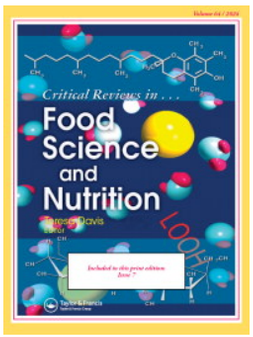

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REVIEW

Polyphenols target miRNAs as a therapeutic strategy for diabetic complications

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ABSTRACT

MiRNAs are a large group of non-coding RNAs which participate in different cellular pathways like inflammation and oxidation through transcriptional, post-transcriptional, and epigenetic regulation. In the post-transcriptional regulation, miRNA interacts with the 3′-UTR of mRNAs and prevents their translation. This prevention or dysregulation can be a cause of pathological conditions like diabetic complications. A huge number of studies have revealed the association between miRNAs and diabetic complications, including diabetic nephropathy, cardiomyopathy, neuropathy, retinopathy, and delayed wound healing. To address this issue, recent studies have focused on the use of polyphenols as selective and safe drugs in the treatment of diabetes complications. In this article, we will review the involvement of miRNAs in diabetic complications' occurrence or development. Finally, we will review the latest findings on targeting miRNAs by polyphenols like curcumin, resveratrol, and quercetin for diabetic complications therapy.

KEYWORDS

Flavonoids; T2DM; microRNAs; phytochemicals; insulin resistance

Introduction

Diabetes mellitus is a metabolic disorder with hyperglycemia that affects 425 million people around the world (Arneth, Arneth, and Shams 2019). Diabetes is a progressive metabolic disorder associated with pancreatic beta cell destruction, which leads to impaired insulin secretion and hyperglycemia (Kolb and Martin 2017). This disorder also associated with increased reactive oxygen species (ROS) production and oxidative stress (Tuttolomondo, Maida, and Pinto 2015). Many studies have shown that obesity, as the crucial cause, creates insulin resistance and type 2 diabetes (T2DM) (Haviland et al. 2016). In diabetic patients, microvascular complications are associated with neuropathy, nephropathy, and retinopathy, while macrovascular complications may lead to cardiovascular disease, stroke, and peripheral artery disease (Regazzi 2018). MiRNAs are non-coding RNA molecules with about 22 to 24 nucleotides in length and play a vital role in regulating genes and protein functions. miRNAs can be positioned inside an untranslated region (UTR) or intron of a protein-coding gene (Annese et al. 2020). After pre-miRNA transportation to the cytoplasm and maturation, they can bind to the 3′-UTR of mRNAs and inhibit their translation (Figure 1) (Bartel 2004). MiRNA expression varies in various pathological conditions, such as cancer, neurological disorders, infectious diseases, autoimmune diseases, and diabetes (Garo and Murugaiyan 2016). In diabetic condtions, there is an association between miRNAs and gene expression alteration resulting in B cells dysfunction, insulin resistance, and secretion (Bartel 2004). In recent decades, evidence has also shown that miRNAs are involved in the pathogenesis of diabetes and its complications. Changes in miRNAs expression are involved in diabetic complications such as neuropathy, retinopathy, nephropathy, cardiomyopathy, and wound healing (Godos et al. 2017). Polyphenols have significant antioxidant properties and are found in abundance in some foods, such as tea, beans, and herbs (Su, Hung, and Chen 2006). Curcumin, resveratrol, and quercetin are among the most important polyphenolic compounds. Resveratrol (3,4%, 5-trihydroxy-stilbene) controls diabetes, reduces blood glucose levels in humans and rodents, and improves insulin secretion (Shishodia et al. 2005; Liu et al. 2016; Huang, Shi, et al. 2020). Quercetin (3,5,7-trihydroxy-2-(3,4-dihydroxy phenyl) 4Hchromen4-one) is a low molecular weight monomeric compound with conspicuous biological activities (Chen et al. 2016). Therefore, based on animal models and early clinical trials, plant polyphenols, phenolic acids, and flavonoids have been suggested as effective supplements to control diabetes and prevent long-term complications. In this review article, we have tried to review the studies on

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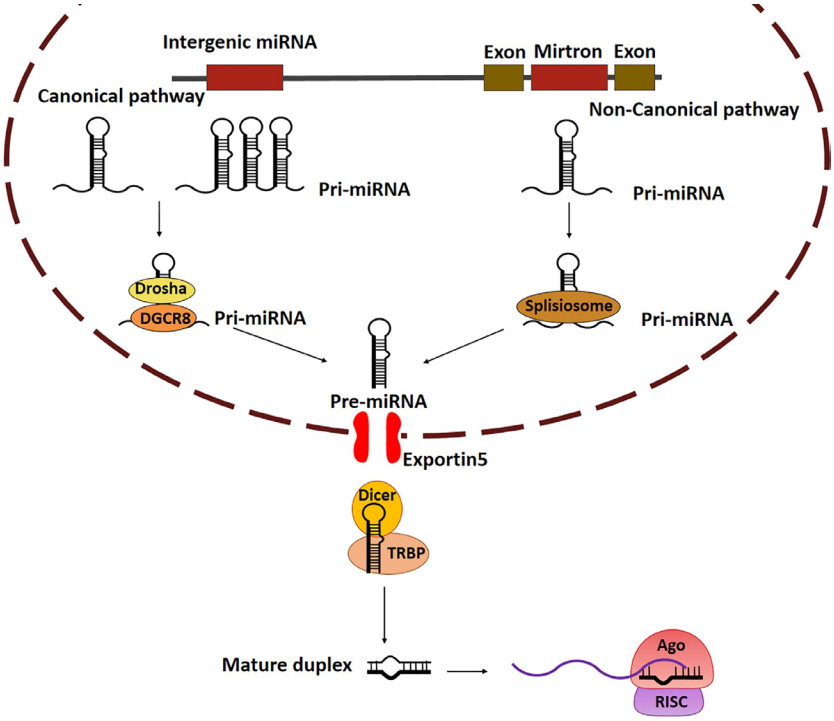

Figure 1. There are two principal biogenesis pathways of miRNAs; canonical and non- canonical. In the canonical pathway, primary miRNAs (pri-miRNAs) are processed in to precursor miRNAs (pre-miRNAs) via Drosha/DGCR8 while in the non-canonical pathway pri-miRNAs are transformed to pre-miRNAs via Splisiosome. In the following, XPO5 exported the pre-miRNAs to the cytoplasm, and Dicer processed them to create a mature miRNA.

the effect of polyphenols on miRNAs involved in the pathogenesis of diabetes and diabetic complications.

Biological significance of miRNAs in diabetic complications

Diabetes is a common disease classified as a metabolic syndrome. Hyperglycemia, caused by abnormalities in insulin production, insulin resistance, and insulin sensitivity, is one of the most common and fastest rising illnesses worldwide, with 693 million individuals anticipated to be afflicted by 2045. Diabetes causes significant disability and premature death, and its complications are becoming more common day by day. Given that diabetes and its complications are a serious threat to life and health, scientists have focused on finding new and safe strategies to reduce its symptoms. (Mastropasqua et al. 2021). Evaluating the changes in the expression level of miRNAs and targeting them is one of the significant and effective pathways that has attracted a lot of attention in the research area. In this section, we are going to discuss the relationship between diabetes or diabetic complications and miRNAs expression.

