chemistry

Review

Dyes Are the Rainbow of Our Health

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Abstract: Natural dyes, obtained without the use of chemical treatment, are derived from naturally occurring sources, such as plants, animals, insects, and minerals. The usage of natural substances and their medicinal properties dates back to the origins of human civilization. The purpose of this review is to highlight the medicinal importance of selected natural colors, which sheds light on the critical role played by these dyes in the pharmaceutical industry. The objective is to showcase the health benefits of each color that can be obtained from nature for medicinal purposes based on their chemical structure. The review presents the reasons for utilizing natural resources in addressing various health issues, with a focus on three specific problems: microbial infections, cancer, and oxidative stress. Our review highlights the potential of natural resource structures, particularly anthocyanins, genipin, carotenoids, phycocyanin, and chlorophylls, in combating these ailments, emphasizing the need to explore their resources further for medicinal purposes. While most reviews provide a survey about colorful crude plant extracts in relation to one or a few categories of human health, our review focuses on the specific chromophore extracted not only from plants but also from any natural resource to provide a specific chromophore effect in a whole resource. The review highlights the significant role performed by organic pigments in the medicinal domain, with organic colorants acting as an essential element of the pharmaceutical sector's weaponry. Hence, it is of paramount significance to actively promote and stress the adoptions of naturally existing chromophores in diverse everyday commodities, while simultaneously acknowledging and valuing their substantial importance and worth in the vast realm of the pharmaceutical industry.

Keywords: anthocyanins; genipin; carotenoids; phycocyanin; chlorophyll

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1. Introduction

Natural dyes are obtained from naturally occurring sources like plants, animals, insects and minerals, without any use of chemical treatment [1]. These sources contain a range of beautiful colors, which vary from yellow to black. These colors are produced by various organic and inorganic molecules, called pigments, that absorb light in the visible region of 400–800 nm. The absorption of light depends on the structure or constituents of the coloring pigment, and the molecules contain various chromophores present in the dye, giving rise to a plethora of colors [2].

The utilization of natural substances and their medicinal qualities dates back to the beginning of human civilization [3]. For a considerable length of time, minerals, plants, and animals were the primary sources of medications. The current inclination towards naturally derived colorants stems from their favorable health attributes and superior performance. Various synthetic colorants have been prohibited due to their tendency to cause symptoms resembling allergies or being carcinogenic. Nowadays, natural dyes are extensively used in the cosmetic industry owing to their lack of side effects, ability to protect against UV rays, and anti-aging properties. These benefits make natural dyes a preferable alternative to synthetic ones [4].

Natural dyes play a significant role in imparting color to a diverse range of materials, including textiles, paper, and wood, among others [5]. However, their utility extends beyond these domains, with widespread usage in the cosmetic, food, and pharmaceutical industries. In particular, these dyes offer a broad spectrum of medicinal benefits, rendering them of immense importance in the pharmaceutical sector. Delving deeper, some crucial natural colors' medicinal importance is highlighted below, shedding light on the critical role played by these dyes in the pharmaceutical industry. Through this review, it becomes evident that natural dyes are not only an essential tool in the coloration of materials but also an indispensable component in the pharmaceutical industry's arsenal. This review aimed to illustrate the health benefits of each color obtained from nature for medicinal purposes based on their chemical structure.

2. Color Categories

The colors visible to the human eye range from 400 to 700 nm (Figure 1), which corresponds to the colors of the rainbow as identified by Newton, namely violet, indigo, blue, green, yellow, orange, and red. The biochromes present in nature can also be classified based on their distinctive chemical structures into different types, such as pyrrole derivatives (chlorophylls), isoprenoid derivatives (carotenoids), and flavonoids (anthocyanins) [6,7].

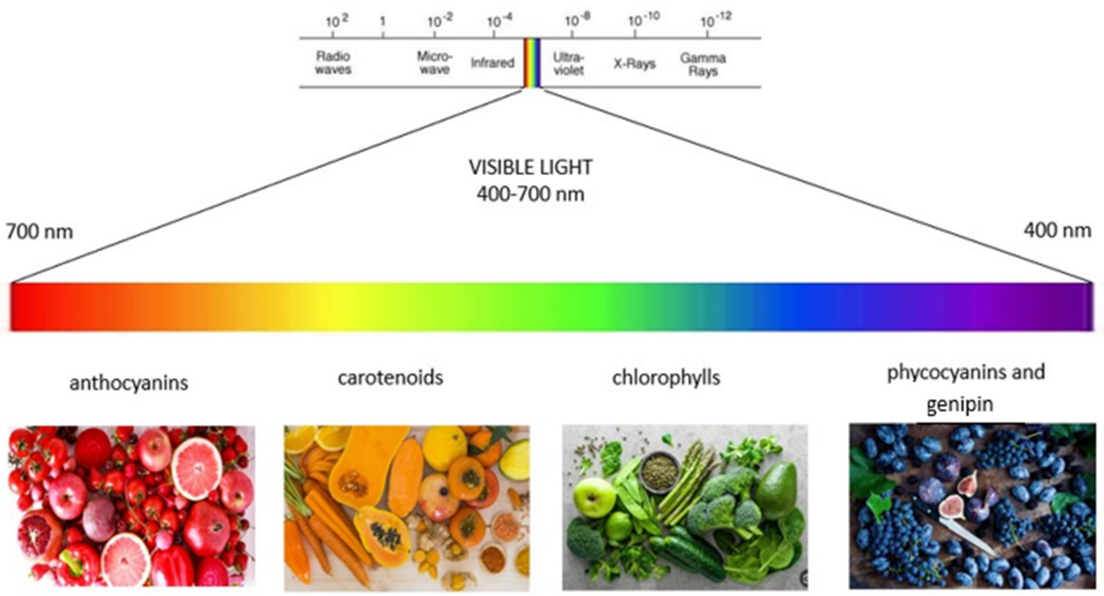

Figure 1. Color categories according to natural resources and chromophore chemical structures.

