Therapeutic Potential of Polyphenols of Marine Origin

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Polyphenols are compounds found in various plants and foods, known for their antioxidant and anti-inflammatory properties. These compounds have unique chemical structures and exhibit diverse biological properties, including anti-inflammatory, antioxidant, antimicrobial and antitumor action. Due to these properties, marine polyphenols are being investigated as possible therapeutic agents for the treatment of a wide variety of conditions, such as cardiovascular disease, diabetes, neurodegenerative diseases and cancer.

Keywords: marine polyphenols; therapeutics; antioxidants; anti-inflammatories

1. Introduction

The maritime environment encompasses more than 70% of the Earth's surface and is the world's biggest ecosystem, with very changeable and hostile physicochemical conditions (low temperature, restricted light availability, high salinity and high pressure). The world's oceans and seas contain approximately 90% of our planet's biological biomass, which is dominated by unicellular microbes.

The search for natural alternatives for the treatment and prevention of diseases has been increasingly relevant, and marine polyphenols have aroused the interest of researchers in this field. These compounds are bioactive molecules that have antioxidant, anti-inflammatory and antitumor properties, in addition to other beneficial health effects. One of the main sources of marine polyphenols is algae, which contains a diverse range of substances, including flavonoids, phenols and organic acids. Other important sources include fish and crustaceans, which are also rich in marine polyphenols such as catechins and phenolic acids.

Marine polyphenols have shown potential for treating and preventing a variety of health conditions. For example, studies indicate that by lowering oxidative stress and inflammation, these substances may help reduce the chance of cardiovascular disease. In addition, marine polyphenols have demonstrated antidiabetic properties, contributing to glycemic control and improving insulin sensitivity. There is also evidence that these compounds may be beneficial for brain health, as they have neuroprotective and anti-inflammatory properties, which may help prevent neurodegenerative diseases such as Alzheimer’s. In addition, marine polyphenols have demonstrated antitumor effects, showing promise in the treatment of several types of cancer. These compounds are believed to help prevent the development of cancer cells, as well as inhibit the growth and proliferation of existing tumors.

Due to the therapeutic potential of marine polyphenols, there is a growing interest in the development of nutraceuticals and pharmaceuticals that contain these compounds as active ingredients. However, more studies are required to assess the safety and effectiveness of these compounds in people, as well as to identify the optimal dose for therapeutic use.

2. Marine Polyphenols

Marine polyphenols are a group of bioactive compounds that are found in a wide variety of marine organisms, including algae, fish and crustaceans. These compounds are characterized by the presence of multiple hydroxyl groups (-OH) in their molecular structures, which give them antioxidant and anti-inflammatory properties. These compounds have a varied chemical structure and are classified into different groups, such as flavonoids, phenolic acids, tannins, lignans and stilbenes. Flavonoids are one of the most studied classes and include compounds such as catechins, quercetin and rutin, which are commonly found in algae and fish.

Marine organisms generate these marine-origin chemicals as a defense strategy against oxidative stress and ultraviolet radiation. Seaweed, for example, is frequently exposed to harsh environmental conditions, and the effects of damage are not visible; as a result, the alga produces a diverse range of metabolites (polyphenols, xanthophylls, tocopherols and polysaccharides) to protect against abiotic and biological factors such as herbivory and mechanical aggression from the
Marine polyphenols have aroused the interest of researchers because they have a wide range of health benefits, including anti-inflammatory, antioxidant, antitumor and neuroprotective properties. They have also been investigated as possible therapeutic agents for various conditions such as cardiovascular diseases, diabetes and cancer [10]. Although most studies have fixed their attention on the antioxidant and anti-inflammatory properties of marine polyphenols, recent studies have highlighted the importance of investigating the other mechanisms of action of these compounds, as well as their bioavailability and metabolism in humans [19].

2.1. Sources of Marine Polyphenols and Other Micronutrient

2.1.1. Algae

These bioactive compounds are found in different types of algae, including green (Chlorophyta), brown (Ochrophyta, Phaeophyceae) and red (Rhodophyta) macroalgae [11]. Each type of seaweed has different chemical compositions, with different types and concentrations of polyphenols. They are rich in various types of polyphenols, such as fucoxanthins, phlorotannins and fucoids [12]. Fucoxanthins are a type of carotenoid found in brown algae and have antioxidant, anti-inflammatory and anti-obesity properties [12]. Phlorotannins are unique phenolic compounds found in brown seaweed that have antioxidant, anti-inflammatory and anti-tumor properties [13]. Fucoids are sulfated polysaccharides found in brown algae and have antitumor, antiangiogenic and anti-inflammatory properties [14].

