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RESEARCH ARTICLE

PERSPECTIVE OF POLYPHENOL COMPONENT FOR THE MANAGEMENT OF DIABETES

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ABSTRACT

Polyphenols are a large and heterogeneous group of phytochemicals containing phenol rings and are divided into flavonoids, phenolic acids, stilbenes, and lignans. Among all polyphenols, the beneficial effects of flavanols (flavan-3-ols) and their primary food sources, including cocoa, chocolate, and red wine, have been most widely examined in clinical trials. Polyphenols can exert a beneficial effect on type 2 diabetes by a number of mechanisms including slowing carbohydrate digestion and glucose absorption by interacting with oral cavity and intestinal α-amylase and intestinal α-glycosidase and sodium-dependent glucose transporter and by stimulating insulin secretion in the pancreas via increasing 5′ adenosine monophosphate-activated protein kinase (AMPK) pathway, and insulin receptor substrate (ISRS) and decreasing β-cell oxidative damage which preserves β-cell integrity. In present paper we have discussed briefly about the role of ploy phenols and diet rich in polyphenols contains antioxidant which help in management of diabetes induced by oxidative stress. we also highlight the mechanism of oxidative stress in induction of diabetes and role of antioxidants in management of diabetes mellitus.

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INTRODUCTION

Diabetes: Diabetes mellitus is a metabolic disorder characterized by failure of glucose homeostasis with disturbances of carbohydrate, fat and protein metabolism resulting defects in insulin secretion, insulin action, or both. Without enough insulin, body tissues, particularly, the liver, muscle and adipose tissues fail to take and utilize glucose from the blood circulation. This results in elevated blood glucose levels, a condition known as hyperglycemia. If blood glucose levels remain high over a long period of time, this can result in long-term damage of organs such as the kidneys, eyes, nerves, heart and blood vessels. Complications in some of these organs can lead to Death Renders *et al.,* 2001.

Pathophysiology of diabetes mellitus

Type -1 diabetes: Type 1 diabetes is an autoimmune disease in which the β-cells of the pancreasis unable to produce sufficient insulin, a hormone which helps use blood sugar (glucose) for energy. Due to which the cells become starved of energy and there will be increase blood glucose level. This condition is called hyperglycemia, high blood sugar. When hypoglycemia develops, cells do not get enough glucose and patients suffer of confusion, loss of consciousness, and coma. Even death can results when the brain is deprived of glucose for too long. Hyperglycemia also result in ketoacidosis, which is accumulation of ketones in the blood. due to prolonged absence of insulin when the body uses fat for energy instead of glucose. This is because fatty acids cannot be converted into glucose at steady state. Ketones make the blood acidic and slow down all body functions. This also leads to a coma and eventually death Weinman *et al.,* 1957.

Type-2 diabetes: The primary cause of development of type-2 diabetes is pathogenic event resuls from occurance of a Chronic fuel surfeit that drives the development of type 2 diabetes in genetically a susceptible people. Many chronic ally over nourished and overweight or obese individuals, however, do not develop diabetes at all or develop it very late in life. Kahn *et al.,* 2003. They remain resistant to type 2 diabetes and safely partition excess calories to subcutaneous adipose tissue (SAT) rather than to the heart, skeletal muscle, liver, and islet β cells, owing to the following mechanisms: successful islet β-cell compensation; maintenance of near-normal blood nutrient concentrations; development of minimal insulin resistance; increased expansion of SAT relative to visceral adipose tissue (VAT); and limited increase in liver fat. In this way, key organs of the body avoid nutrient-induced damage. Susceptible over nourished individuals develop type 2 diabetes owing to

Table 1. Drugs used as antidiabetic

Drug	Mechanism	Side effect
Metformin	Reduce hepatic glucose production, increases Peripheral glucose utilisation and insulin sensitivity	Gastrointestinal complaints and lactic acidosis
Glimepiride	Stimulates insulin release from pancreas	hypoglycaemia and weight gain
Nateglinide	Increases insulin secretion in the pancreas	Mild gastrointestinal complaints and weight gain
Rosiglitazone	Lowers insulin resistance in peripheral tissue	Weight gain, fluid retention and heart failure
Vildagliptin	DPP-4 inhibitors	Few gastrointestinal disturbance
Bromocriptine	Resets abnormally elevated	Fatigue, nausea, vomiting

