

# Urolithins and their possible implications for diabetic kidney

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## Abstract

The increasing prevalence of diabetic kidney disease (DKD), a common complication of type 1 and type 2 diabetes, is becoming a leading risk factor of developing end stage renal disease (ESRD). The multiple mechanisms involved in renal tissue damage are a challenge for effective targeted therapy. Urolithins are metabolites generated by gut microbiota upon dietary intake of plant-derived ellagitannins. Multidirectional effects of these compounds include their anti-inflammatory, antioxidant, anti-proliferatory, anti-migratory and antiglycative properties that are mediated by modulation of signaling pathways and gene expression. Biochemical properties of urolithins indicate their capacity to regulate numerous mechanisms responsible for developing the hyperglycemia-induced tissue injury. The potentially beneficial effects of urolithins on podocytes, the most vulnerable renal cells should be particularly considered. The purpose of this review is to provide the evidence from the *in vivo* and *in vitro* studies showing that urolithin-based therapy could be a useful tool for protecting the kidneys from damage in diabetes.

**Keywords:** urolithins · diabetes · kidney · podocytes

## Citation

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## Introduction

Urolithins (hydroxylated dibenzo [*b,d*]-pyran-6-one derivatives) are a family of bioactive compounds which were first isolated from beaver scent glands in 1949 [1]. Their presence in human and animal intestines is a result of bac-

terial metabolism in gastrointestinal tract of dietary ellagitannins (ETs) and their constituent, ellagic acid (EA) [2]. ETs and EA are naturally occurring polyphenols found in numerous fruits and vegetables, e.g. pomegranates, raspberries and nuts [3]. Their beneficial health properties including anti-inflammatory, antioxidant and antiproliferative effects

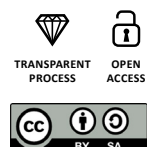
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have been proven in both animal and human models. Various studies demonstrated the protective effects of ETs and EA against chronic diseases of the cardiovascular system, neurodegenerative diseases, diabetes and cancer. However, ETs and EA have poor bioavailability and their biological activity is associated with urolithins that are more easily absorbed in gut [4-8]. The synthesis of urolithins depends on the composition in the gut of specific bacteria that varies between the individuals. The identification of the microorganisms responsible for the complete transformation of EA into the final urolithins is still under research. According to the recent findings, different numbers of *Synergistetes phylum* and members of *Coriobacteriaceae* (genus *Gordonibacter urolithinifaciens* and *Gordonibacter pamelaee*) and *Lachnospiraceae* families can be used to discriminate between individuals producing certain urolithin forms [9-10]. Thus, after absorption and passage through the liver, different urolithins can be found in human body fluids and tissues at nanomolar to micromolar concentrations. Absorbed urolithins undergo phase I and phase II metabolism, resulting in glucuronide, sulfate and methylated derivatives, while small amounts can be found in the form of free aglycones [2, 11-12].

Both the conjugated and unconjugated forms of urolithins can be detected in human plasma and urine even 48 hours after consumption of ET-rich food [6, 13-14]. It is clear therefore that bioactive urolithins directly contact renal tissue during the passage through the nephron. It seems plausible that the cells constituting the glomerular filter, as well as epithelial cells lining the urinary tract may be affected by these compounds. Antioxidant, anti-inflammatory and antimicrobial properties of these compounds could be beneficial in treating several renal diseases, including diabetic kidney disease (DKD) [15-16]. Nevertheless, so far there are not many data on the effects of urolithins on the renal tissue. The purpose of this review is to provide the evidence from the *in vivo* and *in vitro* studies showing that urolithin-based therapy could be a useful tool for protecting the kidneys from damage in diabetes.

## Material and methods

We searched the Medline, Scopus and Science Direct databases for articles published from 2011 to April 2021 using the following keywords: kidney disease, urolithins, ellagic acid, elagitannins, podocytes, polyphenols, diabetes, nephropathy, transforming growth factor and relevant abbreviations (e.g. TGF $\beta$ , CKD, DN). Older articles describe pathomechanisms and serve as context for the presented new information. The inclusion criteria were: full-text article, on-topic. Case reports and letters to the Editor were excluded from the review.

