Frontiers in Natural Product Chemistry

Editor:
Atta-ur-Rahman, *FRS*

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Frontiers in Natural Product Chemistry

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Edited by

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

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CONTENTS

PREFACE

Frontiers in Natural Product Chemistry presents recent advances in the chemistry and biochemistry of naturally occurring compounds. It covers a range of topics, including important research on natural substances. The book is a valuable resource for pharmaceutical scientists and postgraduate students seeking updated and critically important information regarding bioactive natural products.

The chapters in this volume are written by eminent authorities in the field. Sathiyanarayanan et al. present a detailed review of the therapeutic potential of Propolis and its isolated key chemical constituents in chapter 1. Bölek and Tosya, in chapter 2, examine the effects of using omega-3 fatty acids on egg quality in functional egg production. Kumar et al. summarize the anticancer activities of Quercetin (QCT) on various cancer cells in chapter 3 of the book. Ahmad, in chapter 4, suggests that swertiamarin could be considered as a potential therapeutic agent for the treatment of metabolic syndrome. Bhardwaj et al., in the next chapter summarize the various traditional uses, pharmacological properties, and phytochemistry of Peganum harmala L. In chapter 6, Sahari and Ardestani discuss the methods of measurement of antioxidant activity and involved mechanisms. Pirani et al. explain the recent progress in natural and synthetic flavanones and their derivatives in the next chapter. Long et al., in the last chapter, discuss multiple beneficial effects of virgin coconut oil (VCO) and the mechanisms of therapeutic effects towards human health management.

I hope that the readers will find these reviews valuable and thought-provoking so that they may trigger further research in the quest for new and novel therapies against various diseases. I am grateful for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Editorial Director), Mr. Obaid Sadiq (In-charge Books Department), and Miss Asma Ahmed (Senior Manager Publications) at Bentham Science Publishers.

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

List of Contributors

Ajay Sharma	Department of Chemistry, Chandigarh University, NH-95, Chandigarh-Ludhiana Highway, Gharuan, Mohali, Punjab, India
Akshay Kumar	Department of Chemistry, DAV University, Jalandhar, 144012, India
Akshita Sharma	Department of Chemistry, Chandigarh University, NH-95, Chandigarh-Ludhiana Highway, Gharuan, Mohali, Punjab, India
Fatemeh Pirani	Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran
Feyza Tosya	Department of Food Technology, University of Health Sciences, Üsküdar, Istanbul, Turkey
Garima Bhardwaj	Department of Chemistry, Sant Longowal Institute of Engineering and Technology, Longowal, Sangrur, Punjab, 148106, India
Hardev Singh	Department of Chemistry, Chandigarh University, NH-95, Chandigarh-Ludhiana Highway, Gharuan, Mohali, Punjab, India
Harshad S. Kapare	Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, Maharashtra, India
Hossein Eshghi	Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran
Javed Ahamad	Department of Pharmacognosy, Faculty of Pharmacy, Tishk International University, Erbil, Kurdistan Region, Iraq
Kamariah Long	Food Science and Technology Research Center, Malaysian Agricultural Research & Development Institute (MARDI), Persiaran MARDI-UPM, 43400 Serdang, Selangor, Malaysia
Mahsa Khoshnevis	Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran
Mohammad Ali Sahari	Department of Food Science and Technology, Faculty of Agriculture, Tarbiat Modares University, Tehran, Iran
Pankaj Chauhan	Indian Institute of Technology Jammu, Jammu - 181 221 J&K, India
Raymond Cooper	Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong
Sadhana S. Raut	Sinhgad College of Pharmacy, S. No. 44/1, Vadgaon (BK), Off Sinhgad Road, Pune, Maharashtra, India
Samira Berenji Ardestani	Department of Food Science and Technology, Faculty of Agriculture, Tarbiat Modares University, Tehran, Iran
Sarbjit Singh	Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE 68198, USA
Sathiyanarayanan L.	Poona College of Pharmacy, Bharti Vidyapeeth Deemed to be University, Erandwane, Pune, Maharashtra, India
Sibel Bölek	Department of Food Technology, University of Health Sciences, Üsküdar, Istanbul, Turkey

Soo Peng Koh Food Science and Technology Research Center, Malaysian Agricultural Research & Development Institute (MARDI), Persiaran MARDI-UPM, 43400 Serdang, Selangor, Malaysia

Yih Phing Khor Food Science and Technology Research Center, Malaysian Agricultural Research & Development Institute (MARDI), Persiaran MARDI-UPM, 43400 Serdang, Selangor, Malaysia

CHAPTER 1

Propolis and its Key Chemical Constituents: A Promising Natural Product in Therapeutic Applications

Harshad S. Kapare[1], **Sadhana S. Raut**[2] and **L. Sathiyanarayanan**[3,*]

[1] *Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, Maharashtra, India*

[2] *Sinhgad College of Pharmacy, S. No. 44/1, Vadgaon (BK), Off Sinhgad Road, Pune, Maharashtra, India*

[3] *Poona College of Pharmacy, Bharati Vidyapeeth Deemed to be University, Erandwane, Pune, Maharashtra, India*

Abstract: Propolis is a natural resinous and waxy product obtained from honey bee combs. Although propolis has been now explored globally for its wide range of chemical constituents and its therapeutic value, the detailed investigation of pharmacological activities of its key chemical constituents and its analogues is in its infancy. In this study, a detailed review of the therapeutic potential of propolis and its isolated key chemical constituents was carried out to provide basic literature data required for further detailed investigation and discover new therapeutic potential molecules from propolis. Till now, more than 300 isolated chemical compounds are reported from worldwide propolis samples that include the presence of various polyphenols, flavonoids, esters, beta-steroids, aromatic aldehydes, alcohols, *etc*. Some specific chemical constituents of propolis, such as pinocembrin, are reported for its potential neuroprotective action with reduced neurodegeneration in the cerebral cortex and enhanced cognitive function in Aβ25-35-treated mice. Galangin is also well proven for acetylcholinesterase enzyme inhibition and AβPP-Selective BACE inhibitor (ASBI), which may be developed as a new therapeutic agent for Alzheimer's disease. Caffeic acid phenethyl ester is reported as a moiety isolated from European propolis; it is present even in the form of a mixture of caffeic acid esters and phenethyl ester for antibacterial and antifungal properties. *In vitro* and *in vivo* evidence suggested that caffeic acid phenethyl ester has cytotoxic mechanisms, including the activation of p21protein, p38 MAPK, p53, and JNK kinase activity, inhibition of NF-B, and increased caspase-3 or 7 activity. Various pharmacological activities are reported for different propolis extracts, as well as for its constituents that include antioxidant, anti-ulcer, anti-cancer, antiviral, anti-microbial, anti-inflammatory, anti-fungal, *etc*. Propolis possesses tremendous therapeutic potential, and it is also reported worldwide in various traditional systems of medicine. In this study, the key chemical constituents, pharma-

* **Corresponding author Dr. L. Sathiyanarayanan:** Poona College of Pharmacy, Bharati Vidyapeeth Deemed to be University, Erandwane, Pune- 411038, India; Mob: +91 9371085066; Tel:(020) 25437237; E-mail: pharmsathiya@gmail.com

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cological activities, various critical issues in its application in drug delivery, and detailed investigation on approaches for formulation development to enhance biopharmaceutical aspects of propolis have been reviewed.

Keywords: Cytotoxicity, Flavonoids, Neuroprotection, Polyphenols, Propolis.

INTRODUCTION

Natural Products

Natural products have been used as medicinal agents and defensive compounds to slow the progression and effects of different diseases for thousands of years. The use of natural products is reported more than 85-90% of the population for their primary health services. About 73% of the pharmaceutical products are derived from natural products [1]. Natural product study in the pharmaceutical industry has decreased in the last 5-10 years due to the incompatibility of traditional natural product extract libraries with high-throughput screening [2].