Chlorophylls, which are green in color, and carotenoids, which are yellow, red, and orange in color, play a significant role in photosynthesis. These pigments are found in all green plants and are located in plastids. The main function of chlorophylls is to capture light energy and convert it into chemical energy. On the other hand, carotenoids act as accessory light harvesting pigments and photoreceptors. They also protect chlorophylls from photo-oxidation.

In addition to chlorophylls and carotenoids, other pigments such as flavonoids play a vital role in plant growth and development. Flavonoids are responsible for the coloration of flowers and fruits.

These compounds, including carotenoids, anthocyanins or chlorophylls have been extensively studied and found to possess bioactive properties. These bioactive compounds have been linked to numerous health benefits, including antioxidant, anti-inflammatory, and anticancer effects. Therefore, the consumption of natural resources rich in these pigments is essential for maintaining good health and preventing chronic diseases.

2.1. Green Color (Chlorophyll)

Chlorophylls are ubiquitous and visually striking plant pigments, which prominently manifest in foliage and other green plant parts that are exposed to light. Chlorophylls, alongside carotenoids, are situated within chloroplasts, where their physiological function is to absorb light energy and utilize it for photosynthesis. Higher plants possess two distinct types of chlorophyll, specifically chlorophyll-a, which exhibits a green-blue hue, and chlorophyll-b, which displays a green-yellow shade. The structural representation of these chlorophyll variants can be observed in Figure 2. It is important to note that the amounts of these chlorophyll types are subject to variation, influenced by factors such as the plant species, exposure to light, and availability of minerals [6].

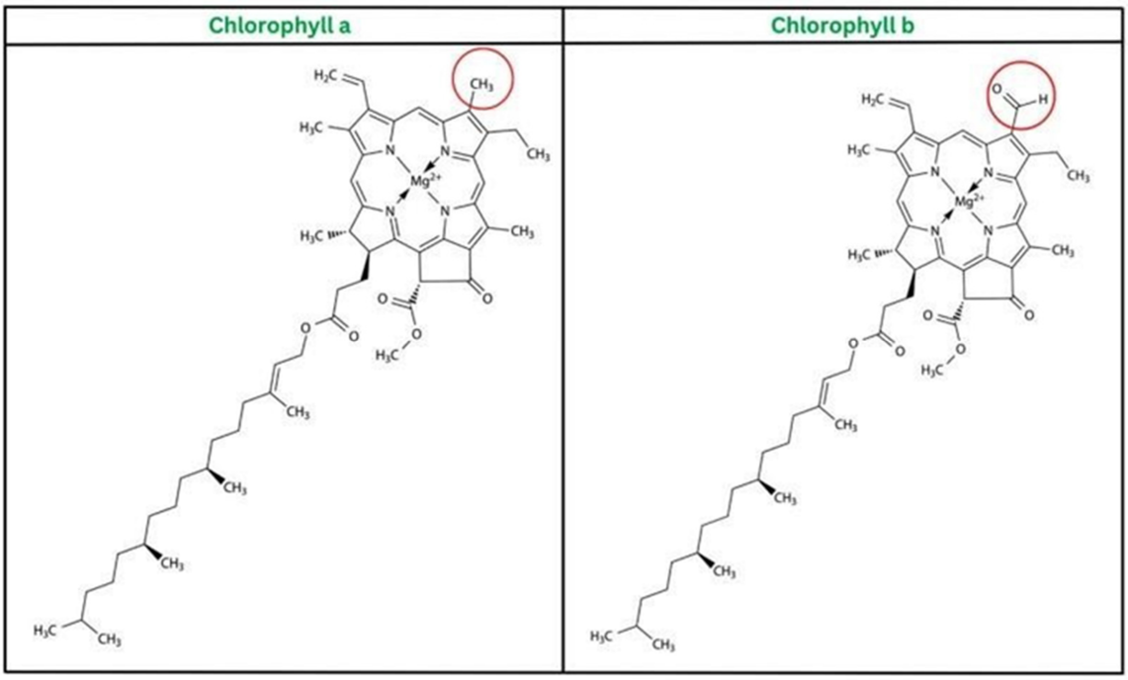

Figure 2. Chemical structures of chlorophyll-a on the left and chlorophyll-b on the right [8].

2.1.1. Chlorophyll as Antimicrobial Agent

The antimicrobial properties of chlorophyll have been the subject of extensive scholarly inquiry [9,10]. The inhibitory effects of chlorophyll have been observed to extend to various bacterial strains including Staphylococcus aureus, Streptococcus pyogenes, and Escherichia coli, as well as fungal strains such as Candida albicans and C. krusei [11,12]. The optimization of chlorophyll's antimicrobial activity can be achieved through the replacement of its metal ion center with alternative ions [13]. Substituting metal ions in derivatives of chlorophyll-a has been demonstrated to enhance the intensity of the intersystem crossing (ISC) mechanism, thereby resulting in the production of singlet oxygen species [14]. Singlet oxygen is recognized to possess antimicrobial properties. Moreover, the incorporation of chlorophyll into vegetation-derived pulp has resulted in the development of antimicrobial pulp, which has demonstrated inhibitory effects against bacteria. Furthermore, the antimicrobial properties of chlorophyll can be attributed to its antioxidant activity and its ability to impede bacterial growth. It has been employed as a natural food coloring agent and a photosensitizer for photodynamic therapy [15]. Chlorophyll is known to exhibit instability and susceptibility to degradation when exposed to environmental conditions such as oxygen, high temperature, or light. Such exposure can result in the loss of its potent antioxidant properties [16]. In order to augment its stability, a technique for encapsulating polymers through the utilization of polycaprolactone (PCL) has been postulated [17]. The PCL particles that encapsulated chlorophylls displayed an extended duration of the chlorophylls' stability, rendering them suitable for application in the food industry. On the other hand, derivatives of chlorophylls have been thoroughly examined and researched as potential photosensitizers for the process of photodynamic inactivation (PDI). This method has the capacity to effectively impede bacterial growth [18]. The physicochemical properties of chlorophylls can be optimized by these derivatives, resulting in the generation of singlet oxygen species which have the ability to inhibit bacterial growth [11]. Chlorophyll, in general, exhibits antimicrobial activity against a wide range of microorganisms, thereby rendering it a promising candidate for antimicrobial applications.

