

Mediterranean Diet: Prevention of Chronic Diseases by Consuming Phenolic Compounds

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Abstract: Dietary polyphenols are the subject of scientific interest due to their phytochemicals and antioxidant potential on human health. Polyphenols are secondary plant metabolites, and consumed as important part of Mediterranean diet. Their role can be crucial in achieving Sustainable Development Goals. Purpose of this review was to evaluate the positive role of phenolic compounds in the prevention of chronic diseases (CDs) such as cardiovascular diseases, cancer, insulin resistance or diabetes and neurodegenerative diseases and some other chronic diseases (urinary tract infection, rheumatoid arthritis, asthma). Fruits and vegetables are the richest sources of polyphenols, and their consumption as a part of daily diet is beneficial for reducing the non-communicable diseases.

Keywords: Berries, Chronic diseases, polyphenols, Mediterranean diet, Olives, Sustainable Development Goals.

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1. Introduction

Non-communicable diseases (NCDs) progress slowly in the body, but adversely affect the health in longer duration (Alwan et al., 2010; Ogoina and Onyemelukwe, 2009). These diseases also called chronic diseases, and are of five main types; including neurodegenerative diseases, diabetes, cancer, chronic respiratory and cardiovascular diseases (Boeing et al., 2012; Bosquet et al., 2011). Globally these chronic diseases are responsible for 36 million (62.5%) deaths per year. The most common chronic disease among them is cardiovascular disease, which causes almost 17 million deaths per year, followed by cancer 7.4 million, respiratory infections 4.1 million and diabetes 1.2 million deaths per year. Approximately 28.5 million (79.9%) deaths are caused by chronic diseases in developing countries (Munro, 2014; Zhu et al., 2014; WHO, 2015). Globally it is imperative to reduce burden of non-communicable diseases (Mendenhall et al., 2017).

Recent data showed that more than 8.9 million of all the deaths happen in low-income countries before the age of sixty. Many risk factors contribute to them, mainly including inadequate dietary patterns, sedentary life-style, smoking and alcohol consumption (Bertram et al., 2018; Munro, 2014; Niessen et al., 2018; WHO, 2015). Long-term exposure to these factors leads towards the alterations in body functions, such as increased blood glucose level, high blood pressure, rise in lipid level and weight gain (Jaspers et al., 2015). The most interesting factor is that they are preventable by healthy eating, enhanced consumption of fruits and vegetables in diet, as well as by improved physical activity or intake of Mediterranean diet (Boeing et al., 2012). Coffee and tea consumption are also beneficial in these conditions, especially in case of heart diseases and cancer (Cornelis et al., 2018; Grosso et al., 2015; Grosso et al., 2015; Navarro et al., 2018). Numerous studies related to them indicated that ingestion of plant diets is inversely related to mortality from cardiovascular diseases (Ciccone et al.,

2013; Nicklett et al., 2012; Woodside et al., 2013). Consuming combined servings of fruits and vegetables were inversely related to the mortality (4%) by heart diseases. This was because plant foods are low in calories and high in healthful compounds, *i.e.* antioxidants, fiber, vitamins, polyphenols, minerals and potassium (Wang, 2014).

World Health Organization recommended an intake of almost 400g per day of fruits and vegetables (WHO, 2015). Alterations in eating habits specifically more intake of fruits and vegetables are linked with decrease in hypertension. According to 8 cohort researches, people who eat > 5 servings of vegetables and fruits indicated 25% decrease in stroke as compare to those whose intake was only about three servings/ day (He et al., 2006). Commonly changeable risk factors in cancer are cigarette smoking, eating pattern and activity. American Institute of Cancer Research exhibited that high consumption of fresh vegetables and fruits lowered the risk of pharynx, lung, colon and rectum cancers. Results from different studies on fruits and vegetables heightened their positive impact on body by lowering the risk of developing cancer (Baena Ruiz and Salinas, 2014; Wang, 2014) and protection against diabetes (Carter et al., 2010). Chen et al. (2013) demonstrated that increased physical activity and greater ingestion of plant foods decreased the initiation of diabetes in Taiwanese. Many studies strongly suggested that fresh fruits and vegetables have capability to reverse these chronic diseases. Recommended quantities (e. g. 400g/day by WHO) must be the part of everyday diet, but many countries have set their own limits e. g. 590g/day by European countries (EUFIC, 2015). American guidelines (USDA, 2010) also emphasize on high ingestion of fruits and vegetables. It is of serious concern that intake of plant foods is very low in developed countries (WHO/ FAO, 2006). Objective of this paper was to review the importance of phenolic compounds from human studies in the prevention of non-communicable diseases (Gonzalez de Mejia and Johnson, 2014).

