders and can even cause mortality in a few cases. For two decades, two novel coronaviruses have already emerged out. These are named Severe Acute Respiratory Syndrome-CoV (SARS-CoV) and Middle East Respiratory Syndrome-CoV (MERS-CoV). SARS-CoV infected over 8000 people, thereby exhibiting 800 fatalities accounting for a whooping mortality rate of 10%, whereas MERS-CoV infected over 851 people and out of which 334 deaths were reported, contributing towards a mortality rate of 35%. SARS-CoV is considered the 7th member of the coronavirus family, which can potentially target the human population. SARS-CoV-2 is considered the sister virus of SARS-CoV, which is wildly responsible for causing respiratory disorders. Anomalous characteristic features of the virus include its contagious behavior and transmission capacity even by asymptomatic individuals, which can cause mass mortality across the globe.

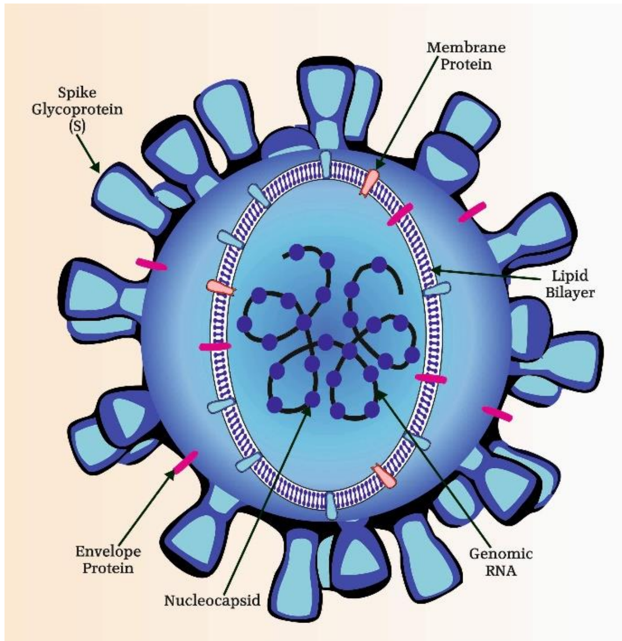

Fig. (1). Structure of SARS-CoV-2.

Originally rooted in the Wuhan City of China, now the virus has spread all across the world. Cases of COVID-19 continue to grow rapidly following an exponential growth rate pattern, and several molecular modeling studies reported a doubling time of 1.8 days for the viral strain. As of 18th December 2020, almost after a year of the emergence of disease, the total number of reported cases across the world was 75,404,230, with 1,671,058 deaths and 52,961,411 recoveries. Although the mortality rate seems significantly lesser compared to recovered cases, the loss of even a single individual cannot be ignored. Of 20,771,761 currently infected patients, 99.5% are mildly symptomatic, whereas 0.5% of this population is critically ill [4, 5].

Zoonotic Origin of Coronaviruses

Based on diverse protein sequences, CoVs are generally classified into four genera named alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV. Based on phylogenetic evidence, it has been revealed that bats and rodents are the genetic sources of alpha & beta-CoV, whereas birds served as the genetic reservoir of gamma & delta-CoV Table **1**. For thousands of years, these CoVs have often crossed species barriers, targeting humans as a pathogen and leading to mortality issues [6, 7].

CHAPTER 4

Application of Mid-Infrared Spectroscopy on Therapeutic Effects of Herbal Medicine in Infectious Diseases

Gulkizilca Yurur[1], **Tugce N. Gedik Kapancık**[2,3], **Mete Severcan**[4], **Nazli Ezer Ozer**[5,6] and **Feride Severcan**[5,*]

[1] *Department of History of Medicine and Medical Ethics, Faculty of Medicine, Altinbas University, Istanbul, Turkey*

[2] *Department of Microbiology, Faculty of Medicine, Altinbas University, Istanbul, Turkey*

[3] *Department of Basic Sciences, Microbiology, Faculty of Dentistry, Burdur Mehmet Akif Ersoy University, Burdur, Turkey*

[4] *Department of Electrical and Electronics Engineering, Faculty of Engineering and Natural Sciences, Altinbas University, Istanbul, Turkey*

[5] *Department of Biophysics, Faculty of Medicine, Altinbas University, Istanbul, Turkey*

[6] *Biomedical Sciences Graduate Program, Altinbas University, Istanbul, Turkey*

Abstract: Although a wide range of drug therapies fighting pathogenic agents have been developed since the late 19th century, infectious diseases such as pneumonia, flu, tuberculosis, AIDS and malaria still cost millions of lives. As per the World Health Organization (WHO) and Center for Infectious Disease Research estimates, the mortality rates of many infectious diseases may have actually worsened over the past few years. Development of new herbal compounds, understanding the effects of interactions between food and herbal medicines, and validating the traditional local combinations of plant use would be sophisticated revenues of research on the therapeutic effects of herbal medicine in infectious diseases. There is certainly a need for further collaborative biological screening of plant extracts in single, or combination forms and further interdisciplinary research in order to understand their interactions with biological systems. Infrared (IR) spectroscopy is a versatile analytical technique that has valuable applications in several areas such as biomedical sciences, pharmacy, engineering, chemistry, biophysics, food, plant science and toxicology. The combination of IR spectroscopy and chemometrics offers fast and powerful techniques for the separation and verification of herbal medicines-disease interactions. IR spectroscopy is widely used for the confirmation (identification), qualitative and quantitative analysis of herbal medicines and pharmaceutical products, and to determine how effective it is in the treatment of diseases. It requires small amounts of

[*] **Corresponding author Feride Severcan:** Department of Biophysics, Faculty of Medicine, Altinbas University, Istanbul, Turkey; E-mail: feride.severcan@altinbas.edu.tr

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samples, and so is relatively nondestructive, accurate and does not require a reagent, so it is more ecofriendly than biochemical processes. There are only a limited number of published studies on the application of FTIR spectroscopy to herbal medicine - infectious disease interactions. Therefore, it is certainly a very promising and open research area.

Keywords: Chemometrics, Herbal Medicines, Infectious Diseases, Infrared (IR) Spectroscopy, Laboratory Methods for Biocompatible Drug Discovery.

INTRODUCTION

Persistent waves of Emerging Infectious Diseases (EID) attest to the adaptive power of microbes, defeating the self-confident optimism of drug developers, health policy makers and medical professionals which was commonplace during the 20th century [1, 2]. Emerging Infectious Diseases (EID) are defined as "infections that have newly appeared in a population or have existed previously but are rapidly increasing in incidence or geographic range" [3]. One powerful recent example of EID is the COVID 19 pandemic, which mobilized researchers, governments and international organizations as a severe global threat to human economies, ecologies and cultures. Global successes such as the eradication of human smallpox (1980), the bovine rinderpest (2011) and most recently, the radical decline in polio cases worldwide should stand proof to the high achievements of synthetic drug and vaccine developers working dominantly with bacterial and fungal sources as antimicrobials [4]. However, the current popular mistrust towards the side effects of bacterial antimicrobial agents is accompanied by evidence-based concerns about increasing microbial resistance to these antimicrobial agents. Possible drug deficiencies in the future treatment of novel bacterial strains are a global threat [5]. Infectious diseases are communicable diseases which are caused by agents rapidly adapting to conditions. As a result, these disease agents easily spread to new geographies, can mutate from being a zoonotic infection to a zoonosis and jump the species barrier from infecting non-humans to infecting humans [6]. Yet, humans also adapt to new infectious diseases, both genetically and culturally. As Inhorn and Brown suggest, "In the human evolutionary process, infectious diseases have played a major role as agents of natural selection [7]. Infectious diseases also lead to cultural transformation, as societies respond to social, economic, political, and psychological crisis conditions brought about by pandemics and epidemics (*e.g.*, measles, influenza) and chronic infectious diseases such as schistosomiasis, malaria and HIV [7]. One can say that even research methods and techniques on novel, safe antimicrobials adapt to the constraints and necessities set by infectious agents. The intimate process of co-evolution between humans and disease also involves plants, whereby the geographical spread of specific medicinal plants may have been influenced by their being collected, carried forth and even buried as funeral gifts already by the Neanderthals, dating as early the Middle Paleolithic [8].

The earliest signs of herbal medicine can be detected from a Neanderthal burial site from 55,000 years ago in Shanidar in Northern Iraq, where individuals were buried with pollen and flower samples from different medicinal plants [9]. Also, the remnants of the possessions of the 5300-year-old 'iceman' discovered in 1991 in the Italian Alps included pieces of birch fungus (*F. betulina*) still today used as a laxative and antibiotic, whereby research provided evidence also about the anti-parasitic, antiviral and anti-inflammatory activities of *F. betulina* preparations [10].

In this chapter, after providing a brief summary of traditional herbal medicinal plants and infectious diseases, the application of infrared spectroscopy as an effective technique in analyzing the therapeutic effect of herbal plants on infectious diseases will be discussed.

Traditional Medicinal Plants

The increasing economic value of traditional herbal medicinal plants, along with the institutionalization and globalization of previously rather localized medical traditions, bring with it a number of questions with regards to the practical strategies to be developed. Questions not only involve regulations in therapeutic use, but also guidelines for any kind of research focusing on medicinal plants as therapeutics or prophylactics. Asian medicine, in particular the Indian Ayurvedic tradition and traditional Chinese medicine, have already gained credibility through an increasing number of randomized controlled trials on herbal medication. China reportedly founded 25 traditional Asian medicine institutes in geographically distant cities. This number will increase along with the rising scientific infrastructure of the Belt and Road Initiative [11]. It is reported from Latin America that governmental funding for the institutional study of traditionally used medicinal plants is continuously rising since as early as the 1980's [12]. By 2018, a big number of member countries of the WHO (World Health Organization) launched national policies on T&CM (Traditional and Complementary Medicine). Even more countries formulated national laws and regulations on T&CM. Almost all countries around the world have today some regulations on the medical use of herbal medicines [13, 14]. As Bussman notes, antibacterial activity is observed in most traditional medicinal plants used to treat infections in Andean healing traditions [15]. In an extensive study by Madureira and co-workers [16], 83% of the extracts derived from 22 most used anti-infectious African medicinal plants showed in vitro antibacterial activity. Similar results are derived from a large number of studies, carried out in varying

CHAPTER 5

Traditional Herbal Uses from Algerian Pharmacopoeia against Infectious Diseases

Djilali Tahri[1,*], Mohammed Seba[2], Fatiha Elhouiti[1], Mohamed Ouinten[1] and **Mohamed Yousfi[1]**

[1] *Laboratoire de Recherche des Sciences Fondamentales, Université Amar TELIDJI, Route de Ghardaïa, BP 37G, 03000 Laghouat, Algérie*

[2] *Institut de Biologie Intégrative de la Cellule, CEA, CNRS, Univ. Paris-Sud, Université Paris-Saclay, Gif-sur-Yvette cedex, France*

Abstract: Man's relationship with his environment has resulted in the development of a very rich traditional pharmacopoeia based mainly on medicinal plants. In Algeria, the plants uses are also oriented by scientific knowledge inherited from Muslim civilization in the books of Rhazes, Avicenna, Dawud El-Antaki, Ibn Beitar and Ibn Hamadouch. The infectious diseases known in the eighteenth and nineteenth centuries were treated by therapeutic formulas made from a plant, a mixture of plants or a mixture of plants and inorganic ingredients. Therefore, therapeutic formulas have been developed to treat measles, smallpox, urethritis, syphilis, malaria, tuberculosis, impetigo, scabies and yaws whose treatment has been imported to other countries and used successfully. These treatments can be prepared by infusion, decoction, maceration, trituration, fumigation, cooking and administered in drinks, eye drops, baths, soft dough and ointments. Currently, natural extracts of medicinal plants rich in biologically active chemical compounds have proven their antimicrobial, antiviral and antiparasitic potential in *in vitro* and *in vivo* studies. The valorization of plant medical resources provides effective alternatives in the treatment of these diseases and against the resistance of infectious agents.

Keywords: Algeria, Anthelmintic, Antimicrobial, Antiviral, Herbal Medicine, Infectious Diseases, Ibn Hamadouch, Syphilis, Smallpox, Scabies, Traditional Pharmacopoeia.

INTRODUCTION

In recent years, numerous studies have investigated the biological potential of natural substances of plant origin. In parallel with these experimental studies, the ethnobotanical approach has led to a screening of plants used in traditional medi-

* **Corresponding author Djilali Tahri:** Laboratoire de Recherche des Sciences Fondamentales, Université Amar TELIDJI, Route de Ghardaïa, BP 37G, 03000 Laghouat, Algérie. Tel: 213698842162 E-mail: d.tahri@lagh-univ.dz

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cine to treat bacterial, fungal, parasitic or viral infections [1]. These substances are considered to be an important medical source to confront the emergence of pathogenic microorganisms resistant to antibiotics or antivirals. According to WHO estimates, around 80% of the populations of Africa, Asia, Middle East, and South America rely on herbal remedies for their primary health care needs [2].

From time immemorial, traditional pharmacopoeia has been developed from generation to generation by an accumulation of purely empirical knowledge until medieval times where scientific developments have improved pharmaco-medical knowledge based on clinical observations and pharmacological tests, thus allowing the appearance of a large number of more or less complex therapeutic formulas, consisting mainly of substances of plant origin and sometimes of animal or inorganic origin. It has also allowed the exploitation of countless plant substances around the world depending on the region of harvest and the desired properties. Medicinal plants were considered a repository of high value for pharmacological research in the early nineteenth century with the aim of isolating pharmacologically active compounds. Later, traditional medicine was gradually discarded with the emergence of techniques for synthesizing active ingredients [3, 4].

In Algeria, traditional pharmacopoeia was enriched by the practical knowledge of the ancient Berber people and the influences of Islamic medicine. In the nineteenth century, healers who practiced medieval medicine still used manuscripts of Avicenna, Rhazes, Dawud Al-Antaki and Ibn elBeitar to prepare their therapeutic formulas. Medical practices in Algeria at this time lacked methodology and scrupulous dosage and it was often associated with mystical and magical practices. However, this medicine was very successful in curing several diseases and gained the confidence of indigenous populations to this day [4, 5].

Recent Algerian ethnobotanical investigations have shown a large number of medicinal herbs used by herbalists from different regions, but these studies have not investigated treatments for infectious diseases based on plant substances. These studies on traditional pharmacological knowledge show to some extent the current state of this knowledge among Algerian populations and more specifically among herbalists and traditional healers. The current state of this declining knowledge reflects the influences of socio-economic progress on the ancestral heritage of natural substances uses in the treatment of contagious diseases.

In this chapter, herbal substances from traditional Algerian pharmacopoeia used in the treatment of infectious diseases have been investigated from the ancient literature of the eighteenth and nineteenth centuries, where the relationship between man and his environment was still strong. At that time, traditional medicine was the only refuge for Algerians to treat their patients, medicine that is generally effective and trustworthy despite the lack of specific principles in the rational composition of drug mixtures.

ORIGINS OF ALGERIAN PHARMACOPOEIA

In Algeria, as in all the Maghreb countries, the traditional pharmacopoeia has been enriched since the dawn of time by an accumulation of purely empirical knowledge in a non-systematic way and by the scientific heritage of Chaldea to Muslim civilization. Therefore, two modes of use of medical material exist either following the practices of local populations according to their empirical experiences limited by the availability of ingredients, or by resorting to practitioners who recommend therapeutic formulas obtained from old manuscripts or from their own composition.

Scientific Knowledge

The people of Mediterranean basin have long used primitive medicine from the time of the Chaldeans and then the Greeks. At the height of Muslim civilization, Greek works were translated and widely studied to deepen knowledge, develop new theories, and implement new techniques. However, practices since Chaldea such as Kahane or the priestly and divinatory method are still used until recent times. Also, until the nineteenth century, the humoral theory was still the galenic doctrine among healers in Algeria [6].

On the arrival of Islam, the Prophet Muhammad by his recommendations and his speech (Hadith) was considered the first physician in Islam, and to this day, healers and practitioners quote his words and verses from the Quran to add spiritual value and a sort of confidence to their remedies or components of their formulas. Among the recommendations of the Prophet, “If you hear of an outbreak of plague in a land, do not enter it; but if the plague breaks out in a place while you are in it, do not leave that place” and “Nigella seed is a remedy for every disease except death” [4, 7].

The healers in Algeria called Tebib, Taleb, Achab or Amdaoui until the nineteenth century used ancient medico-pharmaceutical literature and used ancient manuscripts of Avicenna's Canon, El-Jamî of Ibn elBeithar, Tadhkira of Dawud Al-Antaki, El-Harouniya of Massih Ibn Hakim and Kitab Errahma of Essoyouti. The influences of Greek works were also noticed in their writings and prescriptions, so these are the aphorisms of Hippocrates and the works of Galen (called elHakim elYounani), Aristotle and Dioscorides [4, 6, 7].