There are some advantages of natural products as an entity in drug discovery, given as follows:

There is structural and chemical diversity in natural entities. As a result, researchers are focusing on synthesizing new chemical entities with advanced techniques, such as computational molecular modelling, *etc*. Due to drug-likeness and biological friendliness features, they exhibit advanced binding characteristics.

Natural product structures have biochemical specificity, making them good candidates for drug development lead structures. Enzymatic interactions are responsible for the synthesis of natural products. As a result, protein binding is involved in their biological function.

Secondary metabolites from natural products are very susceptible to have biological activity as compared to synthetic compounds [3].

Over the last few decades, developments in genomics and structural biology have revealed a complete picture of the variety of proteins targeted by natural products. Aside from these factors, emerging lead generation techniques have rekindled interest in natural products in drug development [4].

Propolis

Natural products are increasingly being used to treat a wide range of diseases. Natural products have always been used as an alternative to conventional allopathic formulations in the medical field. Propolis is one such natural substance that has gone unnoticed despite its potential applications in a wide range of diseases, such as acne, herpes simplex and genitalis, and neurodermatitis, and also in wound healing, burn treatment. The term propolis is derived from the Greek word “pro” before, and “polis” city or defender of the city [5]. The Egyptians were well aware of its anti-putrefactive properties and embalmed their cadavers with bee glue. Propolis was used as an antipyretic by the Incas. It was used by Greek and Roman physicians as a mouth disinfectant, antiseptic, and in wound healing treatments for topical therapy of cutaneous and mucosal wounds. In Folk Georgian medicine, propolis ointment was used for the treatment of diseases. There was a custom of placing a propolis cake on the belly button of a newborn baby, and they also rubbed propolis on children's toys. Propolis is widely used in folk medicine, particularly for the treatment of corns. People inhale propolis when they have respiratory tract or lung problems. It is also useful for burns and angina. Propolis has also been used successfully to treat wounds during the Anglo-Boer War and World War II; it was used as an anti-inflammatory with vaseline in the preparation of an ointment to heal war wounds. Because antibiotics were not yet available, this helped save the lives of many soldiers. It was also used in hospitals. 1969, Union of Soviet Socialist Republics (USSR) accepted the use of propolis 30% as anorthomedix medicine (30% alcoholic solution of propolis). As a result, this product has gained popularity as a traditional (folk) medicine for health improvement and disease prevention. It has also been used in mouthwash and toothpaste to prevent caries, treat gingivitis and stomatitis, as well as cough syrups, oral pills, lozenges, ointments, lotions, and vitamins. Propolis is frequently used by therapists to treat inflammations, viral diseases, fungal infections, ulcers, and superficial burns along with acupuncture, ayurveda and homeopathy [6], and the healing properties of propolis were recognized by Greek civilizations. Hippocrates, the father of modern medicine, also used propolis to treat sores and ulcers. Over the last ten years, significant research on propolis has been conducted in the United States, Australia, the United Kingdom, and Europe, particularly in Eastern Europe. Propolis is available in a variety of forms on the global market, including capsules, lozenges, tincture, cream, mouth rinses, and toothpaste [5].

In ancient times, propolis was been widely used by different cultures for various purposes, among which its use in medicine is included. Currently, research is being carried out on its activity, effects, and possible uses in biology and medicine. The most prominent are its application as a dietary supplement, its use in the pharmaceutical industry and clinical applications in animal science [5]. The physical appearance of raw propolis shows a waxy substance with yellowish-brown to dark brown colour, as shown in Fig. (**1**)

CHAPTER 2

Investigation of the Effects of Using Omega-3 Fatty Acids on Egg Quality in Functional Egg Production

Sibel Bölek[1,*] and **Feyza Tosya**[1]

Department of Food Technology, University of Health Sciences, Üsküdar, Istanbul, Turkey

Abstract: Omega-3 polyunsaturated fatty acids (PUFA) have many beneficial effects on health such as lowering the level of inflammatory agents, stimulating fat oxidation in adipose tissue and reducing body weight, reducing the risk of cardiovascular diseases, regulating blood glucose level and increasing insulin sensitivity. However, the intake of omega-3 fatty acids with a normal diet is often insufficient to meet the daily requirement. In this case, besides food supplements, functional foods enriched with omega-3 are an important alternative as an omega-3 source, such as eggs and animal meat. Omega-3 enriched eggs are usually obtained from chickens fed feeds enriched with omega-3 sources. Among these sources, flaxseed, fish meat and fish oil, chia seeds, various microalgae and their combinations used in different proportions can be cited. While the alpha linolenic acid content is higher in flax and chia seeds, fish oil and microalgae have higher levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). It has been observed that the chicken eggs fed with feeds enriched with algae generally have higher fatty acids, antioxidants and carotenoids. However, some studies have reported that chicken eggs fed seafood and flaxseed have a fishy odor or taste. Therefore, in this study, it was aimed to examine and evaluate the changes in egg composition of different chicken feed combinations and to determine the closest option to optimum feed content. The results of this study revealed that enrichment of chicken feeds with a combination of seafood and oilseeds can increase the sensory acceptability.

Keywords: Fish Oil, Flaxseed, Food Enrichment, Functional Egg.

INTRODUCTION

Saturated fatty acids are those with only bond between neighboring carbon atoms in fatty acids, and those with at least one double bond are called unsaturated fatty acids. Polyunsaturated fatty acids, which have two or more double bonds, are named according to the position of these bonds and the total chain length. In addition, the number of double bonds in fatty acids reduces the melting point, which directly affects the fluidity of oils [1].

[*] **Corresponding author Sibel Bölek:** Department of Food Technology, University of Health Sciences, Üsküdar, Istanbul, Turkey; Tel: +90-216-418 9616; Fax: +90-216-418 9620; E-mail: sibel.bolek@sbu.edu.tr

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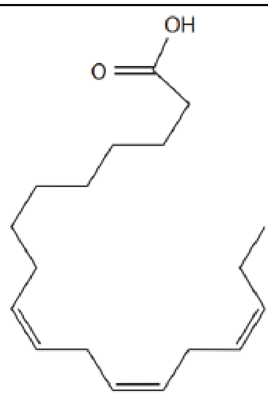
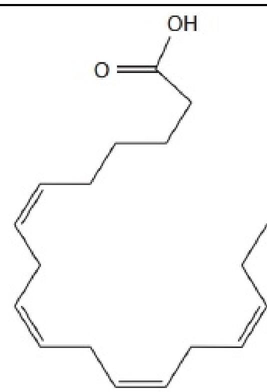
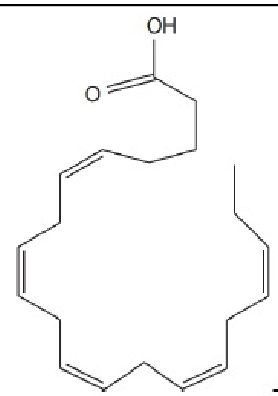
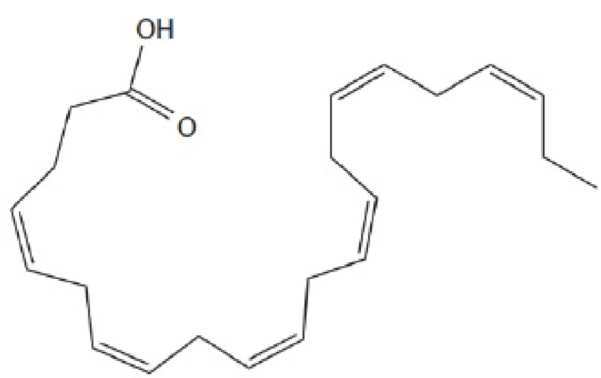
The main effectiveness of polyunsaturated fatty acids (PUFAs) in the diet has been recognized for nearly a century [2, 3]. Originally PUFA was identified as linoleic acid (LA) and α-linolenic acid (ALA). It was later identified as essential fatty acid for the human body. These fatty acids were later named the precursors of two different PUFA series, the omega-6 and omega-3 series, respectively [4].

