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NEPHROPROTECTIVE ACTIVITY OF QUERCETIN IN CISPLATIN-INDUCED ACUTE KIDNEY INJURY

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1. INTRODUCTION

Cisplatin has been in clinical use for several decades and still anchors regimens for testicular, ovarian, bladder, head and neck, lung and cervical cancers [1]. Its main dose-limiting problem is not marrow suppression or nausea, both of which can be managed, but injury to the kidney. A substantial minority of patients show a fall in glomerular filtration after a standard course, and repeated cycles can leave a lasting deficit [2, 3]. The proximal tubule bears most of the damage, and the clinical picture is one of rising serum creatinine, electrolyte wasting (magnesium above all) and, in severe cases, the need to stop or switch treatment [4, 5].

Abstract

Cisplatin remains a mainstay of treatment for many solid tumours, but acute kidney injury limits its dose and sometimes its use. Quercetin, a dietary flavonol with antioxidant and anti-inflammatory activity, has been tested repeatedly as a kidney protectant in rodent models of cisplatin toxicity. This review, which reports no new data, brings together published work on how cisplatin injures the proximal tubule, how quercetin is absorbed and handled, what the animal studies show, and which molecular pathways are probably involved. The experimental literature is consistent in direction, with less tubular damage and lower oxidative and inflammatory stress. Human evidence is absent, bioavailability is poor, and dose, timing and tumour-effect data remain thin.

Because the drug works best at full dose, any strategy that spares the kidney without weakening the antitumour effect has real practical value.

Acute kidney injury is now defined by consensus criteria based on small changes in

serum creatinine and urine output, which allows milder injury to be recognised earlier than in older studies [6, 7]. In oncology practice the main preventive measures remain unglamorous ones: vigorous saline hydration, mannitol or loop diuretics in some centres, magnesium supplementation, and dose reduction or substitution with carboplatin where the tumour allows [8]. Amifostine and a few other agents have been tried, yet none has become a routine standard on which all guidelines agree. This gap explains the steady interest in naturally derived compounds, and quercetin is among the most frequently studied. This review sets out what the published literature reports on quercetin in cisplatin-induced acute kidney injury and where that evidence falls short. It reports no new experimental data.

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavonol found in onions, apples, berries, capers and many leafy vegetables, usually as glycosides rather than as the free aglycone [9, 10]. Interest in it rests on two properties. It scavenges free radicals and chelates transition metals in simple chemical systems, and it dampens the production of inflammatory mediators in cultured cells and animals [9, 11]. Both properties map neatly onto what is known about cisplatin damage in the kidney, which is why the combination keeps being tested. The attraction is partly practical too. Quercetin is cheap, widely sold as a supplement, and consumed in the diet every day without obvious harm [10, 12]. Whether those advantages translate into protection of the human kidney during chemotherapy is a separate question that the literature has not yet answered.

2. MECHANISMS OF CISPLATIN NEPHROTOXICITY

The kidney is exposed to cisplatin more heavily than most organs because it is the main route of elimination, and the proximal tubule concentrates the drug well above plasma levels. Uptake across the basolateral membrane relies substantially on organic cation transporter 2 (OCT2), with the copper transporter Ctr1 also implicated [3, 13, 14]. Mice lacking Oct1 and Oct2 are protected from tubular injury, and co-administration of OCT2 substrates or inhibitors lessens

nephrotoxicity in rodents [15]. Once inside the cell, cisplatin is converted to reactive aquated species and, through further metabolism in the tubule, to thiol-containing products that are more toxic still [2, 3]. This transporter-driven accumulation explains why the proximal tubule, rather than the glomerulus, is the principal target, and it also sets a limit on what an antioxidant given later in the process can achieve.

Inside the tubular cell, cisplatin binds nuclear and mitochondrial DNA, but much of the damage seems to arise outside the nucleus. Mitochondria in proximal tubules are numerous and heavily used, and cisplatin impairs complexes of the respiratory chain, depletes glutathione and drives the formation of superoxide, hydrogen peroxide and the hydroxyl radical [16, 17]. Lipid peroxidation products accumulate, antioxidant enzymes such as superoxide dismutase and catalase fall, and peroxynitrite forms when nitric oxide meets superoxide [16, 18]. Scavenging hydroxyl radicals in cell and animal models reduced p53 activation and tubular apoptosis, which gives experimental support to the idea that oxidant stress is a cause rather than a bystander [19]. Not every study agrees on how much of the injury is oxidant-dependent, and the contribution probably varies with dose and time. That uncertainty is one reason antioxidant strategies need testing with several complementary readouts [16, 19].

