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LETTERS

Dietary Polyphenolics: Mechanistic role in control management of Diabetes and Metabolic Syndrome

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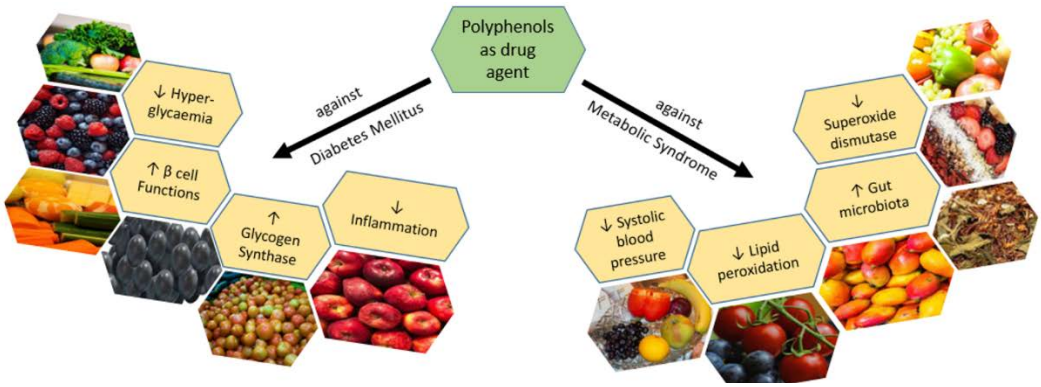
Review

ABSTRACT



The search for an antidiabetic drug is going on three fronts: technological (for instance, development of an artificial pancreas), biological (such as pancreas and islet cell transplants), and pharmacological. Our review focusses on the role of polyphenolics in pharmacological research for T2DM. Being the most abundant antioxidants in human diets, dietary polyphenols have proven efficacy against a variety of diseases in both animal and human trials. Here, the authors present a review of advances in using polyphenols obtained from diet against diabetes and metabolic syndrome. Authors have discussed the role of polyphenols in disease management, and their sources. In addition to that, current knowledge of prevalent pathways of their action in cases of diabetes and metabolic syndrome have been discussed. The future directions and perspectives about diet polyphenols as a good alternative to first-line drug interventions have been included.

Keywords: polyphenols, diabetes, metabolic syndrome, antioxidants, obesity.

INTRODUCTION

Polyphenols or phenolic compounds are secondary metabolism products of plants and comprise over 8000 phenolic compositions. They mainly exist in the conjugated form, where one or more than one sugar residue is attached to the hydroxyl groups, however, direct linkages of an aromatic carbon atom to the sugar unit also exist. The related sugars can be displayed as monosaccharides, disaccharides, and oligosaccharides. Associations with various other compounds, like organic and carboxylic acids, lipids, and amines, and linkages with several other phenols are also quite common.

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'Metabolic syndrome' (MS) is a clustering of insulin resistance, abdominal obesity, dyslipidemia, and increased blood pressure and is related to other comorbidities such as reproductive disorders, pro-thrombotic state, non-alcoholic fatty liver disease, and pro-inflammatory state.[1] As it is a cluster of several conditions and not a particular disease, various concurrent definitions have resulted.

Many MS elements are related to a high risk of evolving diabetes[2] and as defined by the NCEP ATP III, many features of the MS like impaired fasting glucose and impaired glucose tolerance levels, are displayed as predictors of diabetes. Insulin resistance and hyperinsulinemia are also identified as eminent features of diabetes.[3–5] Obesity, dyslipidemia, increased triglyceride levels, hypertension, high blood glucose levels, and reduced high-density lipoprotein (HDL)-cholesterol levels all confer an elevated risk of diabetes. Thus, MS might signal a pre-diabetic state. It is widely approved that lifestyle factors like obesity, smoking, and, a high-caloric diet contributes to the growth of MS, cardiovascular disease, and diabetes. Diabetes seems to be a more potent hazard for stroke and atherosclerotic

cardiovascular disease than MS. But, taken together, the details on diabetes, adiposity, and insulin resistance concerning the occurrence of stroke suggest a vital role for MS and insulin resistance.

Complications arising out of MS

There are several conditions related to MS that need brief attention. Some of these are directly related to the underlying insulin resistance and excess adiposity associated with the syndrome. The common complications arising from MS are also illustrated in figure 1.

1) *Cardiovascular disease*: The collection of metabolic disorders is directly associated with elevated cardiovascular disease risk. The wide majority of findings have found that MS patients have more cardiovascular disease and are at elevated risk for evolving cardiovascular disease.
2) *Type 2 diabetes mellitus (T2DM)*: Various studies have investigated the capability of MS to predict T2DM. The existence of MS elevates the risk and is very predictive of a new outset.[6,7] Numerous studies suggest that MS patients are 5-fold more likely to evolve type 2 diabetes and at twice the risk of heart disease.[8,9] Fascinatingly, the existence of both insulin resistance and MS has an additive impact and therefore these patients display a 6- to 7-times elevated risk for T2DM.[10]
3) *Non-alcoholic fatty liver disease (NAFLD):* The presence of NAFLD is a powerful predictor of MS,[11] and the liver fat corresponds to all the elements of MS. In MS patients, the liver fat content is remarkably elevated up to 4-times greater than those without having MS,[12] and the NAFLD occurrence exhibits elevation of 11-times in women and 4-times in men with MS.[13] Isoflavone and anthocyanin are potential agents to prevent NAFLD.[14]
4) *Polycystic ovarian syndrome (PCOS)*: MS is quite common in women, specifically obese women, with PCOS. The pervasiveness of PCOS is increasing, with reported rates as high as 28% in obese/overweight women.[15] The pathophysiology is highly debated and also unclear.
5) *Obstructive sleep apnea (OSA)*: Individuals with OSA possibly have features of MS. Additionally, disordered sleep is associated with insulin resistance and weight gain.[16,17] Some scientists have even proposed that OSA should be contemplated as an explanation for MS.
6) *Hypogonadism:* Men with MS exhibit greater hypogonadism prevalence.[18] Contrarily, hypogonadism is a threat factor for the growth of T2DM and MS.[19] Additionally, features of MS enhance with the replacement of testosterone. It has been also shown that MS is independently related to a higher prevalence of erectile dysfunction.[20,21]

WHY POLYPHENOLS SHOULD BE EXPLORED?

The polyphenols form a huge group of bioactive phytochemicals which include numerous sub-classes like flavonoids, phenolic acids, stilbenes, and lignans.[22] There exists a bi-directional relation between the microbiome of the human gut and polyphenols,[23] which mimics the relation between polyphenols and symbiotic and pathogenic microbial inhabitants in the root

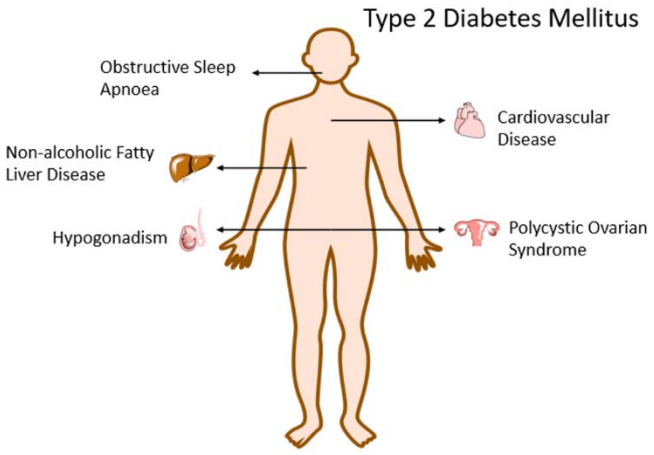

Figure 1: Common complications arising out of MS

complex of plants.[24] Polyphenols can regulate an individual's microbiome composition[25,26] and are metabolized by the microbiome to produce compounds with potent bioactivity.

The prime mechanism of action of the polyphenols was initially thought to be in their direct anti-oxidant impacts. However, various other possible molecular and biochemical mechanisms have been recognized, such as multifarious effects in inter- and intra-cellular signalling paths, like fat metabolism and modulating nuclear transcription aspects, and regulation of inflammatory mediators synthesis, which includes interleukin (IL)-1β, cytokines tumor necrosis factor α, and IL-6.[27–29] For instance, some flavonoids participate in glucose-regulation via downstream signalling which enhances β-cell proliferation, reduces apoptosis, elevates insulin secretion, and reduces inflammation, insulin resistance, and oxidative stress in muscles.[30] Phlorizin which is a dihydrochalcone is found in apples and can be imbibed in the small intestine. It can potentially be transferred by sodium–glucose transporters (SGLT). It is a competitive and specific inhibitor of SGLT in the kidney and intestine and so is useful in alleviating hyperglycemia.[31] Flavonoids consumed in an appropriate amount are believed to have favourable effects on diabetes and obesity.[32,33]

Polyphenols from numerous food sources like cocoa, apples, coffee, and tea, have been related to several health-associated benefits, which include T2DM and cardiovascular disease.[34,35] Possible mechanisms involve effects on blood pressure, cholesterol, endothelial function, platelet function, glucose metabolism, inflammation, and oxidative stress biomarkers, as well as indirect impacts arbitrated by the interaction with the gut microbiome.

ACCESSING POLYPHENOLICS: TYPES AND DIETARY SOURCES

Polyphenols are widespread in plant foods (fruits, vegetables, nuts, cereals, legumes, etc.) and beverages (wine, cocoa, cider, tea, beer, etc.). Their levels greatly vary even between the cultivars of the same species. For instance, flavonol and flavone glycoside formation highly depend on the light; so, their highest concentration is generally found in leaves and the outer portion

of the plants. A few of them are specified to particular food products (like flavanones in citrus food, phloridzin in apples, and isoflavones in soya), whereas others, which include quercetin, is found in almost all plant foods (wine, fruit, vegetables, leguminous plants, cereals, tea, etc.). Normally, food contains a complex polyphenolic mixture. For example, apples, contain chlorogenic acid, oligomers, or flavanol monomers and a small concentration of various quercetin glycosides, other hydroxycinnamic acids, and two glycosides of anthocyanins and phloretin.[36]

The existence of polyphenolic compounds in plant products is greatly influenced by environmental conditions (like climatic or agronomic factors) and genetic factors. Other factors, like germination, storage, degree of ripeness, processing, and variety, also affect the content of plant phenols. Polyphenols are partly responsible for the nutritional and sensory qualities of plant foods. The bitterness and astringency of beverages and foods depend on the polyphenolic content. In cereals and legumes, the prime polyphenols are phenolic acids, tannins, and flavonoids. Legumes are dark varieties with high polyphenolic content, like black gram ***(Vigna mango)***, red kidney beans, and black beans ***(Phaseolus vulgaris).*** Legumes also consist of isoflavones, however, vegetables are primarily made up of flavonoid glycosides. Berries are categorized by their increased anthocyanin content, however, citrus fruits are abundant in flavonoids. The leading phenolic composite in fruits is a flavonol, and its maximum concentrations appear in the skin.[37] Nuts are plentiful in tannins; oil seeds mainly contain phenolic acids, and olive oil involves both hydrolyzable tannins and phenolic acids.[38] Fruit juices usually possess very high flavanone content.[39] Tea fermentation results in differences in the composition of polyphenols: green tea is plentiful in flavanols, however, black tea is abundant in oxidized polyphenols.[40] The prime phenolic component of coffee beans is chlorogenic acid and that of cocoa beans is flavanol epicatechin, anthocyanins, and tannins. The polyphenolic compounds in wine include tannins, phenolic acids, anthocyanins, and other flavonoids.

Depending on the primary chemical structure of polyphenols, they are divided into 10 unique classes. Figure 2 illustrates the primary structure of some of the classes of phenolic compounds.[41] The main polyphenolic groups are flavonoids, phenolic alcohols, stilbenes phenolic acids, and lignans.

Polyphenolics and Diabetes

Due to the chemical structure of polyphenols, they exert several actions by interacting with various molecular pathways specifically relevant to glucose homeostasis. Certain mechanisms relate T2DM risk and polyphenols as shown in figure 3. These include attenuating digestion of carbohydrates and absorption of glucose, triggering insulin secretion, regulation of glucose release, and activation of glucose uptake and insulin receptors in the tissues that are sensitive to insulin.[42] Traditionally, many plants were employed for treating diabetes. These plants contained polyphenols that may explain their therapeutic actions.[43]

Mechanism of action

Polyphenols can act in the gut and besides absorption, they can affect several tissues, which include the adipose tissues, pancreas, liver, and muscle. In the gut, regulation of glycemic response is feasible, by stimulating starch absorption and digestion.[44] Numerous In vitro and animal findings highlight that polyphenols influence the markers of T2DM in various cells and

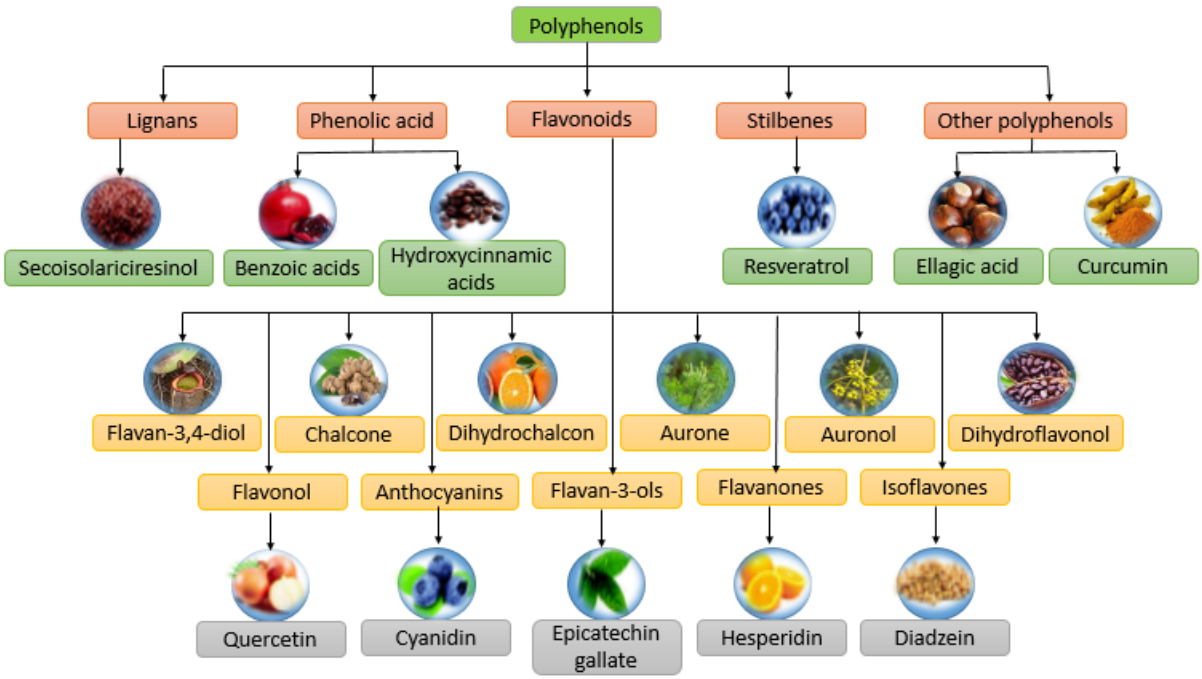

Figure 2: Primary categorization of typical polyphenols[41]

tissues by affecting the metabolism of hepatic glucose, elevating insulin secretion, and sensitivity in the pancreas.[45,46] Comprehending the mechanism of polyphenols is beneficial for the appropriate and correct design of human studies.

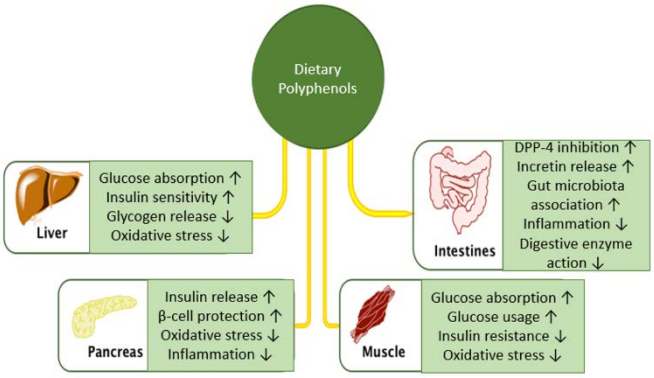

Figure 3: Modes of action of dietary polyphenols against diabetes

In the gut, polyphenols exert hypoglycemic impacts by impairing carbohydrate absorption and digestion. These polyphenols down-regulate the digestion of starch by blocking the hydrolysing enzymes of starch and weakening the absorption of intestinal glucose by either hampering glucose transporters or altering the gene expression associated with these transporters.[47–49] Inhibiting both the starch-digesting enzymes and glucose transporters slows down the glucose release in the circulation thus preventing hyperglycemic events, which is a threat factor for the evolvement of T2DM.[50] Polyphenols not only can block the absorption of glucose in the small intestine but can also restrict their re-absorption in the kidney.

Pancreatic and salivary α-amylases and intestinal α-glucosidases are the main enzymes for hydrolysing dietary starch in humans.[51,52] After a meal, suppression of these enzymes helps in diminishing peaks of postprandial glucose. The inhibitory actions of polyphenols on starch hydrolysing enzymes are well described.[53,54] Orange juice, hesperidin 1, and hesperidin 8 blocked the glucose transporter (GLUT)-5, GLUT-2, and SGLT-1 in Caco-2/TC7 cells.[55] In the small intestine, glucose is chiefly absorbed by GLUT-2 and SGLT-1 transporters, however, GLUT-5 is primarily involved in the absorption of fructose.[56] Furthermore, Naringenin 9 regulated the response of blood glucose in diabetic and normal mice primarily by modulating absorption of intestinal glucose, that too in a dose-dependent manner.[57] In another finding, grapefruit juice enhanced intolerance of glucose in streptozotocin (STZ)-induced diabetic rat models after a dose of glucose, proposing a post-absorptive procedure.[58]

Oxidative stress caused by hyperglycaemia plays a vital role in the evolution of diabetes and its complications. Moreover, oxidative stress affects insulin resistance and inflammation which directly damages the endothelial system. And polyphenols are evidenced by their impact on endogenous antioxidant systems. They are effective in lowering hyperglycaemia, and oxidative stress and preventing complications of diabetes. They elevate uncoupling protein 1 expression and prevent damage to the mitochondrial membrane and apoptosis. It also improves superoxide dismutase (SOD) actions and elevates deacetylation actions of SIRT 3, which in turn elevates the translation of various antioxidative enzymes. And nuclear factor erythroid 2-related factor 2 (Nrf2) activation blocks the transcriptional actions of nuclear factor kappa B (NF-κB), thus averting oxidative stress-induced inflammation (or insulin resistance). This mechanism is displayed in Figure 4.[59]

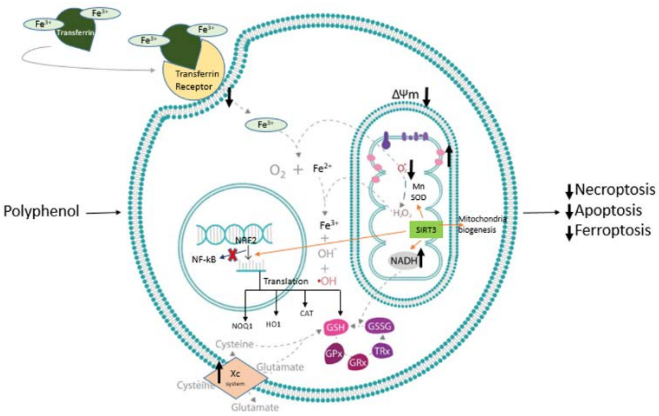

Figure 4: Polyphenolic impact on the antioxidant system. Taken from[59]; licensed under CC-BY-SA-4.0

Resveratrol (stilbenes) enhances the sensitivity of insulin and reduces hyperglycemia by the activation of the AMPK route. It also triggers the phosphatidylinositol 3-kinase (PI3kt)-protein kinase B (Akt) route which eventually elevates the phosphorylation rate of glycogen synthase kinase-3 and ultimately reduces the level of blood glucose. In diabetic cardiomyopathy, resveratrol targets various routes which are focused on mitochondrial dysfunctioning.[60] In a study, the administration of resveratrol enhances the sensitivity of insulin, elevates insulin efficacy, and elevates antioxidative activities during diabetes-induced Alzheimer's disease.[61]

Luteolin (flavone) present in onion leaves, basil, peppers, and broccoli, possesses antidiabetic activity. Of its antioxidant potential, it is capable of restoring brain impairments caused by diabetes.[62] It is a neuro-protective agent which reduces diabetic nephropathy prevalence and elevates deacetylase activity and protects the kidney from diabetic complications. It lowers the resistance of insulin by reducing the Tumor necrosis factor (TNF)-α by affecting β-cell functioning.[63]

Epigallocatechin gallate blocks hepatorenal barriers by managing the phosphoenolpyruvate enzyme which aids in gluconeogenesis. By blocking the gene expressions, catechins lower the level of cholesterol, triacylglycerol, and fatty acids, however, GLUT-4 and GLUT-1 expressions are up-regulated and the level of blood glucose is controlled.[64] Catechins also trigger Sirtuin 1 (SIRT1) expressions, activate proteins against oxidative stress, and lowers cardiovascular outcomes.[65] These also inhibit α-glycosidase and α-amylase and thus lowers hyperglycaemia.

Curcumin (flavonoid) is evidenced as hypoglycaemic agent. It obstructs the prevalence of diabetes by enhancing β-cell functioning, interrupting the death of β-cells, and reducing the resistance of insulin.[66] It regulates the level of blood glucose, enhances the level of fasting glucose by down-regulating G-6-Pase, and eventually reduces gluconeogenesis. It improves the resistance of insulin by blocking TNF-α.[67]

Quercetin (flavonol) is present in blueberries, citrus fruits, apples, beans, cherries, and tea. It has anti-diabetic and anti-inflammatory potentials by aiding in the activated protein kinase (AMPK) phosphorylation and GLUT-4 translocation. It aids in the secretion of insulin and β-cells regeneration. It also reduces the glucoinvertase and GLUT-2 actions thus lowering the glucose oral uptake.[68] It is an anti-hyperglycaemic agent because of its free radical elimination mechanism.

