



4.67
3.38 3.28

Frontiers in Natural Product Chemistry



Editor:
Shazia Anjum



Bentham Books

Frontiers in Natural Product Chemistry

(Volume 11)

Edited by

Shazia Anjum

*Institute of Chemistry
The Islamia University of Bahawalpur
Pakistan*

Frontiers in Natural Product Chemistry

(Volume 11)

Editor: Shazia Anjum

ISSN (Online): 2212-3997

ISSN (Print): 1574-0897

ISBN (Online): 978-981-5136-59-3

ISBN (Print): 978-981-5136-60-9

ISBN (Paperback): 978-981-5136-61-6

©2023, Bentham Books imprint.

Published by Bentham Science Publishers Pte. Ltd. Singapore. All Rights Reserved.

First published in 2023.

BENTHAM SCIENCE PUBLISHERS LTD.

End User License Agreement (for non-institutional, personal use)

This is an agreement between you and Bentham Science Publishers Ltd. Please read this License Agreement carefully before using the ebook/echapter/ejournal (“**Work**”). Your use of the Work constitutes your agreement to the terms and conditions set forth in this License Agreement. If you do not agree to these terms and conditions then you should not use the Work.

Bentham Science Publishers agrees to grant you a non-exclusive, non-transferable limited license to use the Work subject to and in accordance with the following terms and conditions. This License Agreement is for non-library, personal use only. For a library / institutional / multi user license in respect of the Work, please contact: permission@benthamscience.net.

Usage Rules:

1. All rights reserved: The Work is the subject of copyright and Bentham Science Publishers either owns the Work (and the copyright in it) or is licensed to distribute the Work. You shall not copy, reproduce, modify, remove, delete, augment, add to, publish, transmit, sell, resell, create derivative works from, or in any way exploit the Work or make the Work available for others to do any of the same, in any form or by any means, in whole or in part, in each case without the prior written permission of Bentham Science Publishers, unless stated otherwise in this License Agreement.
2. You may download a copy of the Work on one occasion to one personal computer (including tablet, laptop, desktop, or other such devices). You may make one back-up copy of the Work to avoid losing it.
3. The unauthorised use or distribution of copyrighted or other proprietary content is illegal and could subject you to liability for substantial money damages. You will be liable for any damage resulting from your misuse of the Work or any violation of this License Agreement, including any infringement by you of copyrights or proprietary rights.

Disclaimer:

Bentham Science Publishers does not guarantee that the information in the Work is error-free, or warrant that it will meet your requirements or that access to the Work will be uninterrupted or error-free. The Work is provided "as is" without warranty of any kind, either express or implied or statutory, including, without limitation, implied warranties of merchantability and fitness for a particular purpose. The entire risk as to the results and performance of the Work is assumed by you. No responsibility is assumed by Bentham Science Publishers, its staff, editors and/or authors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products instruction, advertisements or ideas contained in the Work.

Limitation of Liability:

In no event will Bentham Science Publishers, its staff, editors and/or authors, be liable for any damages, including, without limitation, special, incidental and/or consequential damages and/or damages for lost data and/or profits arising out of (whether directly or indirectly) the use or inability to use the Work. The entire liability of Bentham Science Publishers shall be limited to the amount actually paid by you for the Work.

General:

1. Any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims) will be governed by and construed in accordance with the laws of Singapore. Each party agrees that the courts of the state of Singapore shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims).
2. Your rights under this License Agreement will automatically terminate without notice and without the

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.

80 Robinson Road #02-00

Singapore 068898

Singapore

Email: subscriptions@benthamscience.net



CONTENTS

PREFACE	i
LIST OF CONTRIBUTORS	ii
CHAPTER 1 MEDICINAL IMPORTANCE OF TURMERIC (<i>CURCUMA LONGA</i>) AND ITS NATURAL PRODUCTS	1
<i>Punit Kumar, Sujata and Archana</i>	
INTRODUCTION	2
TURMERIC (<i>CURCUMA LONGA</i>)	6
General Study: Habitat, Classification & Uses	6
Medicinal Uses of Turmeric	8
<i>Neuroprotective Effects</i>	8
<i>Anticancer Activity</i>	8
<i>Antioxidant Activity</i>	9
<i>Cardioprotective Effects</i>	10
<i>Anti-inflammatory Activity</i>	11
<i>Therapeutic Agent for Sexually Transmitted Infections/Diseases (STD)</i>	11
<i>Hepatoprotective Effect</i>	12
<i>Other Medicinal Uses</i>	13
CURCUMINOIDS	14
CURCUMIN	15
Isolation and Analysis of Curcumin	16
Health Benefits of Curcumin	17
Availability of Curcumin	19
Clinical Investigation of Curcumin as an Anticancer Product	20
CONCLUSION	20
CONSENT FOR PUBLICATION	21
CONFLICT OF INTEREST	21
ACKNOWLEDGEMENTS	21
REFERENCES	21
CHAPTER 2 NOVEL NATURAL COMPOUNDS FOR HEPATOCELLULAR CARCINOMA TREATMENT	32
<i>Çağrı ÖNER and Emine ÇOLAK</i>	
INTRODUCTION	32
NATURAL COMPOUNDS AND THEIR USAGE IN HEPATOCELLULAR CARCINOMA	34
Coumarin and Coumarin Derivatives	34
<i>Coumarin Metabolism in Cells</i>	34
<i>General Functions of Coumarins and Coumarin Derivatives</i>	35
<i>Genetic Markers of Coumarin and Coumarin Derivatives Treatment in HCC</i>	36
Curcumin and Curcumin Derivatives	38
<i>Genetic Markers of Curcumin and Curcumin Derivatives Treatment in HCC</i>	40
Leaf of <i>Olea Europaea</i> and Its Extract	42
<i>Major Derivatives of Olea Europaea Leaf Extract and their Relationship with Various Types of Cancer</i>	42
<i>OLE and OLE Derivatives in HCC</i>	45
Leaf of <i>Cynara Scolymus</i> (globe artichoke) and Its Extract	47
<i>Major Derivatives of Cynara Scolymus Extract and their Relationship with Various types of Cancer</i>	49
<i>CSE and CSE Derivatives in HCC</i>	50
CONCLUSION	51

CONSENT FOR PUBLICATION	51
CONFLICT OF INTEREST	51
ACKNOWLEDGEMENTS	51
REFERENCES	52
CHAPTER 3 HERBAL DRUG SUBSTITUTION (ABHAVAPRATINIDHI DRAVYA): A KEY TO STOPPING ECONOMIC ADULTERATION OF BOTANICAL INGREDIENTS	73
<i>Arun Shivakumar, Atul Namdeorao Jadhav, Ashok Basti Krishnaiah and Rangesh Paramesh</i>	
1. INTRODUCTION	74
2. ECONOMICS OF HERBAL TRADE & ADULTERATION PRACTICES	75
3. CONCEPT OF ABHAVAPRATINIDHI DRAVYAS	76
3.1. Ativisha [Himalayan Aconite or Atis]	77
3.1.1. Introduction	77
3.1.2. Chemistry and Pharmacology	79
3.1.3. Commercial Demand and Supply	79
3.1.4. Potential Substitute, Chemistry And Pharmacology	79
3.1.5. Recommendations	81
3.2. Guduchi [Giloe]	81
3.2.1. Introduction	81
3.2.2. Chemistry and Pharmacology	82
3.2.3. Commercial Demand and Supply	82
3.2.4. Potential Substitute, Chemistry and Pharmacology	83
3.2.5. Recommendations	83
3.3. Bala	84
3.3.1. Introduction	84
3.3.2. Chemistry and Pharmacology	84
3.3.3. Commercial Demand and Supply	85
3.3.4. Potential Substitute, Chemistry and Pharmacology	85
3.3.5. Recommendations	86
3.4. Vidanga	87
3.4.1. Introduction	87
3.4.2. Chemistry and Pharmacology	87
3.4.3. Commercial Demand and Supply	87
3.4.4. Potential Substitute, Chemistry and Pharmacology	88
3.4.5. Recommendations	89
CONCLUSION	90
CONSENT FOR PUBLICATION	91
CONFLICT OF INTEREST	91
ACKNOWLEDGEMENTS	91
REFERENCES	91
CHAPTER 4 SYNTHETIC AND NATURAL AGENTS AS BACTERIAL BIOFILM INHIBITORS	100
<i>Ethiraj Kannatt Radhakrishnan and Anjitha Theres Benny</i>	
INTRODUCTION	100
QUORUM QUENCHERS	102
Natural Products as Quorum Quenchers	104
<i>From Plant Source</i>	104
<i>From Bacterial By-Products</i>	106
Synthetic Compounds as Quorum Quenchers	106
Enzymatic Quorum Quenching	109

