Title

Plant-derived chelators and ionophores as potential therapeutics for metabolic diseases

Journal

Chemical Society Reviews, 52(11)

ISSN

0306-0012

Authors

Lee, Vanessa J

Janisse, Samuel E

Heffern, Marie C

Publication Date

2023-06-06

DOI

10.1039/d3cs00167a

Peer reviewed

HHS Public Access

Author manuscript

Chem Soc Rev. Author manuscript; available in PMC 2024 June 06.

Published in final edited form as:

Chem Soc Rev. ; 52(11): 3927–3945. doi:10.1039/d3cs00167a.

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

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

[a]Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616

Abstract

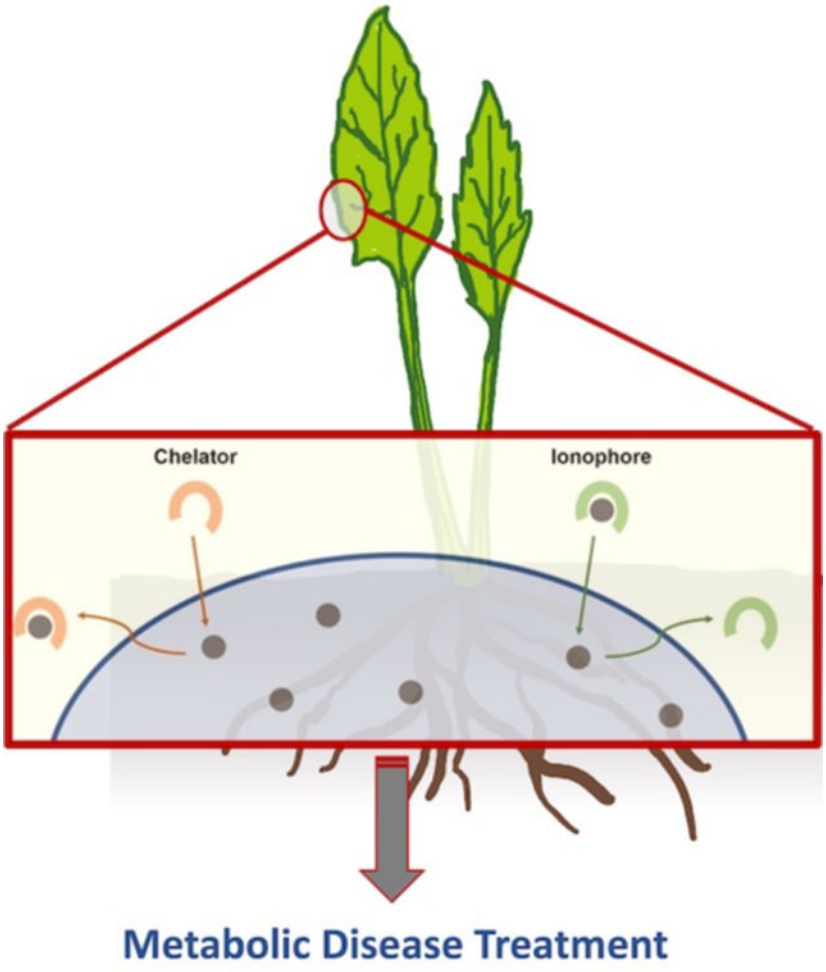
Transition metal dysregulation is associated with a host of pathologies, many of which are therapeutically targeted using chelators and ionophores. Chelators and ionophores are used as therapeutic metal-binding compounds which impart biological effects by sequestering or trafficking endogenous metal 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.

Graphical Abstract

*To whom correspondence may be addressed: mcheffern@ucdavis.edu.

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.



Plant-based molecules are beneficial in treating metabolic disorders. Probing their metal-binding roles are vital to harnessing their function.

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.

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]

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]

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]

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.

Acknowledgements

This work was supported by the National Institutes of Health (NIH MIRA 5R35GM133684 to M.C.H.), and the National Science Foundation (NSF CAREER 2048265 to M.C.H.). We also thank the Hartwell Foundation for their generous support for M.C.H. as a Hartwell Individual Biomedical Investigator, as well as the UC Davis CAMPOS Program and the University of California's Presidential Postdoctoral Fellowship for their support of M.C.H. as a CAMPOS Faculty Fellow and former UC President's Postdoctoral Fellow, respectively.

References

1. Finney LA and O'Halloran VT, Transition metal speciation in the cell: Insights from the chemistry of metal ion receptors, Science, 2003, 300, 931–936. [PubMed: 12738850]
2. Buccella D, Lim MH and Morrow JR, Metals in Biology: From Metallomics to Trafficking, Inorganic Chemistry, 2019, 58, 13505–13508. [PubMed: 31630526]
3. Chang CJ, Searching for harmony in transition-metal signaling, Nature Chemical Biology, 2015, 11, 744–747. [PubMed: 26379012]
4. Umair M and Alfadhel M, Genetic disorders associated with metal metabolism, Cells, 2019, 8, 1–23.

5. Anagianni S and Tuschl K, Genetic Disorders of Manganese Metabolism, Curr Neurol Neurosci, 2019, 19, 33.
6. Gerosa C, Fanni D, Congiu T, Piras M, Cau F, Moi M and Faa G, Liver pathology in Wilson's disease: From copper overload to cirrhosis, Journal of Inorganic Biochemistry, 2019, 193, 106–111. [PubMed: 30703747]
7. Baldari S, Rocco DG and Toietta G, Current biomedical use of copper chelation therapy, International Journal of Molecular Sciences, 2020, 21, 1–20.
8. Moreno RC, Navas-Acien A, Escolar E, Nathan DM, Newman J, Schmedtje JF, Diaz D, Lamas GA and Fonseca V, Potential Role of Metal Chelation to Prevent the Cardiovascular Complications of Diabetes, Journal of Clinical Endocrinology and Metabolism, 2019, 104, 2931–2941. [PubMed: 30869793]
9. Bogie JFJ, Haidar M, Kooij G and Hendriks JJA, Fatty acid metabolism in the progression and resolution of CNS disorders, Advanced Drug Delivery Reviews, 2020, 159, 198–213. [PubMed: 31987838]
10. Xu J, Jiang H, Li J, Cheng KK, Dong J and Chen Z, 1H NMR-based metabolomics investigation of copper-laden rat: A model of Wilson's disease, PLoS ONE, 2015, 10, e0119654. [PubMed: 25849323]
11. Chen J, Jiang Y, Shi H, Peng Y, Fan X and Li C, The molecular mechanisms of copper metabolism and its roles in human diseases, Pflugers Archiv European Journal of Physiology, 2020, 472, 1415–1429. [PubMed: 32506322]
12. Antonucci L, Porcu C, Iannucci G, Balsano C and Barbaro B, Non-alcoholic fatty liver disease and nutritional implications: Special focus on copper, Nutrients, 2017, 9, 1–12.
13. Ding X, Xie H and Kang YJ, The significance of copper chelators in clinical and experimental application, Journal of Nutritional Biochemistry, 2011, 22, 301–310. [PubMed: 21109416]
14. Oliveri V, Biomedical applications of copper ionophores, Coordin Chem Rev, 2020, 422, 213474.
15. Steinbrueck A, Sedgwick AC, Brewster JT, Yan KC, Shang Y, Knoll DM, Vargas-Zúñiga GI, He XP, Tian H and Sessler JL, Transition metal chelators, pro-chelators, and ionophores as small molecule cancer chemotherapeutic agents, Chemical Society Reviews, 2020, 49, 3726–3747. [PubMed: 32525153]
16. Helsel ME, White EJ, Razvi SZA, Alies B and Franz KJ, Chemical and functional properties of metal chelators that mobilize copper to elicit fungal killing of Cryptococcus neoformans, Metallomics, 2016, 9, 69–81.
17. Helsel ME and Franz KJ, Pharmacological activity of metal binding agents that alter copper bioavailability, Dalton T, 2015, 44, 8760–8770.
18. Franz KJ, Clawing back: broadening the notion of metal chelators in medicine, Curr Opin Chem Biol, 2013, 17, 143–149. [PubMed: 23332666]
19. Seidel V, Plant-derived chemicals: A source of inspiration for new drugs, Plants, 2020, 9, 1–3.
20. Wong F-C, Xiao J, Wang S, Ee K-Y and Chai T-T, Advances on the antioxidant peptides from edible plant sources, Trends Food Sci Tech, 2020, 99, 44–57.
21. Tsang T, Davis CI and Brady DC, Copper biology, Curr Biol, 2021, 31, R421–R427. [PubMed: 33974864]
22. Abbate V and Hider R, Iron in biology, Metallomics, 2017, 9, 1467–1469. [PubMed: 29086787]
23. Forrester SJ, Kikuchi DS, Hernandes MS, Xu Q and Griendling KK, Reactive oxygen species in metabolic and inflammatory signaling, Circulation Research, 2018, 122, 877–902. [PubMed: 29700084]
24. Behari M and Pardasani V, Genetics of Wilsons disease, Parkinsonism and Related Disorders, 2010, 16, 639–644. [PubMed: 20708958]
25. Członkowska A, Litwin T, Dusek P, Ferenci P, Lutsenko S, Medici V, Rybakowski JK, Weiss KH and Schilsky ML, Wilson disease, Nature Reviews Disease Primers, 2018, 4, 1–20.
26. Zhong H-J, Xiao P, Lin D, Zhou H-M and He X-X, Cirrhosis in Wilson Disease is characterized by Impaired Hepatic Synthesis, Leukopenia and Thrombocytopenia, Int J Med Sci, 2020, 17, 1345–1350. [PubMed: 32624691]

