List of Publications

- **Rani P**, Kapoor B, Gulati M, Gupta R. Nanoscale self-assembling prodrugs of sulfapyridine for treatment of arthritis: Harnessing the dual approach. **Medical Hypotheses** 2022;165:110896. Doi: 10.1016/j.mehy.2022.110896

- **Rani P**, Kapoor B, Gulati M, Atanasov AG, Alzahrani Q, Gupta R. Antimicrobial peptides: A plausible approach for COVID-19 treatment. **Expert Opinion on Drug Discovery** 2022;17(5):473-87. Doi: 10.1080/17460441.2022.2050693

- Kaur R, **Rani P**, Atanasov AG, Alzahrani Q, Gupta R, Kapoor B, Gulati M, Chawla P. Discovery and development of antibacterial agents: Fortuitous and designed. **Mini Reviews in Medicinal Chemistry** 2022;22(7):984-1029. Doi: 10.2174/1570193X19666211221150119

- Kapoor B, Gulati M, **Rani P**, Gupta R. Psoriasis: Interplay between dysbiosis and host immune system. **Autoimmunity Reviews** 2022 Aug 12:103169. Doi: 10.1016/j.autrev.2022.103169

- Kapoor B, Gulati M, **Rani P**, Kochhar RS, Atanasov AG, Gupta R, Sharma D, Kapoor D. Lycopene: Sojourn from kitchen to an effective therapy in Alzheimer's disease. **Biofactors** 2023;49(2):208-27. Doi: 10.1002/biof.1910

- Kapoor B, Kochhar RS, Gulati M, **Rani P**, Gupta R, Singh SK, Machawal L, Thakur A. Triumvirate to treat mucormycosis: Interplay of pH, metal ions and antifungal drugs. **Medical Hypotheses** 2022;159:110748. Doi: 10.1016/j.mehy.2021.110748

- Kapoor B, Singh A, Gulati M, Singh SK, **Rani P**, Alzahrani Q, Dua K, Dureja H, Corrie L. Orchestration of obesolytic activity of microbiome: metabiotics at centre stage. **Current Drug Metabolism** 2022;23(2):90-8. Doi: 10.2174/1389200223666220211095024

- Alzahrani QE, Gillis R, Harding SE, Pinto LH, Gulati M, Kapoor B, **Rani P**, Singh SK, Adams GG. Potential of the triad of fatty acids, polyphenols, and prebiotics from Cucurbita against COVID-19 in diabetic patients: A review. **Journal of Reports in Pharmaceutical Sciences** 2022;11(1):28-40. Doi: 10.4103/jrptps.JRPTPS_144_21

Pooja Rani 26/8/23
Signature of Applicant
Ms. Pooja Rani

Medical Hypotheses 165 (2022) 110896

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Nanoscale self-assembling prodrugs of sulfapyridine for treatment of arthritis: Harnessing the dual approach

Pooja Rani, Bhupinder Kapoor *, Monica Gulati, Reena Gupta

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India

ARTICLE INFO

Keywords:
Sulfapyridine
Nanoparticles
Self-assembling structures
Rheumatoid arthritis
Inflammation

ABSTRACT

Rheumatoid arthritis is a chronic, autoimmune, inflammatory joint disease, affecting mainly joints of hands, wrists, and knees. Although a number of potent drugs are available for the treatment of arthritis, the management of this life long disease becomes challenging because of their poor bioavailability, frequent administration, toxicity, instability and limitations related to their formulation development. Self-assembling nanoparticles are the emerging class of therapeutic drug delivery systems that have been explored in past few years for the treatment of various diseases. Intra articular administration of these systems prolongs the retention of drug in the target site by virtue of their size as well as two-steps release of the entrapped drugs (disassembly and then lysis of prodrug to release the active drug) and provide a sustained action which is desirable in this condition. Based on the prior reports, it is hypothesized that self-assembly delivery systems of sulfapyridine will provide an effective and sustained treatment of rheumatoid arthritis. Promoieties including saturated, unsaturated fatty acids and amino acids are proposed.

Background

Rheumatoid arthritis (RA), the most common form of inflammatory arthritis, is a chronic, systemic, autoimmune disorder characterized by persistent synovitis, production of auto-antibodies to immunoglobulin G (rheumatoid factor and anti-citrullinated protein antibody), destruction of cartilage and bone, and progressive disability [1–3]. In severe cases, there is a risk of development of extra-articular manifestations including keratitis, pulmonary granulomas (rheumatoid nodules), pericarditis/pleuritis, small vessel vasculitis, and other non-specific extra-articular symptoms, ultimately leading to early death [2]. The global prevalence of RA is approximately 1–2%, and the risk in women is 3 times higher than that in men, which is attributed to the involvement of sex hormones in the pathogenesis of the disease [4,5]. The incidence and prevalence of RA has been increasing over the past 20 years, thereby increasing the economic burden of the disease [6].