<i>Lactonase Enzymes</i>	109
<i>Acylase Enzymes</i>	110
<i>Oxidoreductase Enzymes</i>	110
Nanoparticles as Quorum Quenchers	110
EXTRACELLULAR POLYMERIC MATRIX DEGRADATION	111
Enzymatic Degradation of Extracellular Polymeric Matrix	112
Nano Carriers in Extracellular Polymeric Matrix Degradation	114
Synthetic Compounds in Extracellular Polymeric Matrix Degradation	116
INHIBITION OF BIOFILM FORMATION	116
Natural Products in Inhibition of Biofilm Formation	116
Synthetic Compounds in Inhibition of Biofilm Formation	117
Nanocarriers in Inhibition of Biofilm Formation	117
EFFLUX PUMP INHIBITORS	118
Natural Products as Efflux Pump Inhibitors	118
Synthetic Compounds as Efflux Pump Inhibitors	120
Nanoparticles as Efflux Pump Inhibitors	121
CONCLUSION	121
CONSENT FOR PUBLICATION	121
CONFLICT OF INTEREST	122
ACKNOWLEDGEMENTS	122
REFERENCES	122
CHAPTER 5 QUERCETIN CHEMISTRY, STRUCTURAL MODIFICATIONS, SAR STUDIES AND THERAPEUTIC APPLICATIONS: AN UPDATE	134
<i>Nazia Banday, Prince Ahad Mir, Mudasir Maqbool, Rafia Jan, Nyira Shafi, Roohi Mohi-ud-din and Reyaz Hassan Mir</i>	
1. INTRODUCTION TO FLAVONOIDS	135
1.1. Quercetin Chemistry and Source	135
1.2. Structure of Quercetin and Its Derivatives	138
2. SAR OF QUERCETIN AND ITS DERIVATIVES	141
3. QUERCETIN: THERAPEUTIC APPLICATIONS	142
3.1. Alzheimer's Disease	142
3.2. Cancer	142
3.2.1. <i>Colorectal Cancer</i>	142
3.2.2. <i>Gastric Cancer</i>	142
3.2.3. <i>Prostate Cancer</i>	142
3.2.4. <i>Lung Cancer</i>	143
3.2.5. <i>Breast Cancer</i>	143
3.2.6. <i>Pancreatic Cancer</i>	143
3.3. Cardiovascular Disease	144
3.4. Anti-inflammatory Activity	144
3.5. Anti-Diabetic Activity	145
3.6. Antioxidant Activity of Quercetin	146
3.7. ANTI-OBESITY	147
CONCLUSION	148
CONSENT FOR PUBLICATION	148
CONFLICT OF INTEREST	148
ACKNOWLEDGEMENTS	149
REFERENCES	149
SUBJECT INDEX	383

PREFACE

The 11th volume of **Frontiers in Natural Product Chemistry** maintains the tradition of publishing updated knowledge on the subject. Leading scientists contributed 05 extensive book chapters in this volume including advanced methods of isolation, syntheses, computational studies and SARs. Each chapter bears a uniqueness that will definitely attract readers' and postgraduate students' attention.

For instance, in Chapter 01, Kumar *et al.* discussed the medicinal importance of Turmeric (*Curcuma Longa*)- a blessed plant and its phytochemicals that have diverse medicinal properties.

While Öneri and Çolak reviewed some novel natural compounds for hepatocellular carcinoma treatment. The authors have discussed the effect of these natural compounds on the genetic hallmarks of various signaling pathways and important cellular metabolism molecules of hepatocellular carcinoma.

Shivakumar *et al.* in Chapter 03, explained the prevention of overexploited herbs for balancing a sustainable ecosystem. It has been emphasized that in the Ayurvedic system of medicine, there is an in-depth biochemical classification of herbs, based on which substitutes can be deduced. Moreover, ancient texts also describe alternate herbs for some key ingredients.

Microbial control is an ever-increasing economic burden that is disturbing human beings and as well as animals. Radhakrishnan and Benny, in Chapter 04, discussed the over-smartness of bacteria by forming some biofilms as safety walls for their existence. Therefore, the multi-drug resistance of bacterial biofilm has constantly challenged the existing anti-bacterial drugs. This chapter deals with a few methods by which biofilm inhibition can be achieved by making use of various synthetic and natural compounds.

The updated review on quercetin chemistry, its structural modifications, SARs and therapeutic applications by Banday *et al.* can be found in Chapter 05. Quercetin is a naturally occurring flavone with tremendous medicinal potential and it has a wider scope in medicines as evidenced from this chapter.

It is hoped that this volume will be thought-provoking and trigger further research in the quest for new and novel natural therapies. I am indebted for the great efforts of the entire editorial team, especially Mr. Mahmood Alam (Director Publications) and Ms. Asma Ahmed (Editorial Manager Publications) at Bentham Science Publishers.

Shazia Anjum
Dean, Faculty of Chemical & Biological Science
The Islamia University of Bahawalpur
Pakistan

List of Contributors

Arun Shivakumar	Dubai Science Park, Al Barsha, Himalaya Global Research Center FZ LLC, Dubai, UAE
Atul Namdeorao Jadhav	Himalaya Wellness Company, Bengaluru, Research and Development Centre, Karnataka, India
Ashok Bast Krishnaiah	Himalaya Wellness Company, Bengaluru, Research and Development Centre, Karnataka, India
Anjitha Theres Benny	Department of Chemistry, School of Advanced Science, VIT, Vellore, Tamil Nadu-632014, India
Archana	Department of Morphology and Physiology, Karaganda Medical University, Karaganda-100008, Kazakhstan
Çağrı ÖNER	Medical Faculty, Department of Medical Biology and Genetics, Maltepe University, İstanbul, Turkey
Emine ÇOLAK	Medical Faculty, Department of Medical Biology, Eskişehir Osmangazi University, Eskişehir, Turkey
Ethiraj Kannatt Radhakrishnan	Department of Chemistry, School of Advanced Science, VIT, Vellore, Tamil Nadu-632014, India
Mudasir Maqbool	Pharmacy Practice Division, Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar, 190006, Kashmir, India
Nazia Bandy	Pharmacognosy and Phytochemistry Lab, Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar-190006, Kashmir, India
Nyira Shafi	Pharmacology Division, Department of Pharmaceutical Science, University of Kashmir, Hazratbal, Srinagar, 190006, Kashmir, India
Punit Kumar	Department of Biological Sciences & Bioengineering, Indian Institute of Technology Kanpur, Uttar Pradesh-208016, India
Prince Ahad Mir	Khalsa College of Pharmacy, G.T. Road, Amritsar-143002 Punjab, India
Rangesh Paramesh	Manal Family Office Holdings Ltd, Dubai International Financial Centre, Dubai, UAE
Rafia Jan	Defence Research and Development Organization (DRDO), Hospital, Khonmoh, Srinagar, 190001, Jammu & Kashmir, India
Rooh Mohi-ud-din	Pharmacognosy and Phytochemistry Lab, Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar-190006, Kashmir, India Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu, and Kashmir, India
Reyaz Hassan Mir	Pharmaceutical Chemistry Division, Chandigarh College of Pharmacy, Landran, Punjab-140301, India Pharmaceutical Chemistry Division, Department of Pharmaceutical Sciences, University of Kashmir, Srinagar-190006, Kashmir, India
Sujata	Department of Electronics and Communication Engineering, Kashi Institute of Technology Varanasi, Uttar Pradesh-221307, India

