ANTHOCYANINS: PHARMACOLOGY AND NUTRACEUTICAL IMPORTANCE

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ISBN (Online): 978-981-5223-88-0

ISBN (Print): 978-981-5223-89-7

ISBN (Paperback): 978-981-5223-90-3

First published in 2024.

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PREFACE

This work will provoke a lot of debate as it covers an interesting topic. I feel compelled to share my knowledge, analyses, and conclusions after working for numerous years in the field of pharmacy. I have written many papers and book chapters on various facets. Perhaps this description will increase knowledge of the issue and initiate a discussion that could result in significant ideological transformations. There are two reading categories for this book. First off, it can be read by regular individuals with little to no prior knowledge of science. Professionals from academia and government organizations will be represented by the second set of readers. It is hard to believe that all members of the scientific community will comply with the concepts and ideas presented in this work. But I do hope that the knowledge and information provided will serve as a guide for all the sections of society.

Neglected tropical diseases (NTDs) are a diverse collection of 20 illnesses that are primarily found in tropical regions and impact more than 1 billion people who reside in underdeveloped communities. Numerous pathogens, such as viruses, bacteria, parasites, fungi, and toxins, are responsible for their development. More than one billion people suffer from the terrible health, social, and fiscal effects of these diseases. There are 12 chapters in the book. The introduction to neglected diseases is broadly introduced in Chapter 1 of this book. The strategies to overcome the impact of neglected diseases on the world are discussed in Chapter 2, which also provides a step-by-step process to handle such conditions. The current therapeutic strategy for leprosy, dengue, lymphatic filariasis, dracunculiasis, helminthiasis, Chagas disease, neurocysticercosis, leishmaniasis, rabies, trematodiasis, Buruli ulcer and trachoma is introduced in Chapter 3 to 12, along with an account of possible disease mechanism, transmission and management protocol.

I wish a lot of people read this book. In order to escape the mistakes of the past, we must alter course and begin utilizing knowledge built up by scientists.

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CHAPTER 1

Nutraceutical – An Alternative Pathway in Therapeutics

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Abstract: Nutritional supplements, herbal items, and processed foods, including cereals, soups, and beverages, are all sources of nutraceuticals that have medicinal or health benefits for the prevention and treatment of diseases. Nature has provided us with immeasurable, wonderful gifts, including natural products, herbal medicines, *etc.* All the civilizations, societies, cultures, and ethnic groups from pre-historic times till the present use plants, animals, and minerals to cure diseases. Numerous cultures have a long history of using plants to cure a variety of disorders, which has led to the formation of well-defined medical systems like Ayurveda, traditional African remedies, Chinese herbal medicines, Kampo in Japan, *etc.* Many medicinal plants' healing qualities have been acknowledged on a global scale. Various scientific studies, preclinical studies, clinical studies, *etc.*, are going on to collect scientific evidence to prove their activity. There are safety problems associated with allopathic medicines. Nutraceuticals are foods high in nutrients that are consumed for reasons other than mere nutrition. These medications have shown promising outcomes in recent studies in the treatment of various pathological illnesses, including cancer, diabetes, cardiovascular disease, and neurological problems, with nutritional benefits. The most common nutraceuticals are curcumin from turmeric, glucosamine from ginseng, omega-3 fatty acid from linseed, β-Lactoglobulin from bovine milk, *etc.* This chapter describes the role of nutraceuticals in health and how they are different from foods and medicines.

Keywords: Culinary spices, Herbal medicine, Probiotics, Present therapies.

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INTRODUCTION

Nature has provided us with immeasurable, wonderful things, including natural products. From ancient times to the present, all cultures, civilizations, societies, and ethnic groups have used plants, animals, and minerals to treat illness. There are numerous well-defined medical systems in India as a result of the historical use of herbs for the treatment of various diseases in diverse civilizations (Ayurveda, Siddha, Unani, Yoga, Naturopathy, and Homeopathy), such as in China (acupuncture, herbal medicines, massage (tui na)), Africa (divination, traditional African medicines), Japan (Kampo), *etc* [1 - 3]. Pre-clinical research is now being performed on these plants in order to gather scientific proof of their actions. A vast number of medicinal plants have been recognized for their therapeutic properties. After their successful outcomes in pre-clinical trials, these can be taken further for clinical trials and reach the market in the form of medicine.

Without question, one of the biggest achievements in science and human history is the discovery of pharmaceuticals and treatments. As advancements in science are going on, diseases are also increasing with time. The efforts for new and effective treatments are underway. Life expectancy has also increased with the advancement of medicines, like the treatment of cancer, blood pressure, diabetes, tuberculosis, *etc*. The diseases that were once considered to be untreatable and devastating are also cured now with the advancement of medical science [4].

SAFETY PROBLEMS ASSOCIATED WITH CURRENT THERAPIES

When the first study on a product was conducted in 1956, it was thought to be a non-toxic anxiolytic agent with more sedative effects than other comparable drugs. Pregnant women were initially prescribed this medication to treat morning sickness; however, it was later discovered to cause birth abnormalities in over 10,000 infants and killed almost 2000 newborns [5].

Reye’s Syndrome

A rare yet serious condition known as Reye's syndrome primarily affects children and adolescents but can occasionally also affect adults [4]. Its prevalence in conjunction with severe encephalopathy and acute hepatopathy is described in a study [6]. Reye's syndrome has been associated with the use of acetylsalicylic acid (ASA) for past occurrences of chicken pox, viral infections, or fevers [4, 7].

Astemizole

It is a non-sedative antihistamine but has a connection with the increasing risk of ventricular arrhythmias according to the data obtained from electrophysiological, pharmacovigilance, and pharmacoepidemiological investigations [8 - 11].

Hormone Replacement Therapy (HRT)

As evident by current research on women who use hormone-replacement medication, breast cancer risk has increased. According to Women's Health Initiative and research, acute myocardial infarction has also increased, along with venous thromboembolism and stroke [12 - 14]. In order to prevent osteoporosis, it has been recommended by doctors not to use HRT [15].

Cerivastatin

Even though the side effects of rhabdomyolysis and its connection with the usage of statins have long been recognized, there have been more related cases of rhabdomyolysis compared to other statins [16 - 18].

Cisapride

The growing body of research on cisapride since 1995 has suggested that this prokinetic drug may have arrhythmogenic potential [19]. The decision to restrict its usage to particular situations while strictly enforcing cardiological surveillance was taken by the European Medicine Evaluation agencies [20].

Nimesulide

It is a specific Cox-2 inhibitor for non-steroidal anti-inflammatory drugs (NSAIDs). With a few exceptions, the majority of countries started to discontinue the product in 1999 after reports of the first hepatotoxicity cases associated with Nimesulide [21, 22].

Nutraceuticals

Dr. Stephen DeFelice first used the term “nutraceutical” in 1989. The word “nutraceutical” is made up of two words: nutritional and pharmaceutical. It explains the meaning of the word nutritional products, meaning dietary substances that have nutritional benefits and that provide medical and health benefits, as well as help in the diagnosis or treatment of diseases [23]. These substances provide some kind of pharmaceutical effects, except just being anti-anemic because most of the dietary substances are anti-anemic.

CHAPTER 2

Novel Drug Delivery System for Nutraceuticals

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Abstract: Nutraceuticals have gotten a lot of attention in recent years because of the health-promoting and disease-prevention properties along with their nutritional value. The increasing quantity of widely viable nutraceuticals and their wide range of uses indicate the domination of these products around the world. Nutraceuticals contain a variety of health advantages and functions; however, most nutraceuticals degrade quickly in the gastrointestinal tract and have low bioavailability. Different innovative drug delivery-containing carrier technologies are continually being researched in order to improve the efficacy and bioavailability of herbal medications. To overcome hurdles and enable efficient application, a unique carrier system is becoming increasingly important. This chapter provides an insight into nanoencapsulated nutraceuticals' physical and gastrointestinal stability, as well as their bioavailability, which are all taken into account. The existing limitations, synthesis, and applications of different lipid-based nanocarriers (including niosomes and liposomes) and lipid nanoparticles (SLNs and NLCs) are examined critically. This study also attempts to document the most recent advancements and problems in the field of nanonutraceuticals, a cutting-edge subject that uses nanotechnology to encapsulate bioactive substances in order to enhance their medicinal effectiveness and release profile.

Keywords: Bioavailability, Lipid nanoparticles, Nanocarriers, Nanonutraceuticals.

OVERVIEW OF NUTRACEUTICALS

In 400 BC, Hippocrates said, “Let food be your medicine and medicine be your food”, which signifies the extensive use of herbal products since eras [1]. For treatment and prevention of diseases, different historical civilizations, like Greece,

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Rome, *etc.*, used herbal plants and their products [2]. About 5000 years ago, in Nagpur, on a Sumerian clay tablet, 12 herbal medication recipes were revealed. The book entitled "De Materia Medica" was written in 77 AD by Dioscorides (father of Pharmacognosy) and contained 657 plant-derived medications [3]. These incidents demonstrated how herbal remedies have been a hot topic throughout human civilization. Over the years, numerous renowned plants with medicinal properties have been used. Ginseng, for instance, had been utilized in China to treat and prevent many health issues [4]. Plants like cumin, turmeric, garlic, *etc* were used by the Egyptians as medicines [3]. In the Roman and Egyptian cultures, cinnamon also denoted significant worth [2]. Indians employed natural remedies to treat and prevent a number of diseases before the advent of Ayurveda [5]. Additionally, according to the Holy Quran and the Bible, honey was one of the most widely used treatments in many ancient civilizations [2]. These results have served as an inspiration for numerous inquiries in the nutraceutical industry [2].

To describe nutraceutical compounds, a certain taxonomy and set of guidelines are being discussed [6]. There may not be a universally accepted definition of a nutraceutical [7]. Nutraceutical substances, on the other hand, are health-improving products that enhance the body's physical and mental functions. These are marketed to reduce the hazard elements for certain disorders [8]. In simple terms, nutraceutical supplements are a combination of food and medicine [9]. However, this term is broader and incorporates elements like vitamins, botanicals, herbs, minerals, amino acids, *etc* [10]. As a result, nutraceuticals can be used to describe both beneficial supplements and nourishing foods [11]. The basis for novelty in medication (New York, USA) established the concept of nutraceuticals in 1989 [9]. Defelice stated in 1995: "Dietary or foodstuff components that offer therapeutic or nutritional effects, including the treatment and/or prevention of sickness" [12]. This saying was generated by blending the terms "nutrition" and "pharmaceutical" [9]. In order to differentiate the concepts of dietary supplements, nourishing foods, and nutraceuticals, numerous attempts have been made; however, still some ambiguity in these terms is present [13]. The primary distinction between nutraceuticals and fortified foods is based on their use [7]. Although nutraceuticals are utilized to cure or/and prevent diseases other than anemia, foods that are fortified provide the body with enough levels of minerals, vitamins, carbs, proteins, and other crucial nutritional components to enhance health [7].

INTRODUCTION TO NOVEL DRUG DELIVERY SYSTEM

Due to its simplicity and affordability in formulation, oral delivery is the best practical and widely accepted method of administration. Numerous properties,

including therapeutic impact, bioavailability, and physicochemical stability, contribute to the success of nutraceutical substances. However, a lot of substances have low bioavailability. In order to maintain stability, the bioactive compounds must be absorbed in the gastrointestinal tract before reaching the systemic circulation as lipophilic bioactive substances are poorly water-soluble and have low bioavailability and poor absorption.

Additionally, bioavailability is significantly constrained by metabolism [14]. Various approaches like inclusion complexation, liposome entrapment, co-crystallization, coacervation, and emulsification have been used for the increased bioavailability of nutraceutical compounds.

One of the main fields of formulation research that benefits humanity through the advancement of medicine and technology is nanotechnology [15, 16]. These result in improved half-life, specific release, and similar site-specific targeted administration of medicinal substances [17, 18]. Polymers, metals, and lipids have been used for developing nanocarriers. As lipid-based carriers are biocompatibility and biodegradable, it is the best practice in the nutraceutical area [19].

Although there are many different types of lipid nanocarriers, only a few have been successfully commercialized. These include niosomes, self-emulsifying drug delivery systems, solid lipid nanoparticles, nanoemulsions, *etc* [20].

These nanocarriers may result in the same site-specific targeted distribution of medicinal substances, accurate release-completed short or extended durations, and improved half-life [17, 18]. Polymers, metals, and lipids have all been employed in the creation of nanocarriers, among other materials. Because it is biocompatible and biodegradable, a lipid-based carrier works best in food and nutraceutical industries [19]. Only a few lipid nanocarriers, including niosomes, solid lipid nanoparticles (SLNs), nanoemulsions, liposomes, nanostructured lipid carriers (NLCs), and self-emulsifying drug delivery systems (SEDDSs), have been reported for successful commercialization, despite the fact that there are many different methods using lipid nanocarriers [20].

NDDS FOR NUTRACEUTICALS

Lipid-Based Carriers

Alec D. Bangham invented lipid-based carriers called liposomes in 1965 [21]. They are made up of spherical vesicles with an aqueous cavity and a membrane made of lipid bilayers. Greek words lipid (fat) and soma (body) served as the foundation for this concept. Size, preparation, and lamellarity are used to

CHAPTER 3

Phytoconstituents as Nutraceuticals

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Abstract: Nutraceuticals are nutritional supplements exploited for upgrading well-being, delayingaging, averting ailments, and supporting the appropriate working of the human body. At present, nutraceuticals are gaining significant attention owing to their nourishment as well as therapeutic potential. On the basis of sources, they are classified into nutritional supplements and biologically active plant-derived molecules. These nutraceuticals support fighting some of the foremost well-being complications of the era, including obesity, cardiac ailments, malignancy, osteoporosis, arthritis, diabetes, *etc.* Nutraceuticals have benefits over medication since these are devoid of side effects and are composed of nature-based nutritional supplements. This chapter gives an overview of various bioactive components obtained from secondary metabolites of plants with a diverse era of chemical classes that might act as nutraceuticals (*i.e.*, anthraquinones, alkaloids, saponins, tannins, essential oils, carotenoids, flavonoids, bitters, carbohydrates, protein, and vitamins).

Keywords: Bioactive compounds, Health, Nutraceuticals, Phytoconstituents.

INTRODUCTION

Nutraceuticals are defined as the combination of nutrition and pharmaceutics. Generally, the term refers to products derived from dietary supplements (nutrients), herbal products and specific diets, as well as processed foods like soups, cereals, and beverages used for reasons other than nutritional purposes. The term “nutraceutical” refers to products that are used for purposes other than nutrition [1]. Nutraceutical products are substances that provide physiological benefits or offer protection from chronic diseases. There are many health benefits that can be obtained from dietary supplements, including improved health, delaying the aging process, prevention of chronic diseases, increasing life expectancy, and supporting the body's structure or function. A wide range of

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nutritional, safety, and therapeutic benefits have been associated with nutraceuticals in recent years. The efficacy of these compounds has been demonstrated in a variety of studies in recent years. An effort has been made in this review to introduce new concepts about nutraceuticals based on their potential applications in the treatment of diseases. Herbal nutraceuticals have been emphasized as being effective in treating hard-to-treat disorders associated with oxidative stress, including allergies, Alzheimer's, cardiovascular disease, diabetes, cancer, eye disease, Parkinson's disease, inflammatory disease and obesity [2]. As a drug, a food ingredient, and a dietary supplement, “nutraceuticals” are regulated under US law. A nutraceutical is a substance, which is not patented, as opposed to a pharmaceutical product. It is possible to cure or prevent diseases with both pharmaceuticals and nutraceuticals, but only pharmaceuticals are recognized by the government. As defined by the Food and Drug Administration, a dietary supplement is a product that contains at least one of the following nutritional substances: a vitamin, a mineral, a nutrient or amino acid, a medical herb or botanical, a substance used to augment a person's diet to boost their overall intake or a concentrate, constituent, metabolite, extract, or combination of these substances. It is important to note that nutraceuticals are nutritional supplements used for health purposes other than for nutritional purposes. In addition to green tea, ginseng, Echinacea, glucosamine, omega-3, folic acid, lutein and cod liver oil, there are a number of other popular nutraceuticals [3, 4]. As a result of the safety, potential nutritional, and therapeutic benefits of nutraceuticals, these products are attracting considerable attention these days. A Compound Annual Growth Rate of 8.3% is predicted for the global nutraceutical market by 2027, which is estimated at USD 722.49 billion. Several notable geographic markets are forecast to grow in 2020-2027, including Japan and Canada [5, 6].

ASPECTS OF NUTRACEUTICAL SAFETY

Health authorities do not approve nutraceuticals, yet millions of people take them anyway. Nutraceuticals are generally composed of ingredients that are similar to those found in pharmaceuticals. Nutraceuticals may contain some ingredients that are associated with major and minor health risks. Approximately 25,000 emergency section admissions in the United States are ascribed due to nutritional supplements, according to a recent study based on 3667 cases [7]. There is a 58% female to 42% male gender distribution. Children under the age of four (under 4 years) and teenagers (2034 years old) are at the greatest risk. Firstly, the raw material must be considered as a risk factor since it may not be in accordance with the pharmacopoeia. The presentation of impurities and contaminations is illustrated here, along with the examination of fraudulent practices [8 - 10]. Furthermore, since the control processes are more liberal throughout and post-production, failures are less often revealed, and if they are, they are not constantly

followed by a strict removal procedure. Therefore, serious harm can also be reported in reports. In light of the fact that health authorities do not regularly check the safety of commercially available nutraceuticals or dietary supplements, it is the responsibility of scientists, scientific institutions and non-governmental organizations to monitor the safety of nutritional supplements. In recent years, Vitamin D dosage recommendations with or without calcium supplementation were assessed by the 'United States Preventive Services Task Force' (USPSTF). Despite the current evidence, they concluded that vitamin D and calcium supplementation for preventing ruptures in symptomless males as well as females living in the community are unsatisfactory for evaluating the balance of profits and troubles. Nevertheless, the USPSTF resolved that supplementing with 400 IU of vitamin D and 1000 mg of calcium daily for postmenopausal females of the community has no benefit in preventing fractures in this population. Impurities pose additional risks. Heavy metals, such as lead and cadmium, may be present in herbal dietary supplements. A source of additional risk may be the presence of mercury. This type of contamination has recently been brought to light in a Polish publication [11, 12]. As part of patients' safety, it is important to record the use of dietary supplements and herbal supplements by patients. In spite of this, physicians frequently fail to inquire whether the patient uses DS and to document this in medical records. According to a recent report, 7.5% of all patients' medical records document the use of DS [13, 14]. There is often a similar chemical pathway for the breakdown of prescription medicines and DSs. In certain circumstances (children, gravidity, chronic illnesses, *etc.*), "harmless" products, such as multivitamin pills alone or in combination with minerals, can lead to complications. It should also be noted that timing can also influence the effectiveness of nutraceuticals [15]. In a recent randomized, controlled clinical study, it was shown that these products are safe when used in a mixed population over a period of more than ten years [16, 17].