Although the exact cause of RA still remains unknown, it is believed that a combination of genetic and environmental factors, as well as other auto-immune initiating agents are implicated [7,8]. T cells, B cells and the orchestrated interaction of pro-inflammatory cytokines play key roles in the pathogenesis of the disease. Tumor necrosis factor-α (TNF- α) and interleukin-6 (IL-6) are mainly involved in this process. IL-1 and IL-17 may also play, albeit, less important role in the disease process [9].

Treat-to-target approach, based on tight monitoring of disease activity and change of management if a treatment target is not reached, has been adopted by American College of Rheumatology, European League against Rheumatism, Asia Pacific League of Associations for Rheumatology for the management of RA [10]. The goal of this strategy is disease remission or low disease activity, normalizing the physical function of joints in early stages, maximizing the physical function in established disease, and to prevent the progression of the disease [11]. In the past 30 years, therapeutic resources available for the treatment of RA have grown tremendously. Pharmacotherapy for RA generally involves nonsteroidal anti-inflammatory drugs (NSAIDs) for pain management, with selective use of low-dose oral or intra-articular glucocorticoids, and initiation of a disease modifying anti-rheumatic drugs (DMARDs) that delay the progression of the disease [12]. The available DMARDs are subdivided into conventional synthetic DMARDs (methotrexate, sulfasalazine, chloroquine, hydroxychloroquine and gold salts), targeted synthetic DMARDs (Janus kinase inhibitors like baricitinib, tofacitinib), and biologic DMARDs i.e. TNF-α inhibitors (adalimumab, certolizumab, etanercept, golimumab and infliximab), IL-6 receptor inhibitors (tocilizumab and sarilumab), IL-6 inhibitors (clazakizumab, olokizumab and sirukumab), B cell depleting antibodies,

* Corresponding author.
E-mail address: bhupipharma@gmail.com (B. Kapoor).

https://doi.org/10.1016/j.mehy.2022.110896
Received 13 January 2022; Received in revised form 8 June 2022; Accepted 15 June 2022
Available online 18 June 2022

Pooja Rani
31/8/23

EXPERT OPINION ON DRUG DISCOVERY
https://doi.org/10.1080/17460441.2022.2050693

Taylor & Francis
Taylor & Francis Group

REVIEW

Antimicrobial peptides: A plausible approach for COVID-19 treatment

Pooja Rani [a], Bhupinder Kapoor [a], Monica Gulati [a], Atanas G. Atanasov [b,c,d], Qushmua Alzahrani [e] and Reena Gupta [a]

[a]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India; [b]Ludwig Boltzmann Institute for Digital Health and Patient Safety, Medical University of Vienna, Vienna, Austria; [c]Institute of Genetics and Animal Biotechnology of the Polish Academy of Sciences, Magdalenka, Poland; [d]Department of Pharmaceutical Sciences, University of Vienna, Vienna, Austria; [e]Department of Pharmacy/Nursing/Medicine Health and Environment, University of the Region of Joinville (UNIVILLE) volunteer researcher, Joinville, Brazil

ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19), which emerged as a major public health threat, has affected >400 million people globally leading to >5 million mortalities to date. Treatments of COVID-19 are still to be developed as the available therapeutic approaches are not able to combat the virus causing the disease (severe acute respiratory syndrome coronavirus-2; SARS-CoV-2) satisfactorily. However, antiviral peptides (AVPs) have demonstrated prophylactic and therapeutic effects against many coronaviruses (CoVs).

Areas covered: This review critically discusses various types of AVPs evaluated for the treatment of COVID-19 along with their mechanisms of action. Furthermore, the peptides inhibiting the entry of the virus by targeting its binding to angiotensin-converting enzyme 2 (ACE2) or integrins, fusion mechanism as well as activation of proteolytic enzymes (cathepsin L, transmembrane serine protease 2 (TMPRSS2), or furin) are also discussed.

Expert opinion: Although extensively investigated, successful treatment of COVID-19 is still a challenge due to emergence of virus mutants. Antiviral peptides are anticipated to be blockbuster drugs for the management of this serious infection because of their formulation and therapeutic advantages. Although they may act on different pathways, AVPs having a multi-targeted approach are considered to have the upper hand in the management of this infection.

ARTICLE HISTORY
Received 21 December 2021
Accepted 4 March 2022

KEYWORDS
SARS-CoV-2; COVID-19; peptides; coronavirus; antivirals

1. Introduction

Coronaviruses (CoVs) form the largest cluster of viruses that cause respiratory and gastrointestinal infections [1,2]. The seven CoVs that infect humans are HCoV-HKU1, HCoV-OC43, HCoV-NL63, HCoV-229E, MERS-CoV (Middle east respiratory syndrome-corona virus), SARS-CoV (severe acute respiratory syndrome-corona virus), and SARS-CoV-2 (Figure 1) [3].

In December 2019, a mysterious pneumonia, characterized by fever, cough, chest discomfort, dyspnea, and bilateral lung infiltration was detected in China [6]. The causative agent of the disease was identified as the novel CoV, named later as 'SARS-CoV-2,' while the disease was given the name 'COVID-19' [7–9]. It was declared as a pandemic by WHO in March, 2020 [7].