27. Hermann W, Classification and differential diagnosis of Wilson's disease, Annals of Translational Medicine; Vol 7, Supplement 2 (April 2019): Annals of Translational Medicine (Focus on "Wilson's disease: From Genetics to Management of Disease").
28. Rodriguez-Castro KI, Hevia-Urrutia FJ and Sturniolo GC, Wilson's disease: A review of what we have learned, World Journal of Hepatology, 2015, 7, 2859–2870. [PubMed: 26692151]
29. Sokol RJ, Twedt D, McKim JM, Devereaux MW, Karrer FM, Kam I, Steigman GV, Narkewicz MR, Bacon BR, Britton RS and Neuschwander-Tetri BA, Oxidant injury to hepatic mitochondria in patients with Wilson's disease and Bedlington terriers with copper toxicosis, Gastroenterology, 1994, 107, 1788–1798. [PubMed: 7958693]
30. Nagasaka H, Inoue I, Inui A, Komatsu H, Sogo T, Murayama K, Murakami T, Yorifuji T, Asayama K, Katayama S, Uemoto S, Kobayashi K, Takayanagi M, Fujisawa T and Tsukahara H, Relationship between oxidative stress and antioxidant systems in the liver of patients with Wilson disease: Hepatic manifestation in wilson disease as a consequence of augmented oxidative stress, Pediatric Research, 2006, 60, 472–477. [PubMed: 16940238]
31. Linder MC, Copper Homeostasis in Mammals, with Emphasis on Secretion and Excretion. A Review, Int J Mol Sci, 2020, 21, 4932. [PubMed: 32668621]
32. Tisato F, Marzano C, Porchia M, Pellei M and Santini C, Copper in diseases and treatments, and copper-based anticancer strategies., Medicinal Research Reviews, 2010, 30, 708–749. [PubMed: 19626597]
33. Davis SR and Cousins RJ, Metallothionein expression in animals: A physiological perspective on function, Journal of Nutrition, 2000, 130, 1085–1088. [PubMed: 10801901]
34. Brewer GJ, Zinc and tetrathiomolybdate for the treatment of Wilson's disease and the potential efficacy of anticopper therapy in a wide variety of diseases, Metallomics, 2009, 1, 199–206. [PubMed: 21305118]
35. Weiss KH, Gotthardt DN, Klemm D, Merle U, Ferencifoerster D, Schaefer M, Ferenci P and Stremmel W, Zinc monotherapy is not as effective as chelating agents in treatment of Wilson disease, Gastroenterology, 2011, 140, 1189–1198.e1. [PubMed: 21185835]
36. Denny-Brown D and Porter H, The Effect of BAL (2,3-Dimercaptopropanol) on Hepatolenticular Degeneration (Wilson's Disease), New England Journal of Medicine, 1951, 245, 917–925. [PubMed: 14882450]
37. Purchase R, The treatment of Wilson's disease, a rare genetic disorder of copper metabolism, Science Progress, 2013, 96, 19–32. [PubMed: 23738435]
38. Walshe JM, Penicillamine, a new oral therapy for Wilson's disease, Am J Medicine, 1956, 21, 487–495.
39. Weigert WM, Offermanns H and Degussa PS, D-Penicillamine—Production and Properties, Angewandte Chemie International Edition in English, 1975, 14, 330–336.
40. Pugliese M, Biondi V, Gugliandolo E, Licata P, Peritore AF, Crupi R and Passantino A, D-penicillamine: The state of the art in humans and in dogs from a pharmacological and regulatory perspective, Antibiotics, 2021, 10, 1–15.
41. Khandpur S, Jain N, Singla S, Chatterjee P and Behari M, D-penicillamine Induced Degenerative Dermopathy, Indian journal of dermatology, 2015, 60, 406–409. [PubMed: 26288416]
42. Sarkar B, Sass-Kortsak A, Clarke R, Laurie SH and Wei P, A Comparative Study of in vitro and in vivo Interaction of D-penicillamine and Triethylenetetramine with Copper, J Roy Soc Med, 1977, 70, 13–18.
43. Tümer Z and Møller LB, Menkes disease, European Journal of Human Genetics, 2010, 18, 511–518. [PubMed: 19888294]
44. MENKES JH, ALTER M, STEIGLEDER GK, WEAKLEY DR and SUNG JH, A sex-linked recessive disorder with retardation of growth, peculiar hair, and focal cerebral and cerebellar degeneration., Pediatrics, 1962, 29, 764–79. [PubMed: 14472668]
45. Kaler SG, ATP7A-related copper transport diseasesg-emerging concepts and future trends, Nature Reviews Neurology, 2011, 7, 15–29. [PubMed: 21221114]
46. Kreuder J, Otten A, Fuder H, Tümer Z, Tønnesen T, Horn N and Dralle D, Clinical and biochemical consequences of copper-histidine therapy in Menkes disease, Eur J Pediatr, 1993, 152, 828–832. [PubMed: 8223785]

47. Millichap JG, Neonatal Diagnosis and Treatment of Menkes Disease, Pediatric Neurology Briefs, 2008, 22, 16.
48. Kaler SG, Neurodevelopment and brain growth in classic Menkes disease is influenced by age and symptomatology at initiation of copper treatment, Journal of Trace Elements in Medicine and Biology, 2014, 28, 427–430. [PubMed: 25281031]
49. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, Hu FB, Kahn CR, Raz I, Shulman GI, Simonson DC, Testa MA and Weiss R, Type 2 diabetes mellitus, Nature Reviews Disease Primers, 2015, 1, 1–23.
50. Kahn SE, Hull RL and Utzschneider KM, Mechanisms linking obesity to insulin resistance and type 2 diabetes, Nature, 2006, 444, 840–846. [PubMed: 17167471]
51. Tanaka A, Kaneto H, Miyatsuka T, Yamamoto K, Yoshiuchi K, Yamasaki Y, Shimomura I, Matsuoka TA and Matsuhisa M, Role of copper ion in the pathogenesis of type 2 diabetes, Endocrine Journal, 2009, 56, 699–706. [PubMed: 19461160]
52. Simcox JA and McClain DA, Iron and diabetes risk, Cell metabolism, 2013, 17, 329–341. [PubMed: 23473030]
53. Viktorínová A, Tošerová E, Križko M and Ďuračková Z, Altered metabolism of copper, zinc, and magnesium is associated with increased levels of glycated hemoglobin in patients with diabetes mellitus, Metabolis, 2009, 58, 1477–1482.
54. Dymock IW, Cassar J, Pyke DA, Oakley WG and Williams R, Observations on the pathogenesis, complications and treatment of diabetes in 115 cases of haemochromatosis, The American Journal of Medicine, 1972, 52, 203–210. [PubMed: 5058506]
55. Rajpathak SN, Crandall JP, Wylie-Rosett J, Kabat GC, Rohan TE and Hu FB, The role of iron in type 2 diabetes in humans, Biochimica et Biophysica Acta - General Subjects, 2009, 1790, 671–681.
56. Bao W, Rong Y, Rong S and Liu L, Dietary iron intake, body iron stores, and the risk of type 2 diabetes: a systematic review and meta-analysis, Bmc Med, 2012, 10, 119. [PubMed: 23046549]
57. Cooksey RC, Jones D, Gabrielsen S, Huang J, Simcox JA, Luo B, Soesanto Y, Rienhoff H, Abel ED and McClain DA, Dietary iron restriction or iron chelation protects from diabetes and loss of β-cell function in the obese (ob/ob lep−/−) mouse, American Journal of Physiology - Endocrinology and Metabolism, 2010, 298, 1236–1243.
58. Yan HF, Liu ZY, Guan ZA and Guo C, Deferoxamine ameliorates adipocyte dysfunction by modulating iron metabolism in ob/ob mice, Endocrine Connections, 2018, 7, 604–616. [PubMed: 29678877]
59. Yin H, Xu L and Porter NA, Free radical lipid peroxidation: Mechanisms and analysis, Chemical Reviews, 2011, 111, 5944–5972. [PubMed: 21861450]
60. Nowotny K, Jung T, Höhn A, Weber D and Grune T, Advanced Glycation End Products and Oxidative Stress in Type 2 Diabetes Mellitus, Biomol, 2015, 5, 194–222.
61. Nazari M, Ho KW, Langley N, Cha KM, Kodsi R, Wang M, Laybutt DR, Cheng K, Stokes RA, Swarbrick MM and Gunton JE, Iron chelation increases beige fat differentiation and metabolic activity, preventing and treating obesity, Scientific Reports, 2022, 12, 1–11. [PubMed: 34992227]
62. Yao Z, Gu Y, Zhang Q, Liu L, Meng G, Wu H, Xia Y, Bao X, Shi H, Sun S, Wang X, Zhou M, Jia Q, Wu Y, Song K, Gao W, Guo C and Niu K, Estimated daily quercetin intake and association with the prevalence of type 2 diabetes mellitus in Chinese adults, European Journal of Nutrition, 2019, 58, 819–830. [PubMed: 29754250]
63. Vernarelli JA and Lambert JD, Flavonoid intake is inversely associated with obesity and C-reactive protein, a marker for inflammation, in US adults, Nutrition and Diabetes, 2017, 7, 22–24.
64. Peng J, Li Q, Li K, Zhu L, Lin X, Lin X, Shen Q, Li G and Xie X, Quercetin Improves Glucose and Lipid Metabolism of Diabetic Rats: Involvement of Akt Signaling and SIRT1, J Diabetes Res, 2017, 2017, 3417306. [PubMed: 29379801]
65. Dhanya R, Arya AD, Nisha P and Jayamurthy P, Quercetin, a Lead Compound against Type 2 Diabetes Ameliorates Glucose Uptake via AMPK Pathway in Skeletal Muscle Cell Line, Front Pharmacol, 2017, 8, 336. [PubMed: 28642704]