PLANTS OR PHYTOCONSTITUENTS AS NUTRACEUTICALS

Literature reports numerous plants that can be used to treat disorders of the central nervous system, including *Papaver somniferum L*. (morphine), *Ephedra sinica* (ephedrine), *Physostigma venenosum* (physostigmine), Galanthus, *Hyoscyamus niger L.*(hyoscine), and Narcissus (galantamine). We have been using herbs for a variety of purposes, including as food and medicine, for centuries. Human health and quality of life are greatly enhanced by their use in herbal medicine because of their medicinal importance and other properties like aromatic and flavoring properties. Secondary metabolites, such as lignans, coumarins, flavonoids, carotenoids, saponins, terpenoids plant sterols, contain a variety of chemical compounds like phthalates, phenolic compounds or polyphenols, anthraquinones, and sulfides that are present in plants and are among the most common

CHAPTER 4

Anthocyanins as Nutraceuticals

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Abstract: Anthocyanins are a group of colored, water-soluble flavonoid chemicals that are widely distributed in fruits, leaves, roots, and other portions of plants. They belong to a large group of flavonoids known as glycosides of anthocyanidins. Anthocyanins are often found in foods including cherries, plums, strawberries, raspberries, blackberries, grapes, redcurrants, blackcurrants, vegetable roots, legumes, and grains as colored compounds. Natural foods are known to contain more than 600 anthocyanins. Anthocyanin, which is consumed by humans, is one of the greatest flavonoids. Dietary anthocyanins are not very harmful. They are also helpful for polygenic diseases and managing weight. These actions, which include anti-inflammatory, liver-protective, analgesic, and anti-cancer properties, have given anthocyanins tremendous economic potential and driven researchers to concentrate on studying their chemistry, biological activity, isolation, and quality. Dietary therapies using anthocyanins are being thoroughly researched for the prevention of numerous chronic diseases, including GI cancer.

Anthocyanins have been used in clinical investigations that have demonstrated a substantial reduction in oxidative stress and inflammatory indicators, as well as a positive impact on vascular function and hyperlipidemia by boosting high-density lipoprotein and lowering low-density lipoprotein levels. Additionally, they may have an impact on cognitive decline and glucose homeostasis. The most recent research on anthocyanins as food supplements and nutraceuticals is summarized in this publication. The general structure of anthocyanins is shown in Fig. (**1**).

Keywords: Anthocyanins, Clinical investigations, Disorders, Disease management, Food supplements, Flavonoids, Managements, Natural diet, Nutraceuticals, Phytoconstituents.

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INTRODUCTION

The past few years have witnessed a massive influx in the global "living healthy" concept, including nutritional supplements that are more vital in facilitating access to phytochemicals that would not otherwise be widely accessible in regular eating practices. In North America and Europe, the marketplace for nutraceutical phytochemicals generated an estimated 16.1 billion dollars in sales in 2018 and was projected to reach 24.6 billion dollars in revenue in 2023 [1]. The risk of myocardial infarction, cardiovascular disease (CVD) mortality, and coronary heart disease is often associated with a diet high in flavonoids (CHD) [2 - 4].

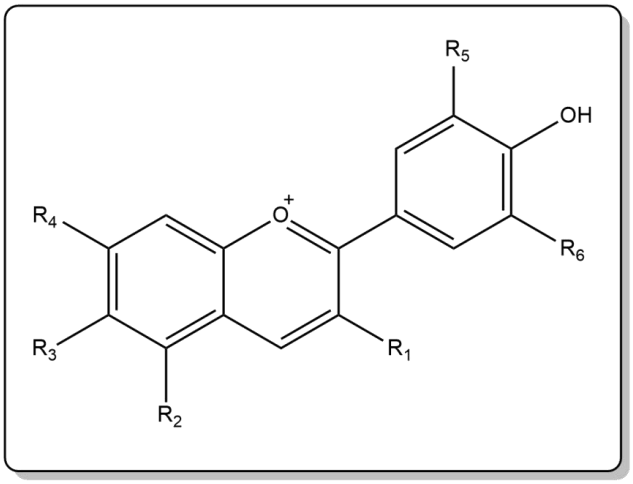

Fig. (1). Basic structure of anthocyanins.

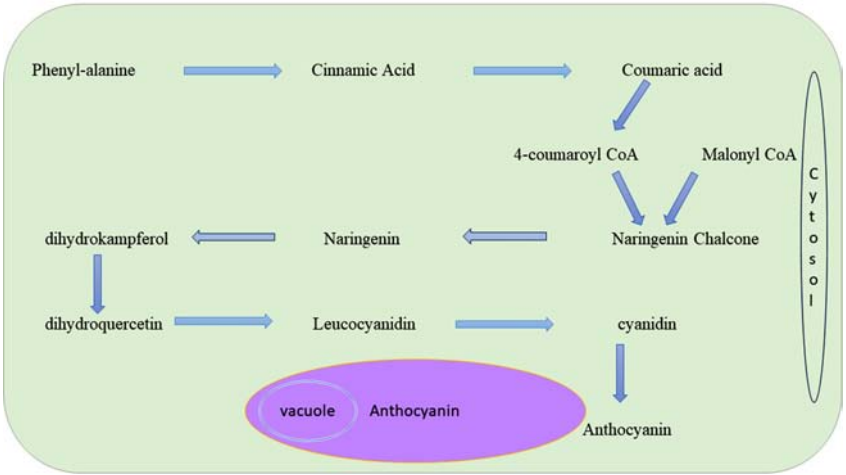

Fig. (2). Biosynthesis of anthocyanin.

The reddish-blue color of numerous fruits and vegetables is due to anthocyanins, a group of naturally occurring pigments with over 700 distinct chemical configurations. Anthocyanins also have potent antioxidant properties. Due to their remarkable ability to impart brilliant colors to a range of compounds as well as their potential health advantages, anthocyanins are of great interest to the agri-food business [5]. The biosynthesis of anthocyanin is presented in Fig. (**2**).

SOURCES OF ANTHOCYANIN AS NUTRACEUTICALS

One of the most intriguing substances in the food, beverage, cosmetic, and nutraceutical sectors is anthocyanins. A detailed evaluation of anthocyanin and anthocyanidin's nutraceutical properties has been done. Primary applications of anthocyanins as a natural food coloring ingredient are discussed in this chapter [6]. An overview of several of the numerous plant sources of anthocyanins, as well as food items derived from them, is presented in Table **1**, together with an estimate of the anthocyanin content in each item [7]. From various plant sources, including fruits, vegetables, roots, legumes, and grains, about 600 anthocyanin chemicals have been extracted and identified. The health advantages of anthocyanins depend on their ingestion from natural sources. Because anthocyanins are a common component of the typical human diet, populations that are unaware of this specific phytochemical's potential as a supplement can still benefit from it. Between 3 and 215 mg are used on a daily basis, according to estimates.

Table. 1. List of Anthocyanin-Containing Food Materials and their Pharmacological Role.

Sr. No	Fruit/Vegetables	Biological Name	Anthrocynins	Function	Concentration[mg/100g]
1	Bilberry	Vaccinium myrtillus	Pelargonidin, Cyaidin, Peonidin, Delphinidin and Malvidin	Antioxidant, Anticancer, Antiinflammatory, Antihyperglycemia, Antihyperlipidemia, prevent cardiovascular diseases and other age-related diseases	300-700
2	Bogberry	Vaccinium uliginosum	Delphinidin, Cyanidin, Petunidin, Peonidin, and Malvidin	Antioxidant, Anti-inflammatory and Anti-cancer	85-270

CHAPTER 5

Targeting Inflammatory Biomarkers and Free Radicals by Anthocyanins

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Abstract: Inflammation and oxidative stress are synergistic partners in the etiopathogenesis of diverse diseases. Polyphenols, such as anthocyanins, are responsible for the regulation of the inflammatory process and activation of the endogenous antioxidant defense system. Anthocyanins modulate the level of inflammatory markers and exert an anti-inflammatory effect. Consequently, translating the research outcomes into clinical practice significantly contributes to the prevention and management of chronic diseases. The chapter summarizes the role of anthocyanins as anti-inflammatory and anti-oxidative molecules in both health and diseases. Anthocyanins downregulate pro-inflammatory markers in chronic disease and thus suppress inflammation as well as oxidative stress in inflammatory disorders. The chapter can help researchers and other healthcare professionals to understand the importance of anthocyanin use in chronic diseases.

Keywords: Biomarkers, Inflammation, Inflammatory mediators, Oxidative stress, Polyphenols.

INTRODUCTION

Anthocyanins (ATNs) belong to the class of polyphenolic compounds and are generally hydrophilic pigments in glycosylated form [1]. Anthrocyanin is considered a class of flavonoids that contain a positive charge at the oxygen atom of C-ring, which is also known as flavylium [2-phenylchromenylium] ion. Among the anthocyanin pigments, cyanin -3-glycoside is the abundant anthocyanin present in plants (Table **1**). The blue pigment is generally found in cornflower and chicory, pink in blossom, purple in purple mint, common violet, lavender, and purple sage. These pigments are edible in nature [2]. ATNs are the most useful pigment of vascular plants. They are non-toxic and caneasily be incorporatedinto aqueous media, making them water-soluble colorants [3]. ATNs have a broad

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spectrum of pharmacological properties that are supported by pre-clinical as well as clinical studies. ATNs are used abundantly in the treatment of cardiovascular disease, cancers, and eye-related diseases, in the prevention of age-related factors and as anti-inflammatory agents and antioxidants. As shown in current *In vitro* studies, they also have the property to inhibit the propagation of viruses such as HIV, syncytial virus and adenovirus [4]. Anthocyanins are the derived products of anthocyanidins with the addition of sugars and are of two types: free anthocyanidin aglycones and anthocyanin glycosides. Delphinidin, Pelargonin and cyanidin are some sugar-free anthocyanidins. They work as building blocks for the production of anthocyanins by reactions like reduction, dehydroxylation and glycosylation inside the plants [5].

CHEMISTRY AND ITS DERIVATIVE

ATN has a cation backbone that is hydroxylated at different positions, giving various anthocyanidins. Glycosylation of anthocyanidinstakes place to produce ATN, which have different hydroxyl moieties in molecules and 3-OH moiety as the highest glycosylation location in nature to form 3-O-β-glucosides. Monomeric anthocyanins, glycosides of malvin, delphilin and cyanidin are most foundable in nature [1]. Anthocyanins are classified as water-soluble pigments; on administration, ATN molecules, with the categorized C6-C3-C6 backbone changed into a large range of different structures and metabolites and interactions with other proteins and lipid-abundant matrices, can become highly stable and strong. As a result, anthocyanins have the ability to change human responses by ingestion, which also has the tendency to regulate human health. ATNs have color-showing properties, which were first explained in 1939 by Pauling. The intensity of the color of anthocyanins is caused by the resonance structures of flavylium ion [3].

