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Review

Deciphering nutritional interventions for podocyte structure and function

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ABSTRACT

Despite increasing awareness and therapeutic options chronic kidney disease (CKD) is still and important health problem and glomerular diseases constitute and important percentage of CKD. Proteinuria/albuminuria is not just a marker; but it also plays a direct pathogenic role in renal disease progression of CKD. Glomerular filtration barrier (GFB) which consists of fenestrated endothelial cells, fused basal membrane and interdigitating podocyte foot process and filtration slits between foot process is the major barrier for proteinuria/albuminuria. Many glomerular diseases are characterized by disruption of GFB podocytes, foot process and slit diaphragm. Many proteinuric diseases are non-specifically targeted by therapeutic agents such as steroids and calcineurin inhibitors with systemic side effects. Thus, there is unmet need for more efficient and less toxic therapeutic options to treat glomerular diseases. In recent years, modification of dietary intake, has been gained to treat pathologic processes introducing the concept of 'food as a medicine'. The effect of various nutritional products on podocyte function and structure is also trending, especially in recent years. In the current review, we summarized the effect of nutritional interventions on podocyte function and structure.

1. Introduction

With improvements in medical technology and innovation, our understanding of kidneys ultrastructure has been greatly improved in recent years. The glomerular filtration barrier (GFB) is composed of fenestrated endothelial cells, fused basal membrane and interdigitating podocyte foot process and filtration slits between foot process. It is now clear that podocyte injury is a major event in many renal diseases, including congenital syndromes and very common conditions – such as diabetic kidney disease (DKD). The ultrastructural organization of GFB is extraordinarily complex and there are numerous connections between slit diaphragm, foot process, actin skeleton of podocytes and glomerular basal membrane. Many glomerular diseases are treated non-specifically by therapeutic agents (including steroids and calcineurin inhibitors) with unwanted systemic adverse effects [1,2]. Thus, there is unmet need for more efficient and less toxic therapeutic options to treat glomerular diseases.

In recent years, modification of dietary intake, has been gained to treat pathologic processes introducing the concept of "food as a medicine". Indeed, there is accelerating research regarding the effect of nutritional interventions in various pathologic states. The effect of various nutritional products on podocyte function and structure is also trending, especially in recent years. With such background in mind, in this review, we summarized the effect of nutritional interventions on podocyte function and structure.

2. Discussion

In the current review, we summarized various nutritional interventions that modify podocyte function and structure and various in vitro and animal studies have shown favorable effects in podocyte function and GFB structure (Tables 1–3).

Glomerular filtration barrier is vital for the process of selective filtration and avoiding passage of albumin and other molecules. Podocytes (an important part of the GFB) and underlying GBM should withstand the transcapillary filtration pressure while permitting filtration. During filtration, plasma passes endothelium and fused GBM, then reaches the slit diaphragm. The slit diaphragm is a specific type of intercellular junction which connects neighboring podocyte foot processes. Any type of stress irrespective of stimulus cause foot process

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Table 1
Summary of animal studies showing the effects of various nutritional interventions on podocyte specific findings.

Ref.	Aim	Methods	Podocyte specific findings
[69]	-To study effects of tRA on PAN-induced interstitial mononuclear infiltration, podocyte death, and proteinuria	-Female Wistar rat study groups (n = 6 in each); control, PAN, tRA, tRA + PAN (tRA treatment 1 day before PAN injection), and PAN + tRA2 (tRA treatment 2 days after PAN)	- tRA treatment, both before and after PAN injection, reduced food process effacement and protected glomerular epithelial cells - tRA treatment inhibited PAN-induced podocytes apoptosis
[70]	-To evaluate effects of genistein on inflammatory and renal parameters in fructose-induced insulin resistance	-Adult male Wistar rats were fed with either starch or fructose containing diet as source of carbohydrate -After development of insulin resistance in fructose-fed rats, rats in each dietary group were divided into two; treatment with either genistein in 30% DMSO or only 30% DMSO for 45 days	-Diffuse podocyte disruption and effacement shown in kidneys of fructose-fed rats -Fructose-fed rats had lower slit pore diameter and higher foot process base than controls -Among fructose-fed group, genistein treatment resulted in higher slit pore diameter and lower foot process base
[71]	-To investigate effects of ferulic acid on podocyte structure	-Obese diabetic OLETF rats and non-diabetic control rats were used -Ferulic acid was applied from weeks 26 to 45	-Ferulic acid treatment prevented podocyte foot process effacement and reduction of slit pores observed in diabetic control rats
[24]	-To investigate whether GSPE decreases podocyte injury by activating PCG-1α in low-dose STZ and high-carbohydrate/high-fat diet-induced diabetic rats	-Rats were first divided into two groups; Group 1 (n = 12), 4 weeks of basal diet, received citrate buffer vehicle; Group 2 (n = 58), 4 weeks of high-carbohydrate/high-fat diet, received STZ -Diabetic rats in Group 2 (n = 48) were evenly randomized to DM control group, and low dose, medium and high doses of GSPE for 16 weeks	-GSPE increased mitochondrial DNA and nephrin, podocalyxin and mitochondrial biogenesis factor mRNA expression in podocytes -GSPE induced expression of PCG-1α, SIRT1 and AMPK -GSPE may improve DN-induced podocyte injury via AMPK-SIRT1-PGC-1α pathway
[26]	-To investigate whether PCB2 enriched fraction of cinnamon prevents AGE accumulation and ameliorates renal disturbances in diabetic rats	-STZ-induced diabetic rats were fed for 12 weeks with either 3% cinnamon or 0.002% PCB2 enriched fraction of cinnamon	-Cinnamon and PCB2 enriched fraction of cinnamon prevented loss of nephrin and podocin expression induced by AGE
[12]	- To investigate effects and mechanism of action of Qiwei granules on podocyte injury in diabetic KK-Ay mice	-Male KK-Ay mice were randomized to receive vehicle or Qiwei granules for 10 weeks -C57BL/6J mice served as controls	-Qiwei granules decreased podocyte foot process fusion and increased nephrin, CD2AP, WT-1 and integrin alpha3beta1 expression -Qiwei granules increased Akt phosphorylation, inhibited expression of caspase-3 and prevented podocyte apoptosis
[28]	-To explore impact of epicatechin on prevention of high fructose-induced kidney injury in rats	-Male Sprague Dawley rats consumed water with 10% fructose with or without epicatechin for 8 weeks	- Expression of nephrin, synaptopodin and WT1 decreased in high fructose consumption -These changes were partly ameliorated by epicatechin
[29]	-To explore whether EA inhibited AGE accumulation in vivo and ameliorated renal disturbances in diabetic rats	- STZ-induced diabetic rats were randomized to a 12-week diet of 0.2% or 2% of EA	-Nephrin and podocin expression was decreased by 35–40% in glomeruli of diabetic rats -EA diminished loss of glomerular nephrin and podocin expression mediated by hyperglycemia
[72]	- To investigate renoprotective effects of RBP in diabetic animals and cultured mesangial cells	- Eight-week-old male *db/m* and *db/db* mice were randomized to 8 weeks of oral tap water or RBP	-Slit pore number and expression of nephrin were decreased in diabetic mice -These changes were diminished by RBPs per unit length of GBM and nephrin expression was significantly decreased in the diabetic control group -These changes were improved by RBP
[86]	-To explore the impact of resveratrol on apoptosis and autophagy in DN mice	- 8 weeks old diabetic db/db and db/m mice with C57BL/KsJ genetic background were evenly randomized (n = 6) into 3 groups; db/m, db/db and db/db + Res) -The db/db + Res mice received resveratrol while other groups received saline by oral gavage for 12 weeks	-Resveratrol decreased of caspase-3 and Bax expression dose-dependently -Resveratrol diminished human podocyte apoptosis induced by glucose and increased proteins related to autophagy (LC3-II, Atg5 and p62) -Resveratrol showed protective effects via miR-383–5p suppression
[49]	-To investigate the effect of AM in DN	- Flower or leaf extracts of AM were tested in mouse DN model constituted by high-fat diet plus STZ after unilateral nephrectomy -The preventive effects of the extracts on DN pathology and changes on autophagy and	-AM increased expressions of nephrin and podocin -AM increased autophagy and decreased mitochondrial fragmentation