## Results

### Bioavailability and metabolism

Similarly to other phytochemicals, ETs are poorly absorbed in the gut. However, following consumption the ETs undergo spontaneous hydrolysis into EA in the upper gastrointestinal tract. Microbes residing in the intestine further transform EA yielding a series of bioactive compounds including urolithins that are characterized by a dibenzopyranone structure and a decreasing number of phenolic hydroxyl groups (Figure 1) [4, 17-18]. Due to their high lipophilicity, urolithins are much more readily absorbed than the original polyphenols.

After absorption in the gut, urolithins rapidly undergo metabolism by phase II enzymes in enterocytes [8, 19]. Once in the bloodstream, conjugated and unconjugated metabolites reach liver via portal circulation and are further subjected to phase II metabolism in hepatocytes. Due to enterohepatic recirculation, part of urolithin conjugates can be secreted with bile back to the small intestine [5, 20]. Analyses of human and animal blood and urine samples indicate that urolithins A and B and their glucuronide and sulfate conjugates are predominant urolithin isoforms. In particular, Uro A is considered to be a major metabolite in humans. However, depending on the study design, the measured final plasma concentrations vary substantially reaching 0.1–35  $\mu$ M [4,8,15]. Human and animal studies have shown that urolithin metabolites accumulate in the gall bladder and urinary bladder [21], prostate gland [22-23], colon and intestinal tissues [22], whereas no accumulation in other tissues (e.g. muscles, adipose tissue, heart, liver, kidney) was observed [21].

Individual variability in the composition of gut microbiome results in significant differences in ET metabolism and urolithin type production, which is defined as different metabolotypes [8]. Specific gut microbiota profile or illnesses generating dysbacteriosis may contribute to different bacteria composition and levels, consequently leading to various potential health effects [24-26]. Therefore, it is essential to consider the influence of factors such as age, gender, race, health condition and geographic origins on the polyphenol profile after consumption of ETs-rich products. Based on the amount and type of urolithins excreted in the urine from healthy volunteers, three different urolithin metabolotypes have been described: metabolotype A (only Uro A metabolites excreted), metabolotype B (Uro B and/ or Uro B metabolites excreted in addition to Uro A and isourolithin A) and urolithin metabolotype O (no urolithins/ urolithin metabolites excreted) [13]. Significant interindividual variability was also reported in the first pharmacokinetic study, that showed for the first time that EA bioavailability was not increased after intake of a high free EA dose. It was concluded that factors such as pH and food protein content have a strong impact on EA bioavailability [19].

## Biological activity

The direct biological effects of urolithins have been examined in different cell models, such as various cancer cell lines, fibroblasts, immune, endothelial and epithelial cells [4, 27-28].

The studies on the chemopreventive potential of EA and its metabolites Uro A and Uro B revealed that their anti-tumor properties, including the influence on cancer cell apoptosis and proliferation involve alterations in the expression of genes involved in signaling (MAPK) pathways, oncogenes (K-Ras, c-Myc), suppressors (DASP6, Fos), p53

protein, growth factor receptors (FGFR2, EGFR) and multiple genes involved in cell cycle [11, 29-33]. EA, as well as urolithins (and principally Uro A) exhibit proapoptotic activity via caspase-dependent pathways, in which activation of caspases 3, 8 and 9 has been reported [34-35]. Inhibition of cancer growth is mediated by suppression by Uro A and Uro B of Wnt/  $\beta$ -catenin signaling [36-37].

Moreover, anti-tumor and anti-metastatic effects of urolithins include inhibition of migration of cancer cells by diverse mechanisms such as suppressing the K-ras/HMGA2 expression or by decreasing actin polymerization [38-39].

