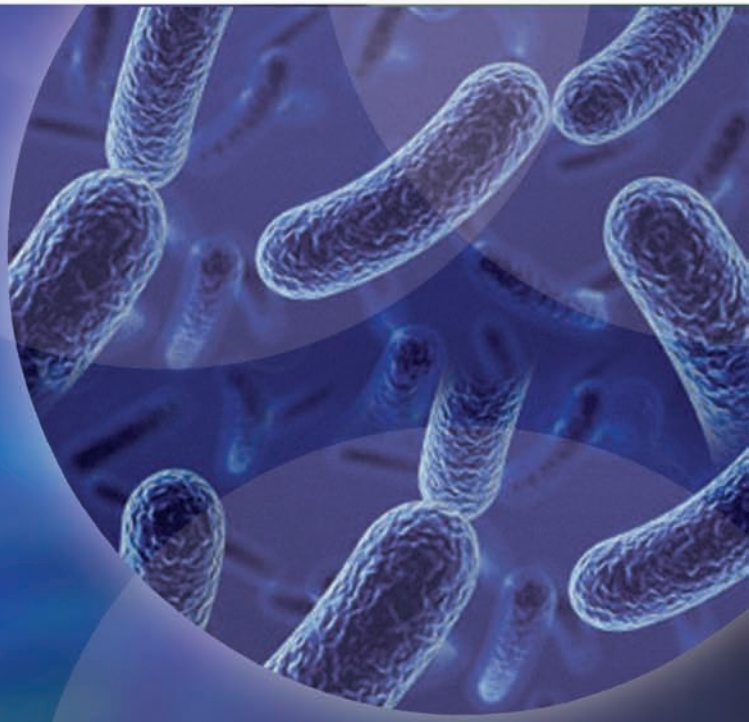
Frontiers in Clinical Drug Research

(Anti Infectives)



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Bentham Books

Frontiers in Clinical Drug Research - Anti-Infectives

(Volume 9)

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Frontiers in Clinical Drug Research-Anti Infectives

(Volume 9)

Editor: Atta-ur-Rahman, *FRS*

ISSN (Online): 2352-3212

ISSN (Print): 2452-3208

ISBN (Online): 978-981-5179-81-1

ISBN (Print): 978-981-5179-82-8

ISBN (Paperback): 978-981-5179-83-5

First published in 2024.

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PREFACE

The 9th volume of ***Frontiers in Clinical Drug Research – Anti-Infectives*** comprises five chapters that cover several important topics, including the role of mature drugs in COVID-19, antivirals to treat COVID-19, ribosomally synthesized bacteriocins as potent anti-infective agents and natural anti-infective agents.

In Chapter 1, Haller *et al*., discuss the potential positioning of three mature innovative drugs—OM-85, calcium dobesilate, and its salt form, etamsylate. These drugs have demonstrated anti-viral and anti-inflammatory properties, which could be of potential use for the treatment of COVID-19. Bhattacharyya, in Chapter 2, addresses the issues associated with available antivirals, including their modes of action, adverse effects, and drug interactions.

Elkhateeb *et al*., in Chapter 3, highlight the importance of bacteriocins as anti-infective agents, describing their common mechanisms of action and recent clinical and therapeutic applications. Bhattacharyya *et al*., in the next chapter, summarize the relationship between oxidative stress, viral infection, and various therapeutic strategies involving antioxidants. Finally, Padwad *et al*., in the last chapter of the volume, discuss phytomolecules, their biological potential, and how these molecules regulate innate and adaptive immune responses in infectious diseases.

I would like to thank all the authors for their excellent contributions, which should be of great interest to readers. I am also grateful for the timely efforts of the editorial personnel, especially Mr. Mahmood Alam (Editorial Director), Mr. Obaid Sadiq (In-charge, Books Department), and Miss Asma Ahmed (Senior Manager, Publications) at Bentham Science Publishers.

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CHAPTER 1

The Place of Mature Drugs in COVID-19 Era

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Abstract: COVID-19 infection, caused by the SARS-CoV-2 virus, is associated with substantial morbidity and mortality. COVID-19 infection has three distinct phases: 1, early infection phase; 2, pulmonary phase; and 3, the hyperinflammatory phase. Despite a major focus on vaccines and new therapeutics, existing drugs sharing some known mechanistic with this virus, have also gained interest. The potential positioning of three mature innovative drugs, which could be of potential use in this pandemic environment, is discussed in this chapter: OM-85 and calcium dobesilate, and their salt form etamsylate, have revealed anti-viral and anti-inflammatory properties. OM-85, a bacterial extract originating from 21 pathogenic strains isolated from human lungs and indicated for the prevention of recurrent respiratory tract infections, stimulates both innate and adaptive immunity, resulting in non-specific loco-regional immune responses. It has shown anti-viral activity in a number of virus infection models, including influenza H1N1, rhinovirus, and more recently, coronaviruses. It has also shown some immunoregulatory properties. Accordingly, there is a rationale for further investigations on OM-85 to be used as prophylaxis for other respiratory infections and potentially in long-COVID. For calcium dobesilate, currently indicated for the treatment of microvascular diseases while preserving microvascular integrity *via* antioxidant and anti-inflammatory properties, there are cumulating data that could promote its potential use for the treatment during phase 2 to protect the vascular endothelium. Calcium dobesilate has anti-viral properties and was recently shown to interfere with the SARS-CoV-2 spike-protein binding to the ACE2 receptor. Accordingly, one could also postulate to use it during phase 1. Etamsylate, an anti-haemorrhagic and antiangiogenic agent that improves platelet adhesiveness and restores capillary resistance, is indicated for the prevention and treatment of capillary haemorrhages. Considering its mechanism of action, etamsylate could be envisage for use as potential treatment during phase 3 for viral-induced complications. Importantly,

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none of these afore mentioned drugs are currently approved for the prevention or treatment of SARS-CoV-2 viral infection. Further, the conduction of well-designed clinical trials is warranted.

Keywords: Angiogenesis, Bacterial Lysate, Calcium Dobesilate, Cell Attachment, Cell Entry, Comorbidities, Coronavirus Disease 2019, COVID-19, Drug Repurposing, Etamsylate, Immune System, Immunotherapy, Inflammation, Infection, OM-85, Respiratory Tract Infection, RTI, SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2, Vascular Endothelium.

INTRODUCTION

The global coronavirus disease 2019 (COVID-19) pandemic, which was declared by the World Health Organization (WHO) on 11 March 2020 [1], is an ongoing infectious respiratory disease caused by the recently identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. SARS-CoV-2, a novel coronavirus, originated in the city of Wuhan, the capital of Hubei Province in China, at the end of 2019, and caused an outbreak of unusual viral pneumonia [2]. Due to its high transmissibility, the virus spread rapidly throughout China and thereafter to the rest of the world [3], resulting in a global pandemic [4].

Although initially identified as viral pneumonia, with symptoms of cough, fever, and dyspnoea plus bilateral lung infiltration in more severe cases [5, 6], COVID-19 has a broad range of clinical manifestations [6, 7]. Cases include asymptomatic infection, mild upper respiratory tract infection (URTI), pneumonia, and severe disease with complications including acute respiratory distress syndrome (ARDS), RNAaemia, acute cardiac injury, and secondary infection, which result in death in many cases [6 - 8]. SARS-CoV-2 RNAaemia and plasma viral RNA load are associated with critical illness, indicating that uncontrolled viral replication may play an important role in the pathogenesis of COVID-19 [8]. However, compared with other respiratory viruses, such as SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), the viral load of SARS-CoV-2 at the time of infection does not always correlate with the severity of COVID-19 disease [9]. There is also evidence that the clinical manifestation of COVID-19 and its associated comorbidities vary between geographic locations, with the highest prevalence of comorbidities seen in the USA, the greatest severity of COVID-19 seen in Asia, and the highest mortality seen in Latin America and Europe [10]. In addition, a number of genetic variants have emerged, with some labelled as variants of concern due to their potentially greater transmissibility, increased morbidity and/or mortality, and resistance to antibodies or vaccines [11].