Portulaca oleracea L. (purslane) includes flavonoids and phenolic acid and can act as a therapeutic drug for diabetes by several action mechanisms, like reduction in resistance of insulin, HbA1C level, and level of glucose, elevation in the level of insulin, and stimulation of translocation of GLUT-4 by triggering AMPK and PI3K routes. This mechanism is schematically displayed in Figure 5.[69]

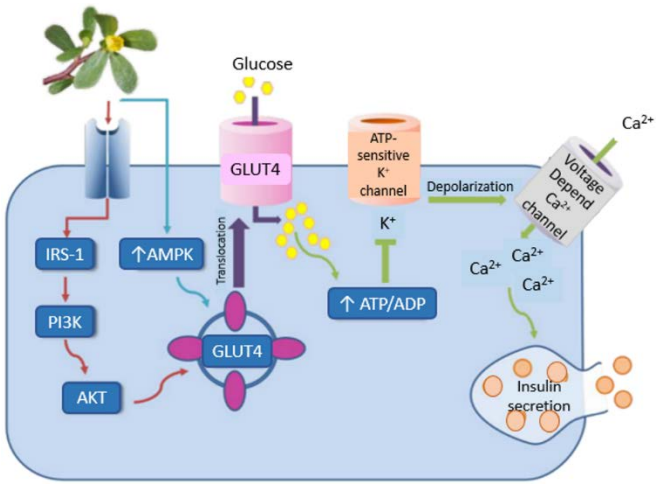

Figure 5: Mechanism of action of purslane in treating diabetes.[69]

The gallic acid present in green tea, dark chocolate, berries, and white tea is evidenced as an antihyperglycaemic agent. It lowers the resistance of insulin via the intraperitoneal pathway by triggering the AMPK route and further activating SIRT1. It plays a vital role in glycaemic control by stimulating the Akt route and down-regulating gluconeogenesis.[70]

Curcumin, catechins, resveratrol, quercetin, capsaicin, and genistein interacted with peroxisome proliferator-activated receptor (PPAR)γ although contradictory impacts were also seen. These polyphenols triggered the AMPK pathway and influenced inflammatory cascades by activating proteasomes and inactivating the transcription factors. Except for capsaicin, all these polyphenols at the inside of the mitochondrial membrane block the respiratory chain and adenosine triphosphate synthetase.[71] The excessive production of reactive oxygen species (ROS) by the chain of mitochondrial electron transfer is central to various independent action mechanisms (like activation of NF-κB and PKC, hexosamine and polyol route flux, formation of AGE) which are involved in adverse impacts of diabetes.[72] Thus all these polyphenols (antioxidants)[73–75] are effective in improving the adverse effects of diabetes.

Clinical Studies

Multiple studies have examined the relationship between different subclasses of flavonoids and T2DM threat with some controversial outcomes. Amongst the flavonol subtypes, only myricetin was related to a low incidence of T2DM. Also, apart from flavan-3-ol, no other flavonoid subgroups (flavonols, isoflavone, flavones, polymeric flavonoids, flavanones, and anthocyanins) were associated with T2DM risk.[76] In humans, proof of the polyphenolic effects on diabetes or glycemia threat is still very finite.

Numerous research studies have displayed that intake of flavan-3-ol brings about positive impacts on the cardio-metabolic effects, such as lowering the threat for diabetes mellitus, and cardiovascular-associated outcomes (i.e. myocardial infarction, cholesterol levels, and blood pressure).[77,78] A meta-analysis of resveratrol remarkably reduced total cholesterol, fasting glucose, diastolic and systolic blood pressure, and C-reactive protein (CRP); these effects were specifically noticed in those subjects with pre-existing non-communicable diseases (e.g. cardiovascular disease, T2DM).[79] A very preliminary and initial track of evidence for the genotype-polyphenol association emerges from the studies of coffee. Decaffeinated coffee consumption did not affect insulinemia or glycemia when absorbed with glucose, however, reduces the glucose-dependent insulinotropic polypeptide secretion and elevated glucagon-like peptide-1 (GLP-1) secretion, proposing that chlorogenic acid lowers the intestinal absorption rate of glucose.[80,81] And therefore, chlorogenic acid can converse the hyperglycemic impacts of caffeine. After the consumption of red-orange supplements involving anthocyanins, phenolic acids, and flavanones, no effect was observed on glycemia in T2DM patients. In another clinical study, patients with type 1 diabetes mellitus ingested high doses of diosmin and hesperidin. Such a supplementation did not affect glycemia, but it considerably lowered the glycated hemoglobin (HbA1c) levels.[82] Thus, polyphenols can limit the threat of diabetic complications. Various spice polyphenols may also enhance the resistance of insulin and glucose homeostasis, which can be seen in Figure 6.[83]

Furthermore, isoferulic and caffeic acid, when intravenously administered in rats, lowers fasting glycemia and also diminishes the plasma glucose elevation in a glucose tolerance test.[84] Whereas both these acids elevate the uptake of glucose by soleus muscle solitary from the streptozotocin-diabetic rats and by mice myoblasts, and rat adipocytes respectively.[85] Conversed results were also noticed for genistein and quercetin on rat adipocytes.[86] Genistein also suppressed the uptake of glucose by erythrocytes and HL-60 cells.[87] More fascinatingly, some hypoglycemic impacts were also seen with polyphenols that are administered orally, soon before the consumption of glucose source.

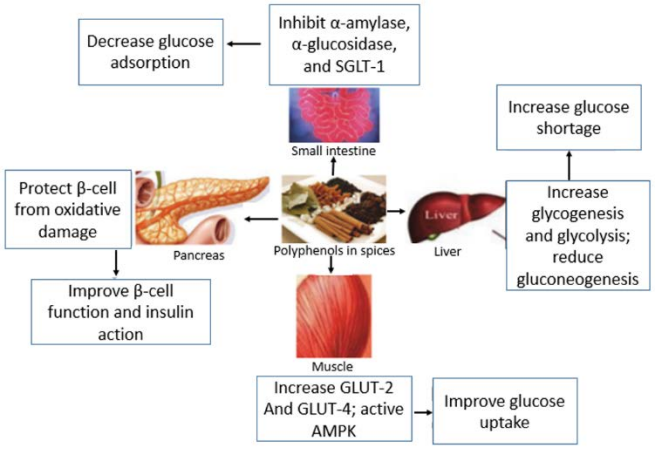

Figure 6: Impact of spice polyphenols on diabetic patients.[88]

In a study, it was observed that a diacylated anthocyanin lowered the glycemia peak persuaded by the consumption of maltose in normal rats.[89] Also, in rats, an imprecise leucodelphinidin reduces fasting glycemia and, the peak of plasma glucose in the glucose tolerance test and equivalent effects were noted with 4-hydroxybenzoic acid.[90] Another is green tea which includes catechins, like epicatechin, epicatechin gallate, gallocatechin, epigallocatechin gallate, and epigallocatechin. Catechins enhanced the glucose tolerance persuaded by sucrose or starch ingestion in rats.[91] Epigallocatechin gallate blocks the oral uptake of glucose by SGLT-1, highlighting its potential to reduce blood sugar levels.[92] In diabetes, the administration of green tea lowers albuminuria when the patients are receiving maximum renin-angiotensin dosage. This is because of the decrease in podocyte apoptosis by the wingless and int-1 route activation.[93] In a study of mice, a fermented tea extract displayed hypoglycemic impacts. Similar effects were noticed in mice or rats rendered diabetic by alloxan or streptozotocin.[94] Although, Streptozotocin diabetic rats displayed elevated sensitivity to thrombosis and platelet aggregation, this anomaly can be ameliorated by various catechins of green tea.[95] Also, in alloxan diabetic rats the oral administration of green tea showed a reduction in serum glucose tolerance and an elevation of the antioxidant power.[96] Apart from this, both in the absence or presence of insulin, green and black tea extracts and epigallocatechin gallate also elevated the uptake of glucose by rat epididymal adipocytes.[97] Until now, it is difficult to elucidate these contradictory outcomes.