Fatty acids mainly in omega-3 form comprise α-linolenic acid, stearidonic acid (SDA), dococosapentaenoic acid (DPA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Chemical descriptions of these omega-3 fatty acids are given in Table **1**.

Table 1. Chemical structures of omega-3 polyunsaturated fatty acids [5].

ALA **(α-linolenic acid)**	**SDA** **(stearidonic acid)**	**EPA** **(eicosapentaenoic acid)**
		
DPA **(docosapentaenoic)**	DHA (docosahexaenoic acid)	
		

While, it involves EPA and DHA, omega-3 polyunsaturated fatty acid has a lower level of DPA [6]. Omega-3 fatty acids participate in the formation of chylomicrons in the gastrointestinal system and they are taken to the liver; EPA and DHA are integrated into triglycerides of very low density lipoprotein structure and they are absorbed into the blood. Omega-3 fatty acids, most of which are bound to albumin, are only present in very small proportions as free fatty acids [7].

Being a major omega-3, ALA is mostly found in plants, while EPA and DHA are mostly found in seafood [8]. ALA is found in small amounts in dark green leafy vegetables, while it is abundant in plant and oilseeds such as flaxseed, chia, soybeans, walnuts and other similar nuts of tree, canola oils and olive oil (Fig. **1**). It is especially found in oils derived from them [5, 9 - 11]. Although ALA can be converted to EPA (Fig. **2**), this conversion mechanism is unfortunately complex and limited [9, 12]. In the human body, 5% of ALA converts to EPA, while a small amount (0-4%) of it converts to DHA [10, 13]. In this context, ALA has possible cardiovascular benefits, but the evidence is generally insufficient. Therefore, it is important to use plant-based omega-3s together as they cannot replace sea-based omega-3s, especially EPA and DHA [11].

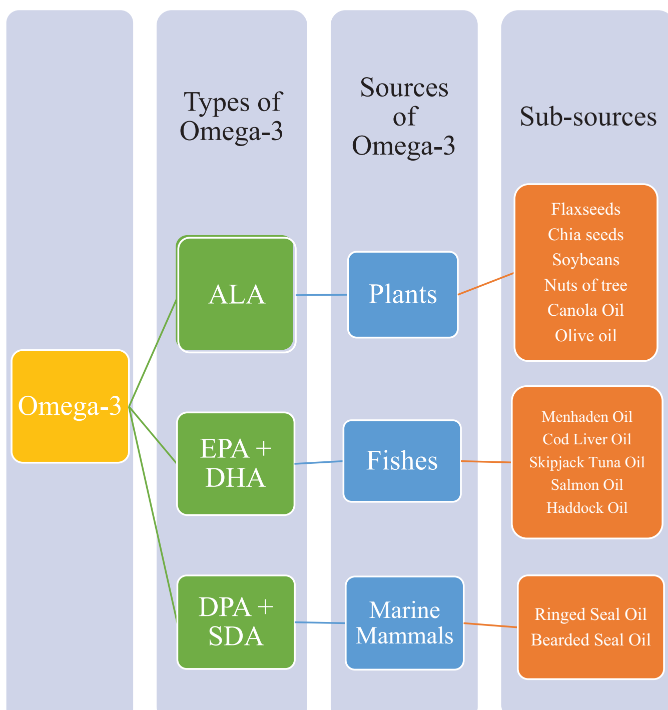


Fig. (1). Foods Containing Omega-3 Fatty Acids.

CHAPTER 3

Quercetin, A Flavonoid with Remarkable Anticancer Activity

Sarbjit Singh[1,*], **Pankaj Chauhan**[2] and **Akshay Kumar**[3]

[1] *Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE 68198, USA*

[2] *Indian Institute of Technology Jammu, Jammu - 181 221 J&K, India*

[3] *Department of Chemistry, DAV University, Jalandhar, 144012, India*

Abstract: Cancer is the second leading cause of death globally and is responsible for about 10 million deaths per year. Several therapeutic options are available currently to treat this deadly disease by targeting various enzymes, receptors, signaling pathways, and nucleic acids. Development of drug resistance, new oncogenic proteins, and recurrence demands sustained discovery of new therapeutic options. Flavonoids are a class of plant polyphenols consisting of 15 carbon skeletons with two benzene rings linked together to a heterocyclic pyrone ring. So far, more than 4,000 flavonoids of different types have been discovered from nature. Flavonoids exhibit several biological activities, including cancer. Quercetin (QCT) is one of the most studied flavonoids that belongs to the flavones subclass. In the recent five years, immense efforts have been made in discovering the anticancer aspect of QCT. This book chapter summarizes the anticancer activities of QCT on various cancer cells (*in vitro*) and tumors (*in vivo*) reported in the last five years.

Keywords: Anticancer, Cancer, Flavonoids, Natural Products, Quercetin.

INTRODUCTION

Cancer is a generic term for a large group of diseases in which cells start growing abnormally beyond their usual boundaries [1 - 7]. In later stages, the cancer cells spread to other organs, the process is known as metastasis. Metastases is the primary cause of death in most cancers [8]. Cancer is the second leading cause of death globally, responsible for about 10 million deaths per year. On average, 1 in 6 deaths is due to cancer worldwide [9]. In 2019, 599,601 people died only due to cancer in the United States [10]. Thus the development of new and advanced therapeutics to cure this deadly disease is highly warranted.

* **Corresponding author Sarbjit Singh:** Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE 68198, USA; E-mail:sarbjit.singh@unmc.edu

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Flavonoids [11 - 14] is a class of plant polyphenols that consist of 15 carbon skeletons with two benzene rings linked together to a heterocyclic pyrone ring. Based upon the level of oxidation and regioselective pattern, these can be subdivided into five main classes, *viz*. flavones, flavanols, flavanones, isoflavones, and anthocyanins (Fig. **1**). Flavonoids find a special place in medicinal chemistry due to the exhibition of several biological activities, including anticancer [15], antiinflammatory [16], antioxidant [17], antidiabetic [18], antidepressant [19], vasorelaxant [20], anticoagulant [21], cardioprotective [22], and neuroprotective [23], *etc*. Plants, vegetables, and flowers are the major source of flavonoids. More than 4,000 types of various flavonoids have been discovered so far from nature.

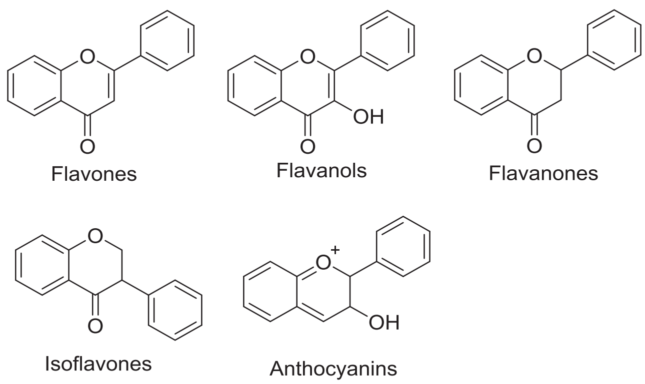

Fig. (1). Structures of different classes of flavonoids.