DERIVATIVES

Red grapes include anthocyanins, which are 3-glucosides of five aglycones: cyanidin, petunidin, peonidin, delphinidin, and malvidin. They exist in glucosylated forms, which are acylated in the glucose moiety by acetyl, caffeoyl, and coumaroyl groups. The anthocyanins found in grapes and wines in the highest concentrations are malvidin 3-glucoside and its derivatives. In the process of making wine, red grape skins and, in certain circumstances, grape pulp are used to extract anthocyanins, which are more prevalent in less-aged red wines. During storage and aging, these pigments are replaced by other anthocyanin-derived pigments, which cause an increase in the transformation of less-aged red wine's red-purple color to a more red-orange color [6 - 8]. The various pigments that have been proposed to contribute to the color of red wine include anthocyanin

oligomers, anthocyanin-flavanol polymers connected by a methylmethine bridge [8], xanthylium salts, pyranoanthocyanins, and many others that are yet to be identified, such as quinonic compounds [1, 17]. Due to the limitations of chromatographic techniques and the lack of pure standards in these pigments, it is difficult to find the color provided by these groups of compounds; at the moment, pyranoanthocyanins are considered to be one of the most valuable classes of anthocyanin derivatives. Between the OH group at C-5 and the C-4 of the anthocyanin pyranic ring, an extra ring D forms in their overall structure. In the initial stage of red wine aging, interactions between anthocyanins and other chemicals lead to the production of pyranoanthocyanins. As anthocyanin levels decline, new anthocyanin derivatives are created as potential precursors to the synthesis of more pyranoanthocyanins. The reaction between carboxypyranoanthocyanins and other compounds produces this second generation of pyranoanthocyanins, which have more complicated structures and distinctive spectroscopic characteristics. A pyranoanthocyanin moiety is connected to a flavanol or phenol unit by a vinyl bridge in the structure of these molecules. They are produced through a process involving vinyl phenolic substances and carboxypyrano-anthocyanins [8]. There are 175 main anthocyanins in *Vitis vinifera*, with malvidin-3-O-glucoside (Mv-glc) and its acylated glycosidic forms being the most abundant. Vitisins, pinotins, flavanyl-pyranoanthocyanins, anthocyanin-flavan-3-ols condensation products, and anthocyanin ethyl-linked flavan-3-ols are the six main structural categories [9].

Table 1. Plant Sources for Anthocyanins.

S. NO	PLANT	COMMON NAME	FAMILY	ANTHOCYANIN	USES
1	*Allium cepa*	Red onion	Amaryllidaceae	Cyanidin and Peonidin	Antioxidants
2	*Acalypha hispida*	Philippines medusa	Spurges	Cyanidin	Anti-fungal and Anti-oxidant properties
3	*Arabidopsis thaliana*	Arabidopsis	Brassicaceae	Cyanidin	Antioxidant activity
4	*Camelia sines*	Teas	Theaceae	Delphinidin and Cyanidin	Antioxidant property
5	*Citrus sineses*	Blood orange	Rutaceae	Cyanidin	Antioxidant property
6	*Fragaria ananassa*	Strawberry	Fragariaceae	Cyanidin and Pelargonidin	Neuroprotective activity
7	*Garcinia indica*	Kokum	Guttiferae	Cyanidin	Treat dysentery, tumors, heat complaints and liver disorders

CHAPTER 6

Role of Anthocyanins in Cancer

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Abstract: Background: Anthocyanins, natural pigments abundantly present in fruits and vegetables, have demonstrated diverse bioactive properties, including antioxidant and anti-inflammatory effects. There is growing interest in exploring their potential role in cancer prevention and treatment due to these properties.

Objective: This study aimed to comprehensively investigate the impact of anthocyanins on cancer, elucidating the underlying mechanisms through *In vitro* and *In vivo* experiments.

Method: The study was conducted to identify studies investigating the effects of anthocyanins on cancer cells. The selected studies encompassed *In vitro* experiments utilizing cell cultures and *In vivo* investigations employing animal models to assess the potential inhibitory effects of anthocyanins on tumor growth. The review focused on molecular and cellular assays from these studies, specifically exploring the modulation of oxidative stress, inflammation, apoptosis, angiogenesis, and cell cycle regulation by anthocyanins. The methodological approaches and key findings from these studies were critically analyzed to provide a comprehensive overview of the current state of knowledge regarding the role of anthocyanins in cancer.

Result: The findings revealed that anthocyanins exerted potent antioxidant effects, mitigating oxidative stress and DNA damage in cancer cells. Anti-inflammatory properties were demonstrated by the suppression of key inflammatory pathways. Anthocyanins induced apoptosis in cancer cells, leading to programmed cell death while sparing normal cells. Furthermore, they exhibited antiangiogenic effects by disrupting the formation of blood vessels essential for tumor growth. The modulation of cell cycle progression was also observed, suggesting a role in preventing uncontrolled cell proliferation.

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Keywords: Anthocyanins, Antioxidants, Anti-inflammatory, Apoptosis, Angiogenesis, Cell cycle regulation, Cancer.

INTRODUCTION

Anthocyanins, plant colors that are blue, crimson or purple, are most prevalent in flowers, fruits vegetables and tubers. In the alkali environment, anthocyanin is a blue colorant, while in acidic ones, it is a red pigment. Anthocyanin is a flavonoid in spite of having a positive charge on the oxygen molecule of the fundamental flavonoid structure's C-ring. It is referred to as the flavylium (2-phenylchromenylium) ion.

Anthocyanin's stability is affected by pH, light, temperature, and its structural makeup [1]. Many plants include anthocyanins in their flowers and fruits. Anthocyanins were detected largely in the flowers' red, purple, and blue colors. Red flowers include pink blossom, red clover, red pineapple sage, red hibiscus plants, red roses, along with red hibiscus. These crimson flowers can be eaten. The most popular edible blossoms are turquoise (cornflower, blue chicory, as well as blue rosemary) and purple (purple mint, purple passion flower, purple sage, common violet, and lavender).

Some of these florae have been utilized as food, dyes, and folk medicine for centuries. Red, purple, and bluish fruits are renowned for their health benefits in addition to their traditional applications.

Berries, in particular, blackcurrants and other berries with a red to blue hue, contain antioxidant-rich anthocyanin pigments. Anthocyanin-rich foods, including purple potatoes, crimson cabbage, and black carrots, have also been utilized to prevent sickness [2]. Plant-derived anthocyanins are employed for a range of reasons. Traditional dye and food coloring methods include extracting blue, crimson, and purple coloring from plants, fruits, and vegetables. Some anthocyanin-rich flora and fruit are typically used as remedies and natural colorants to treat a variety of diseases. Plant anthocyanins, on the other hand, have undergone extensive investigation into their medicinal effects. Anthocyanin is classified as a glycoside, whereas anthocyanidin is classified as an aglycone. Arylated anthocyanins and anthocyanidin glycosides are two types of anthocyanins, whereas three types of anthocyanidins are 3-hydroxyanthocyanidins, 3-deoxyanthocyanidins, and O-methylated anthocyanidins [3].

Cyanidin, delphinidin, pelargonidin, peonidin, petunidin, as well as malvidin are the most prevalent anthocyanidins found in plants’ fruits, flowers, foliage and roots. Plants have been found to contain acylated anthocyanins as well as

traditional anthocyanins. The arylated anthocyanins are further subdivided into arylated, coumaroyl, caffeoylated, and maltosylated anthocyanins. Natural sources of anthocyanins: These occur naturally in flora's fruits, flowers, foliage, and roots. People consume the most anthocyanin-containing foods, such as cherries, fruit, and cereals. Based on publications in science, multiple anthocyanins, along with related compounds, have been discovered from natural sources. Anthocyanins detected in flowers have been shown to be more stable than those found in grapes [4]. Therapeutic and medicinal properties of anthocyanins obtained from botanicals are typically utilized for treating hepatobiliary illnesses such as hyperbilirubinemia, obstructed bile ducts, and anorexia. This section discusses the purported medicinal uses of anthocyanins [5].

Antioxidant effects: Anthocyanins are effective free radical scavengers owing to the conjugated double link of the keto group. Given the high sensitivity and fragility of aglycones in their structure, the pigments have a benefit when acting as antioxidant agents.

Glycosylation reduces their ability to neutralize free radicals, while diacylation increases it. Anthocyanins' antioxidant activity has been studied in a variety of models and systems. Anthocyanins safeguard healthy cells from oxidative stress by enhancing the manufacturing of ARE-regulated phase II enzymes [6].

Antitumor activity: Angiogenesis promotes the growth of cancer cells. Anthocyanins isolated from berries, according to reports, inhibit the growth of certain cancer cell types. Anthocyanins from berries such as blue bilberries and black millet are claimed to possess anti-invasive qualities in both *In vivo* mammal animals and female breast carcinoma cells by lowering the production of the cyclooxygenase-2 gene.

As a black rice anticancer activity, additional methods of activation suppression have been reported. Matrix metalloproteinase (MMP) and mitogen-activated protein kinase (MEK) expression are two examples of metalloproteinases. MMP2 and MMP-9 are two examples of metalloproteinases. A study on the anticancer properties of purple potato anthocyanins in CF-1 mice used cell-cycle arrest induction to simulate the compounds' impact on colorectal cancer [7 - 9].

