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Blueberries in focus: Exploring the phytochemical potentials and therapeutic applications

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ABSTRACT

Blueberries, which belong to the *Vaccinium* spp. Genus, have attracted considerable interest because of their abundant phytochemical composition and potential for medicinal uses. The present study examines the many phytochemicals found in blueberries, such as anthocyanins, flavonoids, phenolic acids, and stilbenes, as well as their biological activities contributing to the health benefits of blueberries. Anthocyanins, the primary pigments that give blueberries their unique color, are renowned for their powerful antioxidant capabilities. These substances counteract oxidative stress by neutralizing free radicals, decreasing the likelihood of developing chronic illnesses such as cardiovascular disease, cancer, and neurological disorders. Furthermore, the presence of flavonoids and phenolic acids in blueberries contributes to their ability to reduce inflammation, prevent cancer, and protect the brain, improving their potential for therapeutic use. This study delves into the bioavailability and metabolism of these phytochemicals, specifically examining the impact of factors like food composition, gut microorganisms, and individual metabolic variations on their effectiveness. Both clinical and preclinical studies provide strong evidence for the beneficial effects of blueberries on multiple health factors, such as enhanced cognitive function, lowered blood pressure, and improved insulin sensitivity. These findings suggest that blueberries may play a significant role in managing conditions like Alzheimer's disease, hypertension, and diabetes. Moreover, this study examines the synergistic impacts of blueberry phytochemicals, suggesting that the health advantages of blueberries arise not alone from individual substances but also from their collective interactions. Proposed future study areas include the advancement of functional foods and nutraceuticals derived from blueberries, as well as the need for standardized clinical studies to determine appropriate dose guidelines and ensure long-term safety. Overall, the significant variety of phytochemicals in blueberries and their potential for therapeutic use make them a promising functional food. Further research into these substances' mechanisms of action and therapeutic uses will clarify their function in enhancing human health and avoiding illness.

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1. Introduction

Blueberries are members of the Vaccinium genus and typically grow in forests or wooded areas throughout the Northern Hemisphere, primarily in North America, Europe, and Asia. Commercial cultivation of blueberries is prevalent in Atlantic Canada, the northeastern US, and various regions of the US and British Columbia [1]. Historically, Indigenous Canadians have consumed wild blueberries, and New Jersey first cultivated high-bush blueberries in the 20th century [2]. Australia, New Zealand, and South America commercially grow native North American blueberries in the southern hemisphere [3]. Wild blueberries exhibit diverse genetics due to cross-pollination and prefer acidic, moist soil, displaying robust cold hardiness in Canada and Maine. High-bush blueberries thrive in sandy or loamy soil, featuring deciduous or evergreen leaves and bell-shaped flowers that mature into a uniform blue color [4]. Water makes up around 84 % of the weight of fresh blueberries. The fruit also contains carbohydrates, which account for approximately 9.7 % of its composition, and proteins, which comprise about 0.6 %. Blueberries contain fats, which constitute around 0.4 % of their overall makeup. A 100-g serving provides approximately 192 kJ of energy, and essential nutrients such as dietary fiber (3 %–3.6 % of fruit weight), vitamin E, vitamin A, vitamin C, minerals (potassium, calcium, iron), and antioxidants. The vitamin C content, approximately 10 mg per 100 g, constitutes 1/3rd of the recommended regular intake [5].

Besides polyphenols, blueberries contain flavonoids, procyanidins, flavonols (kaempferol, quercetin, and myricetin), phenolic acids, and stilbene derivatives. The total polyphenol content varies based on the cultivar, growing conditions, and maturity, ranging from 48 to 304 mg per 100 g of fresh fruit weight [6]. Blueberries' vibrant colors (red, blue, and purple) stem from the glycosides cyaniding, delphinidin, and pelargonidin [7]. The outer layer, rich in anthocyanins and polyphenolic compounds, fundamentally possesses the vital antioxidant characteristics of blueberries [8]. The hydrophobic cuticle surrounds the epicuticular wax, which protects the single layer of the epidermis from desiccation, pathogens, insects, and adverse weather conditions. This protective part regulates the reentry of water molecules and essential chemical moieties [9]. Young blueberries typically hold approximately 3.4 g of alcohol-insoluble solids (AIS) per 100 g of fresh composition, while ripe ones have 2.4 g of AIS. Lignins comprise 27 % of AIS, while cellulose accounts for 16 %. Young fruit contains 0.76 g of neutral non-cellulosic polysaccharides per 100 g, while mature fruit contains 0.41 g [10]. The shape and properties of the outer layer determine how much water is absorbed and released. This, in turn, affects the levels of biologically active substances, especially anthocyanins, right below the epidermis. These dynamics can fluctuate depending on the specific blueberry variety and its degree of ripeness. Researchers have extensively studied these compounds for their anti-carcinogenic, anti-inflammatory, and cardiovascular protective potentials, which reduce the risk of coronary diseases, prevent cholesterol oxidation, and prevent neurodegenerative disorders [11].

Blueberries offer numerous health benefits with their abundance of essential nutrients, antioxidants, and bioactive compounds. Studies have revealed that consuming fresh blueberries can positively impact psychological and physiological health, mitigating non-communicable illnesses such as cardiac ailments, neurological conditions, diabetes mellitus, osteoarthritis, obesity, and certain malignancies [12]. For instance, studies have indicated that blueberries serve as a valuable reservoir of anti-inflammatory polyphenols like anthocyanins, which, when ingested prior to a meal, have the potential to diminish inflammation and counteract oxidative stress [13]. Their small size and ease of transport make them a convenient and recommendable choice for consumption in various situations. It is critical to remember that blueberries' constitution and nutritional content can fluctuate due to a range of factors, including species, variety, maturation stage, farming methods, environmental variables, plant nourishment, soil status, and storage conditions [14].

One of the most remarkable qualities of blueberries is their high antioxidant content. The abundant presence of anthocyanins, a type of flavonoid responsible for the deep blue-purple color, is one of the key contributors to their antioxidant capacity. These antioxidants are crucial in combating inflammation and supporting overall immune health, lowering the likelihood of chronic ailments such as cardiovascular anomalies, specific forms of cancer, and diabetes [15]. Blueberries are known to have a positive impact on heart health. Regular consumption of blueberries has been associated with lower blood pressure levels and improved cholesterol profiles. The bioactive compounds in blueberries promote vessel relaxation and enhance flow, lowering the precipitation of myocardial accidents and strokes [16]. Blueberries are also beneficial for brain health. Studies have shown that consuming blueberries may enhance cognitive function and memory retention, particularly in aging populations [17]. Researchers have discovered that blueberries' antioxidants and various phytochemicals shield brain cells from oxidative stress and diminish inflammation. Consequently, they promote optimal brain performance and diminish the likelihood of neurodegenerative conditions such as Alzheimer's disease [18]. For individuals concerned about weight management, blueberries can be a helpful ally. Blueberries boast a low-calorie content while offering a rich source of dietary fiber, fostering a sense of fullness and aiding in appetite management [19]. Fiber balances the naturally occurring sugars in blueberries, resulting in a slow release of glucose into the bloodstream, making them a suitable fruit option for individuals with diabetes or those aiming to manage blood sugar levels [20]. Blueberries contribute to digestive health due to their fiber content. Dietary fiber plays a role in stimulating regular bowel habits, preventing constipation, and sustaining a well-balanced gut microbiome. The combination of antioxidants and anti-inflammatory compounds in blueberries also supports gut health and reduces the risk of gastrointestinal disorders.

2. Blueberry chemistry

Blueberries are remarkable fruits abundant in diverse phytochemicals, with phenolic molecules being their most prominent components. Within these phytochemicals lie crucial vitamins, minerals, fatty acids, and dietary fibers. Thus, blueberries are significant reservoir of minerals, provitamin A, B-complex vitamins, and vitamin C. With an approximate content of 15 % soluble solids, primarily comprising sugars like fructose, blueberries hold notable value, especially for individuals managing diabetes [21]. Their high dietary fiber content, acting as an intestinal regulator, further enhances their health benefits. The abundance of diverse chemo-preventive compounds in blueberries is responsible for their remarkable health-enhancing properties. Some of these are vitamins, calcium, folic acid, carotene, selenium, lutein, phytosterols (such as stigmasterol and sitosterol), triterpene esters, and a wide range of phenolic compounds (such as flavanols, anthocyanins, ellagitannins, proanthocyanidins, and phenolic acids [22]. The intricate chemistry of these phenolic compounds holds significant sway over their metabolic pathways, bioavailability, and physiological impacts within the body. Changing the structure of blueberry phenolics involves different oxidation levels, hydroxylation, stereoisomerism, glycosylation with sugar and other substituents, and conjugation, all of which create complex molecules like tannins and other compounds [23]. Because they have so many health-benefiting properties, they are a beneficial addition to a balanced diet that helps keep you healthy and avoid getting sick.

2.1. *Anthocyanins*

Blueberries (Vaccinium spp.) contain water-soluble anthocyanins and glycosides that are polyhydroxylated and polyethoxylated derivatives of 2-phenylbenzopyrylium [24]. An aromatic ring binds to a heterocyclic ring containing oxygen, forming a carbon-carbon bond with another aromatic ring, forming the anthocyanins. Nature has identified more than 600 kinds of anthocyanins. There are six common anthocyanins, which are pelargonidin (Pg), cyanidin (Cy), delphinidin (Dp), peonidin (Pn), petunidin (Pt), and malvidin (Mv). The anthocyanins exist in the form of glycosides, each linked to their corresponding aglycones. Various anthocyanidins, such as pmalvidin, malvidin, petunidin, cyanidin, pelargonidin, and delphinidin, generate these aglycones. Different sugars, like galactose, glucose, arabinose, rutinose, and sambubiose, can join with these aglycones through an O-linked bond [25]. The different forms of these anthocyanins in blueberries include 3-monoxides, 3-triosides, 3-biosides, and 3,5-diglucosides [26]. Blueberries showcase a notably diverse array of anthocyanins, a composition that differs among various species. Blueberry anthocyanins are mostly made up of a mix of 3-*O*-galactosides and 3-*O*-arabinosides from delphinidin, cyanidin, and malvidin [27].

2.2. Flavonols

Within blueberries, flavonols and flavan-3-ols represent prominent subcategories of flavonoids. Flavonols in blueberries are mostly made up of compounds like myricetin, quercetin, and kaempferol, which can be hold apart by the hydroxyl group at position 3 of the C-ring [28]. Sugars like rutinose, rhamnose, glucose, galactose, and robinose can also substitute these compounds. Blueberries commonly contain flavonols such as myricetin 3-*O*-glucoside, myricetin 3-*O*-rutinoside, quercetin 3-*O*-glucoside, rutins (quercetin 3-*O*-rutinosides), and quercetin-3-arabinoside [29]. Blueberries contain diverse flavonols, with quercetin 3-glucoside and quercetin 3-galactoside being particularly abundant. Blueberries are rich in flavan-3-ol compounds such as epicatechin, catechin, and epigallocatechin gallate, among the most prevalent [30]. These flavonols and flavan-3-ols are renowned for their robust antioxidant attributes and a myriad of health advantages. They encompass cardiac preventive effects, neuroprotective effects, anti-inflammatory properties, and anticarcinogenic effects, rendering blueberries a promising and advantageous inclusion in one's dietary regimen [31].

2.3. Ellagitannins

Ellagitannins, a category of hydrolyzable tannins widely distributed, are present in blueberries. Red raspberry (297.3 mg/100 g of fresh weight), cloudberry (315.1 mg/100 g of fresh weight), sea buckthorn (1 mg/100 g of fresh weight), and strawberry (77.1 mg/100 g of fresh weight) all contain notable amounts of ellagitannins, which are considered the primary active compounds in these fruits [32]. These ellagitannins can exist in various structures, including monomer units, oligomer units, and complex polymers. Researchers have identified various ellagitannin monomeric to tetrameric units in blackberries, primarily concentrated in the seed tissue [33]. Blueberries contain a significant concentration of ellagitannins, primarily in the form of lambertianin C and sanguiin H-6, responsible for the majority of health benefits [34]. Advanced analytical techniques like high-performance liquid chromatography-electrospray ionization-mass spectrometry (HPLC-MS/ESI) and matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF-MS) further identify ellagitannins with large and diverse types, such as isomeric forms of galloyl-bis-HHDP glucose, pedunculagin, galloyl-HHDP glucose, lambertianin D, sanguiin H-10, lambertianin C, sanguiin H-6/lambertianin A, and castalagin/vescalagin [35].

2.4. Proanthocyanidins

Blueberries, like many other berries, particularly cranberries, contain proanthocyanidins, also known as condensed tannins, which are compounds with A-type bonds.

2.5. Phenolic acids

Researchers have also identified phenolic acids in blueberries, including hydroxybenzoates and hydroxycinnamates [36]. Blueberries typically encounter these acids as conjugated compounds, existing as esters and glycosides, rather than as free acids. Blueberries have a lot of different kinds of phenolic acids, including vanillic, ferulic, caffeic, chlorogenic, neo-chlorogenic, sinapic, ellagic, *p*-coumaric, and protocatechuic acids. They also have β-D-glucosides of tartaric acids and *p*-coumaric [37]. Blueberries also contain low concentrations of other phenolic acids, including coumaric and tartaric acids [38]. In the same way that blackberries can be a good source of gallic and hydroxybenzoic acids, blueberries can also be a good source of glycosidic, vanillic, salicylic, and ester forms of salicylic acid [39].

3. Blueberry pharmacokinetic and pharmacodynamic

Anthocyanins, a subject of extensive research over the past century, have recently been the focus of significant scientific inquiry. This research has delved into the metabolic pathways of anthocyanins in the human body to understand why they have limited bioavailability and how they positively impact health. The ultimate goal is to uncover and enhance these beneficial properties. However, several elements of anthocyanin absorption and metabolism still need more clarification. Therefore, it is essential to elucidate the absorption kinetics and metabolic pathways of anthocyanins upon administration in order to understand their physiological activities when they reach specific tissues or organs. Anthocyanins are mostly absorbed in the mouth cavity, stomach, small intestine, and colon. Because of their short residence time in the mouth cavity, anthocyanins have limited oral digestibility. Oral endocrine enzymes enter the alimentary canal together with anthocyanins, facilitating anthocyanin digestion and absorption. The unprocessed anthocyanins in the mouth pass into the stomach via the upper digestive tract [40].

The stomach's acidic gastric fluid provides an optimal setting for preserving and absorbing anthocyanins. The stomach can efficiently absorb anthocyanins without undergoing hydrolysis, and within 30 min after consumption, the bloodstream can detect them. The pH of the stomach environment typically ranges from 0.9 to 1.5. Anthocyanins have a high level of stability when they are in the form of flavylium AH + at a pH of 2 or below. Gastric epithelial cells absorb around 1–10 % of anthocyanins in their intact form. Furthermore, around 10–20 % of anthocyanins are actively conveyed to the bloodstream via stomach epithelial cells in as primary metabolites. Multiple studies have shown that the stomach plays a crucial role in the absorption of anthocyanins, with the stomach's absorption rate of anthocyanins potentially reaching up to 20 % [40].

The small intestine, the most extensive segment of the digestive system, has a crucial function in assimilating nutrients from ingested food. The undigested anthocyanins pass from the stomach tissue into the small intestine via the lowest part of the digestive tract. In contrast to the stomach's acidic environment, the pH level in the small intestine is nearly neutral, ranging from 4.0 to 7.0. When exposed to neutral or slightly acidic conditions, anthocyanins tend to form quinone bases, pseudobases (B), and chalcones (C). Therefore, these compounds are easily attacked by water through nucleophilic reactions and are unstable. Furthermore, the small intestine rapidly metabolizes anthocyanins through a glycosylation reaction. Anthocyanins may undergo decomposition and transformation by intestinal microbes, producing phenolic acids, aldehydes, and other metabolites that can enhance human health. The breakdown process may be caused by lactase at the edges of small intestinal villi and β-glucosidase in bacteria inside the small intestine. These enzymes break down anthocyanins into free anthocyanins. The digestion of anthocyanins relies on the hydrolysis of glycosidic linkages, since their aglycones are more readily absorbed than the ingested glycosides [40].

The unprocessed anthocyanins in the small intestine migrate to the colon, where the pH level is comparable to that of the small intestine. The intricate physiological circumstances and microbial flora present in the colon can dismantle the ring structure of anthocyanins and break them down into less complicated phenolic acids, such as vanillic acid and hippuric acid. The gut microbiota can alter the composition of anthocyanins by quickly removing sugar molecules and methyl groups from them. The intestinal microbiota can break down anthocyanins' ring structure and eliminate glycosyl complexes, including O-glycosides and C-glycosides. Once anthocyanins are broken down by intestinal flora, the resulting substances may be taken up by epithelial cells and reach the bloodstream to produce their effects. Intestinal flora have a significant role in the process of transforming anthocyanins. The stomach and small intestine digest and absorb anthocyanins, exhibiting their biological effects. Furthermore, the gut microbiota interacts with anthocyanins to facilitate their reabsorption after alteration or destruction. The biological activities and health consequences of anthocyanins result from the original anthocyanins and their metabolites in the intestines. Thus, increasing the stability and absorption of anthocyanins in the gastrointestinal system is essential to enhance their bioavailability. Protoncatechuic acid, ferulic acid, gallic acid, syringic acid, *p*-coumaric acid, and vanillic acid are the main phenolic acids that are made in the cecum by anthocyanins through microbial metabolism. The metabolized phenolic acid has favorable antioxidant, anti-inflammatory, and anti-tumor properties. The absorption and metabolism of berry anthocyanins support their biological actions. Therefore, when consumed as part of the diet, berry anthocyanins contribute to human health in two ways: (a) the stomach and small intestine readily absorb anthocyanins, and (b) the colon subsequently reabstains the breakdown products of anthocyanins [40].