In addition to the rapid development of vaccines to prevent SARS-CoV-2 infection and transmission, drug repurposing has been a major focus of research during the pandemic to find agents that would be suitable for both the prevention [12 - 15] and the treatment [13 - 22] of COVID-19. Agents investigated or proposed as treatment options have included anti-cancer agents [23], anti-virals [17, 21, 24], heparin [14, 25], immunomodulators [13, 17], anti-inflammatory drugs [13, 17], and kinase inhibitors [15]. The anti-viral remdesivir, an inhibitor of the viral RNA-dependent RNA polymerase, was originally developed for the treatment of Ebola [26]. It was shown to be effective for the treatment of COVID-19 in a randomised, double-blind, placebo-controlled, phase 3 study of patients with lower RTI (LRTI), reducing the recovery time [27]. Remdesivir was approved by the U.S. Food and Drug Administration (FDA) in May 2020 for the treatment of adults and children with COVID-19. On 24 June 2021, the FDA issued an emergency-use authorisation (EUA) for the monoclonal antibody tocilizumab for the treatment of hospitalised adults and paediatric patients (2 years of age and older) who were receiving systemic corticosteroids and required supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. The FDA has also issued other EUAs for several monoclonal antibodies for the treatment of mild or moderate COVID-19 in adults and paediatric patients (aged 2 years and older, weighing at least 40 kilograms) with positive results upon direct SARS-CoV-2 viral testing, who are at high risk for progressing to severe COVID-19 and/or hospitalisation. The anticoagulant effects of heparin/low molecular-weight heparin are thought to be responsible for its beneficial effects on mortality [25]. The glucocorticoid dexamethasone has been shown to improve survival in COVID-19 patients who require oxygen, particularly those who need mechanical ventilation [28]. The use of oral or injectable dexamethasone in patients with COVID-19 who require supplemental oxygen therapy was endorsed by the European Medicines Agency (EMA) on 18 September 2020 [29]. Another glucocorticoid, budesonide, was shown to reduce the time to recovery and hospital admission compared with usual care if administered within 7 days of the onset of mild COVID-19 symptoms in a randomised, controlled, open-label, phase 2 clinical study [30]. However, in 2021, the EMA's COVID-19 taskforce (COVID-ETF) pointed out that there was currently insufficient evidence that inhaled corticosteroids were beneficial for outpatients with COVID-19 [31]. Attention should be paid to the duration of corticosteroid therapy and the potential side effects of prolonged use, such as pulmonary fibrosis [32]. Guidelines on the use of corticosteroids were issued by the WHO in 2020, which included a strong recommendation for a 7-10-day course in patients with severe or critical COVID-19 and a conditional recommendation that they should not be used in patients with non-severe COVID-19 [4].

CHAPTER 2

Antivirals to Treat COVID-19

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Abstract: Introduction: COVID -19, caused by the novel coronavirus or SARS-CoV2, has claimed thousands of lives across the world as well as in India as of now. There are many antivirals available to treat COVID-19 at present. Some of them are safe and effective, while many others have been banned by the World Health Organization. Hence, it is very important for clinicians and nurses to know accurately and precisely about the safe and effective antivirals to treat COVID-19. Materials and methods: The purpose of this chapter is to address the issues with available antivirals, their modes of action, adverse effects, and drug interactions. Literature search has been carried out meticulously. Conclusion: Many options are available for treating COVID-19, but treatment needs to be tailored according to the situation.

Keywords: Antivirals, Adverse effects, COVID-19, Dose, Interactions.

INTRODUCTION

The COVID-19 pandemic, caused by the Novel Coronavirus or SARS-CoV2, is now raging across the world. It started way back in December 2019 with several cluster cases of pneumonia in Wuhan City, Hubei province, China, and was recognized in March 2020 as a full-blown Pandemic by the World Health Organization (WHO). The second wave of infections has been particularly severe in India, which is now declining, and the third wave is underway. The overall case-fatality rate was 1.4% in COVID-19 in the early part of the pandemic, with the daily case fatality rate crossing the 1% mark now [1]. This case-fatality rate is now in the range of 1.1%-1.2%. Currently, India's case fatality rate is persisting at about 1.1% to 1.14% [1]. USA and Brazil have so far reported most deaths due to COVID-19, followed by India, Mexico, and Russia. By the end of June 2021, however, the total officially recorded death toll in India due to COVID-19 stood at 2,46,171, which is indeed a grim figure by any standards [2]. This figure has now crossed 500000 deaths in India alone.

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Even taking the world figures into account, by now, more than 5.05 million people have succumbed to the deadly COVID-19 infection since 2020 [3]. The health systems of all countries are hence being stretched to their maximum limits and tested, and healthcare professionals are fighting their best against this pandemic. With subsequent waves of the pandemic, many new mutants and variants of the SARS-CoV2 virus have emerged, raising severe concerns about treatment and vaccination options. Some of these are variants of interest, whereas others are variants of concern. For example, till now, the Delta plus variant of concern (VOC) had been of tremendous public health importance, along with the newly emerged Omicron variant at present. New mutants and variants generally tend to be more contagious than older ones, but the severity or mortality attributed to them may be lesser.