66. Jiang H, Yamashita Y, Nakamura A, Croft K and Ashida H, Quercetin and its metabolite isorhamnetin promote glucose uptake through different signalling pathways in myotubes, Scientific Reports, 2019, 9, 1–15. [PubMed: 30626917]

67. Li D, Jiang C, Mei G, Zhao Y, Chen L, Liu J, Tang Y, Gao C and Yao P, Quercetin alleviates ferroptosis of pancreatic β cells in type 2 diabetes, Nutrients, 2020, 12, 1–15.

68. Hanahan D and Weinberg RA, Hallmarks of cancer: The next generation, Cell, 2011, 144, 646–674. [PubMed: 21376230]

69. Ramchandani D, Berisa M, Tavarez DA, Li Z, Miele M, Bai Y, Lee SB, Ban Y, Dephoure N, Hendrickson RC, Cloonan SM, Gao D, Cross JR, Vahdat LT and Mittal V, Copper depletion modulates mitochondrial oxidative phosphorylation to impair triple negative breast cancer metastasis, Nat Commun, 2021, 12, 7311. [PubMed: 34911956]

70. Davis CI, Gu X, Kiefer RM, Ralle M, Gade TP and Brady DC, Altered copper homeostasis underlies sensitivity of hepatocellular carcinoma to copper chelation, Metallomics, 2020, 12, 1995–2008. [PubMed: 33146201]

71. Safi R, Nelson ER, Chitneni SK, Franz KJ, George DJ, Zalutsky MR and McDonnell DP, Copper signaling axis as a target for prostate cancer therapeutics, Cancer Research, 2014, 74, 5819–5831. [PubMed: 25320179]

72. Kew MC, Hepatic iron overload and hepatocellular carcinoma, Liver Cancer, 2014, 3, 31–40. [PubMed: 24804175]

73. Ishida S, Andreux P, Poitry-Yamate C, Auwerx J and Hanahan D, Bioavailable copper modulates oxidative phosphorylation and growth of tumors, Proceedings of the National Academy of Sciences of the United States of America, 2013, 110, 19507–19512. [PubMed: 24218578]

74. Blockhuys S, Zhang X and Wittung-Stafshede P, Single-cell tracking demonstrates copper chaperone Atox1 to be required for breast cancer cell migration, Proceedings of the National Academy of Sciences of the United States of America, 2020, 117, 2014–2019. [PubMed: 31932435]

75. Tsang T, Posimo JM, Gudiel AA, Cicchini M, Feldser DM and Brady DC, Copper is an essential regulator of the autophagic kinases ULK1/2 to drive lung adenocarcinoma, Nat Cell Biol, 2020, 22, 412–424. [PubMed: 32203415]

76. Chan N, Willis A, Kornhauser N, Mward M, Lee SB, Nackos E, Seo BR, Chuang E, Cigler T, Moore A, Donovan D, Cobham MV, Fitzpatrick V, Schneider S, Wiener A, Guillaume-Abraham J, Aljom E, Zelkowitz R, Warren JD, Lane ME, Fischbach C, Mittal V and Vahdat L, Influencing the tumor microenvironment: A Phase II study of copper depletion using tetrathiomolybdate in patients with breast cancer at high risk for recurrence and in preclinical models of lung metastases, Clinical Cancer Research, 2017, 23, 666–676. [PubMed: 27769988]

77. Liu YL, Bager CL, Willumsen N, Ramchandani D, Kornhauser N, Ling L, Cobham M, Andreopoulou E, Cigler T, Moore A, LaPolla D, Fitzpatrick V, Ward M, Warren JD, Fischbach C, Mittal V and Vahdat LT, Tetrathiomolybdate (TM)-associated copper depletion influences collagen remodeling and immune response in the pre-metastatic niche of breast cancer, Npj Breast Cancer, 2021, 7, 108. [PubMed: 34426581]

78. Yu Z, Yu Z, Chen ZB, Yang L, Ma MJ, Lu SN, Wang CS, Teng CB and Nie YZ, Zinc chelator TPEN induces pancreatic cancer cell death through causing oxidative stress and inhibiting cell autophagy, Journal of Cellular Physiology, 2019, 234, 20648–20661. [PubMed: 31054150]

79. Amano S, Kaino S, Shinoda S, Harima H, Matsumoto T, Fujisawa K, Takami T, Yamamoto N, Yamasaki T and Sakaida I, Invasion inhibition in pancreatic cancer using the oral iron chelating agent deferasirox, BMC Cancer, 2020, 20, 1–10.

80. Yamasaki T, Terai S and Sakaida I, Deferoxamine for Advanced Hepatocellular Carcinoma, New England Journal of Medicine, 2011, 365, 576–578. [PubMed: 21830988]

81. Whitnall M, Howard J, Ponka P and Richardson DR, A class of iron chelators with a wide spectrum of potent antitumor activity that overcomes resistance to chemotherapeutics, Proc National Acad Sci, 2006, 103, 14901–14906.

82. Kalinowski DS and Richardson DR, The Evolution of Iron Chelators for the Treatment of Iron Overload Disease and Cancer, Pharmacol Rev, 2005, 57, 547–583. [PubMed: 16382108]

83. Le NTV and Richardson DR, Iron chelators with high antiproliferative activity up-regulate the expression of a growth inhibitory and metastasis suppressor gene: a link between iron metabolism and proliferation, Blood, 2004, 104, 2967–2975. [PubMed: 15251988]
84. Hatcher HC, Singh RN, Torti FM and Torti SV, Synthetic and natural iron chelators: therapeutic potential and clinical use, Future Med Chem, 2009, 1, 1643–1670. [PubMed: 21425984]
85. Pinnix ZK, Miller LD, Wang W, D'Agostino R, Kute T, Willingham MC, Hatcher H, Tesfay L, Sui G, Di X, Torti SV and Torti FM, Ferroportin and iron regulation in breast cancer progression and prognosis., Science translational medicine, 2010, 2, 43ra56.
86. Brown RAM, Richardson KL, Kabir TD, Trinder D, Ganss R and Leedman PJ, Altered Iron Metabolism and Impact in Cancer Biology, Metastasis, and Immunology, Frontiers Oncol, 2020, 10, 476.
87. Fryknäs M, Zhang X, Bremberg U, Senkowski W, Olofsson MH, Brandt P, Persson I, D'Arcy P, Gullbo J, Nygren P, Schughart LK, Linder S and Larsson R, Iron chelators target both proliferating and quiescent cancer cells, Sci Rep-uk, 2016, 6, 38343.
88. Buss JL, Greene BT, Turner J, Torti FM and Torti SV, Iron Chelators in Cancer Chemotherapy, Curr Top Med Chem, 2004, 4, 1623–1635. [PubMed: 15579100]
89. Srivastava S, Somasagara RR, Hegde M, Nishana M, Tadi SK, Srivastava M, Choudhary B and Raghavan SC, Quercetin, a Natural Flavonoid Interacts with DNA, Arrests Cell Cycle and Causes Tumor Regression by Activating Mitochondrial Pathway of Apoptosis, Sci Rep-uk, 2016, 6, 24049.
90. Lan CY, Chen SY, Kuo CW, Lu CC and Yen GC, Quercetin facilitates cell death and chemosensitivity through RAGE/PI3K/AKT/mTOR axis in human pancreatic cancer cells, Journal of Food and Drug Analysis, 2019, 27, 887–896. [PubMed: 31590760]
91. Quideau S, Deffieux D, Douat-Casassus C and Pouységu L, Plant polyphenols: Chemical properties, biological activities, and synthesis, Angewandte Chemie - International Edition, 2011, 50, 586–621. [PubMed: 21226137]
92. Chaves JO, de Souza MC, da Silva LC, Lachos-Perez D, Torres-Mayanga PC, da F. Machado AP, Forster-Carneiro T, Vázquez-Espinosa M, González-de-Peredo AV, Barbero GF and Rostagno MA, Extraction of Flavonoids From Natural Sources Using Modern Techniques, Front Chem, 2020, 8, 507887. [PubMed: 33102442]
93. Tarahovsky YS, Kim YA, Yagolnik EA and Muzafarov EN, Flavonoid-membrane interactions: Involvement of flavonoid-metal complexes in raft signaling, Biochimica et Biophysica Acta - Biomembranes, 2014, 1838, 1235–1246.
94. Dinda B, Dinda M, Roy A and Dinda S, Dietary plant flavonoids in prevention of obesity and diabetes, Elsevier Ltd, vol. 120.
95. Khan AU, Dagur HS, Khan M, Malik N, Alam M and Mushtaque M, Therapeutic role of flavonoids and flavones in cancer prevention: Current trends and future perspectives, European Journal of Medicinal Chemistry Reports, 2021, 3, 100010.
96. Maiti S, Nazmeen A, Medda N, Patra R and Ghosh TK, Flavonoids green tea against oxidant stress and inflammation with related human diseases, Clinical Nutrition Experimental, 2019, 24, 1–14.
97. Lim MH, Metal-associated amyloid-beta species in Alzheimer's disease, Current Opinions in Chemical Biology, 2012, 16, 67–73.
98. He X, Park HM, Hyung S-J, DeToma AS, Kim C, Ruotolo BT and Lim MH, Exploring the reactivity of flavonoid compounds with metal-associated amyloid-β species, Dalton transactions (Cambridge, England : 2003), 2012, 41, 6558. [PubMed: 22437427]
99. Park S, Yi Y and Lim MH, Reactivity of Flavonoids Containing a Catechol or Pyrogallol Moiety with Metal-Free and Metal-Associated Amyloid-β, B Korean Chem Soc, 2021, 42, 17–24.
100. Nam G, Hong M, Lee J, Lee HJ, Ji Y, Kang J, Baik M-H and Lim MH, Multiple reactivities of flavonoids towards pathological elements in Alzheimer's disease: structure–activity relationship, Chem Sci, 2020, 11, 10243–10254. [PubMed: 34094290]
101. Perez C, Tong Y and Guo M, Iron Chelators as Potential Therapeutic Agents for Parkinsons Disease, Curr Bioact Compd, 2008, 4, 150–158. [PubMed: 19809592]
102. Guo M, Perez C, Wei Y, Rapoza E, Su G, Bou-Abdallah F and Chasteen ND, Iron-binding properties of plant phenolics and cranberry's bio-effects, Dalton T, 2007, 0, 4951–4961.