Studies revealed that blueberry anthocyanins, while resistant to degradation during gastric digestion, lose some stability and antioxidative activity during intestinal digestion. The hydrophobic nature of anthocyanins positively influences their absorption efficiency in the intestines compared to more hydrophilic ones. The glycoside structure of anthocyanins also plays a role in determining their absorption efficiency. Blueberries and their anthocyanin compounds show potential health benefits, but their structural characteristics and susceptibility to gastrointestinal processes may influence their effectiveness [41]. Colonically produced cinnamic and hippuric acids are the predominant metabolites, accompanied by lesser quantities of various phenolic acids, flavonols, and anthocyanins. These compounds collectively contribute to facilitating efficient digestion and absorption [42]. Blueberry polyphenols influence digestion and absorption in the intestine, and the transformation of these compounds into various metabolites, particularly colonically generated cinnamic and hippuric acids, suggests the potential for enhanced health benefits [43]. The research findings suggest that supplementing the diets of older adults with freeze-dried blueberry (BB) powder positively impacts the content of bioactive compounds in their blood serum [44]. Specifically, the consumption of blueberry powder reduced inflammatory signals in microglial cells when exposed to stress-induced inflammation (LPS-induced inflammatory signals) [45]. The serum supplemented with blueberries had a protective effect after 45 days and 90 days of supplementation, with the most pronounced protection observed at the 90-day mark. This implies continuous blueberry supplementation may offer the greatest health advantages over time. The study found that high-fat meal consumption (postprandial conditions) did not hinder the beneficial effects of blueberries. The compounds present in blueberry fruit remained active even after a high-fat meal, and the blueberry-supplemented serum could regulate oxidative and inflammatory stress effectively in both fasted and postprandial states [46]. The metabolic fate of blueberry polyphenols was also examined in some studies, and it was found that blueberry anthocyanins were poorly absorbed in vivo, and extensively metabolized by hepatic enzymes and microbiota to several other compounds (i.e. aglycones, metabolites/breakdown products, methylated, sulfated and glucuronidated compounds) [47]. The breakdown of blueberry polyphenols produces metabolites, particularly phenolic acid derivatives, which may contribute to the observed anti-inflammatory effects [47]. Animal studies correlated cognitive improvements with decreased neuroinflammation, and supplementation with blueberry diets showed reductions in LPS-induced nitrite and TNF-alpha, indicating potential anti-inflammatory effects on brain cells. These findings support that blueberry metabolites circulating in the blood may play an important role in enhancing behavioral performance and cognition by reducing neuroinflammation [48]. The research demonstrates that consuming blueberry powder leads to positive changes in the blood serum, with potential anti-inflammatory effects that could contribute to improved cardiovascular health and cognitive function in older adults. Researchers have connected blueberries, specifically the highbush (*Vaccinium corymbosum*) and lowbush (*Vaccinium angustifolium Aiton.)* varieties, with various metabolic health benefits [49].

The key pharmacological components responsible for these effects are anthocyanins, which are the determinants of the antioxidant capacities of blueberries. Intestinal microorganisms have the ability to break down and modify anthocyanins, producing phenolic acids, aldehydes, and other metabolites that are beneficial to human health. The breakdown process of anthocyanins into free anthocyanins may be caused by the enzymatic activity of β-glucosidase in bacteria within the small intestine and lactase at the periphery of small intestinal villi. The intestinal bacteria may break down the ring structure of anthocyanins, which can also remove the glycosyl complexes of anthocyanins, such as O- and C-glycosides. Protocatechuic acid, ferulic acid, gallic acid, syringic acid, *p*-coumaric acid, and vanillic acid are the main phenolic acids produced by anthocyanins by microbial metabolism in the cecum. The metabolized form of phenolic acid has advantageous anti-inflammatory, antioxidant, and anti-tumor characteristics. The absorption and metabolism of berry anthocyanins support their biological effects [40]. Anthocyanins make up about 35–74 % of the total phenolics in blueberries, followed by hydroxycinnamic acid derivatives, flavan-3-ols, and flavonols [50]. These bioactive compounds, along with folic acid, fibers, and ascorbic acid in blueberries, may exert the observed cardiovascular health effects synergistically. Studies have demonstrated that freeze-dried blueberries can counterbalance oxidative stress aggregates caused by fast-food-style meals in healthy people, indicating their potential to mitigate postprandial effects, especially in conditions like metabolic syndrome [51].

Conversely, blueberry supplementation has demonstrated antioxidant effects by lowering lipid hydroperoxides in smokers, a condition where smoking and inflammation related to metabolic syndrome intensify oxidative stress [52]. Human studies have revealed that freeze-dried blueberries can have antihypertensive effects and improve insulin sensitivity in obese individuals with metabolic syndrome, or insulin resistance [53]. These effects were observed at dietary, achievable doses, indicating the potential for blueberries to aid in managing hypertension and insulin resistance. Exploratory studies conducted in animal models of hypertension provide additional evidence supporting the antihypertensive properties of blueberries. Adding freeze-dried blueberries to the diet significantly reduced the systolic blood pressure in spontaneously hypertensive stroke-prone (SHRSP) rats.

Meanwhile, renal oxidative stress markers decreased, indicating potential protection against oxidative damage in the kidneys [54]. Blueberries also explained improvements in vasoconstriction and endothelial dysfunction in another animal model of spontaneously hypertensive rats, suggesting benefits for blood vessel health [55]. In SHRSP rats, blueberries lowered plasma ACE activity, highlighting another potential mechanism for managing the early stages of hypertension. Blueberries have shown promising effects on atherosclerotic lesions and up-regulated antioxidant enzymes in apolipoprotein E-deficient mice, potentially mitigating atherosclerosis [56]. *In vitro*, studies have shown the ability of blueberries to inhibit α-amylase and α-glucosidase activities, suggesting implications for managing hyperglycemia [57].

4. Bioactive constituents of blueberry

Blueberries are highly sought after not only for their distinctive taste and flavor but also for their abundant nutritional value and health-promoting qualities. They are renowned as a bountiful source of essential nutrients and bioactive constituents, including vital vitamins such as A, C, and E, as well as essential minerals like calcium, iron, and potassium, along with dietary fiber. Furthermore, blueberries are rich in a diverse array of health-related compounds, which encompass organic compounds and different phenolic compounds like malvidin 3-acetylglucoside, quercetin-3-*O*-galactoside, malvidin 3-*O*-glucoside, 3,5-dicaffeoylquinic acid, quercetin-3-*O*-glucoside, cyanidin 3-*O*-arabinoside, kaempferol-3-*O*-glucoside, cyanidin 3-*O*-glucuronide, peonidin-3-*O*-glucoside, petunidin 3-acetylglucoside, petunidin-3-*O*-glucoside, quercetin-3-*O*-rutinoside, quercetin-3-*O*-diglycoside, cyanidin 3-*O*-glucoside, *trans*-5-caffeoylquinic acid, 4,5-dicaffeoylquinic acid, quercetin-3-*O*-arabinoside, and various sugars, including glucose and fructose. These myriad compounds collectively contribute to blueberries' well-deserved reputation as a superfood with the potential for significant health benefits. According to previous studies, the anticipated or observed bioactivities are as follows in Table 1 and Fig. 1.

5. Health benefits

Blueberries have that moniker because of their color. Blueberries are a very popular fruit because of their flavor, which is a combination of sweet and acidic, and they are almost seedless. The heather family includes tiny, spherical, blue, or purple berries, and blueberries. Blueberries come in two main varieties: highbush and lowbush [98]. Commercial blueberry farming occurs throughout the Americas and Europe despite being a North American fruit. They are incredibly popular and delicious. The antioxidants, vitamins, and minerals included in blueberries significantly positively affect on health. For instance, blueberries have a lot of vitamin K, crucial for promoting heart health. Along with bone health and blood coagulation, the vitamin is crucial for both. Berries, such as those from the Rosaceae Rubus family (raspberry and blackberry), the Fragaria family (strawberry), and the Ericaceae *Vaccinium* family (blueberry and cranberry), are the best dietary sources of health benefits (Table 2 and Fig. 2). Their main bioactive compounds include anthocyanins, phenolic acids, ascorbic acid, flavonols, and tannins [99]. The anticancer properties of berry anthocyanidins (cyanidin, malvidin, peonidin, petunidin, and delphinidin) vary [100], but cyanidin and peonidin have properties that are comparable to those of black rice [101].

The key functional components of blueberries for preventing chronic disease are anthocyanins and polyphenols (Ma L. et al., 2016). The presence of total phenolic compounds was higher than that of anthocyanins (33–73 %), although the anthocyanin content of strawberries and blackberries was higher (5). Despite having high levels of total phenolic compounds, berries differ significantly in their effectiveness as antioxidants. Blueberries harbor a wealth of flavonoids, with a particular emphasis on anthocyanidins and polyphenols like phenolic acids, pyruvic acid, and chlorogenic acid, among others. These compounds collectively bestow a wide array of health benefits, including anticancer properties, anti-obesity effects, prevention of degenerative diseases, anti-inflammatory capabilities, vision and liver protection, defense against heart diseases, antidiabetic potential, enhancement of brain function, lung protection, support for strong bones, immune system fortification, prevention of cardiovascular diseases, and improvement in cognitive decline. Existing data further illuminates the mechanisms underlying these health benefits, particularly those associated with anthocyanins and polyphenols, solidifying blueberries' status as one of the most potent functional fruits.

5.1. Cognitive performance

Notably, a blueberry extract high in polyphenols improves the memory function of patients with a wide range of cognitive dysfunctions [102,103]. Polyphenols have a positive impact by mitigating cognitive decline in older adults. In an elderly cohort, a 100 mg blueberry extract intervention spanning three months can improve episodic memory performance and reduce cardiovascular risk factors observed over six months [104]. Anthocyanins, one type of polyphenol found in abundance in blueberries, have been linked in studies to a wide range of cognitive and physical advantages.

Particularly, a blueberry extract high in polyphenols improves the memory function of patients with a wide range of cognitive dysfunctions [102,103]. Polyphenols have a positive impact by mitigating cognitive decline in older adults. In an elderly cohort, a 100 mg blueberry extract intervention spanning three months can result in improved episodic memory performance and a reduction in cardiovascular risk factors observed over a six-month period [104]. Anthocyanins, one type of polyphenol found in abundance in blueberries, have been linked in studies to a wide range of cognitive and physical advantages [105].

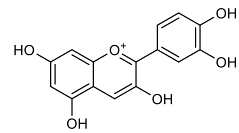
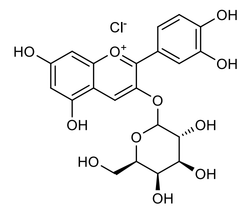
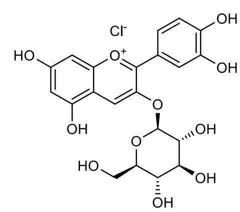
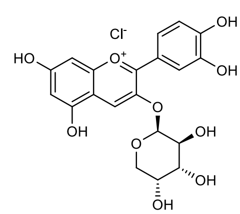
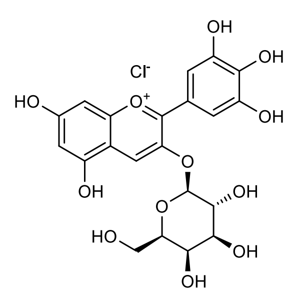
As we get older, blueberries are very advantageous. Epidemiological studies have linked blueberry consumption to lower rates of cognitive impairment as people age [106]. In studies, daily supplementation with blueberry interventions led to increased neural activity, improved working memory performance, and improved memory and executive function performance in older adults [104,106]. These consequences extend beyond healthy aging. For instance, in older people with mild cognitive impairment, daily blueberry supplementation improved memory function and brain activity during a working memory exercise [107]. Berry fruit increases the brain's positive signaling. These findings suggest regular polyphenol intake may benefit neurocognitive function as we age [109].

5.2. Anti-cancer effects

In addition to having lower levels of proliferative, antiapoptotic, and angiogenic transcripts and higher tumor stayers, the pterostilbene, pyruvic acid, phenolic acids, and anthocyanins present in blueberries not only prevented carcinogenesis but also reduced the risk of cancer recurrence and may have potential as a radiosensitizer for treating cervical cancer [110,111]. Blueberry anthocyanin's pyruvic acid ($C_3H_4O_3$), which inhibits the formation of cancer cells, can control the progression of the disease. Blueberry anthocyanin has antiproliferative and apoptotic properties in cancer cells, making it suitable for chemopreventive metastasis. Its concentration varied from 1.02 to 1.95 g/kg of malvidin-3-glucoside for fresh weight [110]. However, when using HepG-2 cells, their anticancer activity is linked to their anthocyanin content [112].

Blueberry anthocyanin extract's defenses against acrylamide toxicity boost mitochondria [110]. With bortezomib treatment, pterostilbene in blueberries can manage significant therapeutic myeloma as well as worsened or obdurate myeloma [113]. Proanthocyanidins from low-bush blueberries can increase apoptosis induction in human colorectal cancer cell lines, a significant nutritional strategy for colorectal cancer treatment [114]. Colon cancer progression can be limited with a dietary supplement of blueberry husks with probiotics [110]. Besides its role as a methylation suppressor for human methylene tetrahydrofolate reductase and DNA methyltransferase 1, as demonstrated by Ref. [110], blueberry juice also demonstrates a comparable anti-premutagenic effect akin to that of vitamin C. Extracts from blueberries that include anthocyanin and anthocyanidin can stop B16–F10 cells from proliferating and cause them to undergo apoptosis [115]. By lowering the levels of COX-1 and COX-2, blueberry eating (400 mg daily) suppressed the proliferation of ovarian cancer cells and greatly reduced tumor size in mice [116]. In a hamster model investigating oral oncogenesis, blueberries and malvidin were employed as STAT-3 inhibitors against the

Table 1
Various bio-actives, their chemical name along with structure present in blueberry.

Bioactive Ingredients Class	Chemical Name	Chemical Structure	Ref.
Anthocyanins	Cyanidin		[58]
	Cyanidin-3-galactoside		[59]
	Cyanidin-3-glucoside		[60]
	Cyanidin-3-arabinoside		[61]
	Delphinidin Glycosides Delphinidin-3-galactoside		[62]

(continued on next page)

Table 1 (*continued*)

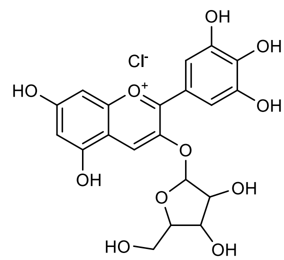
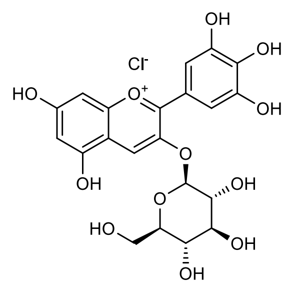
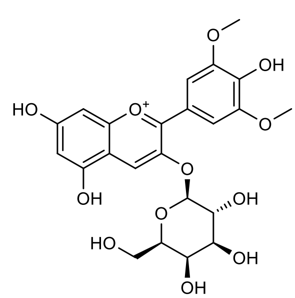
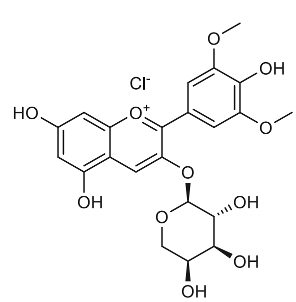
Bioactive Ingredients Class	Chemical Name	Chemical Structure	Ref.
	Delphinidin-3-arabinoside		[62]
	Delphinidin-3-glucoside		[62]
	Malvidin Glycosides Malvidin-3-galactoside		[63]
	Malvidin-3-arabinoside		[64]

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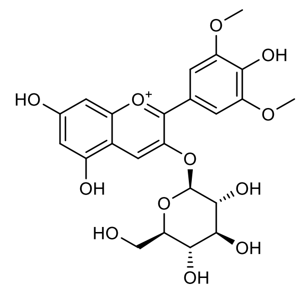
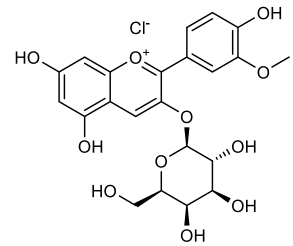
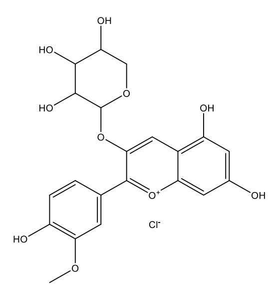
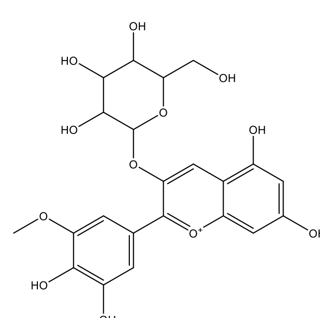
Table 1 (*continued*)

Bioactive Ingredients Class	Chemical Name	Chemical Structure	Ref.
	Malvidin-3-glucoside		[65]
	Peonidin Glycosides Peonidin-3-galactoside		[66]
	Peonidin-3-arabinoside		[67]
	Petunidin Glycosides Petunidin-3-galactoside		[68]

(*continued on next page*)

Table 1 (*continued*)

