Natural Products in Renal-Associated Drug Discovery

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The global increase in the incidence of kidney failure constitutes a major public health problem. Kidney disease is classified into acute and chronic: acute kidney injury (AKI) is associated with an abrupt decline in kidney function and chronic kidney disease (CKD) with chronic renal failure for more than three months. Although both kidney syndromes are multifactorial, inflammation and oxidative stress play major roles in the diversity of processes leading to these kidney malfunctions.

antioxidant anti-inflammatory AKI CKD

1. Introduction

Chronic kidney disease (CKD) and acute kidney injury (AKI) have emerged as major public health burdens with close connections to each other, AKI as a risk factor for CKD and vice versa and both increasing the risk of cardiovascular disease [1]. CKD is defined by a low glomerular filtration rate (GFR) or the presence of kidney damage for more than 3 months [2][3]. Proteins in urine (proteinuria) and decreased GFR as indicators of kidney damage directly reflect the physical properties of the filter between blood and urine constituted by an endothelial layer, the glomerular basement membrane (GMB) and podocytes [4]. While, under physiological conditions, most proteins cannot traverse this barrier, in proteinuria, larger proteins such as albumin, immunoglobulins G and M and α1-microglobulin and β2-microglobulin, correlating with the severity of the histologic lesions [5], can. These proteins can, as a consequence, impair the reabsorption of other, smaller molecules by proximal tubular epithelial cells and ultimately lead to toxic damage [5]. As risk factors of CKD, there has been a global rise in incidences of diabetes and hypertension [6][7].

AKI is defined by a rapid increase in serum creatinine concentrations and/or decline of urine output. The number of incidences is approximately 10–15% of patients admitted to hospital and approximately more than 50% in intensive care units [8][9]. Distinct time intervals of endurance of the pathological conditions are used to distinguish between AKI (<7 days), acute kidney disease (AKD; 7 days–90 days) and CKD (>90 days) [9]. AKI is now regarded as a multiorgan dysfunctional disease and classified as prerenal AKI, acute postrenal obstructive nephropathy and intrinsic acute kidney disease, of which only the latter is a true renal disease [10][11].

2. Plant-Based Extracts with Antioxidant and Anti-Inflammatory Properties

Natural products have, for centuries, been used in the management of various disease. Mother nature has served and is still serving us well. Plant-based extracts serve as natural sources of antioxidant and anti-inflammatory agents in combating stress, inflammation and cell death. Numerous oxygen-based metabolic activities generate reactive oxygen species, which can serve as signalling molecules. These signalling molecules serve as precursors of various beneficial events for the body. Increased levels of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) oxidative stress are an imbalance in the levels of ROS and the body's natural antioxidant capacity. This creates complications due to ROS reacting with membranes and biomolecules such as lipids and proteins, thus leading to organ damage.

Oxidative stress and inflammation are known to cause various diseases, hence the need to have antioxidants and anti-inflammatory agents that will serve in combating oxidative stress-associated diseases. Increased levels of ROS and RNS are known as potential inducers of kidney injury [12][13][14][15], and molecules associated with ROS and RNS are major regulators of solute and water reabsorption in the kidney [16].

In the assessing and diagnosis of AKI, interleukin-6 (IL-6), interleukin-1 (IL-1), tumour necrosis factor (TNF), adipokines, adhesion molecules and the CD40 ligand are proinflammatory cytokines, which are indicative of the extent of stress or inflammation [17][18][19][20]. Ferguson et al. 2008 [21], Shinke et al. 2015 [22] and Zhou et al. 2008 [23] have also stated the importance of kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) as additional urinary biomarkers.

Medicinal plants naturally have antioxidant systems that help in combating oxidative stress. Superoxide dismutase (SOD), catalase, glutathione (GSH), which helps in drug metabolism detoxification, and glutathione peroxidase (GPx) are the systems that help in combating oxidative stress. Each medicinal plant extract has its own antioxidant-based mechanism for managing oxidative stress. Some increase the levels of SOD [24] and activate the SOD and catalase levels [25][26], while some plants increase the levels and activities of all the three antioxidant enzymes: SOD, catalase and GPx [27][28].