CHAPTER 1

Medicinal Importance of Turmeric (*Curcuma Longa*) and its Natural Products

Punit Kumar^{3,*}, Sujata¹ and Archana²

¹ Department of Biological Sciences & Bioengineering, Indian Institute of Technology Kanpur, Uttar Pradesh-208016, India

² Department of Electronics and Communication Engineering, Kashi Institute of Technology Varanasi, Uttar Pradesh-221307, India

³ Department of Morphology and Physiology, Karaganda Medical University, Karaganda-100008, Kazakhstan

Abstract: It is believed that natural products exhibiting medicinal benefits do not cause systemic side effects or they cause acceptable side effects. Due to the increase in research output and increased awareness about the importance of natural products, nowadays, a large fraction of the population is now shifting their orientation towards the use of natural products in daily use. Turmeric (*Curcuma longa*) is one such blessing for all of us. It is one of the most important and abundant spices used in Asian food. It is cultivated around the world and originated in India, Indonesia, and Southeast Asia. Turmeric powder has a bitter, sharp taste and is yellow. It is used to provide color and flavor to various food products such as; butter, mustard, cheese, *etc.* Turmeric belongs to the Zingiberaceae family. It is one of the most commonly used medicinal herbs in India and China and is used for the treatment of jaundice and liver problems. Turmeric is known to have a wide range of pharmacological properties such as anti-microbial, anti-protozoal, anti-malarial, anti-venom, anti-proliferative, anti-aging, anti-inflammatory, anti-tumor, *etc.* It is identified that the yellow color of the turmeric is due to the presence of Curcumin which is the most important and potent bioactive compound of turmeric. Curcumin is a curcuminoid that is extracted from the rhizomes of *Curcuma Longa*. Curcumin possesses remarkable medicinal properties and can also be used in cosmetic products. Curcumin has powerful anti-inflammatory and antioxidant properties. It helps to treat various diseases, some of them are; hay fever, depression, Alzheimer's, treat cholesterol, itching, and osteoarthritis. It is involved in maintaining the functioning of the brain and reduces the risk of brain and heart diseases. Investigators are focusing to find out the therapeutic role of curcumin in asthma, diabetes, cancer, indigestion, and many other disorders. In this chapter, we will discuss the natural compounds present in turmeric and their medicinal importance.

* Corresponding author Punit Kumar: Department of Morphology and Physiology, Karaganda Medical University, Karaganda-100008, Kazakhstan; E-mail: punitdariyapur@gmail.com

Keywords: Anti-inflammatory Activities, Anticancer Activities, Antioxidant Activities, Cardioprotective Protective Properties, *Curcuma longa*, Curcumin, Curcuminoids, Medicinal Herbs, Natural Products, Turmeric.

INTRODUCTION

Natural products are the type of compounds that are produced by living organisms (microbes, animals, plants, *etc.*). These compounds comprise all chemical compounds or substances found in nature and are called natural products if they are produced by a living organism [1]. Natural products may be classified according to their chemical property, biological function, biosynthetic pathway, or source. The estimated number of known natural products around the world is about 326,000 [2]. Natural products may be extracted from the cells, tissues, and secretions of microorganisms, plants, and animals. A crude (unfractionated) extract from any one of these sources will contain a range of structurally diverse and often novel chemical compounds [3].

The natural product can be categorized as a compound that is produced by living organisms and includes the types of biotic materials (*e.g.* wood, silk), bio-based materials (*e.g.* bioplastics, cornstarch), bodily fluids (*e.g.* milk, plant exudates), and other natural materials (*e.g.* soil, coal) [4]. According to Albrecht Kossel's original proposal, natural products are divided into two classes; primary and secondary metabolites [5]. Primary metabolites have an important internal function in the survival of the organism that produces them. The secondary metabolites in contrast have an external function that significantly affects other organisms. Second metabolites are not essential for survival but increase biological competition in their environment. Because of their ability to alter biochemical pathways and signal transduction, some secondary metabolites have beneficial therapeutic properties. The most common classes of secondary metabolites include alkaloids, phenylpropanoids, polyketides, and terpenoids [6]. Although traditional medicines and other biological materials are considered an excellent source of novel compounds, the extraction, and isolation of these compounds can be slow and expensive. Because natural products are usually secondary metabolites with complex chemical properties, their total/semisynthesis is not always commercially viable. In these cases, attempts may be made to design simpler analogs with the same power and safety as the one that combines the essence/structure of the natural product [7]. There is a list of uses of natural compounds in various industries such as medicines, pharmaceuticals, cosmetics, food preservation, food safety, *etc.* Shen *et al.* (2021) reported the antifungal activity of Loquat leaves extract against citrus postharvest pathogens and provided a complete overview of the activity of anti-*Penicillium digitatum* activity. The antifungal activity of this extract against *P. digitatum* was said to be

caused by abnormal cell membranes and disruption of energy metabolism [8]. Jiménez-Gómez *et al.* (2021) explored another potential method to increase crop production: the replacement of chemical fertilizers with biofertilizers (including plant-root-associated beneficial bacteria). They describe their work, which assesses the use of *B. halotolerans* SCCPVE07 and *R. laguerreae* PEPV40 strains as efficient biofertilizers for escarole crops. Natural products have been used since ancient times to enhance food attributes [9]. Plants are added to foodstuff for their aromatic features, but also for preserving and coloring purposes. On the other hand, plants have also been playing an important role in fighting health issues, mostly due to their richness in secondary metabolites. Natural products have been used in the cosmetic industry to avoid side effects with traditional preparations for herbal beauty such as *Embllica officinalis* (Amla), *Acacica concinna* (Shikakai), and *Callicarpa macrophylla* (Priyangu) have been used strongly in skincare and hair care. Moreover, Indian women are still using natural products such as *Pterocarpus santalinus* L. and *Curcuma longa* (skincare), *Lawsonia inermis* L. (hair color), and natural oils such as coconut, olive, shea butter, jojoba, and essential oils in perfumes for their bodies [10].

Natural products may be extracted from the cells, tissues, and secretions of microorganisms, plants, and animals. Crude (unfractionated) extract from any one of these sources will contain a range of structurally diverse and often novel chemical compounds. Chemical diversity in nature is based on biological diversity, so researchers travel around the world to obtain samples to analyze and evaluate in drug discovery or bioassays. This effort to search for natural products is known as bioprospecting [11]. Examples of biological sources along with their natural products are described below Table 1.

Table 1. Medicinal uses of different natural products and their sources.

Source	Strain	Natural Compound	Medicinal Use	Ref.
Bacterium	<i>Streptomyces griseus</i>	Streptomycin	Antibiotic agent	[12]
-	<i>Paenibacillus polymyxa</i>	Polymyxins	Antibiotic agent	[13]
-	<i>Amycolatopsis rifamycinica</i>	Rifamycins	Used to cure tuberculosis and leprosy	[14]
-	<i>Clostridium botulinum</i>	Botulinum toxin	Used cosmetically to help reduce facial wrinkles	[15]
-	<i>Streptomyces verticillus</i>	Bleomycin	Used for the treatment of several cancers including Hodgkin's lymphoma, head and neck cancer, and testicular cancer	[16]
Archaea	<i>Pyrococcus furiosus</i>	Lactase enzyme	breakdown lactose, a disaccharide sugar found in milk	[17]

Novel Natural Compounds for Hepatocellular Carcinoma Treatment

Çağrı ÖNER^{1,*} and Emine ÇOLAK²

¹ Maltepe University, Medical Faculty, Department of Medical Biology and Genetics, İstanbul, Turkey

² Eskişehir Osmangazi University, Medical Faculty, Department of Medical Biology, Eskişehir, Turkey

Abstract: Due to the increase in cancer cases nowadays, an increase in studies related to treatment has been observed. Although many natural or synthetic compounds have been described as therapeutic today, the effects of these treatments are seen in both healthy and cancer cells. In order to reduce these undesirable effects seen in chemotherapy and radiotherapy, alternative treatments that have less effect on healthy cells or alternative attitudes that will allow the minimum use of therapeutics in these treatments continue to be investigated. In particular, such studies focus on natural compounds with phenolic properties. This chapter focuses on the relationship between coumarin derivatives, curcumin, *Olea europaea* leaf extract, and *Cynara scolymus* leaf extract with hepatocellular carcinoma. Furthermore, the effect of these natural compounds on the genetic hallmarks of various signalling pathways and important cellular metabolism molecules of hepatocellular carcinoma are discussed.