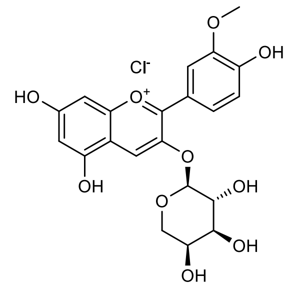
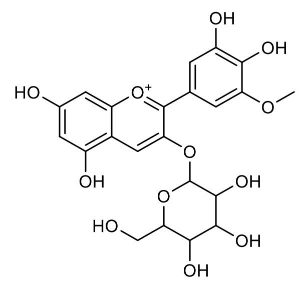
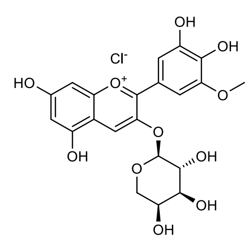
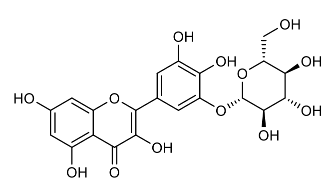
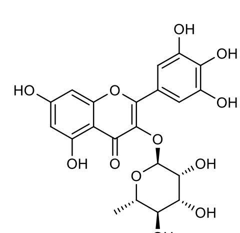
Bioactive Ingredients Class	Chemical Name	Chemical Structure	Ref.
	Peonidin-3-arabinoside		[69]
	Petunidin Glycosides		
	Petunidin-3-galactoside		[70]
	Petunidin-3-arabinoside		[71]
Flavanols	**Myricetin Glycosides**		
	Myricetin-3-glucoside		[72]
	Myricetin-3-rhamnoside		[73]
	Quercetin glycosides		

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Table 1 (*continued*)

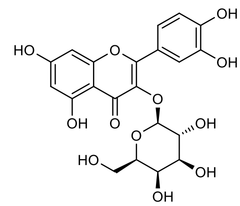
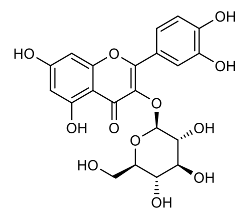
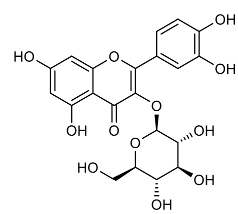
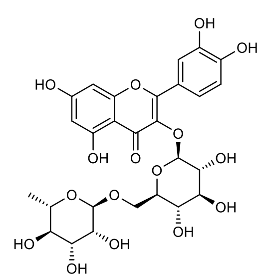
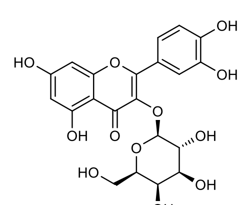
Bioactive Ingredients Class	Chemical Name	Chemical Structure	Ref.
	Quercetin-3-galactoside		[70]
	Quercetin-3-glucoside		[74]
	Quercetin-3-rutinoside		[72]
Others	**Malvidin 3-acetylglucoside**		
	Quercetin-3-*O*-rutinoside		[75]
	Quercetin-3-*O*-galactoside		[76]

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Table 1 (*continued*)

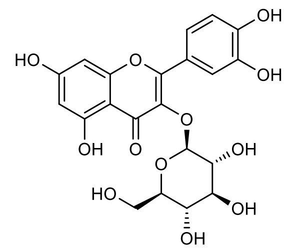
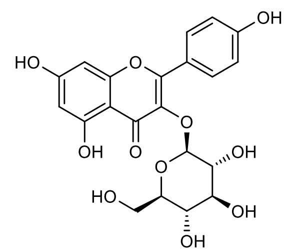
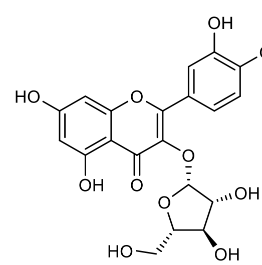
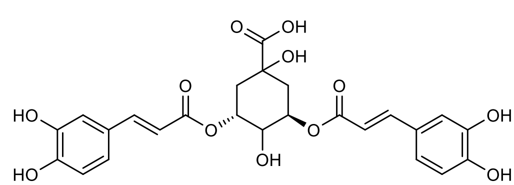
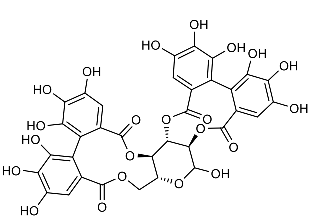
Bioactive Ingredients Class	Chemical Name	Chemical Structure	Ref.
	Quercetin-3-*O*-glucoside		[77]
	Kaempferol-3-*O*-glucoside		[78]
	Quercetin-3-*O*-diglycoside Quercetin 3-*O*-arabinoside		[79]
	3,5-dicaffeoylquinic acid		[80]
Elagitannins	Pedunculagin		[81]

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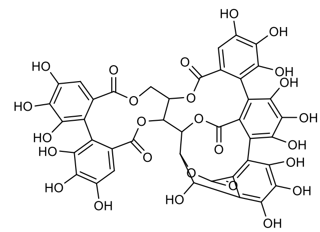
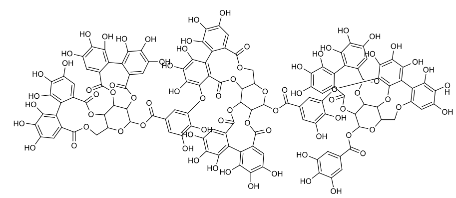
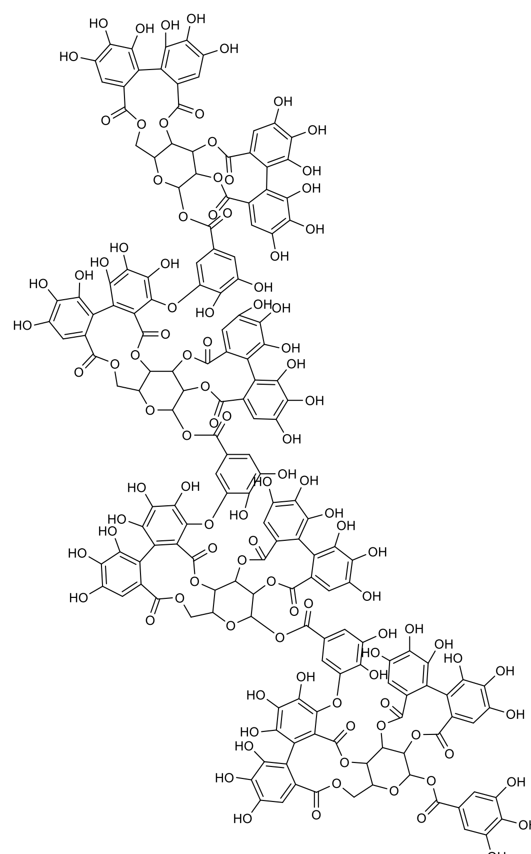
Table 1 (*continued*)

Bioactive Ingredients Class	Chemical Name	Chemical Structure	Ref.
	castalagin/vescalagin Galloyl-HHDP		[82]
	lambertianin C		[83]
	lambertianin D		[84]

(*continued on next page*)

Table 1 (*continued*)

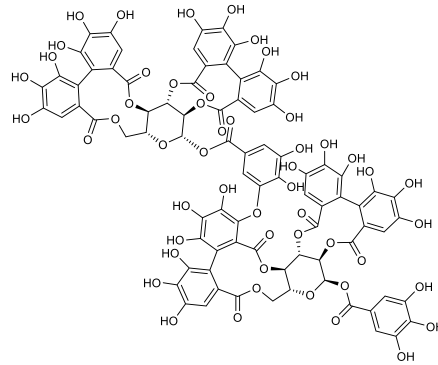
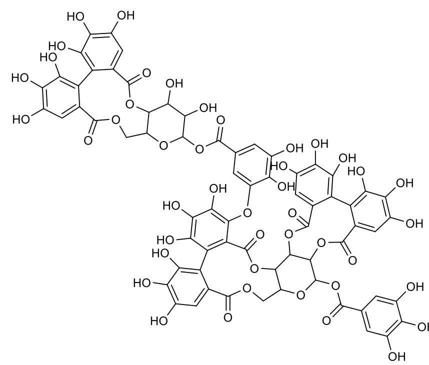
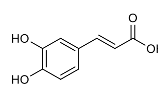
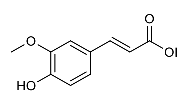
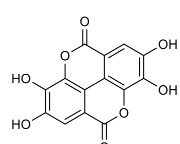
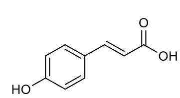
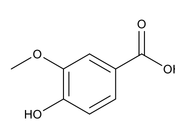
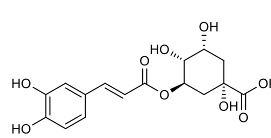
Bioactive Ingredients Class	Chemical Name	Chemical Structure	Ref.
	sanguiin H-6		[85]
	sanguiin H-10		[83]
Phenolic Acids	Caffeic		[86]
	Ferulic		[87]
	Ellagic		[88]
	P-Coumaric		[89]
	Vanillic		[90]
	Chlorogenic		[91]

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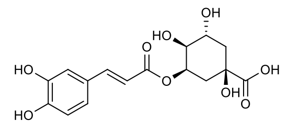
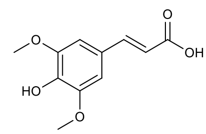
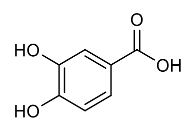
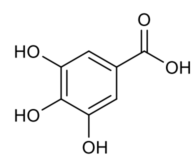
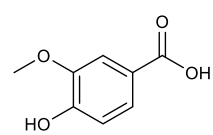
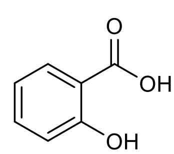
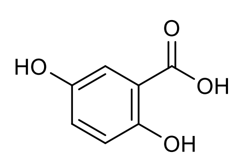
Table 1 (*continued*)

Bioactive Ingredients Class	Chemical Name	Chemical Structure	Ref.
	Neocholorogenic		[92]
	Sinapic		[93]
Hydroxybezoic acids	Protocatechuic		[94]
	Gallic		[95]
	Vanillic		[90]
	Salicylic		[96]
	Gentisic		[97]

SCC131 oral cancer cell line. These inhibitors functioned by interrupting the JAK/STAT-3 signaling pathway, consequently impacting downstream targets that regulate cell proliferation and apoptosis [117].

5.3. Benefits of metabolic disorders

5.3.1. Obesity

Monocyte infiltration into adipose tissue, an obesity-related phenomenon, leads to inflammation and is connected to metabolic issues. Inhibiting insulin signaling within adipocytes reduces insulin-induced glucose uptake and increases glycerol release from these adipocytes [118]. Anthocyanins derived from alcohol-fermented blueberry beverages have demonstrated the capacity to enhance insulin uptake. Moreover, blueberry polyphenols have the potential to substantially curtail adipogenesis and cell proliferation [119]. When mice on a high-fat diet had blueberry leaf extract, their body weight decreased by 20 %, their insulin sensitivity increased, and they were prevented from becoming obese [110]. However, blueberry extract also acts as an effective treatment for obesity-related conditions [120]. Increased intake of wild blueberries resulted in a notable reduction in fatty acid synthase expression in both liver and abdominal adipose tissue [121]. Nevertheless, freeze-dried blueberry powder presents a viable option for managing and preventing chronic conditions associated with obesity and diabetes, emerging global health challenges [120]. The potential metabolic pathways involved in the mechanisms underlying the impact of blueberries on obesity, inflammation, and diabetes are depicted in Fig. 3.

5.3.2. Type-2 diabetes

In rats with metabolic syndrome and obesity, eating wild blueberries

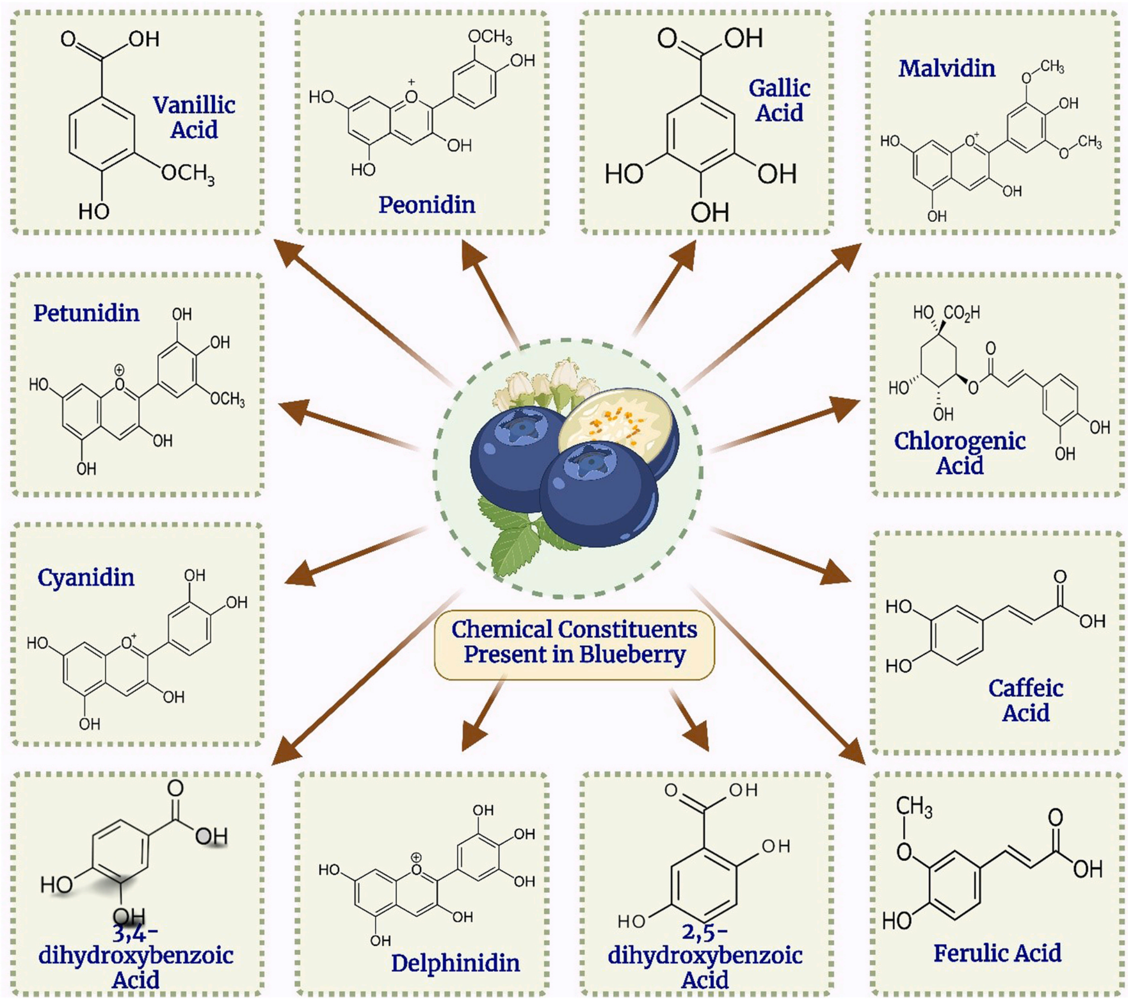


Fig. 1. Major active bio-constituents are present in blueberry.

is related to glucose metabolism [122]. The endothelial dysfunction caused by lipid toxicity is lessened, and the vascular problems related to diabetes are reduced by the metabolism of blueberry anthocyanins [65]. As certain of its metabolites can replenish cell surface glycosaminoglycans and lessen endothelial inflammation, blueberries can lessen vascular problems associated with diabetes [123]. Diabetes and its consequences are significantly influenced by oxidative stress; however, type 1 diabetics can be treated with a blueberry diet [110]. The anti-diabetic and anti-glucolipotoxic effects of anthocyanin-rich wild Chinese blueberries have been reported [124]. The hepatic steatosis and glucose intolerance that are linked to the gene expression of hepatic fatty acid oxidation are prevented by blueberries [110]. However, dietary blueberries can fight obesity-related pathology [125]. Adipose inflammation encourages insulin resistance and other problems. The postprandial glucose response can be moderated by an anthocyanin-rich food, which has implications for type 2 diabetes and cognitive studies [110]. In rats fed a high-fat diet, adding blueberries to the diet improves insulin signaling, overall inflammation, and gut microbiome alterations [126]. The multi-organ influence of blueberries on the evolution of type 2 diabetes mellitus (T2DM) is shown in Fig. 4.

5.4. Chronic inflammation

Blueberry extract is recognized for its antibacterial and anti-inflammatory attributes, primarily attributed to its phenol (6.6 %), flavonoid compound (12.9 %), and procyanidins (2.7 %) content [127]. Consumption of blueberries, particularly those rich in anthocyanins, can lead to a rapid increase in anti-inflammatory cytokines and a reduction in oxidative stress. Interestingly, malvidin-3-glucoside exhibits a more potent anti-inflammatory effect compared to malvidin-3-galactoside despite blueberries being employed as a functional food to mitigate chronic inflammation [110]. In the metabolic syndrome, eating wild blueberries generally reduces inflammation [128].

5.5. Neuroprotection

In the D-galactose-treated rat brain, whole, fresh blueberries alleviated histopathological results and decreased apoptosis [129]. The primary route for the biosynthesis of ascorbic acid in blueberry fruits is the l-galactose pathway. This pathway is associated with the elevated expression of five genes, namely guanosine diphosphate-mannose-3′, 5′-epimerase (GME), guanosine diphosphate-l-galactose phosphorylase (GGP), l-galactono-1,4-lactone dehydrogenase (GLDH), mono-dehydroascorbate reductase (MDHAR), and dehydroascorbate reductase (DHAR). These genes play a crucial role in the production of ascorbic acid in blueberry fruits. [110]. Through the reduction of oxidative stress content and inflammation, improvement of neuronal signaling, and enhancement of neuronal functions when exposed to high-energy particles, diets containing blueberry anthocyanins for animals may serve as a means to mitigate the effects of irradiation [130]. In healthy older individuals, anthocyanins from blueberries increase brain activity and perfusion, which enhances cognitive function [110]. Glucocorticoids, which have neuroprotective and antagonistic effects, and the mono-aminergic systems they regulate may facilitate the antidepressant-like

Table 2
Mechanism of action of different phytoconstituents present in Blueberry for the treatment of various chronic illnesses.

