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Complete List of Authors:	Lee, Vanessa; UC Davis, Chemistry Janisse, Samuel; University of California, Davis, Chemistry Heffern, Marie; University of California, Davis, Chemistry

Plant-Derived Chelators and Ionophores as Potential Therapeutics for Metabolic Diseases

Vanessa J. Lee, Samuel E. Janisse, Marie C. Heffern*

[a]*Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616*
[*]*To whom correspondence may be addressed: mcheffern@ucdavis.edu*

Abstract

Transition metal dysregulation is associated with a host of pathologies, many of which are therapeutically targeted using chelators and ionophores. Chelators and ionophores are used as therapeutic metal-binding compounds which impart biological effects by sequestering or trafficking endogenous metal ions in an effort to restore homeostasis. Many current therapies take inspiration or derive directly from small molecules and peptides found in plants. This review focuses on plant-derived small molecule and peptide chelators and ionophores that can affect metabolic disease states. Understanding the coordination chemistry, bioavailability, and bioactivity of such molecules provides the tools to further research applications of plant-based chelators and ionophores.

1. Brief Introduction to Chelators and Ionophores in Therapy

Transition metals are pervasive in biology and are increasingly recognized for their essential biological activity beyond their traditional role as tightly bound structural cofactors. It has long been established that redox-active transition metals serve as static cofactors for an estimated one-third of all proteins as well as DNA and RNA.[1] Conversely, the main group alkali earth metals that are identified for participation in signaling pathways use labile metal pools.[2] Progressively however, transition metals (most notably copper, iron, zinc, and manganese) are being studied for their involvement in signaling pathways through labile pools.[3] The makeup of these populations remains elusive, but observed differences in labile transition metal pools is associated with a host of disease states.[4–6]

Due to their potential toxicity, transition metals are tightly regulated in biology. Dysregulation of transition metals is correlated with a wide range of pathologies including cancer, cardiovascular disease, neurodegenerative diseases, and metabolic diseases.[7–12] Metabolic diseases include inherited disorders, such as Wilson and Menkes diseases, and chronic conditions including diabetes mellitus and non-alcoholic fatty liver disease (NAFLD). Some metabolic diseases, like Wilson and Menkes diseases, have clear connections to metal metabolism through mutations in metal trafficking proteins. Others, including NAFLD and metabolic syndrome, have no direct relationship to metal metabolism, but have been correlated with transition metal dysregulation[7,12] As such, treatments for these diseases include attempts to restore metal homeostasis through employment of chelators and ionophores (Figure 1).

Chelation therapy is well-established in the treatment of Wilson disease and has gone through clinical trials for the treatment of cancer and Alzheimer's disease.[7,13,14] These treatments use chelators which are small molecules that selectively bind, sequester, and evacuate metal ions from the cell. Conversely, ionophores are small molecules that bind and import metal ions into the cell circumventing standard metal ion importers. While chelators and ionophores serve different purposes, they share necessary properties for metal trafficking. These properties include a low molecular weight, hydrophobicity that is sufficient for crossing cell membranes, and the ability to specifically bind metal ions.[15–18]

Medicinal chemistry has long taken inspiration from nature, with many drug candidates emulate small molecules and peptides found in plants.[19] Due to the association between many chronic metabolic diseases and diet, it is natural to look towards food sources in treatments of such diseases. This review will focus on plant-derived small molecules towards therapy for metabolic diseases. One of the common health benefits of plant products is antioxidant activity.[20] Classes of small molecules such as polyphenols and carotenoids have long been studied for radical scavenging activity and protection against oxidative stress. These small molecules often possess antioxidant activity through interactions with metal ions. Metal ions such as iron and copper perform Fenton or Fenton-like chemistry which is a source of reactive oxygen species (ROS).[21,22] ROS production is linked to metabolic regulation, and as such, perturbation in ROS production is associated with metabolic diseases. For detailed information on the pathways affected by ROS production in metabolic regulation, see the review by Forrester et al.[23] Oxidative damage induced by redox-active metals can be combatted by reduction or chelation of said metal ions. Thus, small molecules that can bind metal ions may reduce their reactivity and thereby reduce oxidative stress. However, some plant-based chelators and ionophores may offer their beneficial effect independent of their redox activity, but the mechanisms for such activity remain uncertain. The bioactivities discussed in this review are subdivided into structural categories of plant-based molecules in an effort to highlight molecular components that may be associated with function.

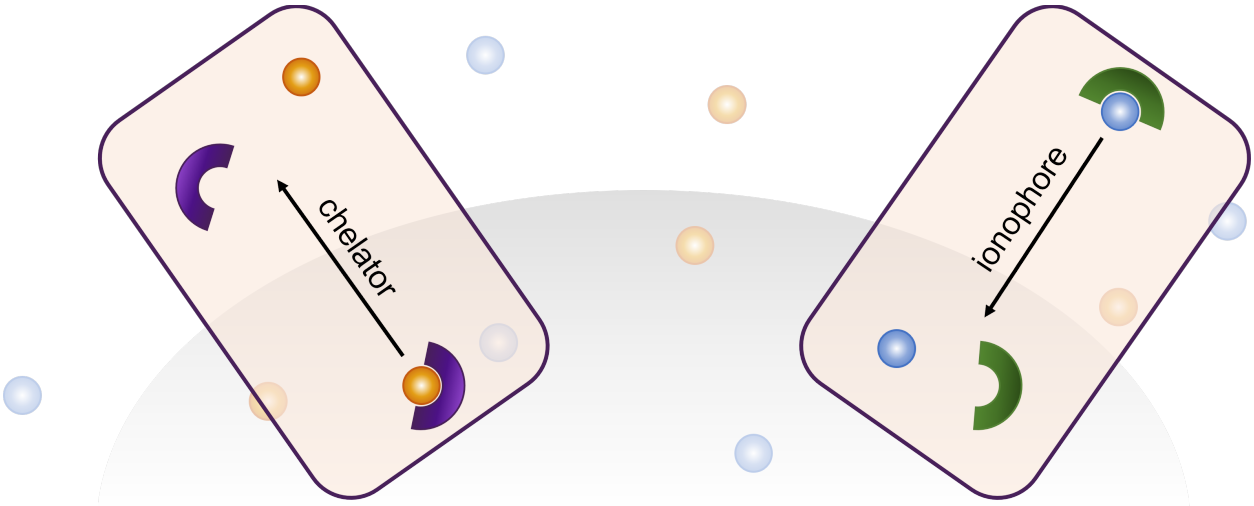

Figure 1: Chelators (purple arcs) are small molecules that can cross cell membranes, bind metal ions (represented by spheres; the different colors – blue and orange – convey the presence of different metal ions), and subsequently evacuate bound ions from the cell. Conversely, ionophores (green arcs) are small molecules that extracellularly bind metal ions and import them into the cell passing through the cell membrane.