Table 2. List of polyphenols-rich dietary materials having anti-diabetic effects

S.No	Dietary materials	Bioactive components	Mechanism of action
1.	Algae(marine)	Polyphenols phlorotannins	Inhibition of α-amylase and α-glucosidase
2	blueberry	Polyphenol anthocyanins	Reduce hyperglycemia, body weight gain and serum cholesterol
3	Blume	polyphenols	Hypoglycaemic and hypolipidemic
4	Cinnamon	Catechin procyanidin cinnamtannin trans-cinnamic acid	Decrease the gene expression of hepatic gluconeogenesis; increase insulin production
5	Chocolate	polyphenols	Protect against acute hyperglycemia-induced endothelial dysfunction and oxidative stress
6	cocoa	Polyphenols methylxanthines	Reduce the plasma total cholesterol,triglyceride and low-density lipoprotein.
7	Red grapes	Resveratrol, querecetin, anthocyanins	Improve β-cell function, protect liver tissue,improve the complication modulation of mitochondrial oxidative stress.

the failure of these adaptive responses to safely dispose of the fuel surfeit Defronzo *et al.,* 2009. The following metabolic defects are important factor for the development of type 2 diabetes: inability of islet β -cells to compensate for the fuel surfeit; results in stimulate glucagon secretion and reduced incretin response; impaired expansion of SAT, hypoadiponectinaemia, and inflammation of adipose tissue; increased endogenous glucose production; and development of peripheral insulin resistance. Importantly, the fuel surfeit is not safely deposited into SAT, such that it has to be disposed of elsewhere Weir *et al.,* 2001.

Polyphenols: Polyphenols are naturally occurring compounds which are found largely in the fruits, vegetables, cereals and beverages. Fruits like grapes, apple, pear, cherries and berries contains up to 200–300 mg polyphenols per 100 grams fresh weight. Polyphenols are also present in the products manufactured from these fruits, in significant amounts. Polyphenols are secondary metabolites of plants and are generally involved in defense against ultraviolet radiation or aggression by pathogens Manach *et al.,* 2004. The polyphenols typically act as antioxidants, which means they can help prevent cellular damage from free-radicals that occur with pollution, smoking, eating rancid foods, and as a byproduct of normal metabolism. It's also thought that polyphenols contribute to the body being in an anti-inflammatory state, which is also associated with a lower risk of several chronic diseases Bouayed *et al.,* 2010.

Classification of plant polyphenols

Polyphenols have been classified by their source of origin, biological function, and chemical structure. Also, the majority of polyphenols in plants exist as glycosides with different sugar units and acylated sugars at different positions of the polyphenol skeletons.

1. **Phenolic Acid**: Phenolic acids are non-flavonoid polyphenolic compounds which can be further divided into two main types, benzoic acid and cinnamic acid derivatives based on C1–C6 and C3–C6 backbones Chandrasekara *et al.,* 2010.
2. **Flavonoids**: Flavonoids have the C6–C3–C6 general structural backbone in which the two C6 units (Ring A and Ring B) are of phenolic nature Tsao *et al.,* 2006.
3. Isoflavones, Neoflavonoids and Chalcones- Isoflavones have their Ring B attached to the C3 position of Ring C. They are mostly found in the leguminous family of plants. Since beans, particularly soybean, are a major part of the diet in many cultures, the role of isoflavones have, thus, great impact on human health Zhao *et al.,* 2005.
4. Flavones, Flavonols, Flavanones and Flavanonols- These flavonoid subgroups are the most common, and almost ubiquitous, throughout the plant kingdom Flavones and their 3-hydroxy derivatives flavonols, including their glycosides, methoxides and other acylated products on all three rings, make this the largest subgroup among all polyphenols Tsao R *et al.,* 2009.
5. Flavanols and Proanthocyanidins- Flavanols or flavan-3-ols are often commonly called catechins. Different from most flavonoids, there is no double bond between C2 and C3, and no C4 carbonyl in Ring C of flavanols. Zamora-Ros *et al.,* 2011.
6. Anthocyanidins:- Anthocyanidins are the principal components of the red, blue and purple pigments of the majority of flower petals, fruits and vegetables, and certain special varieties of grains, e.g., black rice. Anthocyanidins in plants mainly exist in glycosidic forms which are commonly referred to as anthocyanins McCallum *et al.,* 2007.

