Flavonoids

Editors

Ayşegül ÇEBİ

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PREFACE

Nature has long been the ultimate pharmacy, providing humanity with a vast reservoir of bioactive compounds that form the backbone of modern pharmacognosy and nutritional science. Among these, flavonoids and related polyphenolic compounds stand out as one of the most diverse and biologically significant groups of secondary metabolites. This book, designed as a comprehensive reference for researchers, clinicians, and students, aims to bridge the gap between fundamental phytochemical structures and their expanding therapeutic horizons.

The volume opens with a foundational exploration of flavonoids, establishing a clear understanding of their general characteristics and classification. Building upon this framework, the subsequent chapters embark on a molecule-specific journey. From the "king of flavonoids," Quercetin, to the therapeutic potential of Naringenin and the ecological complexities of Isoflavonoids, each chapter dissects the unique molecular architecture and biological mechanisms of these compounds.

Distinguished contributors have provided rigorous analyses of key phytochemicals, including Apigenin, Kaempferol, and the Catechin family, elucidating their roles in cellular signaling and disease prevention. Furthermore, the inclusion of compounds such as Resveratrol, Cyanidin, Rutin, and Anthocyanins broadens the scope to cover critical antioxidants that are pivotal in combating oxidative stress and chronic inflammation.

By synthesizing current research on molecular regulation with practical health applications, this book offers more than just a chemical inventory; it provides a roadmap for future research in functional foods and pharmaceutical development. We extend our deepest gratitude to the esteemed authors who have poured their expertise into these pages. It is our hope that this collection will serve as a vital resource in unlocking the full potential of nature's chemistry for human well-being.

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CHAPTER 1

FLAVONOIDS: GENERAL CHARACTERISTICS AND CLASSIFICATION

Ayşegül ÇEBİ[1]

Introduction

Flavonoids are a large class of plant **polyphenolic secondary metabolites** widely distributed in fruits, vegetables, grains, bark, roots, stems, and flowers. Chemically they share a C6-C3-C6 skeleton (two benzene rings connected by a three-carbon bridge, typically forming a heterocyclic pyran ring) [1]. The term *flavonoid* derives from the Latin *flavus* (yellow), reflecting that many flavonoids are yellow pigments in plants. Historically, flavonoids entered scientific awareness in the 1930s: Albert Szent-Györgyi observed that crude citrus extracts contained unknown yellow compounds that enhanced vitamin C's effect on capillary strength, tentatively calling these substances "vitamin P" [2,3]. Later work revealed that "vitamin P" was not a true vitamin but a mixture of flavonoids, and no deficiency syndrome exists for it.

Flavonoids play critical roles in plant physiology and human nutrition. In plants, they contribute to flower and fruit pigmentation, protect against UV radiation, and mediate signaling in growth and defense [4]. In human health and nutrition, dietary flavonoids are studied for antioxidant, anti-inflammatory, cardioprotective, and anticancer activities (e.g. scavenging free radicals, inhibiting enzymes like xanthine oxidase or COX-2, modulating signaling pathways) [5]. Indeed, flavonoids have been associated with reduced risk of chronic diseases such as cardiovascular disease, diabetes, and cancer, and are regarded as important

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CHAPTER 2

QUERCETIN: FROM MOLECULAR STRUCTURE TO THERAPEUTIC HORIZONS

Fatih Çağlar ÇELİKEZEN[1]

Chemical Structure, Physicochemical Properties and Natural Foundations

Quercetin is a naturally occuring flavonol that possesses polyphenolic structure and is categorised within the subclass of flavonoids. Its International Union of Pure and Applied Chemistry (IUPAC) name is 3,3',4',5,7-pentahydroxyflavone with a molecular formula of $C_{15}H_{10}O_7$ and molecular weight of 302.24 g/mol. Structurally, quercetin consists of a three-ring structure (A,B,C rings) bearing five hydroxyl groups at the C3, C5, C7, C3' and C4' positions (1). These groups have been identified as the fundamental determinants of both the biological and chemical activities of the quercetin (2,3). The chemical reactivity capacities of these hydroxyl groups are subject to variation and can be categorised as follows: the sequnce of numbers is as follows: 3 > 7 > 3' > 4' > 5. The 5-hydroxyl group in the A ring structure exhibits significantly lower reactivity compared to the other hydroxyl groups and also shows resistance to glucuronidation (4). The catechol structure in ring B is defined by the presence of two hydroxyl groups located in adjacent positions at the 3' and 4' positions. This feature signifies a critical structural attribute that confers augmented electron-donating capacity and antioxidant potential in comparison to alternative hydroxylation models (4). It is evident that additional structural elements contribute to the biochemical properties of quercetin, including the C2-C3 double bond (unsaturating in the C ring), the 4 oxo group (carbonyl functionally at the 4 position), and the strategically