Quercetin (QCT) [24 - 35] is one of the most studied flavonoids that belongs to the flavones subclass (Fig. **2**), QCT is chemically known as 3,3′,4′,5,7-pentahydroxyflavone ($C_{15}H_{10}O_7$) and is commonly found in various types of vegetables and fruits, including lovage, capers, cilantro, dill, onions, broccoli, various berries, and tea. QCT is well-known for its antioxidant effects especially for preventing low-density lipoproteins from free radicals impairing [36, 37]. Due to the excellent antioxidant and anti-inflammatory effects exerted by QCT, it is sold commercially over the counter as a health supplement. However, QCT also exhibits several other biological activities, including anticancer [24 - 35]. In the recent past, QCT has gained considerable attention from oncologists for its potential to inhibit various cancer cells and tumors. QCT modulates various cell signaling pathways and inhibits enzymes responsible for the activation of cancer. QCT also binds to several cellular receptors and proteins related to cancer. It induces intrinsic as well extrinsic apoptotic cell death in various cancers [38, 39]. Due to its lipophilic nature, QCT can cross the cellular membranes and trigger several intracellular pathways. The focus of this book chapter is to summarize the anticancer effects of QCT on various cancer cells and tumor models reported in the last five years. The book chapter is divided into fifteen subsections based upon the type of cancer it alleviates.

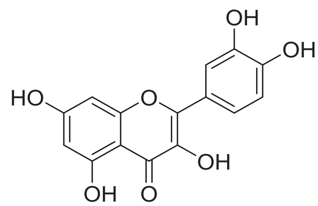

Fig. (2). Structure of Quercetin.

ANTICANCER EFFECTS OF QCT

Breast Cancer

Breast cancer is the leading cancer in women both in the developed and developing world. In 2020, 2.26 million cases of breast cancer were reported causing 685 000 deaths globally [40]. The common treatment options of breast cancer are hormone therapy [41], chemotherapy [42], immunotherapy [43], surgery [44], and radiotherapy [45]. The most severe form of breast cancer is triple-negative (ER, PR, and HER2 negative) breast cancer [46]. Jia and co-workers discovered that QCT can suppress metastasis of breast cancer cells by blocking cell glycolysis and the energy supply of tumor cells [47]. Akt-mTOR was proposed to be the major pathway of induction of autophagy by QCT. Cell viability on MCF-7 and MDA-MB-231 cells revealed a 30 μM dose requirement for *in vitro* studies. QCT effectively suppressed glucose uptake and the production of lactate in breast cancer cells showing its blocking effects on glycolysis. A significant reduction in tumor growth was observed in SPF nude mice after three days in xenograft mouse model.

Drug carriers are the substances used to deliver the drug to specific areas of the body to improve its selectivity, effectiveness, and safety [48]. The drug carriers must have the ability to change their structures under different physiological conditions such as temperature, ionic strength, and pH. High lactic acid production by cancer cells results in low pH in surrounding areas of tumors [49]. Several biopolymers such as chitosan have been developed which exhibit pH sensibility due to the presence of free amino groups. Pedro and co-workers synthesized a chitosan-based pH-responsive drug carrier loaded with QCT [50].

CHAPTER 4

Swertiamarin for the Treatment of Metabolic Syndrome

Javed Ahamad[1,*]

[1] *Department of Pharmacognosy, Faculty of Pharmacy, Tishk International University, Erbil, Kurdistan Region, Iraq*

Abstract: Metabolic syndrome, formerly termed *'Syndrome X',* is a disease of energy metabolism and storage. Metabolic syndrome is characterized by hyperglycemia/impaired glucose tolerance, dyslipidemia, hypertension, and obesity. Swertiamarin is a secoiridoid glycoside extensively found in the Gentianaceae family, which has been reported to cure many diseases, such as diabetes, hypertension, atherosclerosis, arthritis, malaria, and abdominal ulcers. The present book chapter aims to compile up-to-date information on the progress made in the protective role of swertiamarin in metabolic syndrome to provide a guide for future research on this bioactive molecule. In preclinical studies, swertiamarin and its metabolites have shown a wide range of biological activities such as antidiabetic, hypolipidemic, anti-atherosclerotic, anti-inflammatory, and antioxidant activities. These activities were mainly due to its effect on various signaling pathways associated with swertiamarin, such as PPAR-gene upregulation, P-407-induction, inhibition of HMG-CoA reductase, LDL oxidation, lipid peroxidation markers and stimulation of antioxidant enzymes. This book chapter presents evidence supporting that swertiamarin could be considered as a potential therapeutic agent for the treatment of metabolic syndrome.

Keywords: Cardiovascular complications, Diabetes, Metabolic syndrome, Obesity, Swertiamarin.

INTRODUCTION

Metabolic syndrome, formerly termed 'Syndrome X,' is a disease of energy metabolism and storage. Its definition, as diversely described by various organizations, is criterial and metabolic indicators are utilized ordinarily. The most common conditioned are hyperglycemia, impaired glucose tolerance, dyslipidemia, hypertension, and obesity [1]. Epidemiologically, using a combination of presently employed descriptions, its worldwide prevalence in

* **Corresponding author Javed Ahamad:** Department of Pharmacognosy, Faculty of Pharmacy, Tishk International University, Erbil, Kurdistan Region, Iraq; E-mails: jas.hamdard@gmail.com, javed.ahamad@tiu.edu.iq

persons aged 18-30 has been estimated to be 5.2% [2]. A positive correlation between age and incidence is also common in prevalence studies and there is a notifiable higher incidence in western countries, such as America, with some estimates as high as 33-39% [3]. Risk factors associated with these diseases further compound development probability but the commonly known appropriate lifestyle adjustments, such as diet adjustment and exercise adoption, can attenuate risk. The pathophysiology of metabolic syndrome is diverse, resulting from numerous contributory factors. Considering it is not a distinct disease but a combination of multiple factors, the pathophysiology is dependent on the prevalence and progression of its components, namely obesity, hyperglycemia/glucose intolerance, hypertension, and dyslipidemia [4]. Worsening of these elements invariably supports the presence of the syndrome and increases morbidity and mortality. The risk factors are highly interconnected and regularly exist as co-morbidities. Up to 34.4% of the world population was overweight in 2008 and this is an increasing trend [5]. Obesity is essentially due to a poor diet but genetic and epigenetic factors and environmental circumstances contribute. It is also estimated that currently, 463 million suffer from diabetes and by 2045, this will rise to 700 million [6].

Iridoids and secoiridoids are bioactive compounds distributed abundantly in the Gentianaceae family. Swertiamarin is a secoiridoid glycoside present mostly in *Enicostemma littorale* and *Swertia chirata* [7]. *E. littorale* and *S. chirata* are well known bitters and reported to have several health benefits, including antidiabetic, hepatoprotective, antihyperlipidemic, antibacterial properties [8, 9]. Swertiamarin's beneficial effects in preclinical studies have been reported by several authors and it has shown antihyperlipidemic, antioxidant, antiinflammatory, insulinotropic, hypoglycemic, antinociceptive, and hepatoprotective [10]. However, to the best of our knowledge, till date, systemic studies to understand the molecular basis of swertiamarin's action in the metabolic disorder have not been compiled. Hence, the present review aims to compile an up-to-date information on the progress made in the protective role of swertiamarin in metabolic disorders.

SOURCES OF SWERTIAMARIN

Swertiamarin is predominantly found among the members of the Gentianaceae family, mainly *Enicostemma littorale* Blume and *Swertia chirata* Roxb [7, 11]. Swertiamarin was also reported in *Swertia japonica* [12], *Enicostemma hyssopifolium* [13], *Swertia pseudochinensis* [14], *Swertia patens* [15], and *Anthocleista procera* [16].

CHEMISTRY, BIOSYNTHESIS AND DERIVATIVES OF SWERTIAMARIN

Secoiridoids, such as swertiamarin, amarogentin, oleuropein, gentianine, *etc*. are originated from iridoids. Iridoids are monoterpenoids and contain cyclopentanopyran ring system. Iridoids are biosynthesized from 8-oxogeranial. The cleavage of the cyclopentane ring gives rise to a new type of compound known as secoiridoids. Secoiridoids are potent bioactive compounds and have been reported for beneficial actions in several health conditions, including metabolic syndrome. Swertiamarin (Fig. **1**) is a secoiridoid glycoside derived from loganic acid through the mevalonic acid pathway. The possible biosynthetic pathway of swertiamarin is summarized in Fig. (**2**) [17]. Swertiamarin and its derivatives, such as 2'-acetylswertiamarin, amaroswerin, angustiamarin, 6'-glucosylswertia-marin, chironioside, and gelidoside are presented in Fig. (**3**) [18]. Swertiamarin has been reported to have several metabolites, such as gentianine, erythro-centaurin, and 5-(hydroxymethyl)-isochroman-1-one, as given in Fig. (**4**) [19, 20].