The polyphenols found in algae are phenolic compounds, which include catechins [15], phlorotannins, fucoids and fucoxanthins [16]. Catechins are a type of flavonoid that have antioxidant and anti-inflammatory activity, being found mainly in red algae. Phlorotannins are a unique group of polyphenols found in brown seaweed, with antioxidant and anti-inflammatory activity [17]. Fucoids are sulfated polysaccharides found in brown algae, with antiangiogenic, anticancer, anti-inflammatory and immunomodulatory properties [18]. Fucoxanthins are a type of carotenoid unique to brown algae, with antioxidant, anti-inflammatory, anti-obesity and antitumor activity [19].

Many previous studies have been performed where phenolic compounds were isolated from seaweed and include single phenolic compounds or polyphenols such as flavonoids, phlorotannins, mycosporine-like amino acids (MAAs), bromophenols and terpenoids [19]. The biological action of phenolic compounds is determined by the position of the hydroxyl groups and the number of phenyl rings in the structure [20].

Brown algae species contain a large amount of phlorotannins, while green and red algae mainly produce flavonoids, bromophenols, terpenoids and mycosporin amino acids in response to environmental conditions [21]. In the cosmetic industry, phlorotannins enable the activation of hyaluronidase, with anti-allergic, anti-wrinkle, anti-aging, skin whitening, photoprotection and improved skin health benefits. Thus, seaweed-derived phenolic compounds and their chemical structures, along with their skin benefits, are extremely useful in the skincare industry [22].

It is important to emphasize that the concentrations of polyphenols in seaweed vary according to the species, habitat, environmental conditions, stage of development and extraction method. Therefore, it is important to carry out studies to identify the best sources of polyphenols and the best extraction conditions to ensure obtaining products with a high concentration of bioactive compounds [13].

2.1.2. Fish

Fish are also an important source of marine polyphenols and other minor nutrients, particularly fatty fish such as salmon (Salmo salar), tuna (Thunnus orientalis) and sardines (Sardina pilchardus) [23]. Polyphenols found in fish include compounds such as catechins, phenolic acids and carotenoids [24]. Catechins are a type of flavonoid that have antioxidant and anti-inflammatory properties. Phenolic acids are common compounds that are also found in fruits, vegetables and plants that also have antioxidant and anti-inflammatory properties. Carotenoids, such as astaxanthin, are natural pigments found in some types of fish that have antioxidant and anti-inflammatory properties [25].

Catechins are a group of polyphenols with antioxidant and anti-inflammatory properties that are found in many foods, including fish such as tuna and salmon [26]. Catechins are known for their ability to neutralize free radicals, which are unstable molecules naturally produced by the body in response to stress, pollution and other factors. The accumulation of free radicals can lead to cell damage and increase the risk of chronic diseases such as cancer, heart disease and neurodegenerative diseases [27]. Additionally, catechins have anti-inflammatory properties that can help reduce inflammation in the body, which is a natural immune system response to injury and infection, but when persistent can lead
to a number of illnesses. Catechins also have anticancer activities, as they can help prevent the growth of cancer cells and inhibit the formation of new blood vessels that feed tumors.

Quercetin is a flavonol, a type of flavonoid that is found in many plant foods, including fruits, vegetables and some herbs. Furthermore, quercetin can also be found in some fish such, as salmon and trout. This compound is known for its antioxidant and anti-inflammatory properties and is one of the most studied flavonoids in relation to human health. Quercetin acts as an antioxidant, helping to neutralize free radicals, which are unstable molecules naturally produced by the body that can damage cells and lead to chronic disease.