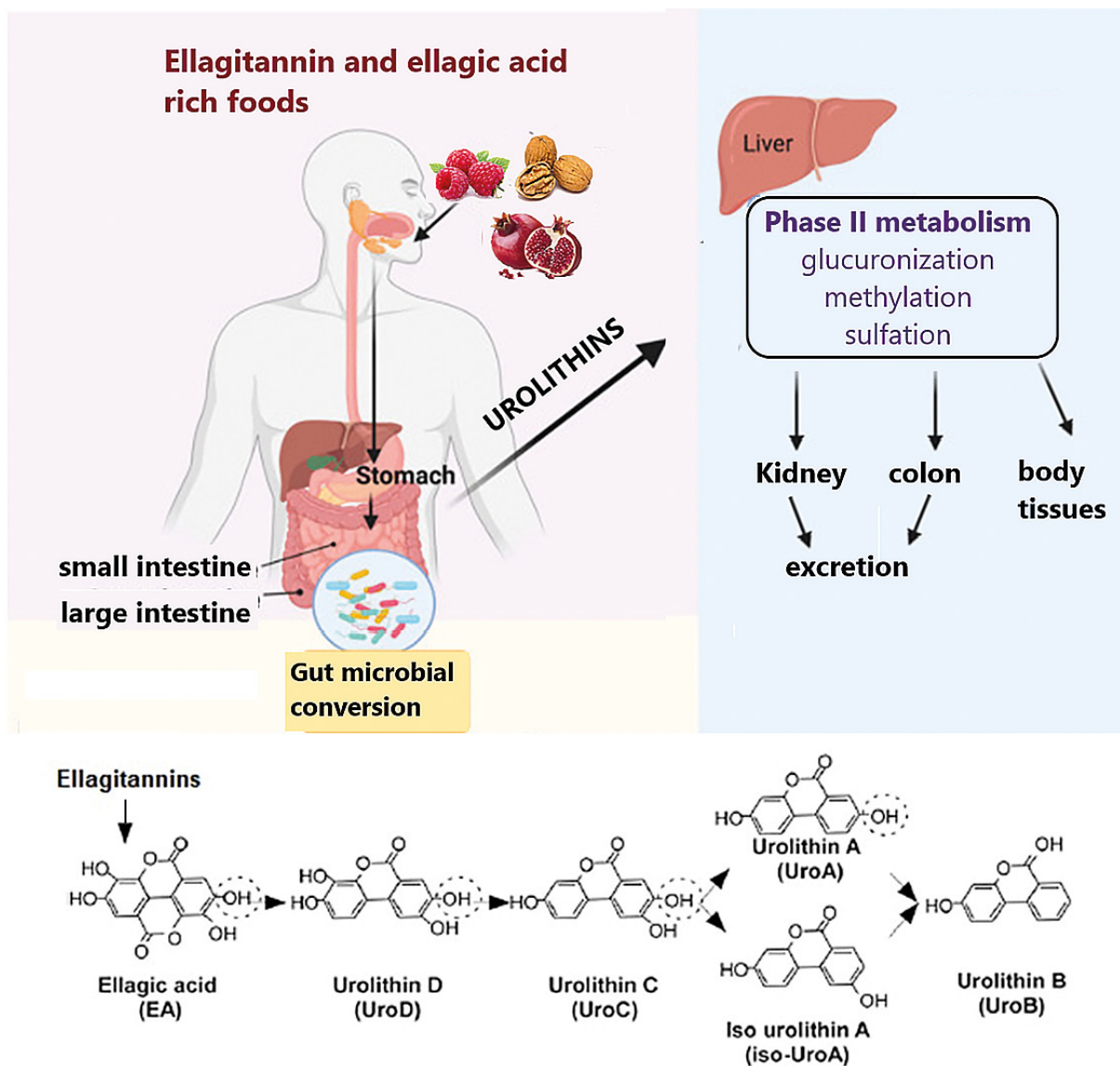


Figure 1. Dietary ellagitannins and ellagic acid are converted by the gut microbiota to urolithins that are readily absorbed to the bloodstream. Most of circulating urolithins undergo II phase metabolism in liver and the conjugates as well as free aglycones reach various peripheral tissues. Urolithins from filtered plasma pass the nephron to be excreted in urine. Some urolithin metabolites are also excreted in faeces [18, 75]

Suppression by urolithins of cell motility accounts also for the mechanisms of their anti-inflammatory activity. By moderate down-regulation of chemokine C-C motif ligand 2 (CCL2), plasminogen activator inhibitor-1 (PAI-1) and decreased expression of IL-8, Uro-A and Uro-A glucuronide inhibited induced by TNF $\alpha$  monocyte adhesion and human fibroblast and aortic endothelial cell migration [40]. The anti-inflammatory and antioxidant activities of Uro A and Uro B involve inhibition of the nuclear factor kappa-B (NF- $\kappa$ B) pathway and modulation of phosphorylation of diverse kinases such as AMPK and MAPK pathway members [41]. In the IL- $\beta$ 1 stimulated rat chondrocytes and in LPS-stimulated macrophages, Uro A pre-treatment inhibited NF- $\kappa$ Bp65 translocation into the nucleus [42-43], while in the HepG2 hepatic carcinomas cell line,