2.1.2. Chlorophyll as Antioxidant Agent

Chlorophyll functions as an agent of antioxidation by means of the elimination of free radicals and the provision of cellular protection against oxidative damage. The aforementioned antioxidant properties of chlorophyll, as indicated by [19], offer significant contributions to its capacity to neutralize reactive oxygen species (ROS) and forestall oxidative stress. The antioxidant activity of chlorophyll has been demonstrated in multiple studies, one such example being the work of [16], who demonstrated that purified chlorophyll extracted from maize leaves exhibits considerable total antioxidant activity, reducing power activity, and DPPH free radical-scavenging activity. Furthermore, Georgiopoulou and colleagues [20] highlighted the possibility of elevating chlorophyll's stability as an antioxidant by implementing techniques like polymer encapsulation.

Chlorophyll also functions as an antioxidant by safeguarding against photo-oxidative degradation and augmenting antioxidant activity. Within liposomal dispersions, the inclusion of monogalactosyl diglyceride prompted the deterioration of chlorophyll-a, whereas a-tocopherol provided complete protection to linolenic acid against photo-oxidative degradation [21]. The stability of chlorophyll-a derived from spirulina powder proved to be greater when compared to the crude extract when subjected to irradiation. Additionally, the antioxidant activity of chlorophyll-a increased subsequent to irradiation [22]. Sunflower oil that contained aromatic raw materials, including dried parsley and basil, exhibited a notably high level of antioxidant activity. Moreover, the chlorophyll content of the oil was observed to be contingent upon the quantity of raw materials employed in the process [23]. The rice mutant with elevated chlorophyll levels exhibited augmented antioxidant enzyme activity, including superoxide dismutase, peroxidase, and catalase, contributing to the challenge of chlorophyll's photo-inactivation and thereby promoting its overall content [24]. Chlorophyll's antioxidant characteristics render it an invaluable resource for a plethora of applications including but not limited to food coloring, photodynamic therapy, and prospective cancer remedies.

2.1.3. Chlorophyll as Anticancer Agent

Phytochemicals, specifically chlorophylls, have been the subject of extensive research due to their potential as agents for combating cancer. These natural compounds derived from plants have exhibited significant promise as highly selective anticancer agents that target only malignant cells while leaving normal cells unaffected [12]. Chlorophylls have been the subject of investigation due to their potential as an anticancer agent, and various proposed mechanisms have been put forth. One such mechanism entails the utilization of chlorophyll as a sonosensitizer in sonodynamic therapy, wherein the application of low-intensity ultrasound activates the cytotoxicity of chlorophyll against human prostatic cancer cells (PC-3) and spheroids (DU-145) in order to selectively eliminate cancer cells [25]. Another mechanism involves the hindrance of cell proliferation, invasion, and migration in highly metastatic melanoma B16-BL6 and human fibrosarcoma HT-1080 cells by taxol, harringtonine, homoharringtonine, and camptothecin [26]. Moreover, chlorophylls that are extracted from green tea has been discovered to possess considerable antioxidation and anticancer properties against colon cancer [27]. Since chlorophyllin is incorporated into traditional Chinese medicine due to its anticancer attributes, Pinelli et al. in their research elucidate on the preparation and cytotoxicity of a reduced chlorophyllin derivative (RCD) on tumor cell lines, demonstrating that this derivative exhibits dose-dependent cytotoxic activity against ZR-75, MCF-7, and HT-29 human tumor cell lines [28]. On the other hand, Vaňková et al. [29] in their study encompass both in vitro and in vivo components. In vitro analyses were carried out on human pancreatic cancer cell lines (PaTu-8902, MiaPaCa-2, 155, and BxPC-3) to evaluate the inhibitory effects of chlorophylls on cell proliferation. while in vivo experiments were performed using xenotransplanted nude mice, in which the administration of chlorophyll-a led to a substantial reduction in the size of pancreatic tumors. The mechanisms underlying the activity of chlorophylls in pancreatic cancer cells involve their ability to impede heme oxygenase (HMOX) mRNA expression and HMOX enzymatic activity, which subsequently influences the redox environment of the cancer cells. This alteration in the redox status is manifested through the generation of reactive oxygen species and changes in the ratio of reduced-to-oxidized glutathione. The modulation of the redox status by chlorophyll in pancreatic cancer cells contributes to their anti-proliferative and anticancer effects. These alterations are thought to be accountable for the diminished occurrence of cancer in individuals who consume chlorophyll-rich green vegetables [29]. Chlorophyll-derived pharmaceuticals have been discovered to possess proficiency as radioprotective agents through the inhibition of radical reactions encompassing lipids, which are fundamental determinants in the process of programmed cellular death and apoptosis [30]. Moreover, the study conducted by Kobayashi [31] revealed that human cancer cell lines' proliferation could be inhibited, and lipid peroxide levels could be increased by derivatives of chlorophylls, namely, Fe-TPPTS and Fe-TTMAPP. Although the precise modus operandi of chlorophyll as an anticancer agent is presently under investigation, the results of these investigations imply that chlorophyll and its derivatives hold considerable promise in cancer therapy and in the prevention of pathological conditions that arise from oxidative stress [32]. These investigations imply that chlorophyll and its derivatives possess a wide range of mechanisms for their anticancer properties, rendering them as prospective subjects for further exploration.

