



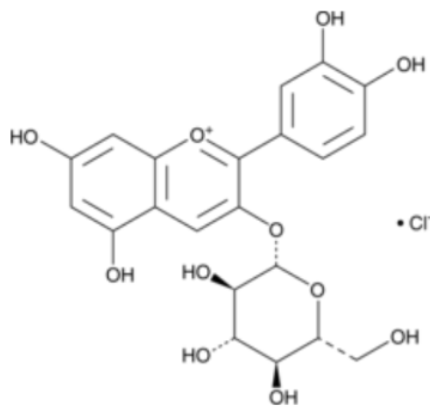
Clinical Insights into the Therapeutic Potential of Bilberry (*Vaccinium myrtillus* L.) and its Extracts:

A review of the literature

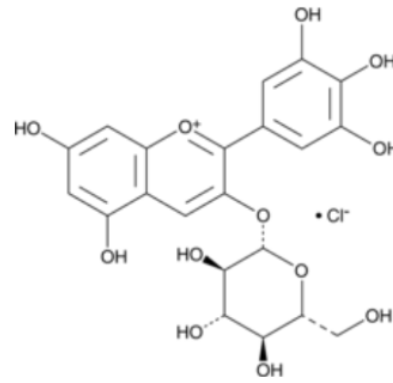
Introduction

Eevia Health's Arctic Bilberry Extract made from Scandinavia's Treasured Superfruit and Its Therapeutic Potential

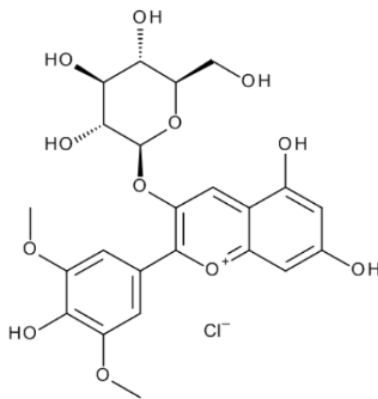
Native to the forests of Scandinavia, the bilberry (*Vaccinium myrtillus* L.) is not just another berry. Distinct from its relative, the blueberry (*Vaccinium* spp.), the bilberry boasts a formidable phytochemical profile, particularly rich in anthocyanins. These compounds, which include derivatives of Cyanidin, Delphinidin, Malvidin and Petunidin (Figure 1.), are powerful antioxidants that not only grant the bilberry its vibrant color but also elevate its status in phytonutrient research¹. Bilberry also has flavanols such as quercetin and myricetin, mainly in glycosylated form.



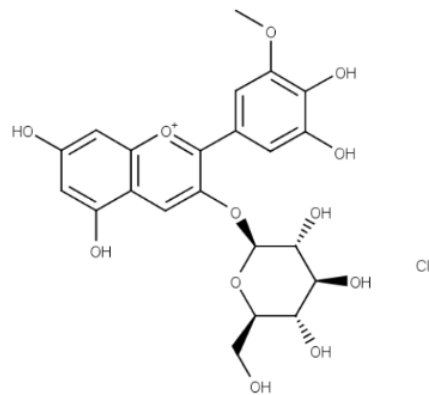
Cyanidin 3-O-glucoside Chloride



Delphinidin-3-O-glucoside Chloride



Malvidin-3-O-Glucoside Chloride



Petunidin-3-O-glucoside chloride

Figure 1. Some of the main anthocyanins found in *Vaccinium myrtillus* L. extracts.