Many antiviral agents and other drugs have been used so far by clinicians to treat COVID-19, albeit all with variable efficacy and safety profiles. Many antiviral agents have already been tested in this regard. Novel categories of drugs are also being employed in numerous trials desperately in an effort to contain this devastating pandemic. These include Remdesivir, protease inhibitors like Lopinavir, Ritonavir, Ribavirin, and numerous other drugs and molecules. Even drugs like Ivermectin have been widely used as repurposed molecules, but there needs to be widespread information about their safety and efficacy before such large-scale use is either encouraged or recommended. Some monoclonal antibodies and signal blocking molecules are also considered to be antivirals against SARS-CoV2 because they can effectively stall the disease process initiated by the virus. All of these molecules have different modes of action. Hence, it is very important for clinicians and other healthcare professionals to keep themselves abreast of the dosage, adverse effects, drug interactions, and mechanisms of action of all these drugs, and when to use them and when not to. Hence, this chapter is aimed to collate information in all these aspects. The scope of this chapter is thus to provide the readers an insight into the existing and upcoming modalities of therapy in COVID-19. As far as feasible, all antiviral and other treatment options have been emphasized and highlighted here.

REPLICATION INHIBITORS AND PROTEASE INHIBITORS

Remdesivir

Introduction And Mechanism Of Action

Because of its ability to inhibit SARS-CoV-2 *in vitro*, Remdesivir (GS-5734), an inhibitor of the viral RNA-dependent RNA polymerase with inhibitory activity against SARS-CoV-1 and the Middle East respiratory syndrome (MERS-CoV),

was identified early as a promising novel therapeutic candidate for COVID-19 [4]. As of October 22, 2020, Remdesivir, an antiviral agent, is the only drug fully approved by USFDA for the treatment of COVID-19. In trials, a 10-day course of Remdesivir was superior to a placebo in the treatment of hospitalized patients with Covid-19 [4]. It is indicated for the treatment of COVID-19 disease in hospitalized adults and children 12 years and older, who weigh at least 40 kgs [5]. An emergency use authorization (EUA) is also in place for treating pediatric patients who weigh 3.5 kg to less than 40 kg or children younger than 12 years who weigh at least 3.5 kg, with Remdesivir [5]. Remdesivir is an intravenous nucleotide prodrug of an adenosine analog. Remdesivir binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by means of premature termination of the RNA transcription. It has earlier demonstrated appreciable inhibitory activity against the causative agent of COVID-19, SARS-CoV2 [6]. However, given the high case-specific mortality despite the use of Remdesivir in clinical trials, it is apparent that treatment with this antiviral drug alone is not likely to be sufficient for all COVID-19 patients [4]. It has to be administered along with Oxygen in admitted patients. However, recently Remdesivir has been prohibited by the WHO (World Health Organization) for lack of adequate efficacy data.

Dose

Timing of therapy: Therapy must be instituted between days 5 and 10 of fever to obtain optimum results. The recommended dose used in most trials is 200 mg intravenously as a loading dose on day 1, followed by 100 mg daily for up to 9 more days.

Adverse Effects

Remdesivir can cause gastrointestinal upset (like nausea), elevated hepatic transaminase enzyme levels, an increase in Prothrombin Time (but with no change in the International Normalized Ratio), and hypersensitivity reactions [6]. Hence, it should be administered carefully and judiciously.

Drug Interactions

Chloroquine or hydroxychloroquine may diminish the antiviral activity of Remdesivir. Hence, coadministration of these drugs with Remdesivir is not advisable. However, till now, there has been no reported reaction with coadministered Dexamethasone [7].

CHAPTER 3

Ribosomally Synthesized Bacteriocins as Potent Anti-infective Agents, Their Medical and Pharmaceutical Applications

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Abstract: The development of multidrug-resistant bacteria (MDRB) and the emergence of new lethal diseases have raised the need for potent anti-infective agents with different killing action mechanisms that contribute to treating and/or supporting the currently used drugs. For this purpose, bacteriocins are considered excellent candidates with promising potential. Bacteriocins are ribosomally synthesized antimicrobial peptides that are produced by many bacterial genera. They are characterized by high thermal stability, being active over a wide pH range, and having specificity against selected bacterial strains by employing specific receptors on their cell membrane, which encourages bacteriocins to use in clinical applications as support and/or alternatives currently used antibiotics. Interestingly, bacteriocins have many advantages over antibiotics, such as the relative difficulty of developing resistance compared to broad-spectrum antibiotics. Moreover, due to their simple biosynthetic mechanisms, bacteriocins can be easily bioengineered, which improves their activity or specificity against selected microorganisms. Additionally, bacteriocins originating from lactic acid bacteria have the extra safety advantage because many LAB and their products are classified by the American Food and Drug Administration (FDA) to be generally recognized as safe (GRAS). Bacteriocins have promising pharmaceutical potentials as anti-infective agents, anti-MDRB agents, antileishmanial, and antiviral agents. Moreover, bacteriocins have been used to treat many ulcers, tumors, and cancers. In this chapter, we highlight the importance of bacteriocins as anti-infective agents, describing their common action mechanisms and recent clinical and therapeutical applications of bacteriocins. Finally, prospects in this field are discussed to discover and develop more diverse and efficient bacteriocins with potent anti-infective activities.