2.2. Orange Color (Carotenoids)

Carotenoids, a class of terpenoid pigments with over 600 compounds, have been identified in photosynthetic bacteria, algae, fungi, and cells of higher plants and animals [6]. This group of pigments can be categorized into two subgroups based on their chemical structure: unsaturated hydrocarbon orange-red carotenes and yellow-orange xanthophylls, which possess additional oxygen atoms in their molecular structure as depicted in Figure 3. The crucial role of these pigments lies in safeguarding the reaction center (RC) of photo system II against photo-oxidative harm through the quenching of triplet chlorophyll or the quenching of singlet oxygen, as described by [33].

2.2.1. Carotenoids as Antimicrobial Agents

Carotenoids have demonstrated the ability to manifest antimicrobial activity against diverse pathogens. These compounds are capable of functioning as antimicrobial agents through the inhibition of pathogenic bacterial growth, thereby preventing or treating bacterial infections [34,35]. The complete understanding of the precise mechanism through which carotenoids exert their antimicrobial effects remains elusive. Nonetheless, empirical research has posited that the disruptive impact of carotenoids on the structural and behavioral aspects of bacterial membranes is an instrumental factor. Computational analysis has provided evidence that carotenoids are capable of condensing membrane lipids, reducing their interactions and augmenting the thickness and rigidity of the membrane [36]. Carotenoids may function as transmembrane radical channels, facilitating the reduction of radicals in a specific compartment while simultaneously being reduced in another. This property could prove advantageous for the regulation of intra- and extracellular redox processes [37]. Furthermore, it has been discovered that carotenoids harbor potent antioxidant characteristics, potentially augmenting their antimicrobial efficacy through the neutralization of intracellularly engendered radical species [38].

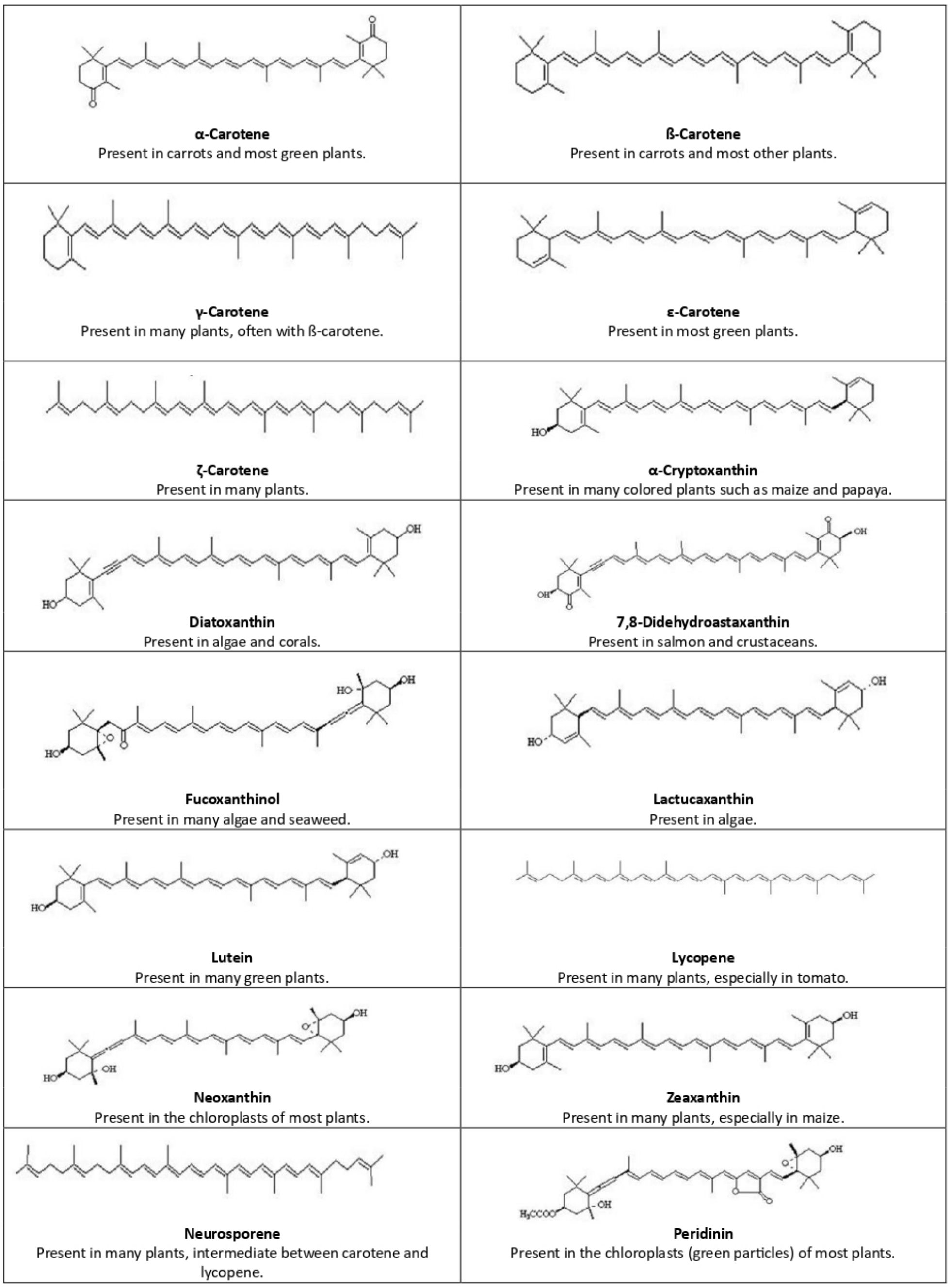

Figure 3. Carotenoids structures and their resources in nature [39].