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Table 1 (*continued*)

Ref.	Aim	Methods	Podocyte specific findings
		mitochondrial proteins were investigated	
			-AM decreased DRP-1 expression (mitochondrial fission marker) and increased fusion markers (MFN-2 and OPA-1)
[50]	-To study effect of retinoic acid receptor b2agonist AC261 in a high-fat diet HFD model of DN in C57BL/6 mice	-Wild-type, 10-week-old, male C57BL/6 mice were randomized to 16 weeks of a laboratory chow or HFD	-HFD-fed mice demonstrated effacement, collapse and reduction in density of podocyte foot process and reduction infiltration slits of glomerular filtration barrier
		-At the end of fourth week, HFD mice were further randomized to continue HFD plus drinking water containing 0.2% dimethylsulfoxide or HFD plus drinking water containing 3.0 mg/100 ml of AC261 for 12 weeks	- Podocyte injury and foot process effacement were lower, foot process density and filtration slits were higher in HFD + AC261 group than in HFD group
			-HFD-fed mice had decreased podocin and WT1 expression, which were normal in HFD + AC261-treated mice
[73]	-To explore whether CMP has protective effects on STZ-induced DN mice.	-DN was induced by STZ-injection in male C57BL/6 mice	-CMP reduced severe foot process effacement induced by STZ
		-CMP (at 200 and 400 mg/kg) or irbesartan were administered to prevent STZ-induced injury	-STZ increased desmin (reflecting injury of podocytes), which was decreased by CMP
			-CMP suppressed STZ-induced CD68, IL-1β, IL-6 and MCP-1
			-CMP counterbalanced STZ-induced autophagy deficiency, increased LC3, beclin1, Atg5 expression and decreased p62 expression
[32]	-To explore impact of fenugreek seeds and onion consumption on glucose transporters and renin angiotensin system related renal disturbances in diabetic rats	-Mechanisms of action of 10% fenugreek seeds and 3% onion consumption on kidneys in STZ-induced diabetic rats were investigated	-Fenugreek normalized kidney podocyte damage markers of podocalyxin, podocin and nephrin and their excretion by urine
			-Fenugreek downregulated KIM-1 expression
[75]	-To investigate effects and mechanism of action of lowering plasma homocysteine by Folic acid reduces HHcy-related glomerular injury in SHRs	-SHRs were randomized to; control, HHcy, HHcy + low-dose FA, and HHcy + high-dose FA groups	-HHcy group of SHRs had enhanced effacement and fusion of foot processes and apoptosis of podocytes; these changes were related with enhanced NOX2 and NOX4 expression and reduced nephrin expression
			- LFA and HFA administration counterbalanced these changes
[62]	- To investigate effects and mechanism of action of LJP61A on adriamycin-induced AKI in mice	-Six-week-old male BALB/c mice were evenly randomized to normal group, model group, low-dose LJP61A group (50 mg/kg/day), middle-dose LJP61A group (100 mg/kg/day), high-dose LJP61A group (200 mg/kg/day) and three control LJP61A groups	- LJP61A dose-dependently counterbalanced adriamycin-related decreased WT1 and nephrin, increased desmin
			- LJP61A suppressed phosphor-JNK, phosphor-ERK1/2, phosphor-p65 and
			- LJP61A suppressed Smad3 and TGF-β1 protein and mRNA
			-LJP61A was protective for AKI by inhibiting TGF-β1-mediated Smad3, MAPKs and NF-κB pathways

tRA, all-trans retinoic acid; PAN, puromycin amino nucleoside; DMSO, dimethylsulfoxide; OLETF, Otsuka Long-Evans Tokushima Fatty; LETO, Long-Evans Tokushima Otsuka; GSPE:Grape seed proanthocyanidin extracts, PCG-1α, peroxisome proliferator-activated receptor-γ coactivator 1, STZ, streptozotocin, SIRT1, silent mating type information regulation 2 homolog 1, AMPK, AMP-activated protein kinase; DN, diabetic nephropathy; PCB2, procyanidin-B2; AGE, advanced glycation end product; WT1, Wilms' tumor 1; EA, ellagic acid, RBP: Rice bran protein, GBM: Glomerular basal membrane, AM: Abelmoschus manihot, DRP-1, dynamin-related protein-1; MFN-2, mitofusin-2; OPA-1, optic atrophy-1; HFD, High-fat diet; CMP, Cordyceps militaris polysaccharides; MCP-1, monocyte chemoattractant protein-1; Atg5, autophagy gene 5; KIM-1, kidney injury molecule-1; HHcy, hyperhomocysteinemia, SHRs; spontaneously hypertensive rats, AKI; acute kidney injury; ERK, extracellular regulated protein kinase; JNK, Jun Nterminal kinase; MAPK, mitogen activated protein kinase; TGF-β1, transforming growth factor-β1; Smad: Mothers against decapentaplegic homolog, NF-κB:nuclear factor kappa-light-chain-enhancer of activated B cells, MAPK, mitogen activated protein kinase.