103. Yi H, Peng H, Wu X, Xu X, Kuang T, Zhang J, Du L and Fan G, The Therapeutic Effects and Mechanisms of Quercetin on Metabolic Diseases: Pharmacological Data and Clinical Evidence, Oxid Med Cell Longev, 2021, 2021, 6678662. [PubMed: 34257817]
104. Fang X, Gao W, Yang Z, Gao Z and Li H, Dual Anti-/Prooxidant Behaviors of Flavonoids Pertaining to Cu(II)-Catalyzed Tyrosine Nitration of the Insulin Receptor Kinase Domain in an Antidiabetic Study, Journal of Agricultural and Food Chemistry, 2020, 68, 6202–6211. [PubMed: 32395994]
105. Cremonini E, Wang Z, Bettaieb A, Adamo AM, Daveri E, Mills DA, Kalanetra KM, Haj FG, Karakas S and Oteiza PI, (−)-Epicatechin protects the intestinal barrier from high fat diet-induced permeabilization: Implications for steatosis and insulin resistance, Redox Biology, 2018, 14, 588–599. [PubMed: 29154190]
106. Miao L, Zhang H, Yang L, Chen L, Xie Y and Xiao J, Flavonoids, Antioxidants Effects in Health: The Bright and the Dark Side, 2022, 58, 353–374.
107. Perron NR and Brumaghim JL, A Review of the Antioxidant Mechanisms of Polyphenol Compounds Related to Iron Binding, Cell Biochem Biophys, 2009, 53, 75–100. [PubMed: 19184542]
108. Říha M, Karlíčková J, Filipský T, Macáková K, Rocha L, Bovicelli P, Silvestri IP, Saso L, Jahodář L, Hrdina R and Mladěnka P, In vitro evaluation of copper-chelating properties of flavonoids, RSC Advances, 2014, 4, 32628–32638.
109. Engelmann MD, Hutcheson R and Cheng IF, Stability of ferric complexes with 3-hydroxyflavone (flavonol), 5,7-dihydroxyflavone (chrysin), and 3′,4′-dihydroxyflavone, Journal of Agricultural and Food Chemistry, 2005, 53, 2953–2960. [PubMed: 15826045]
110. Catapano MC, Tvrdý V, Karlíčková J, Migkos T, Valentová K, Křen V and Mladěnka P, The stoichiometry of isoquercitrin complex with iron or copper is highly dependent on experimental conditions, Nutrients, 2017, 9, 1–14.
111. Chen KTJ, Anantha M, Leung AWY, Kulkarni JA, Militao GGC, Wehbe M, Sutherland B, Cullis PR and Bally MB, Characterization of a liposomal copper(II)-quercetin formulation suitable for parenteral use, Drug Deliv Transl Re, 2019, 10, 202–215.
112. Tang X, Tang P and Liu L, Molecular structure–Affinity relationship of Flavonoids in Lotus leaf (Nelumbo nucifera Gaertn.) on Binding to Human serum albumin and Bovine serum albumin by Spectroscopic Method, Molecules, , DOI:10.3390/molecules22071036.
113. Mira L, Fernandez MT, Santos M, Rocha R, Florêncio MH and Jennings KR, Interactions of flavonoids with iron and copper ions: A mechanism for their antioxidant activity, Free Radical Research, 2002, 36, 1199–1208. [PubMed: 12592672]
114. Cherrak SA, Mokhtari-Soulimane N, Berroukeche F, Bensenane B, Cherbonnel A, Merzouk H and Elhabiri M, In vitro antioxidant versus metal ion chelating properties of flavonoids: A structure-activity investigation, PLoS ONE, 2016, 11, 1–21.
115. Samsonowicz M and Regulska E, Spectroscopic study of molecular structure, antioxidant activity and biological effects of metal hydroxyflavonol complexes, Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy, 2017, 173, 757–771. [PubMed: 27792987]
116. Ansari AA, DFT and 1H NMR molecular spectroscopic studies on biologically anti-oxidant active paramagnetic lanthanide(III)-chrysin complexes, Main Group Chemistry, 2008, 7, 43–56.
117. Karlíčková J, Macáková K, Říha M, Pinheiro LMT, Filipský T, Horňasová V, Hrdina R and Mladěnka P, Isoflavones reduce copper with minimal impact on iron in vitro, Oxidative Medicine and Cellular Longevity, , DOI:10.1155/2015/437381.
118. Lee VJ and Heffern MC, Structure-activity assessment of flavonoids as modulators of copper transport, Front Chem, 2022, 10, 1–15.
119. Azam S, Hadi N, Khan NU and Hadi SM, Prooxidant property of green tea polyphenols epicatechin and epigallocatechin-3-gallate: Implications for anticancer properties, Toxicology in Vitro, 2004, 18, 555–561. [PubMed: 15251172]
120. Kumar N and Goel N, Phenolic acids: Natural versatile molecules with promising therapeutic applications, Biotechnology Reports, 2019, 24, e00370. [PubMed: 31516850]

121. Mandal SM, Chakraborty D, Dey S, Mandal SM, Chakraborty D and Dey S, Phenolic acids act as signaling molecules in plant- microbe symbioses Phenolic acids act as signaling molecules in plant-microbe symbioses, Plant Signaling and Behavior, 2017, 2324, 359–368.

122. Srinivasulu C, Ramgopal M, Ramanjaneyulu G, Anuradha CM and Kumar CS, Syringic acid (SA) − A Review of Its Occurrence, Biosynthesis, Pharmacological and Industrial Importance, Biomedicine and Pharmacotherapy, 2018, 108, 547–557. [PubMed: 30243088]

123. Masella R, Santangelo C, D'Archivio M, LiVolti G, Giovannini C and Galvano F, Protocatechuic Acid and Human Disease Prevention: Biological Activities and Molecular Mechanisms, Current Medicinal Chemistry, 2012, 19, 2901–2917. [PubMed: 22519395]

124. Kalinowska M, Gołębiewska E, Świderski G, Męczyńska-Wielgosz S, Lewandowska H, Pietryczuk A, Cudowski A, Astel A, Świsłocka R, Samsonowicz M, Złowodzka AB, Priebe W and Lewandowski W, Plant-derived and dietary hydroxybenzoic acids—a comprehensive study of structural, anti-/pro-oxidant, lipophilic, antimicrobial, and cytotoxic activity in mda-mb-231 and mcf-7 cell lines, Nutrients, , DOI:10.3390/nu13093107.

125. Juurlink BHJ, Azouz HJ, Aldalati AMZ, Altinawi BMH and Ganguly P, Hydroxybenzoic acid isomers and the cardiovascular system, Nutrition Journal, 2014, 13, 1–10. [PubMed: 24405527]

126. Chang WC, Wu JSB, Chen CW, Kuo PL, Chien HM, Wang YT and Shen SC, Protective effect of vanillic acid against hyperinsulinemia, hyperglycemia and hyperlipidemia via alleviating hepatic insulin resistance and inflammation in High-Fat Diet (HFD)-fed rats, Nutrients, 2015, 7, 9946–9959. [PubMed: 26633482]

127. Sreelekshmi M and Raghu KG, Vanillic acid mitigates the impairments in glucose metabolism in HepG2 cells through BAD–GK interaction during hyperinsulinemia, Journal of Biochemical and Molecular Toxicology, 2021, 35, 1–8.