Keywords: Action mechanism, Anti-infective, Bacteriocins, Biosynthesis, Oral care, Resistance, Skin infections, Spermicide, Systemic infections, Veterinary applications, Woman's care.

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INTRODUCTION

Bacteriocins are those bacterial peptides that are synthesized by ribosomes. Many works of the literature suggest that nearly all bacteria (both Gram-positive and Gram-negative bacteria) produce bacteriocins under certain conditions and can be detected using suitable techniques [1, 2]. However, bacteriocins produced by lactic acid bacteria (LAB) have been involved in biotechnological and food-related applications intensively compared to those secreted by other bacterial groups. Most LAB and their products are 'generally recognized as safe (GRAS) [3, 4].

Bacteriocins are a heterogeneous group of peptides that were discovered about 100 years. The continuous discovery of novel bacteriocins and advances in their identification and characterization have increased the need for LAB bacteriocins classification, which may make their study easier. Klaenhammer proposed the basis of LAB bacteriocins classification [5]. He suggested four classes of bacteriocins as follows; class I, post-translationally modified peptides; class II, unmodified small (<10 kDa), heat-stable peptides; class III, for unmodified large (>30 kDa), heat-labile proteins; and class IV, complex proteins, which include lipid or carbohydrate moieties. All following classification schemes excluded class IV. On the other hand, Nes *et al.* modified class IIc to include bacteriocins containing a typical single peptide and those secreted by the sec-pathway of the cell [6]. Later, Cotter *et al.* suggested a different classification scheme [2] by classifying LAB bacteriocins into two major classes, as shown in Table **1**. In another classification model by Alvarez-Sieiro *et al.*, LAB bacteriocins were similarly classified into 3 classes with some modifications, where class I included the lanthipeptides, cyclized peptides, linear azol(in)e-containing peptides, glycocins, and lasso peptides, while class II bacteriocin was divided into pediocin-like bacteriocins, two peptide bacteriocins, leaderless peptides, and non-pediocin-like single peptides. Finally, class III contained all thermo-labile bacteriocins, including bacteriolysins and non-lytic peptides [7]. However, in a recent classification system proposed by Acedo *et al.*, the leaderless bacteriocins were removed from class IId and were put in subclass (IIc) instead of the circular bacteriocins. In contrast, class III bacteriocins remained to contain large, heat-labile bacteriocins but were reviewed and subdivided into bacteriolysins, non-lytic large bacteriocins, and tailocins [8].

Comparing bacteriocins with conventional antibiotics revealed the promising characteristics of bacteriocins. Antibiotics are secondary metabolites, while bacteriocins are ribosomally-synthesized peptides. Also, bacteriocins have a simpler biosynthetic mechanism which facilitates their bioengineering to improve their activity or alter it to target specific microbes. Bacteriocins show higher

thermal stability and remarkable activity over a wide pH range. Also, bacteriocins have promising applications in food and clinical fields [23]. Moreover, some bacteriocins have high specificity against clinical pathogens, such as multi-dru--resistant strains (MDR) [2].

Table 1. Classification of LAB bacteriocins as proposed by Cotter *et al.* [2].

Class	Characteristics	Examples	References
Class I	Lantibiotics Small (<5 kDa), heat-stable, contain post-translationally modified amino acids such as lanthionine, 3-methyllanthionine, and dehydrated amino acids	Nisin A Nisin Q Nisin Z	Gross and Morell, [9] Fukao *et al*., [10] Mulders *et al*., [11]
Class II	Non-Lantibiotics Small (<10 kDa), heat-stable, do not contain post-translationally modified amino acids, further divided into 4 subclasses:	-	-
	IIa: Pediocin-like bacteriocins	Pediocin PA-1 Enterocin A	Henderson *et al*., [12] Aymerich *et al*., [13]
	IIb: Two-peptide bacteriocins	Lactococcin G Lactococcin Q Plantaricin EF	Nissen-Meyer *et al*., [14] Zendo *et al*., [15] Anderssen *et al*., [16]
	IIc: Circular bacteriocins	Enterocin AS-48 Lactocyclicin Q	Gálvez *et al*., [17] Sawa *et al*., [18]
	IId: Non pediocin-like single linear bacteriocins	Lactococcin A Lactococcin B Lacticin Q Lactococcin Z	Holo *et al*., [19] van Belkum *et al*., [20] Fujita *et al*., [21] Ishibashi *et al*., [22]

Bacteriocins have unique action mechanisms that result in their relatively narrow antimicrobial spectrum. These mechanisms decrease the chances of developing resistance against bacteriocins compared to antibiotics [24, 25]. All these attractive characteristics have encouraged studying bacteriocins and investigating the possibility of employing them in different biotechnological applications. For this purpose, this chapter aims to describe the importance of bacteriocins as anti-infective agents and their common killing mechanisms. Moreover, it highlights the clinical and therapeutical applications of bacteriocins. Finally, it discusses prospects to discover and develop more diverse and efficient bacteriocins with potent anti-infective activity potentials.