effacement and loss of slit diaphragms, leading to proteinuria [3,4]. The close connection between foot process, slit diaphragms, and underlying GBM is not only structural but functional and take role in cellular signaling. Slit diaphragm connects with foot process and podocytes via a variety of proteins (cell–matrix adhesions) including laminins, integrins, α-dystroglycan, type XVII collagen and intracellular linker proteins such as integrin-linked kinase [1,2,5].

3. Podocyte and GBM adhesions

Podocytes connect to underlying basement membrane via their foot processes. The major link between foot process and GBM occurs via α3β1which is the main integrin found on the basolateral aspects of podocyte foot processes. The other β1 integrin causing podocyte GBM adhesion is α2β1 [6]. CD151 is another way of connection which binds the integrin α3β1 and is involved in the augmentation of podocyte adhesion to laminin via integrin α3β1 [2]. Podocytes express cell-surface proteoglycans such as syndecans 1 and 4, and glypican-1 [7–9]. Syndecans not only act with cell matrix connection but along with integrins function as transmembrane receptors for growth factors and extracellular proteins [10]. There are also other linker proteins such as protein tyrosine kinase 2 [11,12] Integrin-linked kinase [2], Kindlin-2 [13]

Table 2
Summary of in vitro showing the effects of various nutritional interventions on podocyte specific findings.

Ref.	Aim	Methods	Podocyte specific findings
[25]	-To investigate effects and mechanism of action of GSPB2 on apoptosis of podocytes induced by high glucose	-NRF-1 and TFAM gene expression was studied in cultured podocytes	-GSPB2 decreased apoptosis of podocytes -Nephrin and podocalyxin expression was increased - mRNA expression of NRF-1 and TFAM was increased -mtDNA copy was increased - AMPK-SIRT1-PGC-1α pathway was activated
[30]	-To investigate effect of Crocin, a plant-derived compound, in experimental diabetes model	- Conditionally immortalized mouse podocytes were incubated with 15- or 25-mM D-glucose	- Expressions of podocin, nephrin, CD2AD were reduced in high glucose milieu -Crocin pretreatment prevented these changes - High glucose milieu upregulated IL-1β, IL-8, TNF-α, ROS levels and phosphorylated IκBα expression and decreased SOD production -Crocin restored these changes
[87]	- To explore effects of EGCG in high-glucose induced mouse podocyte injury	-Conditionally immortalized mouse podocytes were cultured in medium at 37 °C without interferon-γ to induce differentiation for > 2 weeks -Ahead of experiment, growth of cells were synchronized via culturing for 24 h in serum-free medium	- Expressions of WT-1 and nephrin were lower and podocyte apoptosis was higher in high glucose group than normal glucose and mannitol groups -EGCG markedly promoted podocyte proliferation and significantly decreased number of apoptotic cells -EGCG diminished high-glucose induced GRP78, p-PERK and caspase-12 expression
[58]	-To explore whether GTS is protective for podocytes in vitro diabetic milieu	-Conditionally immortalized mouse podocytes were cultured with glucose (normal or high, with or without AGE) and were treated with GTS	- CD2AP is decreased in diabetic milieu and was recovered by GTS -GTS diminished apoptosis of podocytes in diabetic milieu
[78]	-To investigate the impact of plant-derived saponin, AS-IV, on reversal of kidney fibrosis and improvement of kidney function via modulation of autophagy and podocyte EMT	- AS-IV was tested on diabetes models of KK-Ay mice and cultured immortalized mouse podocytes	-AS-IV reduced EMT induced by glucose -AS-IV increased autophagy via reducing NF-κB subunit p65 acetylation and upregulating expression of SIRT1 in podocytes
[33]	To investigate impact of hesperetin on podocytes eliciting EMT	-TGF-β1 was used to induce EMT in podocytes, which were then exposed to hesperetin -Hesperetin induced a slight but nonsignificant decrease in viability of cells at 100 and 200 mM -Hesperetin had no cytotoxic effect on podocytes up to 50 mM concentrations -Highest hesperetin concentration was set to 50 mM	-TGF-β1downregulated ZO-1 and nephrin (epithelial markers) in podocytes - TGF-β1upregulated vimentin, FN and α-SMA (mesenchymal markers) in podocyte -Hesperetin counterbalanced these changes by TGFβ1 via mTOR pathway inhibition
[35]	-To explore whether ferulic acid is protective in diabetic rats	- STZ-induced DN rats were administered 8 weeks of ferulic acid	-Ferulic acid increased the activity of CAT, SOD and GPx, and decreased MDA content -Ferulic acid decreased TGF-β1, TNF-α, NF-κB, p65 and collagen IV expression -Ferulic acid partially counterbalanced decreased podocin and nephrin expression in DN

GSPB2, grape seed procyanidin B2; NRF-1, nuclear respiratory factor 1; TFAM, mitochondrial transcription factor A, AMPK, AMP-activated protein kinase; SIRT1, silent mating type information regulation 2 homolog 1, PCG-1α, peroxisome proliferator-activated receptor-γ coactivator 1, TNF-α, tumor necrosis factor alpha, ROS, reactive oxygen species; IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, EGCG, epigallocatechin-3-gallate; GRP78, glucose-regulated protein 78; PERK: Protein Kinase R-like ER Kinase, *GTS,* ginseng total saponin, EMT, epithelial to mesenchymal transition, NF-κB:nuclear factor kappa-light-chain-enhancer of activated B cells, TGF-β1, transforming growth factor-β1; ZO-1,zonulin-1; FN, fibronectin; α-SMA, α-smooth muscle actin; mTOR, mammalian target of rapamycin, CAT: catalase, SOD: superoxide dismutase, GPx, GPx, glutathione peroxidase. MDA: MDA, malondialdehyde; IL TGF-β1, TGF-β1, transforming growth factor-β1, TNF-α, TNF-α, tumor necrosis factor alpha.