Apart from this, an extract of Aegle marmelos (an edible plant) was investigated for its anti-diabetic activity. It showed cytoprotective ability and cytocompatibility against oxidative stress caused by hyperglycaemia. In diabetic mice, it remarkably improved dyslipidemia state, level of serum blood glucose, pro-inflammatory marker levels, and status of antioxidants.[98] The waste part of fruits like pomace, peels, and seeds also contain various polyphenols (flavonoids, tannins, and phenolic acids). And thus can be used to treat numerous degenerative disorders like diabetes.[99] The mechanism of action of polyphenols to treat diabetes and its complications is displayed in Figure 7.[100]

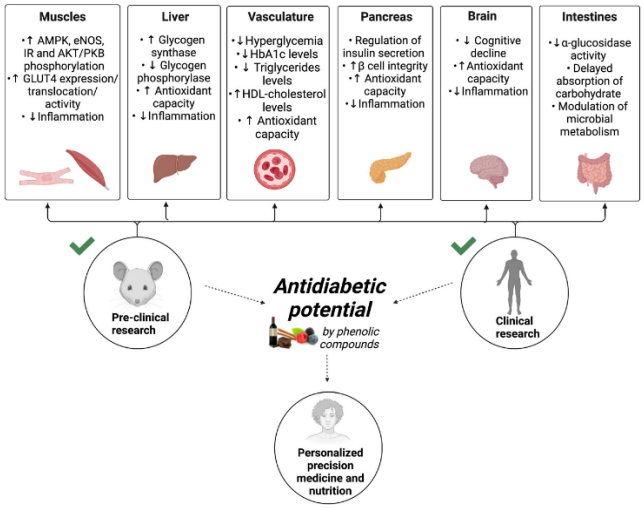

Figure 7: Mechanism of action of polyphenols in clinical and pre-clinical diabetic research. Taken from [100]; licensed under CC-BY-SA-4.0.

The results from various epidemiological research are inconsistent, which may be because of the huge variations between disparate populations and the measurement errors in polyphenolic dietary intake.[101] Some of the meta-analyses of clinical trials of polyphenols against diabetes mellitus are listed in table 1.

Table 1: Clinical Trials of Polyphenols against Diabetes Mellitus

Source And Active Polyphenols	Trial Structure (Method)	Findings	Ref
Extra-virgin olive oil Unidentified	• 11 overweight T2DM patients • 4 weeks on refined olive oil (without polyphenols), then 4 weeks on polyphenol-rich extra-virgin olive oil	• Significant reduction in fasting blood glucose and HbA1c levels • Improved circulatory inflammatory adipokine profile	102
Diet Flavonoids (flavanones, dihydroflavonols), stilbenes	• 3430 non-diabetic elderly subjects studied over an average of 5.51 years on the Mediterranean diet • Observational cohort analysis, part of the PREDIMED trial	• 314 new cases of diabetes • 28% reduction in new-onset diabetes • Reduced risk of diabetes in elderly at high cardiovascular disease risk	103
Diet Flavonoids	• 1111 T2DM case-control pairs from the NHS and NHSII cohorts – US Women • Spot urine sample quantification of eight polyphenol metabolites (naringenin, hesperetin, quercetin,	• Higher urinary excretion of hesperetin linked to lower T2DM risk • No other significant correlation was found, especially in the long-term follow-up	104

	isorhamnetin, catechin, epicatechin, caffeic acid, and ferulic acid) by LC/MS		
Supplements Quercetin	• 22 healthy males under a randomised, double-blinded, placebo-controlled, cross-over trial • 4 weeks of 500 mg daily supplements of quercetin	• Significantly lower uric acid in plasma (a risk factor for T2DM) • No effect on fasting glucose levels, blood pressure, and uric acid excretion	105
Tea or tea extract various	• Meta-analysis of ten trials (608 subjects) studying tea or tea extract benefits to T2DM patients	• In >8-week periods, blood glucose levels and waist circumference reduced	106
Brazilian green propolis various	• Double-blind randomised placebo-controlled study of 80 T2DM patients over 8 weeks	• Prevention of worsening of blood uric acid and EGFR levels in T2DM patients seen	107
Apple extract drink Phlorizin, quercetin, epicatechin	• Randomized, controlled, double-blinded, cross-over acute trial of 30 healthy men and women between 18-70 over 4 h, at 4 visits spread across 28 days • 4 different dosing quantities	• Significant fall in postprandial glucose level in first 30 min, delay in T_{max} • Lowering of postprandial insulin concentrations • No impact on gastric emptying and renal glucose expulsion	108
Red raspberry various	• 32 overweight prediabetic and insulin resistant and healthy individuals, in a randomised, controlled, three-arm, single-blinded, crossover trial • 3 different dosings of frozen red raspberries at breakfast on 3 days, measurements taken after 8 h than 24 h on	• Peak insulin and glucose reduced • Less insulin area under the curve over 2 h which may improve insulin sensitivity • No significant oxidative stress and inflammatory biomarkers detected	109
Cranberries various	• 35 obese individuals with impaired glucose tolerance/high glucose levels • Randomised, double-blind, placebo-controlled, parallel-designed pilot trial over 8 weeks • 450 ml of low-energy cranberry beverage daily	• No notable impact on insulin sensitivity • TAG lowered • Changes are seen in oxidative stress biomarkers in obese and inflamed subjects	110
Green tea extract various	• 120 overweight non-diabetic women in a double-blind, placebo-controlled, randomized trial • Green tea extract and metformin were given individually and in combination over 12 weeks	• No major blood glucose level control observed • Green tea alone had greater fasting glucose reduction, but not when in combination with metformin • Total cholesterol and low-density lipoprotein (LDL)-cholesterol were also reduced significantly by green tea	111
Kiwifruit various	• Meta-analysis of 5 randomised controlled trials with 489 participants including hypertension, T2DM, hypercholesterolemia patients, and male smokers (i.e. all at risk of developing heart disease)	• No direct improvement in the metabolic health of patients • A general trend of improvement seen post-kiwifruit use	112
Soy-based products Genistein	• The offspring of non-obese diabetic (NOD) mice was exposed to genistein with a dosage of 20 mg/kg body weight • From embryonic day (7) to postnatal day (21)	• The gut microbiota-associated immune-modulatory mechanism • A sex-specific impact of genistein was seen on diabetes followed by perinatal exposure	113
Red cabbage extract Anthocyanins	• Diabetic Wistar rats were induced by STZ (60 mg/kg). • After 7 days, STZ rats were given red cabbage extract (800 mg/kg) and administered for 4 weeks	• Decreased level of blood glucose, protected β cells, and elevated serum insulin	114
Red wine Resveratrol	• 13 diabetic patients (men and women both) were subjected to the trial. • Twice daily dosages of resveratrol in 500 mg capsules were given to the patients for 60 days.	• Strong anti-oxidative and anti-diabetic effects were seen	115
Grapes Resveratrol	• STZ-induced mice were ovariectomized and injected with unique 17β-estradiol (0.01, 0.1, or 1 mg/kg) and resveratrol (0.1, 1, or 10 mg/kg) concentrations, subcutaneously for 4 weeks.	• Reduced level of blood glucose, protected pancreatic β cells, enhanced plasma insulin level, and anti-oxidative potential is observed	116
Green tea Epigallocatechin gallate	• 12 NOD mice (32 weeks old) were treated with epigallocatechin gallate for study.	• Increased levels of IL-10 and elevated levels of plasma insulin were observed.	117
Silymarin	• Diabetic-induced rats were	• Hepatic transaminases,	118

