Frontiers in Natural Product Chemistry

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Shazia Anjum

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Frontiers in Natural Product Chemistry

(Volume 12)

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PREFACE

Natural products continue to occupy a central position in contemporary research based on their profound implications for human health and nutrition. Advances in analytical techniques, molecular biology, and interdisciplinary approaches have expanded our understanding of how foods and natural metabolites influence physiological processes, therapeutic outcomes, and quality of life. This book, **"Frontiers in Natural Product Chemistry Volume 12,"** brings together diverse yet complementary perspectives that collectively highlight the chemical diversity, sensory attributes, and biological activities of natural products originating from terrestrial, marine, and dietary sources.

The first chapter establishes the importance of organoleptic evaluation as a cornerstone of virgin olive oil quality assessment. By detailing International Olive Council (IOC)–based methodologies, panel testing procedures, and the classification of virgin olive oils, this chapter underscores how sensory science bridges consumer perception with objective quality control. It sets the foundation for understanding food quality not merely as a chemical construct, but as a multidimensional attribute shaped by sensory, environmental, and processing factors.

Expanding beyond terrestrial food systems, the chapter on the chemical diversity and biological activities of marine fungi of the genus Aspergillus explores their remarkable adaptability. By surveying two decades of research, this contribution highlights marine Aspergillus as a prolific source of bioactive compounds with significant pharmaceutical potential, emphasizing the untapped promise of marine ecosystems in drug discovery.

The third chapter provides a comprehensive overview of melatonin biosynthesis, circadian regulation, and its presence in foods of plant and animal origin. By linking dietary intake to physiological modulation of serum melatonin levels, this chapter integrates nutrition, chronobiology, and health sciences, offering insight into how dietary strategies may complement therapeutic interventions.

The fourth chapter of this volume examines the complex chemistry of tea in relation to processing methods and health outcomes. This chapter presents an in-depth discussion of catechins, theaflavins, L-theanine, and other phytochemicals, illustrating how biochemical transformations during fermentation influence both nutritional value and therapeutic efficacy.

Finally, the fifth chapter addresses an urgent global health challenge by evaluating flavanones as promising antiviral agents. Through a critical analysis of their chemistry, mechanisms of action, and structure–activity relationships, this contribution bridges natural product chemistry with modern pharmacological and computational approaches aimed at combating emerging viral diseases.

This volume is intended to serve as a valuable resource for researchers, academicians, and professionals in food science, biotechnology, pharmacognosy, and related disciplines, fostering cross-disciplinary dialogue and inspiring future research on natural product-based health solutions. I express my profound thanks to the entire editorial team, including Mr. Mahmood Alam, for their diligent work.

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CHAPTER 1

Therapeutic Potential of Flavanones against SARS-CoV-2

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Abstract: The emergence of SARS-CoV-2 in late 2019 and the subsequent COVID-19 pandemic have highlighted an urgent global demand for developing potent antiviral therapies with minimal side effects. Despite advances in current treatments, they remain limited and non-specific medications. Natural phytochemicals, particularly flavanones, a subclass of flavonoids with diverse biological properties, have emerged as promising antiviral candidates. This review explores flavanones' potential against SARS-CoV-2, focusing on their chemistry, occurrence, mechanism of action, key active compounds, challenges to their application, and structure-activity relationships (SARs). A comprehensive literature review was conducted using multiple electronic databases, including Scopus, PubMed, Google Scholar, and ScienceDirect. Evidence from previous computational, cellular, and animal models underscores flavanones' multifaceted mechanisms, including direct viral enzyme inhibition and immunomodulation to mitigate cytokine storms. Flavanones such as hesperidin, naringin, and their aglycones exhibit significant potential for combating the COVID-19 pandemic, though challenges such as poor solubility and insufficient clinical data remain. SAR insights showed how structural modifications, specifically glycosylation, could enhance potency and bioavailability. These findings could position flavanones as valuable scaffolds for developing novel anti-COVID-19 agents and optimizing current therapeutic protocols. Further studies are warranted to transform these research insights into clinical applications.

Keywords: COVID-19, Flavanones, Hesperidin, Hesperetin, *In silico*, *In vitro*, *In vivo*, Naringin, Naringenin, SARS-CoV-2, Structure-activity relationship.