α-actinin-4 [14], which play a role in foot process-GBM connections. As seen there is extensive and complex interaction between foot process and GBM. It was shown that, Qiwei granules increase expression of alpha3beta1 [12], Eucalyptol increases the levels of integrin β1 and α-actinin-4 [15] and also induces focal adhesion proteins of paxillin, vinculin, talin1, FAK, and Src in glucose-exposed podocytes [16].

3.1. *Structure and function of slit diaphragm, foot process and its connections*

The structure of SD is very complex and composed of many proteins. The major component of SD is nephrin which has a central role in determining mechanical strength of the slit junction [3]. In fact, without nephrin, the slit diaphragm does not even form [17], resulting in a loss of the SD, foot process effacement and proteinuria. The intracellular part of nephrin contains tyrosine residues where phosphorylation occurs. After tyrosine phosphorylation, nephrin can serve as binding sites for the SH2 domains of cytoplasmic targets, including phosphoinositide 3-kinase (PI3K) and Fyn [18], leading to activation of AKT pathway which

Table 3
Summary of in vitro and animal studies showing the effects of various nutritional interventions on podocyte specific findings.

Ref.	Aim	Methods	Podocyte specific findings
[61]	-To investigate effects of SE in podocyte injury in STZ-induced DN in mice and cultured mouse podocytes	-STZ-induced DN mice were treated with oral SE for 7 weeks	-SE reduced podocyte loss, preserved slit diaphragm integrity and prevented EMT -SE reversed downregulation of WT1 and discontinuous nephrin expression caused by diabetes - SE restored decreased E-cadherin and increased α-SMA expression in diabetic mice
[88]	-To examine protective effects of TFA on microalbuminuria and podocyte apoptosis in DN rats	- In male Sprague–Dawley rats, DM was induced by STZ -Control group of nondiabetic rats received citrate buffer - STZ-induced diabetic rats were treated with continuous oral TFA -DM rats were randomized; DM rats treated with carboxymethyl cellulose solution (DN group) or a low or high dose of TFA	-Rats treated with TFA had lower urinary microalbuminuria, caspase 3 and caspase 8 levels -Rats treated with TFA had less podocyte apoptosis
[27]	-To investigate effects of fructose and curcumin on insulin signaling in podocyte dysfunction and injury in rats and cultured podocytes	-Rats were fed with 6 weeks of 10% fructose followed by 6 weeks of 10% fructose + curcumin	-10% fructose diet was associated with decreased miR-206 expression, phosphorylation of extracellular signal-regulated kinases 1 & 2, insulin receptor, insulin receptor substrate 1, caveolin-1, protein kinase B and induced expression of PTP1B -Curcumin improved above changes, -Curcumin increased expression of nephrin and podocin, decreased mean FPW and improved and improved foot process effacement - Curcumin increased miR-206 expression, decreased PTP1B and activated podocyte insulin signaling
[89]	-To investigate functional relationship between cav-1 and ROS and curcumin in DN	-High glucose media was used to incubate mouse podocytes -Diabetes was induced by STZ injection in male rats	-Podocyte ROS generation, oxidative stress, apoptosis, and cav-1 phosphorylation were increased by high glucose -These changes were ameliorated by curcumin pretreatment

Table 3 (*continued*)

Ref.	Aim	Methods	Podocyte specific findings
			in a dose-dependent manner
[31]	-To evaluate impact of chrysin on apoptosis of podocytes and deficiency of proteins in slit diaphragm in vitro and in mice in high glucose exposure conditions	- Conditionally immortalized mouse podocytes were used for in vitro studies - Adult male *db/db* mice and their age-matched non-diabetic *db/m* littermates were used for animal studies	-In vitro exposure to high glucose resulted in apoptosis of podocytes, which was diminished dose-dependently by chrysin via attenuation of DNA fragmentation - In podocytes exposed to high glucose, chrysin restored increased Bax/Bcl-2 ratio, and decreased Apaf-1 induction and increased cytochrome *c* release in a dose-dependent manner -In diabetic glomeruli, chrysin decreased podocyte apoptosis and foot process effacement, induced podocin and nephrin -In podocytes, high glucose elevated the unfolded protein response to endoplasmic reticulum stress, as shown by increased by induction of PERK-eIF2α-ATF4-CHOP pathway -Chrysin blocked endoplasmic reticulum stress, which leads to apoptosis of podocytes
[85]	-To investigate whether WGP diet is beneficial in metabolic syndrome-associated chronic kidney disease	-Obese diabetic ZSF1 rats received 6 months of WGP (5%, *w/w*) -Heat-sensitive mouse podocytes were used for in vitro analysis	-WGP diminished H_2O_2-induced apoptosis of podocytes, as demonstrated by positive Annexin-V staining
[15]	-To explore the effects and mechanism of action of eucalyptol on inhibition of slit diaphragm malfunction in podocytes exposed to glucose and diabetic mice	-For in vitro procedures, podocytes were incubated in a glucose and eucalyptol containing media - db/db mice received oral eucalyptol for in vivo model	-Eucalyptol enhanced expression of α-actinin-4, FAT-1, nephrin, podocin and CD2AP in podocytes, which were reduced by glucose -Eucalyptol counteracted RAGE up-regulation in podocytes with glucose -AGE-induced ERK-c-Myc signaling is ameliorated by Eucalyptol with an increase in nephrin and CD2AP expression and induction of α-actinin-4 and integrin β1
[16]	-To explore the protective impact of eucalyptol on formation of F-actin cytoskeleton and focal	-Conditionally immortalized mouse podocytes were used for in vitro experiments	-Mouse podocytes loaded with glucose demonstrated reduced ezrin, cortactin, F-actin

(*continued on next page*)

Table 3 (*continued*)