Natural medicinal plants have showed in vivo and in vitro efficacy in downregulating proinflammatory cytokines and upregulating natural antioxidants such as glutathione, which modulates oxidative stress and inflammation. Though modern treatment approaches have also afforded substantial progress in the fight against AKI, potent therapies are still meagre due to a lack of oxidative stress- and inflammation-specific AKI targets. The cost effects coupled with harsh side effects approaches have led to the search for more novel natural biological products, especially those derived from herbs and natural spices. These can all be accessed in medicinal plants due to the various Phyto components present in them. Their uses and applications are promising, since they are able to react, bind, conjugate and possibly eliminate through excretion all reactive oxygen spices (ROS and RNS), which form the bases of most ailments by cell degradation, lipid peroxidation and inflammation, among others.

3. Plant Sources and Activity

Plants have various phytochemicals with the potential to combat ailments. Research on medicinal plants is being carried out mostly in Asia, followed by Africa and Europe. Below are plants, herbs and spices that have been scientifically proven to manage, protect or cure acute kidney injury.

Aronia melanocarpa of the black chokeberry family mostly found in North America contains anthocyanins (cyanidins), which are able to potentially decrease inflammation, oxidative stress and lipid peroxidation, as well as apoptosis, in acute renal ischaemia effectively [29].

Kang et al. 2021 [30] showed that green tea is rich in bioactive compounds. Its aqueous high content of antioxidants has made it active in managing oxidative stress, resulting in the development of various healthy and nutritious detoxification products.

Punica granatum is a plant originally from India. Administration of the fruit peel ethanolic extract in Wistar rats showed improvement in kidney function biomarkers, exerted antioxidant activity and ameliorated histological changes prerenal and intrinsic gentamicin-induced AKI [31][32].

The methanolic peel extract of passion fruit (*Passiflora* spp.), which is predominantly found in North America, contains gallic acid, ellagic acid, kaempferol and quercetin glycosides. The extract is able to protect the kidneys by maintaining the levels of urea and creatinine at normal units during paracetamol-induced nephrotoxicity in albino rats [33]. The methanolic extract of its upper parts reduced the urea and creatinine levels during thioacetamide-induced nephrotoxicity in Sprague–Dawley rats [34].

Pistacia atlantica, an exotic berry-like fruit plant, is mostly be found in North Africa, the Middle East, Iran and Afghanistan. Leaf hydroethanolic extracts of *Pistacia atlantica* have the ability to decrease the levels of urea, creatinine and uric acid during gentamicin-inducted nephrotoxicity in Wistar rats [35].

Eurycoma longifolia is an herbal medicinal plant mostly found in Southeast Asia, Indonesia. The standardised aqueous extract of the roots has been shown to increase the levels and activities of antioxidant enzymes and improves kidney function during paracetamol-induced nephrotoxicity in rats [36].

Costus afer is an African indigenous plant used traditionally for the treatment of several diseases, such as rheumatoid arthritis, hepatic diseases, measles and malaria, and can also serve as an antidote for snake poisoning [37]. The aqueous extract of the leaf has been shown to decrease the serum potassium and BUN levels [38]. It also uses its antioxidant and anti-inflammatory potential to provide neuroprotection against low-dose heavy metal mixed neurotoxicity [39].

Ocimum americanum (family Lamiaceae) grows in Africa, India, China and Southeast Asia and is used as a spice. In Ghana, it is widely cultivated (called akokobesa) [40] and also used by locals to manage diabetes [41]. Nyarko et al. reported that it reduces blood glucose in mice and improved insulin release in beta cells isolated from rats [41]. Genfi et al. reported a hepatoprotective effect of *Ocimum americanum*, probably due to the inhibition of oxidative stress and the downregulation of proinflammatory cytokines [40].

