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Plant Extracellular Vesicle-Encapsulated Phytometabolites for Reversing Cellular Senescence Associated with Chronic Kidney Disease: A Mechanistic Review and Research Roadmap

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ABSTRACT: CKD is characterized by the presence of senescent tubular epithelial cells in increasing numbers in association with the injury of the nephrons, and the secretory phenotypes associated with these senescent cells are responsible for the fibrosis seen during CKD progression. Natural small molecule senotherapy agents (senolytics and senomorphics) obtained from plant sources like quercetin, fisetin, and curcumin have demonstrated biological activity towards senescent cells, and one senolytic combination drug has even been used in a clinical trial in diabetic kidney disease patients. Despite the biological activity of these drugs, they lack aqueous solubility, fast systemic clearance, and renal bioavailability as free molecules. Extracellular vesicles from edible plants such as ginger, grape, and grapefruit – plant-derived extracellular vesicles (PEVs) – have been proposed as another delivery vehicle for senotherapeutic drugs, providing natural biological activity, good biocompatibility, low manufacturing cost, and ability to load phytometabolite drugs like curcumin. This review summarizes the physiology of cellular senescence in CKD, the evidence for plant-based compounds as senotherapeutic agents, and the rationale behind using PEVs to deliver the drugs. Three areas of literature that have so far been studied largely in isolation are brought together to construct a five-point hypothesis about how PEV-encapsulated plant metabolites can mitigate renal cellular

senescence. The review ends with a proposed step-by-step approach to translating the hypothesis into in vitro and animal studies before human trials. There is no experimental data provided here; each proposed link in the mechanistic chain is a hypothesis formed based on indirect evidence.

1. INTRODUCTION

Histologically speaking, chronic kidney disease is a disease in which nephrons are gradually lost in a situation where the remaining glomeruli and tubular cells experience a chronic cellular stress situation. Recent studies show that there is a significant amount of the stress response in which cells become senescent, i.e., enter a cell cycle arrest situation permanently or irreversibly through the action of the p53/p21 and p16/Rb pathways and remain metabolically active and secreting instead of being inactive [7] [10]. In contrast to the temporary senescence that occurs as part of the healing process for wounds, the senescence seen in CKD is chronic in nature; senescent tubular epithelial cells do not undergo apoptosis and continuously secrete a senescence-associated secretory phenotype (SASP), which consists of inflammatory cytokines (IL-6, TNF-α), matrix remodelers and pro-fibrosis mediators (TGF-β).

However, the relevance of such an approach is not only correlative. Experimental models reveal the beneficial effects of genetic removal of p16-positive senescent cells (through INK-ATTAC transgenic systems) or of p16 knockout on the improvement of renal function and prevention of fibrosis; direct manipulation with p16 and p21 leads to the changes in tubular repair in response to acute kidney injury – a proof that senescence burden is one of the drivers of CKD development rather than a mere indicator [9]. Thus, senescent cells become an actual therapeutic target, and this is the reason why the very first clinical trial in this field has been conducted on the population with kidney diseases: the administration of dasatinib and quercetin reduced the amount of senescent markers and SASP factors in patients with diabetic kidney disease – a pilot open-label trial with a small sample size, but still a proof-of-concept for senotherapy in CKD [12].

It should be mentioned that quercetin is a plant-derived molecule, yet there are others like fisetin, curcumin, resveratrol and dietary polyphenols that demonstrated senolytic or senomorphic effect in their preclinical experiments on renal epithelial cells [13] [14] [15]. The issue is not a lack of promising candidates, but an issue of delivery. These phytochemicals share similar characteristics when it comes to application: poor water solubility, rapid metabolic elimination from liver and kidneys and low oral bioavailability in case of curcumin [20] [22]. It means that these molecules had to be delivered in synthetic nanoparticle vectors such as PEGylated liposomes and polymeric nanoparticles just to reach therapeutic concentrations in kidneys.