Ref.	Aim	Methods	Podocyte specific findings
	adhesion assembly in diabetic kidney podocytes loaded with glucose		and Arp2/3, all were reversed by eucalyptol
		-Adult male db/db mice and their age-matched nondiabetic db/m littermates were randomized to; nondiabetic mice, db/m control mice, and db/db mice -One group of db/db mice received 8 weeks of eucalyptol	- Vinculin, paxillin, FAK, talin1 and Src (focal adhesion proteins) were induced by eucalyptol in podocytes loaded with glucose and diabetic kidneys -Eucalyptol counterbalanced the upregulation of Rho A, ROCK, Cdc42 and GTP-binding Rac1 in podocytes loaded with glucose and diabetic kidneys
[74]	- To assess protective effects of chlorogenic acids enriched STVRE and flavonoids against HU	-Male Kunming mice were randomized to; normal control; model control, positive control (allopurinol 5 mg/kg bw), STVRE (STVRE 100 mg/kg bw), STVRE + Al1 (STVRE 75 mg/kg bw + allopurinol 5 mg/kg bw), and STVRE + Al2 (STVRE 100 mg/kg bw + allopurinol 5 mg/kg bw) -HU was induced by 4 weeks of oral 10% fructose and 150 mg/kg bw potassium oxonate -Allopurinol and STVRE were administered for 4 weeks	- Structural podocyte disorder and fusion of foot process were improved by allopurinol and STVRE, alone or combined
[45]	-To investigate whether taurine was protective for diabetic kidney disease focusing on mitochondrial dysfunction modulated by TRPC6	-STZ-induces diabetic kidney disease model and immortalized mouse podocytes were used	-STZ decreased expression of podocin, nephrin and bcl-2, which were increased by taurine -Taurine decreased calcium overload, improved mitochondrial respiration, and reduced ROS production and podocyte apoptosis -High glucose conditions induce calcium overload, partially via TRPC6 expression, which is decrease by taurine -High glucose increases ROS and MDA, and decreases SOD levels, all partially reversed by taurine -Taurine significantly improved high glucose- induced impaired respiratory functions mediated by CI_{OXPHOS}, $CI + II_{OXPHOS}$ and $CI + II_{ETS}$, -High glucose enhanced TG-induced SOCE and OAG-induced ROCE -Taurine partially diminished calcium overload induced by high glucose
[34]	-To explore protective effects of tangeretin on podocyte injury induced by EMT and fibrosis hyperglycemia-induced hypoxia and oxidative stress	-Mouse podocytes were incubated in glucose containing media with or without tangeretin for up to 6 days	-Tangeretin decreased podocyte expression of N-cadherin and α-SMA (mesenchymal markers)
		- db/db mice were administered 8 weeks of oral tangeretin for in vivo study	-Tangeretin increased P-cadherin and E-cadherin (epithelial markers) -Tangeretin counterbalanced glucose-induced down-regulation of nephrin and podocin -Tangeretin diminished podocyte foot process effacement and loss -Tangeretin counterbalanced glucose-induced 8-hydroxy-2-deoxy guanosine and HIF-1α induction -Submicromolar tangeretin inhibited EMT induced by loss of podocyte junction and slit diaphragm proteins, and hypoxia-evoking cobalt chloride induced EMT
[90]	-To investigate effects of dietary fiber on emergence of DN, gut microbiata and production of SCFAs	-Diabetes in wild-type C57BL/6 and knockout mice lacking genes for G-protein coupled receptors GPR43 or GPR109A was induced by STZ	-High-fiber diet improved loss of podocyte density in DN
		-Mice were randomized to; zero-fiber, high-fiber, normal chow diets or SCFAs	-Dietary fiber enhanced SCFA (propionate, acetate and butyrate) production, which in turn decreased podocyte fibronectin, TGF-β1 and IL6
		- C57BL/6 mouse podocytes and tubular epithelial cells were cultured	-SCFA mediated its effects by GPR43 or GPR109A
[91]	-To investigate the protective effect of TP on podocytes epithelial-mesenchymal transition (EMT) injury model	- Human conditionally immortalized glomerular podocytes for used for in vitro experiments	-TP increased nephrin and NEPH1 levels which were down-regulated by TGF-β1
		-When the differentiated cells grew to 70–80%	-TP increased TET2 protein expression which was decreased by TGF-β1.

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Table 3 (*continued*)

Ref.	Aim	Methods	Podocyte specific findings
		confluence, they were starved in serum-free medium for 24 h, followed by treatment with medium containing either TGF-β1 or TP -Sprague Dawley rats were used to establish the focal segmental glomerulosclerosis (FSGS) model by using uninephrectomy and repeated injection of doxorubicin. - FSGS rats were allocated randomly into the model and TP groups. Intervention with TP started after the proteinuria occurred and FSGS rats were gavaged with triptolide at a dose of 200 μg/kg/d. Control rats were treated with an equivalent volume of normal saline.	-TP decreased methylation at specific promoter sites of nephrin and NEPH1 which was increased by TGF-β1

SE, Schisandra chinensis fruit extract; STZ, streptozotocin, DN: Diabetic nephropathy, EMT, epithelial to mesenchymal transition; WT1, Wilms' tumor 1; α-SMA, α-smooth muscle actin; TFA, total flavone glycosides of Flos Abelmoschus manihot, PTB1B, protein tyrosine phosphatase 1B; FPW, foot process width; ROS, reactive oxygen species, cav-1, caveolin-1, Apaf-1, apoptotic peptidase activating factor 1, PERK, protein kinase RNA-like endoplasmic reticulum kinase; eIF2 α, phospho-eukaryotic initiation factor 2α (eIF2α); ATF4, activating transcription factor 4; CHOP, C/EBP homologous protein; WGP, whole grape powder; RAGE, receptor for advanced glycation endproducts, AGE, advanced glycation endproducts, ERK, extracellular signal-regulated kinases, STVRE, stevia residue extract; HU, hyperuricemia; ROS, reactive oxygen species; MDA, malondialdehyde; CI_{OXPHOS}, complex I-dependent oxidative phosphorylation, CI + II_{OXPHOS}, maximal oxidative phosphorylation; CI + II_{ETS}, complex I + II supported noncoupled respiration; TG-induced SOCE, store-operated calcium entry; OAG-induced ROCE, receptor-operated calcium entry, α-SMA, α-smooth muscle actin; HIF-1, Hypoxia-inducible factor 1-alpha, DN:Diabetic nephropathy, SCFA, short-chain fatty acids; TGF-β1, transforming growth factor-β1, IL-6, Interleukin 6, TP: triptolide, EMT: Epithelial-mesenchymal transition FSGS: Focal segmental glomerulosclerosis, TET2: ten-eleven translocation 2.

mediates actin remodeling when mechanical stress occurs [19–21]. Indeed, diminished nephrin phosphorylation has been associated with various forms of nephrotic syndrome [22,23]. As shown in Table 1 many nutritional interventions increase nephrin expression.