flavonolignans, flavonoids	treated with silymarin (120 mg/kg) for about 10 days	plasma creatinine, blood glucose, and glycaemic levels were decreased. • Protective impacts on DNA were observed	
Coffee various	• Wistar rats were treated with 3.9 g/kg of coffee for 8 weeks	• The activity of α-glucosidase is reduced in the small intestine	119
Silymarin flavonolignans, flavonoids	• Diabetic obese mice were fed orally with silymarin (30 mg/kg) for around 30 days	• Enhanced insulin resistance and glucose intolerance were observed.	120

POLYPHENOLICS AND METABOLIC DISORDERS

A low-grade chronic inflammation and pro-oxidant level are the indications of MS and its seriousness depends on the number of prevalent components. Polyphenols seem to be a good dietary candidate to prevent the progression of MS by their explicit anti-inflammatory and anti-oxidant actions.[121] Also, polyphenols have been described to enhance insulin resistance,[122] to improve lipid profile,[123] and reduce body weight,[124] and blood pressure.[125] Yet, the dietary strategies might be less efficacious for patients having a cluster of threat factors as a whole as compared to those patients having one or two threat factors. Furthermore, the impacts of polyphenolic intake on healthy subjects or low-moderate cardiovascular-risk individuals may differ due to their pathological attributes. So, the outcomes reported in human studies are still contrary, and the metabolic gains of polyphenols greatly depend on the population considered. Also, a latest systematic review proposed that polyphenols are efficient in lowering some MS characteristics, however, there is no single extract, polyphenol, or food which can cleverly act on all MS characteristics.[126]

Pathways of Action against MS

The antioxidant capability of polyphenolic compounds is described by their chemical structure, donor electrons present in the ring structure, position and number of conjugation groups, hydroxyl groups, and degree of glycosylation. Despite their rapid elimination and metabolism, and low bioavailability, the antioxidant effects may be of clinical importance when contemplated in a diet rich in vegetables and fruits. In MS women, cranberry juice elevated plasma anti-oxidant capability and reduced oxidized low-density lipoprotein and malondialdehyde,[127] and freeze-dried blueberries reduced serum oxidized low-density lipoprotein and malondialdehyde and elevated concentrations of hydroxynonenal in both women and men with MS.[128] MS patients getting extra virgin olive oil exhibit elevation in total radical-trapping antioxidant parameter (TRAP), but there was no effect on hydroperoxide levels, advanced oxidation protein product indexes.[129] Cell signalling pathways, enzymes, and gene expression associated with inflammation are also targeted by polyphenols, which can better explain their favourable effects on vascular inflammation, endothelial function, and metabolic disturbances. In MS patients, berry addition in the form of extract, juice, or powder decreases the overall score of inflammation and enhances endothelial activities.[130] It is suggested that MS should be described by a multifactorial approach because of the whole dietary plan and also elevated physical activity, which is known to be an effective anti-inflammatory technique.[131]

Caffeic acid is used for preventing and treating MS as it possesses anti-inflammatory, anti-obesity, and anti-oxidative stress properties. It is used to treat obesity-associated atherosclerosis as it blocks the NF-κB route, averts inflammation, and down-regulates PIC levels, and IL-8 production.[132] The anti-oxidative stress and anti-inflammatory effects were attained by blocking the E-selectin expression, and NF-κB translocation and up-regulating the Nrf2/electrophile responsive route.[133] It is also used to treat diabetes and its complications by increasing C-peptide, leptin, and plasma insulin levels and decreasing HbA1c, fasting glucose, plasma glucose, triglycerides, and total cholesterol levels.[134]

Silibinin or Silymarin (flavonolignans) possess antihypertensive, hepatoprotective, anti-obesity, antioxidant, antidiabetic, antiatherosclerotic, and lipid-lowering impacts. It is used for treating MS by regulating the Nrf2 and blocking the mitogen-activated protein kinase (MAPK) routes. It triggers the Nrf2 route by initiating the estrogen receptors of β-cells and affecting the gut-brain-liver axis. Also, it blocks the p38 MAPK phosphorylation route and aids in hypercholesterolemia treatment.[135] It regulates blood pressure by blocking the aggregation of platelets and regulating the vascular tone. Moreover, it lowers renal damage by reducing the micro-albumins in urine excretion. It regulates lipid profile by reducing hepatic steatosis and focusing on hyperlipidemia and NAFLD. It also enhances liver functioning through its cytoprotective and antioxidant impacts.[136]

Quercetin (flavonol) is very effective in treating and preventing MS. It displays an anti-inflammatory impact by triggering the AMPKα1/ SIRT1 route, lowering PIC levels, and improving white adipose tissue.[137] It displays anti-oxidant potential and averts oxidative stress by lowering the cytochrome P450 2E1 activity. Both its antioxidant and anti-inflammatory effects could be seen in Figure 8.[138] It also stimulates the secretion of adiponectin, and metabolism of lipids and down-regulates expression of PPAR-γ.[139]

Genistein (isoflavone) is used against obesity as it up-regulates glyoxalases and adiponectin expression, and down-regulates PPAR-γ.[140] It also influences the release of insulin by blocking phosphodiesterase and collecting adenosine monophosphate.[141] It also inhibits various other adipocyte-specific proteins, lipogenic enzymes, and SREBP-1c.

Anthocyanins (flavonoids) are very effective in treating MS disorders as they possess anti-inflammatory, antioxidant, and antibacterial properties. It lowers the resistance to insulin and body weight, thus improving glucose tolerance. It displays the anti-inflammatory impact by lowering the PIC levels, blocking the inhibitory κB-α degradation and NF-κB signaling route. It is also studied for its effects on inflammation and cardiovascular

disorder.[142] Down-regulation of blood pressure, malondialdehyde, oxidized LDL, and hydroxynonenal levels were observed in MS patients.