Inflammation amplifies the early tubular injury. Cisplatin raises renal tumour necrosis factor- α (TNF- α), and in mice that cytokine drives the downstream expression of chemokines and further cytokines; blocking or deleting it lessens kidney damage [20]. Interleukin-1 β , interleukin-18 and interleukin-6 also rise, with neutrophil and macrophage infiltration following [21]. Signalling through p38 mitogen-activated protein kinase sits upstream of part of this response, since its inhibition reduced both cytokine induction and functional decline in mice [22]. The picture is of injured tubular cells releasing signals that recruit immune cells, which in turn worsen the damage. Compounds that act on only one arm, antioxidant or anti-inflammatory, may therefore give partial benefit, and a flavonoid

that touches both is an understandable candidate for testing.

Cell death takes several forms. Low concentrations of cisplatin provoke apoptosis in cultured proximal tubular cells, whereas higher concentrations cause necrosis [23]. Apoptosis proceeds through p53 activation, the mitochondrial pathway with caspase-9 and caspase-3, and endoplasmic reticulum stress, while death receptor signalling adds an extrinsic route [2, 3]. More recent work indicates that regulated necrosis, including ferroptosis, contributes to synchronised tubular cell death in kidney injury of several causes, so the older apoptosis-or-necrosis dichotomy is too tidy [24]. The practical consequence for protective agents is that single-marker readouts, such as a caspase assay alone, can understate or overstate benefit, and careful histology remains important. Repair is also at stake: surviving tubular cells must dedifferentiate and proliferate, and a prolonged injury leaves fibrosis behind [25, 26].

In the clinic the injury typically declares itself several days after a dose, with creatinine rising after the glomerular filtration rate has already fallen. Hypomagnesaemia, hypokalaemia and a salt-wasting state may accompany it, and some patients develop a Fanconi-like tubular defect. Recovery is often partial, and repeated cycles can leave chronic kidney disease [5, 25]. Rodent models mimic the acute phase well: a single intraperitoneal dose produces a predictable rise in urea and creatinine within days, which is why most protection studies use that design. The clinical course with fractionated dosing is slower and less dramatic, so the mapping from model to patient is imperfect [4, 26].

3. QUERCETIN: CHEMISTRY AND DISPOSITION

The antioxidant behaviour of quercetin follows from its structure. The catechol group on the B ring, the 2,3 double bond conjugated with the 4-oxo group, and the hydroxyls at positions 3 and 5 together give it a low oxidation potential and the ability to bind iron and copper [9, 10]. In test-tube assays quercetin compares well with many other antioxidants as a radical scavenger. The same

chemistry has a downside: a quercetin radical can form and, under some conditions, quinone products that react with thiols, so the molecule can behave as a pro-oxidant at high concentration or in the presence of metal ions [9]. Biological relevance therefore depends on the concentrations and forms that actually reach the tissue, rather than on what is measured in a cuvette.

Absorption is the main weakness. Dietary quercetin is mostly glycosylated, and in ileostomy volunteers the glycosides from onions were absorbed far better than the aglycone, so the sugar moiety clearly influences uptake [27]. Plasma concentrations after ordinary intake are low, and in humans the compound circulates mainly as glucuronide, sulphate and methylated conjugates rather than as free quercetin [28, 29]. Elimination half-lives measured after oral glycoside intake are long, of the order of a day, so repeated dosing leads to accumulation [29]. For a kidney protection study this matters in two ways: the tubular cell may see conjugates that are less reactive than the parent molecule, and the doses used in rodents, often tens of milligrams per kilogram, produce exposures that are hard to reproduce by diet alone [10, 28].