Various nutritional interventional studies have shown that nephrin levels and expression is increased by grape seed proanthocyanidin extracts (GSPE) [24,25] procyanidin-B2 (PCB2) [26], curcumin [27] Epicatechin [28] ellagic acid [29], Crocin [30], chrysin [31], eucalyptol [15], fenugreek [32], hesperetin [33], tangeretin [34] Ferulic acid [35] (Fig. 1).

NEPH1 is another transmembrane protein located adjacent to nephrin [36] Studies have shown that Neph1 is necessary for normal foot process development [37,38]. NEPH1 interacts with nephrin and this interaction has an important role in normal slit diaphragm function [39]. After phosphorylation, The nephrin–NEPH1 complex transduces signals which result in the assembly of an actin polymerization complex [39].

Another slit diaphragm protein is podocin. This is a membrane associated protein whose C-terminus and N-terminus both face the cytoplasm. This protein seems vital for transmitting the signaling the nephrin-Neph1 complex to the podocyte which in turn regulates podocyte actin dynamics [39]. Podocin mutation results in diminished nephrin recruitment into the rafts, thus altering nephrin signaling [40]. Podocin, also may act as a mechanic sensor and is closely associated with in TRPC6 channel [17]. TRPC6 is a nonselective calcium permeable cation channel. TRPC6 enables podocytes to sense alterations in pressure, fluid flow or filtration rate [41]. This results podocyte to cytoskeleton remodeling according to needs [42–44]. In normal conditions, knockout of TRPC6 induces insulin resistance and exacerbates glomerular injuries. However, in DKD and FSGS, aberrant activation of TRPC6 has been shown to contribute to pathogenesis [45,46]. Augmented activity of TRPC6 channel increase calcium influx into cells resulting downregulating the expression of nephrin at the slit diaphragm and synaptopodin in the cytoskeleton, and stimulates RhoA activity which in turn causes actin derangement and foot processes effacement and inhibits podocyte motility [47,48]. Podocin by balancing TRPC6 activity regulates the cytoskeleton dynamics [42–44].

Podocin is increased in various nutritional interventions such as procyanidin-B2 (PCB2) [26] curcumin [27] ellagic acid [29] crocin [30], chrysin [31], Abelmoschus manihot [49] retinoic acid [50] fenugreek [32] ferulic acid [35]. Taurine also decreased TRPC6 expression which is responsible for the calcium overload during high glucose treatment [45].

The adaptor CD2AP molecule is another protein which localized in the cytoplasm and membrane ruffles of podocytes, and has also important role for regulating podocyte dynamics [51,52]. CD2AP works as

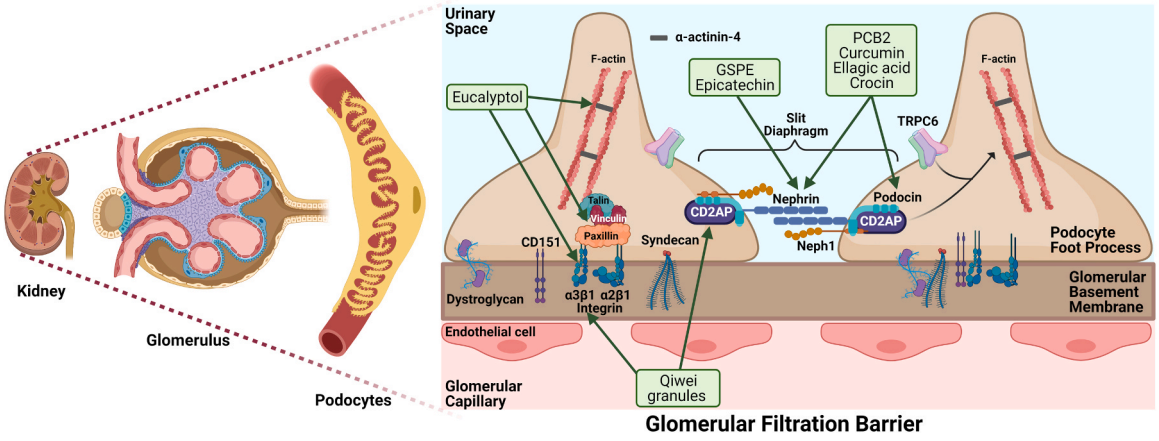

Fig. 1. Overview of Nutritional Interventions and their effects on the components of the glomerular filtration barrier. Transient receptor potential channel 6 (TRPC6), CD2-associated protein (CD2AP), Nephrin-like protein 1 (Neph1).

anchor since it links actin assembly to the formation of the podocyte slit diaphragm by interacting with nephrin and podocin and cell signaling [53,54]. CD2AP and nephrin also interact with the p85 subunit of phosphoinositide 3-kinase (PI3-K) and, subsequently, stimulate the anti-apoptotic intracellular Akt kinase (PI3-K/Akt) pathway, resulting cell survival and actin reorganization [55]. The activation of the PI3-K/Akt signaling pathway by nephrin could protect podocytes against detachment induced podocytes apoptosis. Additionally, the deletion of CD2AP significantly suppressed Akt activation and increased susceptibility to pro-apoptotic transforming growth factor (TGF)-b; however, the reconstitution of CD2AP in transfected CD2AP-/– podocytes might reverse this apoptotic process [56]. CD2AP damage disrupts podocyte cytoskeleton and induces proteinuria [57]. Qiwei granules [12], Crocin [30] ginseng total saponin [58] increased the expression of CD2AP.

Synaptopodin and marker of differentiated podocytes and during nephrogenesis its expression increases. Synaptopodin along with actin filaments plays an important role for foot processes formation [30]. Synaptopodin by binding to α-actinin-4, regulates its actin-bundling activity, and to CD2AP binding. Synaptopodin inhibits filopodia formation while promoting formation of contractile actin stress fibers by blocking the degradation of RhoA [59,60]. Epicatechin increased the expression of Synaptopodin [28]. WT-1 is another biomarker of GFB is a positive marker of podocyte in kidney [12]. Schisandra chinensis fruit extract [61], Epicatechin [28] retinoic acid receptor b2agonist [50] Laminaria japonica polysaccharide [62] have all favorable effects on WT1. The effect of nutritional interventions on TRPC6, CD2AP, PI3K, AKT and RhoA has been shown in Fig. 2.

