Review

Effects of Fruit and Vegetable Polyphenols on the Glycemic Control and Metabolic Parameters in Type 2 Diabetes Mellitus: A Review

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ABSTRACT: The high prevalence of diabetes in recent decades has been associated with lifestyle changes and dietary habits correlated with economic development. Fruits and vegetables are a vital source of nutraceuticals and components of the healthy diet recommended in the medical nutrition therapy for type 2 diabetes mellitus (T2DM) to prevent hyperglycemia and related complications. They are low in calories and rich in dietary fiber, consist of many polyphenols, and are an essential component of a healthy lifestyle. Recently, researchers have developed a significant interest in understanding the effects of polyphenols (flavonoids and non-flavonoids) on blood glucose levels. In this review, the authors summarize the effects of polyphenols commonly found in the fruits and vegetables, such as resveratrol and anthocyanins, on the glycemic control and metabolic parameters, based on human clinical trials. Significant reductions in fasting blood glucose, glycated hemoglobin, and low-density lipoprotein cholesterol levels were reported after resveratrol, anthocyanin, and naringin were administered to patients with prediabetes and diabetes. Decreased insulin levels were observed after resveratrol intervention but not with the other types of polyphenols. These effects of polyphenolic compounds on the glycemic and metabolic parameters might be mediated by multiple pathophysiological mechanisms, such as activating regulator proteins to increase insulin signaling and eventually suppress insulin resistance. The benefits of certain polyphenols on T2DM remain ambiguous; therefore, further studies, especially clinical trials, are required to substantiate the available evidence.

Keywords: diabetes mellitus, glucose, intervention, polyphenol, vegetable

INTRODUCTION

Diabetes mellitus (DM) is a major health issue affecting millions worldwide. It is also one of this century's rapidly escalating health issues. In 2021, the International Diabetes Federation findings revealed that 537 million people were diagnosed with DM globally. This number is anticipated to increase to 643 million by 2030 and 783 million by 2045. According to the latest International Diabetes Federation Diabetes Atlas (2021), there were 90 million diabetic patients in Southeast Asia, 206 million in the Western Pacific, 51 million in North America and the Caribbean, 32 million in South and Central America, 61 million in Europe, 73 million in the Middle East and North Africa, and 24 million in the rest of Africa. DM is a complex metabolic disorder with significant complications resulting in morbidity and mortality. It is catego-

rized into types 1 and 2, depending on the insulin dependency. More than 90% to 95% of diabetic cases are type 2 DM (T2DM) (American Diabetes Association, 2020; Jeong et al., 2020). In individuals with T2DM, there is relative (rather than absolute) insulin deficiency and peripheral insulin resistance (American Diabetes Association, 2020). Prolonged hyperglycemia due to uncontrolled T2DM can destroy the nerves and blood vessels, leading to neuropathy, nephropathy, retinopathy, and cardiovascular diseases. The cost of controlling diabetes has increased by 316% over the last 15 years, such that over 966 billion dollars are spent globally every year (International Diabetes Federation, 2021). The burden of T2DM and its complications are significant as it causes severe disabilities, reduced quality of life, and mortality, imposing substantial economic burdens on societies and governments. Therefore, it is crucial to seek more effective

strategies for modulating glycemic control among patients with T2DM to reduce and prevent the risk of complications.

Diet composition and quality are crucial in T2DM management as these factors influence glycemic control. The Medical Nutrition Therapy Guidelines for T2DM recommend at least five daily servings of fruits and vegetables to help people attain and maintain normal blood glucose levels (Malaysian Dietitian's Association, 2013). Similarly, the healthy plate concept introduced by various health promotion boards worldwide also emphasizes a healthy and balanced meal. A single meal should comprise a quarter plate of carbohydrates (25%), a quarter plate of protein (25%), and half a plate of fruits and vegetables (50%). Fruits and vegetables are vital sources of nutraceuticals and functional foods as they are lower in calories yet rich in dietary fiber and phytochemicals like polyphenols. This can help diversify the intake of nutrients beneficial for various human physiological processes.