Chemical properties and chemical uses of polyphenols

Chemical properties

Polyphenols are aromatic in structure and molecules owing their UV/Vis absorptivity. It contains large conjugated of pi electron configurations; they also have auto fluorescence properties, especially lignin and the phenolic part of suberin. They are reactive species toward oxidation, and used in problem associated with oxidative stress. Polyphenols can form soluble and insoluble protein-polyphenol complexes because they characteristically possess a significant binding affinity for proteins.

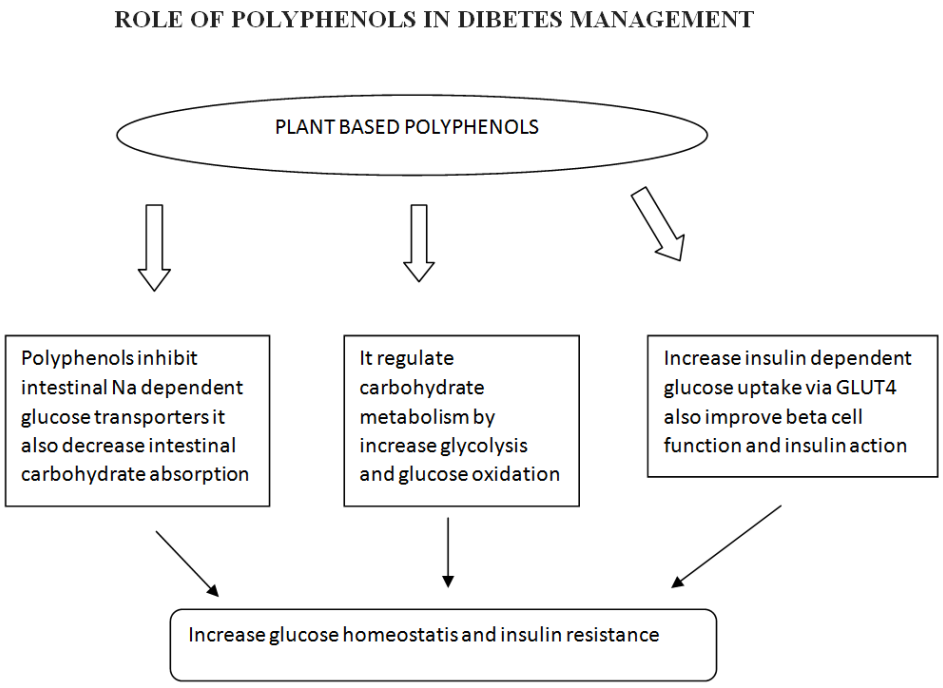

Fig. 1. Role of polyphenols in dibetes management

Chemical uses: Some polyphenols are traditionally used as dyes. For instance, in the Indian subcontinent, the 0pomegranate peel, high in tannins and other polyphenols, or its juice, is employed in the dyeing of non-synthetic fabrics. Polyphenols, especially tannins, were used traditionally for tanning leather and today also as precursors in green chemistry notably to produce plastics or resins by polymerization with or without the use of formaldehyde or adhesives for particleboards Fukuoka *et al.,* 2003. Cashew nut shell liquid (CNSL) is an important phenolic raw material containing mostly cardol, cardanol and anacardic acid., it is used mainly in polymer-based industries for friction linings, paints, varnishes, laminating resins, rubber compounding resins, polyurethane based polymers, surfactants, epoxy resins and wood preservatives.

Beneficial effects of polyphenols on management of blood glucose in diabetes: The hypoglycemic effects of polyphenols are mainly because it delay intestinal absorption of dietary carbohydrate, modulation of the enzymes involved in glucose metabolism, improvement of β-cell function and insulin action, stimulation of insulin secretion, and the antioxidative and anti-inflammatory properties of these components Bahadoran *et al.,* 2013. One of the most well known properties of the polyphenols, especially flavonoids, phenolic acids and tannins, on carbohydrate metabolism is inhibition of α-glucosidase and α-amylase, the key enzymes responsible for digestion of dietary carbohydrates to glucose. Some polyphenols, including green tea catechins and epicatechins, chlorogenic acids, Ferulic acids, caffeic and tannic acids, quercetin and naringenin, could interact with absorption of glucose from intestine via inhibition of Na^+-dependent glucose transporters, SGLT1 and SGLT2. Grassi *et al.,* 2008. Some polyphenols are able to regulate the key pathways of carbohydrate metabolism and hepatic glucose homeostasis including glycolysis, glycogenesis and gluconeogenesis, usually impaired in diabetes. Ferulic acid, a hydroxycinnamic acid derivate, effectively suppresses blood glucose by elevating glucokinase activity and production of glycogen in the liver and increased plasma insulin levels in diabetic rats.