2.2.2. Carotenoids as Antioxidant Agents

Carotenoids are a class of naturally occurring pigments that demonstrate potent antioxidant properties by effectively neutralizing reactive oxygen species (ROS) and providing substantial protection against oxidative stress [40,41]. The presence of electron-enriched polyene chains and triplet energy levels is a key factor in conferring antioxidant properties to them [42]. Carotenoids are capable of serving as reactive nucleophiles, thereby initiating the sequential proton loss electron transfer (SPLET) mechanism, which ultimately results in direct antioxidant activity [43]. The chemical hardness, proton affinities, and bond dissociation enthalpies of carotenoids have been observed to exert an influence on their antioxidant activity [44]. Carotenoids, for instance astaxanthin, β-carotene, zeaxanthin, and lycopene, have displayed noteworthy characteristics as antioxidants. Moreover, their antioxidant mechanism enables carotenoids to impede the onset and progression of numerous medical conditions, including cancer, skin disorders, eye diseases, diabetes, and coronary artery disease [45]. Nevertheless, an arduous task lies in the categorization of carotenoids as either anti- or pro-oxidant compounds due to their multifaceted nature and the diverse oxidation byproducts they produce [46]. It is crucial to conduct further investigations to scrutinize the antioxidant properties of different carotenoids [47].

2.2.3. Carotenoids as Antidiabetic Agents

Carotenoids have evinced antidiabetic properties by mitigating diabetes and its concomitant complications. They possess the ability to abate blood glucose levels and avert oxidative impairment [42,48]. Carotenoids, namely, astaxanthin, zeaxanthin, bixin, β-carotene, lutein, and lycopene, have been observed to demonstrate considerable potential as antidiabetic agents [49]. Several studies have provided evidence of a negative association between levels of carotenoids within the body and the likelihood of developing diabetes. These findings imply that the consumption of foods enriched with carotenoids may have the potential to mitigate or prevent the onset of diabetes [50]. Carotenoids play a significant prophylactic function in mitigating diabetic complications owing to their potent antioxidant properties [51]. Carotenoids have been discovered to possess hypoglycemic properties and potent antioxidant activity that effectively safeguards against oxidative damage and diabetes. However, additional research is necessary to comprehensively comprehend the mechanisms through which carotenoids function as antidiabetic agents.

2.2.4. Carotenoids as Anticancer Agents

Carotenoids exhibit anticancer properties through the targeting of various molecular events, inhibition of cell proliferation, and initiation of apoptosis [42]. The modulation of various cell signaling events results in the possession of noteworthy inhibitory potential against cancer [52]. Carotenoids, including but not limited to lycopene, crocin, β-carotenoid, lutein, zeaxanthin, β-cryptoxanthin, astaxanthin, and fucoxanthin, have demonstrated considerable efficacy in the prevention and treatment of cancer [53]. The phytochemicals exert their effects through multiple mechanisms, such as the stimulation of AMPK, the expression of biochemical markers associated with autophagy, the activation of the Keap1-Nrf2/EpRE/ARE signaling pathway, the suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), the initiation of apoptosis, and the inhibition of cancer cell proliferation [54]. Moreover, it has been discovered that carotenoids, derived from halophilic archaea, possess formidable anti-tumor properties by impeding matrix metalloprotease 9 and stimulating caspase-mediated apoptosis [55]. Carotenoids, such as bacterioruberin and its derivatives, exhibited significant antioxidant and antihemolytic properties. Additionally, they demonstrated both dose-dependent and dose-independent anticancer effects on HepG2 cells [56]. Carotenoids additionally manifest anti-inflammatory properties, a crucial factor in mitigating persistent inflammation that may precipitate the onset of cancer [57]. Although there exists limited clinical evidence that supports the utilization of carotenoids in the prevention and treatment of prostate cancer, in vitro as well as in vivo experiments have demonstrated that carotenoids have the potential to inhibit proliferation, prompt apoptosis, and diminish the metastatic capacity of prostate cancer cells [58].

2.3. Red Color (Anthocyanin)

Anthocyanins, commonly found in plants, particularly in flowers, fruits, and tubers, are pigments that exhibit blue, red, or purple hues [59]. The appearance of anthocyanins in acidic conditions is in the form of a red pigment, while in alkaline conditions, they manifest as a blue pigment. Despite their positive charge at the oxygen atom of the C-ring of the fundamental flavonoid structure (Figure 4), anthocyanins are still considered as one of the flavonoids [60]. It is known as the flavylium (2 phenylchromenylium) ion. The general molecular structure of anthocyanins is illustrated in Figure 4. The stability of anthocyanins varies depending on pH, light, temperature, and its structure [61].

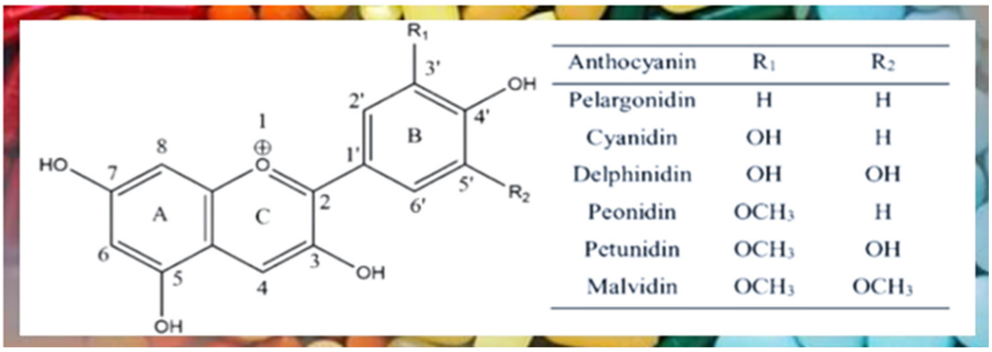

Figure 4. The basic structure of anthocyanin which consists of an anthocyanidin "core" with an attached sugar moiety [62].