Polyphenols are compounds that are naturally abundant in plant-based sources like fruits, vegetables, legumes, and cereals. As secondary metabolites, polyphenols offer protection against ultraviolet radiation and pathogens in plants. The presence of polyphenolic compounds in food can affect oxidative stability and sensory properties such as taste, flavor, color, and odor (Pandey and Rizvi, 2009). Polyphenols are large, heterogeneous phytochemicals with phenol rings. Over 8,000 polyphenolic compounds have been identified in various plants, which differ in the number and bonding structure of phenol rings (Pandey and Rizvi, 2009; Kim et al., 2016). The polyphenols include flavonoids, phenolic acids, stilbenes, and lignans (Kim et al., 2016). Flavonoids can be divided into flavanols, flavonols, flavanones, flavones, isoflavones, and anthocyanins, characterized by the arrangement and number of hydroxyl groups and the extent of their alkylation and glycosylation (Spencer et al., 2008; Pandey and Rizvi, 2009).

Researchers have developed a significant interest in dietary polyphenols, potentially beneficial for human health, including the effects of the flavonoid and non-flavonoid classes of polyphenols on blood glucose levels. Polyphenols in fruits and vegetables are essential because individuals with T2DM are encouraged to consume appropriate portions of fruits and vegetables in their daily diet. This review aims to gather evidence related to the polyphenols in fruits and vegetables, in terms of their effects on the glycemic and metabolic parameters, based on human intervention studies involving T2DM patients. This knowledge is anticipated to help provide directions for future research, which is crucial to support the implementation strategies that aim to introduce polyphenols as an additional component of diet therapy measures directed toward the prevention of T2DM in non-diabetic or prediabetic patients. The knowledge will also help T2DM patients to achieve good glycemic control, thus minimizing the risk of developing complications from uncontrolled T2DM and ultimately reducing the burdens of the disease.

MATERIALS AND METHODS

Search strategy
The publications on the effects of polyphenols (flavonoid and non-flavonoid) on blood glucose control in patients with T2DM were reviewed by applying a search strategy. An advanced search was performed through the PubMed (MEDLINE) database using the terms "flavonoid", "glycemia", and "randomized controlled trial". The articles were considered relevant only if they were published in English in the last 5 years, between January 2016 and August 2021. The literature was extracted based on the titles and abstracts. Full-text articles were subsequently checked according to the criteria listed in Fig. 1. The final selection amounted to nine articles reporting the effects of fruits and vegetable polyphenols on blood glucose control and metabolic parameters, based on human intervention studies.