Keywords: Coumarin, Curcumin, *Cynara scolymus*, Hepatocellular Carcinoma, *Olea europaea*.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most occurring cancer type and cause of cancer-related death worldwide. HCC is seen more in males than females, and its development is also related to the age of individuals. There are some risk factors/diseases which might cause hepatocellular carcinoma to occur. The main diseases that cause hepatocellular carcinoma are chronic liver disease, cirrhosis and obesity; the main risk factors are viral hepatitis and excessive alcohol intake worldwide [1]. Chronic viral hepatitis infections, Hepatitis B and C, were indicated as the main causes of hepatic carcinogenicity and cirrhosis [1 - 4]. Because of this, the surface antigen of Hepatitis B (HBsAg) is the main marker of

* Corresponding author Çağrı ÖNER: Maltepe University, Medical Faculty, Department of Medical Biology and Genetics, İstanbul, Turkey; E-mail: cagri.oner@maltepe.edu.tr

hepatic diseases and HCC. However, HBsAg is useful to determine the HCC, and it is not the only marker to detect HCC. Hepatitis B core antibody (anti-HBc) is another marker to detect HCC earlier.

Furthermore, sometimes HBsAg might be negative while anti-HBc is positive in HCC patients. HBV vaccination is important for reducing the risk of HCC [5]. The impact of hepatitis C on HCC development is observed in patients with cirrhosis and advanced fibrosis [6]. Infection with hepatitis B and C also increases the risk of HCC. Alcohol consumption is the other risk factor for HCC. As known previously, excessive alcohol consumption is the main reason for cirrhosis. Furthermore, HCC development occurs approximately in 40-50% of cirrhosis patients. So alcohol consumption can be the main risk factor for HCC [7, 8].

Hepatocellular carcinogenesis also appears without excessive alcohol consumption; it may arise in obesity, non-alcoholic fatty liver (NAFLD) and diabetes patients. The risk factors of these diseases are the risk factors of hepatocellular carcinogenesis directly. Glucose mechanism failure leads to the observation of diabetes in patients. These deficiencies in diabetic patients result in the pathologies/diseases of the liver, including cirrhosis, fatty liver, chronic hepatitis, and liver failure. Detecting HCC in diabetes patients is 3-4 times higher than in healthy individuals [9, 10]. Anti-inflammatory, proliferative signaling pathways and the related growth hormones cause hepatocellular carcinogenesis. The major genetic markers of diabetes are insulin-like growth hormone, insulin receptor substrate 1, α -fetoprotein (AFP) and des- γ -carboxyl prothrombin (DCP). The other factor which affects HCC occurrence is obesity. As is well known, hepatobiliary disorders, including NAFLD, steatosis, and cirrhosis, are brought on by obesity and can cause people to develop HCC [11].

There are toxins or compounds which lead to observing HCC. The most known compound is aflatoxin. This toxin is related and found in grains, corn, peanuts and soybeans. The carcinogenic effect of aflatoxin is observed in moisture and warm conditions. The amount of aflatoxin intake determines the risk of being hepatocellular carcinoma [1]. Furthermore, alcohol consumption and smoking are the major risk factors for HCC.

In the liver and related organs, there are some essential mechanisms for the survival of individuals. In this chapter, we focus on the carcinogenesis of hepatocellular carcinoma and the effect of natural compounds on hepatocellular carcinoma.

NATURAL COMPOUNDS AND THEIR USAGE IN HEPATOCELLULAR CARCINOMA

Coumarin and Coumarin Derivatives

Coumarins were originally isolated in the 18th century from tonka beans (*Dipteryx odorata Willd.*, Fabaceae), and used for various purposes [12, 13]. Coumarin is a natural compound of many plants and essential oils, including tonka beans, sweet clover, woodruff, oil of cassia, and lavender. Furthermore, its name derives from the *Coumarouna odorata* plant [14]. Coumarin is an odorless complex conjugated to sugars and acids, but is released by the action of acids, enzymes, or ultraviolet (UV) radiation [14]. Coumarin compounds have been used to treat various diseases as antispasmodics, especially in cancer, bums, brucellosis and rheumatic disease [14].

The molecular weight of Coumarin is approximately 146.15, and it is colorless with a characteristic odor. Its melting point is between 68-70°C, and its boiling point is 303°C. In chloroform, coumarin can have a UV absorption maximum of 272 nm. Moreover, it can be easily solved in ethanol, chloroform, distilled water and oils [14].

Coumarin is a member of the benzopyrone family, and can be classified into 4 subgroups: simple coumarins, furanocoumarins, pyranocoumarins and pyrone-substituted coumarins [13, 15, 16]. The hydroxylated, alkoxyated, and alkylated derivatives of coumarins include molecules like 7-hydroxycoumarin and 6,7-dihydroxycoumarin, which are simple coumarins. The difference between Furanocoumarins and Pyranocoumarins is the number of furan rings attached to the coumarin nucleus. Pyranocoumarins are analogous to furanocoumarins. 4-hydroxycoumarin, synthetic coumarin derivatives warfarin and benzopyrones are examples of coumarins substituting in the pyrone ring [13, 16].

Coumarin Metabolism in Cells

Initially, coumarin is metabolized in the cytochrome p450 system in cells. In this system, hydroxylation has occurred. The important and well-known coumarin hydroxylations are 7th and 3rd positions. If the hydroxylation is at the 7th position, it is called 7-hydroxycoumarin. If it is at the 3rd position, it is called 3-hydroxycoumarin. 3-hydroxycoumarin is metabolized non-enzymatically. 0-hydroxyphenyllactic acid (OHPLA), 0-hydroxyphenylacetic acid (OHPAA) and glucuronide conjugate occurred as a result [14]. The activity of 7-hydroxycoumarin is greater in humans than in rodent microsomes. However, 3-hydroxycoumarin activity is observed highly in rodents [14].

CHAPTER 3

Herbal Drug Substitution (*Abhava-Pratinidhi Dravya*): A Key to Stopping Economic Adulteration of Botanical Ingredients

Arun Shivakumar¹, Atul Namdeorao Jadhav^{1,*}, Ashok Basti Krishnaiah² and Rangesh Paramesh³

¹ Himalaya Global Research Center FZ LLC, Dubai Science Park, Al Barsha, Dubai, UAE

² Research and Development Center, Himalaya Wellness Company, Bengaluru, Karnataka, India

³ Manal Family Office Holdings Ltd., Dubai International Financial Centre, Dubai, UAE

Abstract: Dwindling of natural resources coupled with the rising demand for several botanical ingredients in the Indian subcontinent and global market has led to scarcity and extensive adulteration. This may result in altered safety and efficacy of several single and polyherbal Ayurvedic formulations. Foreseeing this, Ayurveda experts have decided to use alternate herbal ingredients with similar properties. Such ingredients are known as *Pratinidhi* (a substitute) and are used in medicinal preparations. Because of the unavailability of a particular herb or the availability of the herb at a prohibitive cost, the usage of substitutes is necessary. This concept of substitution of herbs in Ayurvedic medicines is quite an elaborate and popular practice. In commerce, there are some predominant herbs whose substitutes or adulterants are also being traded. These substitutes belong to the same or different genera or cultivar species and may or may not have similar phytochemical constituents. This also relates to the use mentioned in the authoritative texts of Ayurveda and their modern pharmacological responses and safety. Ayurvedic system of medicine has an in-depth biochemical classification of herbs, based on which substitutes can be deduced. In addition, ancient texts have mentioned alternate herbs for some key ingredients.

In the present article, we are discussing commercially significant herbs, *viz. Ativisha, Bala, Guduchi* and *Vidanga*. These herbs have diverse clinical usage in Ayurveda and are reported to have properties such as immunomodulatory, anti-pyretic, anti-oxidant and anthelmintic. Based on this concept, the development of standard protocols for highly traded botanical ingredients will help the healthcare industry to meet the quality standards for medicinal products. Using substitute herbs will majorly reduce the overexploitation of natural resources and help bring balance to the ecosystem.