The use of extracellular vesicles isolated from edible plants provides an entirely natural carrier system. This refers to small (30-150 nm), lipid bilayer-bound structures that edible plants such as ginger, grapes, grapefruit, and numerous others release in the course of regular intercellular communication within the kingdom as well as in the course of inter-kingdom communication and that, in their isolated state, preserve their inherent biological activity and proven ability to load external drugs [2][21]. Unlike synthetic nanoparticles or exosomes derived from mammalian cells, plant-derived extracellular vesicles can be produced cheaply, are free from ethical and infection safety considerations associated with animal and cell culture-derived materials, and, according to preliminary research results, appear to be characterized by lower immunogenicity and toxicity profiles [1][4][19]. The combination of these three aspects in one particular way – using PEVs to deliver senotherapeutic phytometabolites for treating kidney cellular senescence in CKD patients – has never, to our best knowledge, been studied in the published literature. Separately considered, each of the above-mentioned scientific fields has a reasonably mature status.

The objective of this review, therefore, is: (1) To summarise the mechanistic basis of cellular senescence in CKD and to highlight the scientific basis for its being causally rather than simply associatively related to the pathogenesis of the disease; (2) To summarise the scientific literature regarding the plant-based senolytics and senomorphics, including the human studies conducted to date in patients with kidney disease; (3) To summarise PEV biology and the limited but existing precedent in the delivery of phytometabolites by PEVs to renal tissue; and (4) To formulate a mechanistic hypothesis for how this combination might result in alleviating or reversing renal senescence, and to outline a phased research agenda for testing this hypothesis. Like the scientific literature upon which it is based, the present review presents no novel experimental findings; each mechanistic hypothesis in Section 4 is precisely what it says it is.

2. CELLULAR SENESCENCE IN CHRONIC KIDNEY DISEASE

2.1 Senescence pathways and markers in the kidney

Renal cell senescence involves two major pathways that partially overlap with each other. Senescence occurs as a result of DNA damage and cellular stress, which trigger the ATM/ATR pathway to stabilise p53 and increase p21 expression, which inhibits CDK2, thus stopping G1/S cell cycle transition; the other parallel pathway involves p16, which inhibits CDK4/6 and prevents phosphorylation of retinoblastoma protein, thereby also stopping cell cycle progression [8] [10]. The Wnt/β-catenin pathway activates both pathways via induction of p53 and p16 expression. The renal protective protein, Klotho, whose expression is typically reduced in CKD, as well as sirtuin 1 (SIRT1) block senescence by inhibiting the two pathways and, therefore, form an important target in senescence-CKD research studies. In practice, senescent renal cells are detected using a combination of markers: SA-β-Gal activity as a primary screen, followed by staining for p16, p21, γ-H2AX, and loss of Lamin B1, since there is no fully specific marker [5] [7].

2.2 The senescence-associated secretory phenotype and renal fibrosis

However, it is the products released by the senescent cell, rather than the senescence itself, which poses the pathologic problem for CKD. The SASP includes cytokines involved in inflammation (IL-6, IL-1β, TNF-α), chemokines that attract even more immune cell infiltration, matrix metalloproteinases, and — importantly for the issue of fibrosis – TGF-β1, which promotes fibroblast-myofibroblast transition and deposition of extracellular matrix [6] [11]. As a result, a true vicious circle is created – senescent tubular cells recruit and can turn macrophages into myofibroblasts via SASP signaling, and macrophage-myofibroblast transition has itself been demonstrated in rodent chronic ischemic kidney disease models, thereby connecting senescence directly to the fibrotic end-point that characterizes progressive CKD [11]. Clinical-stage proof strengthens the understanding that this is not simply an artifact of rodent modeling: while SASP-targeting small-molecules (TGF-β1 inhibitors) have yielded results in preclinical fibrosis studies, have failed to do so clinically on their own, driving the field towards senescence cell itself or SASP-targeting altogether rather than focusing on one component of SASP only.