Selection criteria
The studies for polyphenol interventions were randomized controlled trials (RCTs) that involved T2DM patients and used blood glucose regulatory markers, such as fasting blood glucose (FBG) or glycated hemoglobin A1c (HbA1c), and metabolic parameters, such as serum lipid profile (Fig. 1). Following the identification of relevant papers according to the titles, nonhuman studies, non-intervention studies, and review articles were excluded. The abstracts of the remaining articles were then reviewed. The articles were excluded if the subject did not involve patients diagnosed with T2DM. Studies were excluded if they involved healthy individuals or those with other diseases. Studies that used grains, herbs, legumes, or beans as polyphenol sources were also excluded. The authors only selected studies involving fruit or vegetable polyphenols. Finally, nine articles were included in this review.
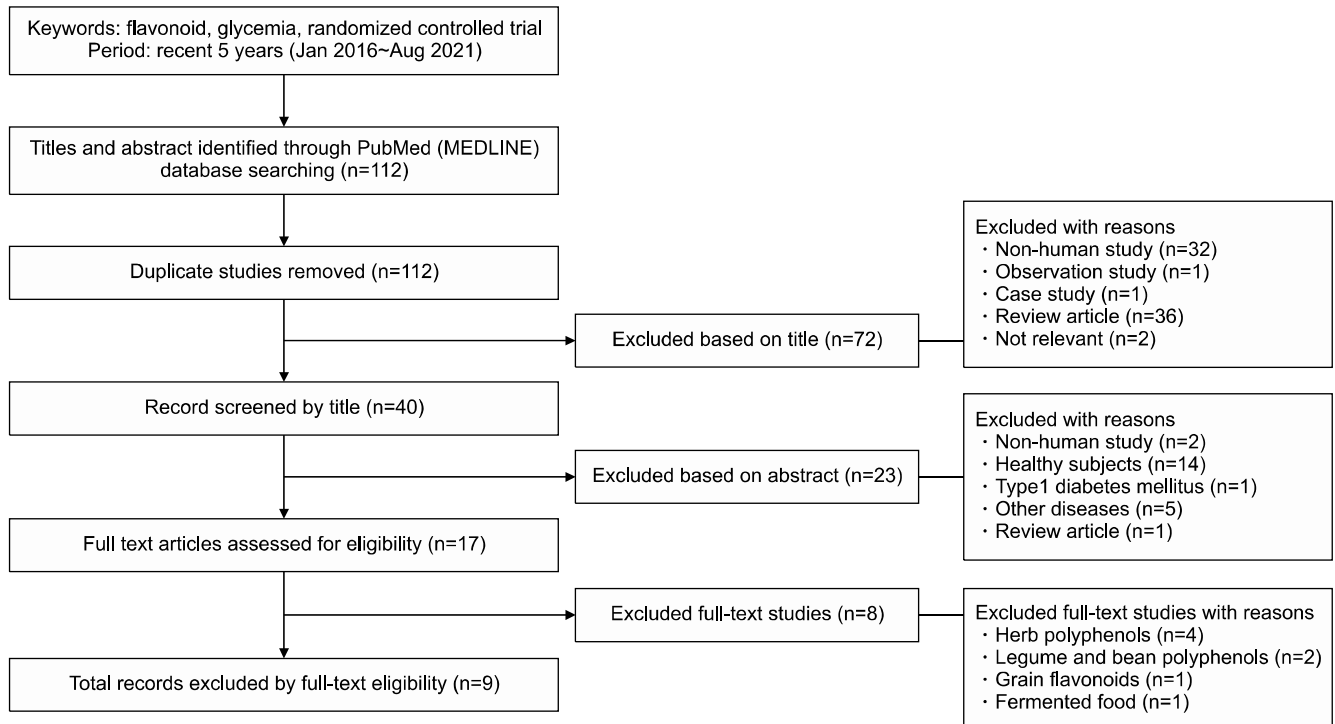
Statistical analysis
The differences between control and treated groups used an independent t-test for numerical analysis of normally distributed data. For nonparametric distributions, the Mann-Whitney U-test was used.

RESULTS

Characteristics of the included studies
Table 1 summarizes the characteristics of the nine in-

Fig. 1. Flow diagram of studies included in the review of effect of fruit and vegetable polyphenols on blood glucose regulation and metabolic parameters in type 2 diabetes mellitus.

cluded trials. Eight parallel RCTs (Yang et al., 2017; Zare Javid et al., 2017; Khodabandehloo et al., 2018; Abdollahi et al., 2019; Mollace et al., 2019; Stote et al., 2020; Nikbakht et al., 2021; Yang et al., 2021) and one crossover RCT (Thazhath et al., 2016) compared the effects of fruit and vegetable polyphenols, resveratrol, or anthocyanin on diabetes-at-risk, prediabetes, type 2 diabetes, and placebos. A total of 623 participants were involved. One trial was on diabetes-at-risk (n=26), two were on prediabetes (n=298), and six were on type 2 diabetes (n=299). The trials involved different populations, including Ameri-

cans, Australians, Chinese, Italians, and Iranians. There were 343 participants in the polyphenol group and 280 in the placebo group. All the participants in the intervention group received polyphenols in capsules or tablets as a supplement while maintaining their daily routine without restrictions. The participants in the control group received identically packaged placebo capsules or tablets. One trial used resveratrol capsules extracted from *Polygonum cuspidatum,* while another two trials that used resveratrol capsules did not specify the extracted source. Three trials used anthocyanin capsules purified from nat-