* Corresponding author Atul Namdeorao Jadhav: Himalaya Global Research Center FZ-LLC, Dubai Science Park, Al Barsha, Dubai, UAE; T: +9714 277 6008, Fax: +9714 277 6009; E-mail: dr.atul@himalayawellness.com

Keywords: Adulterant, *Ativisha*, *Bala*, Bioactive Constituent, Endangered Herbs, *Guduchi*, Herbal Trade, Herbal Medicine, IUCN, Pharmacology, Phytochemical Constitution, *Pratinidhi*, Substitute, *Vidanga*.

1. INTRODUCTION

The usage of herbal medicines for the management of the health and wellness of mankind is gaining interest globally. According to the latest WHO report, 80% of the world's population relies on herbal medicine, resulting in a new trend of integration of alternative and complementary medicine into mainstream healthcare systems gradually [1, 2]. National Health Interview Survey 2012 reveals that more than 56% of the US population suffers from chronic conditions, of which 22% of the population depends on herbal therapies [3]. Medicinal plants contain many phytoconstituents with potential therapeutic value, *viz.* flavonoids, polyphenols, saponins, glycosides, tannins, alkaloids and terpenoids [4]. They exhibit a unique mode of action with very few or no side effects, even after prolonged usage, unlike conventional medicine [5]. Herbal medicines are widely used for the treatment of chronic diseases and also for maintaining the health of the elderly, which is of utmost concern. A clinical study conducted in Turkey in both urban and rural populations with diabetes mellitus, hypertension and hyperlipidemia found that most of the patients believed herbal medicine to be effective (68.3% good effect, 11.1% minor effect) and had no adverse effects (85.7%) [6]. A survey conducted in Thailand for the treatment of arthritis, asthma, cancer, cardiac failure, stroke, coronary artery disease, cardiac arrhythmias, chronic obstructive pulmonary disease (COPD), diabetes mellitus and hypertension revealed that the herbs used for the treatment included herbs such as *Andrographis paniculata* (Burm.f.) Nees, *Curcuma longa* L., *Zingiber officinale* Roscoe, *Boesenbergia rotunda*, *Aloe vera* (L) Burm.f. and *Centella asiatica* (L.) Urb [7]. A comprehensive study involving 1601 participants, both from urban (47.5%) and rural areas (52.5%), was conducted in Vietnam to evaluate the use of herbal medicine in the treatment of chronic medical conditions. Stomach and intestinal diseases (39.6%); followed by gout and other musculoskeletal conditions such as chronic backache (23.8%) and arthritis (22.1%); hypertension (19.6%); cardiovascular disorders (9.6%); liver diseases (9.1%); migraine or frequent headaches (6.9%); diabetes mellitus (6.2%); dyslipidaemia (6.2%); kidney diseases (6.0%); asthma (4.0%), cancer (2.9%), thyroid diseases (2.5%); mental disorders (2.1%); COPD (0.9%); Parkinson's disease (0.7%); and epilepsy (0.3%), were treated with herbal medicines [8]. The global trend for research on herbal ingredients has been increasing exponentially over a decade, with India and China leading in publishing research articles, that is, around 800 to 1100 articles per year [9]. The International Union for Conservation of Nature (IUCN) Red List

of Threatened Species is the world's most comprehensive source for information on the global extinction and risk status of plant and animal species. It is estimated that more than 115,291 plant species have not been evaluated by the IUCN Red List of Threatened Species™ [10]. Threat and extinction of these medicinal herbs force us to adopt the concept of drug substitution, *i.e.*, *Abhava-pratinidhi dravya*, which is well documented (in 15th- and 16th-century literature) and practiced in Ayurvedic medicine [11]. The principle of *Abhava-pratinidhi dravya* describes using potential alternative herbs in clinical practice by an Ayurvedic physician without compromising safety and efficacy.

2. ECONOMICS OF HERBAL TRADE & ADULTERATION PRACTICES

The herbal industry is estimated to be at about US100\$ billion with a consistent annual growth rate of 15% [12]. Herbal trade includes essential oils, extracts, phytopharmaceuticals, gums, spices used in medicine and tannins for pharmaceutical use and cosmetics. The global export market of medicinal plants is contributed majorly by five countries: China (27.1%), Hong Kong (7.6%), USA (7%), India (6.5%) and Germany (6.1%) [13]. The US Food and Drug Administration regulates botanical ingredients and finished products under separate regulations under the Dietary Supplement Health and Education Act of 1994 (DSHEA). “Economically motivated adulteration” (EMA) is defined as the “fraudulent, intentional omission, substitution or addition of a substance in a product to increase the apparent value of the product or reduce the cost of its production, *i.e.*, for economic gain.” The American Botanical Council is continually upgrading the American Botanical Council, the American Herbal Pharmacopoeia and the University of Mississippi's National Center for Natural Products Research Botanical Adulterants Programs, which emphasize both accidental and intentional adulteration of botanical ingredients. These programs are commended by Canada, which involve herbal experts from universities, industry and government bodies to establish quality control for possible adulterants and identify the availability of official or unofficial analytical methods to help detect these adulterants [14].

Adulteration of botanical ingredients may be accidental or intentional for financial gains. Species-level adulteration ranges from 21% (in the case of *Crocus sativus* L.) to 80% (in the case of *Berberis asiatica* Roxb. Ex DC.) [15]. The growing demand for supplements for weight management necessitates herbal supplement manufacturers to add non-plant-derived compounds into the products to compete in the market. A detailed study conducted in Iran on weight management products available in the market has shown that for weight loss, sibutramine, laxative medicines (phenolphthalein) and appetite suppressants (amfepramone) are used in

Synthetic and Natural Agents as Bacterial Biofilm Inhibitors

Ethiraj Kannatt Radhakrishnan^{1,*} and Anjitha Theres Benny¹

¹ Department of Chemistry, School of Advanced Science, VIT, Vellore, Tamil Nadu-632014, India

Abstract: A biofilm is a form of bacterial cluster normally seen in environmental niches. They are immobile communities that colonize and develop on medical implants like sutures, catheters and dental implants, which can be treated only by their removal, leading to unaffordable treatment. The main biofilm consequence is its increased tolerance to negative environmental conditions, which includes resistance to antibiotics and antimicrobial agents. The high resistance of bacterial biofilm towards external stress and antibiotics is due to the extracellular polymeric matrix, which provides a barrier from the external environment. The biofilm development is facilitated by the cell-to-cell communication mechanism of bacteria called quorum sensing, which promotes the bacterial community to mature. There is a huge number of naturally occurring chemical compounds that can act as antibiofilm agents. Different chemical compounds resist bacterial biofilm growth by different mechanisms depending on the chemical structure of the molecule, and the stage of biofilm formation at which we introduce the chemical compound into the biofilm system. The anti-biofilm activity of a natural or synthetic compound mainly depends on certain aspects; some of them will deal with the inhibition of the formation of the polymer matrix, some others may suppress the cell adhesion and its attachment to itself or an external surface, while others deal with the interruption of extracellular polymeric matrix generation and lessening virulence factors production, thereby hindering QS network and biofilm development.

Keywords: Antagonistic, Antibiofilm, Antimicrobial, Autoinducers, Efflux Pump, Extracellular Polymeric Matrix, Multidrug-resistant, N-acyl Homoserine Lactones, Persisters, Photodynamic Therapy, Magnetic Nanoparticles, Violacein, Virulence Factor, Quorum Sensing, Quorum Quenching.

INTRODUCTION

Today microbial control is an ever-increasing economic concern disturbing human beings and animals. There are many phases for this crisis, making it difficult to overcome; the existence of various antimicrobial resistance and

* Corresponding author Ethiraj Kannatt Radhakrishnan: Department of Chemistry, School of Advanced Science, VIT, Vellore, Tamil Nadu-632014, India; Email: ethukr@gmail.com

altering regulations in the bacterial body due to the increased awareness of the bacteria to its surroundings may make the antibiotics inefficient. Antimicrobial resistance occurs naturally in a microorganism and is a dynamic threat due to its capability to evolve and express resistant genes, finally leading to the selection of resistant microbial clones. This fact pointed to the requirement for new, potent antimicrobials, which can overcome the negatives of the existing ones [1]. Recent literature review shows advancements in the field of developing potent antimicrobial compounds. Jaspreet S. Dhau *et al.*, studied the anti-bacterial efficiency of various pyridylselenium compounds like bis[3-(4-chloro-N,N-diethylpyridine-2-carboxamide)] diselenide and bis(3-bromo-2-pyridyl) diselenide against different bacterial strains, including *Bacillus pumilus* (MTCC-1607), *Escherichia coli* (MTCC-1687), *Bacillus subtilis* (MTCC-441), *Staphylococcus aureus* (MTCC-737) and *Pseudomonas oleovorans* (MTCC-617) [2 - 4] .