2. Background on Metal Dysregulation in Metabolic Diseases and Therapeutic Applications of Metal Binders

2.1 Hereditary Diseases Related to Metal Dysregulation

2.1.1 Wilson Disease

Wilson disease (WD) is a hereditary disease affecting an estimated 1 in 30,000[24] people worldwide. WD involves a mutation in the ATPase copper transporting beta protein (ATP7B) resulting in the obliteration of the copper transporter's ability to export copper via the biliary excretion pathway and uncontrolled copper accumulation in several organs (Figure 2).[25] The copper overload in patients with WD leads to deleterious neurological and hepatic outcomes, such as steatosis and cirrhosis.[26–28] While the exact mechanisms of liver damage in WD is unclear, the generation of excess oxidative stress due to the buildup of copper culminating in an increase in lipid peroxidation and hepatic dysfunction.[29,30] Moreover, the reduction in intracellular copper transport from the mutation in ATP7B prevents adequate copper loading into the ferroxidase ceruloplasmin as it matures through the trans-Golgi network.[31] This results in a drastic increase of apoceruloplasmin, or non-copper binding ceruloplasmin, relative to holoceruloplasmin which contains copper. Currently, the diagnostic criteria for WD involves screening patients relies on serum ceruloplasmin and copper levels, which are often significantly lower and higher, respectively.[27,28] The increase in non-ceruloplasmin bound copper is believed to be a direct result of the release of copper from degrading hepatocytes.[27,32]

Although damage can occur if copper imbalance in not remedied, if diagnosed early, WD can be managed.

Current treatments include zinc supplementation and copper chelator therapy. Zinc supplementation is believed to inhibit copper uptake in the gastrointestinal tract by inducing metallothionine production,[33] which in turn results in increased metallothionein bound copper and subsequent excretion by intestinal sloughing.[34]. While zinc supplementation has consistently been effective in WD maintenance, it has been suggested that it is not as effective as chelating therapies in preventing liver damage.[35] Chelation therapy for WD was first suggested in the early 1950's when researchers found that administering 2,3-dimercaptopropalol (also called BAL) lead to a significant decrease in neurological symptoms observed in patients.[36] However, despite BAL showing a profound impact in increasing quality and length of life for patients with WD, it required regular invasive intramuscular injection, prompting the development more accessible treatments.[37]

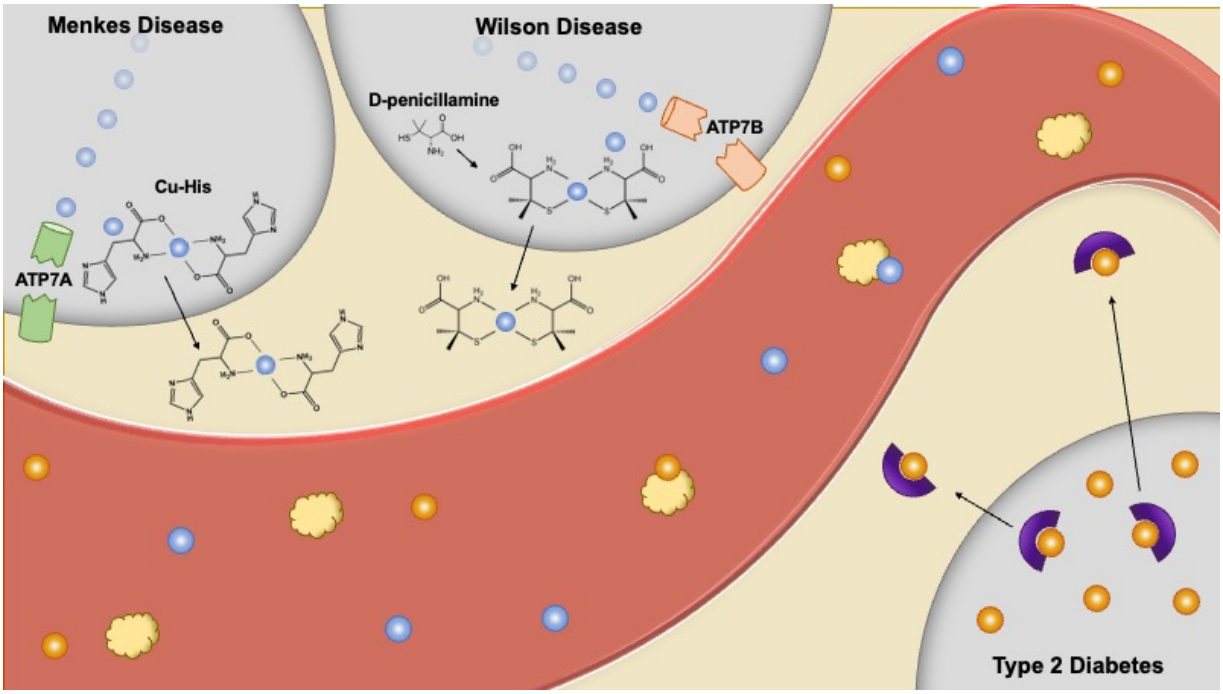

Figure 2: Hereditary diseases including Menkes and Wilson diseases are linked to mutations in copper-trafficking proteins. These mutations result in dysregulation of copper populations and subsequent detrimental symptoms. Chelates are clinically employed for management and treatment of these disease. Symptoms of metabolic disorders such as type 2 diabetes are alleviated by molecules known to have chelation or ionophoric properties (indicated with purple arcs), but their mechanisms of action require further investigation. While blue spheres represent copper centers and orange spheres represent iron centers in the figure, further mechanistic insight is required to determine chelator selectivity *in vivo* as well as the role and interaction metal-binding serum proteins (yellow blobs) may play in metal availability and ligand exchange.

The most common chelators used in current treatments of WD are D-penicillamine (DPA) and trientine (TETA), which are taken orally. DPA, first used as a therapeutic

1956,[38] contains three main functional groups: thiol, amine, and carboxylic acid. D-penicillamine is reported to be a bidentate chelator binding copper(I) with the amine and thiol functional group and a tridentate chelator for copper(II) where the carboxylate is thought to participate.[39] Once binding to copper, the D-penicillamine-copper complex is excreted via the urine. While an improvement to BAL, DPA has been associated with various disadvantageous side effects, such as gastrointestinal irritation, cytopenia, proteinuria, myasthenic syndrome, and degenerative dermopathy.[40,41] Triene is the other commonly administered copper chelator used to treat WD. TETA is a polyamine containing a total of four nitrogen groups with two primary amines and two additional secondary amines separated by two aliphatic carbons (-CH_2CH_2-). The four nitrogen atoms coordinate copper resulting in a square planar complex. Similar to DPA, once copper is bound by TETA it is excreted via the kidneys. Moreover, it has been shown to have efficacy in reducing copper absorption if taken prior to eating. However, despite TETA being distributed throughout various tissues post administration, the copper pool that TETA chelates is believed to be primarily in the blood whereas DPA can extract copper from tissues.[42]

2.1.2 Menkes disease

Menkes disease (MD), and the less severe occipital horn syndrome (OHS), is another hereditary disease involving the dysregulation of copper.[43] The X-linked genetic disorder involves the mutation of the copper transporter ATP7A, which regulates copper by utilizing ATP to transport copper across cell membranes. Classical MD is often lethal with an average life expectancy of less than three years[44] while those with OHS exhibit a longer lifespan. ATP7A is heavily involved in the transport of copper from the intestine after import by CTR1 and DMT1 into the blood where it is transported to the liver and other organs for utilization in various proteins. Mutations in ATP7A result in the aberrant transport of copper through the intestine resulting is low copper levels in serum, liver, and brain.[45] Diagnosis does not usually occur until the age of 3-6 months due to the appearance of hypopigmented hair that is prone to fraying, failure to thrive, vomiting, diarrhea, and loss consistent seizures. Later symptoms often include blindness, respiratory failure, and vascular complications which ultimately lead to death.

Currently, the only treatment of MD and OHS is through the subcutaneous injection of copper histidine (CuHis), which is comprised of copper coordinated by histidine in a 1:2 stochometric ratio. Early and sustained intervention with CuHis leads to an increase in life expectancy and been shown to increase serum copper, CSF copper, and ceruloplasmin levels.[46–48] The mechanism of action has not been fully elucidated, however, the injection of CuHis complex into the subcutaneous tissues bypasses the gastrointestinal track and is introduced in the bloodstream. Once in the bloodstream the copper can be chelated by the various copper chelating proteins, such as albumin, or exist as the CuHis.

2.2 Metabolic Diseases with Genetic and Environmental Contributions

2.2.1 Type 2 Diabetes, Obesity, and Metabolic Syndrome

Type 2 diabetes mellitus (T2D) is a rapidly expanding disease affecting millions of people worldwide. It is a metabolic disorder involving the dysregulation of lipid and glucose metabolism. The dysregulation has been directly linked to impaired insulin secretion by the pancreas and insulin resistance in peripherical tissues such as the liver and adipose.[49,50] Various factors have been associated with the onset of T2D including the dysregulation of metal micronutrients, such as iron, copper, and zinc.[51,52] In patients with T2D, there is a positive association between serum copper to zinc ratios T2D as well as glycated hemoglobin.[53]

The association with iron and T2D has been observed in patients with hereditary hemostasis (HH) which is an iron disorder leading to iron accumulation in various tissues and increased serum ferritin.[54,55] However, there is a growing interest on the role of dietary iron and non-hereditary iron overload with T2D disease progression.[56] The use of iron chelators to treat iron overload has been well documented with various animal studies illustrating their utility. Early studies showed that obese (ob/ob lep-/-) mice were protected from deleterious effects of diabetes onset such as glucose intolerance and insulin resistance by the iron chelator FBS0701 administration.[57] Moreover, it was found that 15 day interparental administration of deferoxamine (DFO) for 15 days led to decreased insulin resistance in adipose tissues of ob/ob mice.[58] The exact mechanism of these preventative outcomes have yet to be fully elucidated. One explanation is there is a reduction of oxidative stress associated with dysregulated iron levels that produce reactive oxygen species (ROS). The increase of ROS can lead to lipid peroxidation and advanced glycation end products.[58–60] There seems to be a link between iron chelation and preventing excess weight gain, which has been linked to a decrease in systemic oxidative stress. A recent study showed that mice who were fed a high fat diet supplemented with the iron chelator deferasirox (DFS) weighed less than non-chelator high fat diet (HFD) control and obese mice on a HFD supplemented with DFS also led to a reduction in weight gained compared to HFD ob/ob mice.[61]

Flavonoids have been linked to a decrease in T2D prevalence, obesity, and involved in glucose metabolism. A cross-sectional study showed a strong negative association between daily quercetin intake and the prevalence of T2D[62] while another study showed that daily flavonoid intake lead to a lower prevalence of diabetes and the inflammation marker – C-reactive protein.[63] Moreover, the daily intake of flavonoids was found inversely related to the prevalence of obesity. Administration of quercetin to Sprague-Dawley rats with streptozocin induced diabetes showed improvements in hepatic glucose and lipid metabolism through increased Akt activity.[64] Studies conducted in skeletal muscle L6 myotubes showed that quercetin acts through the AMPK pathway in a manner similar to metformin,[65] as well as GLUT4 translocation to the membrane in mouse skeletal muscle[66]. A further link between the beneficial aspects of dietary quercetin and the reduction of ferroptosis, a mechanism in which lipid peroxidation catalyzed by iron leads to programmed cell death, was demonstrated in mouse pancreatic islets.[67]

Interestingly, the authors also found that administration of DFO resulted in similar protective outcomes for ferroptosis induced by high glucose, potentially suggesting a mechanism where quercetin directly interacts with iron to prevent the generation of ROS, protecting the cell from the onset of ferroptosis.

2.2.2 Cancer

Cancer is defined by a dysregulation of biochemical processes that govern proper cell homeostasis, leading to uncontrolled cell proliferation and resistance to cell death.[68] Aberrant metal micronutrients levels, such as copper, have been linked to various types of cancers.[69–72] Copper levels in the tumor microenvironment have been directly related to cancer cell proliferation and angiogenesis.[73] The mechanism of how metals such as copper influence tumor progression and metastasis is relatively unexplored. However, recent research has elucidated copper trafficking through ATP7A, ATOX1, and LOX as a key pathway in breast cancer migration.[74] Furthermore, recent studies have elucidated copper as a key regulator of the autophagic kinases ULK1/2 through direct metal binding in lung adenocarcinoma.[75]

Due to the role of copper in cancer progression, there is growing interest in the application of copper depletion therapies for cancer treatments. Application of the copper chelator tetrathiomolybdate (TM) decreases the metastases of triple negative breast cancer to the lungs.[76] The exact mechanism of TM reducing cancer metastasis remains elusive, but recent research illustrates a link between the tumor microenvironment and collagen processing through the lysyl oxidase axis.[77] Additional research has revealed that TM mediates the inhibition of the mitochondrial Complex IV, which is involved in mitochondria energy production, via copper depletion.[69]

Beyond copper, the application the zinc chelator N,N,N,N-Tetrakis(2-pyridylmethyl)-ehtlyenediamine (TPEN) to pancreatic cancer results in increased cell apoptosis and autophagy *in vitro.*[78] Iron chelation by deferasirox (DFX) inhibited the migration and reduced invasiveness of pancreatic cancer by reducing the activity of Rac1 and Cdc42, which are involved in a plethora of pro-cancer mechanisms such as tumor growth, migration, and angiogenesis.[79] This finding was significant as DFX can be given orally in contrast to DFO, which has been shown to decrease in tumor size in patients with hepatocellular carcinoma but requires intravenous application.[80] Beyond this example, the potential role of iron chelation in affecting oncogenic pathways has been a wide topic of interest in the past few decades, and we refer the reader to extensive reviews and recent reports in this area.[81–88]