MiRNAs roles in diabetic nephropathy (DN)

Diabetic nephropathy (DN), a distinctive progressive renal disorder, is considered a crucial diabetes mellitus microvascular complication (SunYM 2013; Khanra et al. 2015; Bhattacharjee et al. 2016; Simpson et al. 2016; Khanra et al. 2017). Numerous miRNAs, namely miR-1207-5p, miR-377, miR-217, miR-216a, miR-200, miR-195, miR-135a, miR-124, and miR-21, are discovered to be upregulated in diabetic kidneys and suppress the expression of reno-protective genes through binding to their 3′UTR, leading to promoting pathological signaling in DN. On the other side, diverse miRNAs, including miR-451, miR-141, miR-93, miR-29, miR-25, and Let-7, are reported to be suppressed in DN. The mentioned miRNAs play an essential role in inhibiting various DN-inducing agents, including Akt, mTORC1, NOX, COL, and TGF-β. The miRNAs expression could be employed as a diagnostic tool and reveal the role of distinctive pathogenic signaling in DN; hence, miRNAs are vastly explored, aiming to design untried therapies or uncover novel therapeutic targets for DN (Wu et al. 2014; Dewanjee and Bhattacharjee 2018).

miRNAs roles in diabetic cardiomyopathy (DCM)

Diabetic cardiomyopathy (DCM) is one of the most dangerous, fatal, and chronic complications of diabetes. Systemic metabolic disorders, abnormalities in the function of the renin-angiotensin-aldosterone system, oxidative stress, inflammation, and immune system along with insulin resistance, hyperinsulinemia, and hyperglycemia are the main factors involved in the development of diabetic cardiomyopathy (Jia, Hill, et al. 2018).

Cardiac miRNAs as gene expression regulators play an essential role in transcriptional and post-transcriptional regulation in diabetic cardiomyopathy and heart failure. The miRNAs are suggested to target vital mechanisms of the

progression of heart failure, cardiac hypertrophy, and remodeling (Chen et al. 2008; Latronico et al. 2008; Rao et al. 2009; Das et al. 2012; Harada et al. 2014; Li et al. 2014; Melman, Shah, and Das 2014; Zhou et al. 2014; Guo and Nair 2017). The expression of apoptosis genes and genes involved in oxidative stress, pyroptosis, cardiac fibrosis, and cardiomyocyte hypertrophy is regulated by miRNAs. miR-451, miR-320, miR-195, miR-142-3p, miR-141, miR-216a, miR-34a, miR-30d, miR-24, and miR-21 have repeatedly reported to be overexpressed while various miRNAs including miR-181a, miR-150, miR-144, miR-143, miR-133a, miR-30c, miR-29, miR-23b, miR-20a, miR-9, and miR-1 are declared to be downregulated in diabetic subjects (Guo and Nair 2017). Higher expression levels of miR-451 and miR-195 have been observed in diabetic cardiomyopathy, and their knockdown significantly reduced cardiac hypertrophy and dysfunction by targeting Calcium Binding Protein 39 (Cab39) and Sirt1 and Bcl-2 respectively (Kuwabara et al. 2015; Zheng et al. 2015). Both miR-155 and miR-195 upregultion are associated with diabetic cardiomyopathy and targeting them can be a selective approach to preventing cardiomyocytes apoptosis and restoring cardiac function (Zheng et al. 2015; Jia et al. 2017). In addition, there is some evidence that miR-133a is down-regulated in the cardiac tissue of diabetic mice, and inducing the expression of this miRNA can target transforming growth factor β1 and reduce extracellular matrix protein and cardiac fibrosis (Chen et al. 2014). Overall, miRNAs are proposed to perform a possible diagnostic, prognostic, and therapeutic role in diabetic cardiomyopathy (Asrih and Steffens 2013; Guo and Nair 2017).

MiRNAs roles in diabetic retinopathy (DR)

Diabetic retinopathy in patients with diabetes includes the damage or dysfunction of the autonomic and/or peripheral nervous system which is occurred due to the effect of increased glucose on normal neural activity and causes glucose-induced stress and nerve cell damage (Ioannou 2017). Just like other complications, miRNAs can be the main players either in DR progression or the healing process. miR-21 upregulation, for instance, affects DR pathogenesis by playing a vital role in inflammation and endothelial dysfunction following diabetes mellitus (Roy et al. 2021), while miR-216a upregulation has been reported to play a protective role against damage to human retinal microvascular endothelial cell (HRMEC) in DR through repressing the NOS2/JAK/STAT axis (Liu et al. 2020). miRNA- 29b-3p has been declared to elevate apoptosis in HRMEC through thwarting SIRT1 in DR. In addition, through targeting VEGFA and HIF-1α, miR-203a-3p overexpression is suggested to hinder retinal neovascularization in retinopathy induced by oxygen in rat models (Zeng et al. 2019). Moreover, MiR-183 knockdown resulted in the suppression of cell growth and tube formation in the vascular endothelium of DR rats via BTG1 overexpression and through the PI3K/Akt/VEGF signaling pathway (Zhang, Qin, and Zhang 2019). Furthermore, inhibiting YAP1 lowers the proliferation, migration, and tube formation of RMECs, leading to attenuating the progression of DR via suppressing MALAT1 and VEGFA expression and promoting miR-200b-3p expression (Han, Zhang, et al. 2020). Overall, miRNAs could be an innovative targets and potential therapeutic agents with the capacity to impact the eye's pathological pathways (Smit-McBride and Morse 2021).

MiRNAs roles in diabetic neuropathy

Diabetic neuropathy refers to nerve damage due to diabetes. Oxidative stress, metabolic dysfunction, and inflammation are some of the pathogenic factors indicated to be associated with diabetic neuropathy. miRNAs functions in oxidative response in diabetic patients have been reported by some studies. When it comes to diabetic neuropathy, miR-25 upregulation in db/db mice is associated with enhanced neurological function through dwindling the production of reactive oxygen species (ROS) mediated by PKC-α phosphorylation in diabetic peripheral nerves. However, miRNAs roles in oxidative response and regulating metabolism in diabetic neuropathy are yet to be elucidated (Fan et al. 2020).

Diabetic neuropathy is also declared to be closely correlated with chronic low-grade inflammation, which is connected to neuropathic pain. Accordingly, miR-190a-5p, miR-155 chr11, miR-9 chr2, miR-25, and miR-146a are linked to inflammation regulation and Let-7i, miR-29b, miR-29c, miR-145-3p, miR-199a, and miR-146a are reported to play crucial roles in neurovascular dysfunctions in diabetic neuropathic (Fan et al. 2020). Raised glucose levels in these patients led to an increase in fibronectin besides inflammatory mediators, including VEGF (vascular endothelial growth factor), IL-6, TNFα, TGF-β (transforming growth factor-β), and NF-κB (nuclear factor-kappa B), resulting in augmented central nervous system sensitization (Andriambeloson et al. 2006; Wang et al. 2006; Finnerup, Sindrup, and Jensen 2010; Rizzo et al. 2010; Hur et al. 2011; Hussain et al. 2016; Pop-Busui et al. 2016). miR-190a-5p and miR-184-5p are found to be correlated with the genes that are linked to inflammation and neuropathic pain pathogenesis in diabetic neuropathic mice, and MiR-155 is reported to mediate neuropathic pain through targeting NF-κB (Khamaneh et al. 2015; Pop-Busui et al. 2016). In this regard, miRNAs can be the mediators in diationabetic neuropathic pain, inflammation, and stress.