Biofilm formation is a significant field to study once dealing with antimicrobials and antimicrobial resistance of bacterial biofilm. Biofilms are aggregates of multicellular organisms found associated with abiotic or biotic surfaces where bacteria are found embedded in extracellular polymeric matrix [5]. They express higher resistance to antibiotics than planktonic ones due to the poor penetration of drugs into the biofilm [6]. The major reason for the increased resistance of biofilm is the presence of an extracellular polymeric matrix [7].

The extracellular matrix, composed of polysaccharides, proteins, lipids, and DNA, slows or nullifies the diffusion of antibiotics into the biofilm. The resistance of biofilm thus leads to its propagation and further development [8]. Along with the inhibition of antibiotic entry into the cells, bacteria can also resist antibiotic drugs by some other mechanisms. Any kind of variations in the microenvironment of biofilm-like, change in temperature, low availability of water, and change in availability of nutrients, oxidative stress, and starvation may activate some adaptive stress responses inherent in bacteria. This response will then further lead to the alteration of the bacterial cell by which it enters into the spore-like persister state, where they are extremely safe. The presence of persisters inside the biofilm is the reason for the high antibiotic resistance [9]. Another mechanism by which bacterial biofilm resists antibiotics is the method known as efflux pumping. The efflux system allows the expelling of antibiotics, biocides, metabolic products, organic solvents, and dyes out of the biofilm system to enhance biofilm development. Hence, in order to overcome its activity, promising modifications are required in developing new antibiotics [10].

In nature, microorganisms rarely live in planktonic form, but rather they prefer communal growth or aggregates. Bacteria achieve the self-immobilisation in aquatic or soil systems by the cell surface hydrophobicity of the organism.

Bacterial cell surface hydrophobicity promotes bacterial colonisation and hence biofilm formation [11]. The studies done by various researchers found that there is a positive correlation between cell surface hydrophobicity and virulence factors and biofilm formation [12]. Hence, drugs that are capable of reducing the thickness and cell surface hydrophobicity of the bacteria can lead to a reduction in biofilm formation.

All the known mechanisms of bacterial resistance to antibiotics make the chemists aware of developing more potent antibiotics which can overcome all the possible resistance mechanisms. The chapter deals with a few methods by which biofilm inhibition can be achieved by making use of various synthetic and natural compounds. The methods include quorum quenching, extracellular polymeric matrix formation, inhibition of biofilm formation, and efflux pump inhibition.

QUORUM QUENCHERS

Due to the overuse of antibiotics, bacteria become multidrug-resistant, and it is an immediate necessity to find an alternative method for antimicrobial therapies. The most promising strategy for that is to target the main physiological property in the biofilm, and it is quorum sensing (QS). QS is the mechanism by which bacteria communicate with each other. The mechanism is based on the constant flow of signalling molecules called autoinducers (AI) [13]. In the case of gram-negative bacteria, N-acyl homoserine lactones (AHLs) play the role of AI, and in gram positive bacteria, it is AIPs. [14].

Quorum quenching (QQ) that can disrupt the communication of bacteria can act as a driving force for the lessening or even complete inhibition of virulence factors and biofilm formation. The quorum quenching approaches include the use of structural analogues of auto-inductors which are QS receptors. The structural analogues of these can be synthesized in laboratories or can be isolated from natural sources. There are a vast number of naturally occurring compounds that can hinder the communication of microbes [15, 16]. There are different methods by which QS can be inhibited, and the mechanisms involved in quorum sensing inhibition are listed below.

- Inhibiting the synthesis of signal molecules by blocking Lux operon proteins [17].
- Enzymatic degradation [18] or inactivation of signal molecules by changing the pH to alkaline [19] or by changing temperature [19] and thereby leading to lactonolysis [20].
- The enzymatic degradation of AHL is the best method of QQ. The enzymatic degradation can be catalysed by enzymes like lactonases, acylases, reductases,

Quercetin Chemistry, Structural Modifications, SAR Studies and Therapeutic Applications: An Update

Nazia Banday¹, Prince Ahad Mir², Mudasir Maqbool³, Rafia Jan⁴, Nyira Shafi⁵, Roohi Mohi-ud-din^{1,6,*} and Reyaz Hassan Mir^{7,8,*}

¹ Pharmacognosy and Phytochemistry Lab, Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar-190006, Kashmir, India

² Khalsa College of Pharmacy, G.T. Road, Amritsar, 143002 Punjab, India

³ Pharmacy Practice Division, Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar, 190006, Kashmir, India

⁴ Defence Research and Development Organization (DRDO), Hospital, Khonmoh, Srinagar 190001, Jammu & Kashmir, India

⁵ Pharmacology Division, Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar, 190006, Kashmir, India

⁶ Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu, and Kashmir, India

⁷ Pharmaceutical Chemistry Division, Chandigarh College of Pharmacy, Landran, Punjab-140301, India

⁸ Pharmaceutical Chemistry Division, Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar-190006, Kashmir, India

Abstract: Natural products are investigated for their remunerative effects on health. Quercetin, a flavonoid, is commonly distributed in vegetables and fruits. Quercetin is used as a supplement in food and as a phytochemical remedy against several diseases, including circulatory dysfunction, neurodegeneration, diabetes, cancer, and inflammation. The most prominent property of quercetin is its antioxidant activity, enabling it to douse free radicals. Derivatives of quercetin are essential metabolites, and even various conjugates are being advocated by the Food and Drug Administration (FDA) for use in humans. So, the biosynthesis of quercetin derivatives is a predominant field of research. Methylation and glycosylation are two essential strategies used to synthesize various metabolites of quercetin that do not exist in nature. This review

* **Corresponding authors Roohi Mohi-ud-din and Reyaz Hassan Mir:** Pharmacognosy and Phytochemistry Lab, Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar-190006, Kashmir, India; Tel: +917006320884; and Pharmaceutical Chemistry Division, Chandigarh College of Pharmacy, Landran, Punjab-140301, India; Tel: +917051433380; E-mails: roohisofi@gmail.com; reyazhassan249@gmail.com

Shazia Anjum (Ed.)

All rights reserved-© 2023 Bentham Science Publishers

summarizes quercetin chemistry, structural modifications, Structure-Activity Relationship (SAR) studies, and therapeutic applications of quercetin.

Keywords: Flavonoids, Quercetin Derivatives, Quercetin, SAR Studies, Therapeutic Applications.

1. INTRODUCTION TO FLAVONOIDS

Flavonoids are a group of plant-derived substances with a similar flavone structure. The basic skeleton comprises two aromatic rings (A and B) attached to a heterocyclic ring (C) that integrates the aromatic rings [1, 2] (Fig. 1). Flavonoids are available in glycoside-bound and free aglycone [3, 4]. There are over 4,000 different types of flavonoids in nature, which are classified as anthocyanidins, flavones, chalcones, flavonols, and isoflavones. Flavonoids exhibit various pharmacological effects, such as antimicrobial, antioxidant, anti-inflammatory, and hepatoprotective [5 - 13].

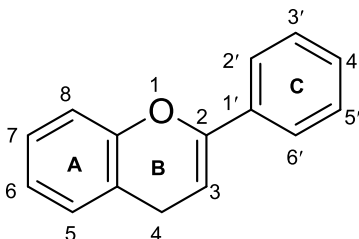


Fig. (1). Fundamental arrangement of flavonoid.