128. Mohan S, George G and Raghu KG, Vanillic acid retains redox status in HepG2 cells during hyperinsulinemic shock using the mitochondrial pathway, Food Bioscience, 2021, 41, 101016.

129. Ramachandran V and Raja B, Protective effects of syringic acid against acetaminophen-induced hepatic damage in albino rats, Journal of Basic and Clinical Physiology and Pharmacology, 2010, 21, 369–386. [PubMed: 21305852]

130. Gao Y, Tian R, Liu H, Xue H, Zhang R, Han S, Ji L, Huang W, Zhan J and You Y, Research progress on intervention effect and mechanism of protocatechuic acid on nonalcoholic fatty liver disease, Critical Reviews in Food Science and Nutrition, 2021, 0, 1–23.

131. Abdelmageed ME, Shehatou GSG, Suddek GM and Salem HA, Protocatechuic acid improves hepatic insulin resistance and restores vascular oxidative status in type-2 diabetic rats, Environmental Toxicology and Pharmacology, 2021, 83, 103577. [PubMed: 33383195]

132. Alam Md. A., Anti-hypertensive Effect of Cereal Antioxidant Ferulic Acid and Its Mechanism of Action, Frontiers Nutrition, 2019, 6, 121.

133. Srinivasan M, Sudheer AR and Menon VP, Ferulic acid: Therapeutic potential through its antioxidant property, Journal of Clinical Biochemistry and Nutrition, 2007, 40, 92–100. [PubMed: 18188410]

134. Xu J, Ge J, He X, Sheng Y, Zheng S, Zhang C, Xu W and Huang K, Caffeic acid reduces body weight by regulating gut microbiota in diet-induced-obese mice, J Funct Food, 2020, 74, 104061.

135. Yang C, Deng Q, Xu J, Wang X, Hu C, Tang H and Huang F, Sinapic acid and resveratrol alleviate oxidative stress with modulation of gut microbiota in high-fat diet-fed rats, Food Research International, 2019, 116, 1202–1211. [PubMed: 30716907]

136. Santana-Gálvez J, Cisneros-Zevallos L and Jacobo-Velázquez D, Chlorogenic Acid: Recent Advances on Its Dual Role as a Food Additive and a Nutraceutical against Metabolic Syndrome, Molecules, 2017, 22, 358. [PubMed: 28245635]

137. Shi A, Li T, Zheng Y, Song Y, Wang H, Wang N, Dong L and Shi H, Chlorogenic Acid Improves NAFLD by Regulating gut Microbiota and GLP-1, Front Pharmacol, 2021, 12, 693048. [PubMed: 34276380]

138. Abdollahi M, Marandi SM, Ghaedi K, Safaeinejad Z, Kazeminasab F, Shirkhani S, Sanei MH, Rezvanian P and Nasr-Esfahani MH, Insulin-Related Liver Pathways and the Therapeutic Effects of Aerobic Training, Green Coffee, and Chlorogenic Acid Supplementation in Prediabetic Mice, Oxidative Medicine and Cellular Longevity, 2022, 2022, 1–14.

139. Mansour A, Mohajeri-Tehrani MR, Samadi M, Qorbani M, Merat S, Adibi H, Poustchi H and Hekmatdoost A, Effects of supplementation with main coffee components including caffeine and/or chlorogenic acid on hepatic, metabolic, and inflammatory indices in patients with non-alcoholic fatty liver disease and type 2 diabetes: a randomized, double-blind, placebo-c, Nutrition Journal, 2021, 20, 1–11. [PubMed: 33388067]
140. Hynes MJ and O'Coinceanainn M, The kinetics and mechanisms of reactions of iron(III) with caffeic acid, chlorogenic acid, sinapic acid, ferulic acid and naringin, Journal of Inorganic Biochemistry, 2004, 98, 1457–1464. [PubMed: 15271524]
141. Truong DH, Nhung NTA and Dao DQ, Iron ions chelation-based antioxidant potential vs. pro-oxidant risk of ferulic acid: A DFT study in aqueous phase, Computational and Theoretical Chemistry, 2020, 1185, 112905.
142. Singh K and Kumar A, Kinetics of complex formation of Fe(III) with caffeic acid: Experimental and theoretical study, Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy, 2019, 211, 148–153. [PubMed: 30530068]
143. Kalinowska M, Sienkiewicz-Gromiuk J, Świderski G, Pietryczuk A, Cudowski A and Lewandowski W, Zn(II) Complex of Plant Phenolic Chlorogenic Acid: Antioxidant, Antimicrobial and Structural Studies, Materials, 2020, 13, 3745. [PubMed: 32847095]
144. Mazzone G, On the Inhibition of Hydroxyl Radical Formation by Hydroxycinnamic Acids: The Case of Caffeic Acid as a Promising Chelating Ligand of a Ferrous Ion, Journal of Physical Chemistry A, 2019, 123, 9560–9566. [PubMed: 31603328]
145. Oke IM, Ramorobi LM, Mashele SS, Bonnet SL, Makhafola TJ, Eze KC, Noreljaleel AEM and Chukwuma CI, Vanillic acid-Zn(II) complex: a novel complex with antihyperglycaemic and anti-oxidative activity, The Journal of pharmacy and pharmacology, 2021, 73, 1703–1714. [PubMed: 34109975]
146. Murata Y, Yoshida M, Sakamoto N, Morimoto S, Watanabe T and Namba K, Iron uptake mediated by the plant-derived chelator nicotianamine in the small intestine, Journal of Biological Chemistry, 2021, 296, 100195. [PubMed: 33334885]
147. Hussain MI, Syed QA, Khattak MNK, Hafez B, Reigosa MJ and El-Keblawy A, Natural product coumarins: biological and pharmacological perspectives, Biologia, 2019, 74, 863–888.
148. Akkol EK, Genç Y, Karpuz B, Sobarzo-Sánchez E and Capasso R, Coumarins and Coumarin-Related Compounds in Pharmacotherapy of Cancer, Cancers, 2020, 12, 1959. [PubMed: 32707666]
149. Hiremathad A, Chand K and Keri RS, Development of coumarin–benzofuran hybrids as versatile multitargeted compounds for the treatment of Alzheimer's Disease, Chemical Biology and Drug Design, 2018, 92, 1497–1503. [PubMed: 29679445]
150. Capra JC, Cunha MP, Machado DG, Zomkowski ADE, Mendes BG, Santos ARS, Pizzolatti MG and Rodrigues ALS, Antidepressant-like effect of scopoletin, a coumarin isolated from Polygala sabulosa (Polygalaceae) in mice: Evidence for the involvement of monoaminergic systems, Eur J Pharmacol, 2010, 643, 232–238. [PubMed: 20599906]
151. Ali Md. Y., Jannat S, Jung HA, Choi RJ, Roy A and Choi JS, Anti-Alzheimer's disease potential of coumarins from Angelica decursiva and Artemisia capillaris and structure-activity analysis, Asian Pac J Trop Med, 2016, 9, 103–111. [PubMed: 26919937]
152. Ali Md. Y., Jung HA and Choi JS, Anti-diabetic and anti-Alzheimer's disease activities of Angelica decursiva, Arch Pharm Res, 2015, 38, 2216–2227. [PubMed: 26152875]
153. Islam MN, Jung HA, Sohn HS, Kim HM and Choi JS, Potent α-glucosidase and protein tyrosine phosphatase 1B inhibitors from Artemisia capillaris, Archives of Pharmacal Research, 2013, 36, 542–552. [PubMed: 23435948]
154. Hussain H, Nazir M, Saleem M, Al-Harrasi A, Elizbit and Green IR, Fruitful decade of fungal metabolites as anti-diabetic agents from 2010 to 2019: emphasis on α-glucosidase inhibitors, Springer Netherlands, vol. 20.
155. Tamrakar AK, Maurya CK and Rai AK, PTP1B inhibitors for type 2 diabetes treatment: A patent review (2011–2014), Expert Opinion on Therapeutic Patents, 2014, 24, 1101–1115. [PubMed: 25120222]

156. Kang KS, Lee W, Jung Y, Lee JH, Lee S, Eom DW, Jeon Y, Yoo HH, Jin MJ, Song IK, Kim WJ, Ham J, Kim HJ and Kim SN, Protective effect of esculin on streptozotocin-induced diabetic renal damage in mice, Journal of Agricultural and Food Chemistry, 2014, 62, 2069–2076. [PubMed: 24484395]

157. Wang J, Lu J, Lan Y, Zhou H, Li W and Xiang M, Total coumarins from Urtica dentata Hand prevent murine autoimmune diabetes via suppression of the TLR4-signaling pathways, Journal of Ethnopharmacology, 2013, 146, 379–392. [PubMed: 23340441]

158. Mergu N, Kim M and Son Y-A, A coumarin-derived Cu2+-fluorescent chemosensor and its direct application in aqueous media, Spectrochimica Acta Part Mol Biomol Spectrosc, 2018, 188, 571–580.