Anthocyanins have been purported to possess diverse health benefits owing to their potent antioxidant attributes. They have been correlated with safeguarding against chronic ailments and have demonstrated potential as natural food pigments. Nonetheless, the recovery of anthocyanins from botanical sources can present a challenging undertaking due to their inherent instability and limited extraction efficiency [63,64]. Several techniques for extraction, including conventional and ultrasonic methods, have been employed for the retrieval of anthocyanins from diverse origins [64]. The inhibitory properties of the extract do not appear to be influenced by the extraction process, as the antimicrobial efficacy of the extracts is primarily contingent upon the quantity of anthocyanins present [63,65]. The study conducted by [65] effectively showcases the practical functionality of anthocyanins in the suppression of bacterial proliferation. It has been conclusively determined that this effect is achieved by means of interfering with the Angpt-Tie-2 ligand-receptor system, which is intricately linked to the renal VEGFR2 signaling pathway.

2.3.1. Anthocyanin as Antimicrobial Agent

Anthocyanins have been demonstrated to possess potent antimicrobial properties against a diverse range of pathogenic microorganisms [66–69], such as Staphylococcus aureus, Escherichia coli, Proteus mirabilis, Acinetobacter baumannii, and Pseudomonas aeruginosa. Furthermore, they have the potential to obstruct the formation of biofilms and bacterial adhesion, thereby diminishing the plausibility of resistance development and subsequent incidence of infection [66]. In the instance of chronic bacterial prostatitis, the utilization of anthocyanins sourced from black soybean exhibited notable anti-inflammatory and antimicrobial properties. When conjoined with ciprofloxacin, a synergistic effect was observed, resulting in an enhanced treatment efficacy [67]. Anthocyanin extracts obtained from *Clitoria ternatea* and *Dioscorea alata* showcased remarkable antibacterial and antifungal activity against a range of carefully selected bacteria and fungi [68]. The antimicrobial efficacy of anthocyanin complexes, extracted from Aronia melanocarpa, black currant, and elderberry, against a panel of bacterial strains, including Staphylococcus aureus, Escherichia coli, Bacillus subtilis, and Pseudomonas aeruginosa, demonstrate that these anthocyanin complexes exhibited significant antibacterial activity against the tested bacterial strains [69]. Moreover, anthocyanin extracts, procured through both conventional methods and ohmic heating, have been found to possess considerable antimicrobial properties against a variety of microorganisms [70]. Anthocyanins, as a whole, have been discovered to exhibit antimicrobial traits, rendering them viable organic substitutes to conventional antimicrobial agents.

2.3.2. Anthocyanin as Antioxidant Agent

The extracts of anthocyanins have exhibited remarkable antioxidant properties, as they possess the capacity to eliminate free radicals and decrease oxidative stress [71]. They possess the capacity to contribute electrons or hydrogen atoms for the purpose of quenching free radicals and impeding cellular harm [64]. The degree of antioxidant capacity exhibited by different anthocyanins is subject to the influence of their chemical structure. This correlation between anthocyanins and their antioxidant activity is well established. It is noteworthy that the chemical structure of anthocyanins plays a vital role in determining their antioxidant activity, thereby highlighting the significance of chemical structure in antioxidant potential [72]. Lipid peroxidation and the generation of reactive oxygen species are two pathways that lead to oxidative damage. However, the inhibitory effects of certain substances can mitigate this damage. Specifically, these substances are capable of reducing lipid peroxidation and curtailing the production of reactive oxygen species, thereby offering protection against oxidative damage [73]. Anthocyanins also possess the capacity to chelate metal ions, thereby augmenting their antioxidant activity. Moreover, extant studies have revealed that anthocyanins are capable of amplifying the activity of endogenous antioxidant enzymes, including superoxide dismutase and catalase [74]. In general, anthocyanins manifest their antioxidant effects via various mechanisms, thus rendering them significant compounds for their prospective health benefits [75].

2.3.3. Anthocyanin as Anticancer Agent

Anthocyanins have been discovered to possess anticancer characteristics through the modulation of diverse cellular functions implicated in the development and progression of cancer. Specifically, they have the ability to alter the redox status of cells, disrupt the regulation of the cell cycle, induce apoptosis, mitigate inflammation, impede angiogenesis, and subdue invasion and metastasis [76,77]. Anthocyanins also have the ability to inhibit cancer cell growth [78]. They can stabilize heat shock factor 1 (HSF1) expression, downregulate insulin-like growth factor II receptor (IGF-IIR) expression, and inhibit caspase 3 activation, thereby protecting cardiomyocytes against doxorubicin-induced injury [79]. Moreover, it has been demonstrated that anthocyanins originating from the Vitelotte potato possess the ability to regulate cell cycle regulators and prompt the maturation of acute myeloid leukemia cells [80]. Flavonoids, notably anthocyanins, have been the subject of clinical usage and have exhibited marked anticancer properties through their regulation of cellular division and proliferation. Evidently, anthocyanins possess the potential to be employed as anticancer agents and act as functional food constituents for both cancer treatment and prevention [81].