MiRNAs roles in diabetic wound

Wound repair process disruption, distinguished by inadequate growth factors, is one of the most critical diabetes mellitus complications. miRNAs dysregulation throughout the process of wound healing has been reported in diabetic mice. Several miRNAs have been reported to show different expression levels in the skin tissue of diabetic and healthy mice, and their expression levels change during the healing process of diabetic wounds. Various miRNAs, including miR-541, miR-452, miR-128, miR-96, miR-20b, miR-10b, and miR-10a, showed alike basal levels between diabetic

and normal skins despite being dysregulated throughout the healing process of diabetic wounds (Madhyastha et al. 2012). Investigating miR-21 also revealed that its expression decreased and increased throughout diabetic wound healing and diabetic skin, respectively, and it contributes to the diabetic wound healing process through fibroblast migration (Madhyastha et al. 2012). Employing miRNAs to make resident cells produce and supply the growth factors to the wound location can serve as an effective method for the treatment of diabetic wounds.

Targeting miRNAs by polyphenols in diabetic complications

Polyphenols have become the center of attention in recent years which create new insight in offering therapies for patients suffering diabetes. One of the most studied polyphenols' mechanisms of action in alleviating diabetic complications is regulating miRNAs expression (Figures 1,2, and Table 1).

Modulation of miRNAs expression in diabetic nephropathy by polyphenols

Diabetic nephropathy (DN) is the most important complication among diabetic patients. The prevalent characterizations of DN are proteinuria, glomerular and renal dysfunction which happen as a result of chronic hyperglycemia and high blood pressure (Samsu 2021). Inflammatory pathways and oxidative stress have been introduced as the main victims of DN development (He et al. 2021). MiRNAs play essential roles during inflammation and immune responses in DN patients. In this regard, it has been suggested that miRNAs can be selective candidates in enhancing diagnosis and therapeutic strategies in these cases (Zhou et al. 2020; Yarahmadi et al. 2021). In addition, a huge number of studies focused on the relationship between DN and polyphenols (Hu et al. 2021) while other studies investigated the relationships between miRNAs and polyphenols (Bladé et al. 2013). Taken collectively, in these years, researchers are concentrating on applying polyphenols for DN treatment through modulating miRNAs.

Podocytes are visceral epithelial cells that take part in glomerular filtration regulation. Podocytes apoptosis is associated with albuminuria in diabetic mice.

Podocyte autophagy is an adaptive response to protect cases against DN (Podgórski et al. 2019). Resveratrol is a poly-phenolic phytoalexin that can be found in natural ingredients like grape and plays role in a variety of biological processes including cell death, autophagy, anti-inflammation, and antioxidant pathways (Galiniak, Aebisher, and Bartusik-Aebisher 2019). In the field of DN, resveratrol not only reduces apoptosis but also increases autophagy in podocytes. For example, in a study several methods were applied to identify the mechanism of DN protection by resveratrol. It has been showed that high glucose concentration in human podocytes leads to the stimulation of apoptotic factors, cleaved caspase-3 and Bax, while resveratrol reverses this effect and prohibits apoptosis. In addition, LC3-II is located on autophagosomes which are representative of autophagy. Immunofluorescence assay has proved that LC3-II expression in resveratrol-treated mice is higher than that of control groups. To make sure that autophagy stimulation is a result of resveratrol application, autophagy inhibitors were used that reversed the resveratrol protective effects. MiR-383-5p is identified to participate in autophagy suppression and apoptosis induction. As final evidence, this valuable study revealed that resveratrol suppresses miR-383-5p expression and consequently modulates autophagy and apoptosis (Huang et al. 2017). Another study also showed that after 12 weeks, resveratrol treatment stimulates autophagy markers LC3-II/LC3-I and reduces apoptotic factors cleaved-caspase 3 and ATM. Relatively, it showed that miR-18a-5p is low in diabetic mice; but when diabetic mice models treated by resveratrol, miR-18a-5p expression level improves significantly which is an apoptosis negative regulator. Indeed, it has been concluded that resveratrol does these functions to protect kidneys in diabetic cases via upregulation of miR-18a-5p (Xu et al. 2017).

As we mentioned before, resveratrol has anti-oxidant and anti-inflammatory functions. A study documented the interconnection whether between resveratrol and Sirt1/HIF-1α or MircroRNA-217 (Mir-217) and Sirt1/HIF-1α (Shao et al. 2016). Hypoxia-inducible factor-1 alpha (HIF-1α) plays role in hypoxia and inflammation. Silent information regulator

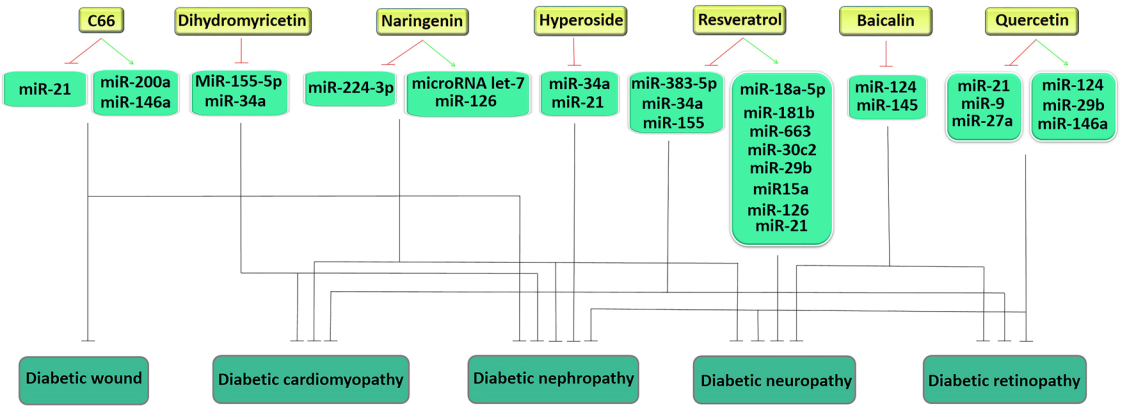

Figure 2. Polyphenols play their protective role against diabetic complications through miRNAs suppression or activation.

Table 1. The cross talk between polyphenols and miRNAs in controlling diabetic complications.