Actin dynamics: Foot process effacement (FPE) is commonly observed in many proteinuric diseases. FPE is associated with actin cytoskeleton disruption. This is important since proper actin dynamics and signaling determines normal podocyte morphology during development and important in response to podocyte injury. Accordingly, the filtration function of podocytes depends on the maintenance of the normal actin dynamics [15]. F-actin, intermediate filaments and microtubules are mostly found on podocyte cell body, however the foot process cytoskeleton is mostly composed of actin fibers [63]. At molecular level, mechanical forces induce cytoskeletal rearrangements through downstream effectors of Rho kinase [64]. Indeed, in various experimental nephropathy models, downregulation of Rho kinase activity has been shown to be beneficial [65]. Apart from Rho kinase, small GTPases, Rac1, and Cdc42, modulate cytoskeletal dynamics through actin nucleation promoting factors such as formin and WASP. The activities of these small GTPases is tightly regulated, to control multiple cellular processes [66,67]. In addition other SD proteins such as FAT1 interact with cellular signaling networks and actin cytoskeleton via scaffolding proteins of CD2AP and ZO1 [68]. Last but not least, α-actinin-4 which mediates actin cross linking interacts with integrins supporting the podocyte-GBM interaction, thereby stabilizing glomerular architecture [14].

Various nutritional interventions restored food process effacement and restore GFB. For example retinoic acid [69], genistein [70], ferulic acid [71], Schisandra chinensis fruit extract [61], Qiwei granules [12], rice bran protein hydrolysates (RBPs) [72], retinoic acid receptor b2agonist [50], Cordyceps militaris polysaccharides (CMP) [73], chlorogenic acids enriched stevia residue extract [74] and folic acid [75] reduce foot process effacement and restoration of GFB. Eucalyptol increased α-actinin-4 [15] and F actin levels [16] and ginseng total saponin increased F actin levels [58].

One of the adverse events regarding podocyte biology is epithelial to mesenchymal transition (EMT). EMT as the name suggest, is characterized by epithelial cells which lose their epithelial characteristics and acquire the mesenchymal features. Podocyte EMT is unwanted phenomenon and during this process the expressions of nephrin, podocin and zonulin-1 (ZO-1) is downregulated in podocyte. The result is altered and disordered slit diaphragm actin cytoskeleton arrangement. On the contrary during podocyte EMT, expression of mesenchymal markers such as desmin, and matrix metalloproteinase proteins were increased in podocytes [76]. One of the inducer of EMT and renal fibrosis is TGF-β1. TGF-β1 via activating Smad dependent and non-Smad-dependent pathways, activates myofibroblasts, increase of extracellular matrix (ECM) production and inhibits of degradation. For example Smad3, an important downstream mediator of TGF-β/Smad signaling, plays a pathogenic role in both renal inflammation and fibrosis [62]. Podocyte EMT has also been observed during hyperglycemia and oxidative stress [61]. It was shown that curcumin prevents EMT in podocytes, in experimental diabetic nephropathy by regulating caveolin-1 Tyr14 phosphorylation [27,77].

Schisandra chinensis fruit extract prevented the EMT of podocytes caused by diabetic nephropathy and decreased E-cadherin and increased

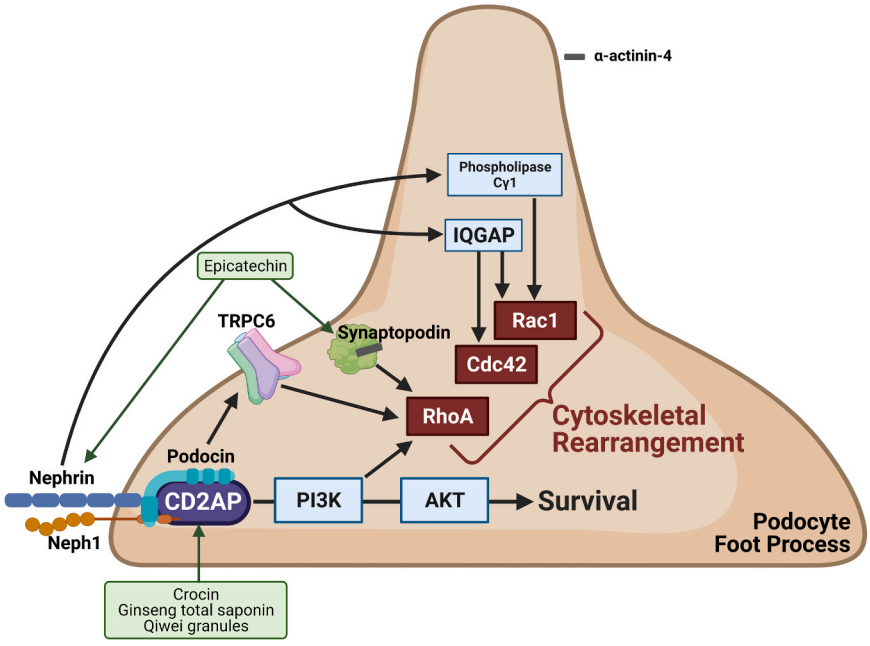

Fig. 2. Overview of the interactions of slit diaphragm proteins and their corresponding signaling pathways within podocytes leading to regulation of the podocyte cytoskeleton and survival. Transient receptor potential channel 6 (TRPC6), CD2-associated protein (CD2AP), Nephrin-like protein 1 (Neph1), cell division control protein 42 (Cdc42), IQ motif containing GTPase activating protein (IQGAP), ras-related C3 botulinum toxin substrate 1 (Rac1), ras homolog gene family member A (RhoA), phosphatidylinositol 3 kinase (PI3K), protein kinase B (AKT).

alpha-smooth muscle actin expressions in diabetic mouse were restored by Schisandra chinensis fruit extract [61] plant-derived saponin astragaloside decreased glucose-induced podocyte EMT and enhanced autophagy by decreasing NF-κB subunit p65 acetylation as well as increasing Sirtuin1 (SIRT1) expression in podocytes [78]. As suggested above TGF-b1 decreased expression of epithelial markers such as nephrin, zonula occludens-1, while it increased the mesenchymal markers, including fibronectin (FN), vimentin, and α-smooth muscle actin (α-SMA) in the podocytes. Hesperetin restored these changes elicited by TGF-b1 by inhibiting the mTOR pathway [33]. Tangeretin inhibited glucose-induced expression of the mesenchymal markers of N-cadherin and α-smooth muscle actin in podocytes and increased epithelial markers of E-cadherin and P-cadherin in diabetic podocytes [34].