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mechanisms stop it from being harmful when it is eaten (76). People generally tolerate quercetin well, and researchers have extensively studied its safety in humans (27,77). Quercetin supplementation has been shown to be generally safe, with only a small number of mild side effect being reported in studies. The most common of these are gastreintestinal disturbances, headaches and tingling sensations, particularly at high doses (27,77). The best amount of quercetin depends on how it is used and how its made. Researchers have administrated doses ranging from 500 to 2000 mg/day in clinical studies (78).Conventional quercetin supplements generally provide daily dose of up to 1000 miligrams (77). It is generally safe for short-term use at common supplemental doses, but not for specific risk groups. Further long-term studies are neccessary to assess its safety for prolonged, high dose consumption (77).

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CHAPTER 3

NARINGENIN

Bahar BİLGİN SÖKMEN[1]

Giriş

Flavonoids are polyphenolic compounds naturally found in plants and known to have multifaceted effects on human health. Plant polyphenols are increasingly being investigated for their potential to prevent chronic diseases and maintain health. Naringenin (4',5,7-trihydroxyflavanone) is found in particularly high concentrations in citrus fruits such as grapefruit, oranges, and tangerines. Its high antioxidant capacity and versatile biological effects have made this compound an important candidate for functional foods and pharmaceuticals.

Structural Properties of Naringenin

The disaccharide derivative naringin has a 2-O-(α-L-rhamnopyranosyl)-α-D-glucopyranosyl group replaced by an α-L-rhamnopyranosyl group at position 7 through a glycosidic bond. The melting point of naringin is reported as 83°C. Its solubility in a given solvent is 1 mg/mL at a temperature of 40°C (1).

Chemically, it is a glycoside made up of the disaccharide neohesperidone and the flavone naringenin. The structure of naringenin features a flavonoid core, a heterocyclic pyran ring, and two phenolic rings. The compound has a molecular weight of 580.54 g/mol and a molecular formula of $C_{27}H_{32}O_{14}$ (2).

The molecular structure of naringin (4',5,7-trihydroxyflavanone) is shown in Figure 1. With rising temperature, the solubility of naringin and its aglycone

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promote synaptic plasticity, nerve cell survival, and prevent neuronal damage, reducing and promoting neuroinflammation (25).

Antidiabetic Effects

Naringin has been shown to increase insulin sensitivity and may improve glucose uptake by cells (26). Naringin has the ability to inhibit certain enzymes involved in carbohydrate metabolism, such as glucosidase. By blocking this enzyme, naringin can lower postprandial glucose levels, which in turn slows the digestion and absorption of carbohydrates.

Naringin is a potent biomolecule with promising potential to improve outcomes in individuals with diabetes. (27). Naringin modulates multiple metabolic processes by limiting insulin secretion and sensitivity, regulating glucose transporters, enhancing peripheral glucose uptake, reducing hepatic glucose production and intestinal glucose absorption, and decreasing cholesterol synthesis, blood lipid levels, oxidative stress, and inflammation (28).

Conclusion

Naringenin, a natural flavanone with broad-spectrum biological activities, holds promise for the prevention and treatment of various chronic diseases. However, its low bioavailability and potential for drug interactions are important issues to address before clinical application. More comprehensive clinical studies will provide clearer information regarding therapeutic doses and the long-term safety profile of naringenin. Naringenin, with its potent antioxidant and anti-inflammatory properties, has significant potential in the prevention and treatment of metabolic, cardiovascular, and neurological diseases. Its multifaceted biological effects and ease of availability from natural sources make it a valuable bioactive compound at the heart of modern health research.