Numerous clinical trials have either been conducted or are underway for repositioning the existing drugs to prevent and treat this disease. Some of these drugs are remdesivir, ivermectin, nelfinavir, cepharanthine, hydroxychloroquine, and dexamethasone [10].

Despite all the efforts, treatment of COVID-19 still remains elusive. Antimicrobial peptides (AMPs) have been reported to treat various viral infections such as AIDS, hepatitis, dengue, and influenza. AMPs, therefore, offer a potential treatment option of COVID-19 [11–13].

1.1. Search strategy and selection criteria

Articles for this review were identified through searches of PubMed for the period from January 2020, to July 2021, by use of the terms 'COVID-19,' and 'SARS-CoV-2.' Articles published in English only were included.

2. Structure assembly and replication of SARS-CoV-2 virus

SARS-CoV-2 virus is a large spherical albeit pleomorphic, enveloped virus, having positive sense RNA (with a length of 29.9 kb), encoding 9860 amino acids [14]. Proteins of SARS-CoV-2 include two polyproteins, i.e. ORF1a and ORF1b, which undergo proteolytic cleavage to form 16 nonstructural proteins, Nsp1-16, four structural proteins: nucleocapsid (N), membrane (M), envelope (E), and spike (S), and nine accessory proteins: Orf_{3a}, Orf_{3b}, Orf_{6}, Orf_{7a}, Orf_{7b}, Orf_{8}, Orf_{9b}, Orf_{9c}, and Orf_{10} [15,16,17]. The N protein forms the capsid outside the genome, while the remaining structural proteins participate in

CONTACT Bhupinder Kapoor bhupipharma@gmail.com School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India

Pooja Rani, Bhupinder Kapoor. These authors Contributed equally

Pooja Rani
31/8/23

Send Orders for Reprints to reprints@benthamscience.net

Mini-Reviews in Medicinal Chemistry, xxxx, xx, 1-46

REVIEW ARTICLE

Discovery and Development of Antibacterial Agents: Fortuitous and Designed

Ravleen Kaur[1,#], Pooja Rani[2,#], Atanas G. Atanasov[3,4,5], Qushmua Alzahrani[6], Reena Gupta[2], Bhupinder Kapoor[2,*], Monica Gulati[2,*] and Pooja Chawla[7]

[1]*Department of Health Sciences, Cape Breton University, Sydney, Nova Scotia, Canada;* [2]*School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India;* [3]*Ludwig Boltzmann Institute of Digital Health and Patient Safety, Medical University of Vienna, Vienna, Austria;* [4]*Institute of Genetics and Animal Biotechnology of the Polish Academy of Sciences, Jastrzebiec, Magdalenka, Poland;* [5]*Department of Pharmacognosy, University of Vienna, Vienna, Austria;* [6]*Department of Pharmacy/Nursing/Medicine Health and Environment, University of the Region of Joinville (UNIVILLE) volunteer researcher, Joinville, SC, Brazil;* [7]*Department of Pharmaceutical Chemistry and Analysis, ISF College of Pharmacy, Ghal Kalan Moga, Punjab 142001, India*

ARTICLE HISTORY

Received: October 4, 2021
Revised: October 12, 2021
Accepted: October 25, 2021

DOI
10.2174/1389557521666211025160139

Abstract: Today, antibacterial drug resistance has turned into a significant public health issue. Repeated intake, suboptimal and/or unnecessary use of antibiotics, and, additionally, the transfer of resistance genes are the critical elements that make microorganisms resistant to conventional antibiotics. A substantial number of antibacterials that were successfully utilized earlier for prophylaxis and therapeutic purposes have been rendered inadequate due to this phenomenon. Therefore, the exploration of new molecules has become a continuous endeavour. Many such molecules are at various stages of the investigation. A surprisingly high number of new molecules are currently in the stage of phase 3 clinical trials. A few new agents have been commercialized in the last decade. These include solithromycin, plazomicin, lefamulin, omadacycline, eravacycline, delafloxacin, zabofloxacin, finafloxacin, nemonoxacin, gepotidacin, zoliflodacin, cefiderocol, BAL30072, avycaz, zerbaxa, vabomere, relebactam, tedizolid, cadazolid, sutezolid, triclosan, and afabiacin. This article aims to review the investigational and recently approved antibacterials with a focus on their structure, mechanisms of action/resistance, and spectrum of activity. Delving deep, their success or otherwise in various phases of clinical trials is also discussed while attributing the same to various causal factors.

Keywords: Antimicrobials, microbial resistance, macrolides, aminoglycosides, pleuromutilins, tetracyclines, fluoroquinolones, oxazolidinones, fatty acid biosynthesis inhibitors, cephalosporins.