Cranberry (*Vaccinium* sp.) natural extracts from North America decrease E. coli adhesion and reduce bacterial motility and biofilm formation in urinary tract infections [42]. Its polyphenols have anti-inflammatory and antioxidant effects and also have positive effects on the gut flora [43].

Descurainia sophia is a dominant weed with several local names and mostly found in Europe and Northern Africa. Csikós et al. 2021 [44] studied its effect on Wistar rats; its aqueous seed extract decreases the deposition of calcium oxalate in ammonium chloride and ethylene glycol-induced gallbladder stones.

An extract of the aerial parts *Equisetum arvense*, a fern-like plant mostly found in Spain, heals urinary retention and urinary infections, among others [45][46].

The aqueous leaf extract of *Anchomanes difformis* decreases the levels of oxidative stress-associated biomarkers and increases the CAT and SOD levels in African Wistar rats. It has anti-inflammatory effects by reducing the expression of NF-κB and Bcl2 and decreasing the levels of IL-10, IL-18 and TNF [47].

Hibiscus sabdariffa is a plant used for indigenous beverages in most parts of Asia, Africa and Central America. The aqueous extract of the dried flower bulb contains anthocyanins and chlorogenic acid, which increase both the enzymatic and nonenzymatic antioxidant systems [48].

Curcuma longa, a rhizome, is found mostly in India but now has been planted in Ghana. It contains polyphenol and is used for antioxidant, anti-inflammatory, antimicrobial and antitumour activity, among others [49].

The Lamiaceae family *Melissa officinalis* (lemon balm) is a well-known herb indigenously used to cure a variety of ailments [50]. It has glycosides that give it antioxidant and cytotoxic properties [51].

Mostly found across Europe is *Digitalis purpurea* L., a member of the Scrophulariaceae family [52]. The glycosides of D. purpurea have antioxidant and cytotoxic properties. Lycopene, β-carotene and the vitamins of tomato fruits also help to reduce oxidative stress and reduce the risk of cancer [53][54]. Oxidative regulation is paramount in the management of AKI. The aerial parts of Tylophora indica contain alkaloid and tylophorine, which serve as anti-inflammatory and immunosuppressive agents [55]. Lavandula intermedia leaves and flowers have been shown to contain polyphenols, which are significant in providing UV protection [56].

4. Active Ingredients

These plants, herbs and spices serve as antioxidants, anti-inflammatories, anti-malarias, anti-hyperglycaemias and hepatic protectants, among others. This is possible due to the active ingredients in them: flavonoids, alkaloids, saponins, tannins, coumarins, cyanides, anthocyanidins, phenols, phenolics, carotenoids, phytoestrogens [57][58], capsaicin [59][60], curcumin [61], β-carotene [62][63], catechins [64][65], resveratrol [66], vitamins, flavonoids (hyperoxide) and xanthones, as well as naphthodianthrone hypericin (antiviral action), the phloroglucinol derivative hyperforin (antibacterial effect) [67], cardiac glycosides [68], flavonoids, anthraquinones and triterpenes [69][70][71][72].