INTRODUCTION

COVID-19, the coronavirus disease first identified in Wuhan, China in December 2019, spread throughout the country and subsequently achieved global pandemic

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status, impacting around 210 territories within a few weeks. SARS-CoV-2, the causative pathogen of COVID-19, was recognized as a single-stranded RNA virus of the beta-coronavirus genus that is phylogenetically related to SARS-CoV. Infected patients may experience an acute and progressive respiratory condition, which can be fatal following massive alveolar impairment and subsequent respiratory failure [1]. As confirmed by the World Health Organization (WHO) situation report on 8th November 2023, the virus had caused approximately 771,820,937 COVID-19 cases globally, including 6,978,175 deaths. The groups at the highest risk for severe COVID-19 outcomes include older adults and those with underlying chronic conditions such as diabetes, hypertension, and cancers (The, 2020). Historical epidemics such as the 2002 SARS-CoV outbreaks in Guangdong, China, and the 2012 Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in Saudi Arabia have demonstrated their high CoVs lethality (Schoeman & Fielding, 2019; Zhong *et al*., 2003). Therefore, a response is desperately needed globally for an effective drug against this pandemic disease. At present, there is no globally approved therapy for COVID-19.

Nevertheless, several protocols were applied, such as azithromycin, chloroquine derivatives, and convalescent plasma, in addition to widely applicable antiviral drugs. Favipiravir and remdesivir, as inhibitors of RNA polymerase, have been evaluated in recent clinical trials. However, systematic reviews did not show significant efficacy against COVID-19 [2].

In early drug discovery, plants were the main source of medicines. The WHO encourages the integration of traditional herbal remedies for the treatment of chronic ailments, especially in developing nations [3]. Several *in silico* studies have pointed out the potential of plant-derived natural products as antiviral agents. Flavonoids, a diverse class of phytochemicals commonly found in many dietary fruits and vegetables, have demonstrated valuable pharmacological actions, including antiviral effects. Such compounds exert their antiviral effect by interfering with essential steps of replication and infection. Among them, the major subclass, flavanones, have shown promising activity against SARS-CoV-2 [2].

Given the continuing global impact of COVID-19 and the urgent need for accessible antiviral options, naturally occurring flavonoids, particularly flavanones, have gained attention for their potential to modulate key viral and host mechanisms. This review, therefore, focuses on summarizing current experimental and computational evidence for flavanones as potential anti-SAR--CoV-2 agents. It was conducted using literature published till December 2024. The main evaluated outcomes include chemistry, inhibitory potencies, selectivity, cytotoxicity indices, mechanistic pathways, and translational prospects.

MATERIALS AND METHODS

Of 753 records identified, 121 duplicates were removed; 684 titles/abstracts were screened; 211 full texts were assessed; and 56 studies were included (Fig. **1**). Records were screened first by title/abstract and then by full text, to include studies assessing flavanones' antiviral or mechanistic activity. Data on compound, model type, potency, and cytotoxicity were extracted using a standardized template. Docking-only studies were analyzed separately from *in vitro* and *in vivo* data to avoid bias. Study quality was appraised using modified SYRCLE and GRADE criteria, focusing on design, controls, and reporting clarity.

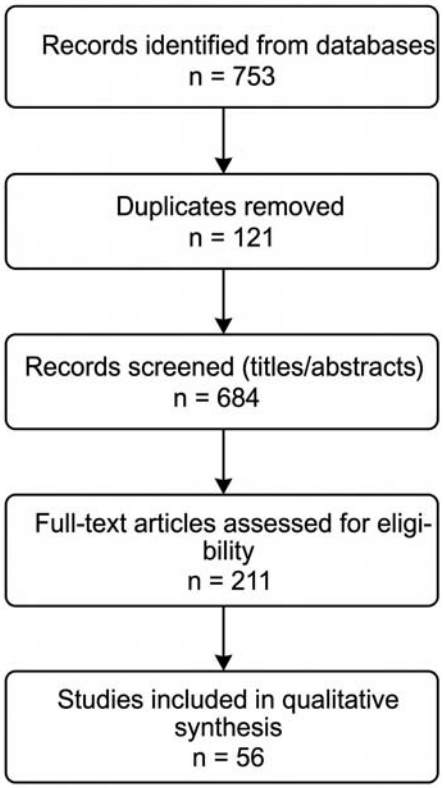

Fig. (1). PRISMA flow diagram summarizing database search and study selection.

A comprehensive search was performed using three electronic databases, including Web of Science, PubMed, and Scopus, until 2024. The applied search strategy used the following query: (SARS OR COVID-19 OR coronavirus [in abstract/title]) AND (extract OR plant OR herb OR flavonoids OR phytochemicals OR flavanones [all fields]). Additionally, the names of common flavanones, such as hesperetin, hesperidin, naringin, naringenin, bailalein, and

CHAPTER 2

Chemical Diversity and Biological Activities of Marine Fungi of Genera *Aspergillus*