Chronic illnesses	Phytoconstituents	Mechanism of action	Ref.
Cognitive Performance	Polyphenols	Food polyphenols can alter neuronal functioning. Neurotoxins, neuroinflammation, and/or certain genetic abnormalities can cause neuronal death in conditions associated with aging and neurodegenerative disorders. Apoptosis pathways are activated, oxidative stress levels rise, and protein aggregates and DNA damage are all promoted by initiating factors. In the hippocampus of APP/PS1 swiss albino mice, the ingestion of blueberry extracts controls the expression of certain proteins (such as dynamin 1), which is associated with improved cognitive impairment. An increase in the hippocampal nerve growth factor's mRNA expression and the inhibition of protein/serine-threonine kinase signaling are what cause polyphenols to ameliorate cognitive decline.	[160]
Anticancer	Phenolic acids, pyruvic acid, anthocyanins, pterostilbene	Blueberry plant extracts demonstrate anti-AML (acute myeloid leukemia) properties when tested against ML cell lines. These effects are particularly pronounced within the leukemia stem cell subpopulation and are attributed, in part, to the regulation of extracellular signal-regulated kinase (Erk) and protein kinase B (Akt) (McGill CM et al., 2018). The anticancer properties of blueberries are linked to their antioxidant and anti-inflammatory capabilities. Furthermore, they exert control over cell proliferation by overseeing signal transduction pathways. Blueberries' bioactive constituents effectively curb the growth and metastasis of breast cancer cells by modulating the PI3K/AKT/NF-κB pathway (Ma L et al., 2018); Blueberry anthocyanins have been found to impact the expression of caspase-9 and cytochrome *c*, along with reducing the methylation of p53. Together, these activities cumulatively impede proliferation, trigger G2/M cell cycle arrest, and stimulate apoptosis in oral cancer cells.	[161]
Anti-obesity	Polyphenols, Anthocyanins	Anthocyanins from blackberries and blueberries can reduce oxidative stress and inflammation while boosting energy expenditure to fight diet-induced obesity. By downregulating three particular genes and lowering levels of the adipogenic factor phospho-Akt, blueberry peel extracts effectively reduction weight gain and lipid accumulation in obese mice. Additionally, blueberries feature around 92 expressed genes involved in the antioxidant biosynthesis pathway. This intricate network includes 862 transcription factors and 1236 transcripts, collectively governing the levels of anthocyanins in the fruit as it undergoes ripening.	[110, 162, 163]
Anti-diabetes	Polyphenols, Anthocyanins	Anthocyanins and polyphenols in blueberries are thought to have anti-diabetic properties; however, they work by increasing insulin secretion in the case of pelargonidin, lowering insulin resistance in the case of cyanidin-3-glucoside, and promoting the regeneration of beta cells	[110]
Neuroprotective	Polyphenols, Anthocyanins	Anthocyanins found in blueberries exert a neuroprotective mechanism by influencing the regulation of gene expression and signal transduction activities in the brain. Such compounds, encompassing anthocyanins and flavanols, possess the ability to permeate the brain and ameliorate alterations in spatial working memory, especially in elderly animals. The outcomes are attributed to the influence of flavonoids on the extracellular signal-related kinase, cAMP-response element-binding protein, and brain-derived neurotrophic factor pathways. Additionally, by enhancing mitochondrial activity and reducing	[110, 164, 165]

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Table 2 (*continued*)

Chronic illnesses	Phytoconstituents	Mechanism of action	Ref.
		intracellular reactive oxygen species (ROS) production and lipid peroxidation, especially in response to H2O2, and by boosting the activity of catalase (CAT) and superoxide dismutase (SOD), cyanidin and cyanidin-containing compounds derived from blueberries may effectively alleviate oxidative stress in neural cells.	
Anti-inflammation	Phenolic acids, Anthocyanins, flavonoids	Blueberry proanthocyanidins represent promising candidates for potential therapeutic agents due to their remarkable properties. These compounds possess the ability to neutralize leukotoxins, exhibit antibacterial effects, and demonstrate anti-inflammatory activities, collectively safeguarding the oral keratinocyte barrier. (Ma L et al., 2018). The nuclear factor-kappa B pathway controlled the anti-inflammatory effects of blueberry with malvidin-3-glucoside and malvidin-3-galactoside in endothelial cells.	[166]
Antioxidant	Polyphenols, anthocyanins, chlorogenic acid	Anthocyanins (malvidin-3-glucoside)/phenolic metabolism inhibited by methyl jasmonate	[110]
Ophthalmol-protective	Polyphenols, Anthocyanins	Against light-induced retinal damage in the eyes, blueberry polyphenols offer retinal protective action (Ma L et al., 2018). Due to their ability to activate Akt signaling pathways and reduce vascular endothelial cell growth factor levels, blueberry anthocyanins proactively contribute to maintaining eye health by averting the onset of age-related macular degeneration. Human retinal capillary endothelial cells are shielded by blueberry anthocyanins via antioxidant and anti-inflammatory processes, which also help to prevent diabetic retinopathy.	[110, 167]
Prevent cardiovascular diseases	Flavonoid, phenolic acids,	In adult cardiomyocytes, blueberry polyphenols inhibit norepinephrine-induced cell death and hypertrophy. The redox enzymes that control the formation of reactive oxygen species from mitochondria, NADPH oxidases, and uncoupled endothelial NO synthase as well as the up-regulation of several antioxidant enzymes are thought to be responsible for polyphenol's antioxidant effects. Blueberry anthocyanins function in preventing cardiovascular diseases through their regulation of Nrf2-mediated antioxidant response proteins in vascular endothelial cells and their inhibition of soluble angiotensin-converting enzyme activity.	[110]
Anti-hypertensive	Anthocyanins, procyanidin, polyphenols	Thanks to their capacity to lower soluble angiotensin-converting enzyme activity, blueberries rich in dietary flavonoids are remarkably effective in managing essential hypertension. Due to their anti-inflammation and antioxidant properties, blueberry anthocyanins are effective at preventing cardiac disorders.	[168]
Hepatoprotective	Polyphenols, Anthocyanins	Inhibiting the activity of hepatic stellate cells, downregulating TIMP1, PCNA, Col-III, -SMA, and upregulating MMP-9 are some of the protective effects of blueberry anthocyanins on CCl4-induced hepatic fibrosis These effects are also associated with a decrease in ROS-producing sources and oxidative damage. Inhibiting hnRNP A2/B1 is how blueberry leaf oligomeric proanthocyanidin inhibits the function of the resistant hepatitis C virus. Through the signaling pathway involving phosphor-Janus kinase-1 and phosphor-signal transducer and activator of transcription-3, blueberry probiotics may combat non-alcoholic fatty liver disease.	[110, 169]
Antimicrobial	Polyphenols	Seven membrane gene's expression was altered by blueberry extract, which also compromised the integrity of cell membranes and prevented bacterial cells from developing correctly. Blueberry extract modifies gene expression patterns and compromises the integrity of cell	[150]

(*continued on next page*)

Table 2 (*continued*)

Chronic illnesses	Phytoconstituents	Mechanism of action	Ref.
		membranes in select strains of V. parahaemolyticus, rendering them unable to undergo proliferation.	
As prebiotics	Polyphenols	In C57BL/6 J mice, blueberry polyphenols extract may have anti-obesity effects by modifying the gut flora.	[170]
Reno-protective	Polyphenols	The consumption of blueberries (BB) safeguards against chronic kidney disease within the Zucker rat model of metabolic syndrome. This protection is achieved by diminishing the expression of TLR4 and alleviating oxidative stress in the renal tissues. 1) In MetS animals with chronic kidney failure, TLR4 signaling, and the accompanying inflammatory cascade induce renal impairment; 2) One possible mechanism for the development of chronic kidney damage in MetS is the activation of ERK and p38 MAPK by TLR4; 3) By blocking TLR4 and therefore reducing MAPK activity, BB can prevent chronic kidney injury in MetS rats; and 4) BB can reduce further MetS risk factors. A significant step in the development of new treatment approaches could be made possible by BB's capacity to suppress TLR4.	[54]
Osteoprotective	Anthocyanins	Due to decreased collagen type I and alkaline phosphatase mRNA levels in the femoral region, blueberries can reduce bone loss and enhance bone mineral density during bone metabolism	[171]
Anti-aging	Polyphenols, phenolics	Numerous animal species' lifespans have been demonstrated to be increased by reducing ROS which also lessens oxidative damage. Because of their ability to scavenge ROS and have anti-aging potential, phytonutrients with antioxidant properties have attracted a lot of research. Of all naturally occurring antioxidants, polyphenols are the most prevalent and extensively researched. Among polyphenols' possible anti-aging mechanisms is enhancing mitochondrial function, concentrating on microRNA, affecting NO bioavailability, avoiding cellular senescence, and, antioxidant signaling.	[172]
As Food Value	Anthocyanins and polyphenols	Numerous novel food products featuring blueberries are currently available on the market, including blueberry fruit juice, wine, vinegar, jam, dried fruit, pulp powder, and additives for color and flavor in items like cakes, biscuits, bread, yogurt, and jelly. These products are enriched with a variety of beneficial compounds from blueberries, such as anthocyanidins, flavonoids polyphenols, phenol, pyruvic acid, and chlorogenic acid. These substances have exhibited an extensive array of health advantages, encompassing their capacity to combat cancer, address obesity, thwart degenerative conditions, diminish inflammation, safeguard vision and liver well-being, fend off heart ailments, regulate diabetes, augment cognitive function, enhance brain function, bolster lung health, support bone strength, boost immunity, mitigate cardiovascular diseases, and promote overall well-being.	[159]

effects of blueberry extract [131].

By boosting antioxidant ability and changing stress signaling, cyaniding-3-*O*-galactoside, a component of blueberries, can preserve the central nervous system and improve cognitive and behavioral performance as people age. Elevated neuronal signaling within the brain, responsible for regulating memory function, glucose disposal, and the postponement of neurodegeneration, has been associated with both blueberry anthocyanins and the ethyl acetate fraction derived from blueberry leaves. Enhancing the antidepressant effect through the induction of miR-155-regulated brain-induced neurotrophic factor [110]. In this at risk population, increased brain activity from blueberries demonstrates neurocognitive benefits. Boespflug EL Anthocyanin, eicosapentaenoic acid, and docosahexaenoic acid are the main components of blueberries that have neurocognitive advantages. The anti-A fibrillation, glycosylation resistance, reactive carbonyl, and microglial neuroprotective actions of six berry extracts, especially blueberry anthocyanins, are effective against the development of Alzheimer's [110]. The reactive oxygen species (ROS) that cause oxidative stress may be the target of polyphenols. (1) Lower levels of damage-associated molecular patterns (DAMPs) may result from reducing ROS; (2) IKK phosphorylation may also be stopped by reducing ROS, which would prevent IB from dissociating from NF–B; and (3) ROS may directly phosphorylate IB, which polyphenols may suppress. Without these pathways, NF–B could not cross the nucleus [132].

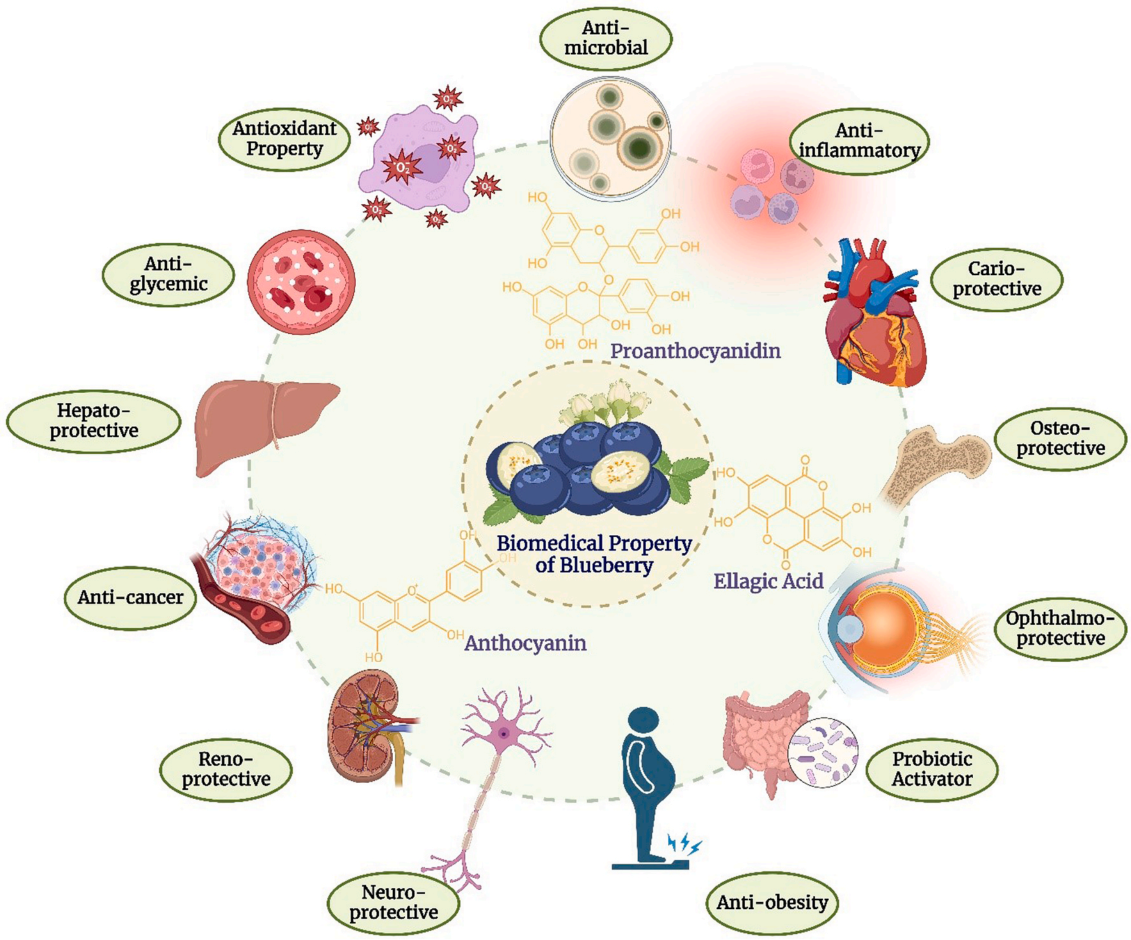

Fig. 2. Role of major active chemical constituents of blueberry in health benefit.

5.6. *Miscellaneous applications*

5.6.1. *Antioxidant effects*

The blueberry's antioxidant and glucosidase inhibitory properties are excellent [133]. Blueberry juice contains anthocyanins, linked to antiproliferative and antioxidant properties; regular consumption of blueberries helps prevent several degenerative illnesses. Anthocyanins can weaken the capabilities of malvidin, superoxide dismutase, and heme oxygenase-1 (HO-1), as well as reactive oxygen species (ROS) and xanthine oxidase-1 (XO-1). Blueberries grown in Suwon contain high anthocyanin and polyphenol content in four cultivars (Elliott, Rubel, Rancocas, and Friendship), with vigorous antioxidant activity [110]. Chlorogenic acid, which lowbush blueberries contain at 0.44 mg/g, mediates the anti-inflammatory effects of the phenolic acid combination by regulating nuclear factor-B activation and inducing the production of inflammatory cytokines at high doses [134]. The antioxidant biosynthesis pathway, which involves 862 transcription factors and 1236 transcripts, engages approximately 92 expressed genes in the blueberry [110].

These genes control the levels of anthocyanins in the fruit as it ripens. Longevity and morbidity rates have been shown to increase with a diet high in fruits and vegetables. The supplementation of polyphenols offers various health-promoting effects, particularly in the elderly population, as shown by extensive dietary intervention studies in humans. Various natural and synthesized phenolic compounds have been used in vitro studies on the anti-aging properties of polyphenols and phenolic chemicals [135]. It is generally accepted that a disturbed balance between oxidants and antioxidants would result in cellular damage and potential organ malfunction (Elks CM et al., 2011), notwithstanding the decade-long controversy surrounding the free radical theory of aging [136]. Antioxidants neutralize the harmful effects of oxidants by joining with pro-oxidants and absorbing hydrogen to create stabilized radicals (Nair AR et al., 2014). They also fight against aberrant oxidative stress and the buildup of excess oxidants, such as ROS, which cause DNA damage [137] and cellular senescence [138]. The aging process and several chronic disorders linked to aging are significantly influenced by oxidative stress.

5.6.2. *Ophthalmoprotective effects*

A total of thirteen anthocyanins were detected in wild Chinese blueberries. Among them, malvidin, which imparts a blue hue, was found to be glycosylated with either hexose ($C_6H_{12}O_6$) or pentose. This particular anthocyanin accounted for more than 46 % of the overall anthocyanin and total polyphenol levels. The chemicals were discovered to improve animal eyesight by 0.60 % and 0.18 %, respectively [139]. Ingesting anthocyanin blueberries enhanced the speed of visual acuity recovery after photobleaching [110]. Anthocyanins, found in berries, are particularly advantageous in avoiding retinal diseases. One specific molecule, cyanidin-3-glucoside, is especially effective [140].

5.6.3. *Cardioprotective effects*

Anthocyanins from blueberries decreased oxidative stress, cardiomyocyte apoptosis, and cyclophosphamide-induced cardiac damage [110]. Procyanidin-rich blueberry pomace has been shown to protect against diabetes, obesity, and coronary heart disease [141]. However, procyanidin monomer and dimer concentrations can increase during extrusion processing.