First, the AMP-activated peptide kinase enzyme, or AMPK, is a crucial regulator of energy balance. It can regulate energy usage and fat accumulation through various methods, such as boosting mitochondrial biogenesis, reducing lipid metabolism, enhancing fatty acid oxidation, reducing hypertriglyceridemia, regulating food consumption, and maintaining triglycerides in the muscles and liver. Second, black soy kernels may promote thermogenesis by increasing the levels of regulatory uncoupling proteins in brown and white fat tissues, preventing

CHAPTER 7

Anthocyanins: Pharmacology and Nutraceutical Importance

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Abstract: Anthocyanins are natural, colored, water-soluble plant pigments that belong to the flavonoid, a subclass of the family polyphenol. Common dietary sources of anthocyanins include red and purple berries, grapes, apples, plums, cabbage, and other foods strong in natural colorants. Cyanidin, delphinidin, malvidin, peonidin, petunidin, and pelargonidin are among the six most prevalent anthocyanidins in nature. Cyanidin-3-glucoside, one of the anthocyanin pigments, is the main anthocyanin present in most of the plants. Following ingestion, anthocyanins are absorbed in the digestive system, with the distal lower colon meant for the major absorption and metabolism. Anthocyanins are extensively broken down by microbes in the colon before being absorbed and used by humans in phase II metabolism. As a result, hybrid microbial-human metabolites are created, which are then ingested and boost the anthocyanins' bioavailability. Colored anthocyanin pigments are traditionally used as natural food colorants. In addition to their usage as natural colors, anthocyanidins and anthocyanins are potential medicinal components that have a variety of positive health effects. Anthocyanins provide several health advantages, particularly in the prevention of oxidative stress-related illnesses, including cardiovascular, metabolic, and neurological disorders. According to new data, the regulation of gut microbiota may also be linked to the health-promoting benefits attributed to anthocyanins. Despite the potentially widespread biological activity of anthocyanins, safety and toxicological concerns are relatively minor. The advantages of anthocyanins for health have been the focus of extensive study over the last two decades. This book chapter focuses on a thorough overview of the most recent research on anthocyanins, their pharmacological properties and nutraceutical values in human health.

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Keywords: Anthocyanin, Anthocyanidin, Antioxidant, Biological activity, Colorant, Cardioprotective, Dietary source, Health benefit, Nutraceutical, Neuroprotective, Nutraceutical, Pigment.

INTRODUCTION

The average life expectancy and life quality of the global population have significantly increased due to improved and better healthcare facilities. However, the widespread availability of high-calorie meals and the rise in processed food consumption, especially in western and developing countries, have contributed to an epidemic of chronic, non-communicable illnesses like cardiovascular, metabolic, and neurological conditions. Fresh foods with bioactive non-nutrients protect the body on several levels, thus encouraging their intake. Fresh foods, especially plant-based meals, include a variety of bioactive substances, such as polyphenolic substances, that can influence many body pathways and processes and exhibit antioxidant, anti-inflammatory, anticancer, antidiabetic, and neuroprotective effects.

Anthocyanins are naturally colored water-soluble plant pigments that belong to the flavonoid group and are categorized under one of the major subclasses of the polyphenol family. These substances are vacuole-specific pigments and are mostly found in fruits and flowers, as well as in vegetative organs. Anthocyanins are basically the glucosides of anthocyanidins, which are phenylpropanoid-derived flavonoid derivative compounds. Higher plants have them in every tissue, including the leaves, stems, roots, flowers, and fruits. Cyanidin, delphinidin, pelargonidin, peonidin, petunidin, and malvidin are the six anthocyanidins that are most frequently present in dietary foods [1, 2]. These pigments' color and stability are affected by physical factors*i.e.*, pH, light, temperature, and structure. Some of the anthocyanins take on a red appearance when exposed to an acidic medium. When the pH is neutral, they have a purple tint, but when the pH rises, the color turns blue. Because anthocyanins change in reaction to pH, it is easy to distinguish them from other flavonoids. They strongly influence the sensory qualities of food because they give fruits and vegetables their distinctive red to blue color. They are essential for pollination in plants and, by absorbing light, shielding them from cold stress and ultraviolet (UV) damage [3 - 5]. Some organs, such as petals of flowers, can change color during development, eventually varying vacuolar acidity and the production of more or fewer anthocyanins [6]. The vacuolar acidification modifies the color, whereas the fluctuation in anthocyanin content changes the color intensity [7]. The primary purpose of anthocyanins, which are found in flowers and fruit skins, is to draw animals and pollinating insects to transfer pollen grains or readily disperse seeds. Although in fact, anthocyanin synthesis is stimulated when unfavorable circumstances are met,

this shows that they are influenced by biotic and abiotic stress factors. Anthocyanins' functions have been related to their ability to scavenge free radicals, as well as to their effects on a variety of enzymes, such as cyclooxygenase and mitogen-activated protein kinase, as well as on the signaling of inflammatory cytokines. Plant-derived anthocyanins are frequently employed as food coloring, food additives, and colors.

Recent studies on animals and humans have shown that these compounds are beneficial and can increase antioxidant protection, and reduce weight, free radical injury, long-term inflammation, and the possibility of mutations, as well as delay or even stop the onset and progression of many non-communicable and degenerative persistent disarrays, such as atherosclerosis, metabolic ailments, ocular disease and renal complications, as well as many cancers [8 - 14]. Along with vitamin A and carotenoids, they are well-recognized for protecting visual function [15]. They also have a lot of positive health benefits, making them suitable constituents for nutraceuticals. The idea of using anthocyanin derivatives in the prevention or treatment of many illnesses is alluring because they have not been shown to have any side effects, even when consumed in extremely large amounts.

SOURCES, CHEMICAL CONSTITUENTS, STABILITY, AND BIOAVAILABILITY OF ACNS

Anthocyanins are phenolic compounds that are odorless, virtually flavorless, have a moderate astringent property and constitute an important group of plant pigments. The brilliant red, blue, and purple colors present in vegetables, fruits, and their derivatives are primarily due to the presence of anthocyanins, which are extensively distributed in nature (Fig. **1**) [16].

Fig. (1). Natural sources of anthocyanins and their chemical constituents.

CHAPTER 8

Therapeutic Efficacy of Anthocyanins in Metabolic Disorders

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Abstract: Metabolic syndrome (MetS) is a chronic disorder developed with cumulative symptoms of diabetes mellitus, hypertension and dyslipidemia. The etiologic causes of metabolic syndrome are a sedentary lifestyle, poor dietary choices, and hereditary factors, which have a negative impact on the health of people by increasing the risk of cardiovascular problems, organ damage, and additional pathology related to MetS. Anthocyanins (ANTs) are plant-based biomolecules that promote health and belong to a polyphenols subclass of flavonoids. Concurrent research reports have found that plants rich in ANTs may have therapeutic advantages for diabetes, obesity and MetS by decreasing insulin resistance, poor glucose resistance, dyslipidemia, high cholesterol levels in serum, hypertension, and inhibiting free radical formation. This chapter reviews the therapeutic advantage of ANTs in the management of MetS, along with their pharmacological mechanisms and biopharmaceutical functions. Similarly, the use of ANT-rich supplements is discussed for their potential in the control of MetS.

Keywords: Anti-oxidative, Anthocyanins, Diabetes, Hypertension, Health, Metabolic syndrome, Obesity, Pharmacological mechanisms, Plants.

INTRODUCTION

MetS is a blend of disorders that include compromised glucose tolerance, high blood pressure, and obesity. It is also termed “syndrome X” or, more specifically, “insulin resistance syndrome”. It is diagnosed using criteria such as atherosclerosis, dyslipidemia (low levels of HDL and high TGs levels), high blood pressure, and insulin impairment. Furthermore, patients who are susceptible to hyperglycemia, hyperlipidemia, and glucose intolerance and also have inflam-

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mation and platelet aggregation-related disorders are in higher danger of the predominance of T2DM and CVD and ultimately MetS [1 - 3]. MetS may be a chronic condition characterized by hyperglycemia as a result of impairment of insulin synthesis or insufficient receptor sensitivity to insulin, as well as a gradual loss in β-cell activity, high BP and other diseases like obesity [4, 5]. MetS is a growing global issue that is predicted to impact around 380 million people by 2025 [6]. Several studies have revealed that plant compounds, like flavonoidsand polyphenols, have a wide variety of cellular actions, with anti-inflammation mediators, antioxidative, and insulin-sensitizing properties [7, 8]. Particularly, anthocyanin-rich herbal formulations and nutraceuticals have a major role in regulating MetS [9-12]. Multiple studies have shown that plants like blueberries, which are rich in anthocyanin, have a variety of useful medicinal potential, including counteracting age-induced oxidative stress and reducing the levels of pro-inflammatory cytokines, demonstrating anti-inflammatory action, which helps in protecting the kidney and treating diabetes, cardiovascular disorders, hyperlipidemia hypertension and obesity *In vitro*and*In vivo* [13]. Additionally, in the obese Zucker rat, a wild blueberry-containing diet guards against the pro-inflammatory state linked with MetS by reducing NF-κB and raising adiponectin production [14]. Thus, in this chapter, we examined ANT-loaded diets as prospective substitute therapy in addition to their potential modes of action for controlling metabolic syndrome.

Epidemiology of Metabolic Syndrome (MetS)-

The rate of occurrence of MetS varies from 10 to 84% in town people, depending on geography and demographic combination (age, gender, and race). According to the Global Diabetes Alliance, roughly one-fourth of the world's population is suffering from MetS, with 28% of males and 34% of females also taking part in Arteriosclerosis Risk in Communities (ARIC) studies [15]. MetS is becoming more popular among adults aged 60 to 69 years old in the United States [16]. According to one research, the frequency of MetS among Iranians was found to be 34.6% [17]. MetS has significant public health implications due to an increased hazard of progressing T2DM and CVD [18]. As per World Health Organization (WHO) figures, MetS is now a worldwide epidemic by means of growing incidence in India and Asia, and it is anticipated to be the seventh leading cause of mortality by 2030 [19].

Pathophysiology

Obesity and insulin resistance, along with the deposition of circulating fatty acids in the bloodstream, are two major pathophysiologic variables that could contribute to MetS development [20] (Fig. **1**). Insulin inhibits lipolysis and activates

lipoprotein lipase in adipose tissue; as a result, when insulin resistance arises, the number of fatty acids increases in the body, which further triggers the lipolysis in adipose tissue, and, therefore, increases the number of lipids in the circulatory system. Further, obesity is associated with an increase in macrophages in adipose tissues as well as an elevation in pro-inflammatory cytokines [21]. In a study, a high-fat diet resulted in elevated arterial pressure, elevated levels of TG in serum, and a decline in HDL-C concentrations because of increased fatty acid re-esterification, which is directly associated with MetS [22].