Antioxidant: An antioxidant is a molecule that inhibits the oxidant of other molecules. Oxidation is a chemical reaction that can produce free radicals, leading to chain reaction that may damage cells. Antioxidant such as thiols or ascorbic acid (vitamin c) terminate this chain reaction and prevent the cellular component from getting damage. The term "antioxidant" is mainly used for two different groups of substances: industrial chemicals which are added to products to prevent oxidation, and natural chemicals found in foods and body tissue which are said to have beneficial health effects. To balance the oxidative state, plants and animals maintain complex systems of overlapping antioxidants, such as glutathione and enzymes (e.g., catalase and superoxide dismutase) produced internally or the dietary antioxidants: vitamin A, vitamin C, and vitamin E. Kanter *et al.,* 1992

Vitamin C: Ascorbic acid or "vitamin C" is a monosaccharide oxidation-reduction catalyst which are found in both animals and plants. Padayatty *et al.,* 2003. It is also known as L-ascorbic acid, is a water-soluble vitamin that is naturally present in some foods, added to others, and available as a dietary supplement. Humans are unable to synthesize vitamin C endogenously, therefore it is an essential dietary component, humans must obtain it from the diet; Most other animals are able to produce this compound in their bodies and do not require it in their diets. Kalt *et al.,* 1999. Ascorbic acid is required for the conversion of the procollagen to collagen by oxidizing proline residues to hydroxyproline. Vitamin C is an important physiological antioxidant and has been shown to regenerate other antioxidants within the body, including alpha-tocopherol (vitamin E) Carr et al., 1999. many research take place which showed vitamin C consist of antioxidants which limiting the damaging effects of free radicals through its antioxidant activity, might help prevent or delay the development of certain cancers, cardiovascular disease, and other diseases in which oxidative stress plays a causal role. Frei *et al.,* 1989

Biological role of free radical: Free radicals play vital role in origin and evolution of life. These are important for activating