Anti-cancer properties of quercetin have been explored and show promise in reducing the severity of cancer. Mice given quercetin via oral gavage post tumor induction had a five-fold increase in life span compared to the vehicle.[89] The authors illustrated that quercetin intercalates with the DNA in cancer cells leading to S phase cell cycle arrest and subsequent apoptosis. Quercetin can also act by repressing expression of the receptor to advanced glycation end products (RAGE) leading to an increase in apoptosis and autophagy in pancreatic cells.[90]

3. Plant-derived with bioactivity related to transition metal interactions

3.1 Phenolic Compounds

Plants have been historically used for medicinal purposes predating modern science. As such, plant metabolites have been extensively studied for their potential biochemical activity, and many drug candidates resemble compounds found in nature. The most well-studied class of plant-derived compounds in applications of metabolic diseases are the phenolic compounds. Plant phenolic compounds, often referred to as polyphenols, are a class of small molecules that include molecules such as flavonoids, coumarins, and lignans. By definition, polyphenols are compounds that are composed of multiple phenolic rings. However, the term has been colloquially used to describe phenolic compounds including diphenols like catechol. To read more about the history and definition of the term polyphenols, you can read a review by Quideau et al.[91]

Polyphenols are secondary metabolites from fruits and vegetables and serve a variety of purposes in plants including aroma and color. Polyphenols are found in all plant products we consume and are often the source of the health benefits advertised for various herbs, fruits, and vegetables. Most plant polyphenols exist as conjugated forms (glycosides, esters, and amides) rather than in their free forms. The seemingly endless identification of novel plant phenols broaches the variety of roles they play in plant biology. Plant phenols are involved in activities ranging from protective effects (against predators or radiation) to reproduction to signaling.[91] The vast range of plant phenols necessitates categorization. Each subgroup of plant polyphenols shares a core structure and has a wide range of substitutions on the ring structure. Of the subgroups of plant polyphenols, flavonoids are the most prevalently studied.

3.1.1 Flavonoids

Over 8000 molecules comprise the largest group of plant polyphenols, flavonoids. Flavonoids all share a core structure consisting of three rings: two phenyl rings (A and B) joined by a heterocyclic pyran ring (C). Subclasses of flavonoids are defined by substitution on and oxidation of the heterocyclic C-ring. There are subclasses of flavonoids: flavanols, flavanones, flavonols, flavones, anthocyanins, isoflavones, and chalcones. Flavonoids, which are found in all parts of plants, are most often isolated via extraction from their natural sources.[91] Extraction is most commonly performed via a mixture of organic and aqueous solvents, though more current methods are continually being optimized.[92] Flavonoids have historic medicinal purposes, and modern techniques have been used to elucidate the bioactivity of flavonoids in diseases ranging from cancer to cardiovascular disease to metabolic diseases.[93–96] In particular, extensive research,

including mechanistic and detailed structure-activity relationship studies, has ushed in important developments, understanding, and applications of flavonoid/metal interactions in neurodegenerative disorders.[2,97–102]

Flavonoids have been used in the treatment of diabetes, non-alcoholic fatty liver disease (NAFLD), and hyperlipidemia.[94,103,104] Yi et al. highlight the advances of the flavonol quercetin in clinical trials for treatment of metabolic diseases.[103] Quercetin has entered clinical trials in the treatment of type 2 diabetes mellitus (T2DM), hyperlipidemia, hypercholesterolemia, and NAFLD. The results from these clinical trials support the use of quercetin for increasing insulin secretion and improving insulin resistance, regulating glucose homeostasis, and reducing oxidative stress. Like quercetin, the flavanol (-)-epicatechin, shows beneficial effects in the treatment of NAFLD-related symptoms.[105] In all of these applications, flavonoids are known to exhibit antioxidant and anti-inflammatory activity.[95,106]

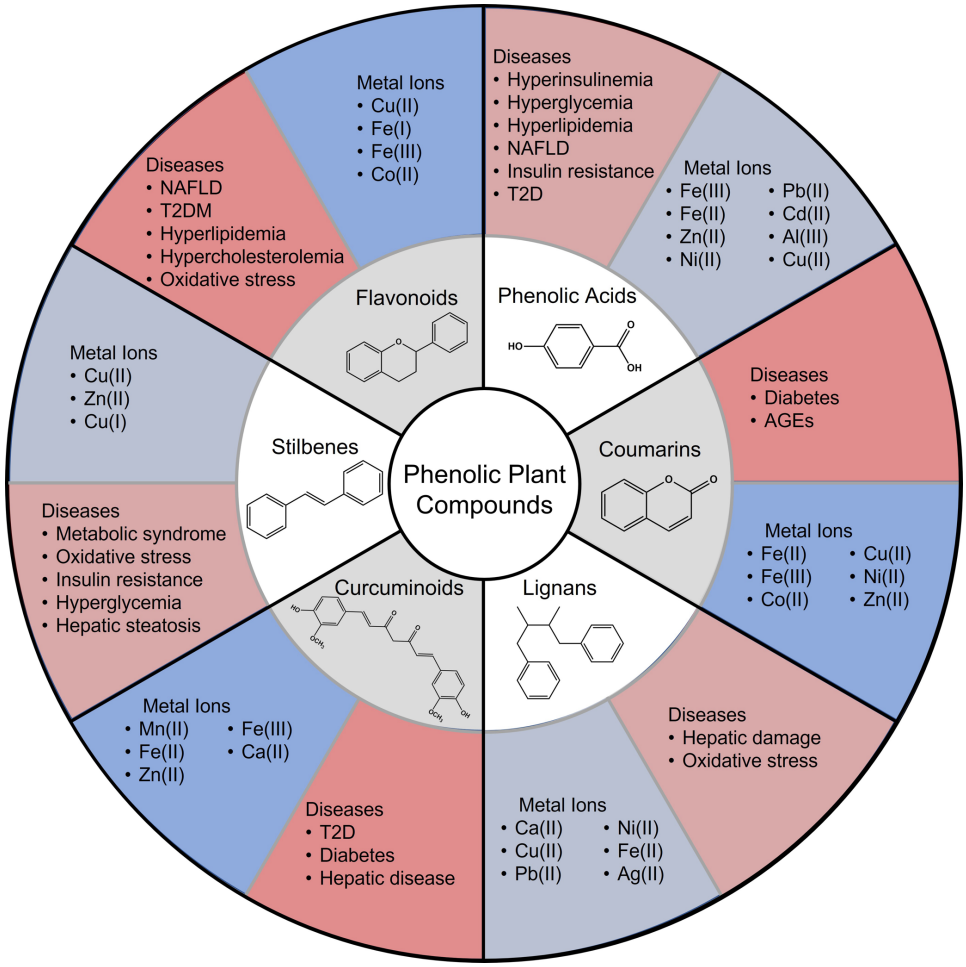

Figure 3: Phenolic plant compounds are known to affect biological function under metabolic disease states. Additionally these phenolic compounds interact with d-block metal ions with little known about the intersection between effects on metabolic disease states.