Table 1. Characteristics of included trials

Reference	Number of subject	Duration of intervention	Subject (country)	Intervention	Comparison
Thazhath et al. (2016)	28	5 wk	T2DM on diet control (Australian)	Resveratrol capsules (n=14)	Placebo (n=14)
Yang et al. (2017)	160	12 wk	Prediabetes or early untreated diabetes (Chinese)	Purified anthocyanins (n=80)	Placebo (n=80)
Zare Javid et al. (2017)	43	4 wk	DM (Iranian)	Resveratrol capsules (n=21)	Placebo (n=22)
Khodabandehloo et al. (2018)	45	8 wk	T2DM (Iranian)	Resveratrol capsules (n=25)	Placebo (n=20)
Abdollahi et al. (2019)	71	8 wk	T2DM (Iranian)	Resveratrol capsules (n=35)	Placebo (n=36)
Mollace et al. (2019)	60	30 d	T2DM (Italian)	Bergamot polyphenolic fraction (n=40)	Placebo (n=20)
Stote et al. (2020)	52	8 wk	T2DM (American men)	Freeze-dried blueberries (n=26)	Placebo (n=26)
Yang et al. (2021)	138	12 wk	Prediabetes or newly diagnosed diabetes (Chinese)	Anthocyanins capsules from natural bilberry and blackcurrant (n=76)	Placebo (n=62)
Nikbakht et al. (2021)	26	4 wk	T2DM, T2DM-at-risk, healthy (Australian)	Anthocyanins capsules from natural bilberry and blackcurrant (n=26)	−

T2DM, type 2 diabetes mellitus.

Table 2. Intervention studies of various polyphenols on glycemic control and metabolic parameters

Sources/types of flavonoids (dose)	Subject	Duration of intervention	Result	Comment	Reference
Purified anthocyanins capsules from natural bilberry and blackcurrant (320 mg/d)	Prediabetes, early untreated T2DM	12 wk	FBG: no change; HbA1c: decrease; Insulin: no change; TC and TG: no change; HDL-C and LDL-C: decrease	Significant differences were observed in the net changes of HbA1c and LDL-C between anthocyanin and placebo groups	Yang et al. (2017)
Resveratrol capsules (480 mg/d)	T2DM	4 wk	FBG: no change; Insulin: decrease; HOMA-IR: decrease; TG: no change	FBG and TG in resveratrol group did not differ significantly from placebo. Insulin level at post-intervention was significantly different in resveratrol compared to placebo groups	Zare Javid et al. (2017)
Resveratrol capsules (800 mg/d)	T2DM	8 wk	FBG: decrease; HbA1c: no change; Insulin: decrease; HOMA-IR: decrease; HDL-C: decrease; TC and TG: no change; LDL-C: decrease	There was significant difference in FBG found in resveratrol group compared with placebo. No mean difference of HDL-C levels between resveratrol and placebo groups	Khodabandehloo et al. (2018)
Resveratrol capsules (1,000 mg/d)	T2DM	8 wk	FBG: decrease; HbA1c: no change; Insulin: decrease; HOMA-IR: decrease; TC, TG, and LDL-C: no changes; HDL-C: increase	Study included overweight participants with body mass index 25~30 kg/m^2 with HbA1c <8%	Abdollahi et al. (2019)
BPF powder (650 mg/d) or BPF phytosome formulation (500 mg/d)	T2DM	30 d	FBG: decrease; TC, TG, and LDL-C: decrease; HDL-C: increase	No significant changes found in placebo group for FBG, TC, TG, LDL-C, and HDL-C. No statistically significant differences detected between BPF and BPF Phyto groups on their hypoglycemic and hypolipemic effect	Mollace et al. (2019)
Freeze-dried blueberries (22 g/d, contain 262 mg anthocyanins)	T2DM	8 wk	HbA1c and TG were significantly lower in freeze-dried blueberries than placebo groups	TC, TG, and LDL-C between groups treated with freeze-dried blueberries and placebo were significantly different	Stote et al. (2020)
Purified anthocyanins capsules from natural bilberry and blackcurrant (320 mg/d)	Prediabetes, newly diagnosed untreated T2DM	12 wk	FBG: no change; HbA1c: decrease; HOMA-IR: no change; TC and TG: no change; HDL-C and LDL-C: decrease	Study included participants with HbA1c 5.7%~6.4%. There was significant difference in HbA1c found between anthocyanin and placebo groups. No significant net change in TC, TG, HDL-C, and LDL-C between anthocyanin and placebo groups	Yang et al. (2021)
Powdered anthocyanins capsules from natural bilberry and blackcurrant (320 mg/d)	T2DM-at-risk, T2DM	4 wk	FBG: decrease; LDL-C: decrease; TC, TG, and HDL-C: no change	FBG and LDL-C was significantly reduced after intervention within T2DM-at-risk group but not in T2DM group	Nikbakht et al. (2021)
Resveratrol capsules (1,000 mg/d)	T2DM	5 wk (crossover)	There were no significant differences in FBG and HbA1c between resveratrol and placebo treatments	Study included T2DM patients on diet control alone	Thazhath et al. (2016)

T2DM, type 2 diabetes mellitus; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; BPF, Bergamot polyphenolic fraction.

ural bilberry (*Vaccinium myrtillus*) and blackcurrant (*Ribes nigrum*); one trial used bergamot polyphenolic fraction (BPF); another used freeze-dried blueberries. The period of intervention follow-up ranged from 4 to 12 weeks. Concerning the crossover RCT (Thazhath et al., 2016), data were taken during both intervention periods as the carryover effects from one intervention period to the other were excluded.

Effect of polyphenol intervention

Glycemic parameters: Table 2 summarizes the polyphenol intervention studies. The changes in FBG were observed to be inconsistent among the included studies. Some studies reported a significant decrease in FBG after resveratrol (Khodabandehloo et al., 2018; Abdollahi et al., 2019), anthocyanin (Nikbakht et al., 2021), and BPF (Mollace et al., 2019) interventions, whereas other studies (Yang et al., 2017; Zare Javid et al., 2017; Yang et al., 2021) found no significant changes in FBG. The between-group comparison revealed no significant differences in FBG among the resveratrol and placebo groups (Zare Javid et al., 2017). Similarly, a 5-week crossover trial using resveratrol and placebo found no significant difference in FBG between the two treatments (Thazhath et al., 2016).

Two studies that included prediabetic and newly diagnosed DM patients showed significant decreases in glycated hemoglobin (HbA1c) but no changes in FBG after anthocyanin interventions (Yang et al., 2017; Yang et al., 2021). In addition, they found a significant difference in HbA1c observed between the anthocyanin and placebo groups. In line with other studies, Stote et al. (2020) reported findings that HbA1c levels were significantly lower in the group consuming freeze-dried blueberries containing anthocyanins compared to the placebo in T2DM patients.

Five trials reported mixed insulin level results according to the type of polyphenols. Insulin levels significantly reduced after intervention with resveratrol (Zare Javid et al., 2017; Khodabandehloo et al., 2018; Abdollahi et al., 2019), whereas intervention with anthocyanin reported no changes in the insulin levels (Yang et al., 2017; Yang et al., 2021). Moreover, resveratrol intervention reported significant insulin reduction and showed a significant decrease in the degrees of β-cell deficiency and insulin resistance indicated by the homeostatic model assessment for insulin resistance (Zare Javid et al., 2017; Khodabandehloo et al., 2018; Abdollahi et al., 2019).

Metabolic parameters: Triglyceride (TG) and total cholesterol (TC) did not significantly change after intervention with resveratrol or anthocyanin (Yang et al., 2017; Zare Javid et al., 2017; Khodabandehloo et al., 2018; Abdollahi et al., 2019; Nikbakht et al., 2021; Yang et al., 2021). On the other hand, intervention with BPF significantly decreased levels of TG and TC in T2DM (Mollace et al., 2019). Stote et al. (2020) reported that significant differences in TG and TC were identified between the anthocyanin intervention and placebo groups. However, Yang et al. (2021) reported no significant changes in TG and TC between the two groups.

There were significant reductions in the levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels within the polyphenol intervention group (Yang et al., 2017; Khodabandehloo et al., 2018; Yang et al., 2021). One study reported no significant change in LDL-C, yet a significant increase in HDL-C was identified after resveratrol intervention (Abdollahi et al., 2019). Interestingly, the intervention conducted by Mollace et al. (2019) reported that the level of LDL-C had significantly reduced, while the level of HDL-C significantly increased post-intervention with BPF compared to baseline. There was no significant change detected in either LDL-C or HDL-C within the placebo group.

DISCUSSION

This review compared the potential effects of certain polyphenols in pre- and post-intervention and reported comparisons between polyphenol-treated and placebo groups. The outcomes of this study were explored, such as the glycemic and metabolic parameters from the included studies. Four studies reported that groups supplemented with polyphenols, resveratrol, anthocyanin, or naringin in BPF showed significant improvements in glycemic control based on the reductions in FBG or HbA1c levels. This aligns with the findings from a systematic review by Zhu et al. (2017), wherein resveratrol supplementation in T2DM resulted in significant and clinically important changes, particularly in the FBG and HbA1c levels. Multiple pathophysiological mechanisms might mediate the effects.

Resveratrol is a potent activator of sirtuin 1, or silent information regulator protein 1 (SIRT1). SIRT1 regulates adiponectin secretion, inflammation, glucose production, oxidative stress, mitochondrial function, and circadian rhythms. The activators of SIRT1, including resveratrol, benefit glucose homeostasis and insulin sensitivity (Kitada and Koya, 2013). Glucose and lipid metabolism were regulated by SIRT1 through its deacetylase activity on many substrates. In pancreatic β-cells, SIRT1 adjusts insulin secretion, protects cells from oxidative stress and inflammation, and modulates insulin signaling in the metabolic pathway (Kitada and Koya, 2013). The activation of intracellular regulators such as SIRT1 and adenosine monophosphate-activated protein kinase (AMPK) by resveratrol might attenuate insulin resistance and restore

its sensitivity by increasing signaling in the skeletal muscle cells (Deng et al., 2008; Um et al., 2010). Polyphenols like naringin and resveratrol ameliorate glucose uptake through the upregulation of glucose transporter 4 gene expression in the skeletal muscle and liver (Yonamine et al., 2017; Vlavcheski et al., 2020). Meanwhile, improved glycemic control can also be seen with anthocyanin supplementation. Scazzocchio et al. (2011) reported that the most common form of anthocyanin, cyanidin-3-O-β-glucoside, can exert insulin-like effects by upregulating peroxisome proliferator-activated receptor γ activity.

Polyphenolic compounds also produce favorable lipid profile results, as shown in several studies. Two of the included studies reported a significant increase in HDL-C (Abdollahi et al., 2019; Mollace et al., 2019). These effects might be contributed by the role of polyphenols in regulating the expression of the main cholesterol transporters, which resulted in the formation of mature HDL granules. This boosts the transportation of excess cholesterol to the liver and intestinal excretion (Zhao et al., 2019). Moreover, a significant reduction in LDL-C were identified after intervention with resveratrol (Khodabandehloo et al., 2018) and anthocyanin (Nikbakht et al., 2021; Yang et al., 2021). Guo et al.'s (2012) study reported that anthocyanin inhibits adipocyte lipolysis by blocking the FoxO1-mediated transcription of adipose triglyceride lipase, the major lipase involved in TG breakdown in adipocytes. It was also suggested that anthocyanin could inhibit the fatty acid synthesis via the SIRT1-AMPK axis through SIRT1 activation and the stimulation of AMPK phosphorylation (Han et al., 2018).

The poor absorption of dietary polyphenols by the enterocytes resulted in a large proportion of the ingested polyphenols reaching the colon, where they can modulate the relative abundance of gut microbiota and hinder dysbiosis, an alteration in the gut microbiota that is associated with obesity and pathogenesis of T2DM (Kho and Lal, 2018; Wang et al., 2021). Some polyphenols can produce prebiotic-like effects by fostering the growth of beneficial bacteria and retarding pathogen growth (Wang et al., 2021). Roopchand et al. (2015) studied mice fed with a high-fat diet, reporting that grape polyphenols enhance the growth of *Akkermansia muciniphila*, which degraded mucin and decreased the proportion of *Firmicutes* to *Bacteroidetes*, a shift that can have protective effects against diet-induced obesity and metabolic disease. Grapes are rich in polyphenols such as anthocyanin, flavanols, flavonols, stilbenes, and phenolic acids (Xia et al., 2010).

However, many studies found that the efficacy of resveratrol and anthocyanin on glycemic control and the metabolic parameters were inconsistent due to factors such as the period of intervention, the form and dose of polyphenol supplementation, and the baseline parameter values. Some statistically significant and clinically rele-

vant outcomes were observed in interventions of a longer duration. Resveratrol supplementations (800 or 1,000 mg/d) for 8 weeks showed a significant decrease in FBG after intervention (Khodabandehloo et al., 2018; Abdollahi et al., 2019), but no changes were identified in a 5-week study (Thazhath et al., 2016). Most polyphenol supplements used in the studies provided purified resveratrol and anthocyanin in capsules, while a minority used freeze-dried fruits and extracts. The contrasting findings contributed to bioavailability, variety, ripeness, culinary technique, storage, region, and environmental conditions (Castro-Barquero et al., 2020).

This review has several advantages. The researchers selected only RCTs in this review, ensuring the inclusion of high-quality studies. Most of the chosen studies used placebos to compare against the intervention with polyphenols, while the participants were blinded to minimize bias and maximize the validity of the trials. The evidence applies to adult males and females diagnosed with prediabetes and T2DM. The data obtained were sufficient for analyzing the primary and secondary glycemic control outcomes and the metabolic parameters.

Nevertheless, the study also had some limitations. The result of this review may not be sufficiently comprehensive as it was not designed as a systematic review with meta-analysis. Other limitations of this review include the difference in the types of polyphenol samples. The polyphenol samples were not controlled between the selected trials. Hence, the properties and efficacy of the bioactive compounds might vary. The studies included in this review had a relatively short follow-up duration, ranging between 4 and 12 weeks. An important indicator of glycemic control, the HbA1c changes, would need to be monitored for at least 12 weeks to evaluate the progression of diabetes. However, only two studies were conducted for 12 weeks. Therefore, more RCTs with a larger number of subjects and a longer follow-up duration are needed to confirm the relationship between polyphenols on one hand and glycemic control and metabolic parameters on the other in adults with prediabetes or T2DM. In addition, the population sizes of these trials ranged from 28 to 160 participants. Therefore, this review may have been underpowered to detect the actual effects. Furthermore, high-quality research might significantly contribute to raising confidence in the estimated effects or potentially changing such estimates.

Overall, this review unveils current evidence from the effects of fruit and vegetable polyphenol interventions, mainly resveratrol and anthocyanin, on blood glucose in prediabetic and T2DM patients. The authors anticipate that the insights presented in this review will guide further investigations on polyphenolic compounds as preventive approaches against complications in T2DM patients and the development of T2DM in non-diabetic and

prediabetic populations. Further research is warranted to evaluate the outcomes rigorously. As for the team involved in this review, the many levels of interest in this topic led the team to conduct a 12-week intervention to determine whether polyphenol from a local vegetable could help to improve the glycemic and metabolic profiles of T2DM patients.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

CAJCMZ conceptualized and designed the article along with WRWI. CAJCMZ and WRWI analyzed and interpreted the results. CAJCMZ prepared the manuscript with inputs from WRWI, WMIWM and NAKK. WRWI, WMIWM and NAKK made critical revisions of the article related to important intellectual content. Finally, all the authors read and approved the final manuscript.

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