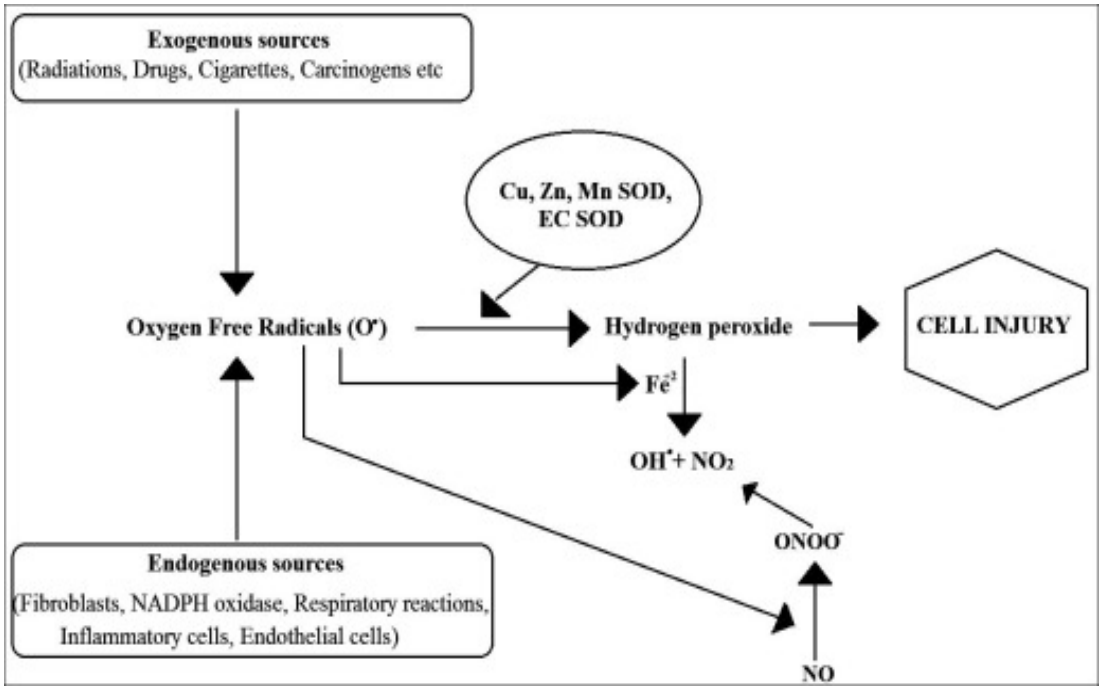

Fig. 2. Free radicals induced cell injury

different casecade signaling pathways inside the cell, such as the Mitogen activated protein kinase (MAPK) and extracellular-signal-regulated kinase (ERK) pathways that alter gene expression, as well as in coordination with superoxide dismutase initiates cell death Cho *et al.,* 2003 some free radical which are produce by neurons also act as neurotransmitters and those which are generated by macrophages act as mediators of immunity. Chevion *et al.,* 1998. These are also responsible for leukocyte adhesion, thrombosis, angiogenesis and vascular tone. Similarly reactive oxygen species (ROS) is involved in gene transcription, single transduction and regulation of other activities in cell.

Role of free radical in progression of diabetes: Since free radical are beneficial for body in some extent but in much amount they are harmful for body because they can chemically interact with components of cell and take their electron and become stable but it makes DNA, protein or lipid unstable Both exogenous and endogenous substances produce free radicals in cells and its surroundings. They can be produced from non-enzymatic reactions of organic compounds with oxygen as well as those initiated by ionizing radiations Pham-Huy *et al.,* 2008. This process may also occur in mitochondrion by oxidative phosphorylation. Different sources include radiations, ROS, RNS, Neutrophils and macrophages production, chemicals, smoking of cigarettes, beedi, cigars and industrial effluents. To prevent such condition antioxidants are use which is either obtained from plants source or prepared in laboratories. From different studies time to time it has been found that (ROS) induced diabetes pathogenesis by change in various physiological pathways like alteration in lipid peroxide and enzymatic system, by impairment of metabolism of glutathione and also by decrease vitamin c level in body. Complications which may arise due to oxidative stress induced diabetes are retinopathy, stroke, and neuropathy.

Mechanism of antioxidant obtained from polyphenols in managenent of diabetes: There are four routes-Chain breaking reaction e.g alphatocopherol which acts as lipid phase to trap ROD radical. Reducing the concentration of ROS e.g glutathione Scavenging initiating radicalse. Gsuperoxidase dismutase which act in aqueous phase to trap superoxide free radical chelating the transition metal catalyst; A group of compound serve as antioxidant function by sequestration of transition metal that are well developed pro-oxidant. Soobrattee *et al.,* 2005. The inhibition of intracellular free radical formation would provide a therapeutic strategy to prevent oxidative stress and the related diabetic vascular complications. Antioxidants may act at different levels, inhibiting the formation of ROS or scavenge free radicals, or increase the antioxidants defense enzyme capabilities. Supplementation with antioxidants and/or factors essential to nitric oxide (NO) production may potentially improve endothelial dysfunction in T2DM by re-coupling eNOS and mitochondrial function, as well as decreasing vascular NAD(P)H oxidase activity Hamilton *et al.,* 2007. Generally, the antioxidant pharmacotherapy can be divided in the use of antioxidant enzyme and substrates, biogenic elements, combined drugs, synthetic antioxidants, and drugs with antioxidant activity Hogan *et al.,* 2001. The enzymatic antioxidant systems, such as copper, zinc, manganese superoxide dismutase, gluthatione peroxidase, gluthathione reductase, and catalase may remove the ROS directly or sequentially, preventing their excessive accumulation and consequent adverse effects. Non-enzymatic antioxidant systems consist of scavenging molecules that are endogenously produced such as glutathione, ubichinol, and uric acid or derivatives of the diet such as vitamins C and E, carotenoids, lipoic acid, selenium, etc da Silva *et al.,* 2010. In a prospective cohort study, vitamin C intake was found to be significantly lower among incident cases of T2DM Feskens *et al.,* 1995.