159. García-Beltrán O, Mena N, Friedrich LC, Netto-Ferreira JC, Vargas V, Quina FH, Núñez MT and Cassels BK, Design and synthesis of a new coumarin-based “turn-on” fluorescent probe selective for Cu +2, Tetrahedron Letters, 2012, 53, 5280–5283.

160. Mladěnka P, Macáková K, Zatloukalová L, Řeháková Z, Singh BK, Prasad AK, Parmar VS, Jahodář L, Hrdina R and Saso L, In vitro interactions of coumarins with iron, Biochimie, 2010, 92, 1108–1114. [PubMed: 20381579]

161. Pecyna P, Wargula J, Murias M and Kucinska M, More than resveratrol: New insights into stilbene-based compounds, Biomolecules, 2020, 10, 1–40.

162. Singh AP, Singh R, Verma SS, Rai V, Kaschula CH, Maiti P and Gupta SC, Health benefits of resveratrol: Evidence from clinical studies, Medicinal Research Reviews, 2019, 39, 1851–1891. [PubMed: 30741437]

163. Chou YC, Ho CT and Pan MH, Stilbenes: Chemistry and Molecular Mechanisms of Anti-obesity, Current Pharmacology Reports, 2018, 4, 202–209.

164. dos S. Lacerda D, Türck P, de Lima-Seolin BG, Colombo R, Ortiz VD, Bonetto JHP, Campos-Carraro C, Bianchi SE, Belló-Klein A, Bassani VL and da R. Araujo AS, Pterostilbene reduces oxidative stress, prevents hypertrophy and preserves systolic function of right ventricle in cor pulmonale model, British Journal of Pharmacology, 2017, 174, 3302–3314. [PubMed: 28703274]

165. Sunilkumar D, Drishya G, Chandrasekharan A, Shaji SK, Bose C, Jossart J, Perry JJP, Mishra N, Kumar GB and Nair BG, Oxyresveratrol drives caspase-independent apoptosis-like cell death in MDA-MB-231 breast cancer cells through the induction of ROS, Biochemical Pharmacology, , DOI:10.1016/j.bcp.2019.113724.

166. Hyo JK, Ki WL and Hyong JL, Protective effects of piceatannol against beta-amyloid-induced neuronal cell death, Annals of the New York Academy of Sciences, 2007, 1095, 473–482. [PubMed: 17404060]

167. Tan HY, Tse IMY, Li ETS and Wang M, Oxyresveratrol supplementation to C57bl/6 mice fed with a high-fat diet ameliorates obesity-associated symptoms, Nutrients, , DOI:10.3390/nu9020147.

168. Choi JH, Song NJ, Lee AR, Lee DH, Seo MJ, Kim S, Chang SH, Yang DK, Hwang YJ, Hwang KA, Ha TS, Yun UJ and Park KW, Oxyresveratrol increases energy expenditure through Foxo3a-mediated Ucp1 induction in high-fat-diet-induced obese mice, International Journal of Molecular Sciences, , DOI:10.3390/ijms20010026.

169. Pan MH, Koh YC, Lee TL, Wang B, Chen WK, Nagabhushanam K and Ho CT, Resveratrol and Oxyresveratrol Activate Thermogenesis via Different Transcriptional Coactivators in High-Fat Diet-Induced Obese Mice, Journal of Agricultural and Food Chemistry, 2019, 67, 13605–13616. [PubMed: 31735033]

170. Kershaw J and Kim KH, The Therapeutic Potential of Piceatannol, a Natural Stilbene, in Metabolic Diseases: A Review, Journal of medicinal food, 2017, 20, 427–438. [PubMed: 28387565]

171. Kitada M, Ogura Y, Maruki-Uchida H, Sai M, Suzuki T, Kanasaki K, Hara Y, Seto H, Kuroshima Y, Monno I and Koya D, The effect of piceatannol from passion fruit (Passiflora edulis) seeds on metabolic health in humans, Nutrients, 2017, 9, 1–17.

172. Pan M, Wu J, Ho C and Lai C, Antiobesity molecular mechanisms of action: Resveratrol and pterostilbene, Biofactors, 2018, 44, 50–60. [PubMed: 29315906]

173. Walle T, Hsieh F, DeLegge MH, Oatis JE and Walle UK, High absorption but very low bioavailability of oral resveratrol in humans, Drug Metabolism and Disposition, 2004, 32, 1377–1382. [PubMed: 15333514]
174. Ullah MF, Ahmad A, Khan HY, Zubair H, Sarkar FH and Hadi SM, The Prooxidant Action of Dietary Antioxidants Leading to Cellular DNA Breakage and Anticancer Effects: Implications for Chemotherapeutic Action Against Cancer, Cell Biochemistry and Biophysics, 2013, 67, 431–438. [PubMed: 22038302]
175. Zheng LF, Wei QY, Cai YJ, Fang JG, Zhou B, Yang L and Liu ZL, DNA damage induced by resveratrol and its synthetic analogues in the presence of Cu (II) ions: Mechanism and structure-activity relationship, Free Radical Biology and Medicine, 2006, 41, 1807–1816. [PubMed: 17157183]
176. Volkart PA, Gassen RB, Nogueira BM, Porto BN, Vargas JE and Souto AA, Antitumor activity of resveratrol is independent of Cu(II) complex formation in MCF-7 cell line, Bioorg Med Chem Lett, 2017, 27, 3238–3242. [PubMed: 28647350]
177. Li Z, Yang X, Dong S and Li X, DNa breakage induced by piceatannol and copper(II): Mechanism and anticancer properties, Oncology Letters, 2012, 3, 1087–1094. [PubMed: 22783397]
178. Tamboli V, Defant A, Mancini I and Tosi P, A study of resveratrol-copper complexes by electrospray ionization mass spectrometry and density functional theory calculations, Rapid Commun. Mass Spectrom, 2011, 25, 526–532. [PubMed: 21259361]
179. Granzotto A and Zatta P, Resveratrol and Alzheimer's disease: Message in a bottle on red wine and cognition, Frontiers in Aging Neuroscience, 2014, 6, 1–7. [PubMed: 24478697]
180. Chiavarino B, Crestoni ME, Fornarini S, Taioli S, Mancini I and Tosi P, Infrared spectroscopy of copper-resveratrol complexes: A joint experimental and theoretical study, Journal of Chemical Physics, , DOI:10.1063/1.4732583.
181. Xueming X, Lignans : Source , Antioxidant.
182. Webb AL and McCullough ML, Dietary lignans: Potential role in cancer prevention, Nutrition and Cancer, 2005, 51, 117–131. [PubMed: 15860433]
183. Senizza A, Rocchetti G, Mosele JI, Patrone V, Callegari ML, Morelli L and Lucini L, Lignans and gut microbiota: An interplay revealing potential health implications, Molecules, 2020, 25, 1–17.
184. Peterson J, Dwyer J, Adlercreutz H, Scalbert A, Jacques P and McCullough ML, Dietary lignans: Physiology and potential for cardiovascular disease risk reduction, Nutrition Reviews, 2010, 68, 571–603. [PubMed: 20883417]
185. Zanella I, Biasiotto G, Holm F and di Lorenzo D, Cereal Lignans, Natural Compounds of Interest for Human Health?, Nat Prod Commun, 2017, 12, 1934578X1701200139.
186. Soleymani S, Habtemariam S, Rahimi R and Nabavi SM, The what and who of dietary lignans in human health: Special focus on prooxidant and antioxidant effects, Trends in Food Science and Technology, 2020, 106, 382–390.
187. guang Li C, lin Ni C, Yang M, zhao Tang Y, Li Z, juan Zhu Y, huan Jiang Z, Sun B and jun Li C, Honokiol protects pancreatic β cell against high glucose and intermittent hypoxia-induced injury by activating Nrf2/ARE pathway in vitro and in vivo, Biomedicine and Pharmacotherapy, 2018, 97, 1229–1237. [PubMed: 29145148]
188. Liu JX, Shen SN, Tong Q, Wang YT and Lin LG, Honokiol protects hepatocytes from oxidative injury through mitochondrial deacetylase SIRT3, European Journal of Pharmacology, 2018, 834, 176–187. [PubMed: 30036533]
189. Kim HY, Kim JK, Choi JH, Jung JY, Oh WY, Kim DC, Lee HS, Kim YS, Kang SS, Lee SH and Lee SM, Hepatoprotective effect of pinoresinol on carbon tetrachloride-induced hepatic damage in mice, Journal of Pharmacological Sciences, 2010, 112, 105–112. [PubMed: 20093790]
190. Kim YW, Kim YM, Yang YM, Kim TH, Hwang SJ, Lee JR, Kim SC and Kim SG, Inhibition of SREBP-1c-mediated hepatic steatosis and oxidative stress by sauchinone, an AMPK-activating lignan in Saururus chinensis, Free Radical Biology and Medicine, 2010, 48, 567–578. [PubMed: 20005944]

191. Ma JQ, Ding J, Zhang L and Liu CM, Hepatoprotective properties of sesamin against CCl4 induced oxidative stress-mediated apoptosis in mice via JNK pathway, Food and Chemical Toxicology, 2014, 64, 41–48. [PubMed: 24287204]

192. Lv D, Zhu CQ and Liu L, Sesamin ameliorates oxidative liver injury induced by carbon tetrachloride in rat, International Journal of Clinical and Experimental Pathology, 2015, 8, 5733–5738. [PubMed: 26191289]

193. Donoso-Fierro C, Becerra J, Bustos-Concha E and Silva M, Chelating and antioxidant activity of lignans from Chilean woods (Cupressaceae), Hfsg, 2009, 63, 559–563.