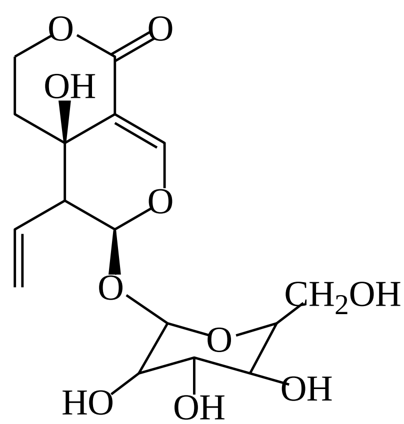

Fig. (1). Chemical structure of Swertiamarin.

CHAPTER 5

Overview of Traditional Uses, Phytochemistry and Pharmacology of *Peganum Harmala L.*

Akshita Sharma[1], **Ajay Sharma**[1,*], **Sharmila Wahengbam**[1], **Raymond Cooper**[3], **Hardev Singh**[1] and **Garima Bhardwaj**[2,*]

[1] *Department of Chemistry, Chandigarh University, NH-95, Chandigarh- Ludhiana Highway, Gharuan, Mohali, Punjab, India*

[2] *Department of Chemistry, Sant Longowal Institute of Engineering and Technology, Longowal, Sangrur, Punjab, India*

[3] *Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong*

Abstract: Mother Nature acts as a source of a variety of therapeutically important plants that have been used directly or indirectly for the wellbeing of the human race. In addition, these plants have also been well known for their applications, especially in agriculture, pharmaceuticals, cosmetics, aroma, food flavors, and food preservatives. These therapeutically important plants are also used by local and tribal peoples as a remedy to cure various infectious illnesses since the dawn of civilization. These medicinal plants serve as a source of eco-friendly drugs that are potentially less toxic as compared to a variety of synthetic drugs. *Peganum harmala* L. belongs to the genus *Peganum* and the recently separated family Nitrariaceae and is now officially included in the family Zygophyllaceae. The plant grows primarily in dehydrated and amorphous conditions, mostly in Africa, Iraq, Uzbekistan, Tajikistan, Russia, China, Afghanistan, Pakistan, and India. The genus *Peganum* comprises six species and *P. harmala L.* is the most explored plant of the genus. The plant is widely known for its pharmacological potential such as antiviral, antibacterial, anticancer, antioxidant, anti-inflammatory, antidepressant and anti-diabetic, *etc*. The wide range of applications of the plant can be attributed to its secondary metabolite composition consisting of alkaloids, flavonoids, triterpenoids, anthraquinones, volatile oils, and dietary components (proteins, fatty acids, vitamins, and minerals). Harmalol and harmine are two key beta-carbolines, which are isolated from different parts of the plant and are mainly responsible for the diverse array of pharmacological potential of the plant. Owing to this, these beta-carbolines serve as an active ingredient for the production of different drugs, which are used to treat various illnesses *viz.* common cold, diarrhea, ulcer, arthritis, asthenia, depression, and dermatologic problems related to hair and skin. These are also effective against Parkinson's disorder and various cancers. Furthermore, different parts of *P. harmala L.* also act as a source of various macro and micro minerals, which are essen-

[*] **Corresponding Author Ajay Sharma:** Department of Chemistry, University Institute of Science (UIS), Chandigarh University, Gharuan, Mohali, Punjab, India-140413; Emails: sharmaajay9981@gmail.com, ajaye7631@cumail.in, garimasliet@gmail.com

Atta-ur-Rahman, *FRS* (Ed.)

tial for the smooth functioning of the human body. The aim of the present chapter is to summarize the various traditional uses, pharmacological properties and phytochemistry of *P. harmala L.*

Keywords: Alkaloids, Anthraquinones, Beta-carboline, Flavonoids, *Peganum harmala* L., Pharmacology, Secondary metabolites, Traditional uses.

INTRODUCTION

Natural products are the chemical compounds obtained from a living organism. These are mainly synthesized from primary metabolites by various metabolic pathways going on in the body of living organisms. Biosynthesis plays an essential role in the elaboration of a variety of natural products and hence the organic chemistry. The plant-based natural products are well known for their immense applications in a variety of industries such as pharmaceuticals, cosmetics, dietary supplements, functional food, food preservatives, paint, aroma and agriculture [1]. The species of the family Nitrariaceae are well recognized for their natural products wealth. The family Nitrariaceae consists of four genera, which includes 17 species that are mainly found in the arid region in the Mediterranean in East Asia, Mexico, Australia. Out of four genera, Peganum is one of them. Genus *Peganum* comprises five species *i.e.*, *viz .P. harmala* L., *P. multisectum* (maxim.) bobrov, *P. nigellastrum* Bunge, *P. mexicanum* Gray and *P. texanum* M.E jones [2].

The species of this genus *Peganum* have a long history of uses in Chinese traditional medicine for the cure of a diverse array of ailments like cough, asthma, hypertension, lumbago, jaundice, colic, diabetes *etc*. Moreover, the species has also been used as a charm against evil-eye, which has become gradually popular in North Africa, Asia and Northwest India, Iran. Apart from various traditional uses, species of genus *Peganum* has also been well known for their wide range of pharmacological potential, such as antitumor, anti-diabetic, antidepressant, antiparasidal, anti-Alzheimer, anti-cholinesterase, anti-Parkinson, anti-leishman iasis, anticoagulant, analgesic, antioxidant, anti-inflammatory, anti-hypertension, anticoagulant, antimicrobial, anti-withdrawal syndrome, and insecticidal [3]. To date, about 308 phytoconstituents have been isolated from different species of genus *Peganum* that mainly belongs to alkaloids, triterpenoids, flavonoids, anthraquinones, steroids, phenylpropanoids, proteins, carotene, carbohydrates and amino acids classes of natural products. Out of different classes of natural products isolated from genus *Peganum* quinazoline (like vasicinone, vasicine, deoxyvasicinone, desoxyvasicine) and β-carboline (like harmaline, harmalol, harmine, harmane, harmol,) alkaloids are the major ones [3].

P. harmala is the most explored species out of different species of the genus *Peganum*. *P. harmala* and its parts have a long history of use in traditional medicines of China, India as well as in Iran [4]. The plant was used to treat cough, asthma, rheumatism, diabetes, and hypertension. It is mainly found in various countries of the Asian subcontinent, where it is used for a variety of purposes from medicinal uses to keep away the devil [5]. Different parts (leaves, roots, seeds, and flowers) of *P. harmala* contained a variety of natural products such as alkaloids, flavonoids, steroids, anthraquinones, amino acids and carbohydrates. The major compounds are beta-carbolines such as harmaline, harmalol, harmol, and tetrahydroharmine which are mainly responsible for their antimicrobial, antidepressant, antiviral, analgesic, antitumor activity [6]. Owing to a wide range of traditional uses, pharmacological potential and phytochemical composition of *P. harmala*, in the present book chapter comprehensive and up-to-date literature analysis of *P. harmala* (botany, traditional uses, phytochemistry, pharmacology, biosynthesis, pharmacokinetics and toxicology) has been carried out, which will help to boost the subsequent research in future on *P. harmala* or on its bioactive phytoconstituents in supplementary clinical and pharmacological applications.