	Polyphenol	miRNA	Effect	Final effect	Ref
	Resveratrol	miR-18a-5p↑ miR-383-5p↓	LC3-II/LC3-I↑, cleaved-caspase 3↓ and ATM↓	Autophagy induction and apoptosis inhibition	(Huang et al. 2017; Xu et al. 2017)
	Dihydromyricetin	MiR-155-5p↓	PTEN↑	Autophagy induction and renal fibrosis inhibition	(Guo, Tan, et al. 2020)
	Quercetin	miR-21↓	PTEN↑ and TIMP3↑	Renal fibrosis inhibition	(Cao et al. 2018)
	Hyperoside	miR-21↓	IV collagen↓ and fibronectin↓ and MMP-9↑	ECM abnormalities inhibition and renal dysfunction inhibition	(Zhang, Fu, et al. 2016)
	Curcumin	miR-124↓	Integrin α3↑	Adhesion damage inhibition and DN preventation	(Li et al., 2013)
Diabetic nephropathy	C66	miR-200a↑	KEAP1↓ and NRF2↑	Renal fibrosis protection	(Wu et al. 2016)
	C66	miR-21↓	Smad7↑	renal fibrosis protection	(Wu et al. 2016)
	Quercetin	miR-124↑	Bcl-2↑, NF-κB↓, MyD88↓, IL-6↓and TNF-α↓	Inflammation and apoptosis	(Guo, Tan, et al. 2020)
	Baicalin	miR-124↑	TLR4↓, NF-κB↓, type IV collagen↓, fibronectin↓	Renal fibrosis protection	(Zhang, Dai, et al. 2020)
	Hyperoside	miRNA-34a↓	ERK↓, CREB↓	Cell proliferation inhibition and renal fibrosis protection	(Zhang, Dai, et al. 2020)
	Naringenin	microRNA let-7↑	TGF-β1↓, TGFBR1↓, smad2↓ and smad7↑	Inflammation inhibition, blood glucose level reduction and proliferation inhibition	(Yan et al. 2016)
	Tea polyphenols	miR-126↑	Akt↓, p53↓, p21↓	Renal cell senescence inhibition	(Cao et al. 2019)
	Apigenin	miR-423-5p↑	USF2↓	Inflammation inhibition and fibrosis preventation	(Hou et al. 2021)
Diabetic cardiomyopathy	Resveratrol	miR-155↓ and miR-34a↓, miR-21↑, miR-181b↑, miR-663↑ and miR-30c2↑	IL-6↓, CCL3↓, IL-1β↓, TNF-α↓	Inflammation, oxidative stress and apoptosis inhibition	(Tomé-Carneiro et al., 2013)
	Resveratrol	miR-34a↓	Sirt1↑	DCM protection	(Yang et al. 2016)
	Resveratrol	miR-34a↓	P21↓, p16↓, Sirt1↑, VEGF↑ and HIF-1α↑	BMSCs viability and heart healing improvement	(Zhang et al. 2021)
	Dihydromyricetin	miR-34a↓	cleaved caspase 3↓, Bax↓ Bcl-2 ↑, p53↑, MAP1LC3B II/ MAP1LC3B I ratio↑, Beclin-1↑and LC3B↑	Apoptosis inhibition and autophagy induction	(Ni et al. 2020)
	Naringenin	miR-126↑	PI3K/AKT↑	Oxidative stress and apoptosis inhibition	(Li et al. 2021)
	Resveratrol	miR-29b↑	SP1↓	Apoptosis and fibrosis inhibition	(Zeng et al. 2017)
	Quercetin	miR-29b↑	PTEN/AKT↑, NF-κB↓	Retinal cell damages protection	(Wang et al. 2020)
Diabetic retinopathy	Baicalin	miR-145↑	NF-κB↓ and p38MAPK↓	DR protection	(Dai et al. 2019)
	Resveratrol	miR15a↑	insulin signaling↑	Retinal cells protection	(Jiang, Liu, and Steinle 2018)
	EVOO	miR-155↓		Inflammation inhibition	(Carpi et al. 2019)
	Resveratrol	miR-155↓		Inflammation inhibition and neuroprotection	(Ma et al. 2020)
Diabetic neuropathy	Resveratrol	miR-126↑	PI3K/AKT↑	Neuroprotection	(Xin et al. 2018)
	Quercetin or QCSPIONs	miR-146a↑, miR-9↓	NF-κB↓	Neurological protection and memory improvement	(Ebrahimpour, Esmaeili, et al. 2020)
	Quercetin or QCSPIONs	miR-27a↓	SOD1↑, CAT↑ and NRF2↑	Neurological protection and memory dysfunction prevention	(Ebrahimpour, Esmaeili, et al. 2020)
	Naringenin	miR-224-3p↓	SOD↑, pro-apoptotic factors↓ and anti-apoptotic factors↓	Apoptosis, inflammation inhibition and neuroprotection	(Li et al. 2020)
Diabetic wound	C66	miR-146a↑	IRAK1↓, NF-κB↓, TNF-α↓, IL-6↓ and IL-8↓	Inflammation inhibition and wound healing	(Huang, Shi, et al. 2020)
	PSF	miR-146a↑	IRAK-1↓ and NF-kB↓	Inflammation inhibition and wound healing	(Coppari et al. 2021)

1 (Sirt1) is the upstream protein of HIF-1α and can suppress HIF-1α activity (Takiyama et al. 2011). It is confirmed that there is a negative regulation between Mir-217 and Sirt1 expression when the glucose concentration is high in rat glomerular mesangial cells (RMCs). Moreover, it demonstrated that resveratrol can stimulate Sirt1activation and HIF-1α inhibition in the same condition. Therefore, the Mir-217 inhibitor or resveratrol can protect glomerular cells with high glucose concentration through Sirt1/HIF-1α signaling pathway (Shao et al. 2016). Nevertheless, the author did not mention the relations between Mir-217 and resveratrol. So further examination is required to elucidate the exact mechanism of action.

Tensin homolog deleted on chromosome ten (PTEN) is the negative regulator of the PI3K/AKT/mTOR signaling pathway and the inhibition of this cascade is conducted to autophagy which involves alleviating DN (Khokhar et al. 2020). MiR-155-5p experienced a rise in DN (Klimczak et al., 2017), whereas PTEN expression down-regulated significantly (Khokhar et al. 2020). Relatively, there is a demonstration that PTEN is the direct target of MiR-155-5p because in a recent study when MiR-155-5p was inhibited by inhibitors, PTEN expression level increased in renal cells. Apart from that, dihydromyricetin as a flavonoid which is abundant in *A. grossedentata* plant has significant role in diabetes and diabetic complications protection through the regulation of cellular signaling pathways (Zhang, Chen, et al. 2018). one resent study tested this component to reveal its mechanism of action in protecting renal fibrosis in diabetes. Results confirmed that dihydromyricetin can improve autophagy and renal fibrosis therapy through MiR-155-5p down-regulation and subsequently PTEN activation (Guo, Tan, et al. 2020).

Quercetin is a member of flavonoids and it can be found in natural ingredients like apples and seeds. Research on quercetin validates that it plays anti-inflammatory, anti-cancer, and anti-diabetes functions in the cells. When it comes to DN, a recent in-vivo study reported that quercetin especially quercetin liposomes can be a selective therapeutic agent in DN (Tang et al. 2020). Moreover, several studies have reported that miR-21 is associated with DN (Gomez et al. 2015; Lai et al. 2015) and it can be a biomarker for diagnosing DN in patients (Krichevsky and Gabriely 2009; Zarjou et al. 2011; Wang, Duan, et al. 2016). In line with these demonstrations, a study investigated kidney biopsies of diabetic patients and found that miR-21 enriches in all parts of the kidney, especially in glomerular cells. Both in-vivo and in-vitro results show that miR-21 overexpression has two effects on kidney cells. First, it stops cell cycle progression and induces mesangial cells' hypertrophy through suppressing cell cycle regulatory components, Cdc25a and Cdk6. Secondly, it increases podocytes' motility or migration via affecting Pten. Indeed, if miR-21 is inhibited by antagonists, it results in reducing cells hypertrophy and dysfunction which overall decreases kidney complications in diabetic patients. This study also proved that silenced-miR-21 appears to ameliorate albuminuria, glomerulosclerosis, fibrosis, DN, and inflammation (Kölling et al. 2017). Taken together, this evidence suggests that pharmacological miR-21 antagonisms can be a place to control renal complications in diabetic patients and increase their survival rate (Kölling et al. 2017; Liu et al. 2019). For example, in a study quercetin selected as a candidate by Yaochen Cao et al to identify its effect on kidney fibrosis. They found that a higher concentration of this flavonoid (15 or 30 mg/ml) can alleviate fibrosis through the downregulation of miR-21. Indeed, when quercetin suppresses miR-21, it indirectly increases miR-21 target genes including PTEN and TIMP3 which are identified as anti-fibrotic components and protect renal fibrosis. In this regard, it is estimated that quercetin might protect nephropathy in diabetic patients (Cao et al. 2018).