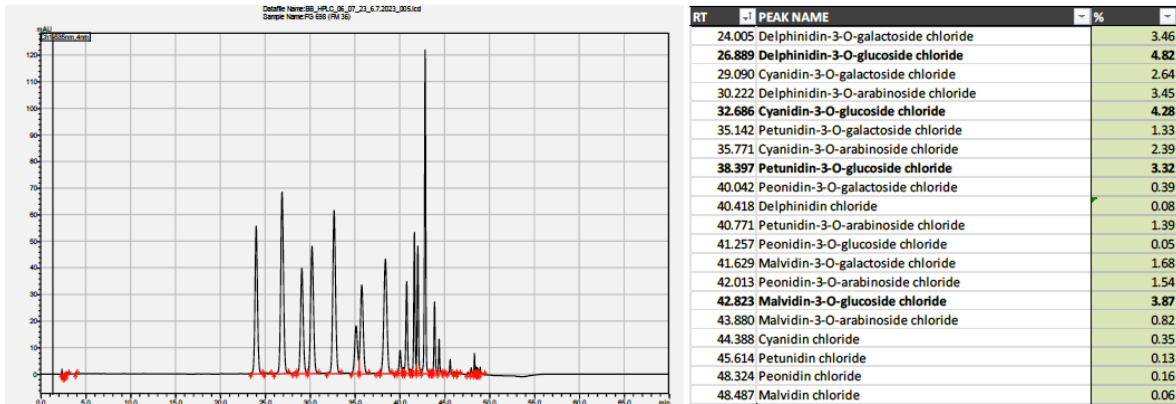


Figure 2. HPLC of Evia Health’s certified organic Fenol Myrtillus 36% arctic *Vaccinium myrtillus* L. extract.

Feno Scandinavian Forest: Nature’s Perfect Anthocyanin Incubator

The unparalleled anthocyanin richness of the bilberry is a tribute to its growth environment the pristine forests of Scandinavia. Here, under the stress of icy temperatures and abundant summer light, bilberries synthesize anthocyanins as a defense mechanism. Evia Health, rooted in this fertile terrain, ensures its bilberries are wild harvested and pollutant free, offering an unmatched Organic Certified Bilberry Extract.

Anthocyanins: Nature's Counterbalance to Today's Lifestyle Stresses

Anthocyanins are more than pigments; they have powerful antioxidants and anti-inflammatory properties^{2,3,4}. Modern lifestyles, rife with digital engagement and artificial light, exacerbate oxidative stress. Evia Health recognizes this and champions anthocyanins for their unparalleled antioxidant and anti-inflammatory properties. However, bioavailability remains a challenge; many anthocyanins are excreted before they can be absorbed^{5,6}. Evia Health's concentrated extracts help bridge this gap, ensuring optimal anthocyanin delivery to combat the health challenges of the digital age.



Bilberry in History and Traditional Herbal Medicine

Bilberries have always been held in high regard. From enhancing visual acuity, as British pilots believed during WWII, to traditional European medicine where they were used for a range of ailments – bilberries have been celebrated for centuries. These traditional uses have provided a roadmap for future clinical research. Some recognized uses of bilberry in herbal medicine, as detailed in the bilberry monograph approved by Health Canada⁷, include:

- Astringent Properties:**
Effective against symptoms like diarrhea^{8,9,10}
- Antioxidant Properties:**
A natural defense against oxidative stress^{7,11}
- Ocular Health:**
Believed to counter specific eye conditions^{7,12,13,14,15}
- Venous Health:**
Used in treating Chronic Venous Insufficiency^{7,16,17,18}

With such a rich history and promising scientific backing, we delve deeper into the clinical studies on bilberries in the subsequent section of this whitepaper.

From Tradition to Evidence: Human Clinical Evaluations of Bilberry Extracts

Introduction to Clinical Investigations

Over the past century, the bilberry (*Vaccinium myrtillus*) has transcended from being a traditionally esteemed berry to an extensively researched therapeutic agent, with a staggering 980 publications registered on PubMed between 1903 and 2023 using the search term "bilberry". Of these, a significant 42 clinical studies specifically evaluated the health effects of bilberry. It's noteworthy to mention that the majority of these studies employed anthocyanin rich bilberry extracts, akin to those offered by Eevia Health. While bilberries are distinguished by their bioactive anthocyanin content, it's imperative to acknowledge that anthocyanins are also prevalent in numerous other natural products such as lingonberry, black currant, and purple potato. This is reflected by the 311 clinical studies on "anthocyanin" found in PubMed. As the contemporary scientific community gravitates towards consolidating evidence based clinical outcomes from traditional botanical knowledge, the spotlight has intensified on standardized and potent extracts. In this setting, Eevia Health has emerged as a forerunner, providing sustainable certified organic, standardized anthocyanins rich bilberry extracts. Such meticulous scientific investigations are pivotal in unraveling the potential health benefits of bilberry, especially in areas such as ocular, metabolic, cardiovascular health, and a spectrum of anti-inflammatory related disorders¹⁹.