The exact mechanisms of flavonoid antioxidant activity continue to be explored. It is understood that one path by which flavonoids prevent oxidative damage is by interacting with reactive metal species including iron and copper ions.[107–110] Flavonoid-metal complexes exhibit different behaviors than flavonoids alone.[111,112] Flavonoids have experimentally been shown to bind and reduce metal ions.[110,113,114] Samsonowicz et al. identify three main interaction sites on the flavonoid core structure at the B-ring 3',4'-dihydroxy group, the C-ring 3-hydroxy or 5-hydroxy group, and the C-ring 4-carbonyl group.[115] These interaction sites have are supported both experimentally and computationally.[108,116] Karlíčková et al. found that isoflavones containing a 5-hydroxy-4-keto substitution pattern were able to chelate ferric, ferrous, and cupric ions. The presence of a free 4'-hydroxyl group and the absence of a 5-hydroxyl group corresponded to redox activity in reducing Cu(II) ions.[117] However, many studies of flavonoid-metal complexes are contradictory in their characterization.[115] Binding affinities, binding ratios, and binding locations are all dynamic under varying experimental conditions. Further investigation of the effects of experimental conditions is warranted, but it is clear that flavonoid-metal interactions contribute to their antioxidant activity.[118]

Conversely, interactions between flavonoids and metal ions have also been implicated in pro-oxidant activity which contributes to observed anticancer and apoptogenic activity.[119] Similar to chelation ability, pro-oxidant interactions of flavonoids with metal ions are structure-dependent. The number of adjacent hydroxy groups and conjugation throughout the molecule affects prooxidant activity.[95] The distinction between anti- and pro-oxidant interactions between flavonoids and metal ions is slight and must be considered when thinking about these complexes in therapeutic contexts.

3.1.2 Phenolic acids

Phenolic acids contain a carboxylic acid and are the most produced phenolic compounds by plants. Plant phenolic acids are most abundant in the seeds, leaves, and skins of fruits.[120] There are two main groups that comprise plant phenolic acids: hydroxybenzoic and hydroxycinnamic acids.[121] Some of the more abundant hydroxybenzoic acids including syringic, vanillic, and protocatechuic acids exhibit many of the beneficial health effects previously discussed.

Hydroxybenzoic acids have been demonstrated to possess protective effects against a host of diseases including cancer, cardiovascular disease, and diabetes.[122–125] Of particular interest to metabolic diseases, Chang et al. found that vanillic acid has protective effects against hyperinsulinemia, hyperglycemia, and hyperlipidemia in a study with HFD fed rats.[126] Treating HFD rats with vanillic acid decreased blood glucose levels and increased expression of proteins associated with insulin signaling and lipid metabolism. Sreelekshmi et al. identify activation of glucokinase and reduction of lipid peroxidation by vanillic acid under hyperinsulinemic conditions in HepG2 cells.[127,128] Similarly, syringic acid protects against fat accumulation in the liver of albino rats treated with acetaminophen as reported by Ramachandran et al.[129] Protocatechuic acid can also affect lipid and glucose metabolism in NAFLD conditions and ameliorate insulin resistance associated with diabetes.[130,131] The biological pathways affected by hydroxybenzoic acids continue to be investigated, but acids such as protocatechuic acid

is known to activate mitogen-activated protein kinases (MAPKs) which are involved in inflammatory responses.[123]

Commonly encountered hydroxycinnamic acids including chlorogenic, ferulic, caffeic, and sinapic acids share biological properties to their hydroxybenzoic counterparts. Notably, ferulic acid derived from cereals demonstrates anti-hypertensive effects which may be attributed in part to its antioxidant activity.[132,133] Additionally, in obese mice and high-fat fed rats, caffeic acid and sinapic acid, respectively, modulate the gut microbiome to produce fewer microbiota associated with disease and inflammation.[134,135] Associated with metabolic disease, chlorogenic acid has been extensively studied *in vivo* and clinical studies for its role as a nutraceutical against metabolic syndrome and related diseases including obesity, diabetes, and hypertension.[136] Shi et al. found that treatment of NAFLD mice with chlorogenic acid leads to decreased activation of inflammatory cytokines (TNF-α and IL-6), reduced fasting blood glucose levels and blood lipids, and reduced insulin resistance.[137] This work is supported by observations that the improved conditions of HFD mice treated with chlorogenic acid was related to changes in mRNA levels of genes involved in glucose metabolism like GYS2, PCK, GK, and PFKL.[138] The same effects of chlorogenic acid were observed in human patients with NAFLD or T2D and exhibited similar results with improved metabolic readings.[139]

Unsurprisingly, phenolic acids are known to interact with transition metal ions through their carboxylic acid and phenol moieties.[140–143] Truong et al. used a density functional theory (DFT) approach to study the antioxidant versus pro-oxidant effects of ferulic acid interactions with iron ions at the carboxyl group.[141] Antioxidant activities of ferulic acid are more prominent than pro-oxidative reduction of Fe(III) except under specific conditions such as high concentrations of ferulic acid. Mazzone also employed DFT to study the interactions of Fe(II) with caffeic acid.[144] Using DFT coupled with experimental UV-Vis data, the binding site of caffeic acid with Fe(II) was identified as the carboxyl group, and caffeic acid-Fe(II) complex formation was found to be more energetically favorable than the production of H_2O_2 through Fenton chemistry. Oke et al. studied the activity of a vanillic acid-Zn(II) complex under hyperglycemic conditions.[145] Similar to previous studies, the anti-oxidant activity was highlighted as a key mechanism of bioactivity. Another plant-derived carboxylic acid, nicotianamine (NA), was shown to aid in Fe(II) import facilitated by the proton-coupled amino acid transporter SLC36A1 (PAT1).[146] Nicotianamine is a small organic molecule that can be obtained through consumption of fruits, vegetables, and legumes. Murata et al. use ^{59}Fe(II) to track iron import in Caco-2 cells by NA. Intracellular Fe(II) levels track with the concentration of NA-Fe(II) treatment, and the complex should be explored for use in iron deficiency treatments. While these studies explain a mechanism of antioxidant activity, there remains room to explore the interplay between metal chelation and protective effects against metabolic diseases of plant phenolic acids.