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CHAPTER 4

ISOFLAVONOIDS: MOLECULAR REGULATION, ECOLOGICAL FUNCTIONS, AND HEALTH APPLICATIONS

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INTRODUCTION

Flavonoids represent one of the most diverse groups of plant specialized metabolites, with more than 10,000 known structures contributing to pigmentation, UV protection, and ecological interactions (2). Among flavonoid subclasses, isoflavonoids occupy a unique position because their biosynthesis depends on the formation of the isoflavone skeleton, catalyzed by a branch-point enzyme, isoflavone synthase (IFS). This structural innovation, found primarily in the Fabaceae (legume) family, underpins both the chemical diversity and the broad functional roles of isoflavonoids (2,3). Isoflavonoids are distinguished not only by their structural diversity but also by the breadth of their ecological and physiological functions: they act as phytoalexins in disease resistance, as signaling molecules that initiate symbiotic nitrogen fixation with rhizobia, and as bioactive phytoestrogens in human consumption (6, 7, 9, 10, 12, 17, 19, 20).

Advances in genomics, transcriptomics, metabolomics, and epigenomics have transformed our understanding of how plants control isoflavonoid biosynthesis (4, 16). Regulatory networks in legumes integrate multiple layers of control, including transcription factors (R2R3-MYB, bHLH, bZIP, NAC, WRKY), epigenetic modifications (DNA methylation, histone acetylation, H3K4me3 enrichment), and post-transcriptional regulators (microRNAs, small interfering RNAs) (18, 21, 24, 25, 27, 29). These regulatory components interact with developmental signals

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In summary, isoflavonoids stand at the intersection of plant defense, ecological communication, metabolic regulation, and human health (1, 4, 8). Continued interdisciplinary research will expand their applications in biotechnology, agriculture, and personalized medicine, while deepening our understanding of the evolutionary and ecological forces that shaped this remarkable class of specialized metabolites.

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CHAPTER 5

APIGENIN

Ozlem AYDIN BERKTAS[1]

Apigenin

Flavonoids are phenolic compounds naturally found in plants that have multifaceted biological effects on human health. They contribute to plant color, aroma, and flavor, as well as playing a crucial role in their defense against environmental stresses. Within this broad biochemical class, apigenin (4′,5,7-trihydroxyflavone) is one of the key flavones of note. (1).

Chemical Structure of Apigenin

Apigenin is a yellow compound belonging to the flavone group and has the chemical formula $C_{15}H_{10}O_5$ (2). Under normal conditions, it exists as yellow crystalline structures and has very limited solubility in water (1.35 μg/mL). However, it exhibits high solubility in organic solvents such as ethanol and DMSO, which is one of the primary factors reducing its bioavailability. It has a melting point between 345–350°C, and storage at −20°C is generally recommended (3-5). The structure of apigenin contains three hydroxyl groups (at positions 4′, 5, and 7). Its basic skeleton consists of two aromatic rings (A and B) and one heterocyclic pyrone ring (C) (Figure 1). This configuration provides apigenin with high stability and strong free radical scavenging capacity (6). Chemically, apigenin differs from other flavones such as luteolin by the absence of a methoxy or additional hydroxyl group. This structural difference enhances the lipophilic properties of apigenin,

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Studies further indicate that apigenin reduces NF-κB activation by preventing p65 phosphorylation and by downregulating Akt-mediated signaling (13).

Conclusion

Considering all these findings, apigenin—owing to its chemical stability, strong antioxidant capacity, and lipophilic characteristics—effectively neutralizes free radicals and mitigates cellular damage caused by oxidative stress. In addition, its anti-inflammatory, anti-proliferative, anti-fibrotic, and anticancer properties make apigenin a remarkable natural therapeutic agent in modern pharmacology. Preclinical and clinical studies have demonstrated that apigenin regulates and protects cellular signaling pathways, particularly in cancer, neurodegenerative diseases, diabetes, and autoimmune disorders. With its low toxicity profile and high biological efficacy, apigenin is regarded as a promising phytochemical candidate for use in future pharmaceutical formulations and complementary therapeutic approaches. However, to achieve effective clinical applications, it is crucial to address the low bioavailability of apigenin through pharmacokinetic optimization strategies. Enhancing its absorption and stability will be a key step in fully realizing apigenin's therapeutic potential in human health applications.