2.3 From acute injury to chronic senescence: the AKI-to-CKD transition

Most of the mechanistic data available regarding renal aging is based on AKI models. In AKI, there is a clear correlation between senescence and outcome which is actually dose- and context-dependent, unlike the detrimental effects seen in the majority of other models [23]. Thus, p21 knockouts enhance proliferation of renal tubular epithelial cells after AKI via ischemia-reperfusion injury, without affecting renal function or mortality; in contrast, during cisplatin-induced AKI, p21 knockout exacerbates necrosis, apoptosis and tissue injury, and thus some degree of AKI is beneficial in terms of senescence being an adaptive response that prevents proliferation of damaged cells until repairs take place [9]. On the other hand, the effect of p16 knockout on tubular proliferation and functional restoration after AKI is mostly positive, and involves reduced atrophy, interstitial fibrosis and collagen deposition [9]. Most importantly for the clinic, what happens when this adaptive response is not resolved and leads to accumulation of senescent cells, with SASP secretion becoming a chronic process and progression of AKI into CKD?

3. SENOTHERAPEUTICS: PLANT-DERIVED SENOLYTICS AND SENOMORPHICS

3.1 Two therapeutic strategies, one target

Senotherapy can be classified into two broad categories of interventions. Senolytics specifically target senescent cells, inducing apoptosis by interfering with the pro-survival (anti-apoptotic) pathways – BCL-2/BCL-xL included – that are upregulated by senescent cells to protect themselves from their pro-cell death signals; while senomorphics, on the other hand, do not necessarily lead to death of senescent cell, rather they inhibit the output of SASP, usually by targeting NF-ϰB or mTOR pathway signaling [13]. There have been a number of plant derived molecules, active in either of the two categories – quercetin and fisetin are categorized as senolytics, curcumin is seen to show senolytic activity in a context-dependent manner, and resveratrol as well-known senomorphic, due to activation of SIRT1 in physiological doses [13,15]. Interestingly, some of these molecules are seen to be dose dependent in nature, with procyanidin C1 exhibiting senomorphic behavior in case of lower doses and senolytic in case of higher doses, mediated by ROS production; which brings out a direct relevance with a delivery system based approach, whereby a PEV-based carrier concentrating cargo in the kidney will make it possible to change the dosage-dependent behavior of a compound [13].

3.2 Renal-specific evidence

Specific evidence for senotherapy in relation to renal cells as opposed to other cell types, such as fibroblasts and more widely investigated senescent-cell models, appears relatively sparse but relevant in the context of this review. One particular example of a study on the impact of selected dietary flavonoids on senescence in senescent human renal cortical and proximal tubular epithelial cells using thermal proteome profiling together with metabolomics screening provided for the first time the protein targets of flavonoid-induced senolysis [14]. Clinically, the only trial in humans assessing the effect of senolytic drugs in reducing senescent cells in a specific population with kidney disease — that of Hickson et al., applying one course of dasatinib together with quercetin in individuals suffering from diabetes-related kidney disease — revealed a decrease in senescent cells in adipose tissue and circulating SASP factors (IL-1α, IL-2, IL-6, MMP-9, MMP-12) in response to treatment [12]. In this study, there were no significant changes observed using the oral form of dasatinib and quercetin in their free forms instead of their nanoparticles encapsulation form, which is in line with our review that calls for an improvement of drug delivery in this case. This is because this particular compound has been shown to have human bioactivity in this particular group of patients, but the reason why its effect is insignificant is simply poor pharmacokinetics.

4. PLANT-DERIVED EXTRACELLULAR VESICLES: BIOLOGY AND RATIONALE AS PHYTOMETABOLITE CARRIERS

4.1 What PEVs are, and why they differ from synthetic nanoparticles

Plant extracellular vesicles (or alternatively, plant exosome-like nanoparticles, PELN, or plant vesicle-like nanoparticles, PDVLN depending on the research team) are nano-sized (typically 30-150 nm) particles enclosed in a lipid bilayer, separated from plant juice or extract via differential centrifugation usually with addition of sucrose-gradient ultracentrifugation. Structurally and chemically, PEVs resemble mammalian exosomes in being vesicular particles encased in a lipid bilayer carrying proteins, lipids, and small RNA molecules; however, they are quite different in their lipid content and proteins present, due to their plant-based origin, and they carry an inherent phytochemical cargo (phenolic compounds, terpenoids, and other plant-specific metabolic products) which is absent in mammalian exosomes. The production scale can be considered as a real strength of the technology since one of the commonly referred articles used a standard juice extractor to process three liters of ginger juice within less than an hour — which in yields equaled to what would normally take 300 cell-culture plates of mammalian cell-derived exosomes' preparation — producing a reported yield of 3×10^{12} particles per liter of juice [16].