1. INTRODUCTION

Antimicrobial resistance, now considered a global issue, has acquired the dimension of an imminent threat to global health, especially to vulnerable patient populations [1]. Irrational and widespread uses of antimicrobials are recognized as the key factors responsible for the development of resistance [2, 3]. The decreasing efficacy of antimicrobials is problematic for medical professionals as it becomes very difficult or sometimes impossible to treat a number of infectious diseases such as pneumonia, tuberculosis, blood poisoning, gonorrhea, and food-borne diseases; and this list is growing day by day [4]. Microorganisms that develop resistance to antimicrobials are also referred to as "superbugs" [5, 6]. These microorganisms gained attention with the publication of a report in "The Lancet" in August 2010 about a multi-drug resistant "superbug" infection. Resistance-mechanism of this microorganism christened as New Delhi Metallo-beta-lactamase (NDM-1). NDM-1 was first reported by Dongeun Yong in 2009 [7] and named after the capital of India, *i.e.*, New Delhi. This was attributed to the assumption that Yang, who reported this, acquired this antibiotic-resistant bacterial infection in India, which eventually led to a controversy about this name [8]. Now, NDM-1 has been detected in almost all the continents except Antarctica and South America [9]. Bacteria resist the effects of antimicrobials by various genetic and biochemical strategies such as the production of destructive enzymes to neutralize antimicrobials, modification of antimicrobial targets by mutation, removal of antimicrobials by efflux mechanism, modification of antimicrobial molecules, preventing the entry of antimicrobials by forming a film (biofilm) or by reducing permeability, and creating bypass mechanism that allows bacteria to

*Address correspondence to these authors at the School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India;
E-mails: monicagulati14@gmail.com; bhupipharma@gmail.com

#*These authors contributed equally to this work*

Pooja Rani
31/8/23

1389-5575/xx $65.00+.00

Autoimmunity Reviews 21 (2022) 103169

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Psoriasis: Interplay between dysbiosis and host immune system

Bhupinder Kapoor [a,*], Monica Gulati [a,b,*], Pooja Rani [a], Reena Gupta [a]

[a] School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India
[b] Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, NSW 2007, Australia

ARTICLE INFO

Keywords:
Psoriasis
Microbiota
Microbiome
Gut dysbiosis
Skin dysbiosis
Probiotics
Fecal Microbiota Transplantation

ABSTRACT

With advancement in human microbiome research, an increasing number of scientific evidences have endorsed the key role of both gut and skin microbiota in the pathogenesis of psoriasis. Microbiome dysbiosis, characterized by altered diversity and composition, as well as rise of pathobionts, have been identified as possible triggers for recurrent episodes of psoriasis. Mechanistically, gut dysbiosis leads to "leaky gut syndrome" via disruption of epithelial bilayer, thereby, resulting in translocation of bacteria and other endotoxins to systemic circulation, which in turn, results in inflammatory response. Similarly, skin dysbiosis disrupts the cutaneous homeostasis, leading to invasion of bacteria and other pathogens to deeper layers of skin or even systemic circulation further enhanced by injury caused by pruritus-induced scratching, and elicit innate and adaptive inflammation. The present review explores the correlation of both skin and gut microbiota dysbiosis with psoriasis. Also, the studies highlighting the potential of bacteriotherapeutic approaches including probiotics, prebiotics, metabiotics, and fecal microbiota transplantation for the management of psoriasis have been discussed.

1. Introduction

1.1. Psoriasis

Psoriasis is a common, chronic, non-communicable, immune-mediated inflammatory disease of skin, nails, and joints that is associated with physical, emotional, and psychological burden [1–3]. The characteristic morphological feature of psoriasis is well-demarcated, erythematous, scaly, pruritic, and often painful skin plaques, which range from pinpoint to larger area, or even generalized erythroderma [4]. Although, plaques can appear on any part of the body, they preferentially appear over elbows and knees as well as on the scalp, the umbilical, and perianal region [5]. Psoriasis has multiple phenotypically distinct subtypes including plaque psoriasis, flexural psoriasis, guttate psoriasis, pustular psoriasis, and erythrodermic psoriasis [6]. The characteristic features of these psoriasis subtypes have been summarized in Table 1.

The hallmark of psoriasis is sustained inflammation, leading to uncontrolled proliferation, and dysfunctional differentiation of keratinocytes. Hyperproliferation of keratinocytes is triggered by proinflammatory cytokines, including tumour necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-17, IL-22, IL-23, and IL-1β [7]. Histopathological examination of psoriatic plaque indicates epidermal hyperplasia (acanthosis), which overlies inflammatory infiltrates composed of dermal dendritic cells, macrophages, T-cells, and neutrophils [8]. In moderate-to-severe psoriasis, there is an increase in systemic level of proinflammatory cytokines leading to asymptomatic inflammation (subclinical inflammation) causing tissue damage over a period of time. It is generally associated with comorbidities including psoriatic arthritis, inflammatory bowel disease, uveitis, cardiovascular diseases, nonalcoholic fatty liver disease, cancer, and chronic obstructive pulmonary disease [9–11].