1.1. Quercetin Chemistry and Source

The chemical name for quercetin is (2-(3,4-dihydroxy phenyl)-3,5,7-trihydroxy-4-H chromen-4-one) Fig. (2) [14, 15]. The word Quercetin is derived from the Latin word Quercetum, which means oak forest. It has a yellow color to it. It is insoluble in cold water, slightly soluble in hot water, and entirely soluble in lipids and alcohol [16, 17]. It's one of the most potent antioxidants, usually found in edible plants [18 - 21]. Quercetin possesses many beneficial qualities, including anti-inflammatory, central nervous system stimulant, anticancer, and anti-infection [22]. Quercetin can also affect blood clotting *via* thrombin inhibition [23]. Quercetin has been shown to have neuroprotective properties in both *in-vivo* and *in-vitro* investigations [24]. Additionally, quercetin is used for ischemia [25], Huntington's disorder [26], and Parkinson's disorder [27].

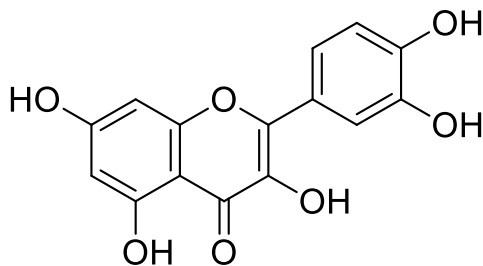


Fig. (2). Chemical structure of quercetin [14, 15].

Quercetin is a di-phenyl propane molecule with 15 carbon atoms in its structure. It is made up of two benzene rings and a pyran ring. 4-oxo-flavonoid is a flavonoid with a carbonyl group at the C-4 position in its 'C' ring. Flavonoids are divided into sub-classes based on pyran ring oxidation and substitutions, flavones, flavonols, flavanones, flavan-3-ols, flavonols, and isoflavones [28, 29]. With a chemical formula of $C_{15}H_{10}O_7$, quercetin belongs to the flavone subclass of flavonoids. According to IUPAC nomenclature, it is also known as 2-(3,5-Dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one. Five hydroxyl groups can be found in quercetin at positions 3, 5, 7, 3', and 4'. It is an aglycone because quercetin lacks an associated sugar moiety. The production of glycosidic quercetin occurs when at position 3 hydroxyl group is replaced by glucose, galactose, rhamnose, or rutinose. Quercetin is water-insoluble or nearly insoluble. The addition of (glucose, rhamnose, or rutinose) to quercetin enhances its solubility in water thus, unlike quercetin, glycosidic quercetin is water-soluble [22, 30]. Due to numerous hydroxyl groups, it has been attributed to the cause of its photo-degradation, in addition to being responsible for its antioxidant capabilities. It has been claimed that the 3,3' and 4' positions hydroxyl groups are principally accountable for their photo-labile feature, while the hydroxyl groups at the 5 and 7 locations play no role [31]. Quercetin is well-known for its anti-inflammatory properties. In addition, glycosylated quercetin has been found to have lower anti-inflammatory properties than quercetin [32]. When quercetin is glycosylated at position 3, it loses its capacity to neutralize free radicals and inhibit Acetylcholine levels [33]. When quercetin is methylated at the 4' and 7' sites, its anticancer capabilities enhance. The metabolic stability of quercetin can be improved by replacing the hydroxyl group with an O-methylated group [34]. The presence of a double bond across carbon 2 and 3 in quercetin, as well as the hydroxyl group in the 'B' ring, is critical for thrombin inhibition. When hydroxyl groups in the 'B' and 'C' rings are replaced with methoxy groups, the inhibiting activity of thrombin is reduced, but replacing hydroxyl groups in the 'A' ring with methoxy groups increases the inhibitory activity of thrombin [35]. Due to the catechol group in the 'B' ring, a 2,3 double bond in the 'C' ring, and a hydroxyl group at C-3 position, quercetin leads to oxidative stress by increasing Reactive

SUBJECT INDEX**A**

- Acid 4, 12, 43, 49, 80, 88, 104, 105, 106, 107
 ascorbic 4, 12
 caffeic 43
 chlorogenic 49
 cinnamic 106
 citric 104
 elenolic 43
 ellagic 105
 hibiscus 105
 linoleic 105
 lyngbyoic 107
 myristic 80
 neochlorogenic 49
 octadecatrienoic 49
 oleic 80
 quinic 49
 salicylic 88, 104
 stearic 80
 Ursolic 4
 vanillic 43, 88
Aconitum heterophyllum 78
Action 18, 106, 116, 146, 147, 149
 antagonistic 106
 anti-inflammatory 18
 antioxidative 146
 enzymatic 116
 hepatic glucokinase 147
 neuroprotective 149
Activity 113, 117, 119, 145, 147, 149
 anti-atherosclerotic 145
 anti-bacterial 117
 antilipogenesis 149
 antimicrobial 113, 119
 immunoregulatory 145
 metabolic 147
Acyl homoserine lactones (AHLs) 100, 102,
 103, 107, 108, 109
Alzheimer's disease 18, 83, 143, 148
Angiogenesis 18, 38, 39, 41, 44, 46, 47, 49
 reduced inflammatory 44
 tumor 47
Antibacterial 4, 13, 47, 49, 87, 88, 89
 activity 13
 agents 47
 drug 4
Antibiofilm activity 105, 114, 115, 116, 117,
 118, 120, 121
Anti-carcinogenic activity 43
Anti-cholinesterase activities 86
Anti-gastric ulcer 36
Anti-inflammatory 7, 11, 18, 36, 136, 145
 activity 11, 18, 145
 agent 7
 effects 36
 properties 11, 136, 145
Antimalarial 86, 100, 112, 113
 activities 86
 agents 100, 112, 113
Antioxidant 2, 9, 10, 13, 44, 46, 50, 134, 147
 activity 2, 9, 10, 134
 enzymes 13, 44, 50, 147
 mechanism 9
 pathways 46
Antitumor 46, 47
 activity 46
 effects 47
Apoptosis 8, 10, 18, 35, 36, 37, 41, 42, 44, 45,
 46, 47, 48, 49, 143, 144
 cancer cell 18
Apoptotic pathway 38, 39, 41, 42
 caspase-dependent 39
Arthritis 4, 17, 74
Asthma 1, 74, 87
Atherosclerosis 4, 10, 18

B

- Bax protein 8
Biofilm 113, 116, 117
 biomass assay 117
 degradation 113, 116
Box-Behnken design (BBD) 11

Shazia Anjum (Ed.)

All rights reserved-© 2023 Bentham Science Publishers

Brassica oleracea 105
Breast carcinomas 148

C

Caenorhabditis elegans 89
Candida albicans 119
Capillary electrophoresis 16
Carcinogenesis 18, 33, 47
 hepatocellular 33
Cardiac fibrosis 10, 145
Cardiovascular disease 10, 18, 19, 145
CDK proteins 44
Chemotherapeutic 41, 49
 agent 49
 effect 41
Chinese hamster ovary (CHO) 9
Chromatography 16
 column 16
 high-performance liquid 16
Chronic 32, 74
 obstructive pulmonary disease (COPD) 74
 viral hepatitis infections 32
Clostridium botulinum 3
Consumption, reducing glutathione 40
Curcumin 1, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16,
 17, 18, 19, 20, 32, 38, 39, 40, 41
 alcoholic 7
 combination 39
 deprotonated 9
 injection 12
 isomer 9
 neutral 9
 synthetic 39
 therapy 39
Cyclooxygenase 36, 145
Cystic fibrosis 113, 118
Cytochrome 34, 37, 44, 50, 143
 releasing 44
Cytokines 145, 146, 149
 inflammatory 145

D

Degradation, neuronal 18
Diabetes 1, 12, 33, 80, 134, 147
 streptozotocin-induced 12
Diabetes mellitus 74, 83, 147
 hyperglycemia 147
Diarrhea 4, 78, 80, 81
Diseases 1, 8, 33, 34, 74, 146, 148
 chronic 74
 chronic obstructive pulmonary 74
 coronary heart 148
 heart 1
 hepatic 33
 inflammatory 146
 intestinal 74
 neurogenerative 8
 rheumatic 34
 thyroid 74
Disorders 4, 6, 20, 33, 74, 83, 84, 87
 cardiovascular 74
 hepatobiliary 33
 mental 74
 metabolic 20
 nervous system 84
 rheumatic 83
 skin 4, 6
 urinary system-related 84
DNA 37, 40, 44, 48, 101, 111, 113
 binding activity 37
 cleaving 113
 damage 37, 40
 fragmentation data 48
Dyslipidaemia 74