BOTANICAL CLASSIFICATION

P. harmala is a wild plant species and a member of the family Nitrariaceae. It is considered as an essential medicinal plant. Seeds are known to have hypothermic and hallucinogenic properties. In America, it was first planted by a farmer in 1928 who wanted to obtain dye known as "Turkish red" from the seeds [7]. *P. harmala* is also known as "Espand" in Iran while in North America, it is known as "Harmel" and is commonly known as African rue, Mexican rue, Turkish rue, wild rue, Syrian rue, African wild rue [8]. The botanical classification of *P. harmala* is given in Table **1** [9], whereas the various vernacular names of *P. harmala* in India are given in Table **2** [10].

Table 1. Botanical classification of *P. harmala*.

Kingdom	Plantae
Division	Angiospermae
Class	Dicotyledonae
Family	Nitrariaceae
Order	Sapindales
Genus	*Peganum*
Species	*Harmala*

CHAPTER 6

Investigation of Measurement Methods of Antioxidant Activity and Involved Mechanisms

Mohammad Ali Sahari[1,*] and **Samira Berenji Ardestani**[2]

[1] *Department of Food Science and Technology, Faculty of Agriculture, Tarbiat Modares University, Tehran, Iran*

[2] *Tarbiat Modares University and Research School of Radiation Applications, Nuclear Science and Technology Research Institute, AEOI, Tehran, Iran*

Abstract: Bioactive food components are active ingredients in food or dietary supplements proven to have a role in health and they are safe for human consumption. These compounds exert their antioxidant effects by different mechanisms such as hydrogen atom transfer (HAT) or single electron transfer (SET) and their efficiencies can be evaluated by several methods such as ferric reducing ability of plasma (FRAP), trolox equivalent antioxidant capacity (TEAC), diphenyl-picrylhydrazil (DPPH), Folin-Ciocaltue method (FCM), *etc*. In this review, these mechanisms and methods will be discussed in detail.

Keywords: Antioxidant, Bioactive Compounds, Hydrogen Atom Transfer, Mechanisms of Antioxidant Activity, Single Electron Transfer.

INTRODUCTION

Bioactive Compounds

Bioactive food compounds are constituents in foods or dietary supplements obtained from animal or herbal sources, containing materials necessary for human major nutritional needs, and materials proven to affect the health and safety of human beings. All active components in foods such as micro and macronutrients should be considered as bioactive food compounds. Bioactive compounds are ordered to various classes on the basis of distinctive chemical structures and functions, for example, phenolic compounds and their subclasses such as flavonoids. The biological activity of a chemical group is affected not only by the differences in chemical composition and structure, but also by factors such as bio-

* **Corresponding author Mohammad Ali Sahari:** Department of Food Science and Technology, Faculty of Agriculture, Tarbiat Modares University, Tehran, Iran, E-mail: sahari@modares.ac.ir

Atta-ur-Rahman, *FRS* (Ed.)

availability, distribution and metabolism. All positive and negative constructive effects of bioactive food components should be investigated in scientific models of risk-benefit. In these experiments, toxic components should not be considered bioactive compounds.

Based on recommended daily intake (RDA), bioactive compounds by definition reflect their safety. Essential and non-essential nutrients should be considered as bioactive compounds according to their specific physiological functions. Bioactive compounds are present in common foods, food additives, dietary supplements and dietary foods. In recent decades, there have been apparent changes in the food's function to promote human well-being. The preliminary role of foods as sources of energy and body constituents has been changed to biologically active components in human bodies. Thus, the new term “functional food” was introduced in 1998, which is a part of the daily human diet that is beneficial for well-being and helps to diminish the hazard of chronic diseases. In 80 AD, the Japanese defined these foods as: “food for specific health purposes.”

Functional foods are:

Conventional foods containing bioactive natural materials such as fiber;

Foods enriched with bioactive substances such as probiotics and antioxidants;

Synthetic commercial nutrients such as prebiotics [1].

Reactive molecules of free radicals have participated in various diseases like cancers, atherosclerosis, diabetes, aging and neurological illnesses. In order to have a healthy body, the destruction caused by free radicals should be neutralized by antioxidants. Nowadays, there is a considerable trend towards natural antioxidants, which include a wide range of bioactive compounds [2]. Factors affecting the type and amount of bioactive compounds in plant tissues, include climate conditions, agronomical practices, harvest management and post-harvest storage conditions, genotypic differences, genus, plant age and species, processing and extraction conditions [1]. Analytical methods for identifying bioactive compounds are as follows; UV-Vis spectrometry; Fourier transformer infrared spectrometry; Mass spectrometry; ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy; Determination of the antioxidant activity of the extract [2].

Present research purposed to review the antioxidant properties of bioactive compounds, sample preparation to measure antioxidant properties, chemical reactions, involved mechanisms and effective factors in antioxidant effects and at last several practical methods for assessing antioxidant activity.

A Brief About Oxidation Reactions

Oxidizing characteristics of oxygen have a vital role in different biological actions, such as electron transport in adenosine-5'-triphosphate (ATP) production. While oxygen is essential for life, it can have destructive effects by means of cellular material oxidation [3]. Auto-oxidation and thermal oxidation of lipids, cellular oxidation pathways, and multiple physiological and biochemical practices in human body under normal circumstances produce two groups of radicals; reactive oxygen species (ROS) such as superoxide anion radical ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($HO^{\bullet}$), peroxyl radicals ($ROO^{\bullet}$), single oxygen ($^1O_2$) and hypochlorous acid (HOCl). The second groups which include reactive nitrogen species (RNS), are nitric oxide ($NO^{\bullet}$) and nitrite proxy ($ONOO^-$) formed in $NO^{\bullet}$ reaction with superoxide during inflammatory processes [4]. Free radicals are highly active and toxic molecules with a short half-life, originating from either inside (normal aerobic respiration, metabolism, and inflammation) or outside (pollution, sunlight, X-ray, extreme sports, smoking and alcohol) body stimuli have one or more non-paired electrons. Thus, they attempt to obtain or lose electrons in the body and consequently cause damages to DNA, proteins, lipids and carbohydrates [2]. One of the most destructive effects of free radicals is lipid peroxidation that leads to cell membrane damage. For example, because the double bonds of unsaturated fatty acids and stimulation of membrane peroxidation chain reactions affect oxygen free radicals, unsaturated fatty acids and cells are ultimately destroyed. Lipid peroxidation impairs membrane of organism and changes the activity of its dependent enzymes and other proteins, which can be potentially harmful to cells by releasing hydroperoxyl and alkoperoxyl radicals [3]. Lipid peroxidation thus changes the structure of unsaturated fatty acids, and reduces their fluidity and so membrane potential negatively affecting cellular membrane permeability. With lipid peroxidation, cellular wall and its performance will be affected. Also, some oxidation products such as malonealdehyde react with biomolecules and show genotoxic and cytotoxic effects. Cytotoxic metabolites derived from the oxidation of low-density lipids (LDL) can cause lipid peroxidation, which acts significantly in the pathogenesis of atherosclerosis. Also, free radicals participate in the mechanism of cytochromes [8].

When fatty foods are exposed to air, light and heat, their taste, color and smell change due to oxidation and eventually, they will spoil. The major products of auto-oxidation of lipids are tasteless and odorless hydroperoxides, which after decomposition, form off-odor and off-flavor products such as aldehydes and ketones. To preserve food quality and increase storage time, natural or synthetic antioxidants must be used [8]. Whenever the production of ROS and RNS in a system is more than the system's capability to neutralize and remove them,

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CHAPTER 7

Recent Progress on Natural and Synthetic Flavanone and its Derivatives

Hossein Eshghi[1,*], **Mahsa Khoshnevis**[1] and **Fatemeh Pirani**[1]

Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran

Abstract: Flavanones with various biological and pharmacological activities which result from their unique structure, a chiral center at C2 and a single bond between C2-C3, are considered as a special subgroup of flavonoids. These naturally occurring compounds with anticancer, antibacterial, anti-inflammatory activity, as well as building blocks and intermediates for organic synthesis have attracted organic and medicinal chemists' attention. Widespread and at the same time interesting application of flavanones in different fields of chemistry and pharmacology, reveals increasing interests in their syntheses from different synthetic methods. In addition, there are many articles published every year about natural flavanones and their novel derivatives from different natural sources and study of their biological activities is also proof of their priority. As a result, herein we have studied recent progresses about flavanones from different aspects such as their: various synthetic methods, different derivatives, biological activities, natural sources reported in articles from 2015 to late 2020.