CHAPTER 4

Therapeutic Interventions Against Free Radicals in Viral Diseases

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Abstract: The delicate balance between oxidants and antioxidants is a dynamic process, and when it hampers, oxidative stress occurs. Oxidative stress is now suggested to have a direct correlation with a viral infection, which in turn induces several oxidants like nitric oxide radicals, superoxide anions, hydroxyl radicals and their by-products (*viz*. hydrogen peroxide). All of these oxidants and their by-products contribute to viral pathogenesis and ultimately cause infectious diseases. The consequences of viral diseases account for considerable economic loss worldwide. In response to this, the scientific fraternity throughout the world is investigating the basic mechanisms underlying such diseases, as well as identifying novel therapeutic strategies for the prevention and treatment of such maladies. Over the last few decades, scientists oriented their research aims mostly towards elucidating the immunological basis of viral replication and pathogenesis, but a little is written about the implications of such research for drug development, which provides the impetus behind the creation of the present chapter enabling the readers to have a comprehensive overview on the involvement of free radicals in viral diseases along with latest updates towards developing novel therapeutic strategies against these diseases. The present chapter summarizes the relationship between oxidative stress, viral infection, and a variety of therapeutic strategies conferred by antioxidants. Antiviral therapeutic strategies based on antioxidants are considered to be a promising area of research against viral infections.

Keywords: Antioxidants, Antiviral therapeutics, Dengue, Free radicals, Hepatitis C Virus, Human Immunodeficiency Virus, Immunomodulation, Inflammation, Influenza, Japanese encephalitis, Proinflammatory cytokines, Reactive oxygen species, Reactive nitrogen species, SARS-CoV-2, Viral pathogenesis.

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INTRODUCTION

Oxidative stress is an indispensable means of defense against viral infection. At the very early stages of a virus-induced immune response, the infected cells of our body get eliminated through free radical-mediated apoptosis or necrosis. But, if unchecked, this virus-induced oxidative stress can be deleterious for both infected and normal cells. The host defense system, upon virus infection, induces phagocytosis through macrophages, dendritic cells, and neutrophils, releasing tumor necrosis factor (TNF) and interleukin-1 (IL-1), which can cause mutations during viral replication, thereby increasing the virulence of the virus [1 - 3]. Oxidative stress due to the generation of free radicals is considered harmful due to its cell-damaging effects. A variety of cellular defensive measures, the so-called "army of antioxidants," is in place to maintain the balance between pro-oxidants and antioxidants in our body. The mutual interaction between a virus and a host is essential in developing an effective antiviral strategy to control viral infection. A virus possesses a unique ability to utilize a variety of metabolic processes of its host for the successful completion of its own life cycle. These virus-induced modifications in the host cell metabolism have been shown to induce oxidative stress inside the host cell, creating an imbalance between free radical production and antioxidant defense system, and thereby disrupting normal cellular physiology. A plethora of research articles gave emphasis on the virus-induced oxidative stress as one of the major pathogenic mechanisms for inflammatory response and tissue injury by a viral infection. In this context, the present chapter is aimed for better understanding of the relationship between virus-induced oxidative stress and antiviral response of a host cell as well as the effective therapeutic strategies to combat various viral diseases [4].

GENERATION OF REACTIVE SPECIES AND NON-RADICAL OXIDANTS AND ITS IMPLICATIONS IN THE BODY

Reactive species (RS), comprise of reactive oxygen species (ROS) and reactive nitrogen species (RNS), are molecules with one or more unpaired electrons in their outer shell. Some of the ROS include hydroxyl ($OH^{\bullet}$), superoxide ($O2^{\bullet -}$), peroxyl ($ROO^{\bullet}$), lipid peroxyl ($LOO^{\bullet}$), lipid peroxide (LOOH), hydrogen peroxide (H_2O_2), ozone (O_3), singlet oxygen ($^1O_2$), hypochlorous acid (HOCl), *etc.*, whereas, nitric oxide ($NO^{\bullet}$), nitrogen dioxide ($NO_2^{\bullet}$), nitrous acid (HNO_2), peroxynitrite ($ONOO^-$) and dinitrogen trioxide (N_2O_3) are some of the examples of reactive nitrogen species. These reactive species are generated from infection, inflammation and immune cell activation, excessive exercise, mental stress, ischemia, aging, cancer, *etc.* (endogenous sources), or from smoking, alcohol intake, consumption of smoked meat, precooked oils, accidental uptake of heavy metals through food and water, use of certain drugs like cyclosporine, tacrolimus,