Uro A decreased p65 expression and increased the activity of intracellular antioxidant enzymes SOD and GSH-Px [41]. Suppression of NO production, decrease of proinflammatory molecules such as TNF- $\alpha$ , IL-6 and IL- $\beta$  at the mRNA and protein levels was observed in the presence of Uro B in the LPS-activated mouse microglial cells and in J774 murine macrophages stimulated with LPS [28,43]. Another study demonstrated that Uro A, by regulating miR-10a-5p, reduced the proliferation of murine CD4+ T cells, that are a trigger to immune response [17]. Furthermore, Uro A exhibited anti-inflammatory effects by directly binding the aryl hydrocarbon receptor (AHR). Acting as a selective AHR antagonist, Uro A inhibited its transcriptional activity which resulted in attenuating cytokine-induced inflammatory signaling in Caco-2 cells [3].

**Table 1. Summarizes diverse biological effects exerted by urolithins**

Biological activity	Cell line	Signaling pathway	References	Urolithin	Urolithin Effect
Anti-tumor (anti-proliferative, anti-metastatic, pro-apoptotic)	Caco-2 cells Caco-2 cells Caco-2 cells SW 480 Caco-2 cells HCT-116, Caco-2 cells HCC cells HepG2 Ishikawa cells (ECACC)	MAPK kinase Oncogenes (K-Ras, c-Myc) Suppressors (DASP6, Fos) p53 protein Growth factor receptors (FGFR2, EGFR) Cell cycle genes (CCNB1, CCNB1IP1) Wnt/ $\beta$ -catenin K-ras/HMGA2 Actin polymerization	[30] [30] [30] [11, 33] [30] [30] [36-37] [35] [38]	UroA, UroB UroA, UroB UroA, UroB UroA UroA, UroB UroA, UroB UroA, UroB UroA UroA	$\uparrow/\downarrow$ $\uparrow/\downarrow$ $\uparrow/\downarrow$ $\uparrow$ $\uparrow/\downarrow$ $\uparrow/\downarrow$ $\downarrow$ $\downarrow$ $\downarrow$
Proapoptotic	T24 cells, HepG2, Caco-2 cells, SW 480, HT-29	Caspases: 3, 8, 9	[34-35]	UroA, UroB, 8-OMe UA	$\uparrow$
Inhibition of the cell motility	Human aortic endothelial cells, monocytes, human fibroblasts	C-C motif ligand 2 (CCL2) plasminogen activator inhibitor-1 (PAI-1) IL-8	[40]	UroA UroA UroA	$\downarrow$ $\downarrow$ $\downarrow$
Anti-proliferative, anti-renal fibrosis	HK-2 cells	TGF- $\beta$ 1/ Smad NF- $\kappa$ B	[66]	UroB	$\downarrow$
Anti-inflammatory and anti-oxidant	Chondrocytes, HepG2 T24 cells HepG2 Murine CD4+ T cells Caco-2 cells Murine kidney HK-2 cells	NF- $\kappa$ Bp65 SOD and GSH-Px AMPK and MAPK kinases MicroRNA-10a-5p Aryl Hydrocarbon Receptor (AHR) TNF- $\alpha$ , IL-18, IL-23, MIP2 TGF- $\beta$ 1, IL-6, NF- $\kappa$ Bp65	[41-43] [41] [41] [17] [3] [63] [66]	UroA	$\downarrow$
Suppression of NO release	Murine microglial cells, macrophages	TNF- $\alpha$ , IL-6 and IL- $\beta$	[28, 43]	UroB, UroA	$\downarrow$
Autophagy	Murine hippocampal tissue J774.1 murine macrophages N2a cells, primary murine cortical neurons Murine kidney	MicroRNA-34a, SIRT1 Akt/mTOR signaling Endoplasmic reticulum stress TFEB $\rightarrow$ CLEAR motif-containing genes	[44] [43-44] [45] [46]	UroA UroA UroA UroA	$\uparrow$ $\downarrow$ $\downarrow$ $\uparrow$