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Abstract: In the marine environment, it is estimated that numerous fungal species on our planet range from 1.5-5.0 million, however, to date, only 10% of fungi have been identified. In the marine ecosystem, the most widely found fungi belong to *Aspergillus* genus. Apart, from the coastal ecosystem and open-ocean, fungi are also found in the deep sea and demonstrated the ability to adapt to extreme environmental conditions. Marine fungi have developed chemical defenses for their survival to combat extreme conditions like variations in pressure, temperature, salinity, desiccation, and pH, resulting in the production of chemically diverse scaffolds. Different strains of genus *Aspergillus* settle on various marine substrates like fauna (sponge, softcoral, tunicates, fish *etc*.), plants (algae), and with the environment (sediments, seawater), have been known to produce numerous secondary metabolites. Bioactive compounds, namely, butyrolactones & terrein (anti-inflammatory), kojic acid (skin whitening agent), pyrrolidinedione, AD0157 (angiosuppressive), asperxanthone (Antiviral), aspergiolide A (cytotoxic), methylhydroquinone (antibacterial), *etc.* from marine *Aspergillus* make them a valuable source for pharmaceutical applications. This chapter gives a comprehensive survey of metabolites isolated from marine *Aspergillus* in the last two decades beginning from 2001, including their occurrence, structural information and biological activities.

Keywords: *Aspergillus*, Bioactivity, Invertebrates, Marine fungi, Marine natural products.

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INTRODUCTION

Aspergillus is a genus of filamentous fungi that belongs to the Phylum Ascomycota, Class Eurotiomycetes and Order Eurotiales. Aspergilli have a world-wide distribution, are ubiquitous and can adapt and grow in various conditions at varying temperatures, salinity, nutrients, *etc*. In terms of species number, *Aspergillus* represents the most abundant genera of filamentous fungi reported from marine contexts [1]. Different species of *Aspergillus* fungi are generally conveyed in marine conditions from intense ocean to polar ice covers. *Aspergillus* fungi have been found in nearly every marine habitat like sessile and mobile invertebrates [2], and marine mammals [3], algae [4], driftwood [5], sediments [6], the water column [7], ranging from surface waters to the deep sea. In situations of nutrient depletion, competition, or other types of metabolic stresses, marine fungi promote the formation and secretion of various secondary metabolites. Marine fungi have been estimated to be greater than 10,000 marine fungal species belonging to the Ascomycota and Basidiomycota phyla. *Aspergillussp.* was first described in the 18th century and 339 species have been reported worldwide, categorized into four subgenera (*Aspergillus*, *Circumdati*, *Fumigati*, and *Nidulantes*) and 20 sections [8]. Marine fungi belonging to genus *Aspergillus* are excellent producers of large number of bioactive secondary metabolites like terpenes, alkaloids, peptides, *etc*., that have gained industrial and therapeutic importance [9,10]. Varieties of chemical scaffolds like fatty acids, peptides, sterols, alkaloids and terpenoids isolated by a marine Aspergillus fungi fungus show potent pharmacological activities like antimicrobial, cytotoxicity, insecticidal, neuroprotective, antiviral and antioxidant activities have been reported [11,12]. The blue biotechnology industry has been using marine organisms to find compounds of therapeutic uses. The marine environment is covered with a huge biomass of microorganisms. Therefore, research in the marine microbiome, including bioactive compounds isolated from marine fungi and bacteria will accelerate the blue biotechnology industry [13]. Interestingly, looking at the number of bioactive compounds isolated from marine fungi *Aspergillus,* it would definitely play a huge role in the development of Blue biotechnology.

A literature search on secondary metabolites produced by extremophilic fungi has been presented by Zhao *et al*., (2018) [14]. The authors have discussed 314 novel compounds describing their chemical structures and their biological potential from 56 fungal cultures reported from 2005-2017. Thousands of natural products exhibiting anticancer activity have been isolated from marine fungi alone. And, these compounds show potency in the development of anticancer drugs [15]. Deshmukh *et al*., (2018) [16], in a review, covered the majority of marine fungi-derived anticancer compounds reported during 2012–2016 that showed activity

towards specific cancer cell lines. Both the reviews have been focused on anticancer compounds derived from a common group of marine fungi (phyla ascomycota and basidiomycota) not specific to any particular type or genus. In this review, we have surveyed bioactive secondary metabolites isolated from marine fungi belonging to genus *Aspergillus* emphasizing their fungal source, the chemical structure of new compounds, and their biological activity, along with references. Based on these compiled data, researchers in the field of chemistry, microbiology, pharmacology and bioinformatics will get an insight into the different bioactive scaffolds that could have the potency to lead to a drug candidate.