Additionally, quercetin prevents apoptosis and inflammation in chronic kidney disease (CKD) with a diabetic background. A study in 2019 documented that this drug can do these functions through upregulation of miR-124 (Guo, Tan, et al. 2020) which previously proved to have a positive effect on reducing inflammation and apoptosis in kidney damages (Li et al. 2018). Mechanistically, miR-124 plays these roles in different ways. First, miR-124 prohibits pro-apoptotic factors Bax and Cleaved-Caspase-3 while increasing the expression level of Bcl-2 to stop apoptosis in HK-2 cells. Secondly, miR-124 is negatively correlated with the NF-κB pathway. Indeed, when the miR-124 expression is low, NF-κB pathway activation increases (Guo, Tan, et al. 2020) because the NF-κB pathway is one of the main inflammatory signalings involved in the progression of chronic diseases (Wu, Lin, et al. 2017). Moreover, miR-124 directly targets MyD88 that appears to activate the NF-κB pathway and inflammation. Finally, miR-124 can suppress inflammation via IL-6 and TNF-α suppression (Li et al. 2018). Taken together, quercetin has valuable effects on these cases by improving the expression level of miR-124 (Guo, Tan, et al. 2020). Along with these findings, another recent study investigated the relationship between baicalin, which is a flavonoid, and the miR-124/TLR4/NF-κB axis in DN. Type IV collagen and fibronectin are renal fibrosis markers. Thus, researchers use them to identify the effectiveness of drugs. For instance, in this study, researchers found that baicalin can reduce type IV collagen, fibronectin, and consequently renal fibrosis in diabetes through the regulation of the miR-124/TLR4/NF-κB pathway. In detail, Toll-like receptor 4 (TLR4) is a component involved in renal fibrosis pathophysiology through NF-κB signaling pathway activation. Thus, baicalin improves miR-124 expression level which interacts with TLR4 and inhibits TLR4/NF-κB signaling, resulting in attenuating inflammation in DN (Zhang, Dai, et al. 2020).

Multiple studies have proved that extracellular matrix (ECM) abnormalities result in DN. matrix metalloproteinases (MMPs) are the main players in regulating ECM (Kolset, Reinholt, and Jenssen 2012; Loeffler and Wolf 2015; Liu et al. 2019); one of the most important ones is MMP-9 because it is demonstrated that MMP-9 down-regulation is interrelated to DN progression (Dimas, Didangelos, and Grekas 2017). On the other side, Hyperoside (quercetin-3-O-D-galactoside) is a flavonol with therapeutic

effects on renal dysfunction in diabetic mice (Zhang, Fu, et al. 2016; An et al. 2017). Hyperoside plays this activity through type IV collagen and fibronectin downregulation and MMP-9 upregulation. Therefore, researchers focused on how hyperoside upregulates MMP-9. In this study, encouraging results showed that this flavonoid post- transcriptionally affects MMP-9 which means that hyperoside causes epigenetic changes and increases MMP-9 protein through modulating miRNA expression. After evaluating, different miRNAs, evidence confirmed that hyperoside gives a rise in MMP-9 protein level through miR-21 down-regulation (Zhang, Fu, et al. 2016).

Glomerular mesangial cells proliferation and hypertrophy are contributed to DN progression. Inhibiting cell proliferation is a good approach to ameliorate DN (Das et al. 2019). Besides, CREB is the downstream transcriptional factor of ERK which plays an instrumental role in regulating genes expression involved in renal cell proliferation and differentiation. Moreover, CREB directly interacts with the miR-34a promoter and increases the transcription of miR-34a which has been proved to take part in cell proliferation and renal fibrosis in diabetes. In this regard, a study observed that hyperoside appears to prohibit ERK/CREB/miRNA-34a signaling pathway, renal cell proliferation, and kidney injuries when glucose concentration is high. As a result, hyperoside can attenuate miRNA-34a expression and subsequently DN development through suppressing ERK/CREB cascade (Zhang, Dai, et al. 2020).

Furthermore, TGF-β1/Smad signaling cascade is responsible for provoking proliferation and ECM production which overall results in renal fibrosis in high glucose concentration. When this pathway is inhibited, it enhances ECM deposition and improves DN treatment. Naringenis as a flavonoid can be found in citrus peel and seeds and mediates positive effects on DN treatment (Al-Rejaie et al. 2015; Orhan et al. 2015). It has been demonstrated that this natural agent can reduce inflammatory cytokines, blood glucose levels, and ECM markers awell a as proliferation to improve its therapy. Mechanistically, when it comes to cell proliferation inhibition, naringenin suppresses TGF-β1/Smad signaling both directly and indirectly. Experimental in-vivo and in-vitro analysis showed that naringenin decreases TGF-β1, TGFBR1, and smad2 expression while increasing smad7 protein expression, leading to TGF-β1/Smad inhibition. Moreover, microRNA let-7 targets and inhibits TGFBR1, and naringenin upregulates microRNA let-7 expression and activation. On this basis, naringenin reduces this signaling pathway through microRNA let-7 expression (Yan et al. 2016).

Curcumin has been identified as the dominant constituent of turmeric, and it plays different positive functions in the cells. One of these situations is diabetes. Curcumin not only reduces insulin resistance and fasting blood glucose but also has a protective role in diabetic mice due to its anti-inflammatory and antioxidant properties. (Qihui et al. 2020). Furthermore, adhesive capacity damage is the hallmark of DN because it generates proteinuria. Integrin α3 as a transmembrane protein is responsible for podocyte cell adhesion to ECM (Blattner and Kretzler 2005). Thus, if Integrin α3 downregulates, it will be associated with podocyte adhesion damage, proteinuria, and consequently DN. miRNAs like miR-124 also regulate podocyte adhesive capacity damage in diabetic rats through modulating cell adhesion molecules (Li et al., 2013). Related to these demonstrations, the experimental analysis showed that miR-124 directly binds to the Integrin α3 3′-UTR region and inhibits its expression and activation, conducting to DN. Another interesting result of this study revealed that curcumin can prevent DN development by inhibiting miR-124 and subsequently activating Integrin α3 (Li et al., 2013).

Furthermore, C66 is an analog of curcumin and is involved in the protection of diabetic nephropathy in mouse models (Pan et al. 2013). C66 appears to play this role through activating nuclear factor E2-related factor 2 (NRF2), which is a protective component against oxidative stress in DN (Liu, Gao, et al. 2014). MiR-200 family has been found to participate in tubular epithelial cells and renal fibrosis protection (Du et al. 2011; Yu et al. 2018). As an example, miR-200a plays these roles through the Keap-1/NRF2 pathway. On this basis, Hao Wu et al. confirmed that C66 induces miR-200a upregulation, which not only disrupts KEAP1 and NRF2 binding and releases NRF2 but also decreases KEAP1 gene expression. This effect leads to kidney disease protection in diabetic mice. However, after testing LNA-200a (miR-200a inhibitor), the C66 renal protection was reduced. So, it is likely that miR-200a/NRF2 DN positive effect is not dependent on C66. This study also proved that C66 activates Smad7, which involves protecting renal cells fibrosis in diabetic mice, through down-regulation of miR-21 (Wu et al. 2016).