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CHAPTER 6

KAEMPFEROL: PHYTOCHEMICAL STRUCTURE AND BIOLOGICAL ACTIVITIES

Tuba ACET[1]

Introduction

Kaempferol is a naturally occurring polyphenolic compound belonging to the flavonol subclass of flavonoids and is widely distributed throughout the plant kingdom. With the growing interest in the bioactivity of phenolic compounds, kaempferol has emerged as a prominent phytochemical with potential roles in antioxidant defense, anti-inflammatory responses, neuroprotection, and cardiometabolic regulation (1). In plants, it predominantly occurs as glycosylated derivatives, and its physiological effects in humans are shaped by both its inherent chemical features and metabolic transformation processes.

Kaempferol is abundant in many fruits and vegetables (2,3) and possesses a wide range of therapeutic attributes (figure 1). Numerous studies indicate that it mitigates oxidative stress—one of the underlying drivers of metabolic disorders—by reducing the formation (4) of reactive oxygen species (ROS) (2). Its antitumor and anti-inflammatory activities have also been demonstrated extensively (5). Furthermore, kaempferol is reported to enhance biological performance through hormetic mechanisms, particularly in aging-associated processes (6). The major biological functions attributed to kaempferol are discussed in the following sections.

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concentrations in cell-culture models (48). Due to insufficient clinical evidence, recommended therapeutic doses are still based solely on experimental data.

Conclusion and Future Perspectives

Kaempferol is a multifunctional flavonoid with protective effects in diverse pathological contexts, including diabetes, obesity, arthritis, glaucoma, osteoporosis, and dermatological disorders. It exerts organ-protective effects on the liver, kidneys, heart, nervous system, and gastrointestinal tract primarily through antioxidant and anti-inflammatory mechanisms. Its anticancer potential is mediated by the modulation of multiple signaling pathways. Nevertheless, limited water solubility, rapid metabolism, and poor oral bioavailability hinder its clinical utility. Novel delivery systems—such as nanocarriers and encapsulation technologies—may help overcome these limitations. However, comprehensive clinical trials are required to confirm its therapeutic efficacy and safety.

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CHAPTER 7

CATECHIN AND ITS DERIVATIVES

Sinem AYDIN[1]

Catechins are categorized under flavanols (1). The catechin term originally comes from the word 'catechu', which is the boiled extract (tannic juices) of the *Mimosa catechu* (2). Fruits and vegetables have catechins at high amounts (1).

They are an important component of tea, making up approximately one-third of the dry weight of tea (3). Non-esterified catechins are catechin, gallocatechin, epicatechin, epigallocatechin and esterified catechins are epigallocatechin gallate, epicatechin gallate, gallocatechin gallate and catechin gallate (1). Catechin derivatives are given in **Fig 1.**

Catechins react easily with oxygen in the air by chemical and enzymatic ways to form condensed tannins (proanthocyanidins). The astringency or bitterness of these compounds is determined by their molecular weights. While proanthocyanidins with sixty-eight monomers create an astringent taste, those with thirty-five monomers create a bitter taste. While short chain molecules are colorless, their color changes from yellow to brown as the degree of polymerization increases (4).

Catechin and type B procyanidin found in legumes. Catechin, epicatechin and epicatechin gallate are found in fruit wine (1). *Camellia sinensis* teas were also studied for their catechins (5).

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in green tea has been shown in various studies to prevent obesity by reducing adipocyte proliferation, lipogenesis, fat absorption, and food intake (22).

L. Antidiabetic Effect

Tea catechins increase insulin activity by protecting pancreatic β cells. Tea polyphenols protect against insulin resistance, the primary cause of Type II diabetes, by improving insulin sensitivity. Jing et al. (19) revealed that tea has a preventing impact towards diabetes, with a modest reduction in Type II diabetes in individuals who drank more than four cups of green tea every day.