E

Efflux pump inhibitors (EPIs) 118, 120, 121
Enterococcus faecalis 115, 117
Enzymes 8, 40, 103, 104, 109, 110, 111, 112,
 113, 114, 116, 145, 146, 148
 alginate lyase 114
 antioxidant defense 8
 oxidoreductase 109, 110

Subject Index

protease 113
proteolytic 114
xenobiotic metabolizing 40
Epilepsy 18, 74
Epithelial-mesenchymal transition (EMT) 36, 40
EPS-degrading/antimicrobial approach (EDA) 113

F

Factors 18, 40, 44, 46, 80, 84, 44, 143, 145
hypoxia-induced 143
immune system-related transcription 44
induced tumor necrosis 145
pro-inflammatory transcription 18
vascular endothelial growth 40, 46
Fatty acids 9, 46, 49, 84, 87
reducing plasma-free 9
synthase activity 46
Fever 1, 4, 78, 81
hay 1
Functions 10, 37, 118, 143, 146
antihyperglycemic 146
anti-inflammatory 146
cognitive 143
mitochondrial 10

G

Gas chromatography-mass spectroscopy (GCMS) 80
Gastric cancer 143
Gastrointestinal disorders 87
GAT mechanism 9
GCM-related autophagy induction 37
GCMS analysis 80
Gel electrophoresis 11
Glucanohydrolase 113
Glutathione 12, 147
peroxidase (GPx) 12
reductase (GR) 12, 147
Glycogenolysis 147
Glycosidase 112

Frontiers in Natural Product Chemistry, Vol. 11 163

Glycosylation process 139
Growth, cardiomyocyte 10

H

Heart disorder 4
Helicobacter pylori 13
Hepatic 32, 147
carcinogenicity 32
gluconeogenesis 147
Hepatitis 32, 33, 40, 87
chronic 33
Hepatocellular carcinoma pathway 51
Hepatoprotective activities 78, 85
Herbal 47, 74, 76
medicines 47, 74, 76
therapies 74
High-performance 16, 80, 84, 89
liquid chromatography (HPLC) 16, 89
thin-layer chromatography (HPTLC) 80, 84
Hodgkin's lymphoma 3
Huntington's disorder 135
Hydrogen peroxidase 115
Hypolipidemic effects 86

I

Immune cell aggregation 146
Immunomodulatory properties 83
Immunosuppressant 80
Inducing DNA fragmentation 48
Industries 75, 79, 85
herbal 75, 79, 85
herbal drug 85
Inflammation 8, 10, 11, 18, 20, 38, 51, 78, 80, 86, 134, 145, 146
adipose tissue 146
chronic 18
diabetes-related 86
irradiation-induced 146
Inflammatory bowel disease 20
Ischemia, myocardial 145

K

Kang's method 16
Klebsiella pneumoniae 115

L

Lactase enzyme 3
Lactonase 103, 104, 109
 enzyme 109
Leukemia 35, 37, 49
 human chronic myeloid 49
Lipid peroxidation 146, 148
Lipogenesis 142, 148, 149
Lipoxygenase 18, 36, 145
Liquid chromatography-mass spectrometry
 11, 84
Liver 13, 33, 47, 74
 cancer 47
 diseases 74
 failure 33
 fibrosis 13

M

Metabolic syndrome 17, 147
Methicillin-resistant *Staphylococcus aureus*
 (MRSA) 116
Microemulsion electrokinetic 16
 chromatography 16
Mitochondrial 41, 45
 apoptosis 45
 dysfunction 41
Mitochondrial membrane 36, 46, 50, 142
 permeability transition (MMPT) 142
 potential (MMPs) 36, 46, 50
Mitogen-activated protein kinases (MAPK)
 12, 18, 19, 40, 44, 49, 143
Moringa oleifera 106
Multiple myeloma 20
Mycobacterium smegmatis 119
Myocardial infarction 10, 18

N

Necrosis, tumor 40
Neurodegenerative diseases 8, 148, 149
Neuroprotective effects 8, 18, 38
Nitric oxide synthase 8, 18, 40
Nuclear factor (NF) 20, 37, 40, 44, 45, 46

O

Osteoarthritis 1, 4
Oxidative 8, 10, 18, 20, 38, 44, 45, 101, 136,
 146, 147, 148
 damage 10, 38, 44, 148
 effects 45
 stress 8, 10, 18, 20, 44, 101, 136, 146, 147,
 148
Oxidoreductase 104, 110

P

Parkinson's disease 8, 18, 74
Pathways 2, 8, 18, 35, 36, 37, 44, 46, 48, 49,
 146, 149
 apoptotic death 46
 biosynthetic 2
 extracellular signal-regulated kinase 49
 mitochondrial-dependent 48
 signal transduction 8
Penicillium 4
 chrysogenum 4
 griseofulvum 4
Plants 2, 3, 5, 6, 42, 47, 75, 76, 77, 80, 81, 82,
 85, 86, 104, 135, 137
 authentic 76
 derived medicinal products 104
 edible 135
 therapeutic 47
Polycystic ovary syndrome 12
Properties 7, 8, 39, 42, 49, 73, 76, 80, 81, 83,
 84, 85, 116, 134, 135
 anti-angiogenic 39
 anti-apoptotic 49
 anti-ulcer 80

Subject Index

cariogenic 116
hypoglycemic 42
neuroprotective 8, 135
wound-healing 85
Proteins 39, 48, 101, 103, 110, 111, 113, 118,
144
 antiapoptotic 144
 sensor 103
Proteoglycans 51
Proteolytic activity 48
Proteus mirabilis 105
Pseudomonas aeruginosa 105, 113, 115

Q

Quinolone-resistant *Pseudomonas aeruginosa*
(QRPA) 116
Quorum quenching (QQ) 100, 102, 103, 104,
105, 106, 108, 109, 110, 116, 121
 activity 104, 105
 approaches 102
Quorum sensing (QS) 100, 102, 103, 104,
105, 106, 107, 108, 110, 111, 118

R

Radiation-induced graft polymerisation 116
Radical adduct formation (RAF) 9
Radiotherapy 32
Reactive oxygen species (ROS) 12, 20, 39, 45,
47, 50, 117, 137, 148
ROS 48, 144
 homeostasis 144
 mediated pathways 48

S

Scanning electron microscopy 117
Skin ulcers 4
Staphylococcus aureus 101, 106, 115, 119,
121
Stroke 10, 18, 74, 84

Frontiers in Natural Product Chemistry, Vol. 11 165

T

Thin layer chromatography (TLC) 16
Triggered apoptosis 44, 46, 50

U

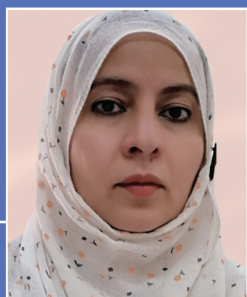
Ultrapformance liquid chromatography 16

V

Vascular endothelial growth factor (VEGF)
18, 40, 41, 46
Virulence factors production 100, 103

W

Wound-healing activity 13



SHAZIA ANJUM

Dr. Shazia Anjum is the Professor of the Chemistry Department and the Director of Cholistan Institute of Desert Studies, the Islamia University of Bahawalpur, Pakistan. She is experienced medicinal and natural product chemist. She has authored and co-authored more than 120 research papers (Impact Factor: 224.8) and a US patent. She has edited 10 books and has published 03 chapters in international books. She has accomplished the synthesis of several naturally occurring aminoglycosides that can be used as antibiotics. Dozen of students have completed their MS degrees under her supervision and couple of others are pursuing for their MS/PhD degrees.

As recognition of her contributions to science, she has been awarded with 03 International awards like Fellowship from Islamic World Academy of Sciences, Postdoctoral fellowship from Ministry of Culture and Education, Spain and a Young Chemist Award from Third World Academy of Sciences, Italy. She also has several national awards on her credit.