It has been demonstrated that there is a correlation between tea polyphenols (TPs) and chronic kidney diseases in diabetic cases. Tea polyphenols (TPs) play important activities in alleviating diabetic complications. Different mechanisms have been identified for accomplishing these functions; one of them is cell senescence regulation (Meng et al. 2019). Generally, high glucose is associated with human glomerular mesangial cells (HGMCs) senescence which is characterized by shortening of telomeres and increasing cell senescence markers like p53 and p21 (Verzola et al. 2008; Sanders and Newman 2013). Additionally, MiR-126 has been regarded as a biomarker for diabetes (Assmann et al. 2018; Beltrami et al. 2018; Park et al. 2018; Lou et al. 2020) since MiR-126 has been reported to be reduced in DN patients, leading to HGMCs senescence (Meng et al. 2012; Al-Kafaji et al. 2016). Mechanistically, MiR-126 overexpression not only reduces inflammatory mediators IL-1b, IL-6, IL-18, and TNF-α but also induces VEGF and PI3K/AKT signaling pathways which potentially improve DN alleviation (Lou et al. 2020). Analysis of different doses of TPs showed that a higher concentration of TPs appears to reduce renal cell senescence in DN through repressing the Akt-p53-p21 pathway and increasing miR-126 (Cao et al. 2019).

Another flavonoid whose anti-diabetic activities have been extensively studied is apigenin with an antioxidant, anti-inflammatory, anti-apoptotic, and anti-fibrotic attributes

(Malik et al. 2017). In 2021, Yi Hou et al. reported that the same as other flavonoids apigenin plays these roles through the downregulation of inflammatory cytokines and fibrotic factors. Moreover, they analyzed apigenin molecular effects on DN both in-vivo and in-vitro and found that miR-423-5p downregulation and upstream stimulating factor 2 (USF2) upregulation, which have functions in DN development, are associated with reducing apigenin effectiveness in DN. In this regard, apigenin mediates its DN protective role depending on the miR-423-5p-USF2 axis (Hou et al. 2021). To sum up, we can conclude that polyphenols mediate their DN protective functions by controlling miRNAs and their target genes.

Modulation of miRNAs expression in diabetic cardiomyopathy by polyphenols

Diabetic cardiomyopathy (DCM) was recognized some decades ago when patients with heart failure had no history of coronary artery disease, hypertension, and valvular heart disease (Rubler et al. 1972).

The initial manifestation of DCM is myocardial fibrosis conducting to ventricular dilation, hypertrophy, and diastolic and systolic dysregulation, which is finally associated with heart failure (Lorenzo-Almorós, Cepeda-Rodrigo, and Lorenzo 2020). It has also been reported that heart failure is a common incidence among diabetic patients (Jia, Hill, et al. 2018). Therefore, oxidative stress, inflammation, metabolism dysregulation, and fibrosis are the most important causes of DCM. The accumulation of Glucose, fatty acids, and cytokines in diabetic patients is associated with reducing cardiac function. In detail, hyperglycemia and consequent oxidative stress increase advanced glycation end products (AGEs) and fibrosis markers like collagen type IV and fibronectin, leading to myocardial stiffness. Moreover, an increasing level of fatty acids involves in lipotoxicity in cardiomyocytes. Besides, the same as nephropathy, cytokines accumulation enhance cardiac hypertrophy (Dillmann 2019; Atale et al. 2020). Neha Atale et al. (Atale et al. 2020) reviewed the effectiveness of natural polyphenols as potential DCM treatment options. In this regard, we will discuss the cross-talk between phytochemicals, including resveratrol, dihydromyricetin and naringenin, and miRNAs in DCM cases.

Immune cells and other cells exposed to inflammation have a higher expression level of miR-155, which amplifies inflammatory responses. Thus, targeting this miRNA can attenuate inflammation (Climent et al. 2020). Resveratrol can reduce miR-155 expression and stimulate miR-663 as an anti-inflammatory miRNA to stop inflammation in different disorders like diabetes (Tili et al. 2010). In addition, miR-21, miR-181, and miR-30c2 have been proved to play a protective role against DCM by reducing ROS accumulation and apoptosis (Raut et al. 2016; Dai et al. 2018; Yin et al. 2019). According to these demonstrations, a study on 35 T2DM and hypertensive medicated patients who took resveratrol enriched (8 mg) grape extract (GE-RES) for 12 months every day showed that the expression level of inflammatory mediators IL-6, CCL3, IL-1β, TNF-α, and also miR-155 and miR-34a reduced, while the expression level of miR-21, miR-181b, miR-663, and miR-30c2 increased in patients' blood samples after one year, resulting in DCM protection (Tomé-Carneiro et al., 2013).

Sirtuin-1 (SIRT1) as a histone deacetylase plays functions in protecting cardiomyocytes by regulating metabolic and physiologic processes (Sundaresan, Pillai, and Gupta 2011; Matsushima and Sadoshima 2015). For example, SIRT1 gives a rise in the expression level of sarcoplasmic calcium ATPase (SERCA2a), which has an effective role in protecting cardiac function in DCM cases (Sulaiman et al. 2010). It has also been proved that SIRT1 is the direct target of miR-34a, which is overexpressed during myocardial infarction (MI). MiR-34a mediates its adverse effect on cardiac function through the down-regulation of SIRT1, Bcl2, and Cyclin D1 (Yang et al. 2015). Previously, it had been documented that resveratrol can improve SIRT1 concentration in DCM, but its mechanism was not investigated (Sulaiman et al. 2010). Therefore, in a study, researchers focused on this issue and found that resveratrol mediates this role by regulating the miR-34a/Sirt1 axis. Indeed, resveratrol downregulates miR-34a and upregulates Sirt1 (Yang et al. 2016).

Another study in 2021 confirmed these results and detected a high concentration level of miR-34a in diabetic rats with MI. Moreover, analysis in this study has three valuable results after resveratrol treatment. First, it found that during hyperglycemia the expression level of miR-34a, P21, and p16 increase in bone marrow mesenchymal stem cells (BMSCs) which overall results in cell senescence, leading to decreasing the effectiveness of repair after MI in diabetes. Resveratrol as a therapeutic strategy can address this situation and increase BMSCs viability through down-regulating miR-34a, P21, and p16. Secondly, SIRT1 decreases, and miR-34a increases in high glucose conditions in BMSCs, while resveratrol appears to reverse their expression levels and enhance the heart healing process. Finally, this in-vivo experiment revealed that pro-angiogenic factors, including VEGF and HIF-1α, which play an essential role in MI recovery, are stimulated in diabetic rats with MI situations treated by resveratrol compared to diabetic rats without intervention (Zhang et al. 2021).

As we mentioned above, miR-34a overexpression has been observed in DCM cases, which exacerbates cardiac dysfunction by inducing apoptosis and reducing autophagy (Zhou et al. 2014; Ghosh and Katare 2018; Climent et al. 2020). Dihydromyricetin (DHM) riches in flavonoids and was proved to have a protective effect on DCM mouse models (Wu, Lin, et al. 2017). A recent study evaluated the dihydromyricetin mechanism of action in DCM mice and its correlation with miR-34a. This study demonstrated that dihydromyricetin mitigates the activation of cleaved caspase 3 and Bax (apoptotic genes) while inducing Bcl-2 and p53 expression (anti-apoptotic genes). Moreover, when it comes to the impairment of autophagy, this study found that dihydromyricetin treatment in DCM mice is associated with inhibiting miR-34a and increasing autophagy markers like MAP1LC3B II/MAP1LC3B I ratio, Beclin-1, and LC3B (Ni et al. 2020).