2. Sustainable Development Goals and Non-Communicable Diseases

Out of total 56.9 million deaths worldwide approximately 71% (40.5 million) deaths were attributed to non-communicable diseases (Bennett et al., 2018). One-third reduction in premature mortality from non-communicable diseases by 2030 is included in target 3.4 of Sustain Development Goals (SDG)3 (Cao et al., 2018). These diseases are

barriers to achieve five Sustainable Development Goals (SDGs 1, 2, 4, 5 & 10) and their management and preventing measures will further contribute to other three SDGs (SDG 8, 11 & 12) (Nugent et al., 2018). Therefore reduction in these diseases will be the key to successfully achieve at least nine SDGs. Achieving target reduction in non-communicable disease will be great challenge for population living in less developed countries (Pullar et al., 2018).

3. Traditional Mediterranean Diet

Mediterranean diet is characterized by excess amount of plant foods including vegetables and fruits, whole grain cereals, pulses, nuts, beans and olive oil, but fewer proteins from animal sources. Olive oil considered being the vital source of fat, while remaining food components are chief contributors of antioxidants in the diet (Ortega, 2006). Besides from known antioxidants including polyphenols, phenolic compound and flavonoids, some less common antioxidants (hydroxy-tyrosol and oleuropein) are also present in plant foods. Study results showed that prevalence of heart disease and cancer are very less in people living in Mediterranean region (Spain, Italy and France) mainly because of their healthy diet pattern (Pitsavos et al., 2005). Numerous studies highlighted the positive impact of Mediterranean diet on hypertension, body mass index, inflammation and lipid metabolism (WHO/FAO, 2006). Several studies demonstrated that the increase in consumption of plant foods contributes to added health benefits, mainly due to the presence of antioxidants, such as polyphenols, vitamin C and carotenoids. Most interesting hypothesis is that the polyphenols present in fruits and vegetables in larger quantities are responsible for protective effects on human body (Davis, 2009).

Polyphenols, secondary plant metabolites, are divided into many categories, such as flavonoids which are made out of a three ring structure and can be subdivided by the proximity of an oxygen gather at position 4 (Heimler et al., 2017; Seca and Pinto, 2018). This class is partitioned into the accompanying essential epigallocatechin, epigallocatechin gallate and procyanidins (Ciesek et al., 2011; Soobrattee et al., 2005; Tsao, 2010). Isoflavones are one of important seems like estrogen in structure and called phytoestrogens; these substances are found in soy products (Barnes et al., 2011). Another class of polyphenols is lignans, having arylbutane structure generally present in flax and sesame seeds (Willfor et al., 2006).

Table 1. Health perspectives or claims of Mediterranean based polyphenols

Health Perspectives	Mechanism	References
Cardiovascular Diseases	Decrease LDL, increase HDL, improve endothelial dysfunction, reduce blood pressure	Wang et al., 2014, Lim; 2012, Siasos et al., 2014; Riso et al, 2013.
Cancer Insurgence	Decrease proliferation rate, Enhance apoptosis of damaged cells. Reduced oxidative damage to DNA	Gonzalez et al., 2012; Woo and Kim, 2013; Hillestorm et al., 2006; Giovannelli et al, 2011.
Neurodegenerative Diseases	Suppress neuro-inflammation, improve memory and cognitive function, reduce dementia and Alzheimer disease	Rodriguez et al., 2014; Devore et al., 2012; Karikorian et al., 2010; Desideri et al., 2012.
Miscellaneous Problems	Reduce the incidence of rheumatoid arthritis, chronic obstructive pulmonary disease, urinary tract infection, insulin resistance and diabetes	Gonzalze and Johnson, 2014; Bullo et al., 2015; Munir et al., 2013; Stull et al., 2010.

The stilbene class is also essential and characterized by resveratrols, which are found in red wine and thought to contain calming properties (Deng et al., 2017). Among them chief antioxidant is phenolic acid (Manach et al., 2004). Various fruits and beverages are rich in polyphenols, and contain about 200 to 300 mg polyphenols / 100 g of fresh weight (Rodriguez-Mateos et al., 2014). Interesting aspect among them is that their antioxidant level is 100-folds than vitamin E and 10-folds than vitamin C (Rodriguez-Mateos et al., 2014).

4. Protective Roles of Phenolic Compounds

4.1. Cardiovascular Diseases

Recently polyphenol rich diet (containing flavones and flavonols) were found to protective against chronic diseases including cardiovascular ailments (Rodriguez et al., 2014; Sakaki et al., 2019). Results exhibited that the consumption of phenolic compounds (Table 1), including flavonols, anthocyanins, flavanones and flavones, decreased the risk of developing heart diseases (Wang et al., 2014). Another study showed that individuals (42, 000), who followed the diet rich in phenolics secured their health from death by 30% (Zamora-Ros et al., 2013).

Mortality rate due to heart diseases generally decreased by increased consumption of flavonoids (Grosso et al., 2017; Ivey et al., 2017; Liu et al., 2017; McCullough et al., 2012). The consumption of polyphenol rich foods improved the resistance to oxidative modification of low-density lipoproteins (LDL) which are considered bad cholesterol and in excess quantities cause the cardiac arrest and various heart problems in humans, and this effect was explained by the quick incorporation of phenolic

acids in LDL (Lim, 2012). Although the role of polyphenols in CVD risk is still controversial, most of the epidemiological and intervention studies indicated a decrease in LDL cholesterol concentrations, increase in high-density lipoproteins (HDL) cholesterol concentrations, and a resistance of LDL to oxidation following the intake of polyphenolic-rich foods in healthy humans (Mursu et al., 2004; Baba et al., 2007; Natella et al., 2007). Siasos et al. (2014) reported that the consumption of grape juice for 2 weeks improved the heart functions in twenty-five smokers. Moreover, intake of grape juice for longer duration reduced the endothelial dysfunctional properties in men having metabolic syndrome (Barona et al., 2012). Scientists believed that resveratrol is the chief reason for the improvement in endothelial functions which is predominantly present in grapes in significant concentrations (Wong et al., 2011).

In addition to the effect of phenolics compounds on heart, several studies also exhibited their beneficial effects on blood lipid profile. Intake of red wine for thirty-five days by the men, who were at risk of developing cardiovascular diseases, showed positive association between red wine intake and high density lipo-proteins (HDL) level (Chiva-Blanch et al., 2013) and negative association with low density lipo-proteins (LDLs) (Yubero et al., 2013). Moreover cocoa phenolics are involved in lowering the blood pressure (Muniyappa et al., 2008). Flavan 3-ol present in cocoa in twenty randomized controlled trails demonstrated that these products significantly lowered blood pressure, and improved the endothelial functions and heart vasomotion by improving the plasma nitric oxide in smokers and in patients with heart failure, respectively (Flammer et al., 2012).A

meta-analysis of forty randomized studies demonstrated that cocoa phenolics increased the HDL concentration by 0.05 mM by decreasing the 0.08 mM of LDL ratio (Hooper et al., 2012). On the other side, phenolic compounds including berries also exhibited high power to enhance the good cholesterol (HDL) in the body (Riso et al., 2013).

4.2. Cancer

The tumorigenesis and carcinogenesis, predominantly in gastrointestinal tract, has been affected by phenolic constituents, reviewed in many epidemiological studies (Gonzalez et al., 2012). The decrease in colorectal cancer is related to the consumption of flavone, anthocyanin (procyanidine), flavonol and flavan-3-ol isoflavone (Theodoratou et al., 2007). Woo and Kim, (2013) found no clear relation between consumption of flavonoids and decreased possibility of stomach and colorectal cancer. The chemoprotective properties of tea and fruits have been studied (Table 1). For example, short-term intervention studies showed the preventive effects of green tea polyphenols against carcinogenesis. A study found that only one tumor was diagnosed among 30 subjects, who took green tea capsules (600mg of flavan-3-ols/day) for 1 year, versus 9 tumors diagnosed in the same sized control group (Bettuzzi et al., 2006). Furthermore, a 4-week study on heavy smokers concluded that the number of damaged cells was reduced by the intake of five cups of green tea per day (400-500mg of flavan-3-ols per cup), by triggering the apoptosis and cell growth arrest (Schwartz et al., 2005). Hakim et al. (2003) found that the consumption of phenolics in green tea for 4 months (4 cups/day, 146 mg total/cup) reduced the urinary level of biomarker of oxidative DNA damage, 8-hydroxydeoxyguanosine. A 12-week randomized, placebo-controlled study showed that the patients with high risk oral premalignant lesions, took green tea extracts (500, 750 or 1000mg/day) and cause changes in cancer progression (Tsao et al. 2009). Nevertheless, FDA claimed that there were no or little sound scientific evidences to support the qualified health claims about intake of green tea and decreased incidence of gastric, colorectal, ovarian, prostate/breast and esophageal cancer.

Chemoprotective effect of intake of fruit juices (orange and anthocyanin-rich juice) is correlated with the reduction in cancer risk (Weisel et al., 2006; Riso et al., 2005). Conversely, there were studies which concluded that the consumption of blackcurrant juice for 3 weeks (666mL/day, 397 mg anthocyanins/day)

and cranberry juices for 2 weeks (750mL/day) had no significant influence on oxidation of DNA (Duthie et al., 2006; Moller et al., 2004). Similarly, Giovannelli et al (2011) investigated that procyanidin-rich-dealcoholized wine (500mL/day), which contained 7 mg/kg body weight had no effect on DNA damage after 4 weeks trial. Contrarily, reduction in oxidative damage to DNA and chemo-preventive effect of berries has been associated in many human intervention studies (Perez-Sanchez et al., 2014).

The relation between olive oil and its effect against carcinogenesis has also been investigated. For this, intake of virgin olive oil and urinary excretion of ethno-DNA adducts were studied, concluding insignificant differences between baseline and after intake of highest phenolic content 150mg/kg (Hillestorm et al., 2006). Although, several studies gave positive results, yet more comprehensive studies are required to support the uncertain protecting effects of polyphenols against DNA damage (Brown et al., 2014).

4.3. Neurodegenerative Diseases

Phenolic compounds in diet perform multiple roles in suppressing neuro-inflammation, improving memory, learning and cognitive functions (Table 1). Some epidemiological studies concluded that there was 50% reduction in incidence of dementia with regular intake of phenolic beverages (Rodriguez et al., 2014). Higher intake of strawberries and berries (anthocyanidins) has been related with a slower development of cognitive degeneration in 70 and over older women (Devore et al., 2012). Several studies showed the relationship of neuro-degenerative disorders and consumption of (poly) phenol-rich foods, like berries or grapes. Flavonoids present in blueberries improved the efficiency of spatial memory by acting on dentate gyrus, which is sub region of hippocampus, and is most sensitive to the effect of aging (Krikorian et al., 2010). A 3-week clinical study on men and women aged 40 to 70 years, reported that there were reductions in plasma concentrations of pro-inflammatory transcription factor (NF-kB), immuno-regulatory cytokines and pro-inflammatory chemokines by daily consumption of 300mg anthocyanin extracts from blueberries (Karlsen et al., 2007). In addition, the consumptions of strawberry and blueberry (flavonoids) improved memory (Krikorian et al., 2010) and reduced the rates of cognitive failure in older adults (Devore et al., 2012).

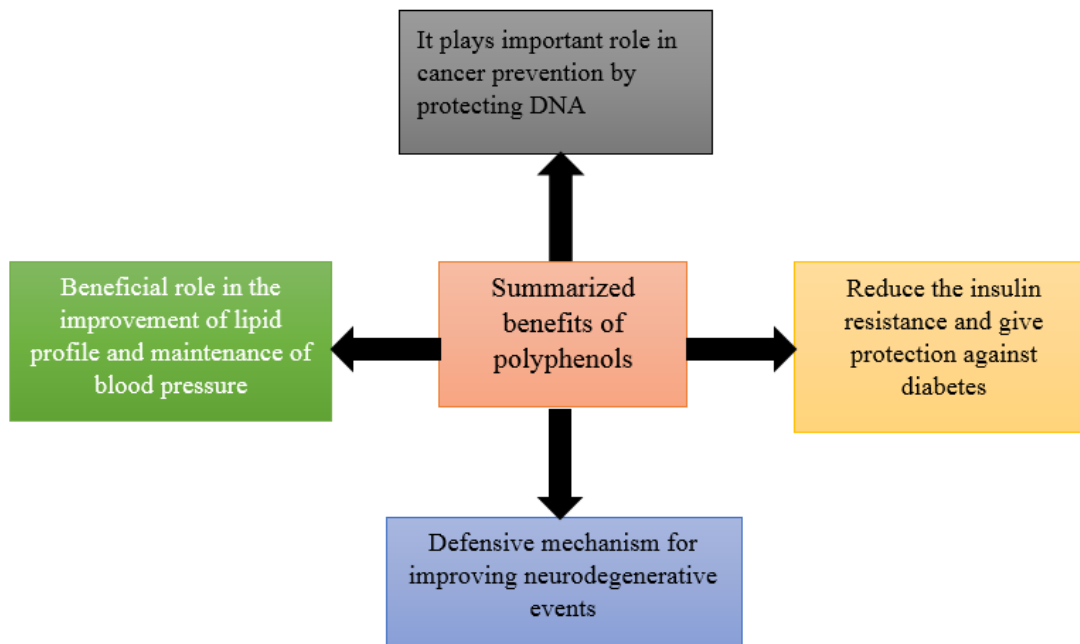


Fig. 1. Summarized benefits of polyphenols

4.4. Phenolic Compounds and Other Chronic Diseases

Moreover, the intake of Concord grape juice for 12 weeks in a group of 12 older adults, who had memory decline, but not suffering from dementia, showed a significant enhancement in verbal learning, but a non-significant improvement in verbal and spatial recall (Krikorian et al., 2010).

Similarly, a human intervention trial resulted that the older individuals, who consumed Concord grape juice showed mild cognitive impairments. The subjects in this study showed decreased semantic interference on memory tasks, and comparatively greater activation in both anterior and posterior parts of the right hemisphere (Krikorian et al., 2012). Francis et al. (2006) concluded in a 5-days study in young healthy female adults, that cocoa has effect on cognitive function, and adults showed an increase in blood oxygenation level-dependent signal intensity in response to a cognitive task by consuming 500mg of cocoa flavanols. The intervention trial showed that cocoa consumption (drinks containing 520 mg, 994 mg cocoa flavonols) improved the cognitive outcomes (Scholey et al.2010), even though there were studies which advocated no fluctuations in neurophysiological outcomes (Francis et al., 2006; Crews et al., 2008).Desideriet al.(2012) did an 8-weeks study on elderly individuals with high risk of dementia, and reported an improvement in verbal

fluency by the consumption of cocoa flavan-3-ol. Moreover, in older healthier volunteers, the mean blood flow velocity increased by 10% after 2 weeks consumption of flavanol-rich cocoa (Sorondet al., 2008).

Polyphenols may prevent chronic diseases, which involve inflammation or oxidative stress, such as rheumatoid arthritis, chronic obstructive pulmonary disease, urinary tract infections, insulin resistance and diabetes (Table 1) due to their anti-inflammatory and antioxidant properties. The effect of phenolic compounds on diabetes has been studied in recent review publication (Gonzalez de Mejia and Johnson, 2014). In this review, the berry anthocyanins improved plasma antioxidant status; and declined the oxidative stress in human feeding trials. Moreover, anthocyanins had many anti-diabetic effects, which prevented free-radical production and reduced blood glucose. Similarly, anthocyanins reduced the secretion of insulin and decreased the digestion of sugars in small intestine and protected beta cells. It was concluded that intake of berries decreased the elevation in post prandial plasma glucose and improved insulin resistance in diabetic type 2 patients.

Some human intervention trials have showed that the intake of nuts may reduce the risk factors of cardiovascular diseases in type 2 diabetic individuals. For instance, the Nurses' Health Study indicated an inverse relationship between nut intake and the risk of

type 2 diabetes (Jiang et al., 2002). These studies are supported by another randomized trial of 8 weeks with 24 individuals of type 2 diabetes taking a diet that had 56 g walnuts/day. This trial suggested that regular intake of walnuts improved endothelial function in type 2 diabetic individuals (Ma et al., 2010). Moreover, current studies concluded that intake of nuts had health benefits on diseases like diabetes and hypertension, cancer, cardiovascular diseases and other inflammatory diseases, due to high levels of phytochemicals (stilbenes, phenolic acids, flavonoids, ellagitannins, ellagic acid plus and proanthocyanidins) (Bulloet al., 2015; Alasalvara and Bollinga, 2015). Conversely, consumption of berries and apples resulted in declined risk of type 2 diabetes due to greater consumptions of quercetin and myricetin (Knekt et al., 2002).

Diabetes and obesity results in insulin resistance that lead to considerable increase in cardiovascular morbidity and mortality (Muniret al., 2013). In addition, there are numerous studies about the beneficial effects of cocoa flavan-3-ol on insulin resistance (Grassiet al., 2008). Though, there was no detectable alterations in insulin resistance after consumption (2 weeks) of flavanol-rich cocoa drink (150 ml twice a day, 900 mg flavonols /daily) in 20 individuals (Muniyappa et al., 2008). This trial also showed enhancements of insulin-resistance in type 2 diabetic subjects without disturbing vascular reactivity and nitric oxide production, after 2 weeks of red wine intake (360 ml/day). Likewise, blueberry extracts have also revealed enhancement on insulin sensitivity over 6 weeks in obese, non-diabetic and insulin-resistant individuals (Stull et al., 2010). Urinary tract infections (UTIs) are the most pervasive of bacterial infections, and have globally high burden on economic and medical costs. Cranberries, best sources of phenolics, have been widely used for many years for the prevention and cure of urinary tract infections (Allan and Nicolle, 2013; Shin, 2014). A review of clinical trials considering the effects of cranberry on UTIs reported that cranberry juice declined the number of indicative UTIs over a time of 12 months, mainly in women with frequent UTIs (Jepson and Craig, 2008).

The relations between the consumption of flavones, flavonols, and flavanones and the occurrences of asthma and rheumatoid arthritis, was considered among a cohort of 10, 000 female and male subjects in the Finnish Mobile Clinic Health Examination Survey (Knekt et al., 2002). A significant opposite relationship was observed only for asthma at

higher consumption of quercetin, naringenin and hesperetin. These findings supported an earlier cross-sectional study, which estimated the protecting effect of flavonoids against chronic lung diseases (Tabak et al., 2001), although such effects were not stable.

Although some studies on cancer, CVD and neurodegenerative diseases, showed positive outcomes, yet a significant number of other studies did not confirm the positive results. This may be accredited to altered trial conditions and diet features. Hence, it would be anticipated that the result of pure phenolics and phenolics containing fruit or vegetables may vary due to the interaction of phenols with other antioxidants in the diet. So, a beneficial role of polyphenols in the prevention of CVDs is not evident, hence needs to be supported by further clinical trials addressing the relations of the phenolics with other dietary compounds, prerequisite for their characterization and standardization, since it is not just the quantity, but also the quality, type and their potential pro-oxidant effect. Summarized benefits of polyphenols are presented in Fig. 1.

5. Conclusion: Dietary polyphenols are the subject of scientific interest due to their phytochemicals and antioxidant potential on human health. Richest source of polyphenols includes fruits and vegetables and their consumption as a part of daily diet responsible for beneficial impact in reducing the non-communicable diseases. Several studies demonstrated that emphasis on Mediterranean diet which contains plant foods like vegetables and fruits, whole grain cereals, pulses, nuts, beans and olive oil. Antioxidant (polyphenols, vitamin C and carotenoids) rich in fruits and vegetables and showed positive impact on human body in preventing chronic diseases (CDs) such as cardiovascular diseases, cancer, insulin resistance or diabetes and neurodegenerative diseases and some other chronic diseases (urinary tract infection, rheumatoid arthritis, asthma).

List of Abbreviations: CD, Chronic Diseases; CVDs, Cardiovascular Diseases; FAO, Food and Agriculture Organization; HDL, High Density Lipoproteins; LDL, Low Density Lipoproteins; NF-kB, Nuclear Factor kappa-B; USDA, United State Department of

Agriculture; UTIs, Urinary Tract Infections; WHO: World Health Organization.

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