Ellagic acid is a naturally occurring phenolic acid that is found in various foods, including fruits, vegetables and some types of fish. Phenolic acids are a type of organic compound that are known for their antioxidant properties and have been associated with a range of health benefits. In the case of ellagic acid, research has suggested that it may have anticancer properties and may be beneficial in the prevention and treatment of various types of cancer. Ellagic acid is also believed to have anti-inflammatory and antimicrobial effects, which may further contribute to its potential health benefits. While ellagic acid is most commonly found in fruits and vegetables, such as strawberries, raspberries and pomegranates, it has also been identified in some species of fish. For example, research has shown that ellagic acid can be found in the muscle tissue of salmon and trout (Oncorhynchus mykiss).

2.1.3. Shellfish

Shellfish, such as shrimps, clams and oysters, are also a source of marine polyphenols and other minor nutrients. The most common compounds found in shellfish are carotenoids such as astaxanthin and zeaxanthin, which have antioxidant and anti-inflammatory properties. These polyphenols are derived from algae and other marine organisms that are consumed by shellfish as part of their diet. One example of a marine polyphenol are the catechins, which are also found in tea, and procyanidins, which are found in various fruits, vegetables and brown seaweeds. These polyphenols are believed to have a range of health benefits, including antioxidant and anti-inflammatory effects.

2.1.4. Sponges

Despite being a rich source of highly bioactive chemicals, there has been little research in the literature on the extraction and identification of polyphenols in sponges. Traditionally, methanol and dichloromethane were utilized for extraction; however, some novel phenolic compounds have been discovered. Bisabolones are polyphenolic chemicals discovered in sponges that are particularly fascinating. All sponge bisabolones have a distinct 7S structure, whereas other marine and terrestrial bisabolones have a 7R structure. (S)-(+) curcuphenol, a member of this family discovered in sponges, has a variety of biological activities.

2.1.5. Marine Fungi

Several Benzaldehyde compounds produced from marine fungus have also sparked interest due to their scavenging characteristics. Wang et al. discovered and characterized chaetopyramin, a scavenging metabolite isolated from the marine fungus Chaetomium globosum (Ascomycota) and the red algae Polysiphonia stricta (formerly Polysiphonia urceolata). Chaetopyramin was synthesized along with known derivatives isotetrahydroauroglaucin and 2-(2′,3′-epoxy-1′,3′-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl)benzaldehyde, having DPPH IC50 values of 35, 26 and 88 g/mL, respectively.

2.1.6. Sea Urchins

The existence of polyhydroxylated naphthoquinone (PHNQ) pigments in sea urchins has long been recognized and investigated. They are concentrated in the shells or gonads, and it has been proposed that they, like other polyphenolic components from edible plants, may be used as antioxidants. Indeed, PHNQs extracted from sea urchin gonads have been demonstrated to be potent antioxidants in lipid peroxidation and food systems.

However, their use may be hampered by their poor yield and restricted by their brown/orange coloration. The structures of polyhydroxylated naphthoquinone pigments reveal that they are easily reduced and re-oxidized. As a result, their stability is critical for future medical applications. Alternatively, their distinctive quinone structure, along with their structural diversity, may lead to the discovery of novel bioactivities that are more relevant to biological applications.

2.2. Phenolic Compounds Metabolomics

There is a natural necessity of extrinsic or intrinsic drivers to make seaweed cellular systems to create naturally and/or enhance trigger its production from one molecule or a class of chemical to be generated by a specimen in nature or in
Marine polyphenols are a diverse group of compounds that include flavonoids, phenolic acids and stilbenes, among others. They are synthesized by marine organisms as a defense mechanism against environmental stressors, such as UV radiation, pathogens and predators [15]. Marine polyphenols have been found to exhibit a wide range of biological activities, including anti-inflammatory, anticancer, antiviral, antimicrobial and neuroprotective effects [17].

One of the key mechanisms by which marine polyphenols exert their biological effects is through their ability to interact with cellular signaling pathways. For example, marine polyphenols have been found to modulate the activity of the enzymes involved in cell proliferation, differentiation and apoptosis [46]. This can lead to the inhibition of cancer cell growth and the induction of cell death. Marine polyphenols can also regulate the expression of genes involved in inflammation, such as cytokines and chemokines, thereby reducing inflammation [47].

One of the primary mechanisms of action of marine polyphenols is their ability to scavenge free radicals and reactive oxygen species (ROS) in the body. Free radicals and ROS can damage cells and tissues, leading to inflammation, aging, and chronic diseases. Marine polyphenols have been shown to neutralize free radicals and prevent oxidative stress, thereby protecting cells and tissues from damage [48].