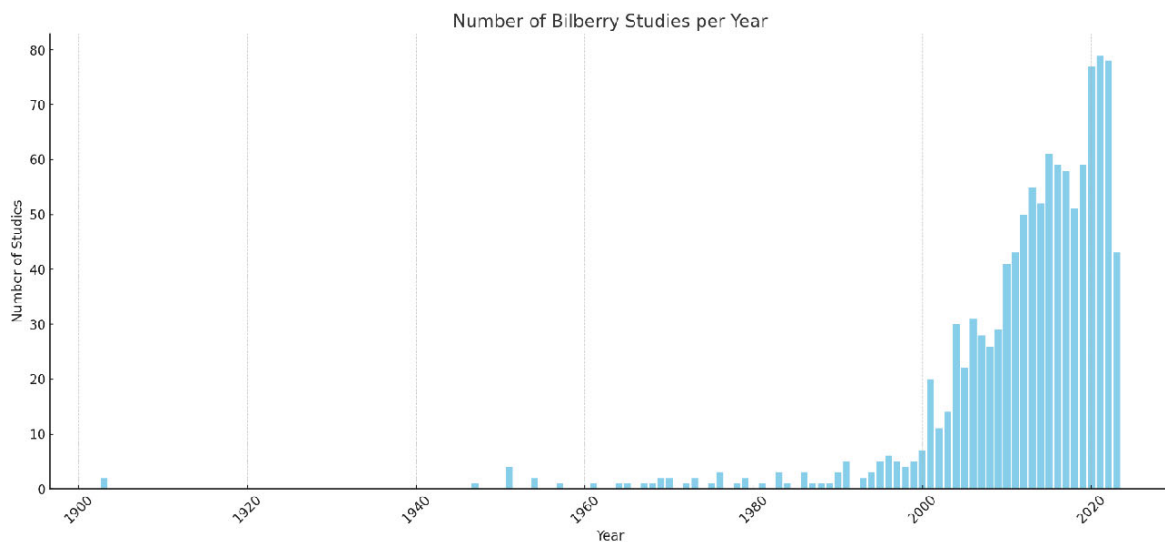


Figure 3. Number of Clinical Trials for Bilberry according to Pubmed search results 2023

Antioxidant Potential and Mechanisms

Oxidative stress, a result of an imbalance between the production of reactive oxygen species (ROS) and the body's ability to counteract their harmful effects, is implicated in numerous pathologies ranging from cardiovascular diseases to neurodegenerative disorders. Anthocyanins, the predominant phytochemicals in bilberries, have attracted attention for their remarkable antioxidant capabilities. These compounds, by virtue of their molecular structure, are adept at stabilizing and neutralizing ROS, thus potentially thwarting the cascade of oxidative damage within the body's cells and tissues²⁰. Bilberries and their extracts, particularly abundant in these antioxidants, offer a promising natural avenue to bolster the body's own defense mechanisms against oxidative damage.

Neutralizing Reactive Oxygen Species:

ROS, such as superoxide radicals, hydrogen peroxide, and hydroxyl radicals, are notorious for causing cellular damage by reacting with essential cellular constituents like DNA, proteins, and lipids. Bilberries' anthocyanins are thought to interact directly with these ROS, rendering them inert and minimizing oxidative harm²¹.

Upregulation of Endogenous Antioxidant Systems:

Beyond direct ROS scavenging, there's evidence to suggest that bilberries might stimulate the body's own antioxidant defenses. They could potentially upregulate the expression of endogenous antioxidant enzymes, amplifying the body's resilience against oxidative stress²².

Clinical Investigation:

Diving deeper into research, several studies have shed light on the profound antioxidant potential of bilberry. For instance, **Erlund I et al. (2003)** probed into the serum quercetin concentrations in subjects after berry consumption, highlighting bilberries as an efficacious source of bioavailable quercetin²³. Another study by **Kuntz S et al. (2014)** underscored the potency of anthocyanin rich beverages in augmenting antioxidant enzyme activities and the overall plasma antioxidant capacity²⁴.