It has been demonstrated that Uro-A exhibits protective properties against brain aging [44] and against ischemic neuronal and ischemia reperfusion renal injury (IRI) [45-46]. These anti-inflammatory and cytoprotective effects include induction by Uro A of autophagic flux, which was confirmed by observed expression of the autophagic markers LC3-II and p62 [43-45]. Some recent studies show that Uro A activates autophagy by upregulating Sirtuin 1 (SIRT1) signaling [44] and by impairing Akt/mTOR signaling [43-44]. Within the kidney, Uro A attenuated IRI by inducing autophagy through activation of transcription factor EB (TFEB) followed by regulation of target genes of Coordinated Lysosomal Expression and Regulation (CLEAR) network [46].

### Safety of urolithin administration

Considering that Uro A is the most representative urolithin form and potential therapeutic agent, safety profile of this compound was evaluated in several studies. A comprehensive study by Heilman et al. [47] indicated that in both 28-day and 90-day observations in rats, orally administered synthetic Uro A did not modify any clinical and blood parameters, did not disrupt homeostasis and did not indicate any specific toxic mechanisms. The 4-week clinical trial in which up to 2000 mg oral Uro A doses were administered to elderly volunteers confirmed that the treatment had no adverse health effects. The observed 31 unfavorable effects were determined to be unrelated to the compound tested [48]. On the basis of the above findings, the US Food and Drug Administration already issued a favorable review for using Uro A as a food ingredient [49].

### Urolithins in diabetes

Pathophysiology of diabetes is strictly linked to metabolic changes and chronic inflammation. Overproduction of multiple pro-inflammatory cytokines, growth factors and reactive oxygen species (ROS) account for the diabetes-related damage of tissues and organs [50-51]. Thus, antioxidant and anti-inflammatory properties of urolithins may exert a protective role in diabetic state [52]. It was reported recently that while the *in vivo* occurring extensive conjugation severely hampers the activity of urolithins, systemic inflammation triggers tissue deconjugation of Uro A glucuronide, yielding free aglycone with remarkably higher biological activity [53]. Indeed, the *in vivo*, as well as the *in vitro* studies confirmed the beneficial effects of unconjugated Uro A and Uro B administration to diabetic rats. Urolithin injections prevented the early cardiac inflammatory response as well as the occurrence of cardiac dysfunction in the streptozocin-induced (STZ) type 1 diabetes rats [54]. In cardiomyocytes cultured in the presence of 25mM glucose, Uro B significantly reduced the glucose-induced high levels of monocyte

chemoattractant protein-1 (MCP-1), the pro-inflammatory cytokine fractalkine and vascular endothelial growth factor (VEGF). In fibroblasts exposed to high glucose, expression of fractalkine was reduced by Uro A, Uro B, Uro C and Uro D [55]. In diabetes, hyperglycemia is also a causative factor for neurodegeneration and development of Alzheimer's disease. Uro A injections in a STZ-induced diabetic mouse prevented mitochondrial ROS accumulation, amyloidogenesis and neuronal cell death, which indicates that Uro A-based therapy may be useful in prevention and treatment of diabetes-associated neuronal impairment [56]. Viability of neuronal cells exposed to oxidative stress was significantly increased in the presence of Uro A and Uro B [57]. In addition, via facilitating L-type Ca<sup>2+</sup> channel opening, Uro A and Uro C have been shown to enhance insulin secretion in cultured INS-1 beta-cells and isolated rat islets of Langerhans [58].

One of the hallmarks of diabetes mellitus (DM) is spontaneous non-enzymatic glycation of proteins, lipids and nucleic acids. Dependent on the level and duration of hyperglycemia this process leads to formation of advanced glycation end products (AGEs) that permanently modify protein structures and functions, contributing to oxidative stress and development of chronic diabetic complications [57, 59-60]. Anti glycative properties of Uro A and Uro B were shown in several *in vitro* experiments in which glycation of the bovine serum albumin (BSA) was strongly hampered by these compounds. The effects were concentration-dependent and the mechanisms included urolithins scavenging for reactive carbonyl species [57, 61].