The global prevalence of psoriasis is 0.09–0.11%, although it varies with the geographical regions [20]. In Asian and some African populations, there is a low prevalence rate, which goes up to 11% in Caucasian and Scandinavian populations [8]. In a number of studies, the age of onset was reported to be bimodal with two peaks of disease-the first between 16–22 and the second between 57–60 years of age [12,20]. It is equally prevalent in both sexes, although affects adults more than children [21,22].

There are several risk factors that increase the susceptibility of individuals to psoriasis. These include genetic, environmental, and behavioural, among them genetic factors being the largest contributor with approximately 35–72% and 12–23% concordance rates in monozygotic and dizygotic twins, respectively [23,24]. Psoriasis is a polygenetic disease in which multiple identified alleles (HLA-C*06:02, HLA-

* Corresponding authors at: School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India.
E-mail addresses: bhupipharma@gmail.com (B. Kapoor), monicagulati149@gmail.com (M. Gulati).

https://doi.org/10.1016/j.autrev.2022.103169
Received 30 July 2022; Accepted 7 August 2022
Available online 12 August 2022

Pooja Rani
31/8/23

Received: 23 August 2022 | Accepted: 5 October 2022

DOI: 10.1002/biof.1910

REVIEW ARTICLE

Biofactors WILEY

Lycopene: Sojourn from kitchen to an effective therapy in Alzheimer's disease

Bhupinder Kapoor[1] | **Monica Gulati**[1,2] | **Pooja Rani**[1] | **Rajpal Singh Kochhar**[3] | **Atanas G. Atanasov**[4,5,6] | **Reena Gupta**[1] | **Deepika Sharma**[7] | **Deepak Kapoor**[8,9]

[1]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India

[2]Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Sydney, New South Wales, Australia

[3]Jagsonpal Pharmaceuticals Ltd., New Delhi, India

[4]Ludwig Boltzmann Institute for Digital Health and Patient Safety, Medical University of Vienna, Vienna, Austria

[5]Institute of Genetics and Animal Biotechnology of the Polish Academy of Sciences, Magdalenka, Poland

[6]Department of Pharmaceutical Sciences, University of Vienna, Vienna, Austria

[7]Institute of Nanoscience and Technology, Mohali, Punjab, India

[8]University Institute of Biotechnology, Chandigarh University, Mohali, Punjab, India

[9]Punjab State Council for Science & Technology (PSCST), Chandigarh, India

Correspondence
Bhupinder Kapoor and Monica Gulati, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab,144411, India.
Email: bhupipharma@gmail.com and monicagulati14@gmail.com

Abstract

Reports on a significant positive correlation between consumption of carotenoid-rich food and prevention of Alzheimer's disease (AD) led to the investigation of carotenoids for the treatment and prevention of AD. More than 1100 types of carotenoids are found naturally, out of which only around 50 are absorbed and metabolized in human body. Lycopene is one of the most commonly ingested members of fat-soluble carotenoid family that gives vegetables and fruits their red, yellow, or orange color. Lycopene has established itself as a promising therapy for AD owing to its neuroprotective activities, including antioxidant, anti-inflammatory, and antiamyloidogenic properties. In this review, we highlight the various in vitro and preclinical studies demonstrating the neuroprotective effect of lycopene. Also, some epidemiological and interventional studies investigating the protective effect of lycopene in AD have been discussed. Diving deeper, we also discuss various significant mechanisms,

Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's disease; ADAM10, A Disintegrin and Metalloprotease 10; APP, amyloid β precursor protein; APP_{sw}, Swedish mutant form of human precursor protein; BACE, beta secretase; Bax, Bcl-2-associated X protein; BDNF, brain-derived neurotropic factor; CAT, catalase; CRP, C-reactive protein; Cyc, cytochrome *c*; GSH, glutathione; HAEC, human amniotic epithelial cell; HFD, high-fat diet; IAL, initial acquisition latency; Iba-1, ionize calcium-binding adapter molecule 1; ICAM-1, intracellular adhesion molecule-1; IL, interleukin; MAO, monoamine oxidase; MAPK, mitogen-activated protein kinase; MCI, mild cognitive impairment; MDA, malondialdehyde; mPTP, mitochondrial permeability transition pore; NHANES, Nutrition and Health Examination Survey; NGF, nerve growth factor; NF-κB, nuclear factor-κB; NFT, neurofibrillary tangle; NLRP3, pyrin domain-containing 3; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; ROS, reactive oxygen species; SOD, superoxide dismutase; *t*-BHP, *tert*-Butyl hydroperoxide; T-AOC, total anti-oxidation capability; TBARS, thiobarbituric acid reactive substances; TGF-β, transforming growth factor-β; TL, transfer latency; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

Pooja Rani 21/8/23

Medical Hypotheses 159 (2022) 110748

Contents lists available at ScienceDirect

Medical Hypotheses

Journal homepage: www.elsevier.com/locate/mehy

Triumvirate to treat mucormycosis: Interplay of pH, metal ions and antifungal drugs