Ocular Health and Visual Acuity

The eye, one of the body's most metabolically active organs, is consistently subjected to oxidative stress due to its exposure to light and high oxygen consumption²⁵. Bilberries, with their rich anthocyanin profile, have garnered scientific interest for potential protective effects on the ocular system²⁶. As researchers aim to capitalize on these effects, the use of potent bilberry extracts, like those produced by Eevia Health, becomes paramount. The unique phytochemical profile of bilberries is believed to counteract the detrimental effects of oxidative stress on many ocular pathologies, from cataract formation to age related macular degeneration²⁷.

Protection Against Oxidative Stress:

Bilberry extracts, due to their high anthocyanin content, can help scavenge free radicals in the retina²⁶, thereby potentially preventing or slowing the progression of diseases instigated by oxidative stress.

Support for Retinal Health:

The retina, being a highly vascular tissue, stands to benefit from the anti-inflammatory and vasoprotective properties of bilberries²⁸. By enhancing microcirculation and mitigating inflammation, bilberries might confer protective effects against conditions like diabetic retinopathy²⁹.

Historically, bilberries have been linked to visual acuity, with legends suggesting that pilots in World War II consumed bilberries to enhance their night vision³⁰. Recent research has sought to validate or refute such anecdotal evidence by probing the effects of bilberry and its extracts on various visual health parameters.

Clinical Investigation:

Studies such as that of **Kosehira M et al. (2020)** have assessed the impact of standardized bilberry extract (SBE) on the tonic accommodation of the ciliary muscle. As the efficacy of such studies relies heavily on the quality of the extracts used, it underscores the importance of manufacturers like Eevia Health who ensure high potency and purity in their bilberry products. The study found that oral consumption of SBE significantly relieved tonic accommodation of the ciliary muscle induced by prolonged VDT tasks³¹

Similarly, other studies have affirmed the positive effects of bilberry extract on eye health, particularly in relation to eye fatigue caused by VDTs³², improvements in subjective

accommodation and mesopic contrast sensitivity in myopic eyes³³, and the potential for treating different types of retinopathies³⁴.

Another noteworthy study by **Riva A et al. (2017)** delved into both antioxidant bioavailability and visual health. Their randomized, double blind trial revealed that standardized bilberry extract not only improves tear secretion but also bolsters the antioxidant potential, further underscoring the multi faceted benefits of bilberries³⁵.

In light of the aforementioned evidence, the clinical implications of bilberry and its extracts are profound. And with manufacturers like Eevia Health ensuring the availability of high quality and potent bilberry extracts, researchers and clinicians are better equipped to harness these benefits. As research continues to evolve , so too does our understanding of how these natural compounds support human.

Cellular Health and Mechanisms of Action in Bilberry Extracts

Vaccinium myrtillus L. (bilberry) is currently being investigated for its prospective role in enhancing cellular integrity and function. Central to its postulated cellular advantages is its capability to mitigate oxidative stress, a prominent contributor to disease pathogenesis and senescence. Bilberry's potential mechanism of action may encompass modulating gene expression, specifically genes modulated by the Nrf2 pathway.

Clinical Investigation:

A research article by **Kropat et al. (2013)** published in the Molecular Nutrition & Food Research journal provided an in depth analysis of this mechanism. The objective of the study was to ascertain if in vivo administration of an anthocyanin enriched bilberry extract (BE) exerts an influence on Nrf2-regulated gene expression in peripheral blood mononuclear cells (PBMC). The Nrf2 pathway is recognized for its critical role in facilitating cellular defense mechanisms against oxidative challenges. The human intervention study presented that bilberry consumption indeed altered Nrf2-regulated gene expression in PBMCs, suggesting systemic effects that are not limited to the gastrointestinal system³⁶. Supplementary in vitro studies proposed that the intestinal anthocyanin degradation product, PGA, might serve as a contributory factor, thereby enhancing the comprehension of the involved metabolic pathways³⁶.

Cardiovascular System: Molecular Mechanisms and Potential Benefits of Bilberry Extracts

The cardiovascular system, encompassing the heart and vasculature, is indispensable for nutrient and oxygen delivery to tissues, as well as for the removal of waste products. Given its vital role, the maintenance of cardiovascular health is imperative. Perturbations within this system, such as atherosclerosis or imbalances in lipid metabolism, can lead to debilitating conditions and remain leading causes of global morbidity and mortality³⁷. Bilberry extracts, especially high quality variants like those manufactured by Eevia Health, are emerging as potential beneficial agents, with their molecular mechanisms offering insights into their cardiovascular benefits.

Bilberries' anthocyanins are postulated to confer several cardiovascular benefits. Mechanistically, anthocyanins from bilberries are believed to:

Enhance endothelial function:

By stimulating the release of nitric oxide (NO), a potent vasodilator, thus aiding in the relaxation of blood vessels and potentially reducing blood pressure³⁸.

Attenuate oxidative stress:

Oxidative modifications of low density lipoproteins (LDL) play a critical role in atherogenesis. Bilberry derived anthocyanins might counteract this process by scavenging free radicals and inhibiting the oxidative modification of LDL³⁹.

Modulate lipid metabolism:

By possibly influencing lipid profiles, especially by reducing LDL and increasing high density lipoprotein (HDL) levels, thereby potentially decreasing the risk of coronary artery diseases⁴⁰.

Exhibit anti-inflammatory properties:

Chronic inflammation is a known contributor to cardiovascular diseases. Bilberries might modulate the expression of inflammatory cytokines and reduce vascular inflammation⁴¹.

Clinical Investigation:

Aboonabi et al. (2020), publishing in *Nutrition Research*, investigated the effects of a 4-week consumption of anthocyanin supplements on cardiometabolic biomarkers in MetS (Metabolic Syndrome) patients. Their results were telling: the supplementation demonstrated anti atherogenic effects by improving various cardiometabolic risk factors and reducing thrombogenicity⁴².

In a study led by **Arevström et al. (2019)**, the effects of freeze dried bilberry supplementation were examined post acute myocardial infarction (AMI). The open label randomized trial, also published in *Nutrition Research*, noted potential benefits in walking distance and lipid profiles, indicating bilberries' potential role in post-AMI recovery⁴³.

Several other studies further corroborate the cardiovascular benefits of bilberries. **Habanova et al. (2016)** demonstrated that regular intake of bilberries could improve lipid profiles, thus reducing cardiovascular disease risk⁴⁴. Meanwhile, **Bryl Górecka et al. (2020)** provided evidence that bilberry extract supplementation could improve the microparticle profile in patient blood and reduce endothelial vesiculation⁴⁵.

Furthermore, **Zhu et al. (2011)** highlighted how anthocyanin supplementation improved endothelium dependent vasodilation in hypercholesterolemic individuals, likely through the NO cGMP signaling pathway. This was complemented by improved serum lipid profiles and a decrease in inflammation⁴⁶.

Finally, a study by **Karlsen et al. (2010)** accentuated the inflammation modulating capabilities of bilberry polyphenols, while **Mink et al. (2007)** reported associations between the intake of flavonoids and a reduced risk of death due to various cardiovascular conditions^{41,47}.

In summary, the vast array of research on bilberries emphasizes its immense potential in supporting cardiovascular health. With the provision of high quality bilberry extracts like those from Eevia Health, there's promising potential to harness these benefits further. From enhancing lipid profiles to reducing thrombosis risk, bilberries might be nature's response to today's cardiovascular challenges.

The Anti-Inflammatory Actions of Bilberry Extracts

Inflammation, a complex physiological response facilitated by the immune system, is a double edged sword in human health. While acute inflammation is a protective mechanism against pathogens and injuries, chronic inflammation poses deleterious effects, becoming a contributory factor in myriad pathologies from cardiovascular ailments to neurodegenerative conditions^{48,41}. Thus, interventions aimed at modulating inflammation, particularly of the chronic variant, are of pivotal importance. In this landscape, bilberry extracts like those cultivated and processed by Eevia Health have garnered attention due to their potential anti-inflammatory properties.

Bilberries, enriched with anthocyanins and other phytochemicals, exhibit their anti-inflammatory potential via multiple molecular pathways:

Downregulation of Pro Inflammatory Mediators:

Bilberries are postulated to inhibit the production or release of pro inflammatory cytokines such as TNF α , IL 6, and IL 1 β , which play significant roles in the propagation of the inflammatory response⁴⁸.

Inhibition of Enzymatic Pathways:

Bilberries might inhibit enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), both of which are involved in the generation of inflammatory mediators⁴¹.

Modulation of Transcriptional Factors

Key transcription factors, notably the Nuclear Factor Kappa B (NF- κ B), regulate the expression of genes involved in inflammation. Bilberry derived compounds might suppress the activation of NF- κ B, thus downregulating the expression of these genes⁴¹.

Regulation of Reactive Oxygen Species (ROS):

Excessive ROS can induce inflammation by damaging cellular structures. Anthocyanins from bilberries are believed to neutralize these species, providing an additional mechanism for their anti-inflammatory action⁴⁹.

Clinical Investigation:

A clinical trial conducted by **Karlsen et al. (2007)** specifically delved into the effects of anthocyanin supplementation on inflammation related mediators³. The results were promising, suggesting that anthocyanin supplementation could inhibit NF-kappaB, a key protein complex involved in inflammatory responses, thereby potentially helping in preventing or treating chronic inflammatory diseases.

Another study spearheaded by **Kolehmainen et al. (2012)** further supports bilberry's anti-inflammatory potential⁴⁸. The researchers examined the impact of regular bilberry consumption on inflammation and gene expression in subjects with metabolic syndrome. Their findings pointed towards a significant reduction in low grade inflammation in those consuming bilberries regularly, hinting at its potential in decreasing long term cardiometabolic risk.

In the context of oral health, a unique aspect of inflammation, **Widén et al. (2015)** explored bilberries' influence on gingival inflammation. Over a seven day period, the study's participants consumed bilberries daily, leading to a notable reduction in markers of gingival inflammation⁵⁰.

In summary, multiple studies underscore the potential of bilberries in managing inflammation, making them an intriguing natural option for addressing chronic inflammatory conditions.

Metabolic Regulation and Benefits

The metabolic system, especially aspects such as blood sugar regulation, plays a central role in overall health. Disruptions or inefficiencies in metabolic function can lead to conditions like type 2 diabetes⁵¹. This has spurred interest in potential interventions, with bilberries emerging as a candidate with potential metabolic benefits.

Bilberries' rich anthocyanin profile is postulated to modulate metabolic functions. Anthocyanins are known to exert multiple physiological effects, including enhancing insulin sensitivity⁵², modulating glucose metabolism⁵³, and regulating lipid profiles⁴⁰. These actions are believed to be facilitated by bilberries' capability to mitigate oxidative stress⁵⁴, modulate inflammatory responses⁴¹, and influence specific signaling pathways pertinent to glucose uptake and utilization⁵⁵.

Clinical Investigation:

Hoggard et al.(2013) embarked on an investigation of a standardized bilberry extract's effect on glucose metabolism in individuals with type 2 diabetes. The findings revealed a significant reduction in postprandial glycaemia and insulin following bilberry extract ingestion⁵².

Studies by **Kianbakht et al. (2013)** and **Chan SW et al. (2021)** further dove into bilberries' influence on type 2 diabetic patients. While the former found that whortleberry, a species related to bilberries, significantly improved glycemic control in conjunction with conventional anti-hyperglycemic drugs⁵⁶, the latter, albeit noting a tendency for improved glycemic control, called for longer term treatments for more pronounced effects⁵⁷.

Lankinen et al.'s research in 2014 and 2011 focused on diets rich in bilberries and their impact on metabolic health. Their findings were consistent with earlier studies, highlighting improvements in glucose metabolism and changes in HDL particles^{58,59}.

Furthermore, the study by **de Mello VD et al. (2017)** revealed an association between increased fasting serum hippuric acid after bilberry consumption and improved insulin secretion and fasting glucose levels⁶⁰.

Wrapping up the metabolic context, **Törrönen et al. (2013)** demonstrated how the consumption of berries, including bilberries, could influence the postprandial insulin response⁶¹.

Drawing from the extensive research, bilberries appear to be a promising natural ally for metabolic health, especially in blood sugar regulation and overall metabolic stability.

Gastrointestinal Health and Digestive Function

Bilberries have been traditionally recognized for their positive influence on the gastrointestinal (GI) system. While they're well known for their antioxidant properties, which can mitigate oxidative stress in various parts of the body, the GI tract can benefit from these properties due to its continuous exposure to dietary and environmental toxins.

Aiding Digestion:

One way bilberries are thought to aid digestion is through their dietary fiber content, which can promote bowel regularity and assist in maintaining a healthy balance of gut flora. The well balanced gut flora is integral for effective digestion and nutrient absorption⁶².