3.1.3 Coumarins

Coumarins have a benzopyrone core and are found in all parts of plants though they are concentrated in fruits.[147] Like the other phenolic compounds previously

mentioned, coumarins are used to treat a range of pathologies including cancer, depression, and Alzheimer's Disease.[148–151] A thorough review by Hussain et al. discusses the biological and pharmaceutical properties of coumarins and their derivatives.[147] Some highlights pertinent to our topic include a study by Ali et al. where methanol extracts of *Angelica decrusiva* exhibited inhibitory activity of protein tyrosine phosphatase 1B (PTP1B) and α-glucosidase.[152] Correspondingly, Islam et al. also found PTP1B and α-glucosidase inhibitory activity of coumarins extracted from *Artemisia capillaris*.[153] As their involvement in diabetes is understood, PTP1B and α-glucosidase are targets for the treatment of diabetes, and thus coumarins which inhibit the activity of these enzymes possess therapeutic potential.[154,155] In animal models, coumarins and their derivates exhibit protective effects against diabetes and associated renal damage.[156,157] Kang et al. administered esculin, a coumarin derivative, to streptozotocin-induced diabetic mice and found that esculin combatted diabetes-associated symptoms including elevated blood glucose levels and increased hepatic glucose-6-phosphotase expression.[156] Non-obese diabetic mice were administered total coumarins extracted from *Urtica dentata*, and Wang et al. found that the treated mice showed decreased expression of the TLR4 gene which is involved in inflammation in type 1 diabetes.[157]

Coumarins are shown to interact with transition metal ions such as iron and copper.[158–160] García-Beltrán et al. synthesized a fluorescent probe sensitive to Cu(II) based on 3-amino-7-hydroxycoumarin.[159] While the proposed mechanism of the probe is through hydrolysis of an imine bond, Mergu et al. also designed a Cu(II)-sensitive probe which employs a coumarin moiety through which the copper ion is chelated.[158] Mladěnka et al. investigated the interactions of coumarins with iron ions *in vitro*.[160] At neutral pH, *ortho*-dihydroxy derivatives of coumarins, specifically, 7,8-dihydroxy-4-methylcoumarin, were able to tightly bind ferrous ions. However, at acidic pH, the same *ortho*-dihydroxycoumarins demonstrated potential pro-oxidant activity through reduction of ferric ions. While the groundwork for coumarin-metal interactions exists, there remains room to investigate the relationship between coumarins, metals, and the protective effects of coumarins against metabolic diseases.

3.1.4 Stilbenes

With a core of 1,2-diphenylethylene, stilbenes are found as either *trans*- or *cis*-isomers.[161] The most known stilbene is resveratrol which is found in edible fruits and seeds such as grapes, pistachios, and berries.[161] Over 250 clinical trials have indicated health benefits of the *trans*- form of resveratrol in addressing cardiovascular diseases, neurological diseases, and metabolic diseases like diabetes.[162] Singh et al. present a summary of clinical trial data of resveratrol in their review article.[162] Some other notable bioactive stilbenes include oxyresveratrol, piceatannol, and pterostilbene.[163] These stilbenes too possess bioactivities such as anticancer and anti-hypertensive effects.[164–166] In the context of metabolic disease, Choi et al. reported that oxyresveratrol combatted metabolic dysregulation in high-fat diet-fed mice by increasing the expression of proteins including AMP-activated protein kinase α, insulin receptor substrate 1, and insulin-dependent glucose transporter type 4 which are involved in lipid and glucose

homeostasis.[167] Two studies by Choi et al. and Pan et al. note the increase of energy expenditure in high-fat diet-fed mice administered oxyresveratrol.[168,169] Both groups identify increasing expression of uncoupling protein 1 (UCP1), a mitochondrial membrane protein in brown adipose tissue, as a mechanism of induced thermogenesis by oxyresveratrol. Piceatannol exhibits anti-inflammatory and antioxidant activity in a variety of cell types and *in vivo* studies.[170] Kitada et al. studied the effects of piceatannol from *Passiflora edulis* on metabolic health in humans.[171] The preliminary results presented indicate that piceatannol increases insulin sensitivity and decreases blood pressure and heart rate. Similarly, pterostilbene reduces adiposity in white adipose tissue at a higher efficacy than resveratrol.[172] Resveratrol, though being the most-studied stilbene, has low oral bioavailability which supports the study of other stilbenes as potential therapeutics.[173]

Stilbenes interact with metal ions, and their complexes have demonstrated biological activity. Stilbene-copper complexes have been studied for their antitumor activity.[174,175] Resveratrol-Cu(II) and piceatannol-Cu(II) complexes induce apoptosis through production of ROS and DNA damage.[175–177] Tamboli et al. use electrospray ionization mass spectrometry (ESI-MS) paired with DFT calculations to understand the mechanisms by which resveratrol interacts with copper.[178] While the previously discussed phenolic compounds interact with metal ions mainly through oxygen-containing groups, resveratrol interacts with copper through its aromatic carbon atoms and alkenyl group. Though resveratrol does exhibit some copper chelating activity, Granzotto et al. suggest that resveratrol poses more of a risk of producing ROS than chelating copper.[179] Metal-interactions with resveratrol have been studied computationally[180] *in vitro*, but the exact mechanisms of interaction *in vivo* remain elusive. Majewski et al. studied the effects of resveratrol on copper deficient Wistar rats and found resveratrol to increase copper and zinc levels as well as superoxide dismutase (SOD) and ferric reducing antioxidant power (FRAP) which are related to antioxidant activity. While the clinical relevance of stilbenes is well-established in diseases associated with metal dyshomeostasis, the direct effects of stilbene-metal interactions on pathological states remains largely unexplored.

3.1.5 Lignans

In plants, lignans serve as structural compounds in the formation of lignin in the cell wall.[181] Lignans have a 2,3-dibenzylbutane structure and are consumed in fibrous foods like grains and legumes.[182] Though relatively low-abundant, lignans, as with other plant phenolic compounds, exhibit a range of biological activity from anti-cancer activity.[182] to gut microbiota modulation[183] to cholesterol reduction.[184] Lignans are consumed largely through cereals in western diets and are known to affect metabolic systems through nuclear receptors (NRs), particularly estrogen receptors (ERs).[185] Zanella et al. highlight the relationship between plant lignans and metabolic syndrome (MetS). Epidemiological studies show an inverse correlation between lignan intake and incidence of T2D, dyslipidemia, and fasting insulin serum levels. Additionally, the structural similarity of lignans to steroid hormones such as estrogen can play a role in modulation of hormone-related tumors by lignans.[186] Lignans including pinoresinol, sauchinone, sesamin, and honokiol can combat hepatic oxidative stress which is often associated with metabolic diseases.[187–192] Mice with liver injury induced by CCl_4 or *tert*-

butyl hydroperoxide were treated with lignans which activated pathways including AMPK, JNK, SIRT3, and Nrf2/ARE. Due to their potent antioxidant activity, it is no surprise that lignans can bind metal ions.