PI3K/AKT signaling is positively correlated with cardiac protection due to its indirect function in modulating muscle contraction and calcium channels myocardium (Viard et al. 2004). Thus, it is not surprising that the dysregulation of this pathway has been observed in DCM (Zhang, Dai, et al. 2020). Besides, studies admitted that miR-126 not only reduces oxidative stress and apoptosis (Wang et al. 2019) but also can activate PI3K/AKT upon MI/R (myocardial ischemia-reperfusion) injury (Zhang, Dai, et al. 2020; Li et al. 2021). A recent study on 50 diabetic rats reported that the application of naringenin for 30 days appears to attenuate DCM through the activation of the miR-126-PI3K/AKT axis (Li et al. 2021). Taken collectively, polyphenols can reduce apoptosis, inflammation, and oxidative stress and also promote autophagy for DCM treatment through miRNAs expression modulation.

Modulation of miRNAs expression in diabetic retinopathy by polyphenols

Diabetic retinopathy (DR), the common cause of blindness in adults, is another complication of diabetes that has been reported to affect one-third of diabetic cases. Multiple mechanisms have been introduced for DR progression; genetic, epigenetic, ROS, inflammatory cytokines, and AGEs accumulation (Wong et al. 2016). In the first steps, there are changes in blood-retinal barrier (BRB) permeability, vascular occlusion, formation of macular edema, and tissue ischemia which are the leading sign of DR development (ValdezGuerrero et al. 2021). In addition to microvascular alterations, retinal neurodegeneration and inflammation are other underlying causes of DR progression (Matos et al. 2020). Different therapeutic strategies are considered to prevent or treat DR progression (ValdezGuerrero et al. 2021); one of them is natural components like flavonoids, curcumin, and resveratrol (Ahmad and Hoda 2020; Matos et al. 2020; Yang et al. 2021). These natural agents apply different ways to play their DR protective role. Among them, a considerable number of studies evaluated the interconnection between these agents and miRNAs in DR treatment.

For instance, both in-vivo and in-vitro examinations revealed that resveratrol mediates DR's protective role due to its anti-apoptotic function on müller cells through the regulation of the miR-29b/SP1 axis (Zeng et al. 2017). MiR-29b and its relationship with DR have been widely investigated (McClelland and Kantharidis 2014; Zhang, Chen, et al. 2018; Dantas da Costa et al. 2019; Han, Zhang, et al. 2020). Ramiro Garzon et al. (Garzon et al. 2009) demonstrated that miR-29b can directly bind to SP1, a transcription factor involved in cellular process regulation (Yoshida-Hata et al. 2010). Both in-vivo and in-vitro analysis reported that the expression level of miR-29b declines in DR, while SP1 expression experiences upregulation in DR. Moreover, this study proved that resveratrol dose-dependently enhances miR-29b expression and consequently downregulates SP1 and apoptotic factors to protect Müller cells apoptosis because these cells are affected by microvascular alterations and they must be protected to stop DR development (Zeng et al. 2017).

Quercetin has various protective effects on retinal cells during high glucose concentration. First, it reduces programmed cell death factors while inducing CyclinD1, CDK4, and Bcl-2 to stop retinal cell apoptosis. Secondly, during hyperglycemia, this flavonoid plays its anti-inflammatory and antioxidant role through the down-regulation of TNF-α and upregulation of superoxide dismutase (SOD) in retinal cells (Yang et al. 2021). Moreover, another study also focused on the interrelation between quercetin and miR-29b on Adult retinal pigment epithelial cell line-19 (ARPE-19) exposed to high glucose. The analysis of data showed that p-AKT reduces in these cells exposed to high glucose while PTEN, p-p65, and IκBα witness a significant rise in these cells. Quercetin can protect retinal cells against damage by reversing this situation. Quercetin activates miR-29b expression, leading to elevating PTEN/AKT and preventing the NF-κB pathway (Wang et al. 2020).

Just like quercetin, baicalin as a flavonoid is extracted from Scutellaria baicalensis, which is a chinese herb with anti-diabetic properties (Fang et al. 2020). baicalin exerts multiple positive effects to improve DR treatment including reducing inflammatory cytokines, ROS accumulation, and apoptotic factors as well as activating apoptosis inhibitors (Xiao, Do, and To 2014; Pan et al. 2021). Apart from that, a considerable number of studies claimed that miR-145 expression levels were repressed in DR conditions, which is related to DR pathogenesis (Gong et al. 2017; Hui and Yin 2018). Thus, a study questioned whether there is an interrelation between baicalin and this miRNA to mediate DR protective functions. Evidence showed that NF-κB and p38MAPK pathways, which are involved in exacerbating DR conditions, are downregulated in DR cells treated by baicalin compared to the control group. This research also revealed that not only does miR-145 have the same functions as baicalin to stop retinal injuries, but also its suppression reverses baicalin effects and reduces retinal cell viability. As a result, it has been suggested that this polyphenol plays its DR protective role through the activation of miR-145 (Dai et al. 2019).

Furthermore, the low expression level of miR15a in DR has been verified in different studies (Chakrabarti 2016; Wang, Duan, et al. 2016; Gong et al. 2019). In retinal cells, miR15a can interact with insulin receptor substrate 1 (IRS-1), reduce TNFα and increase insulin receptor phosphorylation and Akt2, resulting in insulin signaling transduction and consequently protecting retinal cells. Resveratrol has been introduced as a selective pharmacological agent to stimulate miR15a expression to improve insulin signaling in retinal cells (Jiang, Liu, and Steinle 2018). In conclusion, polyphenols participate in diabetic retinopathy protection by increasing the expression level of miR-29b, miR-145, and miR15a.

Modulation of miRNAs expression in diabetic neuropathy by polyphenols

Diabetic peripheral neuropathy (DPN) is a neurodegenerative disorder of the peripheral nervous system that develops

in more than 50% of diabetic patients (Feldman et al. 2019). Different metabolic mechanisms like oxidative stress are attributed to DPN occurrence. Although it is one of the most difficult kinds of pain to control, the guidelines for DPN therapy are restricted to symptomatic and pain management (Zakin, Abrams, and Simpson 2019). However, new evidence climbed that polyphenols can be effective candidates for DPN treatment (Kumar, Negi, and Sharma 2013; Zhang, Dai, et al. 2020; Kabir et al. 2021; Khursheed et al. 2021). On the other side, a huge number of studies confirmed the contribution of miRNAs like miR-155, miR-126, miR-146a, miR-27a, and miR-224-3p in DPN pathophysiology and therapy (Simeoli and Fierabracci 2019; Fan et al. 2020). In this regard, these years, the combination of polyphenols and miRNAs has attracted attention for finding DPN treatment strategies. As we mentioned above, miR-155 involves different diabetic complications like DPN (Chen et al. 2019). It has been suggested that extra virgin olive oil (EVOO) polyphenolic compounds might participate in controlling inflammation in chronic diseases by targeting miR-155 expression (Carpi et al. 2019). Accordingly, a study observed that resveratrol plays its anti-inflammatory and neuroprotective role through the down-regulation of miR-155 (Ma et al. 2020).

Furthermore, miR-126 as an angiogenic miRNA has a low expression level in T2DM-stroke mice and humans (Liu, Gao, et al. 2014; Chen et al. 2017). Exosomes therapy in T2DM-stroke mice by EC-Exo which has a high level of miR-126 exhibits neurorestorative effects like function and cognitive improvement, axon and myelin density, and M2 macrophage polarization. This study also revealed that miR-126 displays diabetic neuroprotective function because when miR-126−/−EC-Exo was applied, neurological and cognitive abilities were attenuated (Venkat et al. 2019). Another study demonstrated that resveratrol is positively correlated with miR-126 and its suppression negatively affects resveratrol's protective function. In this regard, it is estimated that, like diabetic nephropathy, such polyphenols might exert neuroprotective function through miR-126/PI3K/AKT regulation (Xin et al. 2018).

A huge number of studies confirmed the down-expression of miR-146a in DPN (Wang et al. 2014; Leinders et al. 2017; Fan et al. 2021). an In-vivo examination on diabetic mice (db/db) proved that miR-146a mimics are associated with DPN alleviation. Although miR-146a does not have functions in regulating glucose homeostasis, it conducts neuroprotective functions through different mechanisms. In one of them, there is a negative feedback loop between NF-kB and miR-146a. On the other side, IRAK1, and TRAF6 as downstream factors of TLRs are responsible for NF-kB signaling activation and consequently inflammatory responses. This cascade is activated during DPN, while miR-146a can suppress the NF-kB pathway via targeting IRAK1/2 and TRAF6 (Liu, Ao, et al. 2017; Feng et al. 2018). It has been observed that miR-9 expression is high in the DPN situation in rat models (Liu, Ao, et al. 2017) and its expression exacerbates the DPN condition by targeting insulin gene enhancer binding protein-1 (ISL1) and down-regulating sonic hedgehog (SHH) signaling as well as NF-κB activation (Ebrahimpour, Esmaeili, et al. 2020; Sun et al. 2020). A study investigated the expression level of miR-146a, miR-9, and NF-kB in diabetic rats during the application of quercetin and quercetin-conjugated with superparamagnetic iron oxide nanoparticles (QCSPIONs) and found that quercetin therapy, especially in conjugated form, can promote neurological protection and memory improvement in diabetic rats through the regulation of miR-146a/miR-9/NF-κB inflammatory pathway (Ebrahimpour, Esmaeili, et al. 2020).

As we discussed in previous sections, oxidative stress is one of the underlying causes of diabetic complications. Besides, a higher expression level of miR-27a has been verified in diabetic complications (Zhou et al. 2017; Platania et al. 2019; Wu et al. 2021). In the case of neurological protection through controlling oxidative stress, a study on diabetic rats revealed that both quercetin and QCSPIONs not only induce antioxidant enzymes SOD1 and CAT (catalase) but also can reduce miR-27a expression, then increase NRF2 mRNA and protein expression level which finally results in alleviating neurological complications and preventing memory dysfunction. Meanwhile, this study proved that the effectiveness of QCSPIONs is higher than pure quercetin (Ebrahimpour, Esmaeili, et al. 2020). Naringenin is a citrus flavonoid that has effective functions in reducing diabetic neuropathy and enhancing memory in diabetic cases through its anti-oxidant and anti-inflammatory capacity (Rahigude et al. 2012; Singh et al. 2020). For example, it has been reviewed that naringenin mediates its roles via stimulating SOD, CAT, and glutathione (GSH) which have anti-oxidant properties (Zaidun, Thent, and Latiff 2018). In this regard, a study focused on the neuroprotective effect of naringenin by regulating pro-inflammatory miR-224-3p. Encouraging results demonstrated that naringenin mediates this role due to its ability to inhibit miR-224-3p expression and elevate the mRNA and protein expression level of SOD in a dose-dependent manner. Additionally, this flavonoid reduces pro-apoptotic factors, while inducing anti-apoptotic elements to protect PC12 cells (neuronal cell model) (Li et al. 2020). In this regard, these studies show that there is room for further investigation to identify the cross-regulation between phytochemicals and miRNAs for DPN therapy.

Modulation of miRNAs expression in the diabetic wound by polyphenols

There are three major steps in the wound healing process; inflammatory phase, proliferative phase, and remodeling phase (Ayavoo, Murugesan, and Gnanasekaran 2021). The diabetic wound is characterized by delay and incomplete healing, especially in foot ulcers which are the underlying cause of infection, foot deformity, and amputation in diabetic patients (Dixon and Edmonds 2021). Several studies confirmed the participation of miRNAs whether in diabetic wound development or the healing process (Ozdemir and Feinberg 2019; Petkovic et al. 2020). Apart from that, a huge number of studies showed the therapeutic effect of polyphenols like curcumin, resveratrol, and prunus spinosa on diabetic wound healing (Tiboni et al. 2020; Çetinkalp

et al., 2021; Li et al. 2021; Mokhtari, Razzaghi, and Momen-Heravi 2021). Although separate evidence is available about the contribution of miRNAs and polyphenols in improving this complication, few studies evaluate their cross-regulation healing process.

It has been shown that the down-regulation of miR-146a is associated with NF-κB signaling pathway activation and wound healing impairment (Xu et al. 2012; Bi et al. 2022). Moreover, since C66 as the analoge of curcumin has been confirmed to have better anti-inflammatory activities at a lower dose, Jingjuan Huang et al. investigated the role of this analog in diabetic wound healing improvement. Both in-vivo and in-vitro examinations revealed that C66 elevates miR-146a expression, which directly binds to and inhibits IRAK1 to stop NF-κB activation and inflammation. This study also found that other inflammatory mediators, including TNF-α, IL-6, and IL-8, are down-regulated by C66 (Huang, Shi, et al. 2020). In line with these findings, another study investigated that Prunus spinosa L. fruit (PSF), containing polyphenols, has the wound-healing capability through the regulation of miR-146a/IRAK-1/NF-kB anti-inflammatory mechanism (Coppari et al. 2021). Taken together, C66 and PSF have a promising role in diabetic wound healing improvement via miR-146a upregulation.

Conclusions and future research directions

Diabetes and diabetic complications, including diabetic nephropathy, cardiomyopathy, neuropathy, retinopathy, and delayed wound healing are major burdens in societies. The anti-inflammatory, anti-oxidant, and anti-diabetic roles of polyphenols have been discussed widely. Accordingly, these phytochemicals can play their protective role against diabetic complications by targeting miRNAs and their direct effectors which are involved in inflammation, oxidation, apoptosis, and angiogenesis. Mostly, polyphenols appear to upregulate or down-regulate miRNAs to stop inflammatory signaling pathways like NF-kB, inflammatory cytokines like TNF-α, and apoptosis. In addition, polyphenols can induce CyclinD1, CDK4, Bcl-2, VEGF and HIF-1α, SIRT1, and signaling pathways like PTEN/AKT, which are essential in diabetic complications' healing process, through targeting miRNAs. However, a limited number of miRNAs have been evaluated upon polyphenols treatment. Therefore, further studies are required to figure out the association between polyphenols and other miRNAs in diabetic complications therapy. In addition, it is suggested that future clinical studies should examine the effectiveness of polyphenols on diabetic complications.

Author's contributions

FM, EM, MA, DS, ZA, AS and BY contributed in the conception, design, and drafting of the manuscript.

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