Protection to the Gut:

In addition to aiding digestion, bilberries may also provide protection to the gut lining. Anthocyanins, the primary phytochemicals in bilberries, are believed to have protective effects against inflammation, which can help in conditions characterized by inflammation of the GI tract⁶³.

Clinical Investigation:

A noteworthy study focused on the therapeutic potential of bilberries in ulcerative colitis (UC) - an inflammatory bowel disease that causes long lasting inflammation and ulcers in the digestive tract. In a 2013 open pilot trial, **Biedermann L et. al.** investigated the effects of a daily standardized anthocyanin rich bilberry preparation on 13 patients with mild to moderate UC. The trial, lasting nine weeks, assessed clinical, biochemical, endoscopic, and histologic parameters. The findings indicated a promising therapeutic potential of the standardized anthocyanin-rich bilberry preparation in UC in humans⁶⁴.

While this study is insightful, it also hints at the broader potential of bilberries in the management and protection of the GI tract. However, like many areas of nutritional intervention, more in depth, extensive, and controlled studies are essential to consolidate our understanding.

Recommended Dosage:

When considering the effective use of bilberry extracts rich in anthocyanins, it is important to emphasize proper dosing to optimize potential health benefits while ensuring safety. For a bilberry extract standardized to 36% anthocyanins, typical recommendations range between 120 to 750mg per day, with the precise dosage depending on specific health conditions, body weight, and the desired therapeutic effect. Based on the aforementioned clinical investigations and the recognized anthocyanin profile's potency, a starting dose of 250mg per day can be suggested for general health benefits, with considerations for adjustments depending on individual responses and objectives. It is essential for users to consult healthcare professionals when determining the appropriate dosage, especially when utilizing bilberry extracts alongside other medications or for addressing specific health concerns.

Conclusion and Future Perspectives: Bilberry Extracts, Anthocyanins, and Autophagy

As demonstrated in this whitepaper, *Vaccinium myrtillus* L. (bilberry) and its constituent anthocyanins have transitioned from traditional botanical subjects to subjects of rigorous clinical inquiry. As reflected in empirical studies, bilberries exhibit a myriad of bioactivities encompassing antioxidant, anti-inflammatory, metabolic regulatory, glycaemic control, and gastrointestinal protective effects. Such findings provide scientific validation for a multitude of historical anecdotal claims surrounding this phytochemical-rich berry.

In the comprehensive review of clinical literature, a critical consideration pertains to the optimal mode of bilberry administration. While whole fruits and juices offer certain advantages, concentrated bilberry extracts, exemplified by products from Eevia Health, are progressively emerging as potentially superior in terms of bioavailability and therapeutic potency.

Autophagy, a cellular homeostatic process, has recently emerged as a focal point in the context of anthocyanin mediated bioactivities. Preliminary findings indicate that anthocyanins from berries such as *Phillyrea latifolia* L. and *Pistacia lentiscus* L., and *Rubia peregrina* L modulate autophagic pathways⁶⁵. Specifically, anthocyanins from bilberries have shown to exert inhibitory effects on mTOR signaling in liver cancer cells and induce autophagy via the AMPK-mTOR signaling cascades, thereby proposing potential ameliorative effects against oxidative stress, as evidenced in aging female rats⁶⁶.

Another study on anthocyanin extracts from bilberry tested on UV treated male fruit flies, *Drosophila melanogaster*, showcased bilberry's ability to alleviate the aging process and increase lifespan, though the exact correlation with antioxidant and autophagy signaling pathways remains unclear⁶⁷. The concomitant intake of lutein, resveratrol, and bilberry over 6 months has been associated with improvements in AMD symptoms, a condition partly attributed to impaired autophagy⁶⁸. Furthermore, the presence of compounds like resveratrol in bilberries, known for enhancing autophagy via direct competitive inhibition of mTOR⁶⁹, and its suggested use in treating neurodegenerative diseases such as Alzheimer's^{70,71} amplifies the depth and potential of current research trajectories.

In conclusion, bilberries, rich in anthocyanins and other phytonutrients, present a promising avenue for nutritional and therapeutic interventions. Future research will undoubtedly refine our understanding and highlight new areas where these berries can be of potential benefit.

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