Lignans have known interactions with metal ions, particularly iron. Donoso-Fierro et al. extracted, isolated, and studied the iron-binding abilities of lignans from *F. cupressoides* and *A. chilensis*.[193] Five lignans with iron-binding capacity of over 87% were identified as isolariciresinol, isotaxiresinol, matairesinol, methylmatairesinol, secoisolariciresinol, and didemethylmatairesinol. This work was followed up by Fucassi et al. who focused on secoisolariciresinol digucoside (SDG) and found that SDG was able to bind calcium, copper, lead, nickel, iron, and silver ions.[194] While some of these metals are implicated in metabolic diseases affected by lignans, the direct connections between metal chelation, lignan intake, and instance of metabolic disease remain largely unexplored.

3.1.6 Curcuminoids

Curcuminoids are found in the rhizome of turmeric and have gained attention for their bioactivity.[195] The most common curcuminoid, curcumin, is a yellow polyphenolic pigment that contains two ferulic acid residues bridged by a seven-carbon methylene group. Clinical trials implicate curcumin in treatment for a range of disease states from rheumatoid arthritis to inflammatory bowel disease to Alzheimer's disease. Reviews by Pivari et al. and Zheng et al. highlight current understanding of treatment of diabetes with curcumin.[195,196] Yuan et al. performed meta-analysis of the effects of curcuminoids on blood lipids in adults with metabolic diseases.[197] While the results are preliminary, consumption of curcuminoids correlated with decreased levels of triglycerides, total cholesterol, and LDL and an increase in HDL. Newer work by Ibrahim et al. demonstrates hepatoprotective effects of curcuminoids. Hepatic damage was induced in Wistar rats by administration of CCl_4, and curcuminoids were administered in doses of 75, 150, and 300 mg. Liver enzyme levels (alanine transaminase, aspartate transaminase, and alkaline phosphatase) increase with liver damage caused by CCl_4 but are restored upon treatment with curcuminoids.

Expectedly, curcuminoids exhibit antioxidant activity and interact with metal ions. Pitchumani Violet Mary et al. used DFT in gas and DMSO solvent phases to study interactions of curcumin with Mn(II), Fe(II), and Zn(II). Curcumin-Zn(II) complexes are the most stable of the three, though DMSO solvent interactions destabilize the complex. The binding site is identified as the diketone moiety, and metal complexes show increased antioxidant activity as compared to free curcumin. These calculations are supported by experimental results by Hieu et al.[198] Curcumin complexes with Fe(III), Ca(II), and Zn(II) were assessed for their solubility and antioxidant activity. Increased solubility of the metal complexes as compared to free curcumin correlated with increased antioxidant activity as assessed by the DPPH assay. A review by Prasad et al. summarizes the increased pharmacological activity of curcumin when complexed with metal ions.[199] Curcumin-metal complexes modulate a host of biomarkers involved in metabolic diseases including inflammatory cytokines IL-6, TNF-α, and NF-κB. Yuan et al. exploit the anti-inflammatory

effects of curcumin-metal complexes in their Fe-Curcumin nanozyme employed for ROS scavenging and anti-inflammatory activity.[200] The strong chelating behavior of curcumin paired with its therapeutic effects requires further investigation for modulation of metal populations in metabolic disease states.

3.2 Carotenoids

Over 700 compounds comprise the group of natural pigments called carotenoids which impart yellow, red, and orange colors.[201] In plants, carotenoids serve roles in photosynthesis and in protection against oxidative damage.[202] Carotenoids, like the previously discussed compounds found in plants, have been studied for their potential use in therapeutics for pathologies including cardiovascular disease and various cancers.[203] Another key role of carotenoids in human health is as a precursor for vitamin A and antioxidants which implicates their protective activity against oxidative damage.[202]

A study by Christensen et al. of 2003–2014 National Health and Nutrition Examination Survey (NHANES) data showed that increased intake and serum levels of carotenoids correlates with decreased instance of NAFLD.[204] Specifically, α-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin show strong associations with decreased risk of NAFLD which was assessed using ultrasonography.[205] While a healthy diet may largely affect the risk of disease onset, Christensen et al. show that including the healthy eating index of 2015 in their analysis did not eliminate the inverse relationship between increased serum carotenoid levels and risk of fatty liver disease.[204] As such, carotenoids exhibit therapeutic effects towards fatty liver diseases through an unclear mechanism of action. Elvira-Torales et al. highlight some mechanisms by which carotenoids impart their protective effects against liver damage through reduction of oxidative damage and modulation of genes associated with lipid metabolism.[206] Researchers note that levels of inflammatory cytokines including *TNF-α*, *IL-6*, and *MCP-1* are repressed upon oral administration of carotenoids, specifically β-cryptoxanthin.[206,207] These cytokines likewise play a role in diabetes mellitus which is a chronic inflammatory disease. Expectedly, carotenoids present anti-diabetic properties as presented in a review by Roohbakhsh et al.[208] Researchers highlight that carotenoids reduce insulin resistance by affecting JNK, IKKβ, and PPARγ. JNK and IKKβ regulate phosphorylation of insulin receptor substrates, specifically IRS-1; PPARγ assists in metabolism of carbohydrates and decreases inflammation in the cell.

Unlike many of the previously mentioned plant-derived compounds, carotenoids have not been studied for chelation-based interactions with metal ions. Due to their lipophilic nature, the context under which carotenoid-metal ion interactions are studied is in reference to lipid oxidation.[209] Interactions between carotenoids and redox-active metals may contribute to their pro-oxidant activity by producing carotenoid radical cations through electron-transfer.

3.3 Peptides

Another group of plant-derived compounds that is of interest to human health are peptides. Peptide sequences within plant proteins are increasingly being recognized for their potential bioactivity and use as nutraceuticals.[210]

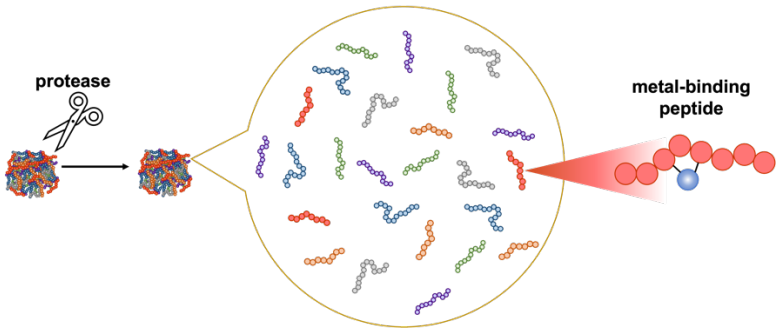

Figure 4: Plant-derived proteins subjected to enzymatic hydrolysis generates bioactive peptides. Such peptides have been found to have metal-interacting properties with potential health benefits.

