

Review

Natural Products to Counteract the Epidemic of Cardiovascular and Metabolic Disorders

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Abstract: Natural products have always been exploited to promote health and served as a valuable source for the discovery of new drugs. In this review, the great potential of natural compounds and medicinal plants for the treatment or prevention of cardiovascular and metabolic disorders, global health problems with rising prevalence, is addressed. Special emphasis is laid on natural products for which efficacy and safety have already been proven and which are in clinical trials, as well as on plants used in traditional medicine. Potential benefits from certain dietary habits and dietary constituents, as well as common molecular targets of natural products, are also briefly discussed. A glimpse at the history of statins and biguanides, two prominent representatives of natural products (or their derivatives) in the fight against metabolic disease, is also included. The present review aims to serve as an “opening” of this special issue of *Molecules*, presenting key historical developments, recent advances, and future perspectives outlining the potential of natural products for prevention or therapy of cardiovascular and metabolic disease.

Keywords: natural products; cardiovascular disease; metabolic disorders; diabetes mellitus; statins; biguanides; dietary constituents; coffee; molecular targets

1. Introduction

It is well known that natural products have been a valuable source of therapeutic agents for millennia and even today, many medicines are natural products or their derivatives [1]. Although natural products have played an important role in lead discovery [1], nowadays the pharmaceutical industry tends to not prioritize natural product research anymore [2]. Instead, common strategies in industry are high throughput screening (HTS) of synthetic compound databases and structural modifications of existing leads. However, the HTS and combinatorial chemistry approaches followed by many pharmaceutical companies have not been very successful. Furthermore, even stakeholders in industry still see a high potential in natural products as drug leads [3]. In line with this view, the number of scientific studies in the area of natural products research is increasing rapidly [1]. The 2015 Nobel Prize in Physiology or Medicine, which was awarded to Youyou Tu, William C. Campbell, and Satoshi Ōmura for the discovery of natural products for the treatment of tropical parasitic diseases [4,5], might

be considered emblematic for the revival of natural product drug discovery. It clearly shows the therapeutic value of natural products and underlines that natural products are an effective source of new drugs.

This review is intended to serve as an “opening” for the *Molecules* special issue entitled “Effects of Natural Products in the Context of Cardiometabolic Disease”. It presents selected prominent illustrative examples of natural products with effects on cardiovascular and metabolic disorders, and is far from being comprehensive. A focus is set on medicinal plants and terrestrial plant-derived natural products, and readers are referred to other recent reviews for an overview on natural products with relevant activities from seaweeds and other marine organisms [6–9].

2. Cardiovascular and Metabolic Disorders—A Global Health Problem

The metabolic syndrome is considered to be a progressive pathophysiological state which is clinically manifested by a cluster of interrelated risk factors (abdominal obesity, atherogenic dyslipidemia, increased blood pressure, insulin resistance, pro-inflammatory and pro-thrombotic state) and associated with an increased expectation for developing diabetes mellitus type 2 and atherosclerotic cardiovascular disease [10,11]. Atherosclerosis, alongside with hypertension, is the main cause of cardiovascular disease representing the leading cause of death in the world. A sedentary life-style together with a diet comprising high calorie intake in westernized societies render the disease prevalence high and atherosclerosis is therefore the underlying cause of approximately 50% of all deaths [12]. Moreover, the prevalence of cardiovascular disease in the world is rising globally and according to the World Health Organization (WHO), this increasing tendency is likely to continue in the next years. While in 2012, cardiovascular disease caused 17.5 million deaths, it is projected to be responsible for 22.2 million deaths in 2030 [13].

Diabetes mellitus is considered one of the most common chronic metabolic diseases in nearly all countries. Especially the prevalence of diabetes mellitus type 2, which accounts for around 90% of all diabetes cases worldwide, continues to increase due to the changing lifestyles that involve reduced physical activity and increased incidence of obesity. In 2014, the prevalence of diabetes reported by the WHO was estimated to be 9% among adults aged 18+ years while in 2012, an estimated 1.5 million deaths were directly caused by this disease [14]. According to projections, its prevalence will further increase [15], becoming the 7th leading cause of death by 2030 [16].

3. Increasing Scientific Interest in Natural Products with Potential Application in Cardiovascular and Metabolic Disorders

Considering the huge morbidity and mortality burden related to cardiometabolic disorders with no end in sight, there is a high interest in the discovery of novel compounds as well as novel pharmacological targets that might be effective in the treatment or prevention of cardiovascular and/or metabolic disorders. Although natural product drug discovery often requires more effort compared to HTS and combinatorial chemistry, nature is still considered as the most productive source of potential drug leads for new medicines [3].

In recent decades, herbal remedies and natural products have undisputedly attracted much research attention in the context of prevention or treatment of cardiovascular and metabolic disease [17–19]. Thus, when searching Scopus using the keywords “cardiovascular disease” and “natural products” (CVD+NP) or “metabolic disease” and “natural products” (MD+NP) it becomes evident that the scientific interest in these areas increased exponentially in the period 2004–2014 (Figure 1).

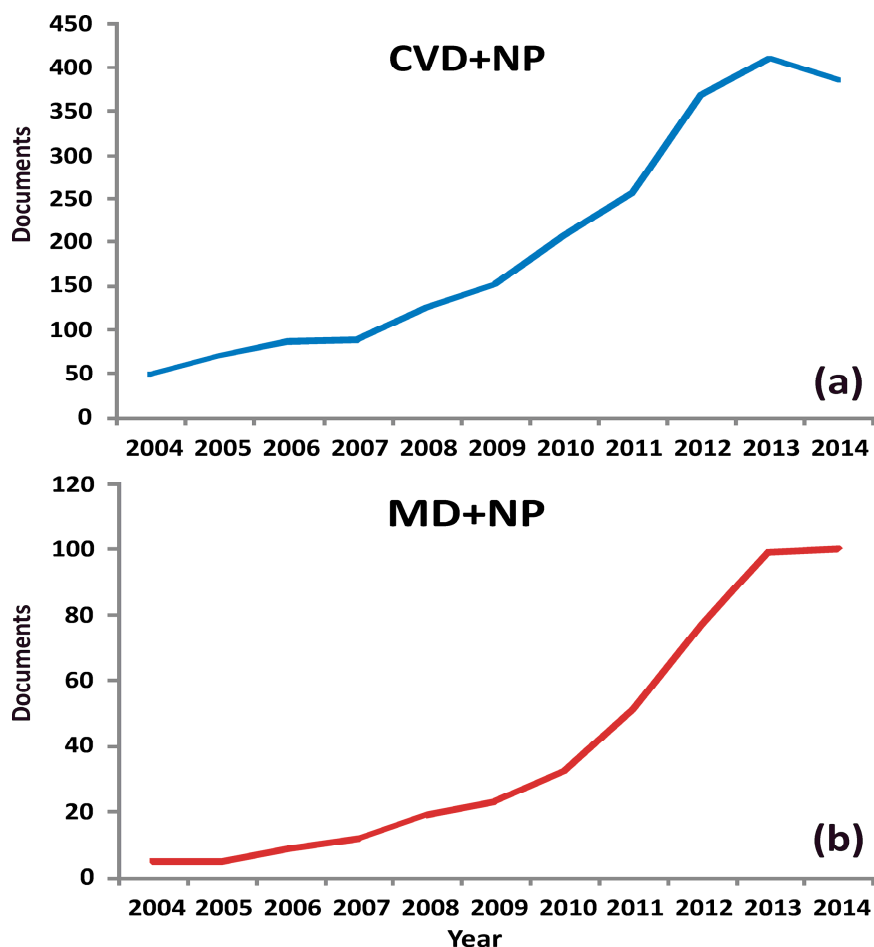


Figure 1. Annual number of publications resulting from the search with the keywords “cardiovascular disease” and “natural products” (CVD + NP) (a) and “metabolic disease” and “natural products” (MD + NP) (b), (Scopus, January 2016).

4. Plants Traditionally Used in the Context of Cardiovascular and Metabolic Disorders

Millenary civilizations rely on plants or other natural resources to sustain or restore health, and in various situations they still represent interesting therapeutic alternatives to synthetic drugs. According to the WHO, over 100 million Europeans and many more people in Africa, Asia, Australia, and North America are users of traditional and complementary medicine. Especially in Africa and some developing countries, traditional medicine is often the primary source of health care [20].

Along with herbal extracts and natural products with validated efficacy and safety proven by randomized controlled clinical trials (further discussed in chapter 5), many other medicinal plants are used world-wide to alleviate cardiovascular and metabolic complaints. Table 1 provides an overview of selected traditionally used plants and their targeted indications.

There is no doubt that medicinal plants and natural products are used for the treatment or prevention of cardiovascular and metabolic disorders, also with rising popularity in western societies. However, in most cases the expected health benefits are not scientifically proven by rigorous clinical trials. Hence, it is vital to provide robust scientific evidence for clinical efficacy and safety.

Table 1. Medicinal plants targeting indications related to cardiovascular or metabolic disease.

| Scientific Name of the Medicinal Plant | Common Name of the Medicinal Plant | Plant Organ | Indications |
|---|--|---|---|
| <i>Aesculus hippocastanum</i> L. | Horse-chestnut | Seeds | Venous insufficiency, varicose veins [21–24] |
| <i>Allium sativum</i> L. | Garlic | Bulbs/whole plant | Hypertension, hypercholesterolemia, diabetes mellitus type 2 [25–30] |
| <i>Aloe vera</i> (L.) Burm. f. | Aloe vera | Leaves | Diabetes mellitus type 2, hypercholesterolemia [31–35] |
| <i>Ammi visnaga</i> (L.) Lam. | Toothpick weed, bisnaga, khella | Fruits | Angina pectoris [36–38] |
| <i>Apocynum venetum</i> L. | Dogbane | Leaves | Hypertension [39–42] |
| <i>Artemisia dracunculus</i> L. | Tarragon | Leaves, aerial parts | Hyperglycemia [17,43–45] |
| <i>Artemisia herba-alba</i> Asso | White wormwood | Aerial parts | Hyperlipidemia, diabetes mellitus [46–50] |
| <i>Aspalathus linearis</i> (Burm. f.) R. Dahlgr. | Rooibos | Leaves | Diabetes mellitus type 2 [51–54] |
| <i>Astragalus membranaceus</i> Moench | Chinese milk vetch | Roots | Angina pectoris, atherosclerosis, diabetic nephropathy [39,55–59] |
| <i>Carthamus tinctorius</i> L. | Safflower | Flowers | Angina pectoris, hypertension, hyperlipidemia [39,60–64] |
| <i>Centaurium erythraea</i> Rafn | Common centaury | Whole plant, leaves | Diabetes mellitus [46,48,65–67] |
| <i>Cinnamomum cassia</i> (L.) J. Presl | Chinese cinnamon | Bark | Diabetes mellitus, diabetic nephropathy [68–70] |
| <i>Cinnamomum verum</i> J. Presl | Ceylon cinnamon | Bark | Diabetes mellitus type 2 [69,71–74] |
| <i>Commiphora mukul</i> (Hook. ex Stocks) Engl. | Gugal, guggul, gugul, Indian bdellium-tree, mukul myrrh tree | Resin | Hypercholesterolemia, hypertriglyceridemia [21,75,76] |
| <i>Coptis chinensis</i> Franch. | Chinese goldthread | Roots, flowers | Hypercholesterolemia, diabetes mellitus, non-alcoholic fatty liver disease [18,77–79] |
| <i>Coriandrum sativum</i> L. | Coriander | Seeds | Diabetes mellitus, hypercholesterolemia [80–83] |
| <i>Crataegus monogyna</i> Jacq./ <i>C. oxyacantha</i> Jacq./ <i>C. laevigata</i> (Poir.) DC./ <i>C. pinnatifida</i> Bunge | Hawthorn | Sprigs with both leaves and flowers, fruits | Angina pectoris, atherosclerosis, hyperlipidemia [84–87] |
| <i>Cynara scolimus</i> L. | Globe artichoke | Leaves | Hypercholesterolemia [88,89] |
| <i>Fraxinus excelsior</i> L. | European ash | Fruits, seeds | Diabetes mellitus type 2, hepatic steatosis [90–95] |
| <i>Galega officinalis</i> L. | French lilac | Aerial parts | Diabetes mellitus [72,96–98] |
| <i>Ginkgo biloba</i> L. | Ginkgo, maidenhair tree | Leaves | Cerebrovascular disease, peripheral vascular disease, hypertension, diabetes nephropathy [75,85,99,100] |
| <i>Glycine max</i> (L.) Merr. | Soybean | Fruits, seeds | Diabetes mellitus, hyperlipidemia [101–103] |
| <i>Glycyrrhiza glabra</i> L. | Licorice | Roots | Atherosclerosis, hypercholesterolemia [85,104] |
| <i>Helianthus tuberosus</i> L. | Jerusalem artichoke | Tubers | Diabetes mellitus type 2, non-alcoholic fatty liver disease [105] |
| <i>Ilex paraguariensis</i> A. St.-Hil. | Yerba mate | Leaves | Obesity, diabetes mellitus [106–111] |
| <i>Lycium barbarum</i> L. | Chinese wolfberry | Fruits, roots | Diabetes mellitus, hyperlipidemia, hypertension [112–119] |
| <i>Momordica charantia</i> L. | Bitter melon | Fruits | Diabetes mellitus type 2 [109,120,121] |
| <i>Morus alba</i> L. | White mulberry tree | Root bark, leaves | Hyperglycemia [122–127] |
| <i>Nigella sativa</i> L. | Black cumin, black seed | Seeds, seed oil | Diabetes mellitus type 2, dyslipidemia [128–132] |
| <i>Ocimum sanctum</i> L. | Holy basil | Leaves, whole plant | Hypertension, dyslipidemia, diabetes mellitus [133,134] |
| <i>Olea europaea</i> L. | Olive | Leaves, fruit oil | Hypertension, atherosclerosis, diabetes mellitus, hepatic steatosis [135–142] |
| <i>Panax notoginseng</i> (Burkill) F.H. Chen ex C.H. Chow | Notoginseng, pseudoginseng | Roots | Angina pectoris, coronary artery disease [21,75,143] |
| <i>Rauwolfia serpentina</i> (L.) Benth. ex Kurz | Indian snakeroot | Roots | Hypertension [75,144,145] |
| <i>Rhodiola rosea</i> L. | Golden root | Roots | Angina pectoris, ischemic heart disease [39,146,147] |
| <i>Rosmarinus officinalis</i> L. | Rosemary | Leaves | Capillary permeability and fragility disturbances [21,148,149] |
| <i>Ruscus aculeatus</i> L. | Rutcher's broom | Rhizomes | Venous insufficiency, varicose veins [21,150] |
| <i>Sambucus nigra</i> L. | European elder, black elder | Flowers | Diabetes mellitus type 2 [151–153] |
| <i>Schisandra chinensis</i> (Turcz.) Baill. | Five-flavor berry | Fruits, seeds | Hypertension, myocardial infarction, hyperlipidemia, diabetic nephropathy, diabetes mellitus [154–158] |
| <i>Silybum marianum</i> (L.) Gaertn. | Milk thistle | Seeds, aerial parts | Diabetes mellitus type 1 and 2 [90,159–163] |
| <i>Stevia rebaudiana</i> (Bertoni) Bertoni | Sweet leaf, candyleaf | Leaves | Diabetes mellitus type 2 [164–167] |
| <i>Trigonella foenum-graecum</i> L. | Fenugreek | Seeds | Metabolic syndrome, diabetes mellitus type 2 [168,169] |
| <i>Vaccinium</i> spp. | Blueberries | Fruits, leaves | Diabetes mellitus type 2, metabolic syndrome [96,109,170–173] |
| <i>Veratrum album</i> L./ <i>V. nigrum</i> L./ <i>V. japonicum</i> (Baker) Loes./ <i>V. viride</i> Aiton | False helleborine/black false hellebore | Rhizomes | Hypertension [75,174,175] |
| <i>Viscum album</i> L. | Mistletoe | Aerial parts | Hypertension [176] |

5. Herbal Products in Recruiting Clinical Trials Targeting Indications Related to Cardiovascular and Metabolic Disorders

Many medicinal plants and natural products are considered by the public as a safe, natural, and cost-effective alternative to synthetic drugs without unambiguous proof by randomized controlled clinical trials. On this background, there is an increased interest in the development of products with validated efficacy and safety, similar to the recently FDA-approved botanical drugs Veregen® (sinecatechins; green tea (*Camellia sinensis* (L.) Kuntze) leaf extract), Fulyzaq® (crofelemer; extract from the red latex of the Dragon's blood tree (*Croton lechleri* Müll.Arg.)), and Grastek® (Timothy grass (*Phleum pratense* L.) pollen allergen extract) [177,178]. Some herbal extracts and pure compounds are currently undergoing clinical trials for cardiometabolic indications; an overview is presented in Table 2.

Table 2. Herbal extracts and natural products in recruiting clinical trials targeting indications related to metabolic or cardiovascular diseases ¹.

| Name of the Product | National Clinical Trial (NCT) Identifier | Phase | Studied Condition |
|---|--|----------------|---|
| BeneFlax® (Flaxseed (<i>Linum usitatissimum</i> L.) lignans) | NCT02391779 | Phase 2 | Hypertension |
| Biscuit containing “Kothala Himbutu” (<i>Salacia reticulata</i> Wight) | NCT02290925 | Phase 3 | Diabetes mellitus type 2 |
| <i>Coleus forskohlii</i> (Willd.) Briq. | NCT02143349 | Phase 3 | Risk factors of metabolic syndrome |
| Combined Rg3-enriched Korean red ginseng and American ginseng | NCT01578837 | Phase 1 and 2 | Diabetes mellitus type 2, hypertension |
| Curcumin | NCT01968564 | - ² | Vascular aging |
| Curcumin | NCT02529982 | Phase 2 | Non insulin dependent diabetes |
| Curcumin | NCT02529969 | Phase 2 | Non insulin dependent diabetes |
| Dantonix® (T89) | NCT01659580 | Phase 3 | Angina pectoris |
| Euiiyin-tang | NCT01724099 | Phase 2 and 3 | Obesity |
| Fibre grain herb | NCT02553382 | Phase 3 | Diabetes mellitus type 2 |
| “Fu-zheng-qu-zhuo” oral liquid | NCT02044835 | Phase 2 and 3 | Ischemic nephropathy |
| Ginger | NCT02289235 | Phase 0 | Non-alcoholic fatty liver disease |
| <i>Phyllanthus niruri</i> L. and <i>Sida cordifolia</i> L. (Vedice) | NCT02107469 | - | Diabetic peripheral polyneuropathy |
| Quercetin | NCT00065676 | Phase 2 | Diabetes mellitus, obesity |
| Red grapes polyphenol supplementation | NCT02633150 | - | Obesity, insulin resistance |
| Resveratrol | NCT02245932 | Phase 3 | Overweight |
| Resveratrol | NCT01564381 | Phase 1 and 2 | Cardiovascular disease |
| Resveratrol | NCT01842399 | Phase 1 and 2 | Vascular resistance, hypertension |
| Resveratrol | NCT02246660 | - | Peripheral arterial disease |
| Resveratrol | NCT02137421 | - | Metabolic syndrome, coronary artery disease |
| Resveratrol | NCT02129595 | - | Pre-diabetes |
| Resveratrol | NCT01997762 | Phase 4 | Gestational diabetes |
| Resveratrol | NCT02216552 | Phase 2 and 3 | Non-alcoholic fatty liver disease, diabetes mellitus type 2, metabolic syndrome |
| Resveratrol | NCT02419092 | - | Obesity |
| Resveratrol | NCT01881347 | - | Diabetes mellitus |
| Resveratrol | NCT02549924 | Phase 2 | Diabetes mellitus type 2 |
| Resveratrol | NCT02244879 | Phase 3 | Diabetes mellitus type 2, inflammation, insulin resistance |

¹ Information retrieved from www.clinicaltrials.gov on 21 January 2016; ² “-” indicates that there is no information for the phase provided on the corresponding trial page at www.clinicaltrials.gov.

6. Dietary Constituents with Potential Benefits in the Context of Cardiovascular and Metabolic Disorders

Ample evidence demonstrates that dietary patterns can affect the development of cardiovascular and metabolic disorders [179,180]. The reduced intake of highly processed foods by replacing them with fruits, nuts, seeds, vegetables, and legumes [181] is considered health promoting. The latter dietary constituents are free of food additives, low in salt content, and rich in phenolics, carotenoids, fibers, minerals, and unsaturated fats. They possess antioxidant effects, lower glycemic indices, and normalize levels of cholesterol in blood. The traditional Mediterranean diet is one example, which is associated with longer life expectancy, lower rates of cardiovascular and metabolic disorders, and even lower rates of certain cancers [182]. This diet is characterized by an abundance of seasonally fresh plant foods (fruits, vegetables, beans, nuts, seeds, *etc.*), minimal food processing, olive oil, and wine consumed in low to moderate amounts, normally with meals [19,182,183].

Another example for a presumably health promoting dietary constituent is coffee, one of the most popular beverages worldwide. It exhibits a range of bioactivities and potential health benefits. Since coffee drinking is very common in Western societies, its bioactivities and in particular its impact on cardiovascular and metabolic parameters have been widely investigated [184–190]. Compared to non-drinkers, coffee consumption of one to five cups/day was associated with lower risk of mortality, while coffee consumption of more than five cups/day did not affect mortality risk. Additionally, coffee consumption (with or without caffeine) was associated with significantly lower death risk due to cardiovascular disease, neurological disorders, and suicide [191]. It was also linked to a lower risk of diabetes mellitus type 2, independent of race, geographic distribution and gender of the studied populations [192]. Major bioactive ingredients in coffee include phenolics (chlorogenic acid and its isomers), diterpenes (cafestol and kahweol), and caffeine (Figure 2). Coffee is considered to be a very prominent source of phenolic compounds, and it appears that it is the number one source of dietary antioxidants in the US [193,194]. The total phenolic content per cup of coffee ranges between 200 and 550 mg, with chlorogenic acid being the main phenolic compound [192].

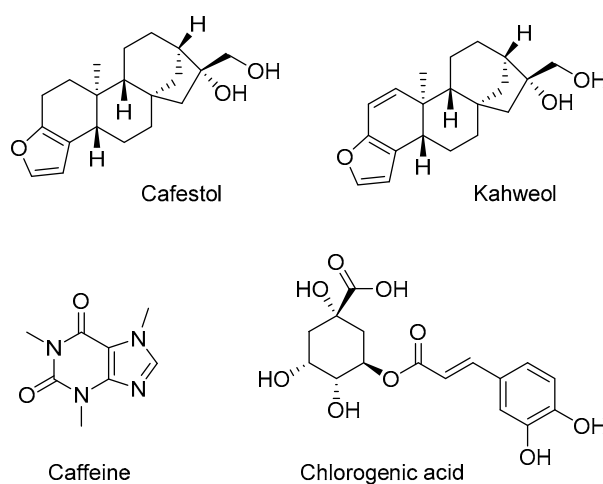


Figure 2. Chemical structures of bioactive compounds found in coffee.

Chlorogenic acid intake leads to lower blood glucose and insulin concentrations 15 minutes after ingestion [195]. In streptozocin-nicotinamide induced diabetic rats, a dose of 5 mg chlorogenic acid/kg body weight exerts antidiabetic effects [195,196]. Additionally, coffee phenolics can intensify energy metabolism and decrease lipogenesis by down-regulation of SREBP-1c and related molecules [197]. Moreover, coffee phenolics are able to modulate whole-body substrate oxidation by suppressing postprandial hyperglycemia and hyperinsulinemia [198].

Another commonly consumed beverage is tea (*Camellia sinensis* (L.) Kuntze). Infusions from tea are enormously rich in phenolic substances, and also contain considerable amounts of caffeine [199–201]. Consumption of tea was found to correlate with several health benefits including beneficial effects on the cardiovascular system [202]. Several studies showed that regular consumption of this polyphenol-rich beverage may exert cardio-protective effects in humans and reduce the risk of cardiovascular disease [203–205]. The phenolics of tea are represented particularly by epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG) [206]. The effects of EGCG (Figure 3) are multifaceted and include among others the inhibition of the activator protein 1 (AP-1), the nuclear factor kappa B (NF- κ B), the tumor necrosis factor α (TNF α) signaling, the inhibition of the vascular endothelial growth factor (VEGF) signaling, the insulin-like growth factor (IGF-1) signaling, and the activation of peroxisome proliferator-activated receptor (PPAR) [207].

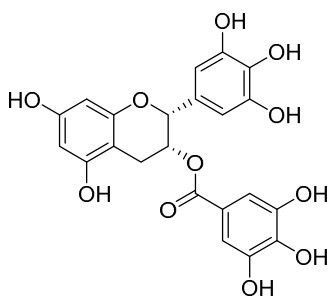


Figure 3. Chemical structure of epigallocatechin-3-gallate (EGCG).

The significance of dietary constituents in the context of metabolic and cardiovascular diseases is also evident in Table 2, which among herbal extracts also lists several prominent dietary constituents (e.g., curcumin and resveratrol).

Detailed studies on the efficacy of dietary constituents and the mechanisms by which they exert beneficial effects on cardiovascular and metabolic diseases are of critical importance in order to better rationalize dietary recommendations, and might also allow the development of novel effective nutraceuticals and functional foods [208–212]. Metabolism, bioavailability, and interaction with the intestinal microbiome will be important aspects to consider in this endeavor and also need to be taken into account for any natural product which is taken up orally.

7. Common Molecular Targets Affected by Natural Compounds in the Context of Cardiovascular and Metabolic Disorders

Diverse natural compounds have been shown to affect cardiovascular and metabolic disorders via different mechanisms, such as anti-inflammatory activity, improvement of blood lipid profiles, improvement of insulin sensitivity, or normalization of blood glucose levels [72,213–217]. Often the underlying molecular targets mediating these beneficial effects are not well understood. However, there are several molecular targets or pathways that are already well established to mediate the beneficial effects of natural compounds in the context of cardiovascular and metabolic disorders. Of those, selected examples, *i.e.*, the AMP-activated protein kinase (AMPK), cyclooxygenase (COX)-1 and -2, the dipeptidyl peptidase-4 (DPP-4), the endothelial nitric oxide synthase (eNOS), the transcription factors NF- κ B, nuclear factor-erythroid 2-related factor 2 (Nrf2), and PPAR γ , the protein-tyrosine phosphatase 1B (PTP1B), and 5-lipoxygenase (5-LO), are listed in Table 3, together with their major physiological consequences and some examples of compound classes of interacting natural products.

Table 3. Selected molecular targets relevant for cardiovascular and metabolic disorders, which are well known to be affected by diverse natural products.

| Molecular Target/Pathway | Major Physiological Consequence | Selected Compound Classes of Interacting Natural Products |
|--------------------------|---|--|
| AMPK | Activation leads among others to inhibition of fat and cholesterol synthesis, promotion of fat oxidation, enhancement of mitochondrial biogenesis, and promotion of glucose uptake in skeletal muscle and fat cells | Alkaloids, chalcones, flavonoids and other polyphenols, galegine, salicylate, terpenoids [214,218–221] |
| COX-1/-2 | Inhibition leads to reduced biosynthesis of pro-inflammatory prostaglandins | Alkaloids, stilbenes, flavonoids and other polyphenols, terpenoids [222–224] |
| DPP-4 | Inhibition leads to decreased incretin degradation (and thus increased insulin secretion) | Alkaloids, flavonoids and other polyphenols, polypeptides, terpenoids [225–227] |
| eNOS | Activation leads to increased availability of anti-inflammatory nitric oxide (NO), a major antiatherogenic factor in the vasculature | Anthocyanidins, fatty acids, flavonoids and other polyphenols, ginsenosides, triterpenic acids [228–234] |
| NF- κ B pathway | Inhibition leads to impaired expression of pro-inflammatory mediators | Alkaloids, curcuminoids, chalcones, diterpenes, flavonoids, iridoids, naphthoquinones, salicylates, sesquiterpene lactones, stilbenes, triterpenes [235–239] |
| Nrf2 pathway | Activation leads to increased expression of cytoprotective (e.g., antioxidant) and reduced expression of lipo- and gluconeogenic genes | Carotenoids, chalcones, curcuminoids, diterpenes, flavonoids and other polyphenols, isothiocyanates, phytylprostanols, sesquiterpenes, sesquiterpene lactones, triterpenes [240–243] |
| PPAR γ | Activation leads to insulin sensitization and normalization of blood glucose levels | Amorfrutins, diterpenequinones, flavonoids, neolignans, polyacetylenes, sesquiterpene lactones, stilbenes [244–249] |
| PTP1B | Inhibition leads to prolonged and enhanced insulin and leptin signaling (increased insulin sensitivity and reduced food intake) | Alkaloids, bromophenols, chalcones, coumarins, diterpenes, flavonoids, lignans, N- or S-containing compounds, sesquiterpenes, sesterterpenes, steroids, triterpenes [250–254] |
| 5-LO | Inhibition leads to reduced biosynthesis of pro-inflammatory leukotrienes | Alkaloids, coumarins, depsides, quinones, flavonoids and other polyphenols, polyacetylenes, sesquiterpenes, triterpenes [222,255–258] |

8. Natural Products (or Their Derivatives) Developed as Drugs for the Treatment of Cardiovascular and Metabolic Disorders

Other than providing a direct remedy, natural products also represent an excellent pool of inspiring lead structures for the development of successful pharmaceuticals to combat cardiovascular and metabolic disorders. This could be demonstrated with historical views on the development of the statins and the biguanides.

Aberrantly high cholesterol is causally connected to atherosclerosis and coronary heart disease. Therefore, in the 1950s and 1960s, companies were searching for compounds which block one of the 30 enzymatic reactions involved in cholesterol biosynthesis. However, none of the developed synthetic inhibitors of cholesterol biosynthesis had an ideal efficacy and safety profile [259]. In the early 1970s, the natural product citrinin (Figure 4) was isolated from fungi and identified as a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [260], the rate-controlling enzyme in the cholesterol biosynthesis. Citrinin also displayed serum cholesterol lowering effects in rats [261]. Shortly after that, mevastatin (compactin; Figure 4), the first statin, was isolated from *Penicillium citrinum* [262]. It was found to be a strong HMG-CoA reductase inhibitor [263] with great structural similarity with HMG-CoA, the substrate of HMG-CoA reductase [259]. Mevastatin potently inhibited cholesterol biosynthesis *in vitro* and *in vivo* [262,264]. Clinical studies started in 1978 but it never came on the market due to side effects in dogs at a dosage of about 200 times the dosage used in human patients [259]. In the 1980s, clinical studies and long-term toxicity studies showed that lovastatin (Figure 4), a natural product isolated from *Aspergillus terreus* [265] and *Monascus ruber* [266], effectively lowered blood cholesterol levels and was well tolerated [259]. In 1987, lovastatin was approved by the FDA and became the first commercial statin. After lovastatin, several synthetic and semi-synthetic statins were also introduced to the market [259,267]. Today, statins represent the first-line pharmacologic intervention for dyslipidemia patients with failed treatment with diet and exercise alone [268] and are one of the most widely prescribed class of drugs worldwide.

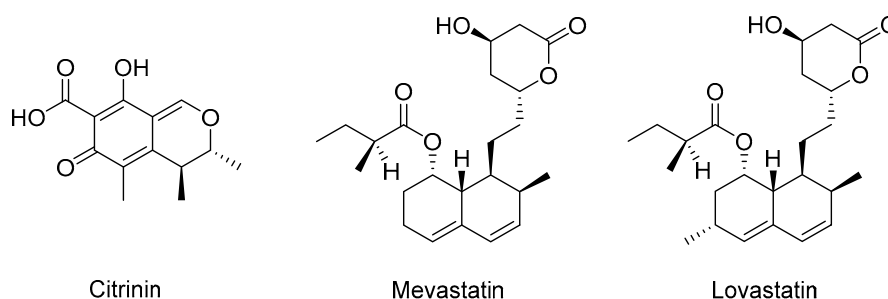


Figure 4. Chemical structures of natural inhibitors of cholesterol biosynthesis.

Since the Middle Ages, *Galega officinalis* (also known as French lilac, Italian fitch, goat's rue) has been known to relieve symptoms (the intense urination) of a disease now described as diabetes mellitus type 2 [98,269]. Galegine (Figure 5), a guanidine derivative which lowers blood glucose levels [270], turned out to be the bioactive constituent in *G. officinalis* [271,272]. Guanidine itself also decreases blood glucose levels [273], but is too toxic for clinical application. Galegine from *G. officinalis* is less toxic, nevertheless, clinical trials conducted with diabetic patients in the 1920s and 1930s, were not successful. However, the identification of the antidiabetic natural product galegine led to the development of the biguanide compound metformin, which is now one of the most important therapeutic agents for the treatment of diabetes mellitus type 2 [98,274,275].

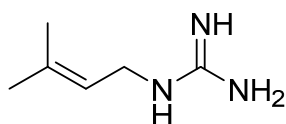


Figure 5. Chemical structure of the natural blood glucose lowering agent galegine.

9. Conclusions and Future Perspectives

The reviewed key examples and recent developments clearly demonstrate the great potential and the future promise of natural products for the treatment or prevention of cardiovascular and metabolic disorders. This work should provide an inspiration for authors who consider preparing further submissions to the special issue “Effects of Natural Products in the Context of Cardiometabolic Disease”. With the present review as well as with the expected valuable contributions to this special issue we do hope to further boost the scientific interest and knowledge on the efficacy of natural products with regard to the prevention and the therapy of cardiovascular and metabolic disease.

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Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---------|---|
| 5-LO | 5-Lipoxygenase |
| AMPK | AMP-Activated Protein Kinase |
| AP-1 | Activator Protein 1 |
| COX-1/2 | Cyclooxygenase-1/2 |
| DPP-4 | Dipeptidyl Peptidase-4 |
| eNOS | Endothelial Nitric Oxide Synthase |
| FDA | US Food and Drug Administration |
| HMG-CoA | 3-Hydroxy-3-Methylglutaryl Coenzyme A |
| HTS | High Throughput Screening |
| IGF-1 | Insulin-Like Growth Factor |
| LDL | Low-Density Lipoprotein |
| NCT | National Clinical Trial |
| NF-κB | Nuclear Factor Kappa B |
| Nrf2 | Nuclear Factor-Erythroid 2-Related Factor 2 |
| NO | Nitric Oxide |
| PPAR | Peroxisome Proliferator-Activated Receptor |
| PTP1B | Protein-Tyrosine Phosphatase 1B |
| TNFα | Tumor Necrosis Factor α |
| VEGF | Vascular Endothelial Growth Factor |
| WHO | World Health Organization |

References

1. Atanasov, A.G.; Waltenberger, B.; Pferschy-Wenzig, E.M.; Linder, T.; Wawrosch, C.; Uhrin, P.; Temml, V.; Wang, L.; Schwaiger, S.; Heiss, E.H.; *et al.* Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnol. Adv.* **2015**, *33*, 1582–1614. [[CrossRef](#)] [[PubMed](#)]
2. David, B.; Wolfender, J.-L.; Dias, D.A. The pharmaceutical industry and natural products: Historical status and new trends. *Phytochem. Rev.* **2015**, *14*, 299–315. [[CrossRef](#)]
3. Amirkia, V.; Heinrich, M. Natural products and drug discovery: A survey of stakeholders in industry and academia. *Front. Pharmacol.* **2015**, *6*. [[CrossRef](#)] [[PubMed](#)]
4. Efferth, T.; Zacchino, S.; Georgiev, M.I.; Liu, L.; Wagner, H.; Panossian, A. Nobel Prize for artemisinin brings phytotherapy into the spotlight. *Phytomedicine* **2015**, *22*, A1–A3. [[CrossRef](#)] [[PubMed](#)]
5. Hertweck, C. Natural products as source of therapeutics against parasitic diseases. *Angew. Chem. Int. Ed. Engl.* **2015**, *54*, 14622–14624. [[CrossRef](#)] [[PubMed](#)]
6. Cardoso, S.M.; Pereira, O.R.; Seca, A.M.; Pinto, D.C.; Silva, A.M. Seaweeds as preventive agents for cardiovascular diseases: From nutrients to functional foods. *Mar. Drugs* **2015**, *13*, 6838–6865. [[CrossRef](#)] [[PubMed](#)]
7. Cornish, M.L.; Critchley, A.T.; Mouritsen, O.G. A role for dietary macroalgae in the amelioration of certain risk factors associated with cardiovascular disease. *Phycologia* **2015**, *54*, 649–666. [[CrossRef](#)]

8. Tierney, M.S.; Croft, A.K.; Hayes, M. A review of antihypertensive and antioxidant activities in macroalgae. *Bot. Mar.* **2010**, *53*, 387–408. [[CrossRef](#)]
9. Wijesekara, I.; Kim, S.K. Angiotensin-I-converting enzyme (ACE) inhibitors from marine resources: Prospects in the pharmaceutical industry. *Mar. Drugs* **2010**, *8*, 1080–1093. [[CrossRef](#)] [[PubMed](#)]
10. Sperling, L.S.; Mechanick, J.I.; Neeland, I.J.; Herrick, C.J.; Després, J.-P.; Ndumele, C.E.; Vijayaraghavan, K.; Handelsman, Y.; Puckrein, G.A.; Araneta, M.R.G.; *et al.* The CardioMetabolic Health Alliance: Working toward a new care model for the metabolic syndrome. *J. Am. Coll. Cardiol.* **2015**, *66*, 1050–1067. [[CrossRef](#)] [[PubMed](#)]
11. Huang, T.H.-W.; Teoh, A.W.; Lin, B.-L.; Lin, D.S.-H.; Roufogalis, B. The role of herbal PPAR modulators in the treatment of cardiometabolic syndrome. *Pharmacol. Res.* **2009**, *60*, 195–206. [[CrossRef](#)] [[PubMed](#)]
12. Lusis, A.J. Atherosclerosis. *Nature* **2000**, *407*, 233–241. [[CrossRef](#)] [[PubMed](#)]
13. World Health Organization (WHO). *Global Status Report on Noncommunicable Diseases 2014*; WHO: Geneva, Switzerland, 2014.
14. World Health Organization (WHO). *Global Report on Diabetes 2016*; WHO: Geneva, Switzerland, 2016.
15. Shaw, J.E.; Sicree, R.A.; Zimmet, P.Z. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res. Clin. Pract.* **2010**, *87*, 4–14. [[CrossRef](#)] [[PubMed](#)]
16. Xiao, J. Natural polyphenols and diabetes: Understanding their mechanism of action. *Curr. Med. Chem.* **2015**, *22*, 2–3. [[CrossRef](#)] [[PubMed](#)]
17. Cefalu, W.T.; Ye, J.; Wang, Z.Q. Efficacy of dietary supplementation with botanicals on carbohydrate metabolism in humans. *Endocr. Metab. Immune Disord. Drug Targets* **2008**, *8*, 78–81. [[CrossRef](#)] [[PubMed](#)]
18. Dong, H.; Lu, F.-E.; Zhao, L. Chinese herbal medicine in the treatment of nonalcoholic fatty liver disease. *Chin. J. Integr. Med.* **2012**, *18*, 152–160. [[CrossRef](#)] [[PubMed](#)]
19. Heber, D. Herbs and atherosclerosis. *Curr. Atheroscler. Rep.* **2001**, *3*, 93–96. [[CrossRef](#)] [[PubMed](#)]
20. World Health Organization (WHO). *Traditional Medicine Strategy 2014–2023*; WHO: Geneva, Switzerland, 2013.
21. Mashour, N.H.; Lin, G.I.; Frishman, W.H. Herbal medicine for the treatment of cardiovascular disease: Clinical considerations. *Arch. Intern. Med.* **1998**, *158*, 2225–2234. [[CrossRef](#)] [[PubMed](#)]
22. Pittler, M.H.; Ernst, E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database Syst. Rev.* **2012**, *11*, CD003230. [[CrossRef](#)] [[PubMed](#)]
23. Suter, A.; Bommer, S.; Rechner, J. Treatment of patients with venous insufficiency with fresh plant horse chestnut seed extract: A review of 5 clinical studies. *Adv. Ther.* **2006**, *23*, 179–190. [[CrossRef](#)] [[PubMed](#)]
24. Siebert, U.; Brach, M.; Sroczynski, G.; Berla, K. Efficacy, routine effectiveness, and safety of horsechestnut seed extract in the treatment of chronic venous insufficiency. A meta-analysis of randomized controlled trials and large observational studies. *Int. Angiol.* **2002**, *21*, 305–315. [[PubMed](#)]
25. Rahman, K.; Lowe, G.M. Garlic and cardiovascular disease: A critical review. *J. Nutr.* **2006**, *136*, 736S–740S. [[PubMed](#)]
26. Sobenin, I.A.; Nedosugova, L.V.; Filatova, L.V.; Balabolkin, M.I.; Gorchakova, T.V.; Orekhov, A.N. Metabolic effects of time-released garlic powder tablets in type 2 diabetes mellitus: The results of double-blinded placebo-controlled study. *Acta Diabetol.* **2008**, *45*, 1–6. [[CrossRef](#)] [[PubMed](#)]
27. Al Disi, S.S.; Anwar, M.A.; Eid, A.H. Anti-hypertensive herbs and their mechanism of action: Part I. *Front. Pharmacol.* **2016**, *6*. [[CrossRef](#)] [[PubMed](#)]
28. Kwak, J.S.; Kim, J.Y.; Paek, J.E.; Lee, Y.J.; Kim, H.R.; Park, D.S.; Kwon, O. Garlic powder intake and cardiovascular risk factors: A meta-analysis of randomized controlled clinical trials. *Nutr. Res. Pract.* **2014**, *8*, 644–654. [[CrossRef](#)] [[PubMed](#)]
29. Stabler, S.N.; Tejani, A.M.; Huynh, F.; Fowkes, C. Garlic for the prevention of cardiovascular morbidity and mortality in hypertensive patients. *Cochrane Database Syst. Rev.* **2012**, *8*, CD007653. [[PubMed](#)]
30. Zeng, T.; Guo, F.F.; Zhang, C.L.; Song, F.Y.; Zhao, X.L.; Xie, K.Q. A meta-analysis of randomized, double-blind, placebo-controlled trials for the effects of garlic on serum lipid profiles. *J. Sci. Food Agric.* **2012**, *92*, 1892–1902. [[CrossRef](#)] [[PubMed](#)]
31. Okyar, A.; Can, A.; Akev, N.; Baktir, G.; Sütlüpinar, N. Effect of *Aloe vera* leaves on blood glucose level in type I and type II diabetic rat models. *Phytother. Res.* **2001**, *15*, 157–161. [[CrossRef](#)] [[PubMed](#)]
32. Rajasekaran, S.; Ravi, K.; Sivagnanam, K.; Subramanian, S. Beneficial effects of *Aloe vera* leaf gel extract on lipid profile status in rats with streptozotocin diabetes. *Clin. Exp. Pharmacol. Physiol.* **2006**, *33*, 232–237. [[CrossRef](#)] [[PubMed](#)]

33. Alinejad-Mofrad, S.; Foadoddini, M.; Saadatjoo, S.A.; Shayesteh, M. Improvement of glucose and lipid profile status with *Aloe vera* in pre-diabetic subjects: A randomized controlled-trial. *J. Diabetes Metab. Disord.* **2015**, *14*. [[CrossRef](#)] [[PubMed](#)]
34. Dick, W.R.; Fletcher, E.A.; Shah, S.A. Reduction of fasting blood glucose and hemoglobin A1c using oral *Aloe vera*: A meta-analysis. *J. Altern. Complement. Med.* **2016**. [[CrossRef](#)] [[PubMed](#)]
35. Devaraj, S.; Yimam, M.; Brownell, L.A.; Jialal, I.; Singh, S.; Jia, Q. Effects of *Aloe vera* supplementation in subjects with prediabetes/metabolic syndrome. *Metab. Syndr. Relat. Disord.* **2013**, *11*, 35–40. [[CrossRef](#)] [[PubMed](#)]
36. Hashim, S.; Jan, A.; Marwat, K.B.; Khan, M.A. Phytochemistry and medicinal properties of *Ammi visnaga* (Apiaceae). *Pak. J. Bot.* **2014**, *46*, 861–867.
37. Durate, J.; Vallejo, I.; Perez-Vizcaino, F.; Jimenez, R.; Zarzuelo, A.; Tamargo, J. Effects of visnadine on rat isolated vascular smooth muscles. *Planta Med.* **1997**, *63*, 233–236. [[CrossRef](#)] [[PubMed](#)]
38. Duarte, J.; Perez-Vizcaino, F.; Torres, A.I.; Zarzuelo, A.; Jimenez, J.; Tamargo, J. Vasodilator effects of visnagin in isolated rat vascular smooth muscle. *Eur. J. Pharmacol.* **1995**, *286*, 115–122. [[CrossRef](#)]
39. Hao, P.-P.; Jiang, F.; Chen, Y.-G.; Yang, J.; Zhang, K.; Zhang, M.-X.; Zhang, C.; Zhao, Y.-X.; Zhang, Y. Traditional Chinese medication for cardiovascular disease. *Nat. Rev. Cardiol.* **2015**, *12*, 115–122. [[CrossRef](#)] [[PubMed](#)]
40. Kim, D.-W.; Yokozawa, T.; Hattori, M.; Kadota, S.; Namba, T. Effects of aqueous extracts of *Apocynum venetum* leaves on spontaneously hypertensive, renal hypertensive and NaCl-fed-hypertensive rats. *J. Ethnopharmacol.* **2000**, *72*, 53–59. [[CrossRef](#)]
41. Xie, W.; Zhang, X.; Wang, T.; Hu, J. Botany, traditional uses, phytochemistry and pharmacology of *Apocynum venetum* L. (Luobuma): A review. *J. Ethnopharmacol.* **2012**, *141*, 1–8. [[CrossRef](#)] [[PubMed](#)]
42. Wang, W.; Liang, X.; Fu, D.; Tie, R.; Xing, W.; Ji, L.; Liu, F.; Zhang, H.; Li, R. *Apocynum venetum* leaf attenuates myocardial ischemia/reperfusion injury by inhibiting oxidative stress. *Am. J. Chin. Med.* **2015**, *43*, 71–85. [[CrossRef](#)] [[PubMed](#)]
43. Aggarwal, S.; Shailendra, G.; Ribnicky, D.M.; Burk, D.; Karki, N.; Qingxia Wang, M.S. An extract of *Artemisia dracunculus* L. stimulates insulin secretion from β cells, activates AMPK and suppresses inflammation. *J. Ethnopharmacol.* **2015**, *170*, 98–105. [[CrossRef](#)] [[PubMed](#)]
44. Watcho, P.; Stavniichuk, R.; Tane, P.; Shevalye, H.; Maksimchyk, Y.; Pacher, P.; Obrosova, I.G. Evaluation of PMI-5011, an ethanolic extract of *Artemisia dracunculus* L., on peripheral neuropathy in streptozotocin-diabetic mice. *Int. J. Mol. Med.* **2011**, *27*, 299–307. [[PubMed](#)]
45. Watcho, P.; Stavniichuk, R.; Ribnicky, D.M.; Raskin, I.; Obrosova, I.G. High-fat diet-induced neuropathy of prediabetes and obesity: Effect of PMI-5011, an ethanolic extract of *Artemisia dracunculus* L. *Mediat. Inflamm.* **2010**, *2010*. [[CrossRef](#)] [[PubMed](#)]
46. Hamza, N.; Berke, B.; Cheze, C.; Marais, S.; Lorrain, S.; Abdouelfath, A.; Lassalle, R.; Carles, D.; Gin, H.; Moore, N. Effect of *Centaureum erythraea* Rafn, *Artemisia herba-alba* Asso and *Trigonella foenum-graecum* L. on liver fat accumulation in C57BL/6J mice with high-fat diet-induced type 2 diabetes. *J. Ethnopharmacol.* **2015**, *171*, 4–11. [[CrossRef](#)] [[PubMed](#)]
47. Boudjelal, A.; Siracusa, L.; Henchiri, C.; Sarri, M.; Abderrahim, B.; Baali, F.; Ruberto, G. Antidiabetic effects of aqueous infusions of *Artemisia herba-alba* and *Ajuga iva* in alloxan-induced diabetic rats. *Planta Med.* **2015**, *81*, 696–704. [[CrossRef](#)] [[PubMed](#)]
48. Hamza, N.; Berke, B.; Cheze, C.; Le Garrec, R.; Lassalle, R.; Agli, A.N.; Robinson, P.; Gin, H.; Moore, N. Treatment of high fat diet induced type 2 diabetes in C57BL/6J mice by two medicinal plants used in traditional treatment of diabetes in the east of Algeria. *J. Ethnopharmacol.* **2011**, *133*, 931–933. [[CrossRef](#)] [[PubMed](#)]
49. Al-Shamaony, L.; al-Khazraji, S.M.; Twaij, H.A. Hypoglycaemic effect of *Artemisia herba alba*. II. Effect of a valuable extract on some blood parameters in diabetic animals. *J. Ethnopharmacol.* **1994**, *43*, 167–171. [[CrossRef](#)]
50. Hamza, N.; Berke, B.; Cheze, C.; Agli, A.N.; Robinson, P.; Gin, H.; Moore, N. Prevention of type 2 diabetes induced by high fat diet in the C57BL/6J mouse by two medicinal plants used in traditional treatment of diabetes in the east of Algeria. *J. Ethnopharmacol.* **2010**, *128*, 513–518. [[CrossRef](#)] [[PubMed](#)]

51. Kawano, A.; Nakamura, H.; Hata, S.-I.; Minakawa, M.; Miura, Y.; Yagasaki, K. Hypoglycemic effect of aspalathin, a rooibos tea component from *Aspalathus linearis*, in type 2 diabetic model *db/db* mice. *Phytomedicine* **2009**, *16*, 437–443. [[CrossRef](#)] [[PubMed](#)]
52. Son, M.J.; Minakawa, M.; Miura, Y.; Yagasaki, K. Aspalathin improves hyperglycemia and glucose intolerance in obese diabetic *ob/ob* mice. *Eur. J. Nutr.* **2013**, *52*, 1607–1619. [[CrossRef](#)] [[PubMed](#)]
53. Mazibuko, S.E.; Joubert, E.; Johnson, R.; Louw, J.; Opoku, A.R.; Muller, C.J. Aspalathin improves glucose and lipid metabolism in 3T3-L1 adipocytes exposed to palmitate. *Mol. Nutr. Food Res.* **2015**, *59*, 2199–2208. [[CrossRef](#)] [[PubMed](#)]
54. Ku, S.K.; Kwak, S.; Kim, Y.; Bae, J.S. Aspalathin and nothofagin from rooibos (*Aspalathus linearis*) inhibits high glucose-induced inflammation *in vitro* and *in vivo*. *Inflammation* **2015**, *38*, 445–455. [[CrossRef](#)] [[PubMed](#)]
55. Chen, W.; Lai, Y.; Wang, L.; Xia, Y.; Chen, W.; Zhao, X.; Yu, M.; Li, Y.; Zhang, Y.; Ye, H. *Astragalus* polysaccharides repress myocardial lipotoxicity in a PPAR α -dependent manner *in vitro* and *in vivo* in mice. *J. Diabetes Complicat.* **2015**, *29*, 164–175. [[CrossRef](#)] [[PubMed](#)]
56. Kim, J.; Moon, E.; Kwon, S. Effect of *Astragalus membranaceus* extract on diabetic nephropathy. *Endocrinol. Diabetes Metab. Case Rep.* **2014**, *2014*. [[CrossRef](#)] [[PubMed](#)]
57. Qin, H.; Liu, P.; Lin, S. Effects of astragaloside IV on the SDF-1/CXCR4 expression in atherosclerosis of apoE^{−/−} mice induced by hyperlipaemia. *Evid. Based Complement. Altern. Med.* **2015**, *2015*. [[CrossRef](#)] [[PubMed](#)]
58. Zhao, P.; Wang, Y.; Zeng, S.; Lu, J.; Jiang, T.-M.; Li, Y.-M. Protective effect of astragaloside IV on lipopolysaccharide-induced cardiac dysfunction *via* downregulation of inflammatory signaling in mice. *Immunopharmacol. Immunotoxicol.* **2015**, *37*, 428–433. [[CrossRef](#)] [[PubMed](#)]
59. Lu, Y.; Li, S.; Wu, H.; Bian, Z.; Xu, J.; Gu, C.; Chen, X.; Yang, D. Beneficial effects of astragaloside IV against angiotensin II-induced mitochondrial dysfunction in rat vascular smooth muscle cells. *Int. J. Mol. Med.* **2015**, *36*, 1223–1232. [[CrossRef](#)] [[PubMed](#)]
60. Bai, Y.; Lu, P.; Han, C.; Yu, C.; Chen, M.; He, F.; Yi, D.; Wu, L. Hydroxysafflor yellow A (HSYA) from flowers of *Carthamus tinctorius* L. and its vasodilatation effects on pulmonary artery. *Molecules* **2012**, *17*, 14918–14927. [[CrossRef](#)] [[PubMed](#)]
61. Nie, P.H.; Zhang, L.; Zhang, W.H.; Rong, W.F.; Zhi, J.M. The effects of hydroxysafflor yellow A on blood pressure and cardiac function. *J. Ethnopharmacol.* **2012**, *139*, 746–750. [[CrossRef](#)] [[PubMed](#)]
62. Chen, J.; Deng, J.; Zhang, Y.; Yang, J.; He, Y.; Fu, W.; Xing, P.; Wan, H.T. Lipid-lowering effects of Danhong injection on hyperlipidemia rats. *J. Ethnopharmacol.* **2014**, *154*, 437–442. [[CrossRef](#)] [[PubMed](#)]
63. Li, L.; Dong, P.; Hou, C.; Cao, F.; Sun, S.; He, F.; Song, Y.; Li, S.; Bai, Y.; Zhu, D. Hydroxysafflor yellow A (HSYA) attenuates hypoxic pulmonary arterial remodelling and reverses right ventricular hypertrophy in rats. *J. Ethnopharmacol.* **2016**, *186*, 224–233. [[CrossRef](#)] [[PubMed](#)]
64. Maneesai, P.; Prasarttong, P.; Bunbupha, S.; Kukongviriyapan, U.; Kukongviriyapan, V.; Tangsucharit, P.; Prachaney, P.; Pakdeechote, P. Synergistic antihypertensive effect of *Carthamus tinctorius* L. extract and captopril in L-NAME-induced hypertensive rats via restoration of eNOS and AT₁R expression. *Nutrients* **2016**, *8*. [[CrossRef](#)] [[PubMed](#)]
65. Sefi, M.; Fetoui, H.; Lachkar, N.; Tahraoui, A.; Lyoussi, B.; Boudawara, T.; Zeghal, N. *Centaurium erythraea* (Gentianaceae) leaf extract alleviates streptozotocin-induced oxidative stress and β -cell damage in rat pancreas. *J. Ethnopharmacol.* **2011**, *135*, 243–250. [[CrossRef](#)] [[PubMed](#)]
66. Stefkov, G.; Miova, B.; Dinevska-Kjovkarovska, S.; Stanoeva, J.P.; Stefova, M.; Petrusevska, G.; Kulevanova, S. Chemical characterization of *Centaurium erythraea* L. and its effects on carbohydrate and lipid metabolism in experimental diabetes. *J. Ethnopharmacol.* **2014**, *152*, 71–77. [[CrossRef](#)] [[PubMed](#)]
67. Eddouks, M.; Bidi, A.; El Bouhali, B.; Hajji, L.; Zeggwagh, N.A. Antidiabetic plants improving insulin sensitivity. *J. Pharm. Pharmacol.* **2014**, *66*, 1197–1214. [[CrossRef](#)] [[PubMed](#)]
68. Yan, Y.-M.; Fang, P.; Yang, M.-T.; Li, N.; Lu, Q.; Cheng, Y.-X. Anti-diabetic nephropathy compounds from *Cinnamomum cassia*. *J. Ethnopharmacol.* **2015**, *165*, 141–147. [[CrossRef](#)] [[PubMed](#)]
69. Medagama, A.B. The glycaemic outcomes of cinnamon, a review of the experimental evidence and clinical trials. *Nutr. J.* **2015**, *14*. [[CrossRef](#)] [[PubMed](#)]
70. Crawford, P. Effectiveness of cinnamon for lowering hemoglobin A1C in patients with type 2 diabetes: A randomized, controlled trial. *J. Am. Board Fam. Med.* **2009**, *22*, 507–512. [[CrossRef](#)] [[PubMed](#)]

71. Mirfeizi, M.; Mehdizadeh Tourzani, Z.; Mirfeizi, S.Z.; Asghari Jafarabadi, M.; Rezvani, H.R.; Afzali, M.; Gholami, M.J. Controlling diabetes mellitus type 2 with herbal medicines: A triple blind, randomized clinical trial of efficacy and safety. *J. Diabetes* **2015**. [[CrossRef](#)] [[PubMed](#)]
72. Ríos, J.L.; Francini, F.; Schinella, G.R. Natural products for the treatment of type 2 diabetes mellitus. *Planta Med.* **2015**, *81*, 975–994. [[CrossRef](#)] [[PubMed](#)]
73. Whitfield, P.; Parry-Strong, A.; Walsh, E.; Weatherall, M.; Krebs, J.D. The effect of a cinnamon-, chromium- and magnesium-formulated honey on glycaemic control, weight loss and lipid parameters in type 2 diabetes: An open-label cross-over randomised controlled trial. *Eur. J. Nutr.* **2016**, *55*, 1123–1131. [[CrossRef](#)] [[PubMed](#)]
74. Beejmohun, V.; Peytavy-Izard, M.; Mignon, C.; Muscente-Paque, D.; Deplanque, X.; Ripoll, C.; Chapal, N. Acute effect of Ceylon cinnamon extract on postprandial glycemia: Alpha-amylase inhibition, starch tolerance test in rats, and randomized crossover clinical trial in healthy volunteers. *BMC Complement. Altern. Med.* **2014**, *14*. [[CrossRef](#)] [[PubMed](#)]
75. Frishman, W.H.; Beravol, P.; Carosella, C. Alternative and complementary medicine for preventing and treating cardiovascular disease. *Dis. Mon.* **2009**, *55*, 121–192. [[CrossRef](#)] [[PubMed](#)]
76. Ojha, S.K.; Nandave, M.; Arora, S.; Mehra, R.D.; Joshi, S.; Narang, R.; Arya, D.S. Effect of *Commiphora mukul* extract on cardiac dysfunction and ventricular function in isoproterenol-induced myocardial infarction. *Indian J. Exp. Biol.* **2008**, *46*, 646–652. [[PubMed](#)]
77. Yuan, L.; Tu, D.; Ye, X.; Wu, J. Hypoglycemic and hypocholesterolemic effects of *Coptis chinensis* Franch inflorescence. *Plant Foods Hum. Nutr.* **2006**, *61*, 139–144. [[CrossRef](#)] [[PubMed](#)]
78. Dong, H.; Wang, J.-H.; Lu, F.-E.; Xu, L.-J.; Gong, Y.-L.; Zou, X. Jiaotai Pill enhances insulin signaling through phosphatidylinositol 3-kinase pathway in skeletal muscle of diabetic rats. *Chin. J. Integr. Med.* **2013**, *19*, 668–674. [[CrossRef](#)] [[PubMed](#)]
79. Yang, Z.; Wang, L.; Zhang, F.; Li, Z. Evaluating the antidiabetic effects of Chinese herbal medicine: Xiao-Ke-An in 3T3-L1 cells and KKAY mice using both conventional and holistic omics approaches. *BMC Complement. Altern. Med.* **2015**, *15*. [[CrossRef](#)] [[PubMed](#)]
80. Eidi, M.; Eidi, A.; Saeidi, A.; Molanaei, S.; Sadeghipour, A.; Bahar, M.; Bahar, K. Effect of coriander seed (*Coriandrum sativum* L.) ethanol extract on insulin release from pancreatic beta cells in streptozotocin-induced diabetic rats. *Phytother. Res.* **2009**, *23*, 404–406. [[CrossRef](#)] [[PubMed](#)]
81. Dhanapakiam, P.; Joseph, J.M.; Ramaswamy, V.K.; Moorthi, M.; Kumar, A.S. The cholesterol lowering properties of coriander seeds (*Coriandrum sativum*): Mechanism of action. *J. Environ. Biol.* **2008**, *29*, 53–56. [[PubMed](#)]
82. Sreelatha, S.; Inbavalli, R. Antioxidant, antihyperglycemic, and antihyperlipidemic effects of *Coriandrum sativum* leaf and stem in alloxan-induced diabetic rats. *J. Food Sci.* **2012**, *77*, T119–T123. [[CrossRef](#)] [[PubMed](#)]
83. Aissaoui, A.; Zizi, S.; Israili, Z.H.; Lyoussi, B. Hypoglycemic and hypolipidemic effects of *Coriandrum sativum* L. in *Meriones shawi* rats. *J. Ethnopharmacol.* **2011**, *137*, 652–661. [[CrossRef](#)] [[PubMed](#)]
84. Chang, W.-T.; Dao, J.; Shao, Z.-H. Hawthorn: Potential roles in cardiovascular disease. *Am. J. Chin. Med.* **2005**, *33*, 1–10. [[CrossRef](#)] [[PubMed](#)]
85. Chrysant, S.G. The clinical significance and costs of herbs and food supplements used by complementary and alternative medicine for the treatment of cardiovascular diseases and hypertension. *J. Hum. Hypertens.* **2016**, *30*, 1–6. [[CrossRef](#)] [[PubMed](#)]
86. Asher, G.N.; Viera, A.J.; Weaver, M.A.; Dominik, R.; Caughey, M.; Hinderliter, A.L. Effect of hawthorn standardized extract on flow mediated dilation in prehypertensive and mildly hypertensive adults: A randomized, controlled cross-over trial. *BMC Complement. Altern. Med.* **2012**, *12*. [[CrossRef](#)] [[PubMed](#)]
87. Pittler, M.H.; Guo, R.; Ernst, E. Hawthorn extract for treating chronic heart failure. *Cochrane Database Syst. Rev.* **2008**, *1*, CD005312. [[PubMed](#)]
88. Bundy, R.; Walker, A.F.; Middleton, R.W.; Wallis, C.; Simpson, H.C.R. Artichoke leaf extract (*Cynara scolymus*) reduces plasma cholesterol in otherwise healthy hypercholesterolemic adults: A randomized, double blind placebo controlled trial. *Phytomedicine* **2008**, *15*, 668–675. [[CrossRef](#)] [[PubMed](#)]
89. Ben Salem, M.; Affes, H.; Ksouda, K.; Dhouibi, R.; Sahnoun, Z.; Hammami, S.; Zeghal, K.M. Pharmacological studies of artichoke leaf extract and their health benefits. *Plant Foods Hum. Nutr.* **2015**, *70*, 441–453. [[CrossRef](#)] [[PubMed](#)]

90. Maghrani, M.; Zeggwagh, N.-A.; Lemhadri, A.; El Amraoui, M.; Michel, J.-B.; Eddouks, M. Study of the hypoglycaemic activity of *Fraxinus excelsior* and *Silybum marianum* in an animal model of type 1 diabetes mellitus. *J. Ethnopharmacol.* **2004**, *91*, 309–316. [[CrossRef](#)] [[PubMed](#)]
91. Eddouks, M.; Maghrani, M. Phlorizin-like effect of *Fraxinus excelsior* in normal and diabetic rats. *J. Ethnopharmacol.* **2004**, *94*, 149–154. [[CrossRef](#)] [[PubMed](#)]
92. Gomez-Garcia, F.; Flanagan, J.; García-Molina, O.; Vilaplana-Vivo, V.; García-Carrillo, N.; Berthon, P.F.; Bily, A.; Roller, M.; Ortega, V.V.; Issaly, N. Preventive effect of a *Fraxinus excelsior* L seeds/fruits extract on hepatic steatosis in obese type 2 diabetic mice. *J. Diabetes Metab.* **2015**, *6*. [[CrossRef](#)]
93. Visen, P.; Saraswat, B.; Visen, A.; Roller, M.; Bily, A.; Mermet, C.; He, K.; Bai, N.; Lemaire, B.; Lafay, S.; et al. Acute effects of *Fraxinus excelsior* L. seed extract on postprandial glycemia and insulin secretion on healthy volunteers. *J. Ethnopharmacol.* **2009**, *126*, 226–232. [[CrossRef](#)] [[PubMed](#)]
94. Bai, N.; He, K.; Ibarra, A.; Bily, A.; Roller, M.; Chen, X.; Rühl, R. Iridoids from *Fraxinus excelsior* with adipocyte differentiation-inhibitory and PPAR α activation activity. *J. Nat. Prod.* **2010**, *73*, 2–6. [[CrossRef](#)] [[PubMed](#)]
95. Zulet, M.A.; Navas-Carretero, S.; Lara y Sanchez, D.; Abete, I.; Flanagan, J.; Issaly, N.; Fanca-Berthon, P.; Bily, A.; Roller, M.; Martinez, J.A. A *Fraxinus excelsior* L. seeds/fruits extract benefits glucose homeostasis and adiposity related markers in elderly overweight/obese subjects: A longitudinal, randomized, crossover, double-blind, placebo-controlled nutritional intervention study. *Phytomedicine* **2014**, *21*, 1162–1169. [[CrossRef](#)] [[PubMed](#)]
96. Bedekar, A.; Shah, K.; Koffas, M. Natural products for type II diabetes treatment. *Adv. Appl. Microbiol.* **2010**, *71*, 21–73. [[PubMed](#)]
97. Perla, V.; Jayanty, S.S. Biguanide related compounds in traditional antidiabetic functional foods. *Food Chem.* **2013**, *138*, 1574–1580. [[CrossRef](#)] [[PubMed](#)]
98. Witters, L.A. The blooming of the French lilac. *J. Clin. Investig.* **2001**, *108*, 1105–1107. [[CrossRef](#)] [[PubMed](#)]
99. Gardner, C.D.; Zehnder, J.L.; Rigby, A.J.; Nicholus, J.R.; Farquhar, J.W. Effect of *Ginkgo biloba* (EGb 761) and aspirin on platelet aggregation and platelet function analysis among older adults at risk of cardiovascular disease: A randomized clinical trial. *Blood Coagul. Fibrinolysis* **2007**, *18*, 787–793. [[CrossRef](#)] [[PubMed](#)]
100. Lu, Q.; Zuo, W.-Z.; Ji, X.-J.; Zhou, Y.-X.; Liu, Y.-Q.; Yao, X.-Q.; Zhou, X.-Y.; Liu, Y.-W.; Zhang, F.; Yin, X.-X. Ethanolic *Ginkgo biloba* leaf extract prevents renal fibrosis through Akt/mTOR signaling in diabetic nephropathy. *Phytomedicine* **2015**, *22*, 1071–1078. [[CrossRef](#)] [[PubMed](#)]
101. Erukainure, O.L.; Ajiboye, J.A.; Lawal, B.A.; Obode, O.C.; Okoro, E.E.; Amisu-Tugbobo, A.O.; Zaruwa, M.Z. Alterations in atherogenic indices and hypolipidemic effect of soybean oil in normocholesteremic rats. *Comp. Clin. Pathol.* **2016**, *25*, 75–78. [[CrossRef](#)]
102. Kwon, D.Y.; Daily, J.W.; Kim, H.J.; Park, S. Antidiabetic effects of fermented soybean products on type 2 diabetes. *Nutr. Res.* **2010**, *30*, 1–13. [[CrossRef](#)] [[PubMed](#)]
103. Jiang, H.; Tong, Y.; Yan, D.; Jia, S.; Ostenson, C.G.; Chen, Z. The soybean peptide vglycin preserves the diabetic beta-cells through improvement of proliferation and inhibition of apoptosis. *Sci. Rep.* **2015**, *5*. [[CrossRef](#)]
104. Fuhrman, B.; Volkova, N.; Kaplan, M.; Presser, D.; Attias, J.; Hayek, T.; Aviram, M. Antiatherosclerotic effects of licorice extract supplementation on hypercholesterolemic patients: Increased resistance of LDL to atherogenic modifications, reduced plasma lipid levels, and decreased systolic blood pressure. *Nutrition* **2002**, *18*, 268–273. [[CrossRef](#)]
105. Chang, W.-C.; Jia, H.; Aw, W.; Saito, K.; Hasegawa, S.; Kato, H. Beneficial effects of soluble dietary Jerusalem artichoke (*Helianthus tuberosus*) in the prevention of the onset of type 2 diabetes and non-alcoholic fatty liver disease in high-fructose diet-fed rats. *Br. J. Nutr.* **2014**, *112*, 709–717. [[CrossRef](#)] [[PubMed](#)]
106. Gambero, A.; Ribeiro, M.L. The positive effects of yerba maté (*Ilex paraguariensis*) in obesity. *Nutrients* **2015**, *7*, 730–750. [[CrossRef](#)] [[PubMed](#)]
107. De Moraes Pontilho, P.; Nunes da Costa Teixeira, A.M.; Yuan, C.; Alves Luzia, L.; Markowicz Bastos, D.H.; Rondó, P.H. Yerba mate (*Ilex paraguariensis* A. St. Hil) and risk factors for cardiovascular diseases. *J. Food Nutr. Res.* **2015**, *3*, 182–190. [[CrossRef](#)]
108. Cardozo, E.L., Jr.; Morand, C. Interest of mate (*Ilex paraguariensis* A. St.-Hil.) as a new natural functional food to preserve human cardiovascular health—A review. *J. Funct. Foods* **2016**, *21*, 440–454. [[CrossRef](#)]

109. Chang, C.L.T.; Lin, Y.; Bartolome, A.P.; Chen, Y.-C.; Chiu, S.-C.; Yang, W.-C. Herbal therapies for type 2 diabetes mellitus: Chemistry, biology, and potential application of selected plants and compounds. *Evid. Based Complement. Alternat. Med.* **2013**, 2013. [[CrossRef](#)] [[PubMed](#)]
110. Kim, S.-Y.; Oh, M.-R.; Kim, M.-G.; Chae, H.-J.; Chae, S.-W. Anti-obesity effects of yerba mate (*Ilex Paraguariensis*): A randomized, double-blind, placebo-controlled clinical trial. *BMC Complement. Altern. Med.* **2015**, 15. [[CrossRef](#)] [[PubMed](#)]
111. Yu, S.; Yue, S.w.; Liu, Z.; Zhang, T.; Xiang, N.; Fu, H. Yerba mate (*Ilex paraguariensis*) improves microcirculation of volunteers with high blood viscosity: A randomized, double-blind, placebo-controlled trial. *Exp. Gerontol.* **2015**, 62, 14–22. [[CrossRef](#)] [[PubMed](#)]
112. Luo, Q.; Cai, Y.; Yan, J.; Sun, M.; Corke, H. Hypoglycemic and hypolipidemic effects and antioxidant activity of fruit extracts from *Lycium barbarum*. *Life Sci.* **2004**, 76, 137–149. [[CrossRef](#)] [[PubMed](#)]
113. Zhao, R.; Jin, R.; Chen, Y.; Han, F.-m. Hypoglycemic and hypolipidemic effects of *Lycium barbarum* polysaccharide in diabetic rats. *Chin. Herb. Med.* **2015**, 7, 310–315. [[CrossRef](#)]
114. Amagase, H.; Nance, D.M. A randomized, double-blind, placebo-controlled, clinical study of the general effects of a standardized *Lycium barbarum* (Goji) juice, GoChi™. *J. Altern. Complement. Med.* **2008**, 14, 403–412. [[CrossRef](#)] [[PubMed](#)]
115. Zhang, X.; Yang, X.; Lin, Y.; Suo, M.; Gong, L.; Chen, J.; Hui, R. Anti-hypertensive effect of *Lycium barbarum* L. with down-regulated expression of renal endothelial lncRNA sONE in a rat model of salt-sensitive hypertension. *Int. J. Clin. Exp. Pathol.* **2015**, 8, 6981–6987. [[PubMed](#)]
116. Lu, S.-P.; Zhao, P.-T. Chemical characterization of *Lycium barbarum* polysaccharides and their reducing myocardial injury in ischemia/reperfusion of rat heart. *Int. J. Biol. Macromol.* **2010**, 47, 681–684. [[CrossRef](#)] [[PubMed](#)]
117. Ming, M.; Guanhua, L.; Zhanhai, Y.; Guang, C.; Xuan, Z. Effect of the *Lycium barbarum* polysaccharides administration on blood lipid metabolism and oxidative stress of mice fed high-fat diet *in vivo*. *Food Chem.* **2009**, 113, 872–877. [[CrossRef](#)]
118. Cai, H.; Liu, F.; Zuo, P.; Huang, G.; Song, Z.; Wang, T.; Lu, H.; Guo, F.; Han, C.; Sun, G. Practical application of antidiabetic efficacy of *Lycium barbarum* polysaccharide in patients with type 2 diabetes. *Med. Chem.* **2015**, 11, 383–390. [[CrossRef](#)] [[PubMed](#)]
119. Zhu, X.; Hu, S.; Zhu, L.; Ding, J.; Zhou, Y.; Li, G. Effects of *Lycium barbarum* polysaccharides on oxidative stress in hyperlipidemic mice following chronic composite psychological stress intervention. *Mol. Med. Rep.* **2015**, 11, 3445–3450. [[CrossRef](#)] [[PubMed](#)]
120. Mishra, A.; Gautam, S.; Pal, S.; Mishra, A.; Rawat, A.K.; Maurya, R.; Srivastava, A.K. Effect of *Momordica charantia* fruits on streptozotocin-induced diabetes mellitus and its associated complications. *Int. J. Pharm. Pharm. Sci.* **2015**, 7, 356–363.
121. Yang, S.J.; Choi, J.M.; Park, S.E.; Rhee, E.J.; Lee, W.Y.; Oh, K.W.; Park, S.W.; Park, C.-Y. Preventive effects of bitter melon (*Momordica charantia*) against insulin resistance and diabetes are associated with the inhibition of NF- κ B and JNK pathways in high-fat-fed OLETF rats. *J. Nutr. Biochem.* **2015**, 26, 234–240. [[CrossRef](#)] [[PubMed](#)]
122. Singab, A.N.B.; El-Beshbishy, H.A.; Yonekawa, M.; Nomura, T.; Fukai, T. Hypoglycemic effect of Egyptian *Morus alba* root bark extract: Effect on diabetes and lipid peroxidation of streptozotocin-induced diabetic rats. *J. Ethnopharmacol.* **2005**, 100, 333–338. [[CrossRef](#)] [[PubMed](#)]
123. Hunyadi, A.; Martins, A.; Hsieh, T.-J.; Seres, A.; Zupkó, I. Chlorogenic acid and rutin play a major role in the *in vivo* anti-diabetic activity of *Morus alba* leaf extract on type II diabetic rats. *PLoS ONE* **2012**, 7, e50619. [[CrossRef](#)] [[PubMed](#)]
124. Butt, M.S.; Nazir, A.; Sultan, M.T.; Schroën, K. *Morus alba* L. nature's functional tonic. *Trends Food Sci. Technol.* **2008**, 19, 505–512. [[CrossRef](#)]
125. Cai, S.; Sun, W.; Fan, Y.; Guo, X.; Xu, G.; Xu, T.; Hou, Y.; Zhao, B.; Feng, X.; Liu, T. Effect of mulberry leaf (*Folium mori*) on insulin resistance via IRS-1/PI3K/Glut-4 signalling pathway in type 2 diabetes mellitus rats. *Pharm. Biol.* **2016**. [[CrossRef](#)] [[PubMed](#)]
126. Mahmoud, A.M.; Abd El-Twab, S.M.; Abdel-Reheim, E.S. Consumption of polyphenol-rich *Morus alba* leaves extract attenuates early diabetic retinopathy: The underlying mechanism. *Eur. J. Nutr.* **2016**. [[CrossRef](#)] [[PubMed](#)]

127. Phimarn, W.; Wichaiyo, K.; Silpsavikul, K.; Sungthong, B.; Saramunee, K. A meta-analysis of efficacy of *Morus alba* Linn. to improve blood glucose and lipid profile. *Eur. J. Nutr.* **2016**. [[CrossRef](#)] [[PubMed](#)]
128. Heshmati, J.; Namazi, N. Effects of black seed (*Nigella sativa*) on metabolic parameters in diabetes mellitus: A systematic review. *Complement. Ther. Med.* **2015**, *23*, 275–282. [[CrossRef](#)] [[PubMed](#)]
129. Heshmati, J.; Namazi, N.; Memarzadeh, M.-R.; Taghizadeh, M.; Kolahdooz, F. *Nigella sativa* oil affects glucose metabolism and lipid concentrations in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *Food Res. Int.* **2015**, *70*, 87–93. [[CrossRef](#)]
130. Kaatabi, H.; Bamosa, A.O.; Badar, A.; Al-Elq, A.; Abou-Hozafa, B.; Lebda, F.; Al-Khadra, A.; Al-Almaie, S. *Nigella sativa* improves glycemic control and ameliorates oxidative stress in patients with type 2 diabetes mellitus: Placebo controlled participant blinded clinical trial. *PLoS ONE* **2015**, *10*, e0113486. [[CrossRef](#)] [[PubMed](#)]
131. Mahdavi, R.; Namazi, N.; Alizadeh, M.; Farajnia, S. Effects of *Nigella sativa* oil with a low-calorie diet on cardiometabolic risk factors in obese women: A randomized controlled clinical trial. *Food Funct.* **2015**, *6*, 2041–2048. [[CrossRef](#)] [[PubMed](#)]
132. Asgary, S.; Sahebkar, A.; Goli-Malekabadi, N. Ameliorative effects of *Nigella sativa* on dyslipidemia. *J. Endocrinol. Investig.* **2015**, *38*, 1039–1046. [[CrossRef](#)] [[PubMed](#)]
133. Husain, I.; Chander, R.; Saxena, J.K.; Mahdi, A.A.; Mahdi, F. Antidyslipidemic effect of *Ocimum sanctum* leaf extract in streptozotocin induced diabetic rats. *Indian J. Clin. Biochem.* **2015**, *30*, 72–77. [[CrossRef](#)] [[PubMed](#)]
134. Thadani, S.; Salman, M.T.; Tewari, S.; Singh, S.; Bhagchandani, D.; Ahmad, A. Renoprotective effect of *Ocimum sanctum* in comparison with olmesartan medoxomil and pitavastatin in metformin treated diabetic rats. *Int. J. Pharm. Sci. Res.* **2015**, *6*, 4433–4441.
135. El, S.N.; Karakaya, S. Olive tree (*Olea europaea*) leaves: Potential beneficial effects on human health. *Nutr. Rev.* **2009**, *67*, 632–638. [[CrossRef](#)] [[PubMed](#)]
136. Poudyal, H.; Campbell, F.; Brown, L. Olive leaf extract attenuates cardiac, hepatic, and metabolic changes in high carbohydrate-, high fat-fed rats. *J. Nutr.* **2010**, *140*, 946–953. [[CrossRef](#)] [[PubMed](#)]
137. Susalit, E.; Agus, N.; Effendi, I.; Tjandrawinata, R.R.; Nofiarny, D.; Perrinjaquet-Moccetti, T.; Verbruggen, M. Olive (*Olea europaea*) leaf extract effective in patients with stage-1 hypertension: Comparison with captopril. *Phytomedicine* **2011**, *18*, 251–258. [[CrossRef](#)] [[PubMed](#)]
138. Efentakis, P.; Iliodromitis, E.K.; Mikros, E.; Papachristodoulou, A.; Dagres, N.; Skaltsounis, A.-L.; Andreadou, I. Effects of the olive tree leaf constituents on myocardial oxidative damage and atherosclerosis. *Planta Med.* **2015**, *81*, 648–654. [[CrossRef](#)] [[PubMed](#)]
139. Wainstein, J.; Ganz, T.; Boaz, M.; Bar Dayan, Y.; Dolev, E.; Kerem, Z.; Madar, Z. Olive leaf extract as a hypoglycemic agent in both human diabetic subjects and in rats. *J. Med. Food* **2012**, *15*, 605–610. [[CrossRef](#)] [[PubMed](#)]
140. Lepore, S.M.; Morittu, V.M.; Celano, M.; Trimboli, F.; Oliverio, M.; Procopio, A.; Di Loreto, C.; Damante, G.; Britti, D.; Bulotta, S.; et al. Oral administration of oleuropein and its semisynthetic peracetylated derivative prevents hepatic steatosis, hyperinsulinemia, and weight gain in mice fed with high fat cafeteria diet. *Int. J. Endocrinol.* **2015**, 2015. [[CrossRef](#)] [[PubMed](#)]
141. Perona, J.S.; Cañizares, J.; Montero, E.; Sánchez-Domínguez, J.M.; Catalá, A.; Ruiz-Gutiérrez, V. Virgin olive oil reduces blood pressure in hypertensive elderly subjects. *Clin. Nutr.* **2004**, *23*, 1113–1121. [[CrossRef](#)] [[PubMed](#)]
142. Quintieri, A.M.; Filice, E.; Amelio, D.; Pasqua, T.; Lupi, F.R.; Scavello, F.; Cantafio, P.; Rocca, C.; Lauria, A.; Penna, C.; et al. The innovative “Bio-Oil Spread” prevents metabolic disorders and mediates preconditioning-like cardioprotection in rats. *Nutr. Metab. Cardiovasc. Dis.* **2016**. [[CrossRef](#)] [[PubMed](#)]
143. Zhang, Y.-G.; Zhang, H.-G.; Zhang, G.-Y.; Fan, J.-S.; Li, X.-H.; Liu, Y.-H.; Li, S.-H.; Lian, X.-M.; Tang, Z. *Panax notoginseng* saponins attenuate atherosclerosis in rats by regulating the blood lipid profile and an anti-inflammatory action. *Clin. Exp. Pharmacol. Physiol.* **2008**, *35*, 1238–1244. [[CrossRef](#)] [[PubMed](#)]
144. Bello, C.T.; Turner, L.W. Reserpine as an antihypertensive in the outpatient clinic: A double-blind clinical study. *Am. J. Med. Sci.* **1956**, *232*, 194–197. [[CrossRef](#)] [[PubMed](#)]
145. Shamon, S.D.; Perez, M.I. Blood pressure lowering efficacy of reserpine for primary hypertension. *Cochrane Database Syst. Rev.* **2009**, *4*, CD007655. [[PubMed](#)]

146. Yu, L.; Qin, Y.; Wang, Q.; Zhang, L.; Liu, Y.; Wang, T.; Huang, L.; Wu, L.; Xiong, H. The efficacy and safety of Chinese herbal medicine, *Rhodiola* formulation in treating ischemic heart disease: A systematic review and meta-analysis of randomized controlled trials. *Complement. Ther. Med.* **2014**, *22*, 814–825. [[CrossRef](#)] [[PubMed](#)]
147. Wu, T.; Zhou, H.; Jin, Z.; Bi, S.; Yang, X.; Yi, D.; Liu, W. Cardioprotection of salidroside from ischemia/reperfusion injury by increasing N-acetylglucosamine linkage to cellular proteins. *Eur. J. Pharmacol.* **2009**, *613*, 93–99. [[CrossRef](#)] [[PubMed](#)]
148. Sinkovic, A.; Suran, D.; Lokar, L.; Fliser, E.; Skerget, M.; Novak, Z.; Knez, Z. Rosemary extracts improve flow-mediated dilatation of the brachial artery and plasma PAI-1 activity in healthy young volunteers. *Phytother. Res.* **2011**, *25*, 402–407. [[CrossRef](#)] [[PubMed](#)]
149. Posadas, S.J.; Caz, V.; Largo, C.; de la Gándara, B.; Matallanas, B.; Reglero, G.; de Miguel, E. Protective effect of supercritical fluid rosemary extract, *Rosmarinus officinalis*, on antioxidants of major organs of aged rats. *Exp. Gerontol.* **2009**, *44*, 383–389. [[CrossRef](#)] [[PubMed](#)]
150. Vanscheidt, W.; Jost, V.; Wolna, P.; Lückner, P.W.; Müller, A.; Theurer, C.; Patz, B.; Grützner, K.I. Efficacy and safety of a butcher's broom preparation (*Ruscus aculeatus* L. extract) compared to placebo in patients suffering from chronic venous insufficiency. *Arzneimittelforschung* **2002**, *52*, 243–250. [[CrossRef](#)] [[PubMed](#)]
151. Ciocoiu, M.; Mirón, A.; Mares, L.; Tutunaru, D.; Pohaci, C.; Groza, M.; Badescu, M. The effects of *Sambucus nigra* polyphenols on oxidative stress and metabolic disorders in experimental diabetes mellitus. *J. Physiol. Biochem.* **2009**, *65*, 297–304. [[CrossRef](#)] [[PubMed](#)]
152. Bhattacharya, S.; Christensen, K.B.; Olsen, L.C.B.; Christensen, L.P.; Grevsen, K.; Færgeman, N.J.; Kristiansen, K.; Young, J.F.; Oksbjerg, N. Bioactive components from flowers of *Sambucus nigra* L. increase glucose uptake in primary porcine myotube cultures and reduce fat accumulation in *Caenorhabditis elegans*. *J. Agric. Food Chem.* **2013**, *61*, 11033–11040. [[CrossRef](#)] [[PubMed](#)]
153. Christensen, K.B.; Petersen, R.K.; Kristiansen, K.; Christensen, L.P. Identification of bioactive compounds from flowers of black elder (*Sambucus nigra* L.) that activate the human peroxisome proliferator-activated receptor (PPAR) gamma. *Phytother. Res.* **2010**, *24*, S129–S132. [[CrossRef](#)] [[PubMed](#)]
154. Li, L.; Zhou, X.; Li, N.; Sun, M.; Lv, J.; Xu, Z. Herbal drugs against cardiovascular disease: Traditional medicine and modern development. *Drug Discov. Today* **2015**, *20*, 1074–1086. [[CrossRef](#)] [[PubMed](#)]
155. Chun, J.N.; Cho, M.; So, I.; Jeon, J.-H. The protective effects of *Schisandra chinensis* fruit extract and its lignans against cardiovascular disease: A review of the molecular mechanisms. *Fitoterapia* **2014**, *97*, 224–233. [[CrossRef](#)] [[PubMed](#)]
156. Liu, H.; Wu, C.; Wang, S.; Gao, S.; Liu, J.; Dong, Z.; Zhang, B.; Liu, M.; Sun, X.; Guo, P. Extracts and lignans of *Schisandra chinensis* fruit alter lipid and glucose metabolism *in vivo* and *in vitro*. *J. Funct. Foods* **2015**, *19*, 296–307. [[CrossRef](#)]
157. Zhang, M.; Liu, M.; Xiong, M.; Gong, J.; Tan, X. *Schisandra chinensis* fruit extract attenuates albuminuria and protects podocyte integrity in a mouse model of streptozotocin-induced diabetic nephropathy. *J. Ethnopharmacol.* **2012**, *141*, 111–118. [[CrossRef](#)] [[PubMed](#)]
158. Li, J.; Wang, J.; Shao, J.-Q.; Du, H.; Wang, Y.-T.; Peng, L. Effect of *Schisandra chinensis* on interleukins, glucose metabolism, and pituitary-adrenal and gonadal axis in rats under strenuous swimming exercise. *Chin. J. Integr. Med.* **2015**, *21*, 43–48. [[CrossRef](#)] [[PubMed](#)]
159. Huseini, H.F.; Larijani, B.; Heshmat, R.; Fakhrzadeh, H.; Radjabipour, B.; Toliat, T.; Raza, M. The efficacy of *Silybum marianum* (L.) Gaertn. (silymarin) in the treatment of type II diabetes: A randomized, double-blind, placebo-controlled, clinical trial. *Phytother. Res.* **2006**, *20*, 1036–1039. [[CrossRef](#)] [[PubMed](#)]
160. Tamayo, C.; Diamond, S. Review of clinical trials evaluating safety and efficacy of milk thistle (*Silybum marianum* [L.] Gaertn.). *Integr. Cancer Ther.* **2007**, *6*, 146–157. [[CrossRef](#)] [[PubMed](#)]
161. Derosa, G.; D'Angelo, A.; Maffioli, P. The role of a fixed *Berberis aristata*/*Silybum marianum* combination in the treatment of type 1 diabetes mellitus. *Clin. Nutr.* **2015**. [[CrossRef](#)] [[PubMed](#)]
162. Ebrahimpour Koujan, S.; Gargari, B.P.; Mobasser, M.; Valizadeh, H.; Asghari-Jafarabadi, M. Effects of *Silybum marianum* (L.) Gaertn. (silymarin) extract supplementation on antioxidant status and hs-CRP in patients with type 2 diabetes mellitus: A randomized, triple-blind, placebo-controlled clinical trial. *Phytomedicine* **2015**, *22*, 290–296. [[CrossRef](#)] [[PubMed](#)]

163. Di Pierro, F.; Bellone, I.; Rapacioli, G.; Putignano, P. Clinical role of a fixed combination of standardized *Berberis aristata* and *Silybum marianum* extracts in diabetic and hypercholesterolemic patients intolerant to statins. *Diabetes Metab. Syndr. Obes.* **2015**, *8*, 89–96. [[CrossRef](#)] [[PubMed](#)]
164. Bhasker, S.; Madhav, H.; Chinnamma, M. Molecular evidence of insulinomimetic property exhibited by steviol and stevioside in diabetes induced L6 and 3T3L1 cells. *Phytomedicine* **2015**, *22*, 1037–1044. [[CrossRef](#)] [[PubMed](#)]
165. Ritu, M.; Nandini, J. Nutritional composition of *Stevia rebaudiana*—A sweet herb and its hypoglycaemic and hypolipidaemic effect on patients with non insulin dependent diabetes mellitus. *J. Sci. Food Agric.* **2016**. [[CrossRef](#)] [[PubMed](#)]
166. Asemi, Z.; Khorrani-Rad, A.; Alizadeh, S.A.; Shakeri, H.; Esmailzadeh, A. Effects of synbiotic food consumption on metabolic status of diabetic patients: A double-blind randomized cross-over controlled clinical trial. *Clin. Nutr.* **2014**, *33*, 198–203. [[CrossRef](#)] [[PubMed](#)]
167. Saravanan, R.; Vengatash babu, K.; Ramachandran, V. Effect of rebaudioside A, a diterpenoid on glucose homeostasis in STZ-induced diabetic rats. *J. Physiol. Biochem.* **2012**, *68*, 421–431. [[CrossRef](#)] [[PubMed](#)]
168. Fuller, S.; Stephens, J.M. Diosgenin, 4-hydroxyisoleucine, and fiber from fenugreek: Mechanisms of actions and potential effects on metabolic syndrome. *Adv. Nutr.* **2015**, *6*, 189–197. [[CrossRef](#)] [[PubMed](#)]
169. Gaddam, A.; Galla, C.; Thummiseti, S.; Marikanty, R.K.; Palanisamy, U.D.; Rao, P.V. Role of fenugreek in the prevention of type 2 diabetes mellitus in prediabetes. *J. Diabetes Metab. Disord.* **2015**, *14*. [[CrossRef](#)] [[PubMed](#)]
170. Basu, A.; Du, M.; Leyva, M.J.; Sanchez, K.; Betts, N.M.; Wu, M.; Aston, C.E.; Lyons, T.J. Blueberries decrease cardiovascular risk factors in obese men and women with metabolic syndrome. *J. Nutr.* **2010**, *140*, 1582–1587. [[CrossRef](#)] [[PubMed](#)]
171. Johnson, M.H.; de Mejia, E.G. Phenolic compounds from fermented berry beverages modulated gene and protein expression to increase insulin secretion from pancreatic beta-cells *in vitro*. *J. Agric. Food Chem.* **2016**, *64*, 2569–2581. [[CrossRef](#)] [[PubMed](#)]
172. Johnson, M.H.; de Mejia, E.G.; Fan, J.; Lila, M.A.; Yousef, G.G. Anthocyanins and proanthocyanidins from blueberry-blackberry fermented beverages inhibit markers of inflammation in macrophages and carbohydrate-utilizing enzymes *in vitro*. *Mol. Nutr. Food Res.* **2013**, *57*, 1182–1197. [[CrossRef](#)] [[PubMed](#)]
173. Vendrame, S.; Daugherty, A.; Kristo, A.S.; Riso, P.; Klimis-Zacas, D. Wild blueberry (*Vaccinium angustifolium*) consumption improves inflammatory status in the obese Zucker rat model of the metabolic syndrome. *J. Nutr. Biochem.* **2013**, *24*, 1508–1512. [[CrossRef](#)] [[PubMed](#)]
174. Elek, S.R.; McNair, J.D.; Griffith, G.C. *Veratrum viride*: Hypotensive and cardiac effects of intravenous use. *Calif. Med.* **1953**, *79*, 300–305. [[PubMed](#)]
175. Nand, V.; Doggrell, S.A.; Barnett, C.W. Effects of veratridine on the action potentials and contractility of right and left ventricles from normo- and hypertensive rats. *Clin. Exp. Pharmacol. Physiol.* **1997**, *24*, 570–576. [[CrossRef](#)] [[PubMed](#)]
176. Singh, B.N.; Saha, C.; Galun, D.; Upreti, D.K.; Bayry, J.; Kaveri, S.V. European *Viscum album*: A potent phytotherapeutic agent with multifarious phytochemicals, pharmacological properties and clinical evidence. *RSC Adv.* **2016**, *6*, 23837–23857. [[CrossRef](#)]
177. Tang, T.Y.; Li, F.-Z.; Afseth, J. Review of the regulations for clinical research in herbal medicines in USA. *Chin. J. Integr. Med.* **2014**, *20*, 883–893. [[CrossRef](#)] [[PubMed](#)]
178. Nelson, H.S. Oral/sublingual *Phleum pretense* grass tablet (Grazax/Grastek) to treat allergic rhinitis in the USA. *Expert Rev. Clin. Immunol.* **2014**, *10*, 1437–1451. [[CrossRef](#)] [[PubMed](#)]
179. Mozaffarian, D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: A comprehensive review. *Circulation* **2016**, *133*, 187–225. [[CrossRef](#)] [[PubMed](#)]
180. Xiao, J.B.; Högger, P. Dietary polyphenols and type 2 diabetes: Current insights and future perspectives. *Curr. Med. Chem.* **2015**, *22*, 23–38. [[CrossRef](#)] [[PubMed](#)]
181. Rohn, S.; van Griensven, L. Grain legumes and further gluten free legumes—Science, technology and impacts on human health. *Food Res. Int.* **2015**, *76*, 1–2. [[CrossRef](#)]
182. Barringer, T.A. Mediterranean diets and cardiovascular disease. *Curr. Atheroscler. Rep.* **2001**, *3*, 437–445. [[CrossRef](#)] [[PubMed](#)]

183. Estruch, R.; Ros, E.; Salas-Salvadó, J.; Covas, M.-I.; Corella, D.; Arós, F.; Gómez-Gracia, E.; Ruiz-Gutiérrez, V.; Fiol, M.; Lapetra, J.; *et al.* Primary prevention of cardiovascular disease with a Mediterranean diet. *N. Engl. J. Med.* **2013**, *368*, 1279–1290. [[CrossRef](#)] [[PubMed](#)]
184. Naismith, D.J.; Akinyanju, P.A.; Szanto, S.; Yudkin, J. The effect, in volunteers, of coffee and decaffeinated coffee on blood glucose, insulin, plasma lipids and some factors involved in blood clotting. *Nutr. Metabol.* **1970**, *12*, 144–151. [[CrossRef](#)]
185. Barone, J.J.; Roberts, H.R. Caffeine consumption. *Food Chem. Toxicol.* **1996**, *34*, 119–129. [[CrossRef](#)]
186. Santos, R.M.; Lima, D.R. Coffee consumption, obesity and type 2 diabetes: A mini-review. *Eur. J. Nutr.* **2016**, *55*, 1345–1358. [[CrossRef](#)] [[PubMed](#)]
187. Morisco, F.; Lembo, V.; Mazzone, G.; Camera, S.; Caporaso, N. Coffee and liver health. *J. Clin. Gastroenterol.* **2014**, *48* (Suppl. 1), S87–S90. [[CrossRef](#)] [[PubMed](#)]
188. Akash, M.S.; Rehman, K.; Chen, S. Effects of coffee on type 2 diabetes mellitus. *Nutrition* **2014**, *30*, 755–763. [[CrossRef](#)] [[PubMed](#)]
189. Zulli, A.; Smith, R.M.; Kubatka, P.; Novak, J.; Uehara, Y.; Loftus, H.; Qaradakhi, T.; Pohanka, M.; Kobylak, N.; Zagatina, A.; *et al.* Caffeine and cardiovascular diseases: Critical review of current research. *Eur. J. Nutr.* **2016**, *55*, 1331–1343. [[CrossRef](#)] [[PubMed](#)]
190. Ding, M.; Bhupathiraju, S.N.; Satija, A.; van Dam, R.M.; Hu, F.B. Long-term coffee consumption and risk of cardiovascular disease: A systematic review and a dose-response meta-analysis of prospective cohort studies. *Circulation* **2014**, *129*, 643–659. [[CrossRef](#)] [[PubMed](#)]
191. Ding, M.; Satija, A.; Bhupathiraju, S.N.; Hu, Y.; Sun, Q.; Han, J.; Lopez-Garcia, E.; Willett, W.; van Dam, R.M.; Hu, F.B. Association of coffee consumption with total and cause-specific mortality in three large prospective cohorts. *Circulation* **2015**, *132*, 2305–2315. [[CrossRef](#)] [[PubMed](#)]
192. Natella, F.; Scaccini, C. Role of coffee in modulation of diabetes risk. *Nutr. Rev.* **2012**, *70*, 207–217. [[CrossRef](#)] [[PubMed](#)]
193. Vinson, J.A.; Proch, J.; Bose, P.; Muchler, S.; Taffera, P.; Shuta, D.; Samman, N.; Agbor, G.A. Chocolate is a powerful *ex vivo* and *in vivo* antioxidant, an antiatherosclerotic agent in an animal model, and a significant contributor to antioxidants in the European and American diets. *J. Agric. Food Chem.* **2006**, *54*, 8071–8076. [[CrossRef](#)] [[PubMed](#)]
194. Bonita, J.S.; Mandarano, M.; Shuta, D.; Vinson, J. Coffee and cardiovascular disease: *In vitro*, cellular, animal, and human studies. *Pharmacol. Res.* **2007**, *55*, 187–198. [[CrossRef](#)] [[PubMed](#)]
195. Van Dijk, A.E.; Olthof, M.R.; Meeuse, J.C.; Seebus, E.; Heine, R.J.; van Dam, R.M. Acute effects of decaffeinated coffee and the major coffee components chlorogenic acid and trigonelline on glucose tolerance. *Diabetes Care* **2009**, *32*, 1023–1025. [[CrossRef](#)] [[PubMed](#)]
196. Meng, S.; Cao, J.; Feng, Q.; Peng, J.; Hu, Y. Roles of chlorogenic acid on regulating glucose and lipids metabolism: A review. *Evid. Based Complement. Altern. Med.* **2013**, *2013*. [[CrossRef](#)] [[PubMed](#)]
197. Murase, T.; Misawa, K.; Minegishi, Y.; Aoki, M.; Ominami, H.; Suzuki, Y.; Shibuya, Y.; Hase, T. Coffee polyphenols suppress diet-induced body fat accumulation by downregulating SREBP-1c and related molecules in C57BL/6J mice. *Am. J. Physiol. Endocrinol. Metab.* **2011**, *300*, E122–E133. [[CrossRef](#)] [[PubMed](#)]
198. Murase, T.; Yokoi, Y.; Misawa, K.; Ominami, H.; Suzuki, Y.; Shibuya, Y.; Hase, T. Coffee polyphenols modulate whole-body substrate oxidation and suppress postprandial hyperglycaemia, hyperinsulinaemia and hyperlipidaemia. *Br. J. Nutr.* **2012**, *107*, 1757–1765. [[CrossRef](#)] [[PubMed](#)]
199. Gramza-Michalowska, A. Caffeine in tea *Camellia sinensis*—Content, absorption, benefits and risks of consumption. *J. Nutr. Health Aging* **2014**, *18*, 143–149. [[CrossRef](#)] [[PubMed](#)]
200. Beecher, G.R.; Warden, B.A.; Merken, H. Analysis of tea polyphenols. *Proc. Soc. Exp. Biol. Med.* **1999**, *220*, 267–270. [[CrossRef](#)] [[PubMed](#)]
201. Li, S.; Lo, C.Y.; Pan, M.H.; Lai, C.S.; Ho, C.T. Black tea: Chemical analysis and stability. *Food Funct.* **2013**, *4*, 10–18. [[CrossRef](#)] [[PubMed](#)]
202. Gormaz, J.G.; Valls, N.; Sotomayor, C.; Turner, T.; Rodrigo, R. Potential role of polyphenols in the prevention of cardiovascular diseases: Molecular bases. *Curr. Med. Chem.* **2016**, *23*, 115–128. [[CrossRef](#)] [[PubMed](#)]
203. Peters, U.; Poole, C.; Arab, L. Does tea affect cardiovascular disease? A meta-analysis. *Am. J. Epidemiol.* **2001**, *154*, 495–503. [[CrossRef](#)] [[PubMed](#)]

204. Zhang, C.; Qin, Y.Y.; Wei, X.; Yu, F.F.; Zhou, Y.H.; He, J. Tea consumption and risk of cardiovascular outcomes and total mortality: A systematic review and meta-analysis of prospective observational studies. *Eur. J. Epidemiol.* **2015**, *30*, 103–113. [[CrossRef](#)] [[PubMed](#)]
205. Basu, A.; Lucas, E.A. Mechanisms and effects of green tea on cardiovascular health. *Nutr. Rev.* **2007**, *65*, 361–375. [[CrossRef](#)] [[PubMed](#)]
206. Sano, M.; Tabata, M.; Suzuki, M.; Degawa, M.; Miyase, T.; Maeda-Yamamoto, M. Simultaneous determination of twelve tea catechins by high-performance liquid chromatography with electrochemical detection. *Analyst* **2001**, *126*, 816–820. [[CrossRef](#)] [[PubMed](#)]
207. Chowdhury, A.; Sarkar, J.; Chakraborti, T.; Pramanik, P.K.; Chakraborti, S. Protective role of epigallocatechin-3-gallate in health and disease: A perspective. *Biomed. Pharmacother.* **2016**, *78*, 50–59. [[CrossRef](#)] [[PubMed](#)]
208. Chen, G.; Wang, H.; Zhang, X.; Yang, S.-T. Nutraceuticals and functional foods in the management of hyperlipidemia. *Crit. Rev. Food Sci. Nutr.* **2014**, *54*, 1180–1201. [[CrossRef](#)] [[PubMed](#)]
209. Magrone, T.; Perez De Heredia, F.; Jirillo, E.; Morabito, G.; Marcos, A.; Serafini, M. Functional foods and nutraceuticals as therapeutic tools for the treatment of diet-related diseases. *Can. J. Physiol. Pharmacol.* **2013**, *91*, 387–396. [[CrossRef](#)] [[PubMed](#)]
210. Liu, R.H. Dietary bioactive compounds and their health implications. *J. Food Sci.* **2013**, *78*, A18–A25. [[CrossRef](#)] [[PubMed](#)]
211. Badimon, L.; Vilahur, G.; Padro, T. Nutraceuticals and atherosclerosis: Human trials. *Cardiovasc. Ther.* **2010**, *28*, 202–215. [[CrossRef](#)] [[PubMed](#)]
212. Zuchi, C.; Ambrosio, G.; Lüscher, T.F.; Landmesser, U. Nutraceuticals in cardiovascular prevention: Lessons from studies on endothelial function. *Cardiovasc. Ther.* **2010**, *28*, 187–201. [[CrossRef](#)] [[PubMed](#)]
213. Lacroix, I.M.; Li-Chan, E.C. Overview of food products and dietary constituents with antidiabetic properties and their putative mechanisms of action: A natural approach to complement pharmacotherapy in the management of diabetes. *Mol. Nutr. Food Res.* **2014**, *58*, 61–78. [[CrossRef](#)] [[PubMed](#)]
214. Hung, H.Y.; Qian, K.; Morris-Natschke, S.L.; Hsu, C.S.; Lee, K.H. Recent discovery of plant-derived anti-diabetic natural products. *Nat. Prod. Rep.* **2012**, *29*, 580–606. [[CrossRef](#)] [[PubMed](#)]
215. Gautam, R.; Jachak, S.M. Recent developments in anti-inflammatory natural products. *Med. Res. Rev.* **2009**, *29*, 767–820. [[CrossRef](#)] [[PubMed](#)]
216. Hermansen, K.; Dinesen, B.; Hoie, L.H.; Morgenstern, E.; Gruenwald, J. Effects of soy and other natural products on LDL:HDL ratio and other lipid parameters: A literature review. *Adv. Ther.* **2003**, *20*, 50–78. [[CrossRef](#)] [[PubMed](#)]
217. Vasanthi, H.R.; ShriShriMal, N.; Das, D.K. Phytochemicals from plants to combat cardiovascular disease. *Curr. Med. Chem.* **2012**, *19*, 2242–2251. [[CrossRef](#)] [[PubMed](#)]
218. Hardie, D.G. AMPK: A target for drugs and natural products with effects on both diabetes and cancer. *Diabetes* **2013**, *62*, 2164–2172. [[CrossRef](#)] [[PubMed](#)]
219. Yuan, T.; Nahar, P.; Sharma, M.; Liu, K.; Slitt, A.; Aisa, H.A.; Seeram, N.P. Indazole-type alkaloids from *Nigella sativa* seeds exhibit antihyperglycemic effects via AMPK activation *in vitro*. *J. Nat. Prod.* **2014**, *77*, 2316–2320. [[CrossRef](#)] [[PubMed](#)]
220. Nguyen, P.H.; Nguyen, T.N.; Dao, T.T.; Kang, H.W.; Ndinteh, D.T.; Mbafor, J.T.; Oh, W.K. AMP-activated protein kinase (AMPK) activation by benzofurans and coumestans isolated from *Erythrina abyssinica*. *J. Nat. Prod.* **2010**, *73*, 598–602. [[CrossRef](#)] [[PubMed](#)]
221. Zimmermann, K.; Baldinger, J.; Mayerhofer, B.; Atanasov, A.G.; Dirsch, V.M.; Heiss, E.H. Activated AMPK boosts the Nrf2/HO-1 signaling axis—A role for the unfolded protein response. *Free Radic. Biol. Med.* **2015**, *88*, 417–426. [[CrossRef](#)] [[PubMed](#)]
222. Chen, S. Natural products triggering biological targets—A review of the anti-inflammatory phytochemicals targeting the arachidonic acid pathway in allergy asthma and rheumatoid arthritis. *Curr. Drug Targets* **2011**, *12*, 288–301. [[CrossRef](#)] [[PubMed](#)]
223. Jachak, S.M. Cyclooxygenase inhibitory natural products: Current status. *Curr. Med. Chem.* **2006**, *13*, 659–678. [[CrossRef](#)] [[PubMed](#)]
224. Chi, Y.S.; Jong, H.G.; Son, K.H.; Chang, H.W.; Kang, S.S.; Kim, H.P. Effects of naturally occurring prenylated flavonoids on enzymes metabolizing arachidonic acid: Cyclooxygenases and lipoxygenases. *Biochem. Pharmacol.* **2001**, *62*, 1185–1191. [[CrossRef](#)]

225. Gao, Y.; Zhang, Y.; Zhu, J.; Li, B.; Li, Z.; Zhu, W.; Shi, J.; Jia, Q.; Li, Y. Recent progress in natural products as DPP-4 inhibitors. *Future Med. Chem.* **2015**, *7*, 1079–1089. [[CrossRef](#)] [[PubMed](#)]
226. Abe, M.; Akiyama, T.; Nakamura, H.; Kojima, F.; Harada, S.; Muraoka, Y. First synthesis and determination of the absolute configuration of sulphostin, a novel inhibitor of dipeptidyl peptidase IV. *J. Nat. Prod.* **2004**, *67*, 999–1004. [[CrossRef](#)] [[PubMed](#)]
227. Saleem, S.; Jafri, L.; ul Haq, I.; Chang, L.C.; Calderwood, D.; Green, B.D.; Mirza, B. Plants *Fagonia cretica* L. and *Hedera nepalensis* K. Koch contain natural compounds with potent dipeptidyl peptidase-4 (DPP-4) inhibitory activity. *J. Ethnopharmacol.* **2014**, *156*, 26–32. [[CrossRef](#)] [[PubMed](#)]
228. Schmitt, C.A.; Dirsch, V.M. Modulation of endothelial nitric oxide by plant-derived products. *Nitric Oxide* **2009**, *21*, 77–91. [[CrossRef](#)] [[PubMed](#)]
229. Waldbauer, K.; Seiringer, G.; Nguyen, D.L.; Winkler, J.; Blaschke, M.; McKinnon, R.; Urban, E.; Ladurner, A.; Dirsch, V.M.; Zehl, M.; *et al.* Triterpenoic acids from apple pomace enhance the activity of the endothelial nitric oxide synthase (eNOS). *J. Agric. Food Chem.* **2016**, *64*, 185–194. [[CrossRef](#)] [[PubMed](#)]
230. Xia, N.; Pautz, A.; Wollscheid, U.; Reifenberg, G.; Förstermann, U.; Li, H. Artichoke, cynarin and cyanidin downregulate the expression of inducible nitric oxide synthase in human coronary smooth muscle cells. *Molecules* **2014**, *19*, 3654–3668. [[CrossRef](#)] [[PubMed](#)]
231. Shen, K.; Leung, S.W.; Ji, L.; Huang, Y.; Hou, M.; Xu, A.; Wang, Z.; Vanhoutte, P.M. Notoginsenoside Ft1 activates both glucocorticoid and estrogen receptors to induce endothelium-dependent, nitric oxide-mediated relaxations in rat mesenteric arteries. *Biochem. Pharmacol.* **2014**, *88*, 66–74. [[CrossRef](#)] [[PubMed](#)]
232. Auger, C.; Chaabi, M.; Anselm, E.; Lobstein, A.; Schini-Kerth, V.B. The red wine extract-induced activation of endothelial nitric oxide synthase is mediated by a great variety of polyphenolic compounds. *Mol. Nutr. Food Res.* **2010**, *54* (Suppl. 2), S171–S183. [[CrossRef](#)] [[PubMed](#)]
233. Leung, K.W.; Cheng, Y.K.; Mak, N.K.; Chan, K.K.; Fan, T.P.; Wong, R.N. Signaling pathway of ginsenoside-Rg1 leading to nitric oxide production in endothelial cells. *FEBS Lett.* **2006**, *580*, 3211–3216. [[CrossRef](#)] [[PubMed](#)]
234. Ndiaye, M.; Chataigneau, M.; Lobysheva, I.; Chataigneau, T.; Schini-Kerth, V.B. Red wine polyphenol-induced, endothelium-dependent NO-mediated relaxation is due to the redox-sensitive PI3-kinase/Akt-dependent phosphorylation of endothelial NO-synthase in the isolated porcine coronary artery. *FASEB J.* **2005**, *19*, 455–457. [[CrossRef](#)] [[PubMed](#)]
235. Golan-Goldhirsh, A.; Gopas, J. Plant derived inhibitors of NF- κ B. *Phytochem. Rev.* **2014**, *13*, 107–121. [[CrossRef](#)]
236. Chan, M.M. Inhibition of tumor necrosis factor by curcumin, a phytochemical. *Biochem. Pharmacol.* **1995**, *49*, 1551–1556. [[CrossRef](#)]
237. Siedle, B.; Garcia-Pineros, A.J.; Murillo, R.; Schulte-Mönting, J.; Castro, V.; Rüngeler, P.; Klaas, C.A.; da Costa, F.B.; Kisiel, W.; Merfort, I. Quantitative structure-activity relationship of sesquiterpene lactones as inhibitors of the transcription factor NF- κ B. *J. Med. Chem.* **2004**, *47*, 6042–6054. [[CrossRef](#)] [[PubMed](#)]
238. Fakhrudin, N.; Waltenberger, B.; Cabaravdic, M.; Atanasov, A.G.; Malainer, C.; Schachner, D.; Heiss, E.H.; Liu, R.; Noha, S.M.; Grzywacz, A.M.; *et al.* Identification of plumericin as a potent new inhibitor of the NF- κ B pathway with anti-inflammatory activity *in vitro* and *in vivo*. *Br. J. Pharmacol.* **2014**, *171*, 1676–1686. [[CrossRef](#)] [[PubMed](#)]
239. Kopp, E.; Ghosh, S. Inhibition of NF- κ B by sodium salicylate and aspirin. *Science* **1994**, *265*, 956–959. [[CrossRef](#)] [[PubMed](#)]
240. Kumar, H.; Kim, I.S.; More, S.V.; Kim, B.W.; Choi, D.K. Natural product-derived pharmacological modulators of Nrf2/ARE pathway for chronic diseases. *Nat. Prod. Rep.* **2014**, *31*, 109–139. [[CrossRef](#)] [[PubMed](#)]
241. Balogun, E.; Hoque, M.; Gong, P.; Killeen, E.; Green, C.J.; Foresti, R.; Alam, J.; Motterlini, R. Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. *Biochem. J.* **2003**, *371*, 887–895. [[CrossRef](#)] [[PubMed](#)]
242. Heiss, E.H.; Tran, T.V.; Zimmermann, K.; Schwaiger, S.; Vouk, C.; Mayerhofer, B.; Malainer, C.; Atanasov, A.G.; Stuppner, H.; Dirsch, V.M. Identification of chromomoric acid C-I as an Nrf2 activator in *Chromolaena odorata*. *J. Nat. Prod.* **2014**, *77*, 503–508. [[CrossRef](#)] [[PubMed](#)]
243. Ahn, Y.H.; Hwang, Y.; Liu, H.; Wang, X.J.; Zhang, Y.; Stephenson, K.K.; Boronina, T.N.; Cole, R.N.; Dinkova-Kostova, A.T.; Talalay, P.; *et al.* Electrophilic tuning of the chemoprotective natural product sulforaphane. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 9590–9595. [[CrossRef](#)] [[PubMed](#)]

244. Wang, L.; Waltenberger, B.; Pferschy-Wenzig, E.M.; Blunder, M.; Liu, X.; Malainer, C.; Blazevec, T.; Schwaiger, S.; Rollinger, J.M.; Heiss, E.H.; *et al.* Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARgamma): A review. *Biochem. Pharmacol.* **2014**, *92*, 73–89. [[CrossRef](#)] [[PubMed](#)]
245. Atanasov, A.G.; Blunder, M.; Fakhrudin, N.; Liu, X.; Noha, S.M.; Malainer, C.; Kramer, M.P.; Cocic, A.; Kunert, O.; Schinkovitz, A.; *et al.* Polyacetylenes from *Notopterygium incisum*—New selective partial agonists of peroxisome proliferator-activated receptor-gamma. *PLoS ONE* **2013**, *8*, e61755. [[CrossRef](#)] [[PubMed](#)]
246. Atanasov, A.G.; Wang, J.N.; Gu, S.P.; Bu, J.; Kramer, M.P.; Baumgartner, L.; Fakhrudin, N.; Ladurner, A.; Malainer, C.; Vuorinen, A.; *et al.* Honokiol: A non-adipogenic PPARgamma agonist from nature. *Biochim. Biophys. Acta* **2013**, *1830*, 4813–4819. [[CrossRef](#)] [[PubMed](#)]
247. Fakhrudin, N.; Ladurner, A.; Atanasov, A.G.; Heiss, E.H.; Baumgartner, L.; Markt, P.; Schuster, D.; Ellmerer, E.P.; Wolber, G.; Rollinger, J.M.; *et al.* Computer-aided discovery, validation, and mechanistic characterization of novel neolignan activators of peroxisome proliferator-activated receptor gamma. *Mol. Pharmacol.* **2010**, *77*, 559–566. [[CrossRef](#)] [[PubMed](#)]
248. Puhl, A.C.; Bernardes, A.; Silveira, R.L.; Yuan, J.; Campos, J.L.; Saidenberg, D.M.; Palma, M.S.; Cvorovic, A.; Ayers, S.D.; Webb, P.; *et al.* Mode of peroxisome proliferator-activated receptor gamma activation by luteolin. *Mol. Pharmacol.* **2012**, *81*, 788–799. [[CrossRef](#)] [[PubMed](#)]
249. Weidner, C.; de Groot, J.C.; Prasad, A.; Freiwald, A.; Quedenau, C.; Kliem, M.; Witzke, A.; Kodelja, V.; Han, C.T.; Giegold, S.; *et al.* Amorfrutins are potent antidiabetic dietary natural products. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 7257–7262. [[CrossRef](#)] [[PubMed](#)]
250. Wang, L.-J.; Jiang, B.; Wu, N.; Wang, S.-Y.; Shi, D.-Y. Natural and semisynthetic protein tyrosine phosphatase 1B (PTP1B) inhibitors as anti-diabetