crystals

MDPI

Review

A Mechanistic Insight into Beneficial Effects of Polyphenols in the Prevention and Treatment of Nephrolithiasis: Evidence from Recent In Vitro Studies

Marija Hefer [1,†], Ivana Mihin Huskic [2,†], Ana Petrovic [1,†], Nikola Raguz-Lucic [1,*], Tomislav Kizivat [3,4], Dominik Gjoni [1], Elizabeta Horvatic [1], Zarko Udiljak [1], Robert Smolic [1], Aleksandar Vcev [1] and Martina Smolic [1]

[1] Faculty of Dental Medicine and Health Osijek, Josip Juraj Strossmayer University of Osijek, 31000 Osijek, Croatia; marija.hefer@fdmz.hr (M.H.); anapetrovic@fdmz.hr (A.P.); dominik.gjoni1@gmail.com (D.G.); horvatic.elizabeta@gmail.com (E.H.); zudiljak@fdmz.hr (Z.U.); rsmolic@fdmz.hr (R.S.); avcev@fdmz.hr (A.V.); msmolic@fdmz.hr (M.S.)
[2] Institute of Public Health Osijek-Baranja County, 31000 Osijek, Croatia; mihin.ivana@gmail.com
[3] Clinical Institute of Nuclear Medicine and Radiation Protection, University Hospital Osijek, 31000 Osijek, Croatia; tkizivat@mefos.hr
[4] Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, 31000 Osijek, Croatia
* Correspondence: nikola.rlucic@gmail.com
† These authors contributed equally to this work.

Abstract: Nephrolithiasis is a pathological condition characterized by the formation of solid crystals in the kidneys or other parts of urinary tract. Kidney stones are a serious public health issue and financial burden for health care system, as well as a painful and uncomfortable condition for patients, resulting in renal tissue injury in severe cases. Dietary habits, low fluid and high salt intake predominantly, contribute to the development of kidney stones. Current research suggests that polyphenols have a protective effect in the pathogenesis of kidney stones. Polyphenols are a group of naturally occurring compounds found in plant-based foods such as fruits, vegetables, tea, and coffee. In this review, we explore mechanisms underlying the beneficial effects of polyphenols, such as oxidative stress reduction and modulation of inflammatory pathways, in various in vitro models of nephrolithiasis. Additionally, certain polyphenols, such as catechins found in green tea, have been shown to inhibit the formation and growth of kidney stones in animal studies. This review highlights the antioxidant and anti-inflammatory effects, as well as the inhibition of crystal formation, as results of polyphenol treatment in vitro. Further research is required to determine the specific effects of polyphenols on kidney stone formation in humans; however, current knowledge implicates that incorporating a variety of polyphenol-rich foods into the diet may be a beneficial strategy for individuals at risk of developing nephrolithiasis.

Keywords: nephrolithiasis; polyphenols; curcumin; quercetin; EGCG; prevention; treatment; antioxidants

Citation: Hefer, M.; Huskic, I.M.; Petrovic, A.; Raguz-Lucic, N.; Kizivat, T.; Gjoni, D.; Horvatic, E.; Udiljak, Z.; Smolic, R.; Vcev, A.; et al. A Mechanistic Insight into Beneficial Effects of Polyphenols in the Prevention and Treatment of Nephrolithiasis: Evidence from Recent In Vitro Studies. *Crystals* **2023**, *13*, 1070. https://doi.org/10.3390/cryst13071070

Academic Editors: Anamarija Stanković, Martina Medvidović-Kosanović and Nives Matijaković Mlinarić

Received: 20 June 2023
Revised: 5 July 2023
Accepted: 6 July 2023
Published: 7 July 2023

1. Introduction

Nephrolithiasis, also known as kidney stones, is one of the most common urological conditions. The term originates from Greek words nephron for kidney and lithos for stone. First description of kidney stones (KS) dates back to ancient medical texts of Mesopotamia [1]. Approximately 12% of the world population is affected during their lifetimes, with recurrence rates greater than 30%. Additionally, in the past decades, the prevalence and incidences of KS have increased globally [2,3].

Epidemiology of KS depends on geographical, climate, ethnic, dietary, and genetic factors, as well as characteristics such as age, sex, and race [4]. Pathological conditions such as obesity, metabolic syndrome (MS), hypertension, diabetes mellitus, and gout also contribute to development and increased risk of KS due to higher urinary excretion of

calcium, uric acid, oxalate, and reduced excretion of citrate. The increased KS prevalence in developed countries is related to increased consumption of salt and protein and the prevalence of MS. In developing countries, it can be related to malnutrition and water deprivation [5]. Vice versa, nephrolithiasis and associated kidney injury may also be a risk factor for diabetes and cardiovascular diseases development [6,7], chronic kidney disease [8], and bone fractures [9]. Chronic kidney disease can occur due to obstruction, infection, renal tissue damage, or urological treatments involved in the treatment of nephrolithiasis. Other causes of KS can also be caused by infections, genetic defects, as well as drug induced [4].

The chemical composition of urine determines the type of crystals, varies depending on the cause of nephrolithiasis, and is influenced by dietary habits, metabolic activity, and lifestyle [10]. Approximately 80% of kidney stones are calcium stones, predominantly calcium oxalate (CaOx) and calcium phosphate (CaP), whereas 9% are uric acid, 10% struvite, and 1% cystine stones [11,12]. The pathophysiological mechanism of KS includes nidation, growth, aggregation, retention, and results in crystal–renal epithelial cell interactions, leading to aberrant oxidative stress, inflammation, and injury to renal tissue [12,13].

Renal colic is usually an extremely painful condition requiring multimodal analgetic monotherapy or polytherapy [14]. The treatment of KS is based on many parameters such as the size, number, location, and constitution of the stones [4]. Surgical intervention may also be an option, depending on stone characteristics, patient anatomy, comorbidities, and patient preferences. Non-pharmacological treatment options include shockwave lithotripsy (SWL), rigid and flexible ureteroscopy (URS), and conventional/mini–percutaneous nephrolithotomy (PCNL) [15].

Nephrolithiasis is a serious public health issue and a financial burden for the health care system. For example, cost estimates for 2010 in England were between £190 million and £324 million [15]. According to the calculation of Antonelli et al., the annual cost of stone disease interventions and treatment in the USA in 2000 was approximately USD 2.81 billion. They also estimated that population growth, independent of other risk factors, would increase the cost of stone disease by USD 780 million in 2030 [16]. All of the above points to the importance of prevention in the management of kidney stones.

General preventive measures include optimal fluid intake, normalization of dietary habits, and lifestyle to minimize the risk factors. Pharmacological treatment is necessary in those at high risk of KS formation [4]. For recurrent KS, thiazide diuretics, potassium citrate, and alopurinol can be used as preventative measures, depending on the type of crystals [14]. In addition to conventional pharmacotherapy, a great number of herbal and dietary compounds have been investigated for prevention and treatment of nephrolithiasis [17]. Polyphenols have demonstrated antilithiatic properties in vitro and in vivo, implicating their potential to contribute to preventative measures for development of KS, due to their antioxidant, anti-inflammatory, and other effects [18–24].

Polyphenols are a group of naturally occurring organic molecules characterized by multiple aromatic rings and hydroxyl groups. Dietary polyphenols are mostly found in plants such as fruit and vegetables, where they are stored either as glycoside conjugates or as non-glycosylated conjugates. Some of the most common polyphenols are found in tea (epigallocatechin-3-gallate, epicatechin, catechin), wine (resveratrol), and cocoa (epicatechin, procyanidins) [25,26]. Polyphenols can be classified as flavonoid and non-flavonoid molecules, with multiple sub-classes. Flavonoids are a group of polyphenols such as flavanols, flavanones, isoflavones, flavones, flavan-3-ols, and anthocyanins, whereas the non-flavonoids include phenolic acids, lignans, tannins, and stilbenes [27,28]. Figure 1 shows some of the representative polyphenols of the two key groups and their structures. Dietary polyphenols have been shown to play a vital role in human organisms, affecting a great number of physiological processes [29,30]. In a great manner, this is due to their antioxidant activity, which makes them suitable for the prevention of reactive oxygen species (ROS)-induced damage. ROS are a group of products resulting from oxygen reduction, where the main reduced forms of oxygen include superoxide anions, hydroxyl radicals, and hydrogen peroxide. ROS accumulation causes oxidative stress in cells, depriving the

cell from its antioxidative defense system, thereby causing various diseases. Polyphenols are also known to induce the activities of antioxidant enzymes and inhibit the activities of some oxidases, thereby resulting in improvement of various pathological states [31–33]. Some studies suggest that a polyphenol-rich diet can prevent the development and further detrimental outcomes in a great number of chronic diseases, including cardiovascular diseases, diabetes, neurodegenerative diseases, and even COVID-19. One of the most common occurring dietary polyphenols, such as epigallocatechin-3-gallate and resveratrol, has been shown to prevent oxidative cellular damage in various chronic diseases, including nephrolithiasis [34–36]. According to previous studies, epigallocatechin-3-gallate, a polyphenol found in green tea, has been shown to increase superoxide dismutase activity, and decrease both CaOx deposition and urinary excretion in rats with induced kidney stones [36,37]. Resveratrol, on the other hand, is found in grapes and wine and is known to increase superoxide dismutase, glutathione peroxidase, and catalase protein levels upon treatment of ethylene-glycol-induced kidney stones in a murine model, resulting in a significant decrease in the concentration of urinary crystals and renal cell injuries [38,39].

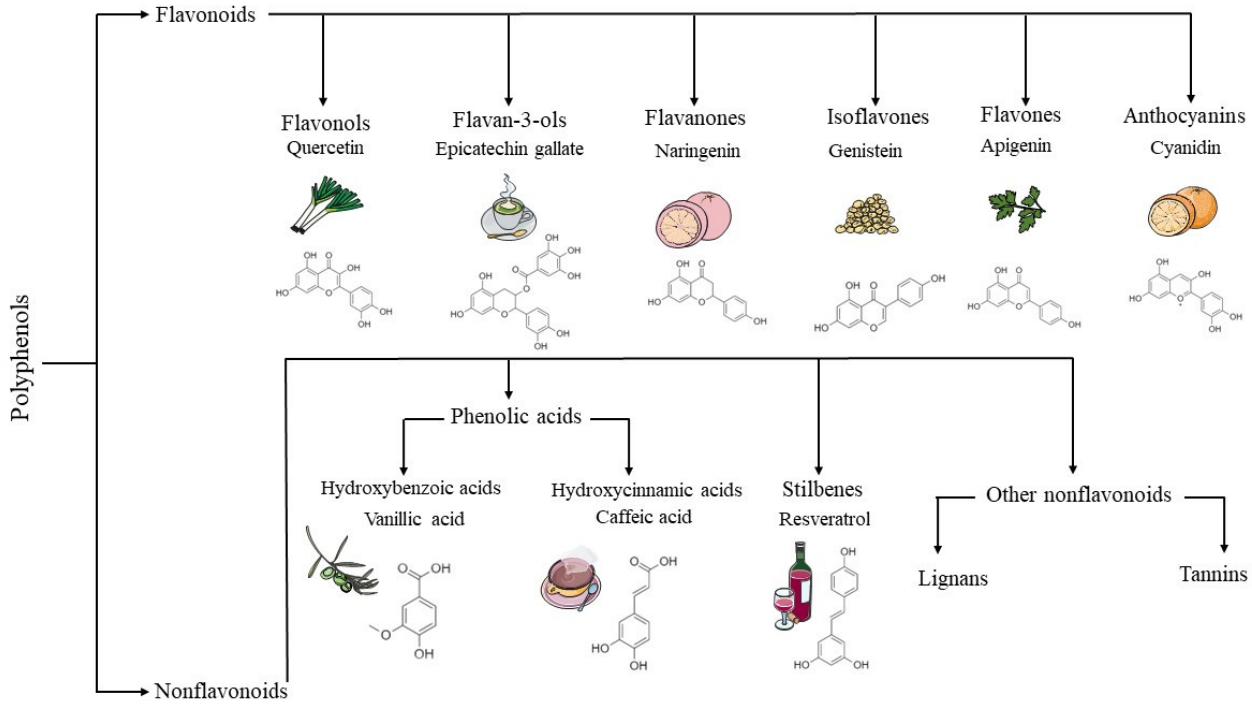

Figure 1. Classification of naturally occurring polyphenols and their representatives. Figure created with Servier Medical Art, https://smart.servier.com/ (accessed on 9 May 2023), and ChemDraw, https://perkinelmerinformatics.com/products/research/chemdraw (accessed on 9 May 2023).

In this review, we examine the role of polyphenols in the prevention and treatment of nephrolithiasis. A specific focus is the elucidation of the underlying mechanisms of their beneficial effects. Also, in aim to better distinguish polyphenols direct nephroprotective effects from pleiotropic and provide a better mechanistic insight, we have opted out for examining the most recent evidence reported by using various in vitro models of nephrolithiasis.

Furthermore, while polyphenols are considered beneficial for health, there are some concerns associated with their concentrations and potential effects on health, such as dosage, interactions, etc. In this review, we also explore some of these issues and progress regarding their elucidation. Finally, we highlight some of the potential therapeutic targets and signaling molecules, reported to be involved in KS pathophysiology.

2. The Cellular Mechanisms of Beneficial Effects of Polyphenols in Nephrolithiasis

Cell membranes are mainly composed of polyunsaturated fatty acids and phospholipids, which make them susceptible to lipid peroxidation caused by relatively high concentrations of ROS. Lipid peroxidation causes the membrane to lose its integrity, as the electrons are removed from the lipid components of a membrane via ROS. On the other hand, oxidation of a phospholipid bilayer generates a signal for cell death and could be a potential cause for the proinflammatory changes. ROS-induced lipid peroxidation results in the overproduction of reactive intermediates [40,41].

2.1. Lipid Peroxidation in Nephrolithiasis

CaOx interaction with renal cells results in enhanced ROS production and lipid peroxidation. ROS cause injury to renal epithelial cells, disrupt the integrities of their membranes, and promote inflammatory responses, contributing to calcium oxalate adhesion, retention, and formation of CaOx stones. Furthermore, the ROS-activated phospholipase A2 results in arachidonic acid production, which further increases ROS and promotes cell injury, inflammation, and crystal formation [42].

Antioxidants, such as polyphenols, are able to inhibit or prevent the damage to the cell membrane caused by lipid peroxidation by scavenging ROS and reactive intermediates. Lipid peroxidation is lowered by increasing the level of antioxidant enzymes and via metal chelation [42,43]. Figure 2 shows a potential mechanism of polyphenol-induced inhibition of CaOx crystal formation and prevention of ROS accumulation.

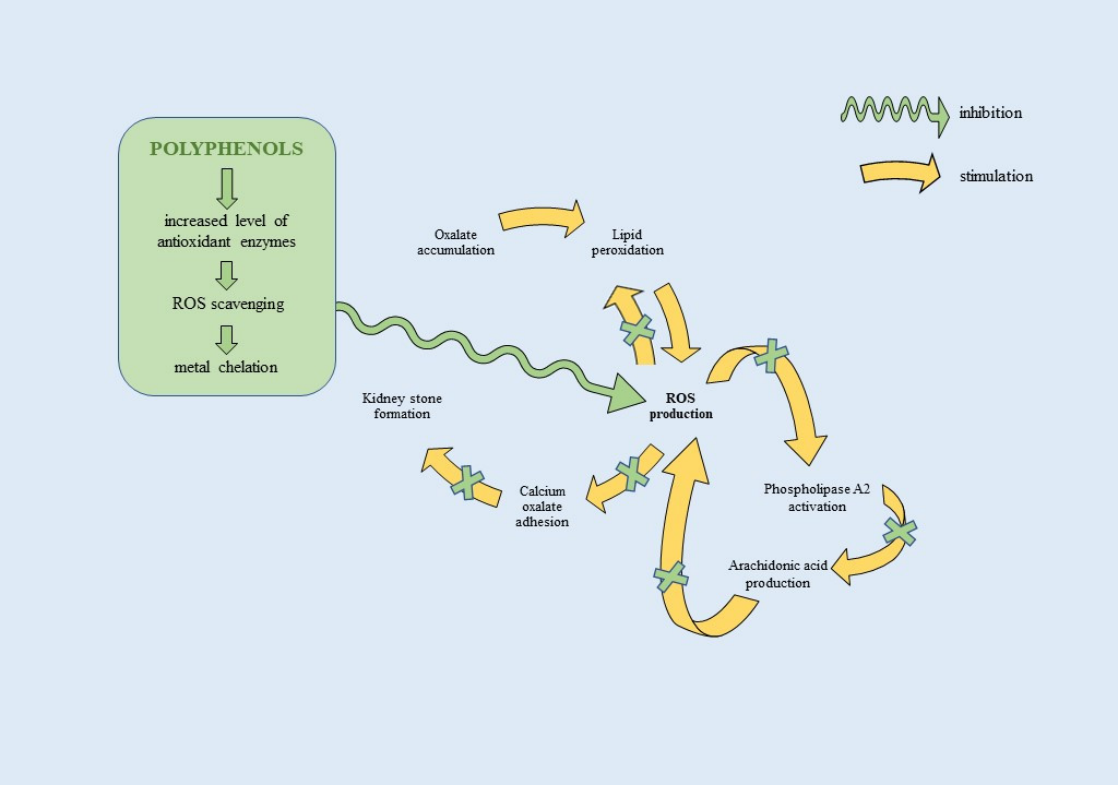

Figure 2. Oxalates initiate lipid peroxidation and ROS production, thereby leading to the formation of kidney stones. Polyphenols reduce kidney stone formation by increasing the level of antioxidant enzymes, ROS scavenging, and metal chelation. Figure created with Servier Medical Art, https://smart.servier.com/ (accessed on 9 May 2023).

Polyphenols exhibit a high antioxidant redox potential, which makes them suitable for inactivating the ROS and acting as chelating agents [43,44]. This makes them valuable

targets for future research in the prevention of ferroptosis in kidney diseases, especially regarding the formation of kidney stones.

2.2. Ferroptosis in Nephrolithiasis

Ferroptosis is a type of cell death caused by accumulation of large amounts of iron, lipid peroxidation, and ROS [45]. This type of apoptosis is induced by ROS accumulation, decreased concentration of glutathione (GSH), inhibition of glutathione peroxidase 4 (GPX4), and the cystine/glutamate antiporter system, as well as by generating ROS-producing molecules, including arachidonic acid. Ferroptosis can be inhibited or even prevented by cellular autophagy, chelating agents, and antioxidants [46–48].

Inhibition of GPX4 in ferroptosis prevents lipid hydroperoxide (LOOH) metabolism, which results in the progression of lipid peroxidation and accumulation of reactive lipid-ROS. GPX4 regulates redox cell potential and is the only GPX in cellular membranes that directly reduces LOOH. Lipid peroxidation in ferroptosis starts with electron transfer from a transition metal, in this case, from iron (II) [49–53]. Figure 3 represents the mechanism of lipid peroxidation of LOOH which accumulates in ferroptosis.

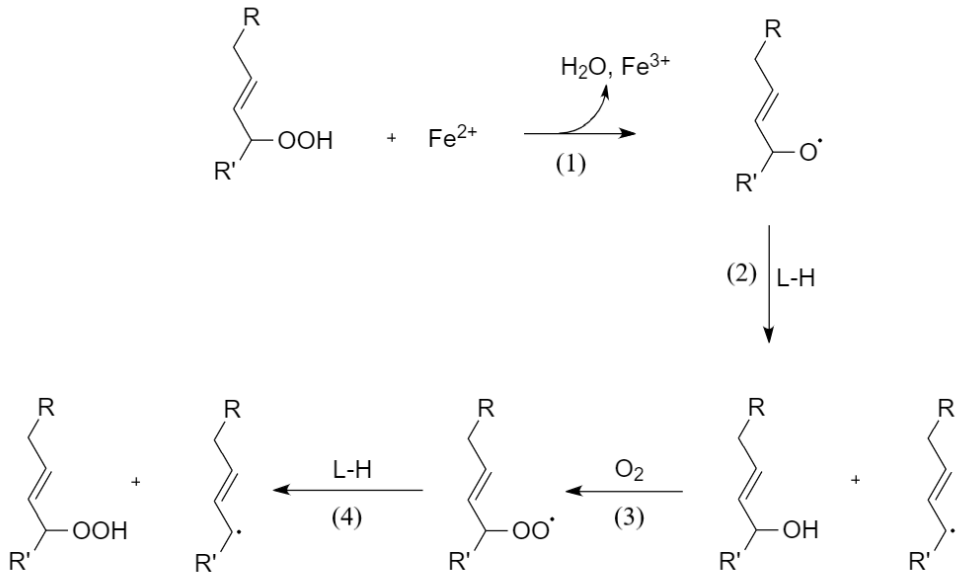

Figure 3. (1) Electron transfer from iron(II) to LOOH generates alkoxy radical (LO•). The radical formed in the previous reaction, LO•, reacts with a new lipid molecule (L-H), which usually results in the formation of a lipid radical (L•). (3) L• then reacts with oxygen, thereby generating lipid peroxyl radical (LOO•), which also reacts with L-H (4), thereby forming LOOH and L•. Figure created with ChemDraw, https://perkinelmerinformatics.com/products/research/chemdraw (accessed on 9 May 2023).

Recent studies have shown that CaOx causes an increase in the ROS concentration and expression of the ferroptosis agonist proteins, whereas ferroptosis inhibitory proteins, such as GPX4, were decreased. The extent of ferroptosis has a great effect on the cellular antioxidant capacity, leading to its eventual weakening [54–57].

2.3. Polyphenols Inhibit Lipid Peroxidation and Ferroptosis as Chelating Agents

In addition to antioxidant properties, polyphenols have also demonstrated chelating functions known to inhibit ferroptosis [58]. In the next few subsections, we have listed some polyphenols known to inhibit and/or even prevent ferroptosis and lipid-peroxidation-induced damage by forming iron chelates. These effects will be discussed in detail in further sections.

3. Beneficial Effects of Polyphenols as Determined by Various In Vitro Models of Nephrolithiasis

In this section, we examine various polyphenol compounds, medicinal plants containing polyphenols, or polyphenol extracts and their effects on experimental in vitro models of nephrolithiasis and consequential renal cell injuries. In vitro studies provide insight into molecular mechanisms underlying these effects in a controlled environment, whereas excluding other pleiotropic effects of these compounds. In this section, we aim to identify potential therapeutic compounds and medicinal herbs, as well as elucidate altered signaling pathways and molecular processes to highlight potential targets for nephrolithiasis prevention and treatment.

3.1. Flavonoids

3.1.1. Quercetin

Quercetin is a polyphenol belonging to a subclass of flavonoids, called flavanols. This yellow-colored plant pigment is well known for its cardiovascular, anti-tumor, immunomodulatory effects and can be found in tea and onion. It is generally insoluble in all common solvents, with exception to its low solubility in some alcohols, basic solvents, and glacial acetic acid [59–61]. This can potentially limit its research use in in vitro studies. When considering its inhibitory effects regarding ferroptosis progression, application of quercetin prevents the ferroptosis-induced morphologic changes in cells. These changes are caused by decreased concentration of GSH, as well as increased levels of malondialdehyde (MDA) and ROS. One of the recent in vitro studies confirmed that quercetin is able to increase the GSH concentration and reduce the levels of both MDA and ROS, suggesting quercetin as a potential target for future research in the prevention of ferroptosis [62–65].

3.1.2. Catechins

One of the most consumed and highly acknowledged polyphenol-rich products for their health benefits is tea. Specifically, three major types of tea—green tea, oolong tea, and black tea. The health benefits of these drinks have been extensively studied, and these benefits are highly related to their various polyphenol compound contents, mostly catechins [66–70]. A recent in vitro study aimed to evaluate the ability of green tea, oolong tea, and black tea to prevent the formation of CaOx crystals by investigating artificial urine spectroscopically and crystallization microscopically. The study concluded that all three teas were effective in inhibiting crystal formation, with green tea being the most effective. This study confirmed the beneficial effects, kidney stone prevention, and treatment potential of green tea [71]. Four primary catechins have been identified in green tea—epicatechin, epigallocatechin, epicatechin-3-gallate, and the most extensively researched epigallocatechin gallate (EGCG), comprising 50–80% of the total catechin content [72]. Therefore, beneficial effects of green tea are most commonly linked to EGCGs' nephroprotective properties [42]. Although considered as a great therapeutic agent in the treatments of various kidney diseases, this tea polyphenol contains a significant amount of oxalate, which usually contributes to CaOx crystal formation. However, a considerable number of studies have demonstrated that treatment with green tea reduces renal injury and CaOx crystal deposition, decreases levels of MDA, and increases GSH concentration, as well as exhibits antiferroptotic activity by activating nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) [73–75]. A significant number of studies have investigated EGCG for its beneficial effects in various diseases. The most recently obtained evidence of in vitro experimental models provide a valuable insight into molecular pathways by which EGCG exerts its nephroprotective properties in nephrolithiasis.

It has been well established that the polarization of the macrophages into M1 and M2 states is a crucial process in inflammatory/immune response, involved in various pathologic conditions, as well as in pathophysiology of nephrolithiasis. In general, M1 macrophages are considered to be pro-inflammatory and antimicrobial, whereas M2 macrophages are regarded as anti-inflammatory states. However, their beneficial effects

vary greatly on the environment. For example, in tumorigenesis, M1 macrophages play an important role as anti-tumor cells, whereas the M2 phenotype is associated with tumor growth [76]. In cell culture models of CaOx-induced nephrolithiasis, M2 macrophage-exposed cells demonstrated reduced inflammation, cell injury, apoptosis, and oxidative-stress-induced damage [17,77], whereas a systematic review by Taguchi et al. indicated the high expression of M1 macrophage proteins in patients with CaOx nephrolithiasis and suggested that targeting M2-like macrophage polarization could serve as a valuable therapeutic strategy against kidney stone formation [78]. A study on the murine macrophage cell line RAW264.7 indicated EGCGs' involvement in the polarization of macrophages. This study demonstrated that EGCG inhibits M1 polarization when stimulated with LPS and IFN-γ, in a dose-dependent manner, whereas no significant effect regarding M2 state was observed. However, the results showed that EGCG could promote M2 polarization in cells treated with EGCG only [79].

3.1.3. Curcumin

Curcumin is a lipophilic polyphenol found in turmeric, a plant commonly used in the form of powder as a flavoring or coloring agent. More than a few studies suggest that curcumin works as an anti-inflammatory, anti-aging, and anti-neoplastic agent. However, curcumin presents great limitations regarding its therapeutic usage due to low solubility in aqueous solutions and poor bioavailability [80–82]. Moreover, due to the metal chelating ability of this compound, curcumin shows a great potential in the prevention of various diseases, including kidney injury [82,83]. The NF-κB signaling pathway shows a great potential as a target for the regulation of inflammatory processes when considering ferroptosis. It has been proposed that curcumin may inhibit ferroptosis and stop the progression of acute renal injury. As an anti-inflammatory agent, curcumin inhibits TLR4/NF-κB axis and activates HO-1, which prevents further progress of ferroptosis in acute kidney injury. This accounts for the therapeutic effect of curcumin in ferroptosis, as both inflammation and oxidative stress make up for this type of apoptosis [83,84].

Gold nanoparticles (GNPs) using the ethanolic crude extract of turmeric (Tur-CE) and curcumin (Cur) have recently been described to have antioxidant, anticholinesterase (anti-ChE), and antilithiatic effects in vitro [85].

3.1.4. Other Flavonoids

Puerarin, a flavonoid polyphenol, has demonstrated protective effects in CaOx-induced renal tubular epithelial cells damage in vitro by inhibition of autophagy, as well as by the attenuation of CaOx cytotoxicity. These protective properties are suggested to be mediated by the activation of the SIRT1/AKT/p38 signaling pathway [86]. Sirtuin 1 (SIRT1) is a crucial regulator of cellular responses in states such as inflammation or oxidative stressors, and chronic inflammation is linked to reduced SIRT1 levels [87].

Another flavonoid, vitexin, has been identified as a potential anti-inflammatory and anti-tumorigenic compound. In an in vitro model of CaOx-treated human proximal renal tubular epithelial cell line (HK-2) and human monocytic cell line (THP-1), vitexin has demonstrated protective properties as well. Vitexin-treated HK-2 and THP-1 cells showed that these effects were mediated through multiple processes. The vitexin-treated cells showed significant increases in cell viability, as well as lower medium lactate dehydrogenase (LDH) levels. Vitexin demonstrated strong inhibition of gene expression of proteins associated with pyroptosis in both cell lines, repressed the epithelial–mesenchymal transition (EMT) of HK-2 cells, and downregulated the expression of Vimentin and alpha-smooth muscle actin (α-SMA) as well as the Wnt/β-catenin signalling pathway. In the THP-1 cells, vitexin was shown to significantly suppress tumor necrosis factor-α (TNF-α) and IL-1β expression. These processes are all hallmarks of nephrolithiasis and its progressive renal tissue damaging states [88].

Kaempferol has been recognized for its anti-inflammatory and ROS-scavenging effects in various in vitro studies [89–92]. In a more recent study regarding nephrolithiasis, it

demonstrated suppression of CaOx-induced HK-2 cell injury, a decrease in adhesion, as well as improved cell viability. The upregulation of pro-inflammatory marker expressions, such as IL-1β, IL-6, TNF-α, OPN, and CD44, was reversed after the kaempferol treatment. On the contrary, the CaOx-associated downregulation of anti-inflammatory factors, such as IL-10, IL-4, and Arg1, was reversed as well when treated with kaempferol. These results indicated the high capability of this flavonoid in ameliorating oxidative stress, renal cell injury, adhesion, and deposition of CaOx, which could be mediated by the AR/NOX2 signaling pathway, suggesting it as a potential target for CaOx nephrolithiasis treatment [93].

Orthosiphon stamineus, a medical herb that contains significant levels of minerals and flavonoids, demonstrated chemolytic effects. *O. stamineus*'s water extract potential in urolithiasis was examined, using 15 stone samples from patients and subjecting them to different concentrations. The extract was found to have a better chemolytic action on calcium oxalate crystals than the potassium citrate solution, concluding that the extract had a dissolving capability of urinary stones to some extent [94].

3.2. Phenolic Acids

In a recent in vitro study, gallic acid, a widely abundant polyphenol in common food, has shown beneficial effects in alleviating the deposition and adhesion of CaOx, inflammation, and cellular damage. The study observed a decrease in intracellular ROS levels, as well as reduced levels of osteopontin and CD44 in HK-2 cells treated with gallic acid. The postulated mechanism is the gallic-acid-induced Nrf2/HO-1 signaling axis, explaining its anti-inflammatory and antioxidant effects [95].

Kalanchoe pinnata, *Emblica officinalis*, *Bambusa nutans*, and *Cynodon dactylon*, rich in caffeic, ferulic, and gallic acid (belonging to phenolic acids group of polyphenols), as well as other polyphenol contents, have also recently demonstrated crystal dissolution and crystal growth inhibition properties in vitro [96].

3.3. Stilbenes (Resveratrol)

Another polyphenol family, stilbenes, its member resveratrol specifically, has been extensively studied for its beneficial effects in various pathological conditions and demonstrated multiple protective antioxidant, anti-inflammatory, renoprotective, hepatoprotective, neuroprotective, cardioprotective, anti-microbial, and anti-tumorigenic effects in previous studies [24,38].

Resveratrol is most famous for its potential health benefits associated with moderate wine consumption, known as the "French Paradox". However, resveratrol's multiple pathway-altering properties have also been postulated to negatively affect some processes. Most reported are its pro-oxidating effects. This has been postulated to vary in a dose-dependent manner and could paradoxically have benefits in some pathological conditions such as tumorigenesis. At lower concentrations, it acts as an antioxidant, whereas it exhibits cell proliferation/cytoprotective or cytostatic/apoptotic effects at a higher dose. Furthermore, resveratrol has demonstrated interactions with CYP enzymes, various transporters, and drugs. This shows the need for further elucidation of pharmacodynamic properties of resveratrol and its dose-dependent biphasic activities, before defining and clinically implementing it beyond its traditional use [97].

In a more recent study, resveratrol pretreatment of normal rat kidney epithelial-like (NRK-52E) cells significantly decreased early and late apoptosis induced by oxalate treatment. Furthermore, expression of the proinflammatory markers BMP2, OPN, and IL-6 mRNA, as well as ROS production, was significantly inhibited by resveratrol treatment. This study also indicated resveratrol's ability to modulate autophagy via the activation of transcription factor EB (TFEB), a major regulator of autophagy and lysosomal function [98]. Another study also associated CaOx renal cell injury with Sirt1 downregulation, whereas resveratrol treatment upregulated Sirt1 expression by lentivirus transfection in vitro and resveratrol administration in vivo, ameliorating CaOx-induced renal cell injury [99].

3.4. Various Polyphenol-Rich Plants and Compounds

Herbal medicines have been extensively researched in nephrolithiasis treatment for decades, mostly due to anecdotal evidence. In this section, we examine some of the most recently in vitro obtained evidence regarding plants constituting various polyphenol compounds.

The medicinal plants *Kalanchoe laciniata* and *Drymoglossum piloselloides*, containing various polyphenols such as flavonoids and tannins, as determined by phytochemical screening, showed significant antilithiatic effects, reducing the nucleation, growth, and aggregation of CaOx. The effects on crystallization were determined using various assays and light microscopy [100]. A traditionally used herb for kidney conditions and diuretic effects, *Mimosa malacophylla* A.Gray, in the treatment of Vero and HEK-293 cells showed no cytotoxicity at concentrations below 300 µg/mL in vitro, whereas it demonstrated antilithic effects in vivo. These effects were attributed to flavonoids but also steroids and terpenes present in this herb, as determined by a phytochemical screening [101].

An interesting study offered a novel solution to utilize crystallization-inhibiting compounds from traditional Chinese medicines (TCMs) for the prevention of nephrolithiasis. Twenty TCMs were extracted and examined for their crystal growth and adhesion of CaOx-inhibiting properties in vitro on human renal epithelial cells. Extracts from 20 kinds of herbs showed almost 100% inhibition percentage. Among all molecules identified from the extracts, polyphenols exhibited the highest inhibition of CaOx crystallization [102].

Costus spicatus (Jacq.) Sw., a traditionally used treatment for nephrolithiasis in Brazil, was recently studied in Wistar rats for its antilithiatic effects, evaluated by in vitro crystallization, and suggested the renoprotective and antilithiatic properties of the herb. Flavonoids and saponins were predominantly identified in *C. spicatus*, as well as other polyphenols [103].

Theaflavin (TF), comprising various polyphenols, is a major compound in black and oolong teas. Its radical scavenging and metal chelation properties and beneficial effects have been reported in various diseases. A recent in vitro study in a HK-2 cell culture model of CaOx-induced nephrolithiasis showed the protective effects of TF treatment in cells exposed to CaOx. A possible mechanism of these nephroprotective effects has also been postulated, suggesting that TF reduced oxidative stress injury and crystal deposition by the downregulating expression of miR-128-3p, thus ameliorating the inhibition of SIRT1, a histone deacetylase known for its anti-inflammatory and anti-oxidative effects. This study provided the elucidation of TFs' nephroprotective mechanisms, as well as suggesting potential miR-128-3p- and SIRT1-targeted therapies of CaOx nephrolithiasis [104].

Hydro-ethanolic and aqueous extracts of *Herniaria hirsuta* L.'s aerial parts, *Opuntia ficus-indica*'s L. flowers, *Zea mays* L.'s stigmata, *Ammi visnaga* L.'s seeds, and *Ziziphus lotus* L.'s fruits have also recently been shown to successfully dissolve CaOx and cystine crystals in vitro [105].

4. Limitations of Current In Vitro Models of Nephrolithiasis Exploring Polyphenols

Although most of the available research on cell culture models of nephrolithiasis and polyphenol's role in its pathophysiology has been performed on cell lines of proximal tubules and greatly elucidate mechanisms of crystal-induced renal tissue injury discussed throughout the manuscript, these cell lines may not be the most appropriate option for exploring the final stone formation, adhesion, and deposition in the renal tissue. Several theories have been acknowledged regarding the pathophisiology of stone formation, postulating that the main site of crystal adhesions and fixations to the urothelium is the terminal part of collecting ducts, as well as the medullary interstitium, where Randall plaques are formed, in which crystals are then deposited [106]. There is a scarcity of in vitro studies examining polyphenols' effects on kidney stone formations in cell cultures using cell lines derived from collecting ducts, as well as their effects on Randall plaques. This highlights the need for the implementation of these approaches to further elucidate polyphenols' effects.

5. Conclusions

Abundant experimental research suggests that dietary polyphenols have a positive impact on human health and potential in prophylactic measures for various diseases. Consuming foods rich in polyphenols, such as quercetin, epigallocatechin-3-gallate, resveratrol, and others explored in this review, has been indicated to lower the risk of various chronic diseases like cardiovascular pathologic conditions, diabetes mellitus, chronic inflammatory disorders, neoplasms, and neurodegenerative disorders. Evidence obtained from both experimental and clinical studies indicate the preventative and therapeutic potential of the intake of a diet rich in polyphenols for these conditions [35,107].

In this review, we have summarized the most recently obtained data regarding underlying mechanisms of antilithiatic and protective properties of polyphenols in nephrolithiasis, as determined by in vitro studies, to distinguish their pleiotropic effects from their direct nephroprotective properties.

We also highlighted some of the recently explored potential therapeutic targets, as well as concerns related to polyphenol implementation into clinical practice, such as the lack of elucidation of their involvement in multiple signaling pathways and variable dose-dependent effects. Despite the evidence supporting the antilithiatic properties of polyphenols, as well as the overall health benefits, extensive in vivo and clinical trials are required for the progression of safe polyphenol-based therapies in clinical practice.

Author Contributions: Conceptualization, M.S., A.P., T.K., M.H. and N.R.-L.; validation, A.P., R.S., M.S., T.K., A.V. and N.R.-L.; formal analysis, M.H., I.M.H., A.P. and T.K.; investigation, M.H., I.M.H., A.P., T.K., Z.U., D.G. and E.H.; writing—original draft preparation, M.H., I.M.H., A.P. and T.K.; writing—review and editing, A.P., T.K., M.H., I.M.H., M.S. and N.R.-L.; visualization, M.H.; supervision, M.S., R.S. and A.V.; project administration, N.R.-L. and M.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Shah, J.; Whitfield, H.N. Urolithiasis through the ages. *BJU Int.* **2002**, *89*, 801–810. [CrossRef]
2. Warli, S.M.; Mantiri, B.J.; Sihombing, B.; Siregar, G.P.; Prapiska, F.F. Nephrolithiasis-Associated Renal Cell Carcinoma in Patients Who Underwent Nephrectomy: A Single-Center Experience. *World J. Oncol.* **2023**, *14*, 94–100. [CrossRef]
3. Chewcharat, A.; Curhan, G. Trends in the prevalence of kidney stones in the United States from 2007 to 2016. *Urolithiasis* **2021**, *49*, 27–39. [CrossRef]
4. Skolarikos, A.; Neisius, J.H.; Petrik; Somani, B.; Tailly, T.; Gambaro, G.; Davis, N.F.; Geraghty, R.; Lombardo, R.; Tzelves, L. EAU Gidelines on Urolithiasis. 2023. Available online: https://uroweb.org/gidelines/urolithiasis (accessed on 20 April 2023).
5. Stamatelou, K.; Goldfarb, D.S. Epidemiology of Kidney Stones. *Healthcare* **2023**, *11*, 424. [CrossRef]
6. Ferraro, P.M.; Taylor, E.N.; Eisner, B.H.; Gambaro, G.; Rimm, E.B.; Mukamal, K.J.; Curhan, G.C. History of kidney stones and the risk of coronary heart disease. *JAMA* **2013**, *310*, 408–415. [CrossRef]
7. Rule, A.D.; Roger, V.L.; Melton, L.J.I.; Bergstralh, E.J.; Li, X.; Peyser, P.A.; Krambeck, A.E.; Lieske, J.C. Kidney Stones Associate with Increased Risk for Myocardial Infarction. *J. Am. Soc. Nephrol.* **2010**, *21*, 1641–1644. [CrossRef]
8. Rule, A.D.; Bergstralh, E.J.; Melton, L.J.I.; Li, X.; Weaver, A.L.; Lieske, J.C. Kidney Stones and the Risk for Chronic Kidney Disease. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 804–811. [CrossRef]
9. Taylor, E.N.; Feskanich, D.; Paik, J.M.; Curhan, G.C. Nephrolithiasis and Risk of Incident Bone Fracture. *J. Urol.* **2016**, *195*, 1482–1486. [CrossRef]
10. Zeng, G.; Zhu, W.; Robertson, W.G.; Penniston, K.L.; Smith, D.; Pozdzik, A.; Tefik, T.; Prezioso, D.; Pearle, M.S.; Chew, B.H.; et al. International Alliance of Urolithiasis (IAU) guidelines on the metabolic evaluation and medical management of urolithiasis. *Urolithiasis* **2022**, *51*, 4. [CrossRef]
11. Evan, A.P. Physiopathology and etiology of stone formation in the kidney and the urinary tract. *Pediatr. Nephrol.* **2010**, *25*, 831–841. [CrossRef]
12. Petrović, A.; Kizivat, T.; Bilić Ćurčić, I.; Smolić, R.; Smolić, M. In Vitro Cell Culture Models of Hyperoxaluric States: Calcium Oxalate and Renal Epithelial Cell Interactions. *Crystals* **2021**, *11*, 735.

13. Aggarwal, K.P.; Narula, S.; Kakkar, M.; Tandon, C. Nephrolithiasis: Molecular mechanism of renal stone formation and the critical role played by modulators. *Biomed. Res. Int.* **2013**, *2013*, 292953. [CrossRef]
14. Mayans, L. Nephrolithiasis. *Prim. Care Clin. Off. Pract.* **2019**, *46*, 203–212. [CrossRef]
15. Geraghty, R.M.; Davis, N.F.; Tzelves, L.; Lombardo, R.; Yuan, C.; Thomas, K.; Petrik, A.; Neisius, A.; Türk, C.; Gambaro, G.; et al. Best Practice in Interventional Management of Urolithiasis: An Update from the European Association of Urology Guidelines Panel for Urolithiasis 2022. *Eur. Urol. Focus* **2023**, *9*, 199–208. [CrossRef]
16. Antonelli, J.A.; Maalouf, N.M.; Pearle, M.S.; Lotan, Y. Use of the National Health and Nutrition Examination Survey to calculate the impact of obesity and diabetes on cost and prevalence of urolithiasis in 2030. *Eur. Urol.* **2014**, *66*, 724–729. [CrossRef]
17. Kizivat, T.; Smolić, M.; Marić, I.; Tolušić Levak, M.; Smolić, R.; Bilić Čurčić, I.; Kuna, L.; Mihaljević, I.; Včev, A.; Tucak-Zorić, S. Antioxidant Pre-Treatment Reduces the Toxic Effects of Oxalate on Renal Epithelial Cells in a Cell Culture Model of Urolithiasis. *Int. J. Environ. Res. Public Health* **2017**, *14*, 109. [CrossRef]
18. Ahmed, S.; Hasan, M.; Mahmood, Z. Antiurolithiatic plants: Multidimensional pharmacology. *J. Pharmacogn. Phytochem.* **2016**, *5*, 4–24.
19. Yasir, F.; Wahab, A.-T.; Choudhary, M.I. Protective effect of dietary polyphenol caffeic acid on ethylene glycol-induced kidney stones in rats. *Urolithiasis* **2018**, *46*, 157–166. [CrossRef]
20. Zhai, W.; Zheng, J.; Yao, X.; Peng, B.; Liu, M.; Huang, J.; Wang, G.; Xu, Y. Catechin prevents the calcium oxalate monohydrate induced renal calcium crystallization in NRK-52E cells and the ethylene glycol induced renal stone formation in rat. *BMC Complement. Altern. Med.* **2013**, *13*, 228. [CrossRef]
21. Ghodasara, J.; Pawar, A.; Deshmukh, C.; Kuchekar, B. Inhibitory effect of rutin and curcumin on experimentally-induced calcium oxalate urolithiasis in rats. *Pharmacogn. Res.* **2010**, *2*, 388–392. [CrossRef]
22. Noorafshan, A.; Karbalay-Doust, S.; Karimi, F. Diosmin Reduces Calcium Oxalate Deposition and Tissue Degeneration in Nephrolithiasis in Rats: A Stereological Study. *Korean J. Urol.* **2013**, *54*, 252–257.
23. Dinnimath, B.M.; Jalalpure, S.S.; Patil, U.K. Antiurolithiatic activity of natural constituents isolated from Aerva lanata. *J. Ayurveda Integr. Med.* **2017**, *8*, 226–232. [CrossRef]
24. Hong, S.H.; Lee, H.J.; Sohn, E.J.; Ko, H.S.; Shim, B.S.; Ahn, K.S.; Kim, S.H. Anti-nephrolithic potential of resveratrol via inhibition of ROS, MCP-1, hyaluronan and osteopontin in vitro and in vivo. *Pharm. Rep.* **2013**, *65*, 970–979. [CrossRef]
25. Shakoor, H.; Feehan, J.; Apostolopoulos, V.; Platat, C.; Al Dhaheri, A.S.; Ali, H.I.; Ismail, L.C.; Bosevski, M.; Stojanovska, L. Immunomodulatory Effects of Dietary Polyphenols. *Nutrients* **2021**, *13*, 728. [CrossRef]
26. Fraga, C.G.; Croft, K.D.; Kennedy, D.O.; Tomás-Barberán, F.A. The effects of polyphenols and other bioactives on human health. *Food Funct* **2019**, *10*, 514–528. [CrossRef]
27. Di Lorenzo, C.; Colombo, F.; Biella, S.; Stockley, C.; Restani, P. Polyphenols and Human Health: The Role of Bioavailability. *Nutrients* **2021**, *13*, 273. [CrossRef]
28. Yahfoufi, N.; Alsadi, N.; Jambi, M.; Matar, C. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. *Nutrients* **2018**, *10*, 1618. [CrossRef]
29. Luca, S.V.; Macovei, I.; Bujor, A.; Miron, A.; Skalicka-Woźniak, K.; Aprotosoaie, A.C.; Trifan, A. Bioactivity of dietary polyphenols: The role of metabolites. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 626–659. [CrossRef]
30. Xiao, J. Stability of dietary polyphenols: It's never too late to mend? *Food Chem. Toxicol.* **2018**, *119*, 3–5. [CrossRef]
31. Shen, N.; Wang, T.; Gan, Q.; Liu, S.; Wang, L.; Jin, B. Plant flavonoids: Classification, distribution, biosynthesis, and antioxidant activity. *Food Chem.* **2022**, *383*, 132531. [CrossRef]
32. Santos-Buelga, C.; González-Paramás, A.M.; Oludemi, T.; Ayuda-Durán, B.; González-Manzano, S. Plant phenolics as functional food ingredients. *Adv. Food Nutr. Res.* **2019**, *90*, 183–257. [CrossRef]
33. Wang, Y.; Qi, H.; Liu, Y.; Duan, C.; Liu, X.; Xia, T.; Chen, D.; Piao, H.L.; Liu, H.X. The double-edged roles of ROS in cancer prevention and therapy. *Theranostics* **2021**, *11*, 4839–4857. [CrossRef]
34. Aneklaphakij, C.; Saigo, T.; Watanabe, M.; Naake, T.; Fernie, A.R.; Bunsupa, S.; Satitpatipan, V.; Tohge, T. Diversity of Chemical Structures and Biosynthesis of Polyphenols in Nut-Bearing Species. *Front. Plant Sci.* **2021**, *12*, 642581. [CrossRef]
35. Rudrapal, M.; Khairnar, S.J.; Khan, J.; Dukhyil, A.B.; Ansari, M.A.; Alomary, M.N.; Alshabrmi, F.M.; Palai, S.; Deb, P.K.; Devi, R. Dietary Polyphenols and Their Role in Oxidative Stress-Induced Human Diseases: Insights into Protective Effects, Antioxidant Potentials and Mechanism(s) of Action. *Front. Pharmacol.* **2022**, *13*, 806470. [CrossRef]
36. Peerapen, P.; Thongboonkerd, V. Kidney Stone Prevention. *Adv. Nutr.* **2023**, *14*, 555–569. [CrossRef]
37. Peerapen, P.; Thongboonkerd, V. Kidney stone proteomics: An update and perspectives. *Expert Rev. Proteom.* **2021**, *18*, 557–569. [CrossRef]
38. Den Hartogh, D.J.; Tsiani, E. Health Benefits of Resveratrol in Kidney Disease: Evidence from In Vitro and In Vivo Studies. *Nutrients* **2019**, *11*, 1624. [CrossRef]
39. Liu, S.; Zhao, M.; Zhou, Y.; Wang, C.; Yuan, Y.; Li, L.; Bresette, W.; Chen, Y.; Cheng, J.; Lu, Y.; et al. Resveratrol exerts dose-dependent anti-fibrotic or pro-fibrotic effects in kidneys: A potential risk to individuals with impaired kidney function. *Phytomedicine* **2019**, *57*, 223–235. [CrossRef]
40. Su, L.J.; Zhang, J.H.; Gomez, H.; Murugan, R.; Hong, X.; Xu, D.; Jiang, F.; Peng, Z.Y. Reactive Oxygen Species-Induced Lipid Peroxidation in Apoptosis, Autophagy, and Ferroptosis. *Oxid. Med. Cell Longev.* **2019**, *2019*, 5080843. [CrossRef]
41. Schreiber, R.; Buchholz, B.; Kraus, A.; Schley, G.; Scholz, J.; Ousingsawat, J.; Kunzelmann, K. Lipid Peroxidation Drives Renal Cyst Growth. *J. Am. Soc. Nephrol.* **2019**, *30*, 228–242. [CrossRef]

42. Ahmed, S.; Hasan, M.M.; Khan, H.; Mahmood, Z.A.; Patel, S. The mechanistic insight of polyphenols in calcium oxalate urolithiasis mitigation. *Biomed. Pharmacother.* **2018**, *106*, 1292–1299. [CrossRef]
43. Gasmi, A.; Mujawdiya, P.K.; Noor, S.; Lysiuk, R.; Darmohray, R.; Piscopo, S.; Lenchyk, L.; Antonyak, H.; Dehtiarova, K.; Shanaida, M.; et al. Polyphenols in Metabolic Diseases. *Molecules* **2022**, *27*, 6280. [CrossRef]
44. Fan, X.; Fan, Z.; Yang, Z.; Huang, T.; Tong, Y.; Yang, D.; Mao, X.; Yang, M. Flavonoids-Natural Gifts to Promote Health and Longevity. *Int. J. Mol. Sci.* **2022**, *23*, 2176. [CrossRef]
45. Li, J.; Cao, F.; Yin, H.L.; Huang, Z.J.; Lin, Z.T.; Mao, N.; Sun, B.; Wang, G. Ferroptosis: Past, present and future. *Cell Death Dis.* **2020**, *11*, 88. [CrossRef]
46. Zhang, J.; Wang, B.; Yuan, S.; He, Q.; Jin, J. The Role of Ferroptosis in Acute Kidney Injury. *Front. Mol. Biosci.* **2022**, *9*, 951275. [CrossRef]
47. Tang, D.; Chen, X.; Kang, R.; Kroemer, G. Ferroptosis: Molecular mechanisms and health implications. *Cell Res.* **2021**, *31*, 107–125. [CrossRef]
48. Messerer, D.A.C.; Halbgebauer, R.; Nilsson, B.; Pavenstädt, H.; Radermacher, P.; Huber-Lang, M. Immunopathophysiology of trauma-related acute kidney injury. *Nat. Rev. Nephrol* **2021**, *17*, 91–111. [CrossRef]
49. Lesjak, M.; Simin, N.; Srai, S.K.S. Can Polyphenols Inhibit Ferroptosis? *Antioxidants* **2022**, *11*, 150. [CrossRef]
50. Hu, W.; Liang, K.; Zhu, H.; Zhao, C.; Hu, H.; Yin, S. Ferroptosis and Its Role in Chronic Diseases. *Cells* **2022**, *11*, 2040. [CrossRef]
51. Xu, S.; Wu, B.; Zhong, B.; Lin, L.; Ding, Y.; Jin, X.; Huang, Z.; Lin, M.; Wu, H.; Xu, D. Naringenin alleviates myocardial ischemia/reperfusion injury by regulating the nuclear factor-erythroid factor 2-related factor 2 (Nrf2) /System xc-/ glutathione peroxidase 4 (GPX4) axis to inhibit ferroptosis. *Bioengineered* **2021**, *12*, 10924–10934. [CrossRef]
52. Lin, C.H.; Tseng, H.F.; Hsieh, P.C.; Chiu, V.; Lin, T.Y.; Lan, C.C.; Tzeng, I.S.; Chao, H.N.; Hsu, C.C.; Kuo, C.Y. Nephroprotective Role of Chrysophanol in Hypoxia/Reoxygenation-Induced Renal Cell Damage via Apoptosis, ER Stress, and Ferroptosis. *Biomedicines* **2021**, *9*, 1283. [CrossRef]
53. Liu, Y.; Wan, Y.; Jiang, Y.; Zhang, L.; Cheng, W. GPX4: The hub of lipid oxidation, ferroptosis, disease and treatment. *Biochim. Biophys. Acta (BBA)-Rev. Cancer* **2023**, *1878*, 188890. [CrossRef]
54. He, Z.; Liao, W.; Song, Q.; Li, B.; Liu, J.; Xiong, Y.; Song, C.; Yang, S. Role of ferroptosis induced by a high concentration of calcium oxalate in the formation and development of urolithiasis. *Int. J. Mol. Med.* **2021**, *47*, 289–301. [CrossRef]
55. Sanz, A.B.; Sanchez-Niño, M.D.; Ramos, A.M.; Ortiz, A. Regulated cell death pathways in kidney disease. *Nat. Rev. Nephrol* **2023**, *19*, 281–299. [CrossRef]
56. Liu, Y.; Wang, J. Ferroptosis, a Rising Force against Renal Fibrosis. *Oxid. Med. Cell. Longev.* **2022**, *2022*, 7686956. [CrossRef]
57. Su, Y.; Liu, Z.; Xie, K.; Ren, Y.; Li, C.; Chen, W. Ferroptosis: A Novel Type of Cell Death in Male Reproduction. *Genes* **2022**, *14*, 43. [CrossRef]
58. Stepanić, V.; Kučerová-Chlupáčová, M. Review and Chemoinformatic Analysis of Ferroptosis Modulators with a Focus on Natural Plant Products. *Molecules* **2023**, *28*, 475. [CrossRef]
59. Singh, P.; Arif, Y.; Bajguz, A.; Hayat, S. The role of quercetin in plants. *Plant. Physiol. Biochem.* **2021**, *166*, 10–19. [CrossRef]
60. Tao, H.; Zhao, Y.; Li, L.; He, Y.; Zhang, X.; Zhu, Y.; Hong, G. Comparative metabolomics of flavonoids in twenty vegetables reveal their nutritional diversity and potential health benefits. *Food Res. Int.* **2023**, *164*, 112384. [CrossRef]
61. Oh, W.Y.; Ambigaipalan, P.; Shahidi, F. Quercetin and its ester derivatives inhibit oxidation of food, LDL and DNA. *Food Chem.* **2021**, *364*, 130394. [CrossRef]
62. Wang, Y.; Quan, F.; Cao, Q.; Lin, Y.; Yue, C.; Bi, R.; Cui, X.; Yang, H.; Yang, Y.; Birnbaumer, L.; et al. Quercetin alleviates acute kidney injury by inhibiting ferroptosis. *J. Adv. Res.* **2021**, *28*, 231–243. [CrossRef]
63. Linkermann, A.; Chen, G.; Dong, G.; Kunzendorf, U.; Krautwald, S.; Dong, Z. Regulated Cell Death in AKI. *J. Am. Soc. Nephrol.* **2014**, *25*, 2689–2701.
64. Wu, X.; Wang, J.; Li, B.; Gong, M.; Cao, C.; Song, L.; Qin, L.; Wang, Y.; Zhang, Y.; Li, Y. Chlorogenic acid, rutin, and quercetin from Lysimachia christinae alleviate triptolide-induced multi-organ injury in vivo by modulating immunity and AKT/mTOR signal pathway to inhibit ferroptosis and apoptosis. *Toxicol. Appl. Pharmacol.* **2023**, *467*, 116479. [CrossRef]
65. Martin-Sanchez, D.; Poveda, J.; Fontecha-Barriuso, M.; Ruiz-Andres, O.; Sanchez-Niño, M.D.; Ruiz-Ortega, M.; Ortiz, A.; Sanz, A.B. Targeting of regulated necrosis in kidney disease. *Nefrología* **2018**, *38*, 125–135. [CrossRef]
66. Zhang, H.; Qi, R.; Mine, Y. The impact of oolong and black tea polyphenols on human health. *Food Biosci.* **2019**, *29*, 55–61. [CrossRef]
67. Heber, D.; Zhang, Y.; Yang, J.; Ma, J.E.; Henning, S.M.; Li, Z. Green Tea, Black Tea, and Oolong Tea Polyphenols Reduce Visceral Fat and Inflammation in Mice Fed High-Fat, High-Sucrose Obesogenic Diets. *J. Nutr.* **2014**, *144*, 1385–1393. [CrossRef]
68. Sun, H.; Chen, Y.; Cheng, M.; Zhang, X.; Zheng, X.; Zhang, Z. The modulatory effect of polyphenols from green tea, oolong tea and black tea on human intestinal microbiota in vitro. *J. Food Sci. Technol* **2018**, *55*, 399–407. [CrossRef]
69. Jeong, B.C.; Kim, B.S.; Kim, J.I.; Kim, H.H. Effects of green tea on urinary stone formation: An in vivo and in vitro study. *J. Endourol.* **2006**, *20*, 356–361. [CrossRef]
70. Chacko, S.M.; Thambi, P.T.; Kuttan, R.; Nishigaki, I. Beneficial effects of green tea: A literature review. *Chin. Med.* **2010**, *5*, 13. [CrossRef]
71. Nasrul, S.I.; Sehgal, A. Antilithogenic potential of green tea, oolong tea, and black tea. *Pharmacogn. Res.* **2020**, *12*, 92. [CrossRef]

72. Higdon, J.V.; Frei, B. Tea catechins and polyphenols: Health effects, metabolism, and antioxidant functions. *Crit. Rev. Food Sci. Nutr.* **2003**, *43*, 89–143. [CrossRef]
73. Kanlaya, R.; Thongboonkerd, V. Protective Effects of Epigallocatechin-3-Gallate from Green Tea in Various Kidney Diseases. *Adv. Nutr.* **2019**, *10*, 112–121. [CrossRef]
74. Huang, J.; Liang, Y.; Zhou, L. Natural products for kidney disease treatment: Focus on targeting mitochondrial dysfunction. *Front. Pharmacol.* **2023**, *14*, 1142001. [CrossRef]
75. Liu, Y.; Bi, S.; Li, H.; Shi, J.; Xia, Y.; Niu, K.; Bai, S. Association between tea intake and hospitalized nephrolithiasis in Chinese adults: A case-control study. *Front. Nutr.* **2022**, *9*, 1014491. [CrossRef]
76. Yunna, C.; Mengru, H.; Lei, W.; Weidong, C. Macrophage M1/M2 polarization. *Eur. J. Pharmacol.* **2020**, *877*, 173090. [CrossRef]
77. Liu, Q.; Liu, Y.; Guan, X.; Wu, J.; He, Z.; Kang, J.; Tao, Z.; Deng, Y. Effect of M2 Macrophages on Injury and Apoptosis of Renal Tubular Epithelial Cells Induced by Calcium Oxalate Crystals. *Kidney Blood Press Res.* **2019**, *44*, 777–791. [CrossRef]
78. Taguchi, K.; Okada, A.; Unno, R.; Hamamoto, S.; Yasui, T. Macrophage Function in Calcium Oxalate Kidney Stone Formation: A Systematic Review of Literature. *Front. Immunol.* **2021**, *12*, 673690. [CrossRef]
79. Hu, Y.; Gu, J.; Lin, J.; Wang, Y.; Yang, F.; Yin, J.; Yu, Z.; Wu, S.; Lv, H.; Ji, X.; et al. (-)-Epigallocatechin-3-gallate (EGCG) modulates polarized macrophages to suppress M1 phenotype and promote M2 polarization in vitro and in vivo. *J. Funct. Foods* **2021**, *87*, 104743. [CrossRef]
80. Kotha, R.R.; Luthria, D.L. Curcumin: Biological, Pharmaceutical, Nutraceutical, and Analytical Aspects. *Molecules* **2019**, *24*, 2930. [CrossRef]
81. Carolina Alves, R.; Perosa Fernandes, R.; Fonseca-Santos, B.; Damiani Victorelli, F.; Chorilli, M. A Critical Review of the Properties and Analytical Methods for the Determination of Curcumin in Biological and Pharmaceutical Matrices. *Crit. Rev. Anal. Chem.* **2019**, *49*, 138–149. [CrossRef]
82. Amalraj, A.; Pius, A.; Gopi, S.; Gopi, S. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives—A review. *J. Tradit. Complement. Med.* **2017**, *7*, 205–233. [CrossRef]
83. Deng, L.; He, S.; Guo, N.; Tian, W.; Zhang, W.; Luo, L. Molecular mechanisms of ferroptosis and relevance to inflammation. *Inflamm. Res.* **2023**, *72*, 281–299. [CrossRef]
84. Guerrero-Hue, M.; García-Caballero, C.; Palomino-Antolín, A.; Rubio-Navarro, A.; Vázquez-Carballo, C.; Herencia, C.; Martín-Sanchez, D.; Farré-Alins, V.; Egea, J.; Cannata, P.; et al. Curcumin reduces renal damage associated with rhabdomyolysis by decreasing ferroptosis-mediated cell death. *FASEB J.* **2019**, *33*, 8961–8975. [CrossRef]
85. Abbas, S. Green Synthesis, Characterization and In-Vitro Bioactivities of Gold Nanoparticles Mediated by Turmeric Crude Extract and Curcumin. Ph.D. Thesis, Universiti Tun Hussein Onn Malaysia, Parit Raja, Malaysia, 2021.
86. Jing, G.H.; Liu, Y.D.; Liu, J.N.; Jin, Y.S.; Yu, S.L.; An, R.H. Puerarin prevents calcium oxalate crystal-induced renal epithelial cell autophagy by activating the SIRT1-mediated signaling pathway. *Urolithiasis* **2022**, *50*, 545–556. [CrossRef]
87. Hadar, A.; Gozes, I.; Gurwitz, D. Chapter 12-RGS2 and SIRT1 Link Renin Angiotensin Aldosterone System to Alzheimer's Disease. In *Neuroprotection in Alzheimer's Disease*; Illana, G., Ed.; Academic Press: Cambridge, MA, USA, 2017; pp. 239–251.
88. Ding, T.; Zhao, T.; Li, Y.; Liu, Z.; Ding, J.; Ji, B.; Wang, Y.; Guo, Z. Vitexin exerts protective effects against calcium oxalate crystal-induced kidney pyroptosis in vivo and in vitro. *Phytomedicine* **2021**, *86*, 153562. [CrossRef]
89. Alam, W.; Khan, H.; Shah, M.A.; Cauli, O.; Saso, L. Kaempferol as a Dietary Anti-Inflammatory Agent: Current Therapeutic Standing. *Molecules* **2020**, *25*, 4073. [CrossRef]
90. Sharma, D.; Gondaliya, P.; Tiwari, V.; Kalia, K. Kaempferol attenuates diabetic nephropathy by inhibiting RhoA/Rho-kinase mediated inflammatory signalling. *Biomed. Pharm.* **2019**, *109*, 1610–1619. [CrossRef]
91. Hyun, S.K.; Jung, H.A.; Chung, H.Y.; Choi, J.S. In vitro peroxynitrite scavenging activity of 6-hydroxykynurenic acid and other flavonoids fromGingko biloba yellow leaves. *Arch. Pharmacal Res.* **2006**, *29*, 1074–1079. [CrossRef]
92. Lin, C.W.; Chen, P.N.; Chen, M.K.; Yang, W.E.; Tang, C.H.; Yang, S.F.; Hsieh, Y.S. Kaempferol reduces matrix metalloproteinase-2 expression by down-regulating ERK1/2 and the activator protein-1 signaling pathways in oral cancer cells. *PLoS ONE* **2013**, *8*, e80883. [CrossRef]
93. Yuan, P.; Sun, X.; Liu, X.; Hutterer, G.; Pummer, K.; Hager, B.; Ye, Z.; Chen, Z. Kaempferol alleviates calcium oxalate crystal-induced renal injury and crystal deposition via regulation of the AR/NOX2 signaling pathway. *Phytomedicine* **2021**, *86*, 153555. [CrossRef]
94. Ambursa, M.B.; Rahman, M.N.G.; Sulaiman, S.A.; Zakaria, A.D.; Mohamed Daud, M.A.; Zakaria, Z.; Zahari, Z.; Wong, M.P. An In vitro Study of Orthosiphon stamineus (Misai Kucing) Standardized Water Extract as a Chemolytic Agent in Urolithiasis. *J. Pharm. Bioallied Sci.* **2021**, *13*, 373–379. [CrossRef]
95. Zhou, D.; Wu, Y.; Yan, H.; Shen, T.; Li, S.; Gong, J.; Li, G.; Mai, H.; Wang, D.; Tan, X. Gallic acid ameliorates calcium oxalate crystal-induced renal injury via upregulation of Nrf2/HO-1 in the mouse model of stone formation. *Phytomedicine* **2022**, *106*, 154429. [CrossRef]
96. Sohgaura, A.K.; Bigoniya, P.; Shrivastava, B. In Vitro Antilithiatic Potential of Kalanchoe pinnata, Emblica officinalis, Bambusa nutans, and Cynodon dactylon. *J. Pharm. Bioallied Sci.* **2018**, *10*, 83–89. [CrossRef]
97. Salehi, B.; Mishra, A.P.; Nigam, M.; Sener, B.; Kilic, M.; Sharifi-Rad, M.; Fokou, P.V.T.; Martins, N.; Sharifi-Rad, J. Resveratrol: A Double-Edged Sword in Health Benefits. *Biomedicines* **2018**, *6*, 91. [CrossRef]

98. Wu, Y.; Xun, Y.; Zhang, J.; Hu, H.; Qin, B.; Wang, T.; Wang, S.; Li, C.; Lu, Y. Resveratrol Attenuates Oxalate-Induced Renal Oxidative Injury and Calcium Oxalate Crystal Deposition by Regulating TFEB-Induced Autophagy Pathway. *Front. Cell Dev. Biol.* **2021**, *9*, 638759. [CrossRef]
99. Ye, Q.L.; Wang, D.M.; Wang, X.; Zhang, Z.Q.; Tian, Q.X.; Feng, S.Y.; Zhang, Z.H.; Yu, D.X.; Ding, D.M.; Xie, D.D. Sirt1 inhibits kidney stones formation by attenuating calcium oxalate-induced cell injury. *Chem. Biol. Interact.* **2021**, *347*, 109605. [CrossRef]
100. Hewagama, S.P.; Hewawasam, R.P. Antiurolithiatic Potential of Three Sri Lankan Medicinal Plants by the Inhibition of Nucleation, Growth, and Aggregation of Calcium Oxalate Crystals In Vitro. *Sci. World J.* **2022**, *2022*, 8657249. [CrossRef]
101. Guillén-Meléndez, G.A.; Soto-Domínguez, A.; Loera-Arias, M.J.; Castillo-Velázquez, U.; Villa-Cedillo, S.A.; Piña-Mendoza, E.I.; Estrada-Castillón, E.; Chávez-Montes, A.; González-Alcocer, A.; Becerra-Verdín, E.M.; et al. Effect of methanolic extract of Mimosa malacophylla A.Gray in vero and HEK-293 cell lines, and in the morphology of kidney and bladder of rats with induced urolithiasis. *J. Ethnopharmacol.* **2022**, *297*, 115552. [CrossRef]
102. Li, S.; Macaringue, E.G.J.; Zhou, D.; Shi, P.; Tang, W.; Gong, J. Discovering inhibitor molecules for pathological crystallization of CaOx kidney stones from natural extracts of medical herbs. *J. Ethnopharmacol.* **2022**, *284*, 114733. [CrossRef]
103. Moreno, K.G.T.; Gasparotto Junior, A.; Dos Santos, A.C.; Palozi, R.A.C.; Guarnier, L.P.; Marques, A.A.M.; Romão, P.V.M.; Lorençone, B.R.; Cassemiro, N.S.; Silva, D.B.; et al. Nephroprotective and antilithiatic activities of *Costus spicatus* (Jacq.) Sw.: Ethnopharmacological investigation of a species from the Dourados region, Mato Grosso do Sul State, Brazil. *J. Ethnopharmacol.* **2021**, *266*, 113409. [CrossRef]
104. Ye, T.; Yang, X.; Liu, H.; Lv, P.; Lu, H.; Jiang, K.; Peng, E.; Ye, Z.; Chen, Z.; Tang, K. Theaflavin protects against oxalate calcium-induced kidney oxidative stress injury via upregulation of SIRT1. *Int. J. Biol. Sci.* **2021**, *17*, 1050–1060. [CrossRef]
105. Yachi, L.; Bennis, S.; Aliat, Z.; Cheikh, A.; Idrissi, M.O.B.; Draoui, M.; Bouatia, M. In vitro litholytic activity of some medicinal plants on urinary stones. *Afr. J. Urol.* **2018**, *24*, 197–201. [CrossRef]
106. Khan, S.R.; Canales, B.K. Unified theory on the pathogenesis of Randall's plaques and plugs. *Urolithiasis* **2015**, *43* (Suppl. S1), 109–123. [CrossRef]
107. Pandey, K.B.; Rizvi, S.I. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid. Med. Cell. Longev.* **2009**, *2*, 270–278. [CrossRef]