Many bioactive peptides are hydrolysis products of plant proteins where the proteins themselves do not present the same bioactivity. The hydrolysis products naturally occur through consumption by digestive enzymes such as trypsin and pepsin.[210] A typical workflow for preparation of plant-protein derived bioactive peptides involves hydrolysis of proteins through one of three methods: gastrointestinal digestion, enzymatic hydrolysis, or fermentation.[211] Enzymatic hydrolysis is the most common method and has been performed with a wide variety of enzymes derived from plants and microbes (Figure 4).[212] The proteolytic enzyme selected for digestion affects the potential bioactivity of the resulting peptides because of the varied cleavage sites.[212] Hydrolysates from a range of foods consumed through diet have been studied for their bioactivity. Similar to their phenolic compound counterparts, plant protein hydrolysates are known to possess biological properties including anti-cancer, anti-inflammatory, and cardiovascular effects.[213–220] Within the realm of metabolic disease, peptides from plant protein hydrolysates have exhibited anti-diabetic, anti-obesity, and anti-oxidant activity.[221,222] Jakubczyk et al. highlight specific peptide sequences that demonstrate bioactivity towards ameliorating metabolic syndrome in their review.[221] Other recent reviews highlight therapeutic effects of plant-derived peptides towards diabetes and related complications.[222,223]

There are known metal-binding amino acid residues, thus it is expected that plant protein-derived peptides have metal-binding capacity.[224] Esfandi et al. hydrolyzed oat bran proteins using four proteases, Alcalase, Flavourzyme, papain, and Protamex.[225] Antioxidant assays and iron-chelating assays support the varied bioactivity of peptides produced by different proteases, with papain-hydrolyzed peptides having the highest iron-chelating activity. Hu et al. further investigated iron chelation by oat bran protein hydrolysates prepared with papain, ficin, and bromelian, separating peptides by size.[226] Larger peptides (> 10 kDa) hydrolyzed by papain have higher iron-chelating capacity than those produced by ficin and bromelian whereas small peptides (< 1 kDa) hydrolyzed by

ficin have higher iron-chelating capacity than those produced by papain and bromelian. Kubglomsong et al. studied rice bran albumin hydrolysates from papain hydrolysis for their copper-chelating activity.[227] Using gradient elution by HPLC, the more hydrophilic peptides demonstrated the highest copper-chelating activity. Identification of the peptides from the strongest chelating fraction showed characteristic moieties such as sulfur-containing amino acids, repeating serine residues, tryptophan, and arginine. Similar to the plant phenolic compounds, the interplay between plant peptides, metal ions, and metabolic disease has much room to be explored.

4. Metal complexes of plant-based molecules as potential therapeutics for metabolic diseases

Current therapeutic design targeting metal dysregulation focuses largely on metal-trafficking small molecules.[14,15] Such molecules can act as metal chelators or metal ionophores. Chelators sequester metal ions from the intracellular space and evacuate them out of the cell; ionophores bind metal ions in the extracellular space and traffic them into the cell across the cell membrane. Physiochemical requirements of small molecule chelators and ionophores include a moderate binding affinity to specific metal ions, sufficient lipophilicity to penetrate the cell membrane, and adequate complex stability.[14] Plant-derived compounds deserve to be considered for their therapeutic potential as metal chelators and ionophores. With known metal ion interactions, a range of binding affinities and lipophilicities, and varying complex stabilities, plant-derived small molecule-metal complexes possess the chemical properties to traffic metal ions. Indeed, small molecules like flavonoids have been studied in these contexts.

Flavonoids are known to interact with redox active metals such as copper and iron which are implicated in metabolic disease states such as diabetes, Wilson and Menkes disease, and metabolic syndrome. To date, much of the research regarding flavonoid-metal interactions focus on their antioxidant activity. A review by Selvaraj et al. highlights the potential of flavonoid-metal complexes as therapeutics mainly for antioxidant and anti-inflammatory activity.[228] However, flavonoids are good candidates to study for their potential chelator or ionophore activity. Dai et al. present their study on flavones as Cu(II) ionophores.[229] Researchers highlight 3-hydroxyflavone as being the most effective copper ionophore. Using human hepatocytes, HepG2 cells, as a model system, 3-hydroxyflavone is shown to import copper into the cell at up to a 150-fold change. While the experimental conditions induce cell death due to cuproptosis[230], the ionophore activity of 3-hydroxyflavone can be harnessed to address diseases under which intracellular copper levels are decreased. Further studies of flavonoid-metal interactions by our lab, show that flavonoids can modulate expression of proteins involved in copper trafficking.[118] Copper chaperone for superoxide dismutase (CCS), which is used as a marker for intracellular copper, shows decreased expression upon treatment with 3-hydroxyflavone and Cu(II) and increased expression when treated with quercetin and Cu(II). Compared to the other molecules studied, 3-hydroxyflavone is the one of the more lipophilic

compounds. The lipophilicity paired with the binding ability of 3-hydroxyflavone maintains the important chemical properties of an ideal ionophore and should serve as inspiration for future investigations.

5. Future Outlook

The health benefits of plant-based molecules are richly reported in the literature, with growing evidence associating plant-based diets with reduced risk of metabolic diseases, including cardiovascular disorders, metabolic syndrome, and type II diabetes.[231,232] Yet, much remains to be elucidated regarding the physicochemical properties of plant-based ingredients, how they differ from animal-based products, and the molecular mechanisms underlying their beneficial effects.[231,233] Even less explored is how their ionophoric and chelating capacities may be linked to their mode of action. The surge in tools for visualizing metal trafficking in complex biological systems has shed new light on the importance of transition metal homeostasis and its perturbation in metabolic diseases.[3,234,235] It is timely to revisit the mechanisms by which plant-derived molecules elicit their function with respect to their interaction with metal homeostatic pathways. Leveraging these new tools should link structural insight to medicinal uses of plant-derived diets and components.

In this review, we brought to the forefront examples wherein metal-binding abilities are associated with beneficial effects on metabolic disorders. The majority of the highlighted studies focus on how the redox chemistry of the metals impact the pro- and antioxidant activity of these molecules. As new roles emerge for labile metal pools in cellular signaling, alternative pathways by which plant-based metal binders may function in disease alleviation should be explored beyond redox-focused interactions. Recent reports have already demonstrated this potential with synthetic or microbe-derived metal binders. Iron-binding siderophores[236,237] are gaining relevance not only in host-pathogen interactions in infection but also in the balance of the gut microbiota in healthy and dysmetabolic states[82,238,239] Tissue-targeted ionophores are finding unique therapeutic mechanisms in shifting metabolic balance.[14,230,240–242] It behooves researchers to consider such metal-trafficking functions when investigating metal associations of plant-derived therapies. These insights should find valuable intersections in determining how nutrition, diet, and natural product-derived therapies might address pressing challenges in metabolic diseases.

Author Contributions

V.J.L., S.E.J., and M.C.H. all contributed to the research and writing of the manuscript. V.J.L. and M.C.H.. organized the manuscript. All authors have given approval to the final version of the manuscript.

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