A mechanism by which marine polyphenols exert their effects is through their interaction with cellular membranes. Polyphenols can interact with the lipid bilayer of the membrane, altering its physical properties, such as its fluidity and permeability. This can lead to changes in membrane-associated signaling pathways, affecting cellular functions such as ion transport, receptor activity, and intracellular signaling [49].

Another mechanism of action of marine polyphenols is their ability to modulate the expression of genes and proteins involved in various cellular pathways. For example, marine polyphenols can activate or inhibit enzymes, such as kinases and phosphatases, involved in signal transduction pathways, leading to altered cellular responses. Marine polyphenols can also regulate the expression of transcription factors, such as nuclear factor-kappa B (NF-κB), which plays a critical role in inflammation and immune responses [47][50].

Marine polyphenols can also modulate the gut microbiota, which has important implications for human health. The gut microbiota plays a critical role in nutrient absorption, immune function and metabolic homeostasis [51]. Polyphenols can affect the composition and activity of the gut microbiota, promoting the growth of beneficial bacteria and reducing the growth of harmful bacteria. This can lead to improved gut health and a reduction in the risk of chronic diseases such as inflammatory bowel disease, obesity and type 2 diabetes [52].

Most of the marine phenolic compounds actuated in enzymes, such as cyclooxygenase (COX), work in tandem with nonsteroidal anti-inflammatory medicines (NSAIDs) to suppress the activity or gene expression of pro-inflammatory mediators. Various phenolic compounds can also operate on transcription factors such as nuclear factor-B (NF-B) or nuclear factor-erythroid factor 2-related factor 2 (Nrf-2) to upregulate or downregulate components in antioxidant response pathways. Phenolic chemicals have been utilized to treat a variety of common human disorders, including hypertension, metabolic difficulties, incendiary infections and neurodegenerative diseases, because they can block the enzymes involved in the development of human diseases. Phenolic chemicals have been used to treat hypertension by inhibiting the angiotensin-converting enzyme (ACE). Carbohydrate hydrolyzing enzyme inhibition is a type 2 diabetes mellitus medication, and cholinesterase inhibition is used to treat Alzheimer’s disease [53].

### 3.1. Therapeutic Potential of Marine Polyphenols

#### 3.1.1. Cardiovascular Diseases

Cardiovascular diseases (CVDs) are a leading cause of morbidity and mortality worldwide, and marine polyphenols have been studied extensively for their potential therapeutic effects in CVDs. Some of the ways in which marine polyphenols may be beneficial in CVDs [33] are as follows:
Antioxidant activity: Marine polyphenols have strong antioxidant properties, which can help reduce oxidative stress in the cardiovascular system. Oxidative stress has been implicated in the development and progression of CVDs, and reducing it may help improve cardiovascular health. Some of the main marine polyphenolic compounds with antioxidant activity include:

Phlorotannins: These are a group of complex polyphenolic compounds found in brown seaweeds. Phlorotannins are known for their potent antioxidant activity, and they have been shown to have a wide range of health benefits, including anti-inflammatory and anti-cancer properties.

Catechins: These are flavonoid polyphenolic compounds found in green tea and some marine sources, such as seaweed. Catechins have been shown to have potent antioxidant properties, and they may help reduce the risk of cardiovascular disease and other chronic diseases.

Anti-inflammatory effects: Chronic inflammation is a key factor in the development of CVDs, and marine polyphenols have been shown to possess anti-inflammatory effects. By reducing inflammation, these compounds may help protect against CVDs. Some of the most commonly studied compounds in this regard include:

Fucoidan: This is a sulfated polysaccharide found in brown seaweed and has been shown to possess anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines.

Phlorotannins: These are polyphenolic compounds found in brown seaweed and have been shown to possess anti-inflammatory effects by inhibiting the production of pro-inflammatory enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS).

Fucoxanthin: This is a carotenoid pigment found in brown seaweed and has been shown to possess anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and reducing oxidative stress.

Eckol: This is a phlorotannin found in brown seaweed and has been shown to possess anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and reducing oxidative stress.

Astaxanthin: This is a carotenoid pigment found in microalgae and has been shown to possess anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and reducing oxidative stress.

Regulation of lipid metabolism: Dyslipidemia, or abnormal lipid levels in the blood, is a major risk factor for CVDs. Marine polyphenols have been shown to regulate lipid metabolism, potentially reducing the risk of CVDs. Some of the main marine polyphenolic and other minor compounds that have been shown to regulate lipid metabolism and potentially reduce the risk of CVDs are:

Fucoxanthin: This is a carotenoid pigment found in brown seaweed. Fucoxanthin has been shown to reduce body weight, decrease total cholesterol and improve lipid metabolism in animal studies. It works by inhibiting the enzymes involved in the synthesis of cholesterol and triglycerides.

Astaxanthin: This is a carotenoid pigment found in microalgae, yeast, salmon, trout, krill, shrimp, crayfish, crustaceans and the feathers of some birds. Astaxanthin has been shown to improve lipid metabolism by decreasing serum triglyceride and cholesterol levels. It also exhibits antioxidant and anti-inflammatory properties.

Vasodilatory effects: Some marine polyphenols have been shown to have vasodilatory effects, meaning they can help relax blood vessels and improve blood flow. This can help reduce blood pressure and improve cardiovascular health. Some of the main marine polyphenolic and other minor nutrients that have been shown to regulate lipid metabolism and potentially reduce the risk of CVDs are:

Fucoxanthin: This is a carotenoid pigment found in brown seaweed. Fucoxanthin has been shown to reduce body weight, decrease total cholesterol and improve lipid metabolism in animal studies. It works by inhibiting the enzymes involved in the synthesis of cholesterol and triglycerides.

Phlorotannins: These are a group of polyphenolic compounds found in brown seaweed. Phlorotannins have been shown to reduce serum lipid levels by inhibiting the absorption of dietary fat and cholesterol. They also exhibit antioxidant and anti-inflammatory properties.
Fucoidan: This is a sulfated polysaccharide found in brown seaweed. Fucoidan has been shown to decrease triglyceride levels and improve lipid metabolism in animal studies. It works by inhibiting the activity of the enzymes involved in the synthesis of triglycerides.

Platelet inhibition: Platelet activation and aggregation play a key role in the development of thrombosis, which can lead to heart attacks and strokes. Marine polyphenols and other minor nutrients have been shown to inhibit platelet aggregation, potentially reducing the risk of thrombosis. Some of the main ones are:

Fucoidan: Fucoidan is a sulfated polysaccharide found in various types of brown seaweed. It has been shown to inhibit platelet aggregation by inhibiting the binding of platelet activating factors to platelet receptors.

Phlorotannins: Phlorotannins have been shown to inhibit platelet aggregation by interfering with the release of platelet activating factors.

Catechins: Catechins, a type of flavonoid found in many types of seaweed, can inhibit platelet aggregation by inhibiting the activity of platelet-activating factors and reducing the adhesion of platelets to the blood vessel wall.

Eckol: Eckol is a type of phlorotannin found in brown seaweeds. It has been shown to inhibit platelet aggregation by interfering with the binding of platelet activating factors to platelet receptors.

3.1.2. Diabetes

Among the marine polyphenols that have been studied for their potential therapeutic effects in diabetes, some of the most commonly studied include:

Fucoxanthin: This polyphenol has been shown to have anti-diabetic effects by improving insulin sensitivity and glucose metabolism in animal studies.

Phlorotannins: These polyphenols have been shown to have anti-diabetic effects by reducing blood glucose levels and improving insulin sensitivity in animal studies.

Fucoidan: This polysaccharide has been shown to have anti-diabetic effects by improving glucose metabolism and insulin sensitivity in animal studies.

Bromophenols: These polyphenols have been shown to have anti-diabetic effects by reducing blood glucose levels and improving insulin sensitivity in animal studies.

Catechins: These polyphenols have been shown to have anti-diabetic effects by improving insulin sensitivity and glucose metabolism in animal studies.

3.1.3. Neurodegenerative Diseases

Neurodegenerative diseases are a group of chronic and progressive disorders that affect the nervous system and lead to the gradual loss of function of neurons. They include Alzheimer’s disease, Parkinson’s disease and Huntington’s disease, among others. The pathogenesis of these diseases is multifactorial and involves oxidative stress, inflammation and the accumulation of misfolded proteins.

Marine polyphenols are natural compounds found in various marine organisms, including seaweeds, algae and marine animals. They have been shown to possess a wide range of biological activities, including antioxidant, anti-inflammatory and neuroprotective effects. Therefore, marine polyphenols have been investigated for their therapeutic potential in the prevention and treatment of neurodegenerative diseases.

The antioxidant properties of marine polyphenols can help reduce oxidative stress in neurons, which is a major contributor to neurodegeneration. These compounds have been shown to scavenge free radicals, prevent lipid peroxidation and enhance the activity of antioxidant enzymes. Moreover, marine polyphenols can also modulate inflammatory pathways, reducing the release of pro-inflammatory cytokines and chemokines that contribute to neuronal damage.

Marine polyphenols have also been found to have neuroprotective effects by inhibiting the aggregation of misfolded proteins, such as amyloid-beta and tau in Alzheimer’s disease and alpha-synuclein in Parkinson’s disease. By preventing the accumulation of these proteins, marine polyphenols can help maintain neuronal function and prevent neuronal death.
Overall, the therapeutic potential of marine polyphenols in neurodegenerative diseases is promising, but more research is needed to fully understand their mechanisms of action and to develop effective treatments. Further studies should focus on identifying the most potent marine polyphenols and optimizing their delivery to the brain to maximize their therapeutic effects.

### 3.1.4. Cancer

As described earlier, polyphenols and other micronutrients are bioactive compounds found in plants and animals, and recently there has been a growing interest in marine polyphenols due to their therapeutic potential in several areas of health, including cancer.

Marine polyphenols are extracted from marine organisms such as algae, mollusks, corals, sponges and fish. They have a wide variety of health benefits, including antioxidant, anti-inflammatory, anticancer and immunomodulatory activities.

The anticancer activity of marine polyphenols has been observed in several in vitro and in vivo studies. They are able to induce cell death in cancer cells, inhibit cell proliferation, inhibit angiogenesis and modulate the immune response. These effects are important because uncontrolled cell proliferation, excessive angiogenesis and suppression of the immune response are hallmarks of tumor development.

Ellagic acid is a polyphenol present in kelp that has been shown to cause cell death in breast and colorectal cancer. It functions by blocking the expression of pro-inflammatory and pro-angiogenic genes in cancer cells. It has also been shown to boost the production of tumor suppressor proteins.

Phloroglucinol acid is another polyphenol found in marine sponges with anticancer activity against lung and prostate cancer cells. This polyphenol induces apoptosis (programmed cell death) in cancer cells and inhibits the formation of capillaries that are necessary for angiogenesis.

Another micronutrient of marine origin with therapeutic potential is fucoidan, a sulfated polysaccharide found in brown algae. Studies suggest that fucoidan has anticancer activity against several cancer cell lines, including breast, lung and colon cancer cells. This sulfated polysaccharide inhibits angiogenesis, modulates the immune response and induces apoptosis in cancer cells.

### 4. Safety and Toxicity of Marine Polyphenols

Marine polyphenols are natural substances found in a variety of aquatic creatures, including seaweed, algae and shellfish. These compounds have received a significant amount of attention because of their possible health advantages, which include antioxidant, anti-inflammatory and anti-cancer properties. However, concerns have been raised regarding their safety and toxicity, mostly regarding their extraction and isolation methods, which can change their relative safety and toxicity; due to the diverse chemical structure and impurities, there is a need to standardize the procedure from extraction until the safety/toxicity assays.

Several studies have investigated the safety of marine polyphenols and their potential toxicity. Overall, the available evidence suggests that these compounds are generally safe for human consumption. However, there are some concerns regarding their potential toxicity at high doses. To date, the bioavailability of seaweeds has not been well researched. More research and study are required in this sector. The majority of seaweed phenolic pharmacological and biological bioavailability investigations have used mice models. Animal investigations and in vitro studies have provided evidence that seaweed phenols protect against various illnesses. As a result, fresh research investigations are required to investigate and completely comprehend their bioavailability in humans (the proportion of the chemical that reaches the human circulatory system and has an active impact).

### References


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