Keywords: Asymmetric Hydrogenation, Benzopyrone, Biological Activity, Biosynthesis, β-Arylation, Chromanone, Claisen-Schmidt condensation, Domino Reaction, Flavanone, Fused Flavanone, Green Synthesis, Hybrid Flavanone, Intramolecular Conjugation Addition, Intermolecular Oxa-Michael Addition, Mannich Reaction, Natural & Synthetic, Polyphenol.

INTRODUCTION

2-Phenyl-2,3-dihydro-chromen-4-ones known as flavanones (Fig. **1**) belong to flavonoids (Fig. **2**), a subclass of a large group of polyphenolic compounds with the core structure of benzo-γ-pyrone [1]. Flavanones as other flavonoids are a class of secondary plant metabolites [2, 3]. As it can be seen from (Fig. **2**), the presence of a single bond between C2-C3 and a chiral center at C2 makes flavanones distinguished from other flavonoids, which determines their biological activity [4, 5].

[*] **Corresponding author Hossein Eshghi:** Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran; Tel: +9851138805549; E-mail: heshghi@um.ac.ir

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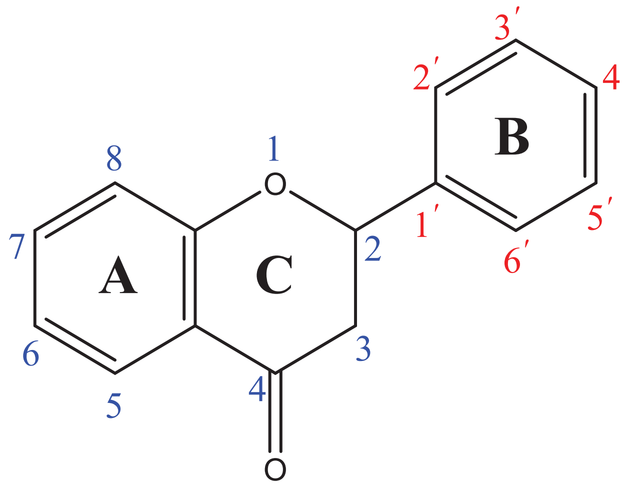


Fig. (1). Flavanone skeleton.

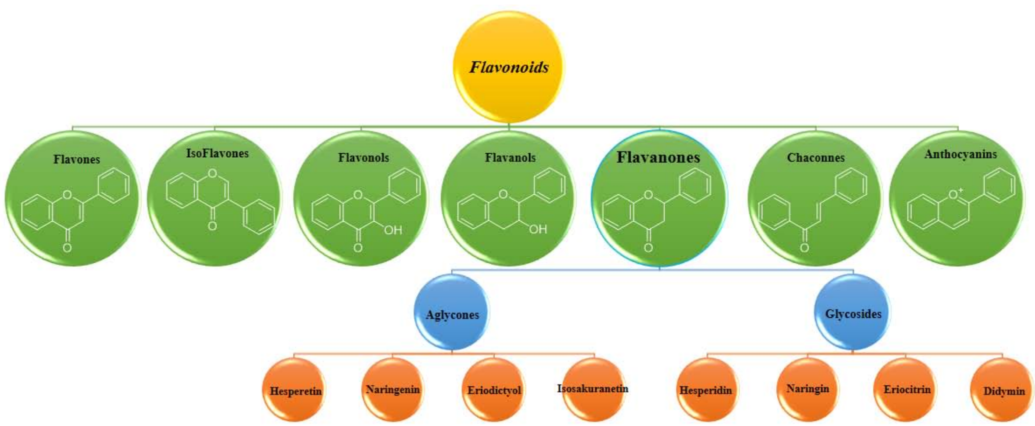


Fig. (2). Some of the most important flavonoids.

Flavanones as a six-member O-based heterocyclic [6] natural compound, with widespread pharmacological and biological properties such as: antifungal [7], anticancer [8], antioxidant [9], antiviral, anti-inflammatory [10], anticholesterolemic, antimicrobial [4], hepatoprotective effects [11], cardioprotective activity [12], gastrointestinal health effects [13] and low toxicity are among the most important flavonoids [14, 15]. Flavanones are divided into two main categories: aglycones and glycosides [16]. Hesperetin, naringenin and eriodictyol are considered as the major aglycones, but mostly the main natural forms of flavanones are glycosides [17]. The most abundant ones are: hesperidin, naringin and eriocitrin (Fig. **3**) [16]. Natural flavanones are found in tomatoes [18], mint [19], honey [20], *etc.* and the main source of flavanones especially glycosides, at high concentrations, are citrus fruits such as: orange, blood orange, lemon, lime, tangerine and grapefruit [11, 21 - 24]; there are hydrophobic structures of aglycones consequences in less concentration of them in citrus fruits [16, 25].

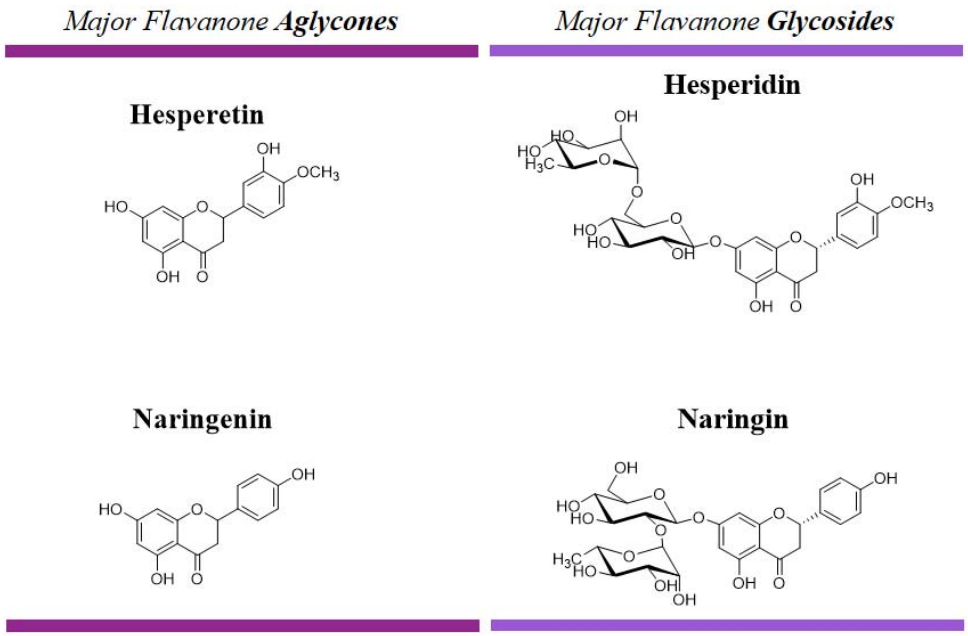


Fig. (3). Chemical structure of some major aglycone and glycoside flavanones.

In recent decades, flavanones due to their diverse biological and pharmacological properties and also great importance as building blocks and intermediates in organic synthesis, have attracted chemists' and pharmacists' attention [26].