ASPERGILLUS ASSOCIATED WITH INVERTEBRATES

Sponges

Sponges are commonly known to harbor diverse microbe, both prokaryotic and eukaryotic. Filamentous fungi are ubiquitous and easily associated with sponge tissue. So far, the highest number of secondary metabolites have been reported from sponge-derived fungi. Aspernigrins A-B **(1-2)** carrying unusual 4-benzyl-1*H*-pyridin-6-one moiety were isolated from a sponge-associated *Aspergillus niger* (Fig. **1**) [17]. These compounds displayed moderate cytotoxic activities towards 10 different human leukemia and carcinoma cell lines at a concentration of 50 µg/ml. The structure of aspernigrin B **(2)** has been revised by Hiort and group [18] based on an X-ray analysis of aspernigrin A **(1)** [19]. The isolation of *A. versicolor*, associated with the sponge *Xestospongia exigua* from Bali, resulted in aspergiones A–F **(3-8)** [20], along with aspergillone **(9)**, aspergillodiol **(10)**, aspergillol **(11)** and 12-acetylaspergillol **(12)** [21]. *A. niger*, associated with sponge *Axinella damicornis* (Italy), produced bicoumanigrin **(13),** pyranonigrins A–D **(14-17)**, along with aspernigrins A-B **(1-2)**. Bicoumanigrin **(13)** showed *in vitro* moderate cytotoxicity against human cancer cell lines, while aspernigrin B **(2)** showed strong neuroprotective activity with a decrease in intracellular calcium in the neuronal cells by 33.6% and 23.5% at a concentration of 1 and 5 µg/ml, respectively. [22]. Cueto *et al*., (2006) isolated the fungal strain *Aspergillus sp.* derived from an unidentified sponge collected from the Bay of Manele in Hawaii. Fermentation of the fungi led to the purification of meroterpenoids, tropolactones A–D **(18-21)** that displayed weakly cytotoxic to human colorectal carcinoma (HCT-116) cells [23]. Tropolactones A, B and C **(18-20)** exhibited cytotoxicity with IC_{50} values of 13.2, 10.9 and 13.9 µg/mL, respectively. A culture *A. ostianus*, isolated from an unidentified marine sponge from Pohnpei, yielded three chlorinated antibiotics, the asperlactone derivatives, 8-chloro-9-hydroxy-8,9-deoxyasperlactone **(22)** and 9-chloro-8-hydroxy-

CHAPTER 3

Sensory Analysis of Virgin Olive Oil

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Abstract: Sensory analysis of virgin olive oil, organoleptic assessment, or panel test (PT), is one of the most important techniques for evaluating the quality of virgin olive oil. Sensory analysis of olive oil is based on the International Olive Council (IOC) standards. It is carried out by trained panelists to evaluate and calculate median values of the positive and negative attributes. This chapter is aimed to discuss the sensory analysis of virgin olive oil, sensory methodology, positive and negative (defects) attributes, classification of virgin olive oils, test conditions, and impact factors on sensory quality.

Keywords: Sensory, Virgin olive oil, Designations, Quality, Organoleptic assessment, Negative attributes, Positive attributes, Tasting glass, Test room, Olfactory test, Panel leader, Panel.

INTRODUCTION

Sensory analysis is a scientific discipline used to evoke, measure, analyze and interpret reactions to those characteristics of foods perceived by the five senses, sight, smell, taste, touch and hearing [1].

Therefore, in sensory analysis, human senses are used to measure, analyze and interpret the organoleptic or sensory properties of food. It means more than just food tasting. Sensory analysis is a recognized science. The term Sensory Analysis is a European term, whereas Sensory Evaluation is an American term. Sensory evaluation, done mainly by trained panelists, involves evaluations in main areas, preference, difference and descriptive tests. Preferences Tests supply information about whether people like or dislike, and are often referred to as “acceptance” or “consumer” tests. Difference Tests are used to detect small differences in foods, and are sometimes called “discrimination” tests. Descriptive Tests are used to describe the perceived sensory characteristics of food.

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The main achievement of sensory analysis is sensory properties evaluation and its effect on consumer product acceptance.

Olive (*Olea europaea L.*) is the most important and well-adapted crop in the Mediterranean region. Virgin olive oil (VOO) is extracted mechanically from olive fruits without a refining process. It achieves basic nutritional needs and reduces common disease risks. VOO has a unique flavor that distinguishes VOO from other vegetable oils [2, 3].

OLIVE OIL DESIGNATIONS AND DEFINITIONS

Olive oil obtained at the mill from olive fruits (*Olea europaea L.),* a traditional tree crop of the Mediterranean Basin, is produced by pressing olives and extracting the oil.

The illustrated Fig. (**1**) shows olive oil designations

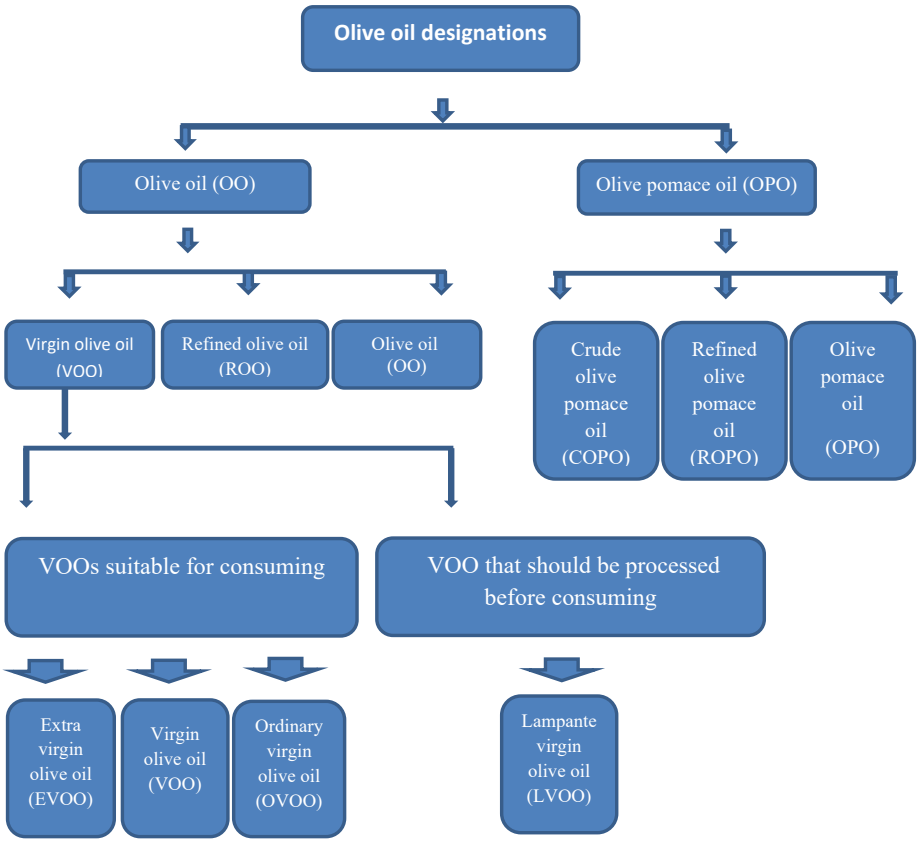

Fig. (1). Designations of olive oil.

Olive Oils

VOOs

VOO**s** are oils which are obtained from the fruit of the olive tree (*Olea europaea L.*) solely by mechanical or other physical means under conditions, particularly thermal conditions, that do not lead to alterations in the oil, and which have not undergone any treatment other than washing, decantation, centrifugation and filtration.

It has a distinctive flavor when compared to edible oils.

International olive council (IOC) categorized VOOs as [4]:

-Virgin Olive Oils Suitable for Consuming:

i. **EVOO:** VOO that has free fatty acids (FFA) ≤0.80 (% as oleic acid) and has physical, chemical and sensory parameters, as shown in Table **1**.
ii. **VOO:** VOO that has free fatty acids (FFA) ≤2.0 (% as oleic acid) and has physical, chemical and sensory parameters, as shown in Table **1**.
iii. **OVOO:** VOO that has free fatty acids (FFA) ≤3.3 (% as oleic acid) and has physical, chemical and sensory parameters, as shown in Table **1**.

- VOO that should be processed before consuming:

LVOO

VOO that has free fatty acids (FFA) >3.3 (% as oleic acid) and has physical, chemical and sensory parameters, as shown in Table 1. It is prepared for refining or for technological purposes.

ROO

The refined VOOs have free fatty acids (FFA) ≤0.30 (% as oleic acid) and have physical, chemical and sensory parameters as shown in Table 1. ROO has no modifications in glyceridic composition.

OO composed of ROO and VOOs

It is a mix between ROO and VOO suitable for consumption. It has free fatty acids (FFA) ≤1.00 (% as oleic acid) and has physical, chemical and sensory parameters, as shown in Table 1.

CHAPTER 4

Promising Therapeutic Approach of Dietary Melatonin on Human Health

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Abstract: Melatonin production and release in the brain are related to the light and dark cycles. The synthesis of melatonin occurs in the pineal gland. The night-time melatonin production is stimulated by neural input from a structure called the suprachiasmatic nucleus, which acts as a master circadian clock for the brain. Tryptophan is an essential amino acid that is used to produce the monoamine neurotransmitter serotonin and the hormone melatonin. In the process of converting tryptophan into serotonin and melatonin, several important cofactors are used, including tetrahydrobiopterin, s-adenosyl methionine (SAM), and co-enzymes. Molecular models have indicated that any disruption in the circadian rhythm of melatonin production or release can cause nocturnal activity and daytime quiescence. Convincing evidence supports the presence of melatonin in plants and foods. The intake of such foods affects circulating melatonin levels in humans. Melatonin dietary supplements have been studied for sleep disorders, such as jet lag, disruptions of the body's internal "clock," insomnia, and problems with sleep among people who work night shifts. The normal melatonin cycle can diminish with age and be disrupted by exposure to electromagnetic pollution and blue-wavelength light. Supplemental melatonin contributes to restoring normal, healthy sleep patterns. The highest melatonin-containing food groups in animals are eggs and fish. Dietary melatonin is absorbed in the gastrointestinal tract and transported into the bloodstream. The ingestion of medicinal and plant foods by mammals as a source of melatonin may be conceived as a key step in serum melatonin modulation and may even cross the blood brain barrier, promoting health. Literature reviews have reported mixed views regarding melatonin supplementation and dosage.

Keywords: Melatonin, serotonin, pineal gland, dietary supplement, circadian rhythm, antioxidant, cancer, mental disorder, metabolism, cardiovascular, insomnia, meta- analysis.

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INTRODUCTION

Age, gender, hormonal imbalance, nutritional deficiency, and pathological conditions exacerbate the disease state in an individual. Administration of dietary formulations or supplements can prevent or delay these consequences. Sleep patterns of all ages, including children, adolescents, and adults, have changed as a result of modern living and technology, which could be a blessing or a curse. Sleep is regulated by two biological rhythms in the body. The circadian rhythm controls the release of hormones related to sleep and wakefulness. It is moderated by sunlight and darkness and typically has a 24-hour cycle. The other rhythm that affects sleep is the homeostatic rhythm, which is our need for sleep.

In the morning, when sunlight hits the photoreceptors in our eyes, our brains begin producing chemicals that make us feel alert and ready for the day. In the evening, when the sun sets, our brain begins producing a hormone called melatonin, which makes us feel drowsy and helps us fall asleep. As we sleep, our brain processes melatonin, and its levels are reduced again, preparing us to go through this cycle again the next day. The homeostatic rhythm works independently of this, and for people who are sleeping normally, these two rhythms are in sync. However, when these cycles are not in sync, we end up feeling alert when we should be feeling sleepy. This leads to insomnia, causing sleep difficulties and decline in the quality of life [1]. The behavioural pattern, or homeostasis, is controlled by the hypothalamus of the brain. In the hypothalamus, there is the suprachiasmatic nucleus (SCN), located directly above the optic chiasm. The SCN is the master pacemaker that controls the sleep-wake cycle. Melatonin regulates the activity of pituitary cells, which in turn affects the synthesis and release of several hormones based on the body's changing functional demands. Melatonin is a highly flexible hormone that varies according to season, time of day, physiological status, life stages, and reproductive behaviours [2]. It is used principally for jetlag (a temporary sleep problem that affects anyone who travels across multiple time zones), for shift workers, and for insomnia. According to accumulating evidence, biochemical and neuroendocrine circadian cycles may be knocked off in cardiovascular and metabolic illnesses. In both human and animal studies melatonin helps prevent a variety of diseases and disorders and lowers anxiety. It is well established in regulating circadian rhythms, which are modulated by the brain's renin-angiotensin system (RAS) [3]. Both hypertension and the circadian regularity of blood pressure appear to be impacted by angiotensin production in the central nervous system. Drugs acting on RAS have been proven potent in the treatment of cardiovascular and metabolic disorders, including hypertension and diabetes mellitus (DM). The positive effects of RAS blockage, however, could be enhanced by combining RAS blockers with melatonin. This is because melatonin has the ability to alleviate metabolic

irregularities in diabetes and insulin resistance [4]. Melatonin was first identified in a plant by Dubbels in 1995; it is also produced in animals and is important for reproductive behaviour and skin coat camouflage. Melatonin is also produced by bacteria, fungi, and plants (leaves, stems, roots, fruits, and seeds) [5]. People travelling at high altitudes (*i.e.*, >2500 m) often end up with reduced physical and mental performance, fatigue, and sleep disturbances. This is mainly due to oxidative stress, and much of the literature has proposed that melatonin could be a remedy. However, if endogenous melatonin is insufficient, exogenous melatonin administration may be required to maintain the potential protective effects. It could be employed as a supplement to medical therapy and could lead to improvements in pathological changes [6].

Unfortunately, in many studies there is a discrepancy in the dose, duration of the study, intensity of the interaction, gender of the patients, or other comorbid disease conditions. There is inconsistency in the scientific data regarding the lowest optimum dose and the long-term safety of melatonin. Further clinical studies are necessary to obtain more conclusive evidence, as each study has its own limitations as previously mentioned [7]. Whether melatonin has autocrine or paracrine effects is still in dispute. Nevertheless, a growing body of literature from molecular approaches and animal models has provided substantial insights into the mechanisms involved in the prevention of pathogenesis by melatonin.

PRODUCTION OF MELATONIN

Melatonin, or 5-methoxy-N-acetyltryptamine, is an indolamine secreted by the pineal gland of the brain through the upregulation of the NAT (N-acetyltransferase) and ASMT (N-Acetylserotonin O-methyltransferase) genes and several other non-pineal tissues. It is produced during the dark phase of the circadian rhythm in both diurnal and nocturnal species [8]. Melatonin has a half-life of approximately 40 minute and is produced from serotonin through two enzymatic steps: acetylation and transfer of a methyl group Fig(**1**).

The initial step in melatonin synthesis is the hydroxylation of tryptophan by tryptophan hydroxylase. The product, 5-hydroxytryptophan, is then decarboxylated *via* 5-hydroxytryptophan decarboxylase to form serotonin. N-acetyltransferase (AANAT) converts serotonin to N-acetylserotonin, the precursor of melatonin, and this is the rate-limiting step in melatonin synthesis. ASMT, on the other hand, modulates the process of melatonin biosynthesis at night Since it is a neuro-hormone produced during the night, it is also called the “hormone of darkness” [9]. AANAT and ASMT are two rate-limiting enzymes in the melatonin synthesis pathway. Light blocks the action of AANAT in melatonin biosynthesis during the daytime. This process is modulated by ASMT at night

CHAPTER 5

Tea made from *Camellia Sinensis*: An Up-To-Date Review of Chemistry and Health Benefits

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Abstract: Since the ancient period, various plants have been used for dietary consumption for their tastes as well as beneficial effects on health. Among them, the tea plant (*Camellia sinensis*) is a notable one. Brewed tea is amongst the top most consumed beverages around the globe. Tea leaves undergo different processes and fermentations to produce tea powder from which brew is prepared. Depending upon its processing, it is divided into various varieties like green, oolong, white, and black tea. Fermentation processes also affect the phytochemical contents in each variety which further determines its dietary significance. Among various phytochemicals present in tea leaves, polyphenolic catechins are the most abundant ones among which epigallocatechin-3-gallate is the dominant catechin. At the time of fermentation, most contents of catechins are found in green tea as oxidation of catechins takes place. Black tea undergoes the most extensive fermentation process and hence catechins get reduced. Most of the catechins in black tea bind with each other and form polymeric structures (*e.g.* theaflavins and thearubigin) which also exhibit prominent health benefits. Theaflavins, one of the categories of polymeric catechin compounds, are antioxidants and also have various medicinal properties. Apart from the entire polyphenolic compound present in tea, various other non-polyphenolic compounds like enzymes, and non-protein amino acids like L-theanine, pigments, *etc*. can also be found that exhibit beneficial properties. A detailed study of polyphenolic green tea catechins mainly EGCG, polyphenolic black tea compound theaflavins, and non-protein L-theanine are described in this chapter containing physical properties, chemical, and biosynthesis process, isolation process, pharmacokinetic study, analytical process, toxicity study, and health beneficial studies.

Keywords: Black tea, Cancer, Catechins, Cardioprotective, Diabetes, EGCG, Green tea, L-theanine, Pharmacokinetics, Obesity, Tea, Theaflavins.

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INTRODUCTION

The tea plant botanically known as *Camellia sinensis* was originally native to Southeast Asia [1]. It was the Portuguese and Chinese who introduced tea drinks during the 16th century [2]. Today, it is notably the most venerable and well-liked aromatic beverage consumed worldwide after water. It is an evergreen tropical plant. Countries with a significant amount of tea production include India, Sri Lanka, Japan, and China [3]. Given the genetic differences, it primarily has two species – *Camellia assamica* and *Camellia sinensis* belonging to the Camelliaceae family. The ideal climate for the growth of this evergreen shrub ranges from 15-to 20 ºC [4].

TYPES OF TEA AND CHEMICAL COMPOSITION OF TEA LEAVES

Buds and leaves from the source plant are being plucked and processed further to make different types of teas and the difference in these types arises from the processing methods. Based on the manufacturing process, tea is of four major types: unfermented green tea, moderately fermented oolong tea, completely fermented black tea, and white tea which is minimally processed.

The approximate percentage of components of tea leaves are polyphenols (30-50%) [5], chlorophyll (0.5%), thiamine (4%), lignin (6.5%), caffeine (approximately 3.5%), theophylline (0.02-0.04%), theobromine (0.15-0.2%) and other flavonoid compounds. Additionally, they have other compounds present such as flavones, carbohydrates, vitamins, minerals, alkaloids, and enzymes [6]. It contains flavanols too, *e.g.* kaempferol, quercetin, and their glycosides. Polyphenols and caffeine (3-6%) give tea its most favorable effects [7]. A tea brew prepared with water (1g leaf/100 mL) will contain tea solids approximately equivalent to 250-350 mg [8]. Soluble components of dry tea leaf are given in Table **2**.

Withering, steaming, and drying of crushed tea leaves are the steps of green tea processing and it contains polyphenolic compounds such as, (–)-epicatechin (EC), 4 (–)-epigallocatechin (EGC), (–)-epigallocatechin-3-gallate (EGCG) and (–)-epicatechin-3-gallate (ECG) [9]. Out of all these catechins, EGCG is most abundantly present. The brewed green tea is typically mild, lemon yellow, or pale green.

Manufacturing of black tea starts with drying, which is a crucial step in maintaining the moisture content (<55%) when compared to the fresh leaf weight. Black tea production involves enzymatic fermentation by polyphenol oxidase and an oxidation process in fixed temperature, humidity, and aerobic conditions. The successive catechin fermentation is condensed and it then leads to thearubigins

(TRs) and theaflavin (TFs) production. It involves the conversion of monomeric polymers to polymeric polyphenols (thearubigins and theaflavins) during fermentation. Theaflavins add taste and color to black tea. Thearubigins, which is a major black tea polyphenol, account for about 20% of the solids in brewed versions [10 - 12]. Polymeric polyphenols (thearubigins and theaflavins) are not absorbed due to their higher molecular mass, whereas, catechins are monomeric polyphenols with low molecular weight [5]. Black tea contains higher concentrations of gallic acid, polymeric polyphenols, and monomeric polyphenols accounting for 3-10% [13]. The polyphenolic content of moderately fermented oolong tea comprises EGCG and epitheflagallin (ETG), among others [14]. Due to its unrivaled fineness and innate flavour, white tea is widely acknowledged by tea connoisseurs. During production, it undergoes minimal processing due to which it is by far a great source of antioxidants when compared to green tea [11].

ABSORPTION AND BIOAVAILABILITY

The tea polyphenols in the brew undergo a complex physiological process after consumption and are degraded into several fragments which are later assimilated in the intestine. “Bioavailability is a term to describe the degree of absorption and fate of an ingested particle that is released from food” [15]. In case of tea catechins, minute amounts are bioavailable after consuming them *i.e.* can be absorbed from the intestine and reach the tissues. Recent research shows that green tea infusions contain between 3250–4410 mg/L of catechins [16]. A laboratory experiment with rats indicated that less than 5% of tea catechins reach the blood after 6 h of oral consumption [17, 18]. After tea was given orally to rats, a pharmacokinetic study showed that around 14% of EGC, 31% of EC, and <1% of EGCG were found in the blood [19]. In humans, 3 g of green tea was administered, and it was noted that the maximal plasma levels of EGCG, EGC, and EC were 0.57, 1.60, and 0.6 μM, respectively [20]. Auger *et al.* [21] collected ileal fluid for 24 h after 200 mg of Polyphenon E ingestion and recorded the tea catechin levels. 27% of the EC and EGC and 59% of EGCG and ECG were recovered in the ileal fluid. The parent catechins showed similar levels of recovery in the ileal fluid after the consumption of green tea [22]. Tea catechins were stable for 4 h at 37°C in the gut. These observations stipulated that in ileal fluid, based on recovery, gallated catechins are less efficiently ingested in the small intestine than nongallated catechins. Higher amounts of tea catechins pass from the small to the large intestine in humans having a fully functional colon and then they are broken down by colonic bacteria. When green tea polyphenols were administered to rats and mice at the rate of 0.6% weight per volume of drinking water, plasma catechin levels showed an increasing trend over 14 days. High concentrations of nongallated catechins were found in the rat bladder (800 ng/g), kidney (450 ng/g), large intestine (300–900 ng/g), esophagus (190 ng/g), lung

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SHAZIA ANJUM

Dr. Shazia Anjum is the Professor of the Chemistry and as well as serving as a Vice Chancellor of the Government Sadiq College Women University, Bahawalpur. She is experienced medicinal and natural product chemist. She has authored and co-authored more than 140 research papers (Impact Factor: 400), a US patent, has edited 17 books and has published 03 chapters in international books. She has accomplished the synthesis of several naturally occurring aminoglycosides- that can be used as antibiotics. Dozens of students have completed their MS degrees under her supervision and couple of others are pursing for their MS/PhD degrees.

Being a senior most Professor of the Islamia University of Bahawalpur, Pakistan she has spearheaded the several R&D projects as a PI. She conceived the idea to have Intra-/Inter-universities Consortium on Climate Change, Sustainability and Conservation. Launched a web portal and have over 87 members from different universities, other organizations (home & abroad) and NGOs as collaborating partners. Led the project of an ancient archaeological site as a Director of Culture & Heritage Research Project

As recognition of her contributions to science she has been awarded with 04 International awards such as 1) selected among top 25 Women Leader Cohort 2022 for 02 years training from Michigan State University (MSU) and Higher Education Commission of Pakistan 2) Fellow of Islamic World Academy of Sciences, 3) Postdoctoral fellowship from Ministry of Culture and Education, 4) Spain and a Young Chemist Award from Third World Academy of Sciences, Italy. She also has several national awards on her credit.