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Mini Review

A Short Review on the Beneficial Effect of Berry Polyphenols on Cardiovascular Diseases

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Received: November 26, 2019; **Published:** December 11, 2019

Abstract

Heart and blood vessel disorders, commonly known as cardiovascular diseases, represent a serious problem worldwide. Due to the vascular complications that this disease causes, diabetic individuals have a higher risk of developing CVDs. Interestingly, recent studies suggested that polyphenols, and in particular berry anthocyanins, may possess vasculo-protective functions. However, the mechanisms of action of these plants by-products have not been fully elucidated yet.

Keywords: *Cardiovascular Diseases; Endothelial Cells; Berry Polyphenols*

Abbreviations

CVDs: Cardiovascular Diseases; ECs: Endothelial Cells; eNOS: Endothelial Nitric Oxide Synthase; HAECs: Human Aortic Endothelial Cells; HUVECs: Human Umbilical Vein Endothelial Cells; IL-1β: Interleukin 1 β; ICAM-I: Intracellular Adhesion Molecule; NO: Nitric Oxide; ROS: Reactive Oxygen Species; TNF-α: Tumour Necrosis Factor- α; VCAM: Vascular Adhesion Cell Molecule

Introduction

Cardiovascular diseases (CVDs) are a group of heart and blood vessel conditions representing by far the major cause of health complications and death globally. Diabetic individuals have a particularly high risk of suffering from CVDs due to the deleterious effects brought about by chronic hyperglycaemia and insulin resistance [1]. Under normal physiological conditions, insulin regulates the uptake of glucose into cells so that this can be broken down to obtain energy [2]. However, when this hormone is not working properly or when hyperglycaemia is persistent, the excessive glucose in the blood is transported into endothelial cells (ECs) by various other mechanisms that lead to an intracellular accumulation of this sugar. Consequently, the cells' metabolism is altered and there is an abnormal production of reactive oxygen species (ROS), which directly or indirectly damage ECs. For instance, superoxide can react with and limit the availability of nitric oxide (NO), a vasodilator and anti-atherothrombotic signalling molecule, forming an apoptosis- and dysfunction-triggering compound called peroxynitrite [3]. Moreover, ROS can stimulate the release of cytokines and adhesion molecules involved in atherogenesis [4]. Taken together, the abnormal production of ROS promotes endothelial dysfunction and the formation of atherogenic plaques in both small and large blood vessels, which explains why vascular injury is one of the main complications diagnosed in diabetic patients and why they are more likely to develop CVDs [5].

To date, a myriad of epidemiological studies has shown that fruits, vegetables and food of plant origin can diminish the incidence of CVDs by means of their rich polyphenolic content [6]. This short review will focus specifically on the cardio-protective benefits of berries, as they contain the largest and most diversified variety of polyphenols. In particular, attention will be given to blue/purple pigments called anthocyanins as they are considered the most efficient polyphenolic compounds for the prevention and the management of CVDs [7].

Polyphenols and their functions

As just mentioned, the association between the consumption of berries, their polyphenolic content and the reduced risk of developing CVDs was proved to be strong by most epidemiological investigations [6]. With approximately 8000 different compounds, polyphenols represent the largest class of plants' secondary metabolites, also known as phytochemicals. Their chemical structure, consisting of at least one phenolic ring to which one or more hydroxyl groups are attached to, suggests that they are very good antioxidants [8]. In fact, polyphenols' aromatic groups can donate electrons to neutralize ROS, thus reducing endothelial damage and slowing down the progression of atherosclerosis by limiting the oxidation of low-density lipoproteins which is mediated by these reactive entities [9,10]. For instance, human aortic endothelial cells (HAECs) and human umbilical vein endothelial cells (HUVECs) previously exposed to stress-inducing chemicals, recorded a lower concentration of ROS following treatment with elderberries and blackberries respectively [11,12]. However, it is hard to determine to what degree this type of intervention might work in humans, as the bioavailability of polyphenols varies considerably compared to *in vitro* samples and animal models.

Apart from their antioxidant function, polyphenols were proved to be also good anti-inflammatory compounds. Interestingly, abundant consumption of berries was associated with a drop in inflammatory biomarkers whose overproduction was previously associated with hyperglycaemia, such as TNF-α, IL-1β, VCAM, ICAM [13]. Moreover, as some studies found that strawberry and blueberry extracts could improve cell migration and capillary-like tube formation in HUVECs subjected to glucose toxicity, it was postulated that polyphenols might interfere with signalling pathways also by targeting kinases [14]. For example, it was suggested that phenolic compounds upregulate the endothelial nitric oxide synthase (eNOS) by enhancing Ca^{2+} concentration and redox-sensitive activation of the phosphoinositide 3-kinase/Akt pathway in ECs. As a result, the production of NO rises, while the synthesis of the pro-inflammatory factor endothelin-1 drops [15]. Finally, polyphenols were also found to lower bad cholesterol, improve platelets' function and reduce blood pressure [16].

Bioavailability of polyphenols

Compound bioavailability is of massive importance when it comes to nutritional studies. In fact, while *in vitro* work shows that polyphenols improve hyperglycaemia-induced endothelial dysfunction, clinical trials cannot always provide the same conclusions because of the inefficient absorption or the rapid metabolization of these compounds. Bioavailability of polyphenols depends on their structure, type and quantity [17], but evidence suggested that *in vivo* absorption of CVDs-relevant berry anthocyanins, is sufficient to produce health effects [18]. According to some epidemiological investigations, the ingestion of berries is followed by the direct absorption and detection of anthocyanin in the plasma. Passamonti and colleagues (2002) found that deglucosylated anthocyanins can reach the bloodstream through gastric mucosal absorption, while others showed that this can occurs also in the gut [7]. However, anthocyanin serum concentration is usually much lower than that in individuals' gastrointestinal tract, indicating that they are being metabolised. In fact, according to the sugar moieties present in their structure, polyphenols can be transformed into conjugated metabolites in either the small or the large intestine. Then, they are transported to the liver for further processing and from there, before being eliminated through the urine or the bile, they are delivered to body tissues via the circulation, or they are returned to the gut. As conjugated metabolites function differently from their parent compounds, and as their identification in biofluids is challenging, investigators are currently struggling to determine anthocyanins' effective bioavailability [20-22].

Conclusion

Taken together, the studies analysed in this review propose that berry polyphenols have the potential to improve and limit endothelial cell damage in diabetic and prediabetic patients. One of the biggest issues limiting the conclusions that could be made from all these investigations is that clinical trials lack racial and ethnic diversity and interventions on large groups are scarce. In addition to this, each berry polyphenol has a specific bioactivity that is also influenced by nutrient interactions taking place within the human body. Finally, these compounds' metabolic processing and the precise dose to obtain consistent beneficial results are still awaiting elucidation. Therefore, robust epidemiological studies should be planned, complemented by *in vitro* investigations so that these gaps could be filled in and dietary guidelines for diabetic people could be created.

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Volume 7 Issue 1 January 2020