etc., industrial solvents and radiation (exogenous sources) [5]. Under the homeostatic condition, RS plays important roles in several biochemical and metabolic processes. Both innate and adaptive immune systems utilize this RS against pathogen infiltration into the host system. After interacting with a pathogen, phagocytes promote oxidative bursts to generate ROS that attacks pathogens. Adaptive immune response, which uses the pathogen-derived antigenic peptides produced by phagocytosis and digestion, is initiated if some pathogens escape the innate immune response. The antigenic peptide-mediated proliferation of T lymphocytes then occurs, producing numerous effector cells capable of eliciting an efficient and antigen-specific immune response [6 - 9]. But overproduction of RS with excessive inflammation harms tissues and may cause damage. As a result, an uncontrolled inflammatory response along with oxidative stress arises, which in turn stimulates inflammatory cells to produce excessive cytokines [10]. Reactive species mainly attack the polyunsaturated fatty acids, leading to a cascade of lipid peroxidation that alters the membrane permeability and function, as well as the immunity of the animal as a whole. ROS oxidizes the membrane lipid and results in the pore opening of the mitochondrial permeability transition (MPT), changes in the mitochondrial transmembrane potential and eventual cell death [11, 12]. Oxidation of cysteine-rich proteins alters its three-dimensional structure, resulting in protein aggregation and altered function. The highly reactive hydroxyl radical results in the formation of carbon-centered radicals, which can readily form alkoxyl radicals by reacting with molecular oxygen, leading to protein cross-linkage, fragmentation, and oxidation of other cellular macromolecules [13].

AN OVERVIEW OF THE ANTIOXIDANT DEFENSE SYSTEM OF OUR BODY

The antioxidant defense system of our body maintains cellular homeostasis by preventing excess reactive species generation and thereby limits the harmful effects of RS. The antioxidant defense system is categorized into two major groups: antioxidant enzymes (Superoxide Dismutase; SOD, Glutathione Peroxidase; GPx and Glutathione Reductase; GR, Catalase; CAT, *etc.*), and nutrient-derived antioxidants (*e.g.*, ascorbic acid, tocopherols carotenoids, glutathione, lipoic acid, *etc.*). Other minor groups include metal-binding proteins (*e.g.*, albumin, lactoferrin, ferritin, and ceruloplasmin) and antioxidant phyto-nutrients present in a wide variety of plant foods [14, 15].

Antioxidant Enzymes

Cells are protected against oxidative stress by an interacting network of antioxidant enzymes which are capable of protecting cells from oxidative stress

CHAPTER 5

A Comprehensive Detail of Natural Anti-Infective Agents

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Abstract: The immune response is an essential regulatory system designed to confer protective ability to hosts against various foreign challenges, including bacteria and viruses. However, self-perpetuation and over-aggravation of the immune system are also responsible for a variety of infectious diseases in humans. Phytochemicals are biologically active, non-nutritive, low molecular weight secondary metabolites that occur in different parts of plants and are well known for their various health-beneficial effects. The non-nutritional plant-based bioactive molecules are amongst the major groups responsible for a majority of immunomodulatory health benefits. These phytomolecules have been shown to possess a significant role in the regulation of various vital cell signaling pathways involved in the pathogenesis of various infectious diseases such as tuberculosis, hepatitis, pneumonia and dengue. Bioactive molecules may play an essential protective role in infectious diseases by interfering with innate and adaptive immune cell regulation, especially proinflammatory cytokine synthesis and cell activation. Considering this, nowadays, most of the natural products are processed and developed as immunomodulators and immunosuppressants for different infectious diseases. In this chapter, we will discuss phytomolecules, their biological potential, and how these molecules regulate innate and adaptive immune responses in infectious diseases. We will also discuss and compare the depth of knowledge available from previous works, which emphasize the importance of developing phytomolecules based preventive and therapeutic approaches as alternatives to synthetic counterparts in infectious diseases.

Keywords: Anti-viral, Clinical claims, Immunity, Infectious diseases, Natural molecules, Pre-clinical claims.

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INTRODUCTION

Infectious diseases have become a major concern of public health and are emerging in unprecedented ways worldwide [1]. This medical discipline is reported as the second foremost reason for death and the major cause of disability-adjusted life years globally [1 disability-adjusted life year is 1 lost year of healthy life] [2]. Infectious disease is an ailment that results from harmful pathogens such as viruses, fungi, parasites and bacteria and their noxious by-products. These diseases are contagious in nature and can transmit easily from one person to another through infected animals and fomites with varying degrees of transmission. To date, several types of infectious diseases have been discovered; however, a dramatic increase in the trend of viral as well as bacterial infection has been observed for a decade. This apparent inclination toward infectious disease patterns occurred due to the emergence of novel and highly morbific infections such as SARS-CoV-2, SARS, Ebola and West Nile virus [3, 4]. Several contributing factors have been identified in the initiation and progression of infectious diseases. Amongst them, changes in lifestyle, environmental conditions and microorganisms are recognized as major plausible aspects in the pathogenesis of infectious diseases [5]. The immune response is an essential regulatory system designed to confer protective ability to hosts against various foreign challenges, including bacteria and viruses. However, self-perpetuation and over-aggravation of the immune system are also responsible for a variety of infectious diseases in humans.

Regardless of the development of several antibiotics, infectious diseases still remain a substantial burden in healthcare, particularly in developing countries. Literature has reported that out of 57 million annual deaths, about 15 million [>25%] are allied with infectious diseases [5, 6]. Due to emerging new infectious diseases, high mortality rates and antimicrobial resistant, there is still a huge demand for alternative strategies that could be used to prevent infections of different origins.

The role of natural molecules from different sources, such as plants, marine and microbial, has gained attention for the prevention of infectious diseases [7]. Of these, medicinal plants have been considered a lead source of anti-infective agents for millennia. Several studies at the preclinical and clinical levels proved their relevance and potential for infectious diseases caused by bacteria, viruses and fungi [7 - 9]. Phytochemicals are biologically active, non-nutritive, low molecular weight secondary metabolites that occur in different parts of plants and are well known for their various health-beneficial effects. Phytomolecules have been shown to possess a significant role in the regulation of various vital cell signaling pathways involved in the pathogenesis of various infectious diseases such as

tuberculosis, hepatitis, pneumonia and dengue. Bioactive molecules may play an essential role in protective infectious diseases by interfering with innate and adaptive immune cell regulation, especially proinflammatory cytokine synthesis and cell activation. Considering this, nowadays, most of the natural products are processed and developed as immunomodulators and immunosuppressants for different infectious diseases. In this chapter, we will discuss infectious diseases, phytomolecules, their biological potential and how these molecules modulate infectious diseases. We will also discuss and compare the depth of knowledge available from previous works, which emphasizes the importance of developing phytomolecules-based preventive and therapeutic approaches as alternatives to synthetic counterparts in infectious diseases.

INFECTIOUS DISEASES

Infectious diseases have, for eras, been recognized as a threat to mankind. Though, an increase in life expectancy and a decrease in infectious disease mortality have been observed since 1950, which might be due to improvements in medical and healthcare systems in context to therapeutics and diagnostic strategies, availability of antibiotics, vaccines, nutrition and clean water [10, 11]. These diseases have become major challenges in terms of economic perspective due to their long-term regime burden and the emergence of new infectious diseases as well as causative agents. Infectious diseases are usually instigated by microorganisms. Different pathogens, namely bacteria, fungi, viruses, helminths, prions and protozoa, are known as causative agents of infectious diseases [12]. These diseases are mainly categorized as emerging and re-emerging infectious diseases [10]. Emerging infectious diseases mean newly established and recognized diseases whose global health influence had not been experienced in the past, such as AIDS and SARS-Cov-2. However, the term re-emergence is generally used for already experienced infections that reappeared in new geographical ranges in a more virulent form than existed previously, like the influenza A pandemic of 1918, 1957, and 1968 [2, 10, 13]. This concept of emerging infectious diseases gained consideration in the late 1960s to mid-1970s with the sudden advent of viral hemorrhagic fevers such as Ebola fever, Crimean-Congo hemorrhagic fever, and Lassa fever.

Burden of Infectious Disease

A significant and remarkable increase in the number of infectious diseases has occured over time. Reports have claimed approximately 1400 species of infectious agents that cause diseases in humans [14]. From 1904 to 2004, studies reported global emergence of 335 infectious diseases [15]. This increase trend has

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PROF. DR. ATTA-UR-RAHMAN, *FRS*

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has over 1559 international publications in several fields of organic chemistry (h index 76, citations 38,200) including 86 international patents, 70 chapters in books, 875 research publications, and 391 books (11 authored and 380 edited). 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.