SYNTHETIC METHODS OF FLAVANONES

Asymmetric Hydrogenation of Chromones

Prof. J. Wang *et al*. decided to use copper instead of rhodium and ruthenium which is abundant and cheaper. For this purpose, they applied $Cu(OAc)_2$ and (R)-DM-Segphos as a chiral bisphosphine ligand which resulted in extremely good yields and ee% (up to 99%) (Fig. **4**) [27]. This catalyst either showed acceptable results in the synthesis of thiochromanones and also preparation of C3-substituted chromanones.

CHAPTER 8

Role of Virgin Coconut Oil as Multiple Health Promoting Functional Oil

Soo Peng Koh[1,*], **Yih Phing Khor**[1] and **Kamariah Long**[1]

[1] *Food Science and Technology Research Center, Malaysian Agricultural Research & Development Institute (MARDI),Persiaran MARDI-UPM, 43400 Serdang, Selangor, Malaysia*

Abstract: Numerous scientific studies have confirmed the effectiveness of virgin coconut oil (VCO) as having multiple health-giving properties, as demonstrated both *in vivo* and *in vitro* findings. The functional properties of VCO as antimicrobial, antiobesity, antiulcerogenic, antiinflammatory, antipyretic, analgesic effect, antidiabetic, and antioxidants properties have been widely reported. The remedial effect of VCO was due to the presence of medium-chain triacylglycerols, micronutrients (Vitamin E, provitamin A, plants sterols, polyphenols), and antioxidants. The partially hydrolysed VCO, also known as activated virgin coconut oil, is more potent than VCO as it contains more free medium-chain fatty acids (caprylic, capric, and lauric acids) and their corresponding monoglycerides (monocaprylin, monocaprin, and monolaurin); it has a broad spectrum of antimicrobial properties. In this review, we summarized the major research, which provided evidence of multiple beneficial effects of VCO and the mechanisms of therapeutic effects towards human health management.

Keywords: Antimicrobial, Functional Food, Human Health, Medium-Chain Fatty Acids, Monoglycerides, Virgin Coconut Oil.

INTRODUCTION

Coconut palm (*Cocos nucifera*) belongs to the family Arecaceae, subfamily Cocoideae, and it is the only species of the genus *Cocos*. Coconut contains microminerals, antioxidants and is rich in nutrients, which are essential to human health. It is also recognized as healthy food and used as Ayurvedic medicine by people all over the world, particularly in tropical countries. This unique palm plant is mainly cultivated for multiple uses, particularly for its nutritional and therapeutic value, because of its high proportion of triacylglycerols with medium-

* **Corresponding author Soo Peng Koh:** Food Science and Technology Research Center, Malaysian Agricultural Research & Development Institute (MARDI),Persiaran MARDI-UPM, 43400 Serdang, Selangor, Malaysia; Tel:+603-89536097; E-mail:karenkoh@mardi.gov.my

Atta-ur-Rahman, *FRS* (Ed.)

chain fatty acids (MCFA), predominantly lauric acid (46–48%). Various products are derived from all parts of the coconut fruit, including tender coconut water, copra, coconut oil, raw kernel, coconut leaves, coconut toddy, coconut shell, coconut cake, coir pith, wood-based products, *etc* [1]. Furthermore, the dry kernel or copra is one of the important international commodity that contributes to the yield of coconut oil. Recently, the demand for coconut products has increased, and global production of coconut has been steadily increasing with more public awareness of the health benefits of coconut oil.

The Philipines, the world's largest supplier of coconut oil and the global leader in of coconut trade, accounts for approximately 57.1% of total export trade [2]. The idea of producing VCO is inspired by the well-known virgin olive oil. Virgin oil has become a widely sought-after commodity because it contains beneficial minor components and is well preserved [3]. Similar to virgin olive oil, VCO holds promise as a new functional food oil, gaining popularity and public attention for the reasons stated above. Unsurprisingly, the VCO market is expanding rapidly. The rising demand for VCO is drawing the interest of both small- and large-scale entrepreneurs, mainly because its production restores the once near-stale coconut industry. VCO is particularly abundant in Southeast Asia, including the Philippines, Thailand, Indonesia, and Malaysia.

The Processing and Nutritional Value of Virgin Coconut Oil (VCO)

In terms of oil composition, VCO consists of 92% saturated fatty acids (SFA), predominantly of 65% MCFA (caprylic acid, capric acid, and laurin acid). VCO is more beneficial than other plant oils since the mode of extraction preserves most of its bioactive components, including Vitamin E, polyphenol components, antioxidants, phospholipids, and plant sterols [4 - 8]. VCO plays a distinct role in the diet as an important functional food due to the abundance of medium-chain triacylglycerols (MCT) and micronutrients. It was widely recognized as nutritious food for infants, premature babies, the elderly, and immune-compromised patients due to its quick energy-giving and multiple health-promoting properties, which had been proven in numerous scientific studies Table **1**.

Table 1. Multiple health benefits of virgin coconut oil (VCO).

Case Study	Health Benefits	References
Effect of VCO inhalation on airway remodelling in a rabbit model of allergic asthma	Significant improvement in alleviating asthma symptoms more than preventing the onset of asthma	Kamalaldin *et al*. (2018) [8]
VCO-enriched diet in ameliorating the oxidative stress, transcriptional regulation of fatty acid synthesis and oxidation	Improve oxidative stress *via* increased activities in catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase by preventing lipid peroxidation and protein oxidation products formation	Arunima and Rajamohan (2014) [9]
Effect of topical virgin coconut oil in mild to moderate pediatric atopic dermatitis	Significant improvement in skin capacitance and hydration	Evangelista *et al*. (2014)[10]
Impact of VCO diet on the blood glucose and cholesterol lowering effect	Significant improvement in the reduction of blood glucose, total cholesterol, triacylglycerols and low density lipoprotein	Arumugan *et al*. (2014) [7]
Anti-inflammatory, analgesic and antipyretic activities of VCO	Exhibit moderate anti-inflammatory, analgesic and antipyretic properties *in vivo* model studies	Intahphuak *et al*. (2010) [11]; Zakaria *et al*. (2011)[12]
Anticoccidial activity of modified VCO	Significant reduction in the oocytes level in faecal and cecal dramatically after 4 days post-treatment on broiler chicken coccidiosis	Tan and Long (2012) [13]
Antimicrobial effect against mastitis pathogens of modified VCO	Capable to control the growth of mastitis pathogens as confirmed in both *in vivo* and *in vitro* studies.	Koh and Long (2014)[14]; Koh *et al*. (2016)[15]
Remedial effect on renal dysfunction in diabetic rats	Effectively in preventing renal damage in diabetic rat supplemented with VCO	Akinnuga *et al*. (2014) [16]
Minor recurrent aphthous stomatitis (RAS) treatment with VCO	Significant in relieving pain and reducing the size of ulcer after treated with VCO	Daddy *et al*. (2014) [17]
Antiulcer activity of VCO	VCO demonstrates cytoprotection effect in antiulcer mechanism for the ulcer formed in pylorus ligated rats	Selvarajah *et al*. (2015) [18]
To protect the postmenopausal osteoporotic bone with VCO	VCO helps to protect bone in osteoporotic rat model by increasing the expressions of antioxidant genes and genes which increase the osteoblast activities	Hayatullina *et al*. (2012) [19]; Abdul-Hamid *et al*. (2016) [20]
Cognitive function study of VCO treated-rats	Potential as memory enhancer	Rahim *et al*. (2017) [21]
Anti-acne activity of modified VCO	Clinically proven for the deduction in the acne grading	Halina *et al*. (2012) [22]

SUBJECT INDEX

A

Atta-ur-Rahman, *FRS* (Ed.)

B

C

D

E

F

G

H

I

J

L

M

N

O

P

R

S

T

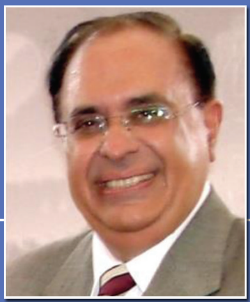
U

V

W

X

Z



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

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