4.2 Demonstrated capacity to carry exogenous phytometabolite cargo

The specific assumption which is being made in this particular review — that PEVs can be loaded with an exogenous senotherapeutic phytometabolite and delivered effectively to a target tissue — does have precedent in the scientific literature, even if it is not necessarily for renal senescence in particular. Grape-derived exosome-like particles loaded with curcumin (GELP-Cur) have been shown, in a collection of patent-published and peer-reviewed studies, to protect mice against LPS-induced septic shock, collagen-II induced arthritis and AOM/DSS induced colon cancer after oral administration through preferential targeting of inflammatory myeloid cells via the vesicle carrier mechanism [18]. In parallel with this, curcumin-loaded synthetic nanoparticles (not derived from plants but providing important insights for the mechanism) have been shown to have renal-protecting activity in models of ischemia-reperfusion and rhabdomyolysis induced AKI by improving cell viability, oxidative stress markers and down-regulating apoptosis in renal tubular epithelial cells, thus proving that curcumin nanoparticles in renal tissue can provide exactly the protective mechanism necessary for renal senescence-related CKD progression [20] [22]. Most directly pertinent of all, a 2025 study that applied folic acid-functionalised ginger-derived exosome-like nanoparticles to deliver the kinase inhibitor sunitinib showed a detectable localisation of vesicle-drug complex in the kidneys within a mouse model of renal cell carcinoma, with good biodistribution and decreased side effects compared to drug alone [17], which, as far as we are aware, is the most directly applicable evidence for the ability of a vesicle from plants containing an exogenous therapeutic agent to enter and act on kidney tissue, even though that particular study applied to a tumour and not senescent tubules.

Table 1 below lists the main sources of PEVs considered in this review and the bioactive agents known to be either natively contained or delivered in them.

Table 1. Selected plant-derived extracellular vesicle sources and their documented or plausible relevance to renal cellular senescence

PEV source	Reported bioactive cargo	Relevance to renal senescence
Ginger (Zingiber officinale)	6-gingerol, 6-shogaol; anti-inflammatory lipids and miRNAs	Suppresses NF-κB/ROS signalling; caveolin-mediated uptake by macrophages; direct renal-tissue accumulation demonstrated in a renal cell carcinoma model [16,17]
Grape / grapefruit (Vitis vinifera / Citrus paradisi)	Native lipids capable of encapsulating exogenous curcumin (GELP-Cur); flavonoid cargo	Oral GELP-Cur preparations have shown anti-inflammatory, myeloid-cell-targeting activity in murine models of systemic and mucosal inflammation [18]
Broad fruit/vegetable/herb sources	Phenolics, terpenoids, small RNAs, structural lipids	General cross-kingdom antioxidant, anti-inflammatory, and anti-fibrotic bioactivity reported across PELN/PDVLN reviews [3,5,6]

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4.3 The open delivery-route question

It would not be appropriate to consider oral PEV delivery as a solved issue. In some PEV reviews, it is highlighted that intravenous delivery has been proved to be more consistent in the existing studies just because of the fact that, like other nanoparticle systems, PEVs can be sensitive to pH fluctuations, temperature changes, and enzymes of the gastrointestinal system, despite oral delivery being more convenient and realistic for the disease that requires continuous treatment – in our case, it is CKD [17]. In the case of ginger-based vesicles, some studies show that despite the oral delivery, there is sustained anti-inflammatory activity with the upregulation of IL-10 and HO-1 levels and downregulation of IL-6 and TNF-α levels without any toxic effect on the gastrointestinal region or the rest of the body; however, it does not solve the problem completely, and the roadmap developed in section 6 considers this question as a first-order question, not an assumption [3].