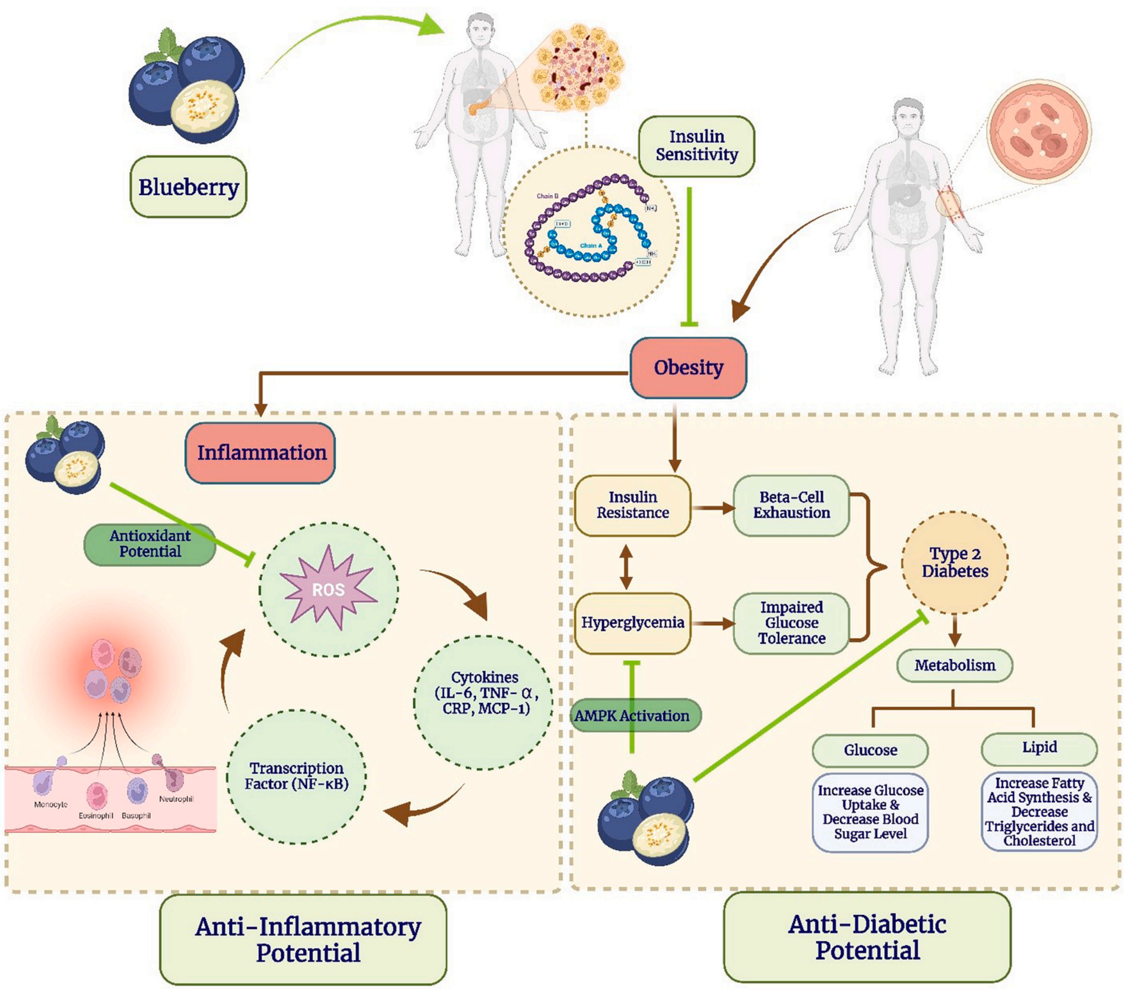

Fig. 3. The potential metabolic pathways implicated in the mechanisms underlying the impact of blueberry on obesity and its associated comorbidities are as follows: Blueberry may exert inhibitory effects on obesity and type 2 diabetes by enhancing the regulation of hyperglycemia through the activation of 5′ adenosine monophosphate-activated protein kinase (AMPK) and the augmentation of insulin sensitivity. These inhibitory effects may include the decrease in blood glucose levels, triglyceride levels, and total cholesterol levels, as well as the rise in glucose uptake, glucose tolerance, and fatty acid oxidation. Blueberry consumption has been proposed as having potential anti-inflammatory attributes through the inhibition of reactive oxygen species (ROS) generation, including hydroxyl radicals (OH) and superoxide radicals (H). Additionally, blueberries and their extracts exhibit strong antioxidant activity, which may contribute to the suppression of inflammatory cytokines including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor (TNF-x), and monocyte chemoattractant protein-1 (MCP-1). The nuclear factor-kappa B (NF-kB) pathway serves as a prominent signaling mechanism.

5.6.4. *Antihypertensive effects*

In both smokers and nonsmokers, blueberry polyphenols can control vascular remodeling and enhance endothelial function [110]. Fermented blueberries with antihypertension effects can decrease the risk of cardiovascular illnesses [142]. Vascular endothelial cells can be attracted by aglycone phenolic acids from blueberries, controlled by Nrf2 [110]. Due to their capacity to generate higher levels of nitric oxide compared to other fruits and vegetables, blueberries have demonstrated their potential to confer health advantages to humans. These benefits include reduced blood pressure, diastolic pressure, artery systolic pressure, arterial stiffness, and a lowered risk of various types of cancer.

5.6.5. *Hepatoprotective effects*

On the other hand, the oligomeric proanthocyanidin found in blueberry leaf can prevent the hepatitis C virus from expressing RNA. The hepatitis C virus, which is a member of the genus Hepacivirus and infects around 170 million individuals worldwide, has a high incidence of chronic hepatitis (>75 %). By exerting vigorous antioxidant activities and dramatically reducing DNA damage in hepatic cells, blueberry-rich diets significantly corrected the changes in the liver caused by acrylamide [110]. Anthocyanin from blueberries can prevent mitochondrial damage and even malfunction in mouse livers by inhibiting the production of reactive oxygen species.

The four enzymes that human hepatocytes and microsomes use for catalysis can be specifically inhibited by the anthocyanidins and anthocyanins found in blueberries. Notably, CYP450 was significantly inhibited by cyanidin-3-*O*-rhamnoside and two glycosides of delphinidin [110]. Blueberry polyphenols, particularly chlorogenic acid and flavonols, exert strong antioxidant protective effects (Ferlemi AV et al., 2015) and were linked to a redox response to a toxic selenite dosage in the rat brain and liver. The antioxidative, anti-inflammatory, and metal-chelating capabilities of blueberry extract make it an effective therapeutic agent for treating the tissue damage caused by Cd (II) on mouse livers (Ma L et al., 2018). The liver arginase activity and ornithine levels were dramatically reduced by the hepatoprotective effects of blueberry and chitosan, while nitric oxide and glutathione levels were elevated [143]. Rats afflicted with hepatic fibrosis could experience enhanced liver function and improved liver fibrosis indicators by modulating histone acetylation through the anthocyanins found in blueberries. These anthocyanins activate genes that promote apoptosis and mitigate the antihepatic fibrosis effects [144].

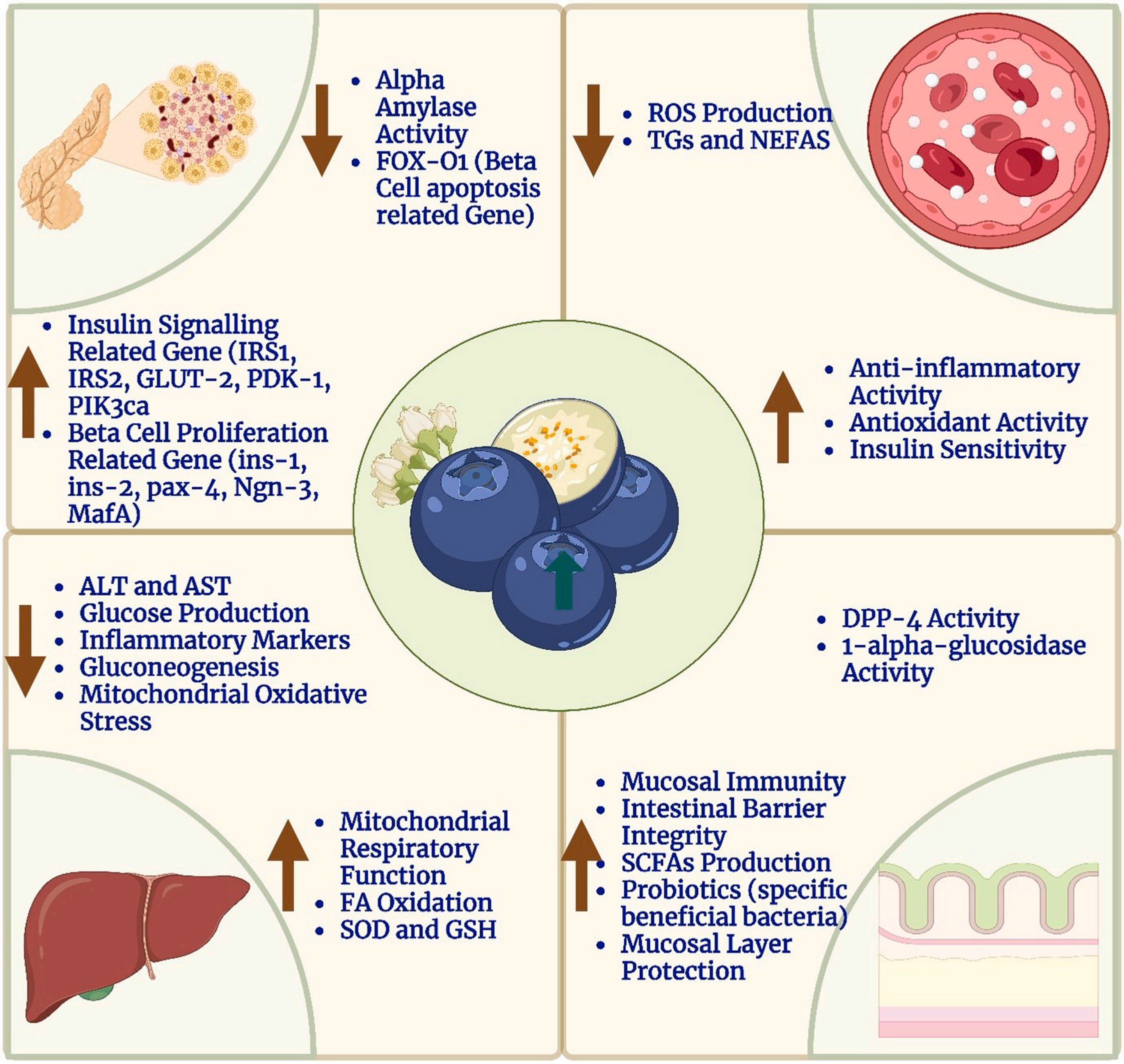

Fig. 4. The multi-organ influence of blueberry consumption on the advancement of type 2 diabetes mellitus (T2DM) is a multifaceted phenomenon with various functional properties. Preclinical and clinical investigations have shown a diverse array of systemic and tissue-specific (such as pancreas, liver, and gut) advantageous processes. These findings further establish BB as a compelling nutraceutical option for mitigating the transition from prediabetes to overt type 2 diabetic mellitus (T2DM).

5.6.6. Prebiotics

Prebiotics are beneficial for advancing human nutrition and health. Eating foods rich in polyphenols, like blueberries, offers health benefits. It is generally recognized that blueberry polyphenol extract (PPE) has potential as a prebiotic agent. Prebiotics are substances that the host cannot digest but that the probiotics can use and ferment to increase the growth and metabolism of intestinal probiotics for overall body wellness [145]. Probiotics have demonstrated their efficacy in clinical and healthcare settings for preventing or managing various conditions, including infections of the intestines, respiratory system, and urogenital tract, as well as allergic reactions, inflammatory bowel disease, irritable bowel syndrome, and other related ailments. Because the human colon lacks the enzymes required to hydrolyze the prebiotics' polymer bonds, prebiotics typically resist digestion in the small intestine. These prebiotics are transmitted intact by humans to the large intestine, where they are fermented and broken down by the intestinal flora to produce specific secondary metabolites [145]. These physiological processes regulate immunity, protect against infections, improve intestinal barrier performance, and increase bile production. Acetate, butyrate, and propionate are produced during the metabolism of the most prevalent SCFAs in the colon by helpful bacteria, which is advantageous for preserving intestinal and overall health [146].

Additionally, prebiotics stimulate the growth of target microbes, which is a unique benefit. By safeguarding or encouraging the creation of advantageous fermentation products, particular prebiotics (such as inulin, FOS, and GOS) can help the growth of beneficial flora to compete with other species [147,148]. The central neurological, immunological, and cardiovascular systems are just a few of the other body systems prebiotics protect besides the gastrointestinal system. In C57BL/6 J mice, blueberry polyphenol extract may have anti-obesity effects by modifying the gut flora.

5.6.7. Antimicrobial effects

A gram-negative bacterium called Vibrio parahaemolyticus typically adheres to or invades zooplankton, fish, shellfish, and other aquatic goods [149]. Infections caused by eating raw or undercooked seafood are also frequently linked to V. parahaemolyticus [150]. Adhesions, thermostable direct hemolysin (TDH), TDH-related hemolysin (TRH), and type III secretion systems are the main virulence factors in V. parahaemolyticus. When V. parahaemolyticus infects the small intestine of animal models, it becomes pathogenic and causes disease [151]. The type III secretion systems play a crucial role in the virulence of this organism. Instances of the V. aeruginosa foodborne illness have also been reported.

Currently, V. parahaemolyticus-related foodborne illnesses are a significant issue that endangers the public's health and food safety. V. parahaemolyticus can induce acute gastroenteritis with diarrhea, nausea, vomiting, low-grade fever, and abdominal pain after being consumed in large enough quantities. In addition, V. parahaemolyticus can result in septicemia and wound infections [152]. Antibiotic therapy is the most typical treatment for bacterial illnesses, but the rise of germs resistant to antibiotics is a big issue everywhere. Global health is seriously threatened by the high incidence of antibiotic resistance [150]. Scientists are looking at natural antibiotic alternatives to prevent and treat infections and diseases. According to Sun XH et al., 2020, blueberries have various favorable defensive characteristics and several chemicals that promote optimal health. In addition, blueberries may inhibit the growth of harmful microorganisms [153].

5.6.8. Renoprotective effects

A collection of health conditions known as metabolic syndrome (MetS) raises the possibility of renal failure and heart conditions. Obesity, diabetes, hypertension, and hyperglycemia are frequent conditions that lead to the development of MetS. When nutritional intake, sedentary behavior, glucose metabolism, and cardiac regulation are out of balance, MetS can ensue [154]. It is fascinating to note that each variable is essential for the kidneys to operate correctly. Renal damage may also result from oxidative stress brought on by excessive reactive oxygen species (ROS) or ineffective antioxidant systems [135]. The variables that cause MetS can be addressed with a wide variety of pharmacological therapies, which are replaced with herbal formulations, as more side effects are associated with these therapies. Antioxidant components, including phenolics and anthocyanins, are abundant in many fruits, notably berries, according to research [137]. The antioxidant capacity of blueberries (BB) (Vaccinium sp.) is the greatest among fruits [136]. The anti-inflammatory and antioxidant effects of BB are well established. Berries include antioxidants that can help reduce inflammation and oxidative damage. TLR4 activation regulates redox-sensitive molecules and the mitogen-activated protein kinase (MAPK) pathway, which causes inflammation-induced kidney damage. Proinflammatory cytokines (PIC) and renin-angiotensin system (RAS) components are produced at higher levels in hypertensive rats [135], and they also exhibit decreased oxidative stress and better nephropathy when fed a BB diet [136]. BB can prevent acute kidney injury due to LPS by regulating the expression of TLR4 [137].

5.6.9. Osteoprotective effects

Bone mineral density significantly differed at the distal epiphysis of the blue and blackberry fruits. This suggests that each fruit's anthocyanin content may affect bone turnover [110]. Myosin synthesis increases osteoblast development and slows interstitial cell senescence [155]. Promotes the molecular processes by which blueberries in the diet can prevent ovariectomy-induced bone loss in rats.

6. Food value and prospects of blueberries

The blueberry (*Vaccinium* spp.), regarded as the "king of the world fruit" and one of the top five healthy foods for people, has generated much interest in the photogenic prebiotics market. The popular blueberry fruit is prized for its mouthwatering flavor and a variety of therapeutic benefits (antioxidant, anti-inflammatory, anti-cancer, neuroprotective, and vision-improving characteristics) provided by its functional constituents, including organic acids, phenolics, minerals, and vitamins [156]. On the other hand, fresh blueberries have a short shelf life due to their susceptibility to mechanical damage and microbiological decomposition, which inevitably leads to financial losses. The derived bioactive compounds of blueberries have become functional foods due to their significant seasonal availability and short storage life. The blueberry's functional components provide the greatest health benefits.

To address the challenges posed by the short shelf life of fresh blueberries, several strategies can be implemented to improve efficiency and enhance the value of their application. One approach is utilizing innovative packaging technologies to extend shelf life and maintain fruit quality. Modified atmosphere packaging (MAP) and active packaging systems incorporating antimicrobial agents or oxygen scavengers can mitigate microbial growth and oxidative deterioration, prolonging blueberry freshness [156]. Additionally, postharvest treatments such as edible coatings enriched with natural antioxidants or bioactive compounds can create a protective barrier against physical damage and microbial spoilage while enhancing fruit preservation [157]. Furthermore, advancements in cold chain logistics and storage facilities equipped with controlled atmosphere storage and humidity control can optimize storage conditions, minimizing physiological deterioration and preserving blueberry quality during distribution and retailing [158]. By integrating these technologies and practices into the blueberry supply chain, stakeholders can improve efficiency, reduce losses, and enhance the overall value proposition of fresh blueberries.