Conclusion

Free radical is very reactive species which cause oxidative stress and produce harmful effect to our body. Environmental factors and unhealthy lifestyle influence oxidative stress in human's Free radicals are not only generated internally in our body system but also trough external sources like environmental pollution, toxic metals, cigarette smoke,

pesticides, etc., which add damage to our body system. Inhaling these toxic chemicals in the environment has become unavoidable in modern civilization. Use of antioxidant obtain from different plant contain adequate quantity of vitamin c can be used for terminating chain reaction involve in oxidative stress and prevent the danger of diabetes induced by oxidative stress. Antioxidant play important role in preventing diabetes complications because they destroyed free radical and enhance insulin secretion and and insulin sensitization.

REFERENCES

Bahadoran Z, Mirmiran P, Azizi F. 2013. Dietary polyphenols as potential nutraceuticals in management of diabetes: a review. *Journal of Diabetes & Metabolic Disorders,* 12(1): 43.

Barf T, Vallgårda J, Emond R, Häggström C, Kurz G, Nygren A, Larwood V, Mosialou E, Axelsson K, Olsson R, Engblom L. 2002. Arylsulfonamidothiazoles as a new class of potential antidiabetic drugs. Discovery of potent and selective inhibitors of the 11β-hydroxysteroid dehydrogenase type 1. *Journal of medicinal chemistry,* 29; 45(18):3813-5.

Bouayed J, Bohn T. 2010. Exogenous antioxidants—double-edged swords in cellular redox state: health beneficial effects at physiologic doses versus deleterious effects at high doses. Oxidative medicine and cellular longevity, 3(4):228-37.

Carr AC, Frei B. 1999. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. *Am J Clin Nutr.,* 69:1086-107.

Chandrasekara A, Shahidi F. 2010. Content of insoluble bound phenolics in millets and their contribution to antioxidant capacity. *Journal of agricultural and food chemistry,* 13; 58(11):6706-14.

Chevion M. 1988. A site-specific mechanism for free radical induced biological damage: the essential role of redox-active transition metals. *Free Radical Biology and Medicine,* 1;5(1):27-37.

Cho K.H., O. Wolkenhauer, 2003. Analysis and modelling of signal transduction pathways in systems biology, *Biochem. Soc. Trans.,* 31 (6), pp. 1503-1509

Da Silva SB, Costa JP, Pintado ME, Ferreira DC, Sarmento B. 2010. Antioxidants in the Prevention and Treatment of Diabetic Retinopathy - A Review. *J Diabetes Metab*., 1:111.

Defronzo RA. 2009. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*, 58: 773–95.

Dubey GP, Agrawal A, Dubey N, Dubey S, Dubey R. 2012. Deborah SM, inventors; SRM Univ, assignee. Novel herbal formulation for the prevention and management of type-2 diabetes mellitus and vascular complications associated with diabetes. United States patent application US 13/162,778, 14.

Feskens EJ, Virtanen SM, Rasanen L, Tuomilehto J, Stengård J, Pekkanen J, et al. 1995. Dietary factors determining diabetes and impaired glucosetolerance: A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetes Care,* 18:1104–12.

Frei B, England L, Ames BN. 1989. Ascorbate is an outstanding antioxidant in human blood plasma. Proc Natl Acad Sci U S A, 86:6377-81.

Fukuoka T, Uyama H, Kobayashi S. 2003. Synthesis of ultrahigh molecular weight polyphenols by oxidative coupling. *Macromolecules*, 4;36(22):8213-5.

Grassi D, Desideri G, Necozione S, Lippi C, Casale R, Properzi G, Blumberg JB, Ferri C. 2008. Blood pressure is reduced and insulin sensitivity increased in glucose-intolerant, hypertensive subjects after 15 days of consuming high-polyphenol dark chocolate. The Journal of nutrition, 1;138(9):1671-6.

Hamilton SJ, Chew GT, Watts GF. 2007. Therapeutic regulation of endothelial dysfunction in type 2 diabetes mellitus. *Diab Vasc Dis Res.,* 4:89–102

Hogan S, Zhang L, Li J, Sun S, Canning C, Zhou K. 2010. Antioxidant rich grape pomace extract suppresses postprandial hyperglycemia in diabetic mice by specifically inhibiting alpha-glucosidase. *Nutrition & metabolism,* 7(1): 71.

Kahn SE. 2003. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia*, 1;46(1):3-19.