194. Fucassi F, Heikal A, Mikhalovska LI, Standen G, Allan IU, Mikhalovsky VS and Cragg PJ, Metal chelation by a plant lignan, secoisolariciresinol diglucoside, Journal of Inclusion Phenomena and Macrocyclic Chemistry, 2014, 80, 345–351.

195. Pivari F, Mingione A, Brasacchio C and Soldati L, Curcumin and Type 2 Diabetes Mellitus: Prevention and Treatment, Nutrients, 2019, 11, 1837. [PubMed: 31398884]

196. Zheng J, Cheng J, Zheng S, Feng Q and Xiao X, Curcumin, A Polyphenolic Curcuminoid With Its Protective Effects and Molecular Mechanisms in Diabetes and Diabetic Cardiomyopathy, Front Pharmacol, 2018, 9, 472. [PubMed: 29867479]

197. Yuan F, Dong H, Gong J, Wang D, Hu M, Huang W, Fang K, Qin X, Qiu X, Yang X and Lu F, A Systematic Review and Meta-analysis of Randomized Controlled Trials on the Effects of Turmeric and Curcuminoids on Blood Lipids in Adults with Metabolic Diseases, Adv Nutr, 2019, 10, 791–802. [PubMed: 31212316]

198. Hieu TQ and Thao DTT, Enhancing the Solubility of Curcumin Metal Complexes and Investigating Some of Their Biological Activities, Journal of Chemistry, , DOI:10.1155/2019/8082195.

199. Prasad S, Dubourdieu D, Srivastava A, Kumar P and Lall R, Metal–curcumin complexes in therapeutics: An approach to enhance pharmacological effects of curcumin, International Journal of Molecular Sciences, , DOI:10.3390/ijms22137094.

200. Yuan R, Li Y, Han S, Chen X, Chen J, He J, Gao H, Yang Y, Yang S and Yang Y, Fe-Curcumin Nanozyme-Mediated Reactive Oxygen Species Scavenging and Anti-Inflammation for Acute Lung Injury, ACS Central Science, 2022, 8, 10–21. [PubMed: 35106369]

201. Rodriguez-Concepcion M, Avalos J, Bonet ML, Boronat A, Gomez-Gomez L, Hornero-Mendez D, Limon MC, Meléndez-Martínez AJ, Olmedilla-Alonso B, Palou A, Ribot J, Rodrigo MJ, Zacarias L and Zhu C, A global perspective on carotenoids: Metabolism, biotechnology, and benefits for nutrition and health, Prog Lipid Res, 2018, 70, 62–93. [PubMed: 29679619]

202. Bonet ML, Canas JA, Ribot J and Palou A, Carotenoids in Nature, Biosynthesis, Regulation and Function, 2016, vol. 79.

203. Carotenoids: Structure and Function in the Human Body, 2021.

204. Christensen K, Lawler T and Mares J, Dietary carotenoids and non-alcoholic fatty liver disease among US adults, NHANES 2003–2014, Nutrients, 2019, 11, 1–12.

205. Cao Y, Wang C, Liu J, Liu ZM, Ling WH and Chen YM, Greater serum carotenoid levels associated with lower prevalence of nonalcoholic fatty liver disease in Chinese adults, Scientific Reports, 2015, 5, 1–8.

206. Elvira-Torales LI, García-Alonso J and Periago-Castón MJ, Nutritional importance of carotenoids and their effect on liver health: A review, Antioxidants, , DOI:10.3390/antiox8070229.

207. Kobori M, Ni Y, Takahashi Y, Watanabe N, Sugiura M, Ogawa K, Nagashimada M, Kaneko S, Naito S and Ota T, B-Cryptoxanthin Alleviates Diet-Induced Nonalcoholic Steatohepatitis By Suppressing Inflammatory Gene Expression in Mice, PLoS ONE, 2014, 9, 1–11.

208. Roohbakhsh A, Karimi G and Iranshahi M, Carotenoids in the treatment of diabetes mellitus and its complications: A mechanistic review, Biomed Pharmacother, 2017, 91, 31–42. [PubMed: 28445831]

209. Jomova K and Valko M, Health protective effects of carotenoids and their interactions with other biological antioxidants, European Journal of Medicinal Chemistry, 2013, 70, 102–110. [PubMed: 24141200]

210. Uraipong C and Zhao J, In vitro digestion of rice bran proteins produces peptides with potent inhibitory effects on α-glucosidase and angiotensin I converting enzyme, Journal of the Science of Food and Agriculture, 2018, 98, 758–766. [PubMed: 28677835]

211. Ashaolu TJ, Soy bioactive peptides and the gut microbiota modulation, Applied Microbiology and Biotechnology, 2020, 104, 9009–9017. [PubMed: 32945899]

212. Chakrabarti S, Guha S and Majumder K, Food-derived bioactive peptides in human health: Challenges and opportunities, Nutrients, 2018, 10, 1–17.

213. Chalamaiah M, Yu W and Wu J, Immunomodulatory and anticancer protein hydrolysates (peptides) from food proteins: A review, Food Chemistry, 2018, 245, 205–222. [PubMed: 29287362]

214. Ramkisson S, Dwarka D, Venter S and Mellem JJ, In vitro anticancer and antioxidant potential of Amaranthus cruentus protein and its hydrolysates, Food Science and Technology (Brazil), 2020, 40, 634–639.

215. Jahanbani R, Ghaffari SM, Salami M, Vahdati K, Sepehri H, Sarvestani NN, Sheibani N and Moosavi-Movahedi AA, Antioxidant and Anticancer Activities of Walnut (Juglans regia L.) Protein Hydrolysates Using Different Proteases, Plant Food Hum Nutr, 2016, 71, 402–409.

216. Avilés-Gaxiola S, León-Félix J, Jiménez-Nevárez YB, Angulo-Escalante MA, Ramos-Payán R, Colado-Velázquez J and Heredia JB, Antioxidant and anti-inflammatory properties of novel peptides from Moringa oleifera Lam. leaves, S Afr J Bot, 2021, 141, 466–473.

217. Rodriguez-Martin NM, la Paz SM-D, Toscano R, Grao-Cruces E, Villanueva A, Pedroche J, Millan F and Millan-Linares MC, Hemp (Cannabis sativa l.) protein hydrolysates promote anti-inflammatory response in primary human monocytes, Biomolecules, , DOI:10.3390/biom10050803.

218. la Paz SM, Rodriguez-Martin NM, Villanueva A, Pedroche J, Cruz-Chamorro I, Millan F and Millan-Linares MC, Evaluation of Anti-Inflammatory and Atheroprotective Properties of Wheat Gluten Protein Hydrolysates in Primary Human Monocytes, Foods, , DOI:10.3390/foods9070854.

219. Lammi C, Aiello G, Boschin G and Arnoldi A, Multifunctional peptides for the prevention of cardiovascular disease: A new concept in the area of bioactive food-derived peptides, Journal of Functional Foods, 2019, 55, 135–145.

220. Angeles JGC, Villanueva JC, Uy LYC, Mercado SMQ, Tsuchiya MCL, Lado JP, Angelia MRN, Bercansil-Clemencia MCM, Estacio MAC and Torio MAO, Legumes as functional food for cardiovascular disease, Applied Sciences (Switzerland), 2021, 11, 1–39.

221. Jakubczyk A, Karas M, Rybczynska-Tkaczyk K, Zielinska E and Zielinski D, Current trends of bioactive peptides - New sources and therapeutic effect, Foods, , DOI:10.3390/foods9070846.

222. Patil SP, Goswami A, Kalia K and Kate AS, Plant-Derived Bioactive Peptides: A Treatment to Cure Diabetes, International Journal of Peptide Research and Therapeutics, 2020, 26, 955–968. [PubMed: 32435169]

223. de Medeiros AF, de Queiroz JLC, Maciel BLL and de A. Morais AH, Hydrolyzed Proteins and Vegetable Peptides: Anti-Inflammatory Mechanisms in Obesity and Potential Therapeutic Targets, Nutrients, , DOI:10.3390/nu14030690.

224. Jover J, Bosque R and Sales J, A comparison of the binding affinity of the common amino acids with different metal cations, Dalton T, 2008, 0, 6441–6453.

225. Esfandi R, Willmore WG and Tsopmo A, Peptidomic analysis of hydrolyzed oat bran proteins, and their in vitro antioxidant and metal chelating properties, Food Chemistry, 2019, 279, 49–57. [PubMed: 30611511]

226. Hu R, Chen G and Li Y, Production and characterization of antioxidative hydrolysates and peptides from corn gluten meal using papain, ficin, and bromelain, Molecules, , DOI:10.3390/molecules25184091.