A study by Iso et al. (19) declared that consuming more than six cups of green tea per day was inversely linked with incidence of diabetes, while the same effect was not observed for black and oolong teas. Tea exerts a preventive influence to diabetes and its complications by increasing insulin effect, improving insulin resistance, activating insulin signaling and defending β cells. Researchs from different countries demonstrated that tea increases fasting insulin levels and that consuming more than four cups every day reduces the risk of Type II diabetes (19).

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CHAPTER 8

FLAVANOLS

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Introduction

Flavanols represent a significant subgroup of flavonoids, which are naturally occurring polyphenolic molecules broadly found throughout the plant kingdom (1,2). They are found abundantly in foods such as cocoa, tea, apples, grapes, and various berries (3). In recent decades, flavanols have attracted significant scientific interest because of their possible positive impacts on human health, especially in relation to cardiovascular, neurological, and metabolic systems (4–7). Their biological activity stems not only from their direct antioxidant properties but also from their ability to modulate cellular signaling pathways, gene expression, and enzymatic activity (8–10).

The health-promoting potential of flavanols is closely linked to their structure and metabolism. While early research emphasized their role as antioxidants that neutralize reactive oxygen species, recent findings suggest that their physiological effects are more complex and involve interactions with endothelial cells, the gut microbiota, and the immune system (11–13). This chapter reviews the essential chemical structures, sources, bioavailability, biological activities, and clinical evidence surrounding flavanols, along with an outlook on future research directions.

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CHAPTER 9

RESVERATROL

Zeliha KAYA[1]

1. Introduction

Free radicals are harmful compounds that can lead to oxidative damage and cause chronic degenerative diseases. Substances that prevent the formation of these radicals or neutralize them are referred to as "antioxidants." Resveratrol, one of these antioxidants, is a phytoalexin found in more than 70 plant species, particularly in grapes and grape-derived products (1). On an industrial scale, it is predominantly obtained from the roots of Polygonum cuspidatum (Japanese knotweed)(2). Owing to its beneficial effects on human health, resveratrol has attracted significant global attention in recent years. Numerous experimental systems have been used to thoroughly examine its in vitro and in vivo biological activity (3). Resveratrol has been reported to exhibit numerous therapeutic properties, including anti-inflammatory, antioxidant, antidiabetic, antiaggregatory, antihyperlipidemic, immunomodulatory, cardioprotective, vasorelaxant, and neuroprotective effects (4,5). However, clinical outcomes remain inconsistent due to factors such as low bioavailability, rapid metabolism, and dosage variations (6–8). These pharmacokinetic limitations have recently prompted a shift toward innovative approaches, including nanoformulations, polymeric and bioceramic hybrid systems, and green extraction technologies (9,10).

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CHAPTER 10

CYANIDIN AND HUMAN HEALTH: MECHANISMS AND APPLICATIONS

Sevim İpek ACAR CÖMERT[1]

Introduction

The Place of Cyanidin within the Flavonoid Family

Flavonoids represent a diverse family of plant-derived polyphenolic compounds with significant health implications. Within this family, anthocyanins constitute a pigmented subclass responsible for the characteristic red, purple, and blue hues observed in numerous fruits and vegetables. Six major anthocyanidin structures—pelargonidin, cyanidin, delphinidin, peonidin, petunidin, and malvidin—predominate in nature, with cyanidin exhibiting particularly pronounced biological activity. Contemporary investigations have characterized cyanidin's antioxidant, anti-inflammatory, and metabolic regulatory properties. Berry species including red raspberry (*Rubus idaeus* L.), blue honeysuckle (*Lonicera caerulea* L.), and mulberry have long traditions in folk medicine, and their extracts now attract scientific interest for potential applications in cardiovascular disease, obesity, neurodegeneration, hepatic dysfunction, and oncology. Cyanidin-3-glucoside predominates in fruits and edible flowers, while cyanidin-3-galactoside also occurs abundantly across fruit species. The aglycone form is principal in vegetables, whereas cyanidin-3-glucoside appears notably in certain cereal grains (1).