Kalt W, Forney CF, Martin A, Prior RL. 1999. Antioxidant capacity, vitamin C, phenolics, and anthocyanins after fresh storage of small fruits. *Journal of Agricultural and Food Chemistry,* 15;47(11):4638-44.

Kanter MM, Eddy DE. 1992. Effects of Antioxident Supplementation On Serum Markers Of Lipid Peroxidation And Skeletal Muscle Damage Following Eccentric Exercise. Medicine & Science in Sports & Exercise, 1; 24(5): S17.

Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. 2004. Polyphenols: food sources and bioavailability. The *American Journal of Clinical Nutrition,* 1;79(5):727-47.

McCallum JL, Yang R, Young JC, Strommer JN, Tsao R. 2007. Improved high performance liquid chromatographic separation of anthocyanin compounds from grapes using a novel mixed-mode ion-exchange reversed-phase column. *Journal of Chromatography A, 27*;1148(1):38-45.

Modak M, Dixit P, Londhe J, Ghaskadbi S, Devasagayam TP. 2007. Recent advances in Indian herbal drug research guest editor: Thomas Paul Asir Devasagayam Indian herbs and herbal drugs used for the treatment of diabetes. *Journal of clinical biochemistry and nutrition,* 40(3):163-73.

Mossa JS. 1985. A study on the crude antidiabetic drugs used in Arabian folk medicine. *International Journal of Crude Drug Research,* 1;23(3):137-45.

National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes. 1979 Dec 1;28(12):1039-57.

Padayatty SJ, Katz A, Wang Y, Eck P, Kwon O, Lee JH, Chen S, Corpe C, Dutta A, Dutta SK, Levine M. 2003. Vitamin C as an antioxidant: evaluation of its role in disease prevention. *Journal of the American college of Nutrition,* 1;22(1):18-35.

Pham-Huy L.A., H. He, C. 2008. Pham-HuyFree radicals, antioxidants in disease and health IJBS, 4 (2), pp. 89-96.

Renders CM, Valk GD, Griffin SJ, Wagner EH, Assendelft WJ. 2001. Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systematic review. *Diabetes care,* 1;24 (10):1821-33.

Sedighi M, Bahmani M, Asgary S, Beyranvand F, Rafieian-Kopaei M. 2017. A review of plant-based compounds and medicinal plants effective on atherosclerosis. *Journal of research in medical sciences: The official Journal of Isfahan University of Medical Sciences,* 22.

Soobrattee MA, Neergheen VS, Luximon-Ramma A, Aruoma OI, Bahorun T. 2005. Phenolics as potential antioxidant therapeutic agents: mechanism and actions. Mutation

Research/Fundamental and Molecular Mechanisms of Mutagenesis, 11;579(1):200-13.

Tsao R, McCallum J. 2009. Chemistry of flavonoids. Fruit and vegetable phytochemicals: chemistry, nutritional value and stability, 13;5:131-53.

Tsao R, Papadopoulos Y, Yang R, Young JC, McRae K. 2006. Isoflavone profiles of red clovers and their distribution in different parts harvested at different growing stages. *Journal of agricultural and food chemistry,* 9; 54(16):5797-805.

Weinman EO, Strisower EH, Chaikoff IL. 1957. Conversion of fatty acids to carbohydrate: application of isotopes to this problem and role of the Krebs cycle as a synthetic pathway. *Physiol. Rev.,* 37: 252–272.

Weir GC, Laybutt DR, Kaneto H, Bonner-Weir S, Sharma A. 2001. Beta-cell adaptation and decompensation during the progression of diabetes. Diabetes, 50 (suppl 1): S154–59.

Xiao JB, Hogger P. 2015. Dietary polyphenols and type 2 diabetes: current insights and future perspectives. *Current medicinal chemistry,* 1;22(1):23-38.

Zamora-Ros R, Knaze V, Luján-Barroso L, Slimani N, Romieu I, Touillaud M, Kaaks R, Teucher B, Mattiello A, Grioni S, Crowe F. 2011. Estimation of the intake of anthocyanidins and their food sources in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *British Journal of Nutrition,* 106(7):1090-9.

Zhao F, Watanabe Y, Nozawa H, Daikonnya A, Kondo K, Kitanaka S. 2005. Prenylflavonoids and phloroglucinol derivatives from hops (Humulus lupulus). *Journal of natural products,* 28; 68(1):43-9

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