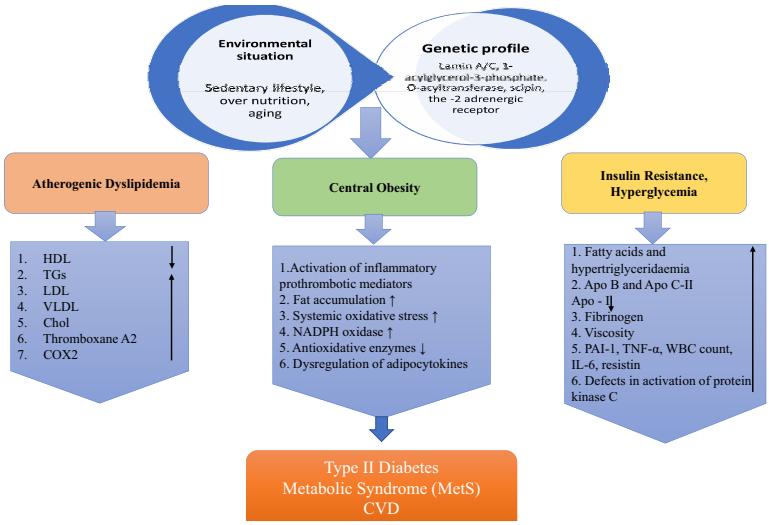

Fig. (1). Pathophysiological mechanism of metabolic syndrome.

Association of Oxidative Stress in MetS Pathogenesis

Oxidative stress is defined as a disturbance in the reactive state of the cellular functions of the body due to the destruction of biomolecules such as proteins, lipids, and DNA [23]. The excessive production of free radicals in fatty tissue reduces the muscle uptake of glucose and insulin production from cells, which may have a major effect on the advancement of insulin resistance, diabetes, and CVD [24]. Multiple studies have revealed that an increase in ROS production from stored fat in the peripheral blood is linked to the onset of insulin resistance. Insulin resistance disrupts several key oxidization processes, resulting in an increase in ROS production at the cellular and mitochondrial levels. According to researchers, people with T2DM have greater concentration of lipid peroxidation, while concentration of plasma glutathione (GSH) and GSH-metabolizing enzymes are lower [25]. Further studies also showed that in lab animals, hyperglycemia causes radical and oxidative stress [26]. Injecting 10-20 mM glucose into posterior root ganglion neurons leads to the production of oxygen, hydrogen

CHAPTER 9

Anthocyanins as Nutraceutical for Gastric Disorders

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Abstract: Vegetables are a crucial part of the human diet and a significant source of physiologically active nutraceuticals. Due to their safety, effectiveness, possible nutritional value, and therapeutic effects, they have attracted a lot of attention in the diet world. Customers are expressing a desire for wholesome food items made with natural, health-improving components, which is primarily fostering the expansion of companies involved in the anthocyanin market. Anthocyanin helps to prevent skin damage and aging, creating potential for suppliers in the nutraceutical and cosmetics industries. Common phytonutrients include lycopene from tomatoes and carotenoids from carrots, among others. There are numerous metabolic and degenerative diseases, most of which are caused by nutritional deficiencies, now increasingly affecting the population. Nutraceuticals are any ingredient used as food or as a component of food that has normal nutritional value and offers health advantages, such as illness prevention or health promotion.

The practice of relieving gastric discomfort with particular foods has long recognized the impact of nutrition on gut health, and more recently, a link between certain diets and decreased incidences of a number of gastrointestinal disorders has been established.

For the purpose of human disease prevention, the focus of this analysis is on grape seed nutraceuticals' most recent developments and prospective applications in the future.

Keywords: Disease, Gastrointestinal disorders, Herbals, Nutraceuticals, Vegetables.

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INTRODUCTION

Everyone needs food to satiate their desire, maintain their health, and consequently lead fulfilling lives. According to the ancient Hindu holy text known as the Vedas, "You are what you eat". Thomas Edison, who lived more than 2000 years after Hippocrates, agreed with him. "The doctor of the future would heal and prevent disease through nutrition rather than using medications to treat the human body," he stated [1].

Although Stephen DeFelice, the founder and executive director of the "Foundation for Medical Innovation", has a precise definition for the term "nutraceutical", which was first used in 1989,. According to him, a nutraceutical is "Any substance that is a part of a meal or a meal itself that has health or medical benefits, such as the ability to treat or prevent diseases" [2].

The previous fifty years have seen a significant shift in human lifestyles as a result of urbanization, industrialization, stressful schedules, and shifting cultural norms. These influences have altered human eating patterns and forced people to rapidly consume quickly prepared meals, fast food, and junk food. The nutritional value of our diet has been directly impacted by these habits, which have gradually reduced nutrient quantity and quality. Due to these modified eating patterns, immunological dysfunctions, metabolic problems, and degenerative diseases are now more common. Biologically active compounds (BAC) are abundant in fruits and vegetables because they are a key source of phytochemicals with potent immunomodulatory, antimicrobial, and anti-inflammatory properties that may promote health. Inhibiting low-density lipoprotein and reducing the risk of cardiovascular illnesses are additional benefits [1, 2].

In the current market, nutraceuticals are frequently used for a number of therapeutic purposes, such as insomnia, digestive issues, cold and flu treatments, and the prevention of illnesses including osteoporosis, cancer, high blood pressure, diabetic pain relievers, depression, and cholesterol. Nutraceuticals include substances including dietary fiber, probiotics, prebiotics, polyphenols, antioxidant vitamins, polyunsaturated fatty acids (PUFA), and spices [3].

A food component or supplement known as a nutraceutical is one that is also used to promote wellness or fend off disease. A fermented beverage called "Kanji", which is laden with probiotics and anthocyanins, is produced from the black carrot kinds cultivated in northern India. Among the vegetables with the greatest nutrients per serving are pumpkin and sweet potatoes (varieties with orange flesh) [3, 4].

CLASSIFICATION OF NUTRACEUTICALS

Dietary Supplement

An oral consumption-only item with a "dietary component" that is intended to supplement food is referred to as a dietary supplement. Examples of "dietary constituents" include vitamins, minerals, herbs or other botanicals, amino acids, as well as substances including enzymes, organs, tissues, glandular tissues, and metabolites.

There are different nutritional supplements like nutrients, herbals, phytochemicals, probiotics, prebiotics, nutraceutical enzymes, and dietary fibers [3].

Functional Food/fortified Nutraceutical

Made with additional nutrients or substances, it is a fortified food. Examples include milk with vitamin D, orange juice with calcium, and cereal flour with folic acid and fiber.

Farmaceuticals/Recombinant Nutraceuticals

In agricultural circles, the word "farmaceuticals" is more usually connected with the medical uses of genetically modified animals or plants. Biotechnology is used to produce foods that provide energy, including bread, wine, fermented starches, yogurt, cheese, and vinegar, among others [4].

THERAPEUTIC AGENTS IN NUTRACEUTICALS

The majority of dietary supplements have been shown to provide several therapeutic benefits, as well as physiological advantages or the ability to defend against a variety of diseases, as shown by cardiovascular drugs, anti-obesity drugs, diabetes drugs, and anti-cancer drugs, immune enhancers, medications for chronic inflammatory conditions, and treatments for degenerative diseases [5].

Nutraceuticals can be categorized in a variety of ways, such as according to their dietary origins, mode of action, chemical makeup, *etc*. All-natural food sources are used to make nutraceuticals. The primary agents responsible for the gastroprotective properties of polyphenols include catechins, curcuminoids, and anthocyanins. Tea, wine, olives, grapes, chocolate, turmeric, and other plants all contain polyphenols, which possess a range of anti-inflammatory, antibacterial, antioxidant, and anti-carcinogenic qualities. Anthocyanins' potential to further battle degenerative illnesses has also been investigated to alter gene regulation and signaling pathways [4, 5].

CHAPTER 10

Anthocyanins as Nutraceutical for Infertility and Impotency

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Abstract: Anthocyanins comprise polyphenols having recognized antioxidant capacity, whichare involved in several biological processes such as the protection or reduction of heart disease, arthritis, diabetes, and cancer and also play an important role in infertility as well as impotency. Such qualities, including stability and bioavailability, are determined by their chemical composition. The current study provides a brief overview of anthocyanin's chemical components, bioavailability, as well as anti-inflammatory properties. If a couple has already been attempting to conceive for more than a year without success, then they may be regarded ashaving fertility problems. Worldwide, 20% of all couples are unable to have offspring. Subfertility canaffect either female, male, or even both partners. Nevertheless, for some couples, the source of infertility cannot be determined, which is known as unexplained infertility. Antioxidants are expected to reduce the harm resulting from oxidative stress, which is known to be implicated in the pathogenesis of infertility. Antioxidants are commonly available and reasonably priced. However, there is currently insufficient high-quality research to establish whether consuming antioxidants would benefit or damage infertile women.

Keywords: Anti-inflammatory properties, Anthocyanins, Antioxidants, Bioavailability, Infertile, Impotency, Oxidative stress, Oonceive, Reactive oxidative species, Subfertility, Worldwide.

INTRODUCTION

Anthocyanins are often regarded as the most abundant and significant group of solubilized pigments found in the environment [1]. These are accountable for so many fruits as well as vegetables' red, purple, and orange hues. The term anthocyanin is derived from the Greek words anthos, which means flowers, and kyanos, which means dark blue [2]. Ras pb erries, blueberries, cherries,

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strawberries, black currants, purple grapes, and red wine are great sources of anthocyanin. These are members of the flavonoid family; they are distinguishable from other flavonoids by their ability to produce flavylium cations [3].

Increasing evidence suggests that reactive oxygen species (ROS) plays a significant role in the progression as well as the pathogenesis of significant health issues such as cardiac disorders, eye disorders, joint disorders, kidney and lung disorders, atherosclerosis, pancreatic and liver diseases, cancer, aging, infertility, as well as neurodegenerative disorders [4] There is growing evidence suggesting oxidative stress-damaged DNA is linked to decreased sperm function as well as male infertility. 8-OHdG is thought to be a precise, highly sensitive indicator of DNA oxidation. Fig. (**1**) shows the effect of reactive oxygen species on male infertility (H.M. *et al.*, 1999). Thus, the current study was conducted to assess the degree of DNA oxidation in sperm and its relationship to male infertility by measuring 8-OHdG concentrations of man's sperm specimens [5].