References

1. Chawla, L.S.; Eggers, P.W.; Star, R.A.; Kimmel, P.L. Acute Kidney Injury and Chronic Kidney Disease as Interconnected Syndromes. N. Engl. J. Med. 2014, 371, 58–66.
2. Levey, A.S.; Coresh, J. Chronic Kidney Disease. Lancet 2012, 379, 165–180.
3. Levey, A.S.; Coresh, J.; Balk, E.; Kausz, A.T.; Levin, A.; Steffes, M.W.; Hogg, R.J.; Perrone, R.D.; Lau, J.; Eknoyan, G.; et al. National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Ann. Intern. Med. 2003, 139, 137–147.
4. Wruck, W.; Boima, V.; Erichsen, L.; Thimm, C.; Koranteng, T.; Kwakyi, E.; Antwi, S.; Adu, D.; Adjaye, J. Urine-Based Detection of Biomarkers Indicative of Chronic Kidney Disease in a Patient Cohort from Ghana. J. Pers. Med. 2022, 13, 38.
5. D'Amico, G.; Bazzi, C. Pathophysiology of Proteinuria. Kidney Int. 2003, 63, 809–825.
6. Schena, F.P.; Gesualdo, L. Pathogenetic Mechanisms of Diabetic Nephropathy. J. Am. Soc. Nephrol. 2005, 16, S30–S33.
7. Webster, A.C.; Nagler, E.V.; Morton, R.L.; Masson, P. Chronic Kidney Disease. Lancet 2017, 389, 1238–1252.
8. Al-Jaghbeer, M.; Dealmeida, D.; Bilderback, A.; Ambrosino, R.; Kellum, J.A. Clinical Decision Support for In-Hospital AKI. J. Am. Soc. Nephrol. JASN 2018, 29, 654–660.
9. Ronco, C.; Bellomo, R.; Kellum, J.A. Acute Kidney Injury. Lancet 2019, 394, 1949–1964.
10. Makris, K.; Spanou, L. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. Clin. Biochem. Rev. 2016, 37, 85–98.
11. Erichsen, L.; Thimm, C.; Wruck, W.; Kaierle, D.; Schless, M.; Huthmann, L.; Dimski, T.; Kindgen-Milles, D.; Brandenburger, T.; Adjaye, J. Secreted Cytokines within the Urine of AKI Patients Modulate TP53 and SIRT1 Levels in a Human Podocyte Cell Model. Int. J. Mol. Sci. 2023, 24, 8228.
12. Wu, L.; Gokden, N.; Mayeux, P.R. Evidence for the Role of Reactive Nitrogen Species in Polymicrobial Sepsis-Induced Renal Peritubular Capillary Dysfunction and Tubular Injury. J. Am. Soc. Nephrol. 2007, 18, 1807–1815.
13. Bonventre, J.V.; Zuk, A. Ischemic Acute Renal Failure: An Inflammatory Disease? Kidney Int. 2004, 66, 480–485.
14. Nath, K.A.; Norby, S.M. Reactive Oxygen Species and Acute Renal Failure. Am. J. Med. 2000, 109, 665–678.

15. Zhu, Y.; Huang, J.; Chen, X.; Xie, J.; Yang, Q.; Wang, J.; Deng, X. Senkyunolide I Alleviates Renal Ischemia-Reperfusion Injury by Inhibiting Oxidative Stress, Endoplasmic Reticulum Stress and Apoptosis. Int. Immunopharmacol. 2022, 102, 108393.
16. Ishimoto, Y.; Tanaka, T.; Yoshida, Y.; Inagi, R. Physiological and Pathophysiological Role of Reactive Oxygen Species and Reactive Nitrogen Species in the Kidney. Clin. Exp. Pharmacol. Physiol. 2018, 45, 1097–1105.
17. Su, H.; Lei, C.-T.; Zhang, C. Interleukin-6 Signaling Pathway and Its Role in Kidney Disease: An Update. Front. Immunol. 2017, 8, 405.
18. Magno, A.; Herat, L.; Carnagarin, R.; Schlaich, M.; Matthews, V. Current Knowledge of IL-6 Cytokine Family Members in Acute and Chronic Kidney Disease. Biomedicines 2019, 7, 19.
19. Bonventre, J.V.; Yang, L. Cellular Pathophysiology of Ischemic Acute Kidney Injury. J. Clin. Investig. 2011, 121, 4210–4221.
20. Xu, C.; Chang, A.; Hack, B.K.; Eadon, M.T.; Alper, S.L.; Cunningham, P.N. TNF-Mediated Damage to Glomerular Endothelium Is an Important Determinant of Acute Kidney Injury in Sepsis. Kidney Int. 2014, 85, 72–81.
21. Ferguson, M.A.; Vaidya, V.S.; Bonventre, J.V. Biomarkers of Nephrotoxic Acute Kidney Injury. Toxicology 2008, 245, 182–193.
22. Shinke, H.; Masuda, S.; Togashi, Y.; Ikemi, Y.; Ozawa, A.; Sato, T.; Kim, Y.H.; Mishima, M.; Ichimura, T.; Bonventre, J.V.; et al. Urinary Kidney Injury Molecule-1 and Monocyte Chemotactic Protein-1 Are Noninvasive Biomarkers of Cisplatin-Induced Nephrotoxicity in Lung Cancer Patients. Cancer Chemother. Pharmacol. 2015, 76, 989–996.
23. Zhou, Y.; Vaidya, V.S.; Brown, R.P.; Zhang, J.; Rosenzweig, B.A.; Thompson, K.L.; Miller, T.J.; Bonventre, J.V.; Goering, P.L. Comparison of Kidney Injury Molecule-1 and Other Nephrotoxicity Biomarkers in Urine and Kidney Following Acute Exposure to Gentamicin, Mercury, and Chromium. Toxicol. Sci. 2008, 101, 159–170.
24. Choucry, M.A.; Khalil, M.N.A.; El Awdan, S.A. Protective Action of Crateva Nurvala Buch. Ham Extracts against Renal Ischaemia Reperfusion Injury in Rats via Antioxidant and Anti-Inflammatory Activities. J. Ethnopharmacol. 2018, 214, 47–57.
25. Liu, Y.; Shi, B.; Li, Y.; Zhang, H. Protective Effect of Luteolin Against Renal Ischemia/Reperfusion Injury via Modulation of Pro-Inflammatory Cytokines, Oxidative Stress and Apoptosis for Possible Benefit in Kidney Transplant. Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 2017, 23, 5720–5727.
26. Punuru, P.; Sujatha, D.; Kumari, B.P.; Charisma, V.V.L. Evaluation of Aqueous Extract of Murraya Koenigii in Unilateral Renal Ischemia Reperfusion Injury in Rats. Indian J. Pharmacol. 2014, 46, 171–175.

27. Long, C.; Yang, J.; Yang, H.; Li, X.; Wang, G. Attenuation of Renal Ischemia/Reperfusion Injury by Oleanolic Acid Preconditioning via Its Antioxidant, Anti-Inflammatory, and Anti-Apoptotic Activities. Mol. Med. Rep. 2016, 13, 4697–4704.
28. Meng, Q.; Liu, H.; Wang, J. Polydatin Ameliorates Renal Ischemia/Reperfusion Injury by Decreasing Apoptosis and Oxidative Stress through Activating Sonic Hedgehog Signaling Pathway. Food Chem. Toxicol. 2016, 96, 215–225.
29. Ren, Y.; Frank, T.; Meyer, G.; Lei, J.; Grebenc, J.R.; Slaughter, R.; Gao, Y.G.; Kinghorn, A.D. Potential Benefits of Black Chokeberry (Aronia melanocarpa) Fruits and Their Constituents in Improving Human Health. Mol. Basel Switz. 2022, 27, 7823.
30. Kang, H.G.; Lee, H.K.; Cho, K.B.; Park, S.I. A Review of Natural Products for Prevention of Acute Kidney Injury. Medicina (Mex.) 2021, 57, 1266.
31. Mestry, S.N.; Gawali, N.B.; Pai, S.A.; Gursahani, M.S.; Dhodi, J.B.; Munshi, R.; Juvekar, A.R. Punica Granatum Improves Renal Function in Gentamicin-Induced Nephropathy in Rats via Attenuation of Oxidative Stress. J. Ayurveda Integr. Med. 2020, 11, 16–23.
32. El Bohi, K.M.; Abdel-Motal, S.M.; Khalil, S.R.; Abd-Elaal, M.M.; Metwally, M.M.M.; ELhady, W.M. The Efficiency of Pomegranate (Punica granatum) Peel Ethanolic Extract in Attenuating the Vancomycin-Triggered Liver and Kidney Tissues Injury in Rats. Environ. Sci. Pollut. Res. 2021, 28, 7134–7150.
33. Nerdy, N.; Ritarwan, K. Hepatoprotective Activity and Nephroprotective Activity of Peel Extract from Three Varieties of the Passion Fruit (Passiflora sp.) in the Albino Rat. Open Access Maced. J. Med. Sci. 2019, 7, 536–542.
34. Al-Yousef, H.M.; Alqahtani, A.S.; Ghani, A.S.A.; El-Toumy, S.A.; El-Dougdoug, W.I.A.; Hassan, W.H.B.; Hassan, H.M. Nephroprotective, Cytotoxic and Antioxidant Activities of Euphorbia Paralias. Saudi J. Biol. Sci. 2021, 28, 785–792.
35. Heidarian, E.; Jafari-Dehkordi, E.; Valipour, P.; Ghatreh-Samani, K.; Ashrafi-Eshkaftaki, L. Nephroprotective and Anti-Inflammatory Effects of Pistacia atlantica Leaf Hydroethanolic Extract Against Gentamicin-Induced Nephrotoxicity in Rats. J. Diet. Suppl. 2017, 14, 489–502.
36. Chinnappan, S.M.; George, A.; Thaggikuppe, P.; Choudhary, Y.; Choudhary, V.K.; Ramani, Y.; Dewangan, R. Nephroprotective Effect of Herbal Extract Eurycoma longifolia on Paracetamol-Induced Nephrotoxicity in Rats. Evid. Based Complement. Alternat. Med. 2019, 2019, 4916519.
37. Anyasor, G.N.; Onajobi, F.D.; Osilesi, O.; Adebawo, O. Proximate Composition, Mineral Content and in Vitro Antioxidant Activity of Leaf and Stem of Costus afer (Ginger Lily). J. Intercult. Ethnopharmacol. 2014, 3, 128–134.
38. Ezejiofor, A.N.; Udowelle, N.A.; Orisakwe, O.E. Nephroprotective and Antioxidant Effect of Aqueous Leaf Extract of Costus Afer Ker Gawl on Cyclosporin-a (Csa) Induced Nephrotoxicity.

Clin. Phytoscience 2017, 2, 11.

39. Anyanwu, B.O.; Orish, C.N.; Ezejiofor, A.N.; Nwaogazie, I.L.; Orisakwe, O.E. Neuroprotective Effect of Costus Afer on Low Dose Heavy Metal Mixture (Lead, Cadmium and Mercury) Induced Neurotoxicity via Antioxidant, Anti-Inflammatory Activities. Toxicol. Rep. 2020, 7, 1032–1038.
40. Genfi, A.K.A.; Larbie, C.; Emikpe, B.O.; Oyagbemi, A.A.; Firempong, C.K.; Adjei, C.O. Modulation of Oxidative Stress and Inflammatory Cytokines as Therapeutic Mechanisms of Ocimum Americanum L Extract in Carbon Tetrachloride and Acetaminophen-Induced Toxicity in Rats. J. Evid.-Based Integr. Med. 2020, 25, 2515690X2093800.
41. Nyarko, A.K.; Asare-Anane, H.; Ofosuhene, M.; Addy, M.E. Extract of Ocimum Canum Lowers Blood Glucose and Facilitates Insulin Release by Isolated Pancreatic β-Islet Cells. Phytomedicine 2002, 9, 346–351.
42. Ranfaing, J.; Dunyach-Remy, C.; Louis, L.; Lavigne, J.-P.; Sotto, A. Propolis Potentiates the Effect of Cranberry (Vaccinium macrocarpon) against the Virulence of Uropathogenic Escherichia Coli. Sci. Rep. 2018, 8, 10706.
43. Amin, R.; Thalluri, C.; Docea, A.O.; Sharifi-Rad, J.; Calina, D. Therapeutic Potential of Cranberry for Kidney Health and Diseases. eFood 2022, 3, e33.
44. Csikós, E.; Horváth, A.; Ács, K.; Papp, N.; Balázs, V.L.; Dolenc, M.S.; Kenda, M.; Kočevar Glavač, N.; Nagy, M.; Protti, M.; et al. Treatment of Benign Prostatic Hyperplasia by Natural Drugs. Molecules 2021, 26, 7141.
45. Carneiro, D.M.; Freire, R.C.; Honório, T.C.D.D.; Zoghaib, I.; Cardoso, F.F.D.S.E.S.; Tresvenzol, L.M.F.; De Paula, J.R.; Sousa, A.L.L.; Jardim, P.C.B.V.; Cunha, L.C.D. Randomized, Double-Blind Clinical Trial to Assess the Acute Diuretic Effect of Equisetum arvense (Field Horsetail) in Healthy Volunteers. Evid. Based Complement. Alternat. Med. 2014, 2014, 760683.
46. Pallag, A.; Filip, G.A.; Olteanu, D.; Clichici, S.; Baldea, I.; Jurca, T.; Micle, O.; Vicaş, L.; Marian, E.; Soriţău, O.; et al. Equisetum arvense L. Extract Induces Antibacterial Activity and Modulates Oxidative Stress, Inflammation, and Apoptosis in Endothelial Vascular Cells Exposed to Hyperosmotic Stress. Oxid. Med. Cell. Longev. 2018, 2018, 3060525.
47. Alabi, T.D.; Brooks, N.L.; Oguntibeju, O.O. Leaf Extracts of Anchomanes Difformis Ameliorated Kidney and Pancreatic Damage in Type 2 Diabetes. Plants 2021, 10, 300.
48. Rodríguez-Fierros, F.L.; Guarner-Lans, V.; Soto, M.E.; Manzano-Pech, L.; Díaz-Díaz, E.; Soria-Castro, E.; Rubio-Ruiz, M.E.; Jiménez-Trejo, F.; Pérez-Torres, I. Modulation of Renal Function in a Metabolic Syndrome Rat Model by Antioxidants in Hibiscus sabdariffa L. Molecules 2021, 26, 2074.
49. Benzer, F.; Kandemir, F.M.; Kucukler, S.; Comaklı, S.; Caglayan, C. Chemoprotective Effects of Curcumin on Doxorubicin-Induced Nephrotoxicity in Wistar Rats: By Modulating Inflammatory

Cytokines, Apoptosis, Oxidative Stress and Oxidative DNA Damage. Arch. Physiol. Biochem. 2018, 124, 448–457.

50. Akhondzadeh, S. Melissa Officinalis Extract in the Treatment of Patients with Mild to Moderate Alzheimer's Disease: A Double Blind, Randomised, Placebo Controlled Trial. J. Neurol. Neurosurg. Psychiatry 2003, 74, 863–866.
51. Zarei, A.; Changizi-Ashtiyani, S.; Taheri, S.; Hosseini, N. A Brief Overview of the Effects of Melissa Officinalis L. Extract on the Function of Various Body Organs. Zahedan J. Res. Med. Sci. 2015, 17.
52. Haji, S.A.; Movahed, A. Update on Digoxin Therapy in Congestive Heart Failure. Am. Fam. Physician 2000, 62, 409–416.
53. Sesso, H.D.; Liu, S.; Gaziano, J.M.; Buring, J.E. Dietary Lycopene, Tomato-Based Food Products and Cardiovascular Disease in Women. J. Nutr. 2003, 133, 2336–2341.
54. Viuda-Martos, M.; Sanchez-Zapata, E.; Sayas-Barberá, E.; Sendra, E.; Pérez-Álvarez, J.A.; Fernández-López, J. Tomato and Tomato Byproducts. Human Health Benefits of Lycopene and Its Application to Meat Products: A Review. Crit. Rev. Food Sci. Nutr. 2014, 54, 1032–1049.
55. Chaudhuri, K.N.; Ghosh, B.; Tepfer, D.; Jha, S. Genetic Transformation of Tylophora Indica with Agrobacterium rhizogenes A4: Growth and Tylophorine Productivity in Different Transformed Root Clones. Plant Cell Rep. 2005, 24, 25–35.
56. Brglez Mojzer, E.; Knez Hrnčič, M.; Škerget, M.; Knez, Ž.; Bren, U. Polyphenols: Extraction Methods, Antioxidative Action, Bioavailability and Anticarcinogenic Effects. Molecules 2016, 21, 901.
57. Sirotkin, A.V.; Harrath, A.H. Phytoestrogens and Their Effects. Eur. J. Pharmacol. 2014, 741, 230–236.
58. Velasquez, M.T.; Bhathena, S.J. Dietary Phytoestrogens: A Possible Role in Renal Disease Protection. Am. J. Kidney Dis. 2001, 37, 1056–1068.
59. Ríos-Silva, M.; Santos-Álvarez, R.; Trujillo, X.; Cárdenas-María, R.; López-Zamudio, M.; Bricio-Barrios, J.; Leal, C.; Saavedra-Molina, A.; Huerta-Trujillo, M.; Espinoza-Mejía, K.; et al. Effects of Chronic Administration of Capsaicin on Biomarkers of Kidney Injury in Male Wistar Rats with Experimental Diabetes. Molecules 2018, 24, 36.
60. Sharma, S.K.; Vij, A.S.; Sharma, M. Mechanisms and Clinical Uses of Capsaicin. Eur. J. Pharmacol. 2013, 720, 55–62.
61. Hewlings, S.; Kalman, D. Curcumin: A Review of Its Effects on Human Health. Foods 2017, 6, 92.
62. Akkara, P.J.; Sabina, E.P. Pre-Treatment with Beta Carotene Gives Protection Against Nephrotoxicity Induced by Bromobenzene via Modulation of Antioxidant System, Pro-