2.3.4. Anthocyanin as Antidiabetic Agent

Anthocyanins have demonstrated efficacy as antidiabetic agents via diverse mechanisms. Their effects are directed towards numerous organs and tissues that play a role in glucose metabolism, including but not limited to the pancreas, liver, muscle, and adipose tissues [82,83]. Anthocyanins possess the capacity to ameliorate insulin resistance, augment insulin secretion, and safeguard beta-cells [84]. They also inhibit enzymes involved in glucose metabolism, such as alpha-glucosidase and alpha-amylase [85]. Furthermore, as previously stated, anthocyanins exhibit antioxidant characteristics, which can effectively mitigate oxidative stress and ameliorate glucose homeostasis. Additionally, these substances have the ability to alter gene expression and metabolic pathways associated with glucose metabolism, including AMPK [86]. Moreover, research has demonstrated that anthocyanins possess the ability to reduce blood glucose levels, enhance liver performance, and restrain carbohydrate hydrolyzing enzymes. In general, anthocyanins exhibit promises as a natural and efficacious remedy for diabetes.

2.4. Blue Color (Phycocyanins and Genipin)

In the realm of natural colorants, red-colored dyes and their yellow or orange derivatives, such as curcumin or carotenoids, are considerably more ubiquitous than their blue counterparts. This is particularly evidenced in the plant kingdom, where the blue color is solely conferred by anthocyanins in an alkaline milieu. Notably, blue hues are also observed in bacteria (as a blue oil slick) and fungi, as well as in cyanobacteria, algae, and certain avian species. However, the manifestation of this coloration is not contingent upon the presence of a dye or pigment, but rather on the cell structure or, in the case of birds, the structure of the feathers [87]. Furthermore, blue pigments or dyes are infrequently encountered in food; this infrequency may account for the color's distinctive appeal to children. The primary natural blue colorants documented in the literature include anthocyanins, genipin, and phycocyanins (Figure 5). Anthocyanins can be derived from a variety of plants, phycocyanins can be extracted from algae, and genipin can be obtained from Gardenia jasminoides Ellis and Genipa americana. These blue colorants can be extracted through classical techniques based on organic solvents or through more advanced methods such as supercritical fluid extraction, ultrasound-assisted extraction, high-pressure extraction, and pressurized liquid extraction [88].

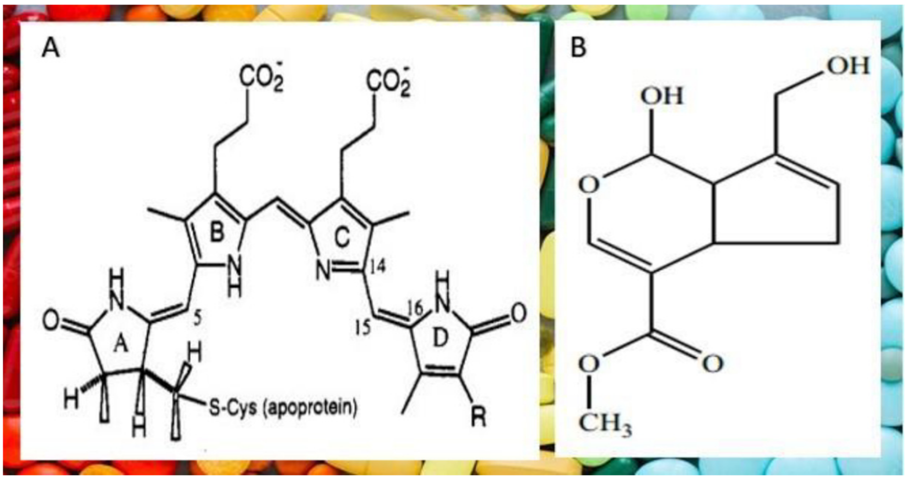

Figure 5. (**A**). Chemical structure of phycocyanobilin (PCB), the chromophore that is found in phycocyanins [89] Reprinted (adapted) with permission from Szalontai, B.; Gombos, Z.; Csizmadia, V.; Bagyinka, C.; Lutd, M. Structure and Interactions of Phycocyanobilin Chromophores in Phycocyanin and Allo-phycocyanin from an Analysis of Their Resonance Raman Spectra. Biochemistry 1994, 33, 11823–11832. Copyright © 1994, American Chemical Society. (**B**). Chemical structure of genipin [90].

2.4.1. Phycocyanin Health Benefits

Phycocyanins, which are pigments found in cyanobacteria and algae, have been shown to possess antioxidant properties. They have the ability to scavenge free radicals and reduce oxidative stress in the body [91,92]. Phycocyanins have been found to exhibit antioxidant activity through various mechanisms, including the scavenging of reactive oxygen species (ROS) such as hydrogen peroxide and hydroxyl radicals [93]. They also have the ability to reduce lipid peroxidation, which is a process that can lead to cellular damage. Additionally, phycocyanins have been shown to possess immunomodulatory effects, further contributing to their antioxidant properties [94]. These findings suggest that phycocyanins can act as neuroprotective agents and have potential therapeutic applications in the treatment of various diseases associated with oxidative stress and inflammation.

As previously noted, a number of scholars have expounded upon the antioxidant capabilities of Phycocyanins [95–97]. They possess the capacity to scavenge unbound radicals and safeguard against the deleterious effects of oxidative stress [98]. Phycocyanins have been shown to possess antioxidant properties and can function as radical scavengers, reducing agents, and metal chelators [99]. This antioxidative capacity has been demonstrated via a range of assays, including DPPH radical-scavenging activity, ferric reducing antioxidant power (FRAP), and Fe^{2+}-chelating activity [100]. Additionally, they have been observed to enhance tolerance against thermal and oxidative stress [101]. The antioxidative potential of phycocyanins renders them a fitting choice for employment as natural antioxidants in a variety of food products [102]. In summary, phycocyanins fulfill their role as antioxidants through the scavenging of free radicals, reduction in oxidative stress, and protection against cellular damage [103].