The kidney handles quercetin as it handles other conjugated flavonoids, taking up and excreting metabolites in urine, though the fraction recovered is small compared with the amount ingested [28, 29]. Some conjugated metabolites keep part of the antioxidant activity of the parent compound, though generally less than the aglycone [9]. Another point is that quercetin inhibits several drug-metabolising enzymes and transporters in vitro, so interactions with co-administered cancer drugs cannot be dismissed [10, 12]. Formulation approaches such as nanoparticles, phospholipid complexes and cyclodextrin inclusion aim to improve exposure, and some animal data show better effects with such carriers, but the evidence is early and the carriers add their own variables [10]. A realistic expectation is modest tissue exposure with a long residence time. Dosing schedules in the animal studies, mostly repeated daily doses around the time of cisplatin, should be read with that in mind

[28, 30].

4. PRECLINICAL EVIDENCE

Most of the experimental work uses rodents given a single intraperitoneal injection of cisplatin, with quercetin delivered by oral gavage or intraperitoneal injection for a few days before, during or after the challenge. In one widely cited rat study, quercetin lessened the rise in plasma creatinine and urea, reduced histological tubular damage, limited markers of oxidative stress and apoptosis and, importantly, did not weaken the antitumour effect of cisplatin in the tumour systems examined [30]. The principal studies and comparator agents are summarised in table 1, which also groups them by type. The direction of effect is consistent across reports, although the magnitude differs and few designs include a positive control or a dose-response arm.

Table 1: Published findings on quercetin and comparator approaches in cisplatin nephrotoxicity

Agent or target	Reported finding	Ref.
Quercetin rat cisplatin model	Lower creatinine, urea and tubular damage with less oxidative stress; antitumour effect preserved	[30]
Quercetin redox chemistry	Catechol ring and conjugation give radical scavenging and metal binding; pro-oxidant at high levels	[9, 10]
Quercetin glycosides absorption	Glycosides absorbed better than aglycone; long plasma half-life after oral intake	[27, 29]
Quercetin anti-inflammatory action	Reduced release of cytokines and mediators through NF- κ B and kinase signalling	[11]
Hesperidin rat model	Less lipid peroxidation, inflammation and DNA damage in injured kidney	[31]
Genistein mouse model	Kidney protected from cisplatin injury with reduced tubular cell death	[32]
Curcumin rat model	Lower inflammation and oxidative stress after cisplatin	[33]
TNF- α and p38 signalling	Blocking either reduces cytokine induction and kidney damage in mice	[20, 22]

Agent or target	Reported finding	Ref.
Hydroxyl radical scavenging	Reduced p53 activation, tubular apoptosis and nephrotoxicity	[19]
OCT2 inhibition	Less tubular uptake of cisplatin and milder nephrotoxicity in rodents	[13, 15]
Hydration and magnesium clinical	Standard preventive measures; no single protectant agreed in guidelines	[8]

Quercetin is not unique. Hesperidin, genistein and curcumin each reduced renal injury in cisplatin models, again with lower oxidative stress, less inflammatory signalling and a smaller histological score [31, 32, 33]. Genistein, a soy isoflavone, protected the kidney in mice and the effect was linked to reduced injury signalling and tubular cell death [32]. Hesperidin, a citrus flavanone glycoside, decreased lipid peroxidation, cytokine levels and DNA damage in rats [31], while curcumin reduced inflammation and oxidant stress in the same kind of model [33]. Read side by side, these studies suggest that the benefit comes from properties shared by polyphenols and not from a unique action of quercetin, a point that tempers the claims sometimes made for any single compound.

Cell culture work fills in some of what animal studies cannot show. Proximal tubular cell lines and primary cells exposed to cisplatin lose mitochondrial membrane potential, release cytochrome c and activate caspases, and the extent of death depends on concentration and exposure time [17, 23]. Adding antioxidant flavonoids to such cultures generally improves viability and lowers reactive oxygen species, but the concentrations used are frequently higher than anything reachable in plasma after oral dosing [11, 28]. That gap is a recurring weakness. A result that holds at 50 micromolar in a dish says little about a tubule bathed in nanomolar to low micromolar conjugates, and the more careful papers test physiologically plausible concentrations or the metabolites themselves.