Inflammatory Cytokines and Pro-Apoptotic Factors. Appl. Biochem. Biotechnol. 2020, 190, 616–633.

63. Pryor, W.A.; Stahl, W.; Rock, C.L. Beta Carotene: From Biochemistry to Clinical Trials. Nutr. Rev. 2009, 58, 39–53.
64. Higdon, J.V.; Frei, B. Tea Catechins and Polyphenols: Health Effects, Metabolism, and Antioxidant Functions. Crit. Rev. Food Sci. Nutr. 2003, 43, 89–143.
65. Wongmekiat, O.; Peerapanyasut, W.; Kobroob, A. Catechin Supplementation Prevents Kidney Damage in Rats Repeatedly Exposed to Cadmium through Mitochondrial Protection. Naunyn. Schmiedebergs Arch. Pharmacol. 2018, 391, 385–394.
66. Baur, J.A.; Sinclair, D.A. Therapeutic Potential of Resveratrol: The In Vivo Evidence. Nat. Rev. Drug Discov. 2006, 5, 493–506.
67. Schempp, C.M.; Pelz, K.; Wittmer, A.; Schöpf, E.; Simon, J.C. Antibacterial Activity of Hyperforin from St John's Wort, against Multiresistant Staphylococcus Aureus and Gram-Positive Bacteria. Lancet 1999, 353, 2129.
68. Prassas, I.; Diamandis, E.P. Novel Therapeutic Applications of Cardiac Glycosides. Nat. Rev. Drug Discov. 2008, 7, 926–935.
69. Harvey, A. Natural Products in Drug Discovery. Drug Discov. Today 2008, 13, 894–901.
70. Thomford, N.; Senthebane, D.; Rowe, A.; Munro, D.; Seele, P.; Maroyi, A.; Dzobo, K. Natural Products for Drug Discovery in the 21st Century: Innovations for Novel Drug Discovery. Int. J. Mol. Sci. 2018, 19, 1578.
71. Alice, C.B.; Vargas, V.M.F.; Silva, G.A.A.B.; De Siqueira, N.C.S.; Schapoval, E.E.S.; Gleye, J.; Henriques, J.A.P.; Henriques, A.T. Screening of Plants Used in South Brazilian Folk Medicine. J. Ethnopharmacol. 1991, 35, 165–171.
72. Adebayo, J.O.; Krettli, A.U. Potential Antimalarials from Nigerian Plants: A Review. J. Ethnopharmacol. 2011, 133, 289–302.