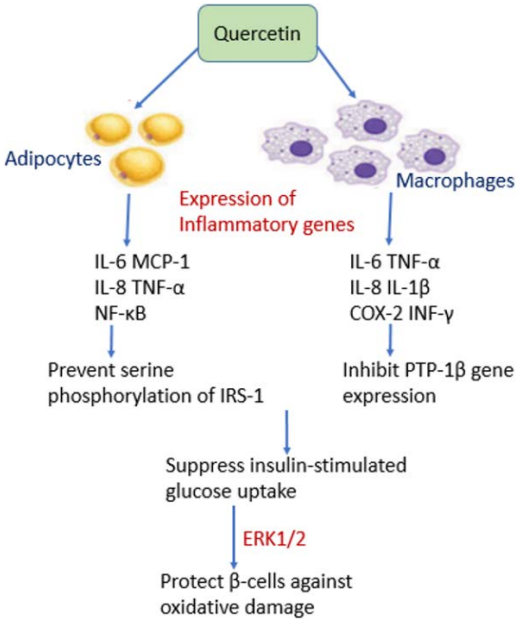

Figure 8: Quercetin shows both anti-inflammatory and antioxidant effects.135

Purslane displays various therapeutic properties like anti-inflammatory, hypolipidemic, antipyretic, analgesic, hypoglycemic, and many more. It also lowers inflammation, lipid profiles, and oxidative stress; enhances glucose absorption, weight gain, and insulin level. Thereby, lowering MS complications, which can be seen in Figure 9.[69]

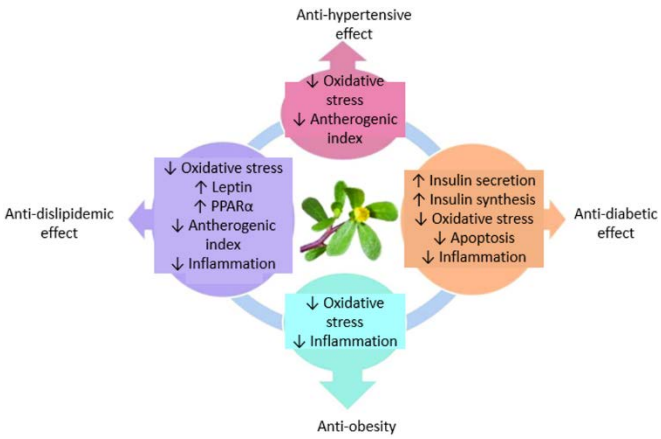

Figure 9: Schematic description of purslane in averting complications of metabolic syndrome.[69]

Baicalin (flavonoid) possesses lipid-reducing, antioxidant, and anti-inflammatory impacts and could be employed against obesity, the resistance to insulin, NAFLD, atherosclerosis, and many more. It down-regulates SREBP-1c, fatty acid synthase, and TNF-α and up-regulates acetyl-coenzyme A carboxylase phosphorylation, GLUT-4, and AMPK.[143] It also shows anti-adipogenic properties by regulating the Wnt/β-catenin route. Moreover, it elevates the expression of carnitine palmitoyltransferase-1, and PPAR-α, blocked NF-κB and p38 mitogen-activated protein kinase signalling routes, down-regulates pro-inflammatory cytokines (PIC) levels and up-regulates antioxidant potential by elevating glutathione peroxidase, catalase and SOD activities.[144]

Green tea can effectively prevent MS. It is a strong anti-oxidising agent as it can elevate the glutathione peroxidase and catalase activities, restore the SOD and malondialdehyde levels, and decrease the TNF-α expression. Lowering the accumulation of fat plays an important role in treating NAFLD. Tea catechins are also effective in enhancing the metabolism of the liver by reducing the levels of SREBP-1c, hormone-sensitive lipase, Fas, alanine transaminases, and fatty acids.[145]

Naringenin (flavanones) is an anti-atherosclerosis, analgesic, anti-inflammatory, hypolipidemia, and antioxidant agent. To reduce the blood lipid, it elevates the expression of uncoupling protein-2, carnitine palmitoyltransferase-1, and PPAR-α, and down-regulates the levels of a phospholipid, and triglycerides. Moreover, by elevating the expression of adiponectin, blocking liver X receptors-α, and triggering PPAR, it may treat atherosclerosis and adiposity. It is also evidenced to down-regulate inflammatory infiltration, NF-κB route, and PIC levels.[146]

Clinical Studies

Currently, clinical trials are the best way to illustrate the impacts of polyphenolic foods on human health. A single polyphenol can modulate various biomarkers associated with MS and that may not suggest the enhancement of MS progression. The consumption of blueberries has been demonstrated to reduce oxidative stress and blood pressure[147] and enhance insulin sensitivity and endothelial functioning[148] in MS patients. Whereas, neither cranberry nor bilberry supplementation exhibited differences in body weight, lipid, or glucose metabolism, in contrast to the control group.[149] Intake of red wine remarkably diminished C-reactive protein, systolic blood pressure, glucose, triglycerides, diastolic blood pressure, total cholesterol, and elevated levels of HDL in MS patients.[150,151] A meta-analysis of grape polyphenols suggested that they are capable of lowering only systolic and not diastolic blood pressure in MS patients. Numerous prospective and cross-sectional studies have concluded that the Mediterranean diet possesses favourable effects on various components of MS and its related pro-oxidative status and low-grade inflammation. It might be a promising implementation for both MS management and prevention.[152]

Multiple animals and in vitro studies have suggested unique mechanisms where polyphenols play a potent role in lowering obesity. In a Chinese cohort, the regular tea consumers exhibited less percentage of waist-to-hip ratio and body fat in contrast to the people who do not consume tea.[153] A Netherlands cohort research demonstrates that a high intake of catechins, flavones, and flavonols, is related to a lower elevation of body mass index (BMI).[154] Similarly, the intake of chocolate in a cohort study was

associated with diminished BMI in patients under statin treatment.[155] Besides, the beneficial effects of polyphenolic foods on lowing body weight, the latest review highlighted that the weight loss persuaded by polyphenolic compounds is not clinically pertinent in obese and overweight individuals. Thus, a long randomized interventional assessment of polyphenolic foods is required.

Polyphenolic intake has been associated with a reduced risk of T2DM and insulin resistance. At high cardiovascular risk, in a Mediterranean cohort, total polyphenol intake was related to a diminished risk of T2DM.[156] In Nurses' Health Studies (NHS), high anthocyanins intakes are remarkably related to reduced risk of T2DM.[157] Moreover, in a cohort study, it was observed that dimers and trimers of proanthocyanidin and monomers of flavan-3-ol are related to a diminished risk of T2DM.[158] However, in the Women's Health Study, no relation was seen between T2DM risk and flavonoid consumption.[159] Nevertheless, consumption of tea and apple was related to decreased risk of T2DM. On the other hand, in a Japanese cohort, the intake of green tea is inversely related to diabetes risk.[160]

A meta-analysis demonstrates that consumption of green tea reduces LDL and total cholesterol with no impact on HDL cholesterol, though few studies exhibited that consumption of green tea elevated HDL cholesterol levels.[161] A meta-analysis of hibiscus tea effects exhibited that this sour tea reduced blood pressure levels,[162] whereas consumption of green tea reduces systolic blood pressure.[163] In a study of T2DM patients, high intake of polyphenols is related to decreased triglycerides and LDL levels and increased HDL cholesterol levels.[164] Similar results were observed in the Moli-Sani cohort research.[165] In another cohort, a high intake of polyphenols was inversely related to the levels of triglyceride but not to the levels of HDL, total, or LDL cholesterol.[166]

Numerous observational findings have disclosed a positive association between diminished hypertension prevalence and a high intake of vegetables and fruits.[167] At increased cardiovascular risk, in a Mediterranean population, total intake of polyphenols was correlated with diminished hypertension prevalence and blood pressure levels. Whereas, in Brazilian research, an inverse correlation was found between hypertension and polyphenolic intake.[168] In the NHS cohort, it was observed that high strawberries and blueberries intake has been correlated with lowered risk of hypertension.[169] However, the latest meta-analysis highlights that blueberry supplementation does not reduce blood pressure. Thus polyphenols, especially flavonoids, exhibit potent antihypertensive impacts, which can differ in association with the disease status. Moreover, while treating metabolic parameters, flavonoids do not affect BMI and body weight.[170]

Studies have displayed that polyphenolic compounds have decreased fasting and postprandial hyperglycemia and enhanced insulin sensitivity and secretion. Gut microbiota is an attractive target for identifying the polyphenolic roles in weight loss and metabolic balance.[171] Studies related to the implications of polyphenols in averting diabetes, insulin resistance, and metabolic syndrome are limited. A major shortcoming in clinical research is the quick metabolism and heterogeneous bioavailability of polyphenols. Some findings of the meta-analysis of polyphenols against MS are listed in table 2.