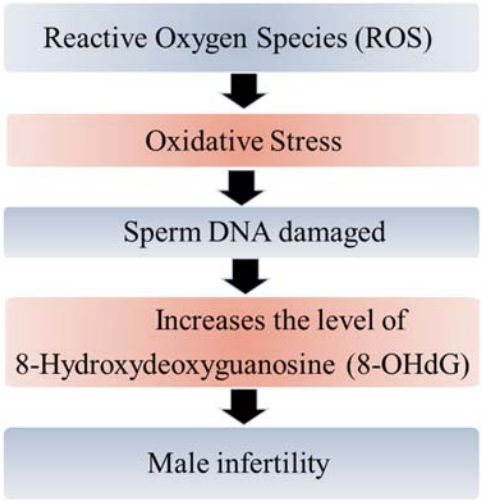

Fig. (1). Effect of ROS on male infertility.

Varicocele is the leading cause of infertility in men and is linked to oxidative stress. The anthocyanin therapy improved left testicle volume, mobility, and cellular density of spermatogenic in the varicocele-associated rat model while decreasing 8-OHdG levels with apoptosis in the testicle tissues. It has recently been proposed that all these effects are attributable to anthocyanin's antioxidant function in reducing oxidative damage caused by varicocele-associated ROS. Thus, anthocyanin treatment may be useful in decreasing or avoiding testis damage caused by the varicocele, as shown in Fig. (**2**) (Jang H *et al.*, 2012) [6]. Anthocyanin reduces the ROS and decreases the level 8-OHdG biomarker.

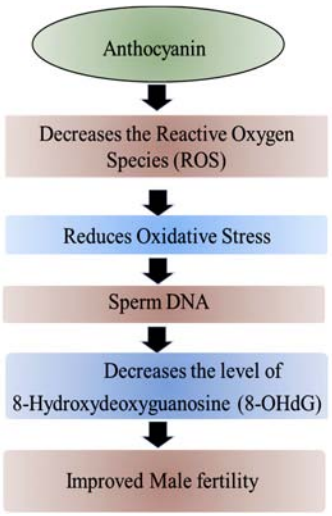

Fig. (2). Mechanism of action of anthocyanin.

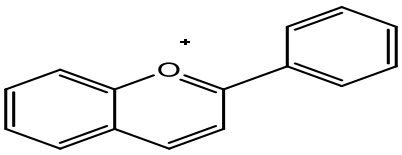

Fig. (3). Anthocyanin structure.

They are most commonly found as glycosides of their corresponding aglycone chromophores of anthocyanidin, even with a moiety of sugar connected at the C-3 position on the carbon ring or even the 5-position in the A-ring [7]. There are approximately 17 anthocyanidins found in nature, although just six (delphinidin, cyanidin, peonidin, petunidin, pelargonidin, and malvidin) are the most common (Fig. **3**). The structures and colors of various anthocyanin derivatives are shown in Table. **1** (Miguel MG, 2011), which are widely distributed and important in human nutrition [1, 8]. In accordance with a recent analysis on the position of anthocyanins in preventing cancer, the daily dose of anthocyanins in the American diet is approximated to be somewhere around 180 as well as 215 mg, which is significantly higher than that of many other dietary flavonoids like genistein, quercetin, and apigenin, which is only 20-25 mg per day [9].

CHAPTER 11

Role of Anthocyanins in Neurological Disorders

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Abstract: Anthocyanins, natural pigments abundantly found in various fruits and vegetables, have attracted increasing attention for their potential role in mitigating neurological disorders. This review explores the multifaceted neuroprotective effects of anthocyanins, focusing on their ability to counteract oxidative stress, modulate neuroinflammatory responses, and influence cognitive function. Drawing on a diverse range of studies, both *In vitro* and *in vivo*, we examine the impact of anthocyanins on neuronal health and their potential therapeutic applications in neurodegenerative diseases. The antioxidant properties of anthocyanins play a crucial role in reducing oxidative damage, while their anti-inflammatory effects contribute to the attenuation of neuroinflammation, a common feature in neurological disorders. Furthermore, anthocyanins exhibit promising potential in preserving cognitive function and preventing neurodegenerative conditions. This comprehensive analysis highlights the emerging significance of anthocyanins as potential neuroprotective agents and emphasizes the need for further research to unlock their full therapeutic potential in the context of neurological disorders.

Keywords: Anthocyanins, Cognitive Function, Neuroprotection, Neuroinflammation, Neurodegenerative Diseases, Oxidative Stress, Therapeutic Potential.

INTRODUCTION

Anthocyanins are the most important plant metabolites, fundamentally colored, water-soluble pigments that are predominantly phenol group members and exist in glycosylated forms (Fig. **1**). Anthocyanins make up the majority of the colorful

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plant pigments, with the exception of chlorophylls. These anthocyanins belong to the group of “flavonoids”, aggregate in vacuoles, and give fruits, vegetables, and flowers their vibrant and distinctive colors. The term “Anthocyanins” is made up of the words “Anthos” and “Kyanous”, where the former implies flowers and the latter, a deep blue color [1]. Compared to other anthocyanin pigments, which are typically found in most plants, cyanidin-3-glucoside is the predominant anthocyanin. These specific groups of chemicals are often regarded as powerful “anti-oxidants”, significantly influencing human health. The colors of anthocyanin salts indicate that they are amphoteric in nature; acidic anthocyanins are red, alkali anthocyanins are blue, and free anthocyanins (neutral) are violet. These pigments' hue and consistency are highly affected by light, pH, temperature, and configuration. Polyphenols derived from plants are used for a variety of applications. The extraction of cyan, red, and magenta colorants from flower petals, vegetables, and fruits is a conventional use for pigment and food coloring. Some alkaloid-rich flowers and fruits have historically been used as drugs to treat a number of disorders and are also used as natural dyes. Chemists and biologists have long been fascinated by anthocyanins, researching their biosynthesis patterns, metabolism, and physiological functions. The therapeutic efficacy of plant anthocyanins has also undergone much research. Anthocyanins have the ability to protect against cardiovascular diseases (CVDs), as well as diabetes, cancer, inflammation, infection, and obesity [2]. Polyphenols have been conclusively demonstrated to have antibacterial and antioxidative characteristics by research studies on culturing, laboratory animals, and human clinical trials that elevate neurological and visual health and safeguard against a range of non-communicable ailments. Anthocyanins produced from food plants are, therefore, possible components for pharmaceuticals. The focus of the above-mentioned points is all on anthocyanins as natural food coloring agents and their health-promoting nutraceutical effects [3].

TYPES OF ANTHOCYANINS

Different types of anthocyanin have different health benefits, that are listed in Table **1**. Following information will brief about the various types of anthocyanin and its use:

Cyanidin

Cyanidins are water-soluble anthocyanins that exist as glycosides, hence the name anthocyanidines. They are pigments, which are essentially natural polymer compounds that give hues to fruits and flowers such as blue, red, and orange. The sources of cyanidins are different red berries like grapes, cranberry, blackberry, cherry, blueberry and so on. Additionally, it can be discovered in other fruits like plums and apples, along with red onion and red cabbage. Cyanidins appear to have the highest absorption rate, the least degradation, and the most clinical significance of all anthocyanin subcomponents, making them the most pharmaceutically useful anthocyanin subcomponent. They have a diverse range of

effects in cells, the majority of which can be characterized as anti-diabetic and may tangentially aid other factors linked to the "metabolic syndrome" (anti-inflammatory, anti-oxidant, *etc.*). However, cyanidin does have some absorption issues; therefore, the outcomes of *In vitro* (lab) research might not be applicable to actual consumption. Studies on human intervention are crucial because there are concerns about the substance's bioavailability (percent absorbed). It is generally manufactured from the hydrolysis of cyanin or the synthesis of pyrocatechol derivatives as the crimson-brown crystalline chloride $C_{15}H_{11}ClO_6$). Berry plants can generate cyanidin using the shikimate pathway and polyketide synthase (PKS) III. The shikimate pathway uses erythrose 4-phosphate and phosphoenol pyruvic acid (PEP) as starting ingredients to create shikimic acid, which then endures more such reactions to produce specified fragrant amino acids [4]. L-phenylalanine is generated using the shikimate pathway and is necessary for the production of cyanidin. Because of their potent antioxidant and radical-scavenging abilities, cyanidins lower the risk of developing cancer. The proliferative and cytodifferentiation actions in the treatment of human prostate gland cancer cell lines are likewise mediated by cyanidin.

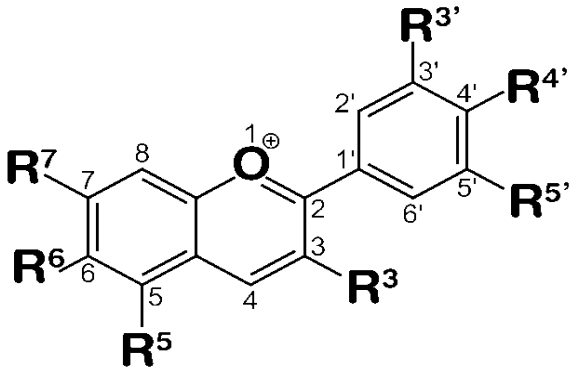

Fig. (1). Core Structure of Anthocyanins, 2-phenylbenzopyrylium(Flavylium cation).