227. Kubglomsong S, Theerakulkait C, Reed RL, Yang L, Maier CS and Stevens JF, Isolation and Identification of Tyrosinase-Inhibitory and Copper-Chelating Peptides from Hydrolyzed Rice-Bran-Derived Albumin, Journal of Agricultural and Food Chemistry, 2018, 66, 8346–8354. [PubMed: 30016586]

228. Brown T, Deisign thinking, Harvard Business Review, 2008, 86, 84–92. [PubMed: 18605031]

229. Dai F, Yan WJ, Du YT, Bao XZ, Li XZ and Zhou B, Structural basis, chemical driving forces and biological implications of flavones as Cu(II) ionophores, Free Radical Biology and Medicine, 2017, 108, 554–563. [PubMed: 28431962]

230. Oliveri V, Selective Targeting of Cancer Cells by Copper Ionophores: An Overview, Frontiers in Molecular Biosciences, 2022, 9, 1–14.

231. McClements DJ and Grossmann L, A brief review of the science behind the design of healthy and sustainable plant-based foods, Npj Sci Food, 2021, 5, 17. [PubMed: 34083539]

232. McGrath L and Fernandez M-L, Plant-based diets and metabolic syndrome: Evaluating the influence of diet quality, J Agric Food Res, 2022, 9, 100322.

233. Jose CG, Jacob RH and Gardner GE, Alternative cutting methods and dry aging reduce the shear force of hot boned beef striploin in Bos indicus cattle, Meat Sci, 2020, 163, 108036. [PubMed: 31951922]

234. Ge EJ, Bush AI, Casini A, Cobine PA, Cross JR, DeNicola GM, Dou QP, Franz KJ, Gohil VM, Gupta S, Kaler SG, Lutsenko S, Mittal V, Petris MJ, Polishchuk R, Ralle M, Schilsky ML, Tonks NK, Vahdat LT, Aelst LV, Xi D, Yuan P, Brady DC and Chang CJ, Connecting copper and cancer: from transition metal signalling to metalloplasia, Nat Rev Cancer, 2022, 22, 102–113. [PubMed: 34764459]

235. Qiu F, Wu L, Yang G, Zhang C, Liu X, Sun X, Chen X and Wang N, The role of iron metabolism in chronic diseases related to obesity, Mol Med, 2022, 28, 130. [PubMed: 36335331]

236. Saha M, Sarkar S, Sarkar B, Sharma BK, Bhattacharjee S and Tribedi P, Microbial siderophores and their potential applications: a review, Environ Sci Pollut R, 2016, 23, 3984–3999.

237. Butler A and Theisen RM, Iron(III)–siderophore coordination chemistry: Reactivity of marine siderophores, Coordin Chem Rev, 2010, 254, 288–296.

238. Ellermann M and Arthur JC, Siderophore-mediated iron acquisition and modulation of host-bacterial interactions, Free Radical Bio Med, 2017, 105, 68–78. [PubMed: 27780750]

239. Nairz M, Ferring-Appel D, Casarrubea D, Sonnweber T, Viatte L, Schroll A, Haschka D, Fang FC, Hentze MW, Weiss G and Galy B, Iron Regulatory Proteins Mediate Host Resistance to Salmonella Infection., Cell host & microbe, 2015, 18, 254–261. [PubMed: 26190773]

240. Su TA, Shihadih DS, Cao W, Detomasi TC, Heffern MC, Jia S, Stahl A and Chang CJ, A Modular Ionophore Platform for Liver-Directed Copper Supplementation in Cells and Animals, J Am Chem Soc, 2018, 140, 13764–13774. [PubMed: 30351140]

241. Meggyesy PM, Masaldan S, Clatworthy SAS, Volitakis I, Eyckens DJ, Aston-Mourney K and Cater MA, Copper Ionophores as Novel Antiobesity Therapeutics, Molecules, 2020, 25, 4957. [PubMed: 33120881]

242. El-Lababidi RM and Rizk JG, Cefiderocol: A Siderophore Cephalosporin, Ann Pharmacother, 2020, 54, 1215–1231. [PubMed: 32522005]

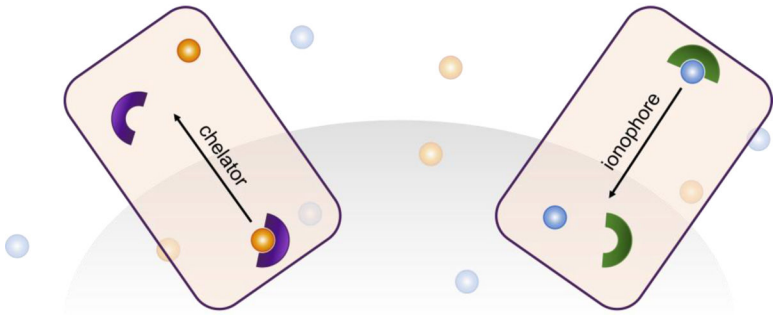


Figure 1:

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.

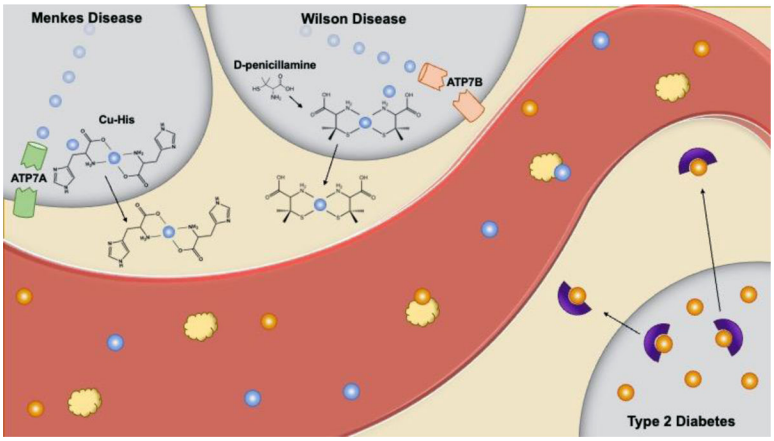


Figure 2:

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.

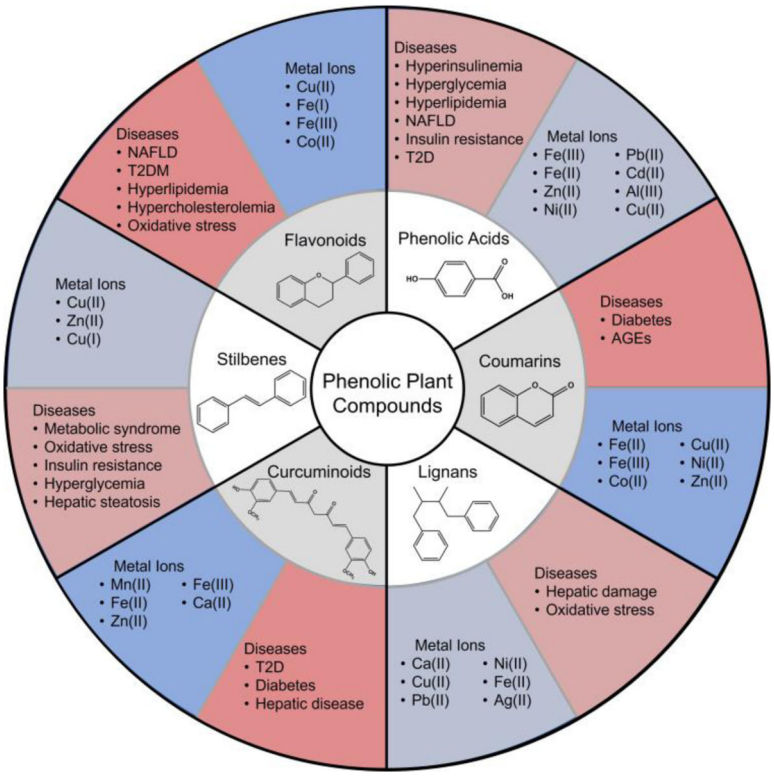


Figure 3:

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.

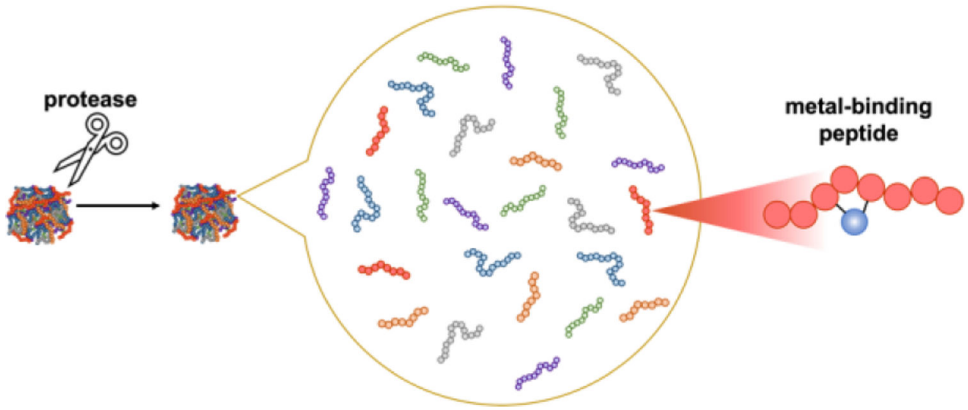


Figure 4:
Plant-derived proteins subjected to enzymatic hydrolysis generates bioactive peptides. Such peptides have been found to have metal-interacting properties with potential health benefits.