Phycocyanins have been found to possess anticancer effects by hindering the tumor cell cycle, triggering tumor cell apoptosis and autophagy, thereby conferring an additional health benefit [104]. The inhibition of cancer cell growth can be achieved through the process of decreasing DNA synthesis and inducing cellular accumulation in the G-1 phase [105]. Phycocyanins also possess the ability to selectively infiltrate biological structures, such as tumors, thereby augmenting the imaging of these structures [106]. Phenazines, which are structurally related to phycocyanins, have also been associated with anticancer activity [107]. In vitro studies have evinced the cytotoxicity of phycocyanins and their derivatives, which endows them with the potential of serving as efficacious anticancer agents [108].

Phycocyanins, conversely, exhibit antimicrobial characteristics and function as antibacterial agents. Evidently, they fortify the vitality, resilience, and antagonistic potential of probiotic bacteria, thereby augmenting their holistic health advantages [109]. Moreover, phycocyanins have demonstrated promising antineoplastic characteristics, particularly in melanoma cells. These compounds regulate the patterns of protein synthesis and participate in the GRB2-ERK1/2 pathway, which is accountable for impeding the proliferation of melanoma cells [103]. Moreover, phycocyanins that have been extracted from spirulina, which is a type of cyanobacterium, have been utilized in the manufacturing of soap that generates foam due to its anti-inflammatory and tissue-preserving attributes [94]. In summary, phycocyanins, which are phycobiliproteins, possess water solubility and bioactivity, and exhibit antioxidant, anti-inflammatory, and anti-tumor characteristics. As a result, they are emerging as promising biomolecules for use in various industrial applications.

2.4.2. Genipin Health Benefits

Genipin has been identified as possessing several advantageous attributes for human health, including its potential usage as an effective antimicrobial agent [110,111]. The utilization of this particular compound as a cross-linking agent has been observed in diverse fields of application, encompassing the creation of antimicrobial films [112,113]. The utilization of genipin cross-linking has been demonstrated to enhance the mechanical characteristics and antimicrobial efficacy of films produced from diverse substances, including sodium caseinate and gelatin [114]. The antimicrobial effect of genipin-crosslinked films has been ascribed to the regulated release of antimicrobial agents, specifically lysozyme and nisin, which are incorporated into the films [115]. Additionally, genipin has been observed to restrain Toll-like receptor (TLR) signaling, a vital mechanism for the stimulation of hyperinflammatory responses and tissue damage in the course of sepsis [116]. This curbing of TLR signaling by genipin has been demonstrated to abate the occurrence of multiple organ dysfunction and mortality in sepsis. In summary, the antimicrobial activity of genipin can be attributed to its cross-linking properties and its aptitude to regulate immune responses [110].

Another advantage of genipin is its ability to function as an anticancer agent via multiple mechanisms. One such mechanism involves the inhibition of uncoupling protein 2 (UCP2) activity, which leads to a reduction in the production of reactive oxygen species (ROS) and, as a result, the apoptosis of malignant cells [117–119]. Genipin is also known to induce an upregulation in the expression of tissue inhibitors of matrix metalloproteases (MMP-2), which have been implicated in tumor promotion and metastatic processes, leading to a concomitant reduction in MMP-2 activity [120,121]. Additionally, it has been demonstrated that genipin elicits caspase-dependent apoptosis in cancerous cells [122]. It has also been observed that genipin sensitizes cancer cells to the cytotoxic effects of oxaliplatin, a chemotherapy drug, by inducing autophagy and p53 expression [123]. Moreover, genipin restrains the accumulation of hypoxia-inducible factor-1α (HIF-1α) and the expression of vascular endothelial growth factor (VEGF), thereby impeding cancer progression [124]. The aforesaid discoveries imply that genipin possesses the potential to serve as a novel anticancer agent with multiple mechanisms of action [124,125].

On the contrary, genipin functions as an antioxidant through the suppression of lipid peroxidation and the removal of hydroxyl radicals [117]. It has been demonstrated that it exerts a noteworthy anti-inflammatory influence through the inhibition of inducible nitric oxide synthase (iNOS) expression and nitric oxide (NO) production [126]. Genipin additionally demonstrates antiangiogenic properties and impedes the stimulation of nuclear factor-kappaB (NF-κB), a transcription factor involved in the generation of pro-inflammatory mediators [127]. Furthermore, it has been discovered that genipin has the ability to reinstate hampered autophagic flux, a mechanism responsible for safeguarding cells, and also serves as a protective measure against septic injury [128]. It has been postulated that genipin possesses the potential to serve as a therapeutic agent for the management of sepsis. Overall, the antioxidant properties of genipin, in conjunction with its anti-inflammatory and cytoprotective effects, contribute to its potential as a highly promising compound for a diverse range of medical and tissue regeneration applications [129].

3. Conclusions

According to the aforementioned data, it is evident that natural chromophores possess not only the ability to dye materials but also a wide range of medicinal benefits that cannot be overlooked. As such, it is highly encouraged to utilize natural dyes in the production of day-to-day food products. Additionally, the usage of such chromophores as an alternative in the pharmaceutical industry is also strongly advocated due to their non-toxic nature, minimal side-effects, and abundant medicinal values. By delving deeper into the subject matter, the critical role played by these natural colors' medicinal importance in the pharmaceutical industry is brought to light. Through careful review and analysis, it becomes increasingly apparent that natural dyes are not only an indispensable tool in the coloration of various materials but are also an essential component in the pharmaceutical industry's arsenal. Therefore, it is of utmost importance to recognize and acknowledge the significance of natural chromophores in the pharmaceutical industry and actively promote their usage in day-to-day products.

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