Bhupinder Kapoor [a], Rajpal Singh Kochhar [b], Monica Gulati [a,*], Pooja Rani [a], Reena Gupta [a], Sachin Kumar Singh [c], Lalit Machawal [c], Abhishek Thakur [a]

[a] School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India
[b] Jagsonpal Pharmaceuticals Ltd., New Delhi, India
[c] Medical Affairs and Clinical Research, Sun Pharmaceuticals Industries Limited, India

ARTICLE INFO

Keywords:
Mucormycosis
COVID-19
Antifungal drugs
Iron chelators
Zinc chelators
Alkalizer

ABSTRACT

Mucormycosis is a rare fungal infection mainly affecting immunocompromised patients. Recently, an alarming rise in cases of mucormycosis was observed in patients undergoing COVID-19 treatment. Commonly, this fungal infection is caused by *Rhizopus* spp., *Mucor* spp., and *Lichtheimia* spp., although the genera of other Mucorales such as *Saksenaea*, *Rhizomucor*, *Cunninghamella*, and *Apophysomyces* may also be involved. A number of factors such as high concentration of zinc, iron and hypoxia induced acidosis promote the growth of fungi, thereby increasing the risk of mucormycosis multiple folds. Iron chelators (deferasirox and deferiprone) and zinc chelators (clioquinol, phenanthroline and *N,N,N',N'*-tetrakis(2-pyridylmethyl)ethane-1,2-diamine) have been reported to inhibit the growth of fungi in a number of in vitro and animal studies. Correction of metabolic acidosis by administration of bicarbonate or glycine reduces the susceptibility of patients to the invasion by fungal species. However, these factors have largely been ignored while deciding the treatment strategy for mucormycosis and first line treatment for the management of mucormycosis continues to be the expensive lipid based formulation of amphotericin B. Treatment with isavuconazole which is proposed as the second choice is reported to be more cost effective. Therefore, it is proposed that a combination of antifungal agent (isavuconazole) with zinc and iron chelators (deferasirox and clioquinol respectively) along with alkalizer (glycine buffer) could be an effective and multi-target approach for the treatment of mucormycosis while being cost effective also.

Background

Coronavirus disease 2019 (COVID-19) caused by novel coronavirus (CoV) caused a pandemic of acute respiratory disease [1]. As the COVID-19 continued the devastation in its first, second and third wave all over the world, an increase in the number of opportunistic mucormycosis infection was also observed in patients with COVID-19, which has been named as COVID-19 associated mucormycosis (CAM) [2].

Mucormycosis, the third most common opportunistic fungal infection after candidiasis and aspergillosis, is a rare angio-invasive infection caused by a group of fungi in the phylum Zygomycota. Due to this reason, the terms zygomycosis and mucormycosis are used interchangeably for this infection [3]. The most common causative agents of mucormycosis infection to humans belong to two orders i.e. Mucorales and Entomophthorales. The genera *Rhizopus*, *Mucor*, *Lichtheimia (formerly Absidia)*, and *Cunninghamella* belong to order Mucorales while *Conidiobolus* and *Basidiobolus* belong to Entomophthorales [4]. Among the various pathogens, *Rhizopus arrhizus (formerly Rhizopus oryzae)* remains the most common cause of mucormycosis, accounting for ~70% of mucormycosis cases world-wide [5]. Spores of these ubiquitous fungi commonly found in air, soil and on variety of decaying material can be inhaled and may infect the lungs, sinuses, and even extend into the brain and eyes [6,7]. Through paranasal sinuses it gets transmitted to the mouth, leading to palatal perforation or to the orbit via the nasolacrimal duct and medial orbit. As the infection advances towards the orbit and skull, it may result in multiple issues, such as orbital cellulitis, chemosis, proptosis, loss of vision, ophthalmoplegia, superior orbital fissure syndrome, sagittal sinus thrombosis, epidural or subdural abscess formation. A bloody nasal discharge indicates that disease has invaded into the brain via turbinates which may result in cerebral ischemia, brain infarction, and eventually death [8,9]. Although non-contagious, in very few cases especially in immunocompromised patients, the infection may

* Corresponding author.
E-mail address: monicagulati14@gmail.com (M. Gulati).

https://doi.org/10.1016/j.mehy.2021.110748
Received 26 October 2021; Accepted 28 December 2021
Available online 3 January 2022

Pooja Rani
31/8/23

Send Orders for Reprints to reprints@benthamscience.net

Current Drug Metabolism, 2022, 23, 90-98

MINI-REVIEW ARTICLE

Orchestration of Obesolytic Activity of Microbiome: Metabiotics at Centre Stage

Bhupinder Kapoor[1], Apoorva Singh[2], Monica Gulati[1,*], Sachin Kumar Singh[1], Pooja Rani[1], Qushmua Alzahrani[3], Kamal Dua[4], Harish Dureja[1] and Leander Corrie[1]

[1]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India; [2]Department of Anesthesia and Intensive Care, Post Graduate Institute of Medical Education and Research, Chandigarh, India; [3]Department of Pharmacy/Nursing/Medicine Health and Environment, University of the Region of Joinville (UNIVILLE), Joinville, SC, Brazil; [4]Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, Australia; [5]Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India