5. A PROPOSED MECHANISTIC MODEL: PEV-ENCAPSULATED PHYTOMETABOLITES AND RENAL SENESCENCE REVERSAL

No research paper has ever reported a study where a plant source extracellular vesicle delivery vector has been loaded with senotherapy plant metabolites to be tested on the effect against cellular senescence in kidney cells. The following model can therefore be considered a synthesis of three different fields of literature which have until now progressed independently from each other - renal cellular senescence (section 2), senotherapy from plants (section 3), and PEVs (section 4).

Table 2. Proposed mechanistic model linking PEV-encapsulated phytometabolites to reversal of renal cellular senescence in chronic kidney disease. Every linkage is a hypothesis synthesised from indirect, adjacent-context evidence; none has been tested directly in this combination

Step	Proposed mechanistic link	Supporting (indirect) evidence
1	PEVs protect encapsulated phytometabolites (quercetin, fisetin, curcumin-class senotherapeutics) from gastrointestinal and systemic degradation en route to renal tissue	PEV structural/compositional reviews; demonstrated encapsulation and oral delivery of curcumin via grape-derived vesicles [4,18]
2	PEV nanoscale size and native surface composition enable preferential uptake by renal tubular and inflammatory cells	Documented renal tissue accumulation of ginger-derived exosome-like nanoparticles; caveolin-dependent uptake by macrophages [17,16]

3	Delivered phytometabolites inhibit p16/p21-mediated cell-cycle arrest and restore proliferative capacity in senescent tubular epithelial cells	p16/p21 knockout and pharmacological inhibition studies in renal senescence models; renal-specific senolytic flavonoid screening [9,14]
4	Phytometabolite cargo suppresses NF-κB-driven SASP output (IL-6, TNF-α, TGF-β), limiting paracrine propagation of senescence to neighbouring cells	SASP/renal fibrosis mechanistic reviews; senomorphic activity of curcumin, quercetin, and resveratrol in other tissue contexts [11,13,15]
5	Reduced SASP burden and restored Klotho signalling attenuate downstream myofibroblast activation and interstitial fibrosis	Klotho-mediated p16/p21 pathway studies; senescent-cell clearance associated with reduced fibrosis in animal models [7,8]

These two aspects of the model bear emphasizing. First, the model does not insist that the PEV be biologically inert; according to the reviewed literature, the natural PEV payload of ginger or other sources contains anti-inflammatory properties in addition to the ability to transport senolytics, which means that an appropriate choice of the PEV source can result in both an anti-inflammatory contribution (step 4) and a potential senomorphic property of the PEV itself (step 4), in addition to the delivery of a senolytic compound (step 3). This aspect is, again, untested within this particular combination. Secondly, in line with the honest framework maintained throughout the review, the evidence used in the steps 3 and 4 has been derived in contexts outside of renal or vesicle delivery, while the renal targeting evidence used in the step 2 has been derived from tumour models, not from CKD models; the hypothesis is biologically consistent but is built out of adjacent pieces of evidence (Table 2).

6. TRANSLATIONAL ROADMAP: FROM HYPOTHESIS TO EVIDENCE

In order to test the hypothesis put forward in Section 5, a multi-step programme will be needed; none of this work has yet been carried out, and what follows is merely a suggested methodology.

6.1 Phase 1 — PEV production, loading, and in vitro senescence screening

As a first step, it will be necessary to isolate candidate PEVs (ginger and grape/grapefruit extracts having precedence from Sections 4.1-4.2) via repeatable differential-centrifugation protocols, then load these with a senotherapeutic candidate (quercetin, fisetin, or curcumin, in view of the precedent already cited for these phytometabolites), and finally carry out physicochemical characterisation of the resultant particles (size, zeta potential, encapsulation efficiency, release kinetics). This will then allow the biological activity to be tested in vitro using an established model of renal senescence, such as ionising radiation- or doxorubicin-induced senescence in HK-2 or primary renal proximal tubular epithelial cells (the same cells that were used in the flavonoid senolytic screening method described earlier), measuring the activity of SA-β-Gal, expression of p16/p21 protein markers and SASP cytokines (IL-6, TNF-α) to determine whether there really is an improvement on the free phytometabolite.