Table 2: Clinical Trials of Polyphenols against MS

Source and Active Polyphenols	Trial Structure (Method)	Findings	Ref
Red wine various	• 3897 elderly patients at cardiovascular disease risk under the PREDIMED study	• Moderate drinkers were found to have a reduced risk of MS, lower risk of abnormal waist size, lower HDL • High BP and higher fasting glucose levels observed in moderate drinkers • Stronger association in female subjects • Overall lower prevalence of MS	172
Coffee various	• 93179 subjects in a Mendelian randomization study to check if high coffee intake is capable of reducing obesity, MS and T2DM • Also evaluated genetic variants associated with obesity, MS, and T2DM to correlate with high coffee intake	• Coffee intake is related to higher BMI, waist size, blood pressure, and total cholesterol, but not to glucose levels • No notable correlation between genetically derived coffee intake and associated diseases	173
Coffee various	• Meta-analysis of 15691 Korean women to evaluate the relation between coffee intake and risk of MS	• Inverse correlation between coffee consumption and MS prevalence among subjects • If lifestyle, socioeconomic factors, etc. included, a 40% lower risk seen in the highest coffee intake cohort	174
Diet Phenolic acids, stilbenes	• 8821 Polish adults surveyed for dietary habits and total phenolic intake calculated	• Subjects with higher polyphenolic intake demonstrated lower BMI, waist circumference, BP, and triglycerides • The inverse association with MS	175
Green tea Catechins	• Zucker Fatty rats were treated with green tea extract (200 mg/kg) for 8 weeks	• Reduction in visceral fat, insulin resistance, body weight, glucose level, and insulin level were observed	176
Cocoa beans	• Zucker diabetic male fatty rats were fed with 10% cocoa-rich diet for 10 weeks	• Elevated intestinal integrity, glucose homeostasis, and improvement of	177

Flavanol epicatechin, anthocyanins, and tannins		gut microbiota were observed	
Red wine Resveratrol	• Hypertensive rats were treated with 50 mg/kg of resveratrol for 28 days	• A reduction in systolic blood pressure was observed	178
Curcumin flavonoid	• Wistar rats induced with STZ and high-fat were treated with 80 mg/kg curcumin for 8 weeks	• Reduction in lipid peroxidation, insulin resistance, glucose levels, and lipid levels was observed	179
Red grape pomace Anthocyanins, flavan-3-ol, procyanidins	• 12 healthy men (20-40 years) were treated with grape pomace for about a week	• Reduction in postprandial insulin level and insulin secretion and elevation in insulin sensitivity was observed.	180
Mango Gallic acid, flavonoids	• 9 obese and 12 lean subjects were fed with mango for around 6 weeks	• Reduction in systolic blood pressure: In lean subjects • Reduction in plasminogen activator inhibitor-1 and HbA1c levels: In obese subjects	181
Cherry juice Gallic acid	• 20 women and 17 men were fed with tart cherry juice for 12 weeks	• Reduction in LDL cholesterol and systolic blood pressure is observed	182
Grape pomace Flavan-3-ol, anthocyanins	• Atleast 1 MS phenotype common in all 50 subjects • Dried grape pomace was given for around 6 weeks	• Elevation in insulin sensitivity and reduction in insulin resistance and fasting insulinemia were observed	183
Pomegranate extract Flavonoids	• Zucker diabetic male fatty rats with MS were fed with pomegranate extract with a dosage of 100-200 mg/kg.	• An increase in catalase activity and a reduction in oxidised LDL, SOD, and ROS levels were observed • kidney injury markers were reduced	184
Silymarin flavonolignans, flavonoids	• Obese mice suffering from NAFLD • 30 mg/kg silymarin was given for about 4 weeks	• Down-regulation of liver steatosis • Up-regulation of metabolism and lipid profile was observed	185
Mulberry fruit Flavonoids and anthocyanins	• Obese mice with MS were taken for study. • The mulberry fruit was studied alone and in association for about 14 weeks.	• A decrease in the accumulation of fat and body weight, enhancement of insulin resistance, and dyslipidemia regulation were observed. • The association studies showed better results. • Improvement in fecal metabolites and the composition of gut microbiota was also observed.	186
Strawberries various	• MS subjects (adults) were studied with strawberry powder for 14 weeks.	• Reduction in targeted metabolites, insulin resistance, and endothelial dysfunctioning was observed. • Elevation in untargeted metabolites, and enhancing the cardiometabolic functioning of adults were seen.	187
Silymarin flavonolignans, flavonoids	• The subjected obese mice were fed a high-fat diet • Silymarin (30 mg/kg) oral was given orally for 4 weeks	• Mitochondrial dysfunctioning was preserved • Improvement in oxidative stress	188

CONCLUSION AND FUTURE PERSPECTIVES

It is evident from the wide body of work compiled herein that polyphenols do show a positive impact on the prevention of T2DM and MS, as well as improving patient outcomes. The wide availability and diversity of polyphenol sources in diets across the world make it an equitable and accessible means of lowering the prevalence and risk of these debilitating conditions. Polyphenols assist in the protection of pancreatic β-cells, help in the improvement of blood glucose level by the activation of the mechanistic signaling pathway which reduces oxidative stress, help in the inhibition of the activity of α-amylase /α-glucosidase and assist glucose uptake in adipocytes and muscle cells. Due to all these, they are a wonderful tool in controlling the complications of diabetes such as neuropathy, retinopathy, nephropathy, and cardiovascular diseases. However, it is natural that with such an enormous and varied class of compounds, due attention must be devoted to understanding underlying mechanisms and pathways, including potential side effects. As the impacts of polyphenolic compounds in clinical trials and human studies are still limited. It is needed to identify and validate the major health benefits of polyphenolics on T2DM and Met-S. That would be possible only if factors such as standardization of dosage, biopharmaceutical and pharmacokinetic properties, bioavailability and bio-accessibility of polyphenols, duration of intake, effect of 'pure compounds vs extract', identification of key targets and clarifications of the clinical indications of polyphenolic compounds are taken care of. There is, thus an urgent need of optimization and modification of the structures of polyphenolics so that synthesis of polyphenolic derivatives having first-rate properties such as increased bioavailability, steady metabolism, good solubility, low toxicity, fewer side effects and excellent biological activity can be achieved. One other very important factor that makes dietary polyphenols significant with respect to diabetes and Met-S is the fact that pathogenesis of these diseases involve dialogue between

the gut microbiome and human genome and the dietary habits of the host affect the structure of the intestinal flora.

Various studies have begun evaluating polyphenols for specifically targeted usage, for instance against diabetic neuropathy and retinopathy.[189,190] There is also work being done on developing combinatorial approaches using polyphenols from different sources, including artificial supplements, to provide customized benefits, as was the case in traditional diets across the globe. Lastly, with growing advancements in analytical techniques, data analysis, and improved understanding of the role and mechanism of polyphenols across diseases, we believe that they may have the potential to substitute the need for first-line drug interventions.

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