Delphinidin

The brownish red or shadowy purple crystalline chloride $C_{15}H_{11}ClO_7$, which is frequently produced as the prominent anthocyanidin delphinidin, is one such anthocyanidin (as by synthesis from pyrogallol derivatives and by hydrolysis of glycosides) and also a plant pigment, as well as an antioxidant that gives fruits and flowers their blue color [5]. Delphinidin is the blue dye found in the flowers belonging to the genus Delphinium and Viola. It is also found in cranberries, bilberries, grapes, pomegranates, and the cyan-red hue of the Cabernet Sauvignon grape. Delphinidin is a pH-sensitive anthocyanidin that also functions as a natural pH biomarker. It turns blue in an acidic solution and red in a basic solution. It is a

CHAPTER 12

Current Global Scenario for Anthocyanin-Based Nutraceuticals

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Abstract: In recent years, the world population has been very conscious about having a healthy lifestyle. Anthocyanin is nowadays popular as a nutraceutical and hasalready been part of traditional medicines. It is not only employed as a colored pigment but also as a potent ingredient in pharmaceutical preparations in several food industries. Various *In vitro* (scavenging assays) and *In vivo* (animal and human cell line studies, various animal models, and clinical trials) evaluations have revealed that anthocyanins are rich in dietary supplements when consumed either through food or beverages and have always been beneficial for humans. According to several studies, it is reported that these anthocyanins possess various activities such as antioxidant, anti-aging, anti-inflammatory, anti-diabetic, and antiviral and also manage illnesses related to neuroprotection and neurodegeneration. The size of the worldwide nutraceuticals market, estimated at USD 454.55 billion in 2021, is anticipated to rise at a 9 percent compound annual growth rate between 2021 and 2030. Over the course of the forecast period, the market is anticipated to be driven primarily by the rising demand for functional foods and dietary supplements. A positive view of medical nutrition in light of its growing use to treat cardiovascular disease and malnutrition is predicted to stimulate the market for dietary supplements. The significant characteristics of anthocyanin-based nutraceuticals are efficiency in cost, a wide safety view for both animals and humans, acceptability and easy availability. Regardless of a wide safety view, some of the nutraceuticals-based products are considered to be negotiated owing to adulteration with poisonous pesticides, abusive drug molecules, heavy metals, harmful plants, mycotoxins and lethal fertilizers. Thus, future broad research from both the pharmaceutical area and academia is required to ensure their effectiveness and safety concerns.

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Keywords: Antioxidant, Anti-inflammatory, Anthocyanin pigments, Color, Dietary, Effectiveness, Food industries, Global market scenario, Health benefits, Nutraceuticals, Regulatory aspects, Safety considerations, Supplements.

INTRODUCTION

In recent years, the world population has been very conscious about having a healthy lifestyle. In order to attain it, supplements containing phytochemicals have increased over time as theyare very vital for healthy living and cannot be attained from our daily diet. In 2018, the estimated revenue of the nutraceutical phytochemicals was reported to be $16.1 billion in Europe and North America. However, it was further evaluated that it will increase up to $24.6 billion in 2023 [1]. The subgroup of flavonoids is anthocyanins, which are present in plants/herbs and are commonly found in berries as coloring agents [2]. According to several studies, it is reported that these anthocyanins possess various activities such as antioxidant, anti-aging, anti-inflammatory, anti-diabetic, and antiviral and also manage illnesses related to neuroprotection and neurodegeneration [3, 4]. The demand for dietary supplements containing berry or berry-derivatives has increased that comprise various extracts of anthocyanin-rich berries, namely *Vacciniumcorybosum* (blueberry), *Vacciniummyrtillus* (bilberry), *Prunuscerasus* (tart cherry), *Ribesnigrum* (blackcurrant) and *Aristoteliachilensis* (maquiberry) [5]. Anthocyanins (ACs) are utilized as a natural colorant instead of synthetic colorants in various food industries [6, 7]. ACs show instant absorption, and after their consumption, they can be immediately traced in the bloodstream. ACs may potentially monitor inflammation-derived obesity as well as other severe illnesses, and they influence the metabolism in several *In vivo* and *In vitro* research. These potentials of ACs neutralize the levels of oxidative stress, protect organs, delay the progression of inflammation as well as work against damage to cells [8].

Several advancements in delivery systems have been made to overcome the drawbacks related to the instability and degradation of active constituents during the formulation of pharmaceutical products containing phenolic compounds [9]. Various research reports exhibited that the nanoformulations of anthocyanin with few modifications aid in better absorption and metabolization with increased biological action [10]. The stability and bioavailability of a drug are enhanced by the encapsulation of ACs so as to study their uses and actions. Thus, ACs are utilized worldwide in several nutraceuticals, as natural colorants instead of synthetic colorants in various food industries as well as in various pharmaceutical-marketed products [11, 12].

About 1.7 million deaths are reported worldwide due to lower ingestion of various fruits and vegetables, out of which 14% of the deaths are due to gastrointestinal

malignancies, 11% are due to cardiovascular disorders, and 9% are due to stroke [13]. Hence, it can be said that anthocyanins play a vital role in the enhancement of human health [14]. Various *In vitro* (scavenging assays) and *In vivo* (animal and human cell line studies, various animal models, and clinical trials) evaluations have revealed that anthocyanins are rich in dietary supplements when consumed either through food or beverages and have always been beneficial for humans [15].

Scenario of Health Benefits of Anthocyanin Pigments Globally

Anthocyanins are pigments that are extracted from plants and used as food additives for introducing colour to food items. Although currently, artificial colorants are quite popular as per many studies, they have been proven to be associated with several adverse effects [16]. Thus, nowadays, more focus is on natural food colorants and anthocyanins as promising alternatives. Anthocyanin is nowadays popular as a nutraceutical and has already been part of traditional medicines. Its main use is as a colorant, an appetite stimulant, and for many diseases. It is employed as a colored pigment but also as a potent ingredient in pharmaceutical preparations. However, good bioavailability is the limiting factor for any anthocyanin to act potentially as an ingredient in pharmaceutical preparations. The decreasing order of the bioavailability of anthocyanin is found in peonidin, followed by cyanidin glycosides, then malvidin, delphinidin, and lastly, petunidin [17]. The lowest bioavailability is exhibited in red wine. A brief overview of the health benefits of anthocyanin pigments is summarized in Fig. (**1**).

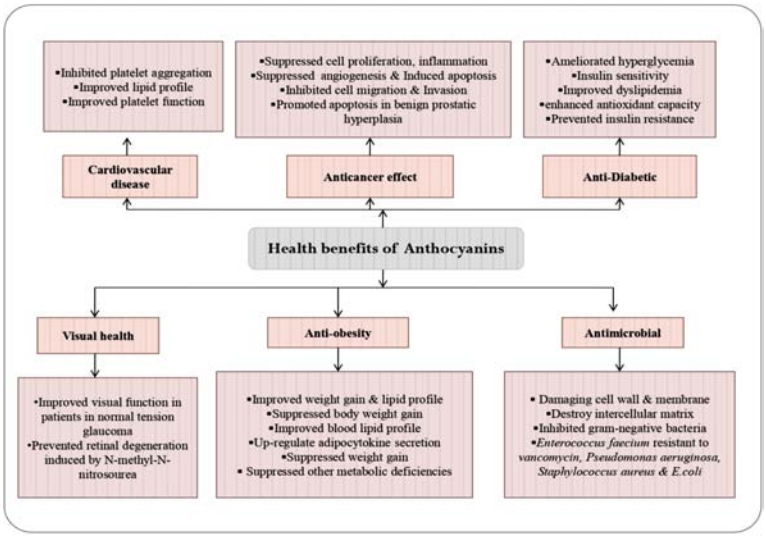

Fig. (1). Brief overview of health benefits of anthocyanin pigments.

SUBJECT INDEX

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Prerna Sharma

Dr. Prerna Sharma is currently working as an assistant professor in Shri Krishna Ayush University, Kurukshetra. She has 11 years of teaching experience as assistant professor and training & placement officer and she is selected as panel expert for AICTE STTP programme. Her field of specialization is pharmacognosy and she has completed his master in pharmaceutical sciences (2012) honor with gold medalist / appreciation in RITS, Sirsa, India. Her field of expertise is standardization of herbal plants/ herbal formulation. Her research area includes pharmacognostical & phytochemical investigation of Indian medicinal plants. She has 20 research/review publication national/international journals of repute to her credit, 40 copyrights, 2 patents and delegated more than 30 national/international conferences /workshops. She is honored with a young research scientist award by SPER and TIPA in Thailand.

Peeyush Kaushik

Prof. Peeyush Kaushik is currently working as an associate professor at Chandigarh College of Pharmacy, Landran Mohali Punjab. His field of specialty is pharmaceutics and completed his master in pharmaceutics from Lovely Professional University, Phagwara. He has 11 years of experience as an assistant professor and 5 years in industry as QA executive experience. His field of expertise in research is solubility enhancement and dissolution modification. He has guided around 25 master's students and published more than 25 research/review/book chapters in national and international journals. He also has 4 patent designs and 2 formulation patents and delegated more than 50 conferences/workshops/FDPs.

Sumeet Gupta

Dr. Sumeet Gupta working as dean and principal, M. M. College of Pharmacy, M. M. (deemed to be University) Mullana, Ambala, Haryana. His main research interests include the scientific validation of plant based compounds in the treatment of metabolic disorders including complications. He has more than 22 years of teaching and research experience in the area of "Preclinical and Clinical Pharmacology". He has published various research & review articles. He has also published 4 books and 6 chapters with international publishers. He has been awarded 5 patents and 2 copyrights.

Hitesh Malhotra

Prof. Hitesh Malhotra is an assistant professor at Guru Gobind Singh College of Pharmacy, Yamuna Nagar. He has 8 years of experience as an assistant professor and expertise in animal experimentation. His field of expertise in research is ethnopharmacology as well as isolation and characterization of phytochemicals. He has guided around 15 master's students and published more than 20 research/review/book chapters in national and international journals. He also has 2 patents and delegated more than 50 conferences/workshops/FDPs. He also has life membership of APTI, IPGA and IHPA.

Pharkphoom Panichayupakaranant

Dr. Pharkphoom Panichayupakaranant is a professor of the Department of Pharmacognosy and Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Thailand. His research interests involved development of herbal products using a green extraction and standardization method, preparation of active constituent-rich herbal extracts, and medicinal plant tissue cultures. His research publications include 139 documents indexed in Scopus and Web of Science, h-index= 32 (SCOPUS), 27 (Web of Science), 15 patents, and 19 petty patents.