### Urolithins in diabetic and non-diabetic kidney disease

Although urolithins do not accumulate in the kidney, the circulating urolithin-rich plasma has continuous contact with renal structures [2, 6, 14], possibly affecting the renal tissue. Indeed, in the experimental rat model based on cisplatin-induced nephrotoxicity, Guada et al. revealed that Uro A effectively attenuated kidney damage by inhibiting the inflammatory cascade and apoptosis pathway. Furthermore, anti-inflammatory cytokine IL-10 was markedly increased in the kidneys of Uro A-treated animals [62]. Similarly, in the cisplatin-induced acute kidney injury (AKI) mouse model, orally given nanoparticle-encapsulated Uro A not only reduced mortality but also protected the kidneys from oxidative stress and cytotoxic injury including necrosis, tubular atrophy and glomerular hypertrophy [16]. Also, in another experiment, Uro A pretreatment of mice receiving cisplatin for 3 days not only improved renal parameters but also attenuated oxidative and nitrative stress and downregulated the expression of pro-inflammatory cytokines and chemokines TNF $\alpha$ , IL-23, IL-18 and MIP2 [63]. Beneficial properties of Uro A were also documented in the kidney ischemia

reperfusion injury (IRI) in mice. Attenuation of renal injury was associated with Uro A – dependent reduction of pro-inflammatory cytokines TNF $\alpha$ , IL1 $\beta$ , MIP1 $\alpha$  and promotion of autophagy [46]. Subcutaneously administered Uro A also increased activity of antioxidant enzymes and attenuated expression of pro-inflammatory cytokines in the kidneys of aging mice [64].

### Modulation of the renal TGF $\beta$ system

The transforming growth factor beta (TGF $\beta$ ) family of multipotential cytokines controls numerous physiological and pathological events such as embryogenesis, carcinogenesis and the immune response [15, 65]. Regulation of cell proliferation, differentiation, migration and apoptosis involves ability of TGF $\beta$  to affect the transcription and translation processes. The hyperglycemia and inflammation associated with diabetes strongly activate the TGF $\beta$  system, resulting in undesirable changes within tissues. In diabetic kidney disease (DKD), overactive TGF $\beta$  plays a prominent role in promoting renal cell hypertrophy, fibrosis and stimulating extracellular matrix (ECM) accumulation. So far, urolithins have been shown to counteract the TGF $\beta$ -dependent effects in unilateral ureteral obstruction (UUO) rats and in cultured renal epithelial cells. In the UUO model, Uro B treatment abolished renal damage and fibrosis, maintained tubular and glomerular structure and reduced inflammatory cell infiltration. Moreover, expression levels of TGF $\beta$ 1, NF- $\kappa$ B p65, angiotensin II, collagen IV and several pro-inflammatory factors was significantly reduced. In cultured proximal tubular HK-2 cells, Uro B inhibited stimulated by TGF $\beta$  cell proliferation and restored cell morphology. It was demonstrated that in the *in vivo*, as well as in the *in vitro* experiments, protective effects of Uro B were related to the down-regulation of TGF- $\beta$ 1/Smad, most likely via inhibition of the NF- $\kappa$ B signaling [66]. Overproduction of the plasminogen activator inhibitor (PAI-1) results in accumulation of ECM in acute and chronic kidney diseases, including diabetic nephropathy. In stimulated by TGF $\beta$  renal epithelial NRK-52e cell line significant increase of PAI-1 release was inhibited by Uro A in a dose-dependent manner [67]. The positive feedback loop between TGF $\beta$  and PAI-1 has also been documented in diabetic kidney [68]. Hence, targeting the TGF $\beta$ - and PAI-1-related pathways by urolithins might be an effective approach in treating renal fibrosis and inflammation, particularly in the DKD.