6.2 Phase 2 — In vivo proof-of-concept

A proven CKD model with a well-defined component of senescence such as adenine nephropathy or 5/6 nephrectomy in rodents, which have the highest precedent as they are used for renal senescence studies in general, as reviewed in Section 2, would permit both the oral and intravenous routes of administering the lead PEV phyto-metabolite to be compared directly without any assumption of which one is better to use, in line with the delivery method question that emerged in Section 4.3. Measures of success would be assessed by SA-β-Gal, p16 and p21 immunohistochemistry, circulating and local SASP cytokines, Masson's trichrome or Sirius Red interstitial fibrosis, blood creatinine and blood urea nitrogen levels, and even biodistribution of the PEV carrier itself, following the example of the ginger EV renal targeting study from Section 4.2.

6.3 Phase 3 — Early-phase human evaluation

If Phases 1-2 were to confirm our hypothesis, the logical subsequent step would be the development of a safety and feasibility trial in patients with early to moderate CKD (as opposed to patients with late stages of the disease where fibrosis has advanced

beyond the point where intervention based on our hypothesis can make a meaningful difference) following the methodological approach of Hickson et al. study due to the early stage at which our hypothesis exists, we believe that it makes sense to have as the primary endpoints feasibility, safety, and biomarker endpoints (markers of senescent cells and their products which are available through blood and kidney biopsy).

7. CHALLENGES AND LIMITATIONS

Some issues that need to be considered before accepting the above hypothesis include the lack of standardization of PEVs fabrication and loading procedures, as well as batch-to-batch reproducibility which is a common issue in literature dealing with plant-based nanomedicine for different applications but has not been resolved for the purpose of treating renal conditions [1]. There is still an open issue of oral bioavailability, as stated in Section 4.3, and it might turn out that a suitable formulation is not possible orally, thus making intravenous administration more likely, which would greatly affect the feasibility of treatment of patients with CKD [17]. The evidence about renal targeting provided in this paper relies mainly on a study with a renal cell carcinoma model rather than on a CKD animal model. The altered distribution pattern due to tumor vasculature and inflammatory microenvironment is another issue that needs to be taken into account when generalizing results to CKD conditions. The evidence base regarding the senolytics/senomorphics properties of the particular phytometabolites considered is itself a nascent field of investigation, especially concerning kidney-specific cell lines, where only one direct study utilizing thermal proteome profiling of renal cellular targets has been performed [14]. In addition, the human trial evidence this review can cite in support, that of the Hickson et al., used free rather than encapsulated compounds, and was a small, open-label study focusing on biomarkers of SASP activity rather than renal function or fibrosis, and certainly did not demonstrate whether an encapsulated form would produce different effects, let alone improved effects [12]. Similarly to the gastrointestinal and retinal axis and postbiotics hypothesis upon which the methodological approach of this review was modeled, what is provided is a mechanism-based rationale derived from separate, but adjacent bodies of literature.

8. CONCLUSION

It is becoming clear that renal cell senescence is causative, not simply associated, with the progression of CKD, and plant-based compounds are already at the heart of the tiny human evidence base for senotherapy in this context. The missing element has been a delivery system that can deliver the relevant compounds to the kidney at a level and time period with clinical significance — a function that may be performed by plant-based extracellular vesicles because of their proven ability to load exogenous cargo and preliminary but promising data suggesting renal tissue localization. The aim of this review has been to present that potential as realistically as possible, which is to say as a hypothesis formed from the intersection of three separate bodies of research, ripe for testing in the staged process outlined in Section 6.

Data Availability Statement

It is a narrative/mechanistic review article. No new experimental data were created or analyzed. All sources reviewed are referenced in the reference list.

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