The endpoints reported are fairly uniform. Serum creatinine and blood urea nitrogen serve as functional markers; kidney malondialdehyde, glutathione, superoxide dismutase and catalase describe redox state;

TNF- α and interleukin levels give the inflammatory side; and tubular necrosis, cast formation and brush border loss are scored on histology [16, 30]. Some papers add tubular injury biomarkers, which respond earlier than creatinine [26]. Serum creatinine rises only after considerable function is lost, and in rodents it is also influenced by hydration, so it can hide or exaggerate differences between groups. Studies that combine functional, biochemical and histological readouts, and report blinded scoring, are more convincing than those relying on a single measure.

Timing deserves comment. Pre-treatment, where quercetin is given before cisplatin, tests prevention and is easy to run in a model with a defined moment of injury. Post-treatment designs, where the flavonoid starts after the insult, test rescue and are closer to what could happen on a ward, yet they are much less common [30, 33]. The spread of the studies in table 1 by type is shown in fig. 1. Entries on quercetin itself account for four of the eleven rows, other agents and pathway targets for three each, and clinical prevention for a single row, a pattern that mirrors the literature as a whole. Doses of quercetin also differ by an order of magnitude between laboratories. Dosing schedules vary from a single administration to two weeks, and species and strain differences in susceptibility to cisplatin add further variation [4, 8].

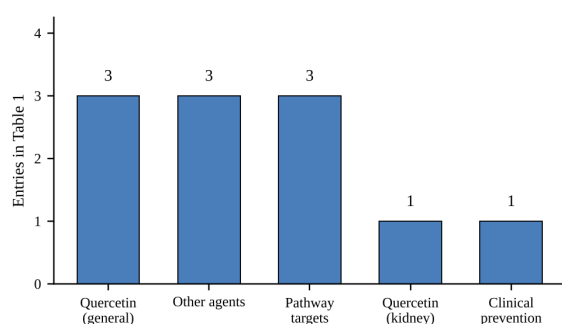


Fig. 1: Number of entries in table 1 by type of agent or target

5. MOLECULAR TARGETS OF PROTECTION

One of the better-supported mechanisms is activation of the Nrf2 pathway. Under basal conditions Nrf2 is held in the cytoplasm by Keap1 and degraded; electrophiles and oxidants release it, allowing it to drive genes for haem oxygenase-1, glutathione-synthesis

enzymes and other cytoprotective proteins [34]. Quercetin and several related polyphenols can raise Nrf2 activity, which would amount to an indirect antioxidant action and may be more durable than simple radical scavenging, given the low plasma concentrations noted above [11, 28, 29]. The protective studies describe higher glutathione and lower lipid peroxidation, which is compatible with such induction [16, 30]. The causal link, however, usually rests on correlation of Nrf2 target expression with protection and not on knockout experiments. Nrf2-deficient animals treated with the flavonoid would show whether the pathway is needed for benefit, and to date such experiments have rarely been reported for this indication [34].

The inflammatory arm is addressed through nuclear factor κ B and mitogen-activated protein kinases. Quercetin reduces production of TNF- α , interleukins and nitric oxide in immune cells, partly by limiting NF- κ B activation and kinase signalling [11]. Since p38 inhibition and TNF- α blockade each reduce cisplatin nephrotoxicity in mice [20, 22], interference with the same axis is a plausible route for a flavonoid, and rodent studies of related compounds report lower renal cytokines and less inflammation [31, 33]. As with the Nrf2 data, the evidence for the pathway is mostly correlative. Specific inhibitors or genetic models that abolish the benefit when the pathway is blocked would be much stronger tests than the endpoint comparisons now available.

Protection at the level of cell fate has received less attention. Reduced p53 activation, a lower Bax to Bcl-2 balance and weaker caspase-3 signalling are reported with quercetin and with other antioxidants, matching the observation that hydroxyl radical scavenging blunts p53 activation and tubular apoptosis [19, 30]. Whether quercetin acts on ferroptosis, in which iron-dependent lipid peroxidation kills cells, is an obvious question given its iron-chelating chemistry, but direct tests in cisplatin kidney models are still sparse [9, 24]. Mitochondrial protection, either by limiting superoxide leakage or by preserving respiratory complex activity of the kind that cisplatin disturbs, offers another

route that merits study [17, 18].