### Potential effects of urolithins on podocytes

Podocytes are terminally-differentiated, highly specialized cells of epithelial origin covering the outer aspect of glomerular capillaries. Due to their inability to replenish in mature kidney, podocyte loss is believed to initiate irrevers-

ible impairment of the glomerular filter [69-70]. Clinical and experimental data suggest a key role of podocytes in the development of diabetic nephropathy (DN) [71]. Podocyte depletion is considered to be the first indicator of glomerular destruction in diabetic patients, even before the appearance of proteinuria [72]. For preventing detachment, podocytes rearrange their structure and migrate to seek attachment in other sites of glomerular basement membrane. However, increased migration may disrupt the slit diaphragms between neighboring cells and the tightness of glomerular filter resulting in proteinuria [73]. Recently performed in our laboratory experiments showed that Uro A effectively inhibited induced by high (30 mM) glucose motility of mouse podocytes (unpublished data), which could be beneficial in the diabetic kidney.

Diabetic milieu induces multiple mechanisms in podocytes that directly affect functions and viability of these cells. In addition to AGEs and direct cytotoxic effects of hyperglycemia, primarily via increased production of ROS, deleterious for podocytes is up-regulation of their local renin-angiotensin and TGF $\beta$  systems and increased synthesis of VEGF. Moreover, angiotensin II, TGF $\beta$  and VEGF reciprocally modulate their production, this way perpetuating podocyte and glomerular impairment [74]. So far, our knowledge on urolithin-mediated effects on the podocytes is very limited. However, it seems likely that similarly to other cells, urolithins in podocytes may regulate the activities of TGF $\beta$ , VEGF, antioxidant systems and multiple signaling pathways and kinases that are sensitive to urolithins in other cell types. The urolithins' ability to attenuate the harmful hyperglycemia-induced effects could protect these vulnerable cells from injury.

## Conclusions

A growing body of evidence suggests that urolithins are potent multifunctional compounds capable of regulating a variety of cellular processes. Since they do not act through specific receptors, urolithins may affect various cell and tissue types. Not all body tissues accumulate urolithins but all urolithins present in plasma pass the glomerular filter, thus directly contacting kidney cells. However, so far relatively little is known about the effects of urolithins on kidney function and data concerning action of urolithins on glomerular cells is particularly sparse. Yet, the available reports definitely show that urolithin administration prevents inflammation and diabetes-induced changes in renal tissue. Figure 2 summarizes the current state of knowledge on urolithin-dependent protective effects in the kidney. The research on urolithins is growing and it can be expected that in the near future the beneficial effects of urolithins in kidney disease will be supported by ample evidence.

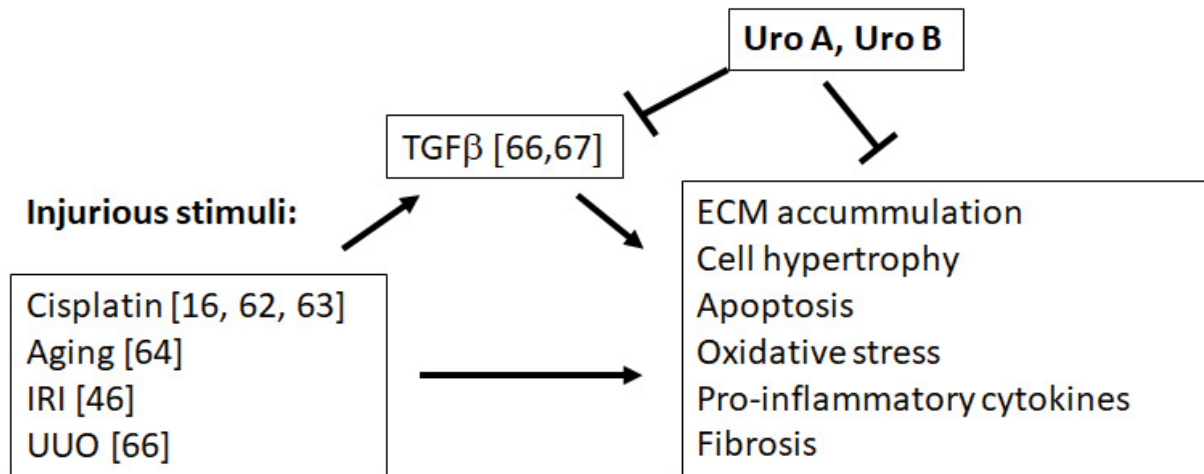


Figure 2. Protective effects of urolithins in the kidney. IRI -ischemia-reperfusion injury. UUO – unilateral ureteral obstruction [66]

### Funding

None.

### Conflicts of interest

None.

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