ARTICLE HISTORY

Received: July 29, 2021
Revised: December 23, 2021
Accepted: December 24, 2021

DOI
10.2174/1389200223666220121093154

Abstract: Metabiotics have emerged as the safer alternatives to probiotics in last decade. Unlike probiotics that are live microbes, metabiotics are the low molecular weight bioactive metabolites produced by the gut microbiota. While offering a similar profile of health benefits as that of probiotics, metabiotics are free from the risks and uncertain responses associated with administration of live bacteria into the body. Metabiotics have demonstrated substantial effectiveness across the ethnicities, age, gender and nutritional habits in a number of metabolic disorders, including obesity. Obesity is attributed to the offsetting of the energy homeostasis of the body due to a number of genetic, endocrinological, and environmental factors leading to obesity. The obesogenic mechanisms are quite complicated as they result from a complex interplay among a number of factors. Owing to a variety of constituents exerting their action through different pathways, metabiotics offer a pragmatic option for treatment as well as prevention of obesity by addressing heterogeneous aspects of its aetiology. In this review, we categorize various components of metabiotics and discuss their cross-talk with host cells at the molecular level. We also discuss the challenges in understanding these interactions and their potential effects on obesity treatment and prevention strategies. Considering the alarming rise in obesity all over the world, metabiotics offer an attractive non-pharmacological approach to spearhead the strategies being designed to combat the challenges posed by the obesity epidemic.

Keywords: Bacteriotherapeutics, obesity, adipose tissue, short chain fatty acids, bacteriocins, metabiotics.

1. INTRODUCTION

Treatment of obesity through the manipulation of gut microbiota has emerged as an effective non-pharmacological option in the last decade. It is attributed to the advent of knowledge regarding the repertoire of metabolic processes of the gut microbiont, their significant role in treatment of diseases, existence of food-gut axis and gut-endocrine axis [1]. The approach has been tried and tested by the use of various bacteriotherapeutics, including probiotics, prebiotics, metabiotics and fecal microbiota transplant (FMT) [2]. Among these bacteriotherapeutics, probiotics have enjoyed maximum popularity. However, interest in probiotics has somewhat declined in last few days. This is attributed to the scepticism regarding their viability on their transition through gut, specificity for a disease condition, safety in paediatric, geriatric, pregnant population and hospitalized patients, especially those on chemotherapy [3]. Use of prebiotics, on the other hand, is limited by their lack of targeted functions, production of certain harmful fermentation products like phenolics, amines and ammonium compounds, and side effects like intestinal discomfort [4]. FMT has not been widely accepted because it is aesthetically unappealing, poses risks for infection transmission, and faces a number of challenges in standardization and regulation policies [5]. Metabiotics, however, emerge as more specific and measurable therapeutic agents with known chemical structures that are free from any risk for infections or uncertain metabolic processes [6]. A portmanteau formed from the combination of words "metabolites" with "probiotics", the word metabiotic literally and functionally means the metabolites produced by the health imparting bacteria of the gut. The major constituents of metabiotics *i.e.* short chain fatty acids (SCFAs), polyunsaturated fatty acids (PUFAs), peptides, peptidoglycan-derived muropeptides, enzymes, polysaccharides, vitamins, and plasmalogens, act in a different manner to exert their obesolytic effect [7]. Metabiotics have been dichotomised into postbiotics and parapro-biotics. Postbiotic is a portmanteau derived from "post" and "biotic", thereby indicating the products secreted by probiotics including enzymes, proteins, short chain fatty acids, vitamins, biosurfactants, amino acids, peptides, organic acids, *etc.* while, parapeobiotics are the components of dead/inactivated cells of probiotics and include peptidoglycans, teichoic acids, surface proteins, *etc.* The individual and overlapping effects of various components of metabiotics that contribute to prevention and treatment of obesity include thermogenesis in brown adipose tissue, browning of the white adipose tissue, reduction in appetite, regulation of the immune function, down-regulation of inflammatory mediators [8].

2. ROLE OF DYSBIOSIS IN OBESITY

Obesity has been rising rapidly, affecting more than 603.7 million adults worldwide [9]. In fact, as per WHO report, worldwide, approximately 38.2 million children under the age of 5 years are overweight or obese [10]. The role of gut dysbiosis *i.e.* perturbations in homeostasis of microbiota in terms of characteristic changes in bacterial phyla, bacterial translocation, inflammation and a decrease in α as well as β diversity, is well established now, albeit some mechanisms involved therein are still unclear [11].