We undertook systematic preventative measures for the functional elements in blueberries, based on thorough databases, to better understand the health role of blueberries in chronic disease [159]. Blueberries contain anthocyanins and polyphenols, which are major functional components for the prevention of chronic disease.

7. Blueberry combination and supplementation with foods

Krikorian and colleagues demonstrated that nine older patients suffering from dementia were being ingested blueberry juice, and in the twelfth week, they showed better learning because blueberries contain anthocyanin and other polyphenolic compounds. Anthocyanin is responsible for better memory function and increased glucose disposal, and it also shows some reducing effects in neurodegeneration [173]. Besides fruits, blueberry flowers are rich in polyphenols, which is why they are mixed with milk and probiotics to prepare blueberry yogurt. Blueberry flower pulp is compatible with yogurt, and it improves the consistency of the yogurt, increases the growth of *Lactobacillus plantarum* and *Streptococcus thermophilus*, and promotes amino acid production [174]. Goat milk yogurt is supplemented with Aronia juice and blueberry juice, which improves the growth of lactic acid bacteria, and the unsaturated fatty acid content was increased from 6.9 to 8.5 % compared with the control group [175].

Scientists investigated and showed that the addition of 25 % blueberry and black current powder to the oat bran paste increased the IC50 by increasing the α-amylase and α-glucosidase inhibitory effects; thus, blueberry supplementation with oats can show a better antidiabetic property [176]. Researchers utilized lipopolysaccharide-stimulated RAW264.7 macrophages to examine the intracellular antioxidant activity of oatmeal paste containing blueberry powder. It was observed that this oatmeal paste, both before and after digestion, effectively prevented the macrophages from accumulating intracellular reactive oxygen species stimulated by lipopolysaccharide, thereby demonstrating its antioxidant potential [177]. Blueberry-fermented vinegar has been identified as possessing antioxidant and antimicrobial characteristics. For some decades, researchers have concluded that some cooked meat and fish foods contain carcinogenic heterocyclic amines. The epidemiological study reports evidence that the consumption of red meat can increase the risk of cancer. That is why a study performed by marinating the meat with blueberry juice and increasing the marination time reduced the heterocyclic amines, thus lowering the precipitating risk of malignancy.

8. Clinical manifestations of blueberry allergy

Nowadays, food allergies are considered one of the most problematic health hazards in the human population because of the more significant presence of allergens [178]. Recent research has classified food allergies into two categories. An IgE-mediated reaction causes the first category, and an immediate allergy occurs in the oral mucosa. Another category is pollen-mediated. Food allergens are resistant to heat and digestive enzymes [179]. In the case of food-mediated allergies, the condition initially remains a minor breathing problem but then worsens to anaphylaxis shock [180]. Gebhardt and colleagues have reported only a single case of blueberry-mediated allergy [181]. Like some other plants, blueberries also contain salicylates, which can cause allergies in some patients. Angioedema is a common allergic reaction that occurs as symptoms like swelling in the face, lips, tongue, and throat. This angioedema is an IgE-mediated immune reaction that is severe and can be fatal [182]. Scientists Wolbart and Baldwin demonstrated through the results of IgE RUST testing that fresh blueberries showed very few but actual cases of allergic reactions [183].

9. Role of blueberry in various disease models

9.1. Blueberry phytochemicals in cardiovascular models

Blueberries are rich in phytochemicals, particularly anthocyanins, which offer a range of cardiovascular benefits. These compounds actively combat cholesterol-triggered atherosclerosis, mitigate oxidative stress, quell endothelial inflammation, and shield against ischemic damage. They also bolster cardiomyocyte survival and counteract age-related cognitive decline. Blueberry consumption holds immense promise for supporting cardiovascular health, with studies such as those by Ref. [184] demonstrating their multifaceted potential. Beyond anthocyanins, various phenolic acids in blueberries contribute to cardiovascular well-being. Chlorogenic acid, protocatechuic acid, rosmarinic acid, ferulic acid, ellagic acid, gallic acid, vanillin acid, and caffeic acid have shown diverse mechanisms in cardiovascular models, influencing aspects such as inflammation, oxidative stress, blood pressure regulation, endothelial function, and cardiac protection. These findings underscore the potential of blueberry phytochemicals as a valuable dietary approach for cardiovascular health promotion and risk reduction (Table 3) [185].

Phenolic acids, abundantly present in various fruits, including blueberries, exhibit remarkable potential for modulating cardiovascular health (Table 4). These compounds have garnered attention for their diverse protective effects across a spectrum of cardiovascular models. We will talk about the many roles that phenolic acids like protocatechuic acid, rosmarinic acid, chlorogenic acid, gallic acid, ferulic acid, ellagic acid, vanillic acid, and caffeic acid play, focusing on how they work and how they affect heart health.

9.2. Blueberry phytochemicals in oxidative stress models

Oxidative stress primarily shapes chronic illnesses, resulting from an imbalance between the body's antioxidant defense mechanisms and the reactive oxygen species (ROS) حقخیعزفهخد. Environmental factors, lifestyle choices, and underlying pathologies fuel this state by amplifying ROS production, surpassing the cellular defense capacity, and triggering a cascade of damaging events. Protein and nucleic acid oxidation, as well as lipid peroxidation, impair critical cellular processes, including enzymatic functions, DNA stability, and cell viability. In this intricate web, oxidative stress interconnects with inflammation, as inflammatory cells release cytokines and chemokines that further stimulate ROS production. As a result, ROS activate proinflammatory pathways such as NF-κB, which maintain oxidative and inflammatory stress [203]. This unfavorable environment facilitates the progression of chronic ailments, encompassing cancer, cardiovascular disorders, neurodegenerative conditions, and more. Blueberry phytochemicals have emerged as promising contenders in the fight against oxidative stress. Researchers have shown over and over again that blueberry extracts and phenolic fractions can reduce the damage caused by oxidative stress in different cell models. The protective effects primarily manifest as a reduction in ROS formation, increased scavenging activity, and mitigation of lipid peroxidation. These benefits are particularly apparent in neuronal cells treated with blueberry juice and Caco-2 cells exposed to polyphenol-rich blueberry extracts [204].

Table 3
Various Phytochemical role in Cardiovascular Model.

Chemical Name	Study Description	Ref.
Blueberries (Anthocyanins)	Actively combat cholesterol-triggered atherosclerosis, mitigate oxidative stress, quell endothelial inflammation, shield against ischemic damage, bolster cardiomyocyte survival, and counteract age-related cognitive decline.	[186]
Flavonoids in General	Demonstrate antihypertensive, anti-oxidative, antidiabetic, anti-obesity, anti-inflammatory, anti-hyperlipidemic, and anti-cholesterol emic effects, enhance cardiovascular biomarkers and lower blood pressure.	[187]
Flavanols, Anthocyanidins, Proanthocyanins, Flavones, Flavanones, Flavanols	Consumption is associated with reduced CVD risk, particularly for flavonols with a dose-response reduction in risk, and a notable decrease in CVD mortality with flavonoid-rich diets.	[188–190]
Flavonoids	Improves vascular function, potentially contributing to CVD prevention, in overweight men.	[191]
Quercetin	Demonstrates cardio-protective properties against heart injury in rat studies.	[192]
Puerarin	Exhibits potential for suppressing atherosclerosis.	[193]
Baicalin	Displays protective effects against atherosclerosis and myocardial ischemic injury in animal models.	[194]
Luteolin	Improves systolic and diastolic function in rat hearts subjected to ischemia/reperfusion.	[110]

While the upregulation of antioxidant enzymes plays a role, it does not solely account for the observed effects. The complex regulatory network through which blueberry compounds interact with antioxidant enzymes and metabolite derivatives makes them even better at fighting free radicals. Notably, the impact of blueberry compounds extends to DNA protection against oxidative damage, demonstrating shielding against oxidative stressor-induced DNA damage. Anthocyanin fractions in blueberries have shown considerable promise in protecting DNA integrity and reducing cell death in liver and pulmonary epithelial cells, especially when exposed to light or ionizing radiation. Even though there were differences between cell types and stressors, the overall trend shows that blueberry phytochemicals help fight oxidative stress and protect vital parts of cells needed for health.

Blueberries may be a natural way to boost antioxidant defenses and lower the risk of chronic diseases linked to oxidative stress by changing key pathways, such as NF-κB. In this work, we summarize the proposed cellular regulatory mechanisms for blueberry extracts and their impact on inflammatory and oxidative stress pathways. The investigation primarily focuses on cell-based models to elucidate these processes. Tables 5 and 6 depict the role of phytoconstituents in blueberry and phenolic compounds on oxidative stress, respectively. Fig. 5 concisely overviews the cellular regulatory mechanisms hypothesized for blueberry extracts and their effects on inflammatory and oxidative stress pathways.

Table 4
Phenolic acids on cardiovascular models.

Chemical Name	Study Description	Ref.
Gallic Acid	Collaborates with calycosin to attenuate myocardial infarction-induced neutrophil infiltration and MPO activity, improves endothelium-dependent vasorelaxation, and mediates antihypertensive effects. Counteracts metabolic alterations, oxidative stress, and inflammatory markers.	[195]
Protocatechuic Acid	Modulates inflammatory mediator expression inhibits monocyte adhesion, and exerts conflicting immunomodulatory effects.	[196]
Rosmarinic Acid	Ameliorates cardiac dysfunction, oxidative stress, and fibrosis. Alters ACE and ACE2 expression suppresses inflammation, improves vascular function, and decreases myocardial infarct size.	[197]
Chlorogenic Acid	Enhances NO production, antioxidant, anti-inflammatory, ACE inhibitory effects, preserves cell viability, reduces apoptosis, improves endothelial function, limits oxidative damage, and confers cardioprotective effects.	[193]
Ferulic Acid	Alters the expression of inflammatory mediators, improves lipid profiles, insulin sensitivity, blood pressure, and vascular function, and attenuates vascular remodeling.	[198]
Ellagic Acid	Decreases endothelial ROS levels, ameliorates vascular relaxation impairment, and improves ventricular remodeling. Improves blood pressure, and attenuates plasmatic alkaline phosphatase activity, calcium content, and vascular hypertrophy.	[199]
Vanillic Acid	Reduces infarct size, improves ventricular function, limits cardiac injury markers, ameliorates cardiac stress, and exerts anti-apoptotic effects.	[200]
Caffeic Acid	Exhibits vasorelaxation effects, increases NO release, angiogenesis, and proliferation, and inhibits leukocyte adhesion, and endothelial cell apoptosis. Attenuates lipid peroxidation maintains cell viability and alleviates ROS-induced damage.	[201, 202]

Table 5
Blueberry phytochemicals on oxidative stress models.

Chemical Name	Study Description	Ref.
Anthocyanins	Natural antioxidants with strong free radical scavenging ability, particularly anthocyanins with simple chemical structures show high antioxidant activity.	[204]
	Enhance antioxidant enzyme activity and efficiency of free radical scavenging, prevent radiation-induced damage	[205]
	Relieves liver ischemia–reperfusion effects induced by oxidative stress, induces antioxidant response element pathway.	[206]
Proanthocyanidins	Reduce ROS and nitrite levels in neutrophils and macrophages, inhibit myeloperoxidase activity, superior scavenging ability to vitamins C and E.	[207]
	Restore mitochondrial enzyme activities, maintain antioxidant enzyme levels, and decrease lysosomal enzyme activity. Maintain GSH, GPx, SOD, and CAT activities, and prevent oxidative damage. Maintain GSH, GPx, SOD, and CAT activities, and prevent oxidative damage.	[208]

9.3. Blueberry phytochemicals in inflammation models

Inflammation is a fundamental response of the body to various insults, yet when it becomes chronic or excessive, it can lead to a range of health issues, including skin disorders. Blueberry phytochemicals have emerged as promising agents for mitigating inflammation and promoting skin well-being. Anthocyanins, for instance, exhibit a multifaceted ability to modulate the expression of inflammatory cytokines and endothelial adhesion molecules (Table 7). By suppressing NF-κB activity and reducing levels of pro-inflammatory factors like MCP-1 and TNF-α, anthocyanins play a role in dampening the inflammatory response. Apigenin is another compound that comes from blueberries. It reduces inflammation by working with different signaling pathways, including PI3K/ERK/mTOR, JAK/STAT, and NF-κB. It also has antioxidant properties [123].

Table 6
Phenolic acids on oxidative stress models.

Chemical Name	Study Description	Ref.
Caffeic Acid	Demonstrates antioxidant activity through radical scavenging, contributing to the reduction of oxidative stress.	[178]
Ferulic Acid	Exhibits antioxidant properties, contributing to the mitigation of oxidative stress and its potential detrimental effects.	[209]
Gallic Acid	Functions as an antioxidant by engaging in radical scavenging activities, playing a role in attenuating oxidative stress.	[210]
Protocatechuic Acid	Contributes to the reduction of oxidative stress through its antioxidant properties, helping to counteract the harmful effects of ROS.	[211]
p-Coumaric Acid	Displays anti-oxidant effects, participating in the neutralization of radicals and alleviating oxidative stress in various systems.	[212]

On the other hand, baicalin shows that it can protect the skin from UVB-caused damage and lower inflammation by changing the activity of NF-κB, COX-1, and iNOS [210]. Quercetin can help stop the production of inflammatory enzymes like COX-2 and MMP-1 when UV light hits cells, and it can also slow down the aging process in different models [213]. Fisetin can stop enzymes like iNOS and MMPs from working and make the skin make more protective proteins. This helps protect against photo-inflammation and dryness [214]. Caffeic acid's ability to quell neuroinflammation and ferulic acid's influence on brain regions associated with mood disorders demonstrate that the effects of blueberry phytochemicals extend beyond the skin. Additionally, gallic acid reduces cytokine levels in microglia cells and safeguards neurons against neurotoxicity. These findings collectively underscore the potential of blueberry-derived compounds as versatile agents for counteracting inflammation and promoting overall health.

9.4. Blueberry phytochemicals in neuroinflammation models

Neuroinflammation, a complex immune response within the central nervous system (CNS), is instigated by factors like infection, brain injury, autoimmunity, and aging. Activated microglia and astrocytes release pro-inflammatory molecules, causing tissue dysfunction and contributing to brain disorders. Anthocyanins and proanthocyanidins emerge as potential mitigators of neuroinflammation. Anthocyanins display antioxidant and anti-inflammatory properties, with data suggesting their ability to attenuate chronic inflammatory states in neurological conditions [220]. Proanthocyanidins, which can cross the blood-brain barrier, promote functional recovery in spinal cord injuries and inhibit apoptosis. Neuroinflammation is pivotal in various brain disorders, including Alzheimer's, Parkinson's, and autism [221]. Anthocyanins have exhibited neuroprotective potential by down-regulating neuroinflammatory processes. Flavonoids, such as baicalin, morin, quercetin, and kaempferol, have been shown to reduce inflammation in the brain by changing several pathways, including the NLRP3 inflammasome, MAPKs, and NF-κB [222]. Although the focus has mainly been on flavones and flavonols, these flavonoids exhibit common mechanisms for countering neuroinflammation [223]. Phenolic acids like caffeic acid, ferulic acid, and gallic acid also show neuroprotective traits. Caffeic acid reduces neuroinflammation and oxidative stress, while ferulic acid influences mood-related neurotransmitters [225]. Gallic acid's inhibition of NF-κB and cytokines rescues cognitive deficits in an Alzheimer's model [226]. Table 8 illustrates the role of blueberries' phytoconstituents in managing neuro-inflammation.