6. SAFETY, TRANSLATION AND LIMITATIONS

Human data on quercetin are mostly from healthy or cardiometabolic populations, not from cancer patients. In a randomised crossover trial, daily flavonoid supplements were well tolerated, but the effects on vascular function and cardiometabolic markers were modest [35]. Reviews of safety conclude that doses used as supplements are generally tolerated, with gastrointestinal complaints and headache the commonest reports, and that very high intravenous doses have been linked to renal toxicity in earlier clinical experience [12]. That last point should not be lost: a compound that protects the tubule at one dose may stress it at another, and the therapeutic window in a patient already receiving a nephrotoxic drug is unknown.

Existing preventive practice provides the yardstick against which any new protectant has to be judged. Hydration with isotonic saline lowers the concentration of platinum in tubular fluid, magnesium supplementation reduces the electrolyte loss that often accompanies treatment, and a lower or split dose remains the simplest option when the tumour allows it [5, 8]. These measures reduce, but do not abolish, kidney injury, and they require inpatient time or extra infusion visits. A quercetin-type compound would have to show benefit on top of good hydration, not merely against an unhydrated control, and the hydration status of control animals in published models is rarely described in a way that allows this to be judged [7, 8].

The question that matters most to oncologists is whether protection comes at the price of efficacy. Cisplatin kills tumour cells in large part through DNA damage and oxidative stress, so an antioxidant could in principle blunt it. The rat work already mentioned found no loss of antitumour activity [30], and some flavonoids appear to sensitise certain tumour cells to platinum drugs [10], yet this is far from a general finding and has not been tested in controlled clinical trials. Interactions through cytochrome P450 enzymes and efflux

transporters add uncertainty, particularly for patients on several drugs at once [10, 12]. Any trial would therefore need pharmacokinetic sampling of platinum alongside renal and tumour endpoints [8, 15].

The main limitations can be stated briefly. Nearly all positive findings come from small rodent experiments with a single cisplatin dose, a short follow-up and surrogate endpoints, and long-term outcomes such as fibrosis or chronic kidney disease are rarely examined [25, 26]. Dose conversion from rodent to human is uncertain, and the poor bioavailability noted above makes it hard to know what exposure to aim for [28, 29]. Future work could usefully include dose-response and post-treatment designs, platinum tissue measurement, standardised formulations, and a modest phase 2 trial in patients with a measurable risk of cisplatin kidney injury, using KDIGO-based endpoints and hypomagnesaemia as a secondary measure [7, 8].

7. CONCLUSION

Cisplatin injures the proximal tubule through a chain that starts with transporter-mediated uptake and runs through mitochondrial dysfunction, oxidant stress, inflammatory signalling and several forms of cell death [2, 3, 20, 24]. Quercetin has chemical and biological properties that fit those steps, and rodent studies consistently report less functional and histological injury when it is given, with no loss of antitumour effect in the systems examined [9, 11, 30]. Similar benefits with other polyphenols suggest that the effect is a class property, not a unique feature of this compound [31, 32, 33]. Readers should keep that in mind when single compounds are promoted as kidney protectants.

The evidence is still preclinical. Bioavailability is low, dose and timing are inconsistently studied, mechanistic claims are largely correlative, and no human study has tested quercetin against cisplatin nephrotoxicity [12, 28, 29]. Until pharmacokinetic and tumour-interaction data are available, it should be regarded as a promising experimental protectant and not as a supplement to recommend to patients

receiving cisplatin [7, 8]. The next useful step is a well-designed study that links exposure, platinum handling and kidney outcome, rather than another report of the same biochemical changes in a similar rat model [15, 30].

8. ABBREVIATIONS

AKI-Acute kidney injury, KDIGO-Kidney Disease: Improving Global Outcomes, NF- κ B-Nuclear factor kappa B, Nrf2-Nuclear factor erythroid 2-related factor 2, OCT2-Organic cation transporter 2, TNF- α -Tumour necrosis factor alpha, Keap1-Kelch-like ECH-associated protein 1, p38-p38 mitogen-activated protein kinase, ROS-Reactive oxygen species

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Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

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