CHAPTER 6

Traditional Chinese Medicine for Treating Infectious Diseases: History, Progress, and Perspectives

Zehua Jin[1,2], Yunru Yu[2], Bin Qu[3], Yu Wang[1], Han Zhang[1] and **Yi Wang[2,4,*]**

[1] *State Key Laboratory of Component-based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China*

[2] *Pharmaceutical Informatics Institute, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, China*

[3] *Biophysics, Center for Integrative Physiology and Molecular Medicine (CIPMM),School of Medicine, Saarland University, Homburg, Germany*

[4] *Innovation Institute for Artificial Intelligence in Medicine of Zhejiang University, Hangzhou, China*

Abstract: Infectious diseases impose global challenges to public health. Infectious diseases can be caused by various pathogens, such as bacteria, parasites, fungi, or viruses. Over 1 million people worldwide die from viruses such as HIV, hepatitis C or B virus (HCV or HBV) in 2016. Recent outbreaks of Zika, Ebola and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) bring serious threats to global health security. On account of the high probability of an unpredictable virus pandemic, there is an urgent need for broad-spectrum antiviral drugs. Herbal medicine (HM) is a valuable source for the treatment of infectious diseases. A conventional traditional Chinese medicine (TCM) treatise 'Shanghan Zabing Lun', which recorded over 200 herbal formulae (known as Zhongjing's formulae), also known in English as the 'Treatise on Cold Damage Diseases' has a history of around 1800 years. However, these ancient TCM formulae and theories are rarely used in nowadays methodologies for developing curative from HB. In this perspective review, we summarize the ancient theory of herbal medicine for treating infectious diseases including flu and malaria. The novel strategies for developing novel anti-infection drugs by modern integrated techniques for example, knowledge mining, high-content screening, phenotypic assays are also discussed, which will shed light on revealing novel properties and biological functions of phytochemicals inspired by ancient medical knowledge.

* **Corresponding author Yi Wang and Han Zhang:** Pharmaceutical Informatics Institute, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, China; E-mail: zjuwangyi@zju.edu.cn and State Key Laboratory of Component-based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China; E-mail: zhanghan0023@126.com

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Keywords: Active compounds, COVID-19, Herbal medicine, Infectious diseases, Influenza, Knowledge discovery, Pharmacology, Shanghan Zabing Lun, Traditional Chinese medicine, Zhongjing's formulae.

INTRODUCTION

Infectious diseases occur when the host is invaded by pathogenic microorganisms, for example, viruses, chlamydia, mycoplasma, rickettsia, bacteria, spirochetes, fungi, and parasites. Pathogens enter the host to live, grow and multiply. Entrance of pathogens is normally through the mucosa in the mouth, eyes, nose, genitals, or open wounds especially on the skin. Then pathogens release toxic substances, causing different degrees of pathological changes in the body and interfering with the normal function of the immune system [1]. For thousands of years, infectious diseases have been the main diseases that endanger human health. Compared with the progress in the prevention of non-communicable diseases such as cancer, diabetes, cardiovascular diseases in recent years, the progress in the prevention and control of communicable infectious diseases is rather insufficient. Especially in low-and middle-income countries and regions, effective infectious disease interventions are a huge challenge for the health system [2], leaving infectious diseases an important public safety issue that causes not only human deaths but also affects economic and social development. The statistics from World Health Organization (WHO) show that lower respiratory tract infections are the deadliest infectious disease, costing 3 million lives worldwide in 2016. The death rate of diarrheal diseases decreased by nearly 1 million between 2000 and 2016, but it still caused 1.4 million deaths in 2016. Although AIDS is no longer one of the top ten causes of death in the world, it still killed 1 million people in 2016, compared with 1.5 million in 2000 [3]. Of note, as of 15 May 2021, the pandemic of COVID-19 (Corona Virus Disease 2019) has costed more than 3 million lives worldwide, according to the WHO [4]. This ongoing pandemic spotlights the urge for adequate and effective response measures, especially upon exposure to unknown and/or deadly infectious diseases.