Proper insulin signaling is important for healthy podocytes [79]. Indeed like smooth muscle cells, insulin is needed for glucose uptake by podocytes [80]. Protein tyrosine phosphatase 1B (PTP1B) is inhibitor of insulin signaling which dephosphorylates insulin receptor (IR) and insulin receptor substrate 1 (IRS-1), thus negatively regulates downstream insulin signaling protein kinase B (Akt)/extracellular signal-regulated kinases 1 and 2 (ERK1/2) pathway activation.

Curcumin by activating miR-206 expression downregulates PTP1B, which result in improvement in insulin signaling and protect against fructose-induced glomerular podocyte injury [27].

Endoplasmic reticulum stress (ERS) – now considered as a pathologic process in many disease states and is related with unfolded protein response (UPR). Nutritional interventions may also impact on EMT (Fig. 3). GRP78, a major protein involved UPR, accepted as marker for ERS [81,82]. The Protein Kinase R-like ER Kinase (PERK) cleaves from GRP78, rendering autophosphorylation by oligomerization. This in turn lead to phosphorylation of the α subunit of translation initiation factor 2 (eIF2α) ERS [83]. Caspase-12, which is specifically located in the cytoplasm of the ER and can be activated during ERS [84] Caspase-12, when activated can directly enter cytosol and activate other caspases mainly including caspase-3, leading to apoptosis [82] Thus GRP78 work as inductor of ERS and caspase-12 work as executor of ERS induced apoptosis. Chrysin has shown to ameliorate ERS and restore UPR. Hyperglycemia has shown to induce UPR and ERS in podocytes, along with up-regulation of PERK-eIF2α-ATF4-CHOP. Chrysin treatment blocked such ERS pertinent to podocyte apoptosis [31].

Nutritional interventions have impact on apoptosis, autophagy, mitochondrial function in podocytes. It was shown that Retinoic acid [69] Flos Abelmoschus manihot [49], Qiwei granules [12] rape seed procyanidin B2 [25], curcumin [77] whole grape powder [85], Resveratrol [86] Epigallocatechin-3-gallate [87], ginseng total saponin (GTS) [58] taurine [45] decreased apoptosis in podocytes. Abelmoschus manihot (AM) increased autophagy and decreased mitochondrial fragmentation -AM decreased DRP-1 expression (mitochondrial fission marker) and increased Fusion markers (MFN-2 and OPA-1[49]. Cordyceps militaris polysaccharides increase autophagy, promote the expression of Atg5, beclin1, LC3 protein, and decrease the expression of p62 protein in kidney [73]. Saponin astragaloside IV augments autophagy by decreasing NF-κB subunit p65 acetylation [78]. Grape seed proanthocyanidin extracts increased mRNA expression of mitochondrial biogenesis factors and mitochondrial DNA content in podocytes and also activate AMPK-SIRT1-PGC-1a signaling in podocytes [24].

3.2. Future perspectives

Recent data demonstrate that nutritional interventions may be pragmatic and feasible approach for treating non-communicable diseases and chronic kidney disease is no exception. Collectively podocytopathies are important in various congenital and acquired nephrotic syndromes. There are numerous complex interactions between foot process GBM, and slit diaphragm. Pathological alterations of any of these interactions may be ended with severe disease. Today non-specific treatments including steroids and calcineurin inhibitors are used to treat podocyte injury but with potential serious side effects. Nutritional interventions on the other hand showed promising preliminary results. However before using them as potential therapeutics some very important issues must be clearly acknowledged. First, as the studies are in vitro and animal studies, the toxic effects of these interventions to other organs should be clearly documented. Second, the dosages of these interventions for humans are not known. Third, the consequences of combination of these therapies with conventional drugs (steroids, calcineurin inhibitors etc.) is not known. Fourth, we should only know the effects of nutritional interventions on hard outcomes (GFR decline dialysis initiation) after clinical investigations were completed. Given these facts, we believe that although promising there is a long path before using these interventions routinely.

4. Conclusion

Nutritional interventions seems promising strategy to treat podocytopathies. However, these studies are explored in vitro studies and animal models. The systemic side effects to other organs is not known precisely and the human studies regarding hard outcomes are lacking. Future studies are needed to highlight these issues.

Author statement

BA, owner of the project, collected the data, wrote the manuscript. REA, helped writing the paper and intellectual content, helped for tables and formatting manuscript. AD, helped collecting data and organization of figures. AC, helped intellectual content and final approval. MK, helped intellectual content, organization of figures and final approval.

Role of the funding source

None.

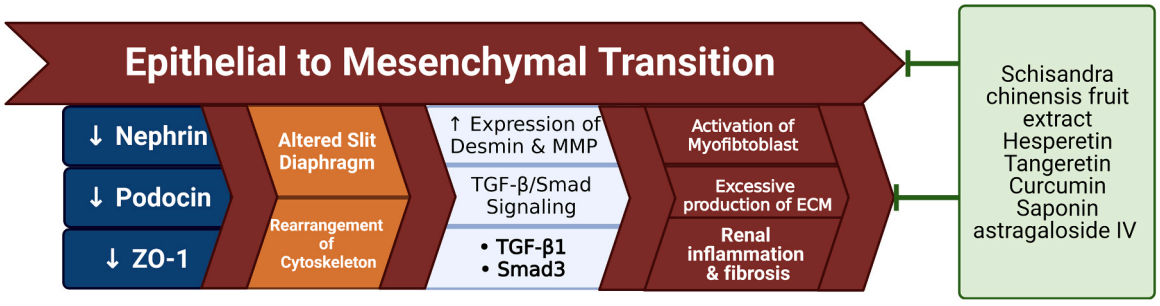

Fig. 3. Overview of epithelial to mesenchymal transition and nutritional ınterventions to ameliorate EMT. Zonulin-1 (ZO-1), Transforming growth factor-beta (TGF-β), Matrix metalloproteinases (MMP), Mothers against decapentaplegic homolog (Smad), Extracellular matrix (ECM).

Conflict of interest

None.

Acknowledgments

None.

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