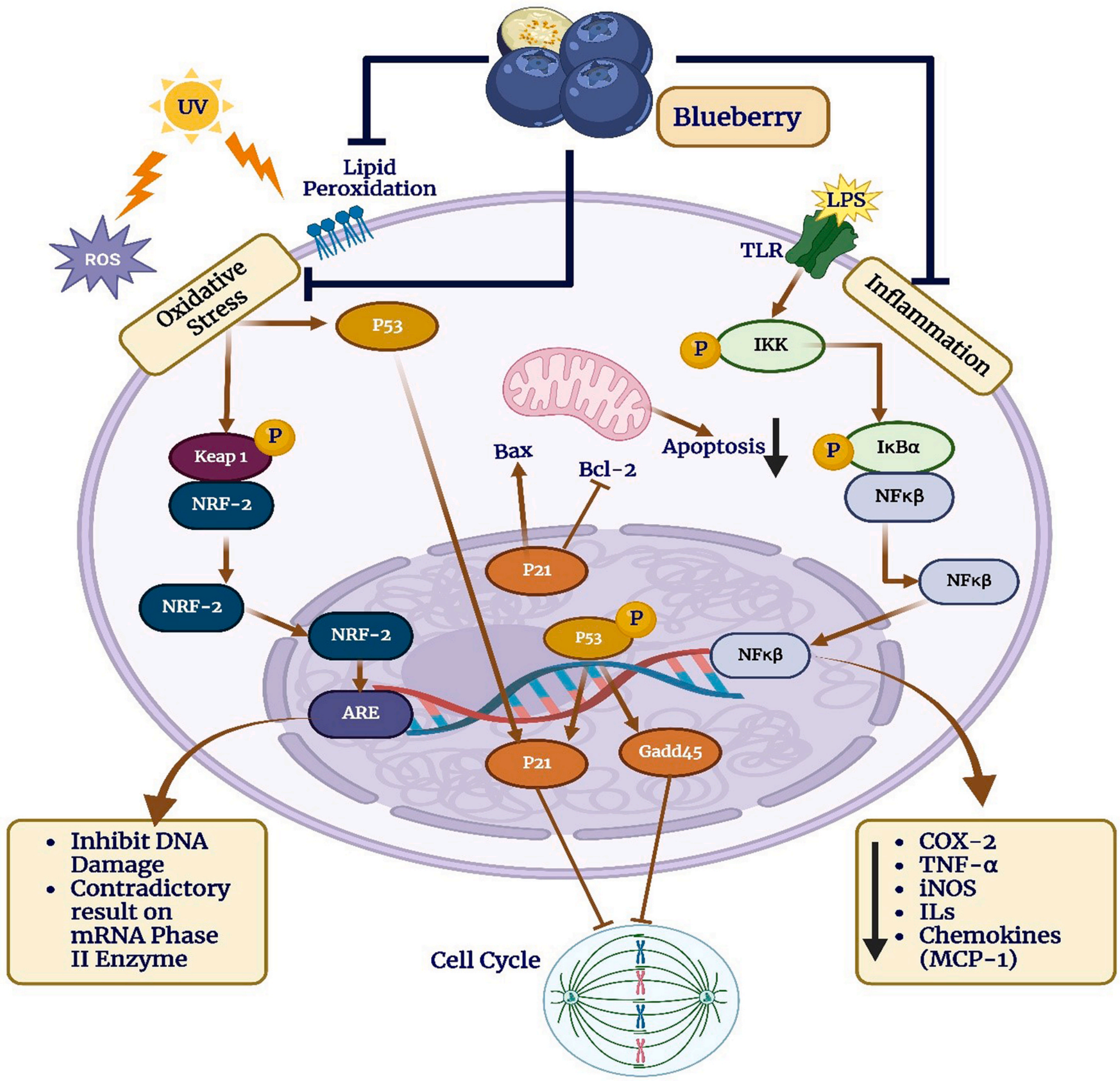

Fig. 5. The concise overview of the cellular regulatory mechanisms hypothesized for blueberry extracts in relation to their effects on inflammatory and oxidative stress pathways. The investigation primarily focuses on cell-based models to elucidate these processes. The abbreviations used in this study are as follows: ARE, which stands for antioxidant response element; Bax, which refers to Bcl-2-associated X protein; Bcl-2, which represents B-cell lymphoma 2; COX-2, which denotes cyclooxygenase-2; IKK, which stands for inhibitory kappa B kinase; iNOS, which refers to inducible nitric oxide synthase; and Ik Ba, which represents inhibitor of nuclear factor kappa B-alpha. The abbreviations used in the text are as follows: Keap-1, which stands for Kelch Like erythroid-derived CNC homology Associated Protein 1; Nrf-2, which refers to nuclear erythroid 2-related factor 2; P, which denotes phosphorylated; and TLR, which stands for toll-like receptor.

9.5. Blueberry phytochemicals in dermal inflammation models

Dermal inflammation is a complex physiological response to various external and internal factors, often leading to skin damage and compromised healing processes. The modulation of this inflammatory response is crucial for maintaining skin health and promoting effective wound healing [228]. Blueberry phytochemicals like apigenin, baicalin, quercetin, and fisetin have shown great promise in reducing inflammation in the skin and speeding up the healing process [229]. With its multifaceted properties, including induction of apoptosis and inhibition of proliferation and angiogenesis in cancer cell lines, Apigenin plays a pivotal role in dampening inflammatory processes [230]. Baicalin's ability to protect against UVB-induced photodamage and its anti-inflammatory effects through the modulation of NF-κB, COX-1, and iNOS activity contributes to maintaining skin integrity [231]. By inhibiting UV-stimulated COX-2 and MMP-1 expression and its combination with dasatinib to eradicate senescent fibroblasts, quercetin shows the potential to mitigate age-related skin alterations (Shin et al., 2019). Fisetin can help protect against skin inflammation and dryness by stopping key enzymes like iNOS, MMP-1, MMP-2, and COX-2 from working. It can also boost the expression of skin proteins like filaggrin and aquaporins [232]. These blueberry phytochemicals are a promising avenue for developing interventions that can mitigate dermal inflammation, accelerate wound healing, and support overall skin health (Table 9).

10. Interaction of blueberries with different organ systems

Blueberries are called "superfoods" because of their abundant nutrient content, resulting in immense benefits to nutrition and the immune system [234]. Though they do not directly affect immune boosting, they contain many compounds that enhance immunological functions. Blueberries contain antioxidants, particularly anthocyanins, which give them vibrant color [235]. Antioxidants help to neutralize harmful molecules called free radicals in the body, which can cause oxidative stress and damage cells. By reducing oxidative stress, blueberries can help support the immune system's functioning and reduce inflammation [236]. Like other fruits, blueberries are not that rich in

Table 7
Blueberry phytochemicals on inflammation models.

Compound	Study Description	Ref.
Anthocyanins	Modulate inflammatory cytokine expression and mitigate endothelial adhesion molecule manifestation. Suppress NF-κB activity and reduce MCP-1 and TNF-α levels. Reduce VEGF and ICAM-1 expression on endothelial cells.	[215]
Apigenin	Promotes apoptosis, hinders proliferation, and suppresses angiogenesis in cancer cells. Interacts with multiple signaling pathways (PI3K/ERK/mTOR, NF–B, MAPK, and JAK/STAT, and Wnt/-catenin). Has antioxidant and anti-inflammatory properties.	[216]
Baicalin	Protects against UVB-induced photodamage. Uses NF–B, COX-1, and iNOS activity to modulate anti-inflammatory and antioxidant effects.	[210]
Quercetin	Suppresses COX-2 and MMP-1 production that is caused by UV exposure and collagen deterioration in human skin. Interacts with PKC δ and JAK2. Eliminates senescent fibroblasts and reduces senescence in vivo.	[213]
Fisetin	iNOS, MMP-1, MMP-2, and COX-2 are all inhibited. Increases the skin's expression of aquaporins and filaggrin, preventing skin dryness and photo-inflammation.	[214]
Caffeic Acid	Reduces LPS-induced sickness behavior and neuroinflammation in mice, decreasing TNF-α level and rescuing antioxidant defense systems.	[217]
Ferulic Acid	Exhibits antioxidant and anti-inflammatory properties, influencing serotonin and norepinephrine levels in brain regions associated with mood disorders.	[218]
Gallic Acid	Decreases cytokine levels in microglia cells, protects neurons from Aβ-induced neurotoxicity,	[219]

Table 8
Blueberry phytochemicals on Neuro-inflammation models.

Compound	Study Description	Ref.
Anthocyanins	Significantly reduce chronic inflammatory state in neuroinflammatory conditions.	[222]
Proanthocyanidins	Can cross the blood-brain barrier, promote functional recovery following SCI, and inhibit H2O2-induced apoptosis in PC12 cells.	[224]
Caffeic Acid	Attenuates LPS-induced sickness behavior and neuroinflammation in mice reduces TNF-α levels and rescues antioxidant defense.	[225]
Ferulic Acid	Exhibits antioxidant and anti-inflammatory properties, and influences serotonin and norepinephrine levels in brain regions.	[227]
Gallic Acid	Decreases cytokine levels in microglia cells, protects neurons from Aβ-induced neurotoxicity, and reduces neuroinflammation.	[226 \
Flavonoids	Exhibit beneficial anti-neuroinflammatory effects, down-regulating pro-inflammatory mediators and promoting anti-inflammatory responses.	[223]

vitamins and minerals. However, it has been found that in *Vaccinium angustifolium* Ait, or low bush blueberries, 11 different types of nutrients like K, Ca, P, Mg, Al, B, Cu, Fe, Na, Mn, and Zn and five types of vitamins are present in significant quantities. These nutrients are vital in maintaining the body and balancing the immune system [237].

Blueberries are a beneficial source of dietary fiber, essential for maintaining a healthy gut microbiome. A healthy gut microbiome is increasingly recognized as crucial for immune system function, as it helps regulate the immune response and contributes to overall immune system health [238]. According to reports, blueberry consumption has significantly reduced the incidence of atherosclerosis. Researchers have found that atherosclerosis is the primary cause of all forms of cardiovascular disease. In this disorder, lipid plaque formation progresses within the blood vessels. Blueberries contain anthocyanins, the pigments responsible for colors like blue, red, and purple in ripe berries, which have antioxidant and anti-inflammatory activity, thus improving cardiovascular health [239–241]. Anthocyanins present in blueberries can improve glucose metabolism, modify endothelial function, and

Table 9
Blueberry phytochemicals on dermal inflammation models.

Chemical Name	Study Description	Ref.
Apigenin	Induces apoptosis, and inhibits proliferation and angiogenesis in cancer cell lines. Interacts with various pathways including PI3K/ERK/mTOR, NF-κB, JAK/STAT, MAPK, and Wnt/β-catenin. Exhibits antioxidant and anti-inflammatory properties.	[230]
Baicalin	Offers skin defense against UVB-triggered photodamage while exhibiting anti-inflammatory and antioxidant properties by regulating NF-κB, COX-1, and iNOS activity.	[231]
Quercetin	Prevents the breakdown of collagen in human skin and skin fibroblasts by preventing COX-2 and MMP-1 production that is stimulated by UV light. Combined with dasatinib, eliminates senescent fibroblasts. Exhibits potential in reducing senescence in various models.	[233]
Fisetin	iNOS, MMP-1, MMP-2, and COX-2 are all effectively suppressed. Meanwhile, it elevates the skin's levels of aquaporins and filaggrin, providing protection against both skin dryness and photo-inflammation.	[232]

maintain plasma lipid levels [242,243].

Blueberries also safeguard vascular health by regulating vasodilation and vasoconstriction in response to appropriate stimuli, and by preserving blood pressure and arterial stiffness. As we know, obesity is one of the significant risk factors for cardiovascular disorders, which first lead to hypertension and then cardiovascular disorders. Comparative studies were done among the ingestion of sixteen other fruits, and the ingestion of blueberries resulted in the least weight gain because, among the six flavonoids, the anthocyanin compound is related to lesser weight gain [239]. A study was performed on two healthy women who increased their anthocyanin intake, resulting in a significant weight reduction and lesser adiposity in blood vessels. It is also reported that the higher blueberry intake in twin studies resulted in reduced adiposity [244]. A clinical trial treated 58 diabetic patients with metabolic disorders and those prone to cardiovascular disorders with blueberries, resulting in reduced obesity [245]. Studies have shown that blueberries can interact with the gut microflora of rats, resulting in an anti-inflammatory effect that modulates cardiovascular health [246,248,249]. Blueberry administration significantly decreased both systolic and diastolic blood pressure [249]. The following outlines the effects of blueberry constituents on the endocrine system and glucose metabolism.

10.1. Interaction with hormones

As per previous reports, blueberries are rich in antioxidants, vitamins, and phytochemicals that help regulate other body systems. Among those systems, the hormonal system is one such system and has potential health benefits. Blueberries contain certain phytochemicals with estrogenic activity. Phytoestrogens are certain chemical compounds that can regulate estrogenic activity. These phytoestrogens also stimulate uterine growth. For example, soy and blueberries have less phytoestrogen content than other plants, but they have an acceptable impact on maintaining estrogen levels [250]. Phytoestrogens are some secondary metabolites of plants that have structural and functional similarities with human estrogen and help maintain several estrogenic functions in the CNS and in women's genital growth [251]. These phytoestrogens have a complex mechanism of action with two nuclear estrogen receptor isoforms, ERα and ERβ, and they bind to those receptors in the same way as endogenous estrogens [252]. On the other hand, blueberries contain vitamin C, which is associated with higher progesterone levels [253].

10.2. Interaction with glucose metabolism

Blueberries contain anthocyanin and other polyphenols that help with metabolism, especially carbohydrate metabolism [254]. The dietary fibers in blueberries slow down the absorption of carbohydrates, reducing the risk of a sudden increase in blood glucose levels [255]. Patients suffering from prediabetes and type 2 diabetes mellitus show reduced insulin stimulation or insulin resistance, followed by decreased insulin uptake and metabolism in the tissues sensitive to insulin [256]. Muraki and his research team conducted three prospective studies, revealing that among various fruits, blueberries displayed remarkable efficacy in reducing risk factors associated with T2DM, ultimately lowering the risk by as much as 26 % [257].

It has also been found that dietary intake of blueberries reduces diabetes-induced dysbiosis, depending on treatment duration and dosage [258]. In a Polish cohort study, the higher anthocyanin intake resulted in a lesser risk of T2DM [259]. Scientists conducted a placebo-controlled study on obese, insulin-resistant adults. They found that consuming blueberries for six weeks enhanced their insulin sensitivity. They used a hyperinsulinemic-euglycemic clamp to measure this sensitivity, which showed the body's ability to eliminate glucose. Glucose tolerance and insulin uptake also increased in mice when their diet was supplemented with blueberries [260]. Roopchand et al. demonstrated that obese hyperglycemic mice showed better oral glucose tolerance and fasting glucose balance than the control group, and they were fed blueberry powder with defatted soy powder [261].

11. Clinical trials

Researchers have conducted clinical trials to explore the potential health benefits of blueberries on various aspects of human health. Blueberries are known for their rich antioxidant content, particularly anthocyanins, which are believed to have potential health-promoting properties. While many studies have shown promising results regarding the health benefits of blueberries, more research is necessary to establish clear cause-and-effect relationships and determine optimal consumption levels. The outcomes of clinical trials can vary, and individual responses to blueberry consumption may differ. Table 10 describes the ongoing clinical research regarding blueberries for different health conditions.

12. Industrial value and global market

Blueberry is commonly known as the "king of the world fruit" because of its multitherapeutic values like anti-inflammatory, antioxidant, neuroprotective, anticancer, and vision improvement characteristics, and this fruit has a prestigious reputation in the market for prebiotics. Different sectors cultivate blueberries for fresh consumption, therapeutic product processing, and processed food preparation. A large population enjoys the delicious taste and health benefits of fresh blueberries. During the peak season of blueberry cultivation, consumers incorporate this fruit into their diets, leading to a surge in market demand and, consequently, a rise in production. Among all the countries, North America is a pioneer in the global market's cultivation, production, and supply of blueberries [262].

In addition to fresh blueberries, processed blueberries are highly popular on the market, and freezing and juicing are the two most essential characteristics of blueberry processing. Blueberries undergo extensive dewatering or drying processes, paving the way for creating innovative blueberry products. However, some of those processing technologies may affect the molecular structure of the bioactives present in fresh blueberries [263]. Blanching is a technique for processing and storing blueberries, performed by inactive microorganisms and the inactivated polyphenol oxidase enzyme responsible for fruit browning. This blanching method results in the degradation of anthocyanin [264, 265]. Reports indicate a significant increase in high-bush blueberry production since the 1990s, particularly after 2000. Fresh blueberry demand is the most critical factor for increased production [266].

Conversely, juice production and winemaking represent two significant blueberry industries. Some blueberry phenolic and antioxidant byproducts are obtained through winemaking, which is later used in food processing [267]. During winemaking, one obtains blueberry pomace, typically regarded as a waste product, but this substance is abundant in anthocyanins, polyphenols, and dietary cellulose. Blueberry dregs have some social and economic benefits as they have made some low-precision flour in some food industries like jam, jelly, bread, and high-fiber biscuit making. These products have some health benefits and taste good [268]. Upon drying the extract, blueberry powder is prepared, but this may lead to some physical properties due to dehydration. This blueberry powder has a high fiber content and antioxidant properties; it is popular when mixed with a muffin, as it improves the physical texture and adds food value, thus gaining popularity among consumers [269].

The worldwide market for blueberry ingredients had a value of USD 2277.4 million in 2022 and is expected to have a compound annual growth rate (CAGR) of 7.3 % from 2023 to 2030. The expansion of the blueberry ingredients market is primarily driven by the heightened health consciousness among customers and their preference for nutrient-dense, low-sugar, and high-protein goods. In addition, the component is being used to enhance goods' nutritional value. Blueberries have become a favored choice among food and beverage makers worldwide. The component is used to augment the caliber and flavor of culinary goods, particularly bread products. The increasing popularity of this substance is ascribed to its antioxidant qualities, which safeguard the human body from oxidative stress induced by free radicals [270].

The global blueberry extract market, with an anticipated size of $394.92 million by 2026, is a promising sector. It is projected to grow at a compound annual growth rate (CAGR) of 10.09 % over the period of 2021–2026. Blueberries, known for their medicinal properties, are used in the treatment of various ailments, including cataracts, urinary tract infections, and diarrhea. They offer a wide range of health benefits and can be consumed as whole fruits or in the form of extracts. Blueberry extract, derived from concentrated blueberry juice, is a rich source of anthocyanins, surpassing other popular fruits in this aspect [272].

The global market value of blueberries has risen in recent years due to increasing consumer demand for healthy and convenient food options. The worldwide blueberry market has been experiencing consistent growth, primarily driven by rising consumer awareness of the health advantages of consuming blueberries [272]. Several factors, like cultivation, production and export, demand and consumption, and market challenges, can determine the market status. Various countries worldwide, including North America, Europe, South America, and Asia, cultivate blueberries. Major blueberry-producing countries include the United States (particularly in states like Michigan, Washington, and Oregon), Canada, Chile, and some European countries.

The demand for blueberries has risen due to their perceived health benefits and versatile uses in culinary applications. They are consumed as fresh fruit, in smoothies, as ingredients in various products, and as part of the growing trend toward healthier snacking options [273]. Some surveys are done to determine consumer acceptance and desire to pay for blueberries, and those studies showed that consumers are enthusiastic about paying for blueberry products [274]. From the cultivation to the production of blueberry products, numerous challenges arise, including weather fluctuations and variable environmental conditions that generally affect harvests, the need for labor-intensive cultivation, and competition from other fruit-derived food industries [275].