CHALLENGES IN THE PREVENTION OF INFECTIOUS DISEASES

Emerging infectious diseases refer to newly-emerging infectious diseases or infectious diseases that already exist but have a rapid increase in incidence due to drug resistance or mutations [5]. The discovery of new infectious diseases mainly falls into three categories: firstly, previously existing diseases are re-defined due to the discovery of pathogens; secondly, past non-communicable diseases are classified as infectious diseases due to new discoveries of the cause; thirdly, infectious diseases that have newly occurred due to complex reasons such as pathogen mutations [6]. Since 2000, there have been 2525 outbreaks of new infectious diseases recorded by the WHO [7], including new major infectious diseases such as COVID-19, Ebola, avian influenza (H7N9), and Middle East respiratory syndrome (MERS), H1N1, and severe acute respiratory syndrome (SARS). The spread of diseases that have been controlled in the past such as syphilis, cholera, tuberculosis, and infectious diseases such as dengue fever, influenza, AIDS still exists. Because of its uncertainty and unpredictability, new infectious diseases may cause extremely high mortality rates and have a huge impact on social stability and economic development. The very recent example is COVID-19 featuring acute pneumonia in critical cases that broke out in 2019 and then quickly transmitted to more than 100 countries and regions worldwide. COVID-19 is a severe acute respiratory syndrome caused by SARS-CoV-2, a type of coronavirus, to which family the viruses cause SARS and MERS also belong [8]. Up to now (15 May 2021), more than 160 million cases infected with SARS-CoV-2 have been confirmed. For prevent spread of COVID-19, many countries and regions have implemented full or partial lockdown as well as international travel restrictions. Effective drugs to prevent the disease from worsening to critical/sever stages are still under development.

This pandemic highlights the threat of newly emerging infectious diseases to society and the challenges to the health care system:

1. Lack of effective drugs. For emerging infectious diseases, the key is to identify the responsible pathogens in a timely manner. It was difficult before, for instance in 2003 the coronavirus-caused SARS was identified only many months later. Thanks to the advanced sequencing techniques, it is technically feasible now in a few days. Nevertheless, it remains very challenging to develop effective drugs against this newly identified virus despite the devotion of pharmaceutical companies and the academy.

2. Pathogen mutation. Pathogens can mutate due to changes in the host, environmental conditions or genetic factors, thereby enhancing the emergence and recurrence of infectious diseases. For example, due to the lack of correction mechanism of RNA polymerase, the replication error rate of influenza virus is relatively high, so the influenza virus can produce a large number of mutations [9], which often leads to the failure of existing vaccines. Concerning SARS-Co--2, numerous mutations have been identified, which show already resistance to the available vaccines (ref).

3. Drug resistance. The abuse of antibiotics has led to an increasingly serious problem of bacterial resistance. Antibiotics impose evolutionary pressure on bacteria, which rapidly reproduce. This leads to evolutionary changes through random genetic mutations, selective survival advantage of which enables bacteria to acquired drug-resistance [10]. Currently, infections with resistant pathogens

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Ferid Murad *(Nobel Laureate)*

Ferid Murad is the winner of the 1998 Nobel Prize in Physiology or Medicine. He received his MD and pharmacology Ph.D. degrees from Case Western Reserve University in 1965. He has 131 international publications in the field of physiology, medicine, and pharmacology. He was awarded the Ciba Award Recipient in 1988 and Albert Lasker Basic Medical Research Award in 1996.

He was the Vice President, Pharmaceutical Research & Development, and Corporate Officer in Abbott Laboratories, USA during 1990-92. He was the CEO/President, Molecular Geriatrics Corporation, USA during 1993-95. Currently he is Senior Research Advisor at the Palo Alto Veterans Hospital, California, USA.

Atta-ur-Rahman, *FRS*

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.

Ka Bian

Dr. Bian's research has been focused on NO / cGMP signaling. Through the research on human adult and/or embryonic and cancer stem cells, Dr. Bian has proposed that NO/ cGMP signaling exerts its pathologic effects with two major mechanisms: Up-stream iNOS centered pathway is involved in the enhanced pro-inflammatory status that is key element for cellular damage and cancer micro-environment formation. Down-stream sGC / cGMP mediated pathway is responsible to proliferation, differentiation and self-renewal of stem/cancer cells. Dr. Bian is expanding the research into the area of cancer metastasis and therapeutic resistance since deciphering the role of NO-sGC signaling would facilitate development of strategies to interfere with malignant and metastasis processes.