*Address correspondence to this author at the School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India;
Tel: 9915020408; E-mail: monicagulati14@gmail.com

Pooja Rani
31/8/23

1875-5453/22 $65.00+.00

Review Article

Potential of the Triad of Fatty Acids, Polyphenols, and Prebiotics from Cucurbita against COVID-19 in Diabetic Patients: A Review

Qushmua E. Alzahrani[1], Richard B. Gillis[2], Stephen E. Harding[3,4], Luciano Henrique Pinto[5], Monica Gulati[6], Bhupinder Kapoor[6], Pooja Rani[6], Sachin Kumar Singh[6], Gary G. Adams[2]

[1]Department of Pharmacy/Nursing/Medicine Health and Environment, University of the Region of Joinville (UNIVILLE) volunteer researcher, Joinville, Santa Catarina, Brazil, [2]University of Nottingham, Faculty of Medicine & Health Sciences, Queens Medical Centre, Nottingham, United Kingdom, [3]University of Nottingham, National Centre for Macromolecular Hydrodynamics, School of Biosciences, Loughborough, United Kingdom, [4]Universitetet I Oslo, Oslo, Norway, [5]Department of Pharmacy/Nursing/Medicine Health and Environment, University of the Region of Joinville (UNIVILLE), Joinville, Santa Catarina, Brazil, [6]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India

Received: 06 Oct 2021
Accepted: 09 May 2022
Published: 29 Jun 2022

Address for correspondence:
Dr. Qushmua E. Alzahrani, Department of Pharmacy/Nursing/Medicine Health and Environment, University of the Region of Joinville (UNIVILLE) volunteer researcher, Joinville, SC, 89219-710, Brazil. E-mail: drqushmua.alzahrani@hotmail.com

Access this article online
Website: www.jrpsjournal.com
DOI: 10.4103/jrpbs.JRPTPS_144_21
Quick Response Code:

Abstract

Though the scientific community of the entire world has been struggling to create preventive and therapeutic drugs for coronavirus disease 2019 (COVID-19), the role of nutraceuticals has been hitherto neglected. Established role of fatty acids and polyphenols in combating lifestyle disease can be harnessed to play a significant role in the prevention of this disease. The synergistic effect of these phytonutrients and prebiotics is anticipated to prove beneficial for prevention as well as attenuation of COVID-19 infection. Presence of fatty acids, polyphenols and prebiotics in vegetables from the Cucurbitaceae family makes them an attractive choice for being used as a nutritional supplement during COVID-19. These are known to attenuate the excessive immune response which may prove to be beneficial in preventing and mitigating COVID-19. Use of prebiotics to promote the growth of probiotics has also been recommended for the prevention and cure of COVID-19. However, no such report exists in literature that throws light on such role of cucurbita plants. The present review focuses on the role of the triad of fatty acids, prebiotics and polyphenols present in cucurbita plants in controlling systemic inflammation and endothelial damage, the two main etiopathological factors involved in COVID-19. Cucurbita plants are rich in all these components and their inclusion in diet would be an effective strategy to combat COVID-19. The main focus of the review is to discuss the role of various components of the plants of Cucurbita family, taken as dietary component, in prevention and control of the ongoing pandemic COVID19.

Keywords: *Diabetes mellitus, fatty acids, microbiome, polyphenols, prebiotics, SARS-CoV-2*

Introduction

Diabetes mellitus

Diabetes mellitus (DM) which is a group of metabolic disease has acquired epidemic proportions in the twenty-first century. More than 460 million people in 2019 are reported to be suffering from some form of DM and the number is anticipated to reach approximately 580 million by the end of this decade.[1] Diabetic patients are susceptible to a number of co-morbidities, generally resulting in reduced quality of life. It also predisposes patients to a number of opportunistic infections.[2]

DM is a chronic metabolic disorder of endocrine origin arising because of the failure of the body to respond to the elevated blood glucose levels. This abnormality in carbohydrate metabolism is attributed either to deficiency of insulin secretion or to dysfunction of pancreatic β cells responsible for producing, storing and releasing insulin. Failure of the body to utilize insulin because of insulin resistance can be another etiopathological factor.[3,4] However, apart from insulin deficiency or lack of utilization, there are many other causes of DM including various pathophysiological changes.[5] In fact, the causes of diabetes popularly known as "Dirty Dozen" include pancreatic β-cell failure, insulin resistance, hepatic gluconeogenesis, deranged adipocyte metabolism, hyperglucagonemia, incretin defect, increased renal glucose reabsorption, neurotransmitter dysfunction, central appetite dysregulation, gut microbiota, deregulation of the immune system and abnormal activity of hormones, namely dopamine, testosterone, vitamin D, and renin-angiotensin system.[6]

Diabetes can be categorized into are four types as classified by The American Diabetic Association. These include two forms of idiopathic diabetes, that is, type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes. Third category is that of gestational diabetes which develops during pregnancy while the fourth one, that is, secondary diabetes is associated with other specific conditions.[7,8] Fourth type, that is, pre-diabetes is a state in

How to cite this article: Alzahrani QE, Gillis RB, Harding SE, Pinto LH, Gulati M, Kapoor B, *et al.* Potential of the triad of fatty acids, polyphenols, and prebiotics from cucurbita against COVID-19 in diabetic patients: A review. J Rep Pharma Sci 2022;11:28-40.

Pooja Rani 31/8/23