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CHAPTER 11

RUTIN

Bengü TEMİZEL[1]

Introduction

Natural products have been the primary source of many life-saving medicines, cosmetics and dietary supplements throughout history (1). Many health products, including the semi synthetic drugs used today, are either derived directly from natural sources or are inspired by the structures of natural products (2). Today, thousands of natural molecules, particularly those derived from plants, have been studied for their biological activity against various human diseases and a large number of them have been identified as having therapeutic potential (3).

Flavonoids, which have long attracted the attention of scientists due to their positive effects on human health, are particularly popular today thanks to their antioxidant and membrane-stabilizing properties (4). Rutin (quercetin-3-O-rutinoside), a prominent member of the flavonoid group, is a natural compound widely found in plants. It takes its name from the *Ruta graveolens* plant, which contains high amounts of rutin. It is also known by other names such as rutoside, quercetin-3-O-rutinoside and sophorin. Rutin, which plays a protective role in plants, is abundant in a wide variety of plant species, including buckwheat, apples, citrus fruits and berries.

Numerous studies have demonstrated the antioxidant, anti-inflammatory, anticancer, antimicrobial, cardioprotective and neuroprotective properties of rutin. These effects are underpinned by rutin's ability to neutralize free radicals, bind metal ions and regulate intracellular signaling pathways. Furthermore, rutin's

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CHAPTER 12

ANTHOCYANIN

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Introduction

Growing recognition of the potential adverse health implications associated with synthetic colorants, coupled with an expanding interest in the functional properties of naturally occurring pigments, has markedly increased the value of plant-derived colorants within the food, nutraceutical, and pharmaceutical industries (1). The term *anthocyanin*, derived from the Greek words *anthos* (flower) and *kyanos* (blue), reflects the extensive chromatic diversity that these compounds impart to plant tissues. As members of the flavonoid subclass, anthocyanins represent one of the most abundant and functionally consequential categories of secondary metabolites in higher plants. Within the broader family of polyphenolic compounds, anthocyanins are of particular scientific interest due to their substantial structural heterogeneity and the correspondingly wide range of physiological and biological processes they influence.

Anthocyanins are water-soluble vacuolar pigments that accumulate predominantly in fruits and floral tissues, although they are also detected in leaves, stems, roots, and other vegetative organs. They are responsible for the characteristic red, purple, and blue coloration of numerous horticultural and agricultural commodities, thereby playing a critical role in defining the sensory attributes and market value of these products. From a biological perspective, anthocyanins contribute to plant reproductive success by attracting pollinators and exert protective functions through the absorption of ultraviolet (UV) radiation.

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Conclusion

Anthocyanins, characterized by their extensive structural diversity and wide-ranging biological activities, constitute a class of natural compounds with considerable potential for both health promotion and industrial applications. Their capacity to modulate oxidative stress, attenuate inflammation, regulate apoptotic pathways, and influence critical cellular signaling cascades underscores their promise as therapeutic agents for the prevention and management of various chronic conditions, including cardiovascular, neurodegenerative, metabolic, and cancer-related disorders. Nonetheless, limited bioavailability and chemical instability under physiological and environmental conditions continue to pose significant obstacles to their effective clinical application.

Recent technological advancements, including nanoformulations, microencapsulation, and other innovative delivery systems, have markedly improved the stability and bioavailability of anthocyanins, addressing key limitations in their clinical application. Moreover, accumulating evidence indicates that interactions between anthocyanins and the gut microbiota, as well as the biological activity of their metabolites, are critical determinants of their systemic effects. Beyond their established role as natural colorants, anthocyanins are increasingly incorporated into functional foods and nutraceutical products, highlighting their relevance as bioactive dietary constituents.

Future research should aim to elucidate the pharmacokinetics, biotransformation pathways, and tissue-specific molecular targets of anthocyanins. The development of standardized formulations, coupled with long-term clinical investigations, will be essential to fully establish their safety, efficacy, and therapeutic potential. In conclusion, anthocyanins are more than mere plant pigments; they are potent phytochemicals with diverse biological activities. Continued scientific and technological exploration is expected to broaden their applications across the food, health, and pharmaceutical sectors, thereby contributing meaningfully to strategies for disease prevention and the promotion of human health.

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