Blueberries have gained popularity in various markets thanks to their potential health advantages, encompassing enhancements in heart health, cognitive function, and a reduced risk of chronic illnesses. They are widely available in supermarkets and grocery stores, making them easily accessible to consumers. This convenience has fueled consumption. Blueberries are sold fresh and used in various processed products such as frozen berries, juices, jams, and baked goods. This diversification has expanded the market and grown in various regions worldwide, and the globalization of supply chains has enabled the year-round availability of blueberries, further boosting consumption. The global market

Table 10
Investigation of blueberry in several diseased conditions: Clinical trials, therapeutic intervention (https://clinicaltrials.gov/search?cond=blueberry/20&page=1).

Study	Study Type	Trial No.	Intervention	Dose	Phase
Rice-Pea-Blueberry Sport Gel Formulation for Exercise-Induced Oxinflammation	Randomized	NCT05596500	Blueberry-protein gel	500 mg/day	Not Applicable (Completed)
Blueberry Intake and Infant Gut Health, inflammation and innate immunity in breastfed infants during early complementary feeding	Randomized	NCT05006989	Blueberry Powder	10 g/day	Not Applicable (Recruiting)
Blueberry Supplementation for Osteoarthritis Pain, Intra-articular Inflammation, and Post-operative Recovery in Total Knee Replacement Patients	Interventional	NCT05784545	Blueberry powder supplement	–	Not Applicable (Recruiting)
Blueberry Supplementation and Inflammation Resolution After Exercise	Interventional	NCT05184855	Blueberry powder	1 cup/day	Not Applicable (Completed)
The Effect of Blueberry Consumption on Brain Health in Older Adults: In Vivo Measures of Cerebral Antioxidant and Cerebral Blood Flow	Interventional, Randomized	NCT05024916	Blueberry powder	26 g packets of freeze-dried blueberries (equivalent to 1 cup of fresh blueberries)	Not Applicable (Recruiting)
Consumption of blueberries has an impact on the cardiometabolic parameters in type 2 diabetic men.	Randomized	NCT02972996	blueberry powder	22 g freeze-dried whole blueberry powder	Not Applicable (Completed)
Effect of Blueberry Supplementation on Alzheimer's Biomarkers	Interventional	NCT05172128	Lyophilized blueberry supplement	18 g twice daily	Not Applicable (Completed)
An Investigation into the Effects of Wild Blueberry Powder and Wild Blueberry Extract on Cognitive Function in Older Adults.	Randomized	NCT02446314	Wild Blueberry Powder	450 mg	Not Applicable (Completed)
Comparison of Bioavailability and Urinary Metabolite Profile After Consumption of Blueberry Extract and Whole Blueberry Powder Confections in Healthy Men and Women	Randomized	NCT04329962	Blueberry Powder Food Product	–	Not Applicable (Active, Not Recruiting)
Impact of Blueberry Consumption on Intestinal Permeability, Gut Microbiota, and Gut-Derived Inflammation in Individuals With Elevated Risk of a Pro-Inflammatory Gut Milieu	Randomized	NCT03934177	Blueberry powder	24 g/day	Not Applicable (Completed)
Enhancing the Benefits of Blueberry Polyphenols With Plant and Whey Proteins	Randomized	NCT05967897	freeze-dried blueberry powder	22 g	Not Applicable (Recruiting)
The Clinical and Physiological Effects of Blueberry Consumption in Older Adults	Randomized	NCT05358210	Blueberry Consumption	1 cup of frozen blueberries daily	Not Applicable (Recruiting)
Does Blueberry Intake Alleviate Postprandial Lipemia-induced Inflammation?	Interventional	NCT01594008	blueberry powder	24.1 g and 48.2 g	Not Applicable (Completed)
Evaluation of Eye Health Benefits of Blueberry Chewable Tablets	Randomized	NCT04348110	Blueberry Chewable Tablets	2 tablets per day	Not Applicable (Completed)
Metabolic Advantages of Blueberry Tea Consumption in Type 2 Diabetes.	Randomized	NCT02629952	Blueberry Tea	3 cups of blueberry tea per day	Not Applicable (Unknown Status)
Short-term Health Effects of Wild Blueberry Juice Consumption	Randomized	NCT02139878	Wild blueberry juice	240 ml wild blueberry juice	Not Applicable (Completed)
Prebiotic Properties of Blueberries in Overweight/Obese Individuals: Exploring the Potential Influence of Gut Microbiota on Mitigating the Metabolic Syndrome.	Randomized	NCT03266055	blueberry powder	50 g/day	Not Applicable (Active, Not Recruiting)
Effects of Blueberry Consumption on Vascular Function, Physical Activity, and Cognition in Sedentary Older Adults	Randomized	NCT04049162	Lyophilized blueberry powder	18 g	Not Applicable (Completed)
Long-Term Blueberry Consumption and its Impact on the Urinary Excretion of Anthocyanins.	Interventional	NCT01789359	Blueberry Juice	250 ml/day	Not Applicable (Completed)
Omega-3 and Blueberry Supplementation in Age-Related Cognitive Decline	Randomized	NCT01746303	Blueberry powder	2.4 g/day	Not Applicable (Completed)
Effects of Blueberries on Vascular Function and Blood Pressure in Healthy Men	Randomized	NCT01292954	freeze-dried blueberry	31.4 g	Not Applicable (Completed)
Impacts of Wild Blueberries on Appetite and Weight Regulation	Randomized	NCT05736432	Blueberries	1 C frozen wild blueberries along with ¾ C low-fat Mountain High yogurt	Not Applicable (Not Yet Recruiting)
Sustained Effects of Blueberry Polyphenols on Vascular Function in Healthy Individuals	Randomized	NCT02520830	freeze-dried blueberry powder	22 g/day	Not Applicable (Completed)
The Effects of Blueberry Anthocyanin Metabolism on Acute Cardiometabolic Health	Randomized	NCT03869086	Freeze-dried blueberry powder	36 g	Not Applicable (Terminated)
Effect of a Blueberry-Enriched Diet on Skeletal Muscle Progenitor Cells	Interventional	NCT04262258	Blueberry enriched diet	19 g/day	Not Applicable (Completed)
Highbush Blueberries, the DNA-damage of Obesity, Somatic Mutations and Metabolic Syndrome	Randomized	NCT02075307	Blueberry Powder	1 cup of whole Blueberries twice a day	Not Applicable (Completed)
The Effect of a Novel Blueberry Supplement on Dry Eye Disease (PLUM)	Randomized	NCT05027087	Blueberry gummy	–	Phase III (Completed)
Characterization of Wild Blueberry Polyphenols Bioavailability and Kinetic Profile Over 24 h	Randomized	NCT02167555	Wild Blueberry Beverage	–	Not Applicable (Completed)
The Health Effects of a Blueberry-Enriched Diet on Obese Children: A Feasibility Study	Randomized	NCT01809795	Blueberry Smoothie	1 1/2 cups	Not Applicable (Completed)
The Effects of Wild Blueberries on Depressive Symptoms in Young Adults	Double-blind, Placebo-controlled Trial	NCT04647019	Wild blueberry powder	22 g/day	Not Applicable (Completed)

(continued on next page)

Table 10 (*continued*)

Study	Study Type	Trial No.	Intervention	Dose	Phase
Salvage Therapy With Docetaxel and Blueberry Powder in Non-Small Cell Lung Cancer	Interventional	NCT01426620	Blueberry powder	2-3 packages (15 g per package)	Phase-II (Terminated)
Sustained Impact of Blueberry Supplementation on Cognitive Health in Elderly Individuals.	Randomized Placebo-controlled Trial	NCT05764824	Blueberry powder	20 g per day	Not Applicable (Recruiting)
Effect of Whole Blueberry Powder Consumption on Depression	Double-blind, Placebo-Controlled, Crossover	NCT04398784	Freeze Dried Blueberry Powder - 71,717	22.5 g	Not Applicable (Completed)
Effect of Hydro-Thermodynamic (HTD) Processed Blueberries on Postprandial Blood Glucose Control and Antioxidant Status in Human Adults	Randomized	NCT04396262	–	–	Not Applicable (Completed)
Evaluate the Effect of Blueberry Dry Powder on Prediabetes	Double-blind	NCT02023320	Blueberry dry powder	0.5 g twice a day	Not Applicable (Completed)
The use of anthocyanins in blueberry powder to improve insulin sensitivity in insulin-resistant and obese people.	Pilot study	NCT01005420	Blueberry Powder	45g/day	Not Applicable (Withdrawn)
The Effect of Blueberry Consumption on Cognition and Body Composition in Elderly Who Are Experiencing Mild Cognitive Decline	Randomized	NCT01515098	Freeze-dried blueberries	37 g/day	Not Applicable (Completed)
Effects of a Single Dose of Wild Blueberries on Mood and Executive Function in Healthy Emerging Adults	Single-Blind, Randomized Controlled Trial	NCT05717452	blueberry powder	22 g blueberry powder mixed with 250 ml water.	Not Applicable (Recruiting)
Blueberry Consumption for Improving Vascular Endothelial Dysfunction in Postmenopausal Women with Elevated Blood Pressure and Stage 1-Hypertension	Randomized	NCT03370991	freeze-dried Blueberry Powder	22 g/day	Not Applicable (Completed)
Daily Incorporation of Blueberries into a Diet Favorably Improves Vascular Function and Lowers Aortic Blood Pressure in Postmenopausal Women With Pre- and Stage 1-Hypertension.	Randomized	NCT01686282	Freeze-dried Blueberry Powder	22 g	Phase II (Completed)
Effect of Bilberry (European Blueberries) and Grape Polyphenols on Cognition and Blood Parameters in Normal, Aged Men with Subjective Memory Decline	Randomized	NCT00972972	bilberry (European blueberries) and red grape juice	300 ml	Early Phase 1 (Unknown status)
The Effect of Blueberry Powder Supplementation on Cardiovascular Risk Factors in Subjects with Metabolic Syndrome	Randomized	NCT01399138	Blueberry Powder	45 g	Not Applicable (Withdrawn)

value of blueberries can vary from year to year based on factors such as weather conditions affecting crop yields, changing consumer preferences, and economic conditions [276].

13. Future directions

The article explores the potential future developments of blueberries, specifically emphasizing their changing significance in health, agriculture, and market dynamics. Due to their high nutritional value and wide range of bioactive compounds, blueberries are renowned for their abundant health advantages. This suggests that there will be a growing focus on utilizing these benefits to prevent diseases and promote health by encouraging greater consumption and inclusion in dietary guidelines. The current scientific study indicates that future findings will clarify the function of blueberries in illness prevention and health promotion, highlighting the ongoing focus on discovering more health advantages and understanding the underlying processes. The language promotes the inclusion of blueberries in a well-balanced diet and encourages individuals to seek guidance from healthcare experts for tailored recommendations. This aligns with the trend towards personalized nutrition and the use of blueberries in customized health programs. The emphasis on genetic research and breeding programs is on showcasing the genetic variability across various *Vaccinium* species and the need for additional genes to boost the agronomic significance of blueberry varieties. This focus aims to improve blueberries' production, disease resistance, and nutritional quality.

Given the enhanced antioxidant activity of wild blueberries and the need to save wild genotypes, it is advisable to prioritize conservation initiatives and include wild genotypes in breeding programs. Enhancements in pest control and storage techniques are necessary to minimize losses and enhance the longevity and excellence of products, which is crucial for worldwide distribution. By acknowledging the significance of blueberry skin as a significant repository of compounds and taking measures to prevent its waste during processing, one demonstrates a commitment to sustainable practices and the optimal use of all parts of the blueberry. By boosting worldwide distribution and acknowledging their natural antibacterial properties and potential as dietary supplements, efforts are underway to enhance blueberries' commercial reach and use in functional foods and nutraceuticals. The points indicate a diverse and complex future for blueberries, including health studies, genetic enhancement, sustainable farming practices, new processing methods, and market growth to fully unlock their potential.

Blueberry is generally referred to as one of three types of *Vaccinium* species: lowbush blueberry (*V. angustifolium* Aiton), highbush blueberry (*V. corymbosum* L.), and rabbit eye blueberry (*V. virgatum* Aiton). Scientific studies have demonstrated that a single genotype is inadequate to address the entirety of genetic diversity found within a population or group. This is why auxiliary genes have emerged as a new target to enhance agronomic significance [277]. The antioxidant activity is a parameter that establishes the fact that wild blueberries are more efficacious than cultivated ones, and for that reason, wild genotypes are to be protected. The COMET assay proved that wild blueberries facilitate stronger action in DNA protection. The most concerning aspect is the need for improvements in pest management and storage, as well as a global distribution of blueberries. Researchers have stated that blueberry skin serves as a potential reservoir of anthocyanin, cinnamic acid derivatives, and flavanol-glycosides, and it is crucial to prevent their wastage during the processing of blueberry products. Blueberries have immense potential for managing cardiovascular ailments, have anticancer properties, and also help to control some pathogens. That is why blueberries must be added as a dietary supplement as a natural or organic antimicrobial agent [278].

14. Conclusions

The expansion of global blueberry production due to increased consumption and successful marketing campaigns promoting the health benefits of blueberries is a notable trend in the agricultural and food industries, particularly in the pharmaceutical fields. The journey of blueberries from their natural habitat to clinical applications in human health has been intriguing and promising. This article has unveiled a remarkable story of how a humble fruit has transformed into a potential powerhouse of health benefits. Blueberries are rich in health benefits due to the presence of some essential body-building compounds, including anthocyanins, flavonoids, and antioxidants, which have been studied extensively for their potential to improve human health and fight against various diseases. Blueberries' journey to clinical applications has included meticulous laboratory studies, preclinical trials, and human clinical trials.

These investigations have provided compelling evidence for blueberries' potential to support cognitive function, cardiovascular health, diabetes management, and cancer prevention. These compounds' antioxidant and anti-inflammatory attributes have been associated with enhanced brain health, reduced risk of heart disease, improved insulin sensitivity, and reduced risk of developing chronic ailments. The conventional view of blueberries in the therapeutic field is that they are natural fruits with significant safety margins, making them suitable for inclusion in daily diets, pharmaceutical product preparation, and food industry use. In conclusion, we can demonstrate that blueberries are a common natural treasure, becoming a daily necessity for maintaining good health and their exceptional taste. The future market for blueberries is steadily growing. The expansion of blueberry production has brought economic benefits to many regions and contributed to improved dietary choices for consumers. However, there are also environmental and sustainability considerations associated with increased cultivation. These include the need for responsible water management, pest control, and soil health maintenance to ensure the long-term sustainability of blueberry production.

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Sumel Ashique: Writing – review & editing, Writing – original draft, Supervision, Resources, Conceptualization. **Tuhin Mukherjee:** Writing – original draft, Conceptualization. **Satyajit Mohanty:** Writing – original draft. **Ashish Garg:** Data curation. **Neeraj Mishra:** Writing – original draft. **Monika Kaushik:** Writing – original draft. **Mithun Bhowmick:** Writing – original draft. **Bornika Chattaraj:** Writing – original draft. **Sourav Mohanto:** Writing – original draft. **Shriyansh Srivastava:** Writing – review & editing, Conceptualization. **Farzad Taghizadeh-Hesary:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Abbreviation List

US	United States
BC	British Columbia
g	grams
kJ	kilojoules
AIS	Alcohol-Insoluble Solids
mg	milligrams
μg	micrograms
MALDI-TOF-MS	Matrix-Assisted Laser Desorption/Ionization-Time-of-Flight Mass Spectrometry
LPS	Lipopolysaccharide
TNF-alpha	Tumor Necrosis Factor Alpha
STAT-3	Signal Transducer and Activator of Transcription 3
JAK/STAT-3	Janus Kinase/Signal Transducer and Activator of Transcription 3
AMPK	5′ Adenosine Monophosphate-Activated Protein Kinase
ROS	Reactive Oxygen Species
OH	Hydroxyl Radicals
H	Superoxide Radicals
CRP	C-Reactive Protein
IL-6	Interleukin-6
MCP-1	Monocyte Chemoattractant Protein-1
NF-kB	Nuclear Factor-Kappa B
T2DM	Type 2 Diabetes Mellitus
GME	Guanosine Diphosphate-Mannose-3′,5′-Epimerase
GGP	Guanosine Diphosphate-l-Galactose Phosphorylase
GLDH	l-Galactono-1,4-Lactone Dehydrogenase
MDHAR	Monodehydroascorbate Reductase
DHAR	Dehydroascorbate Reductase
IB	Inhibitor of κB (IkB)
miR-155	MicroRNA 155
Aβ	Beta-Amyloid (related to Alzheimer's disease)
RNA	Ribonucleic Acid
DNA	Deoxyribonucleic Acid
CYP450	Cytochrome P450 (a group of enzymes involved in drug metabolism)
Cd (II)	Cadmium (a toxic heavy metal)
PPE	Polyphenol Extract
SCFAs	Short-Chain Fatty Acids
FOS	Fructooligosaccharides
GOS	Galactooligosaccharides
TDH	Thermostable Direct Hemolysin
TRH	TDH-Related Hemolysin
MetS	Metabolic Syndrome
TLR4	Toll-Like Receptor 4
BMD	Bone Mineral Density
iNOS	Inducible Nitric Oxide Synthase
PKC δ	Protein Kinase C Delta
MMP-1	Matrix Metalloproteinase-1
PI3K	Phosphoinositide 3-Kinase
ERK	Extracellular Signal-Regulated Kinase
mTOR	Mammalian Target of Rapamycin
CNS	Central Nervous System
MAPKs	Mitogen-Activated Protein Kinases
NLRP3	Nucleotide-Binding Domain, Leucine-Rich Repeat Pyrin Domain-Containing 3
ERα	Estrogen Receptor Alpha
ERβ	Estrogen Receptor Beta
gE	Immunoglobulin E
IgE RUST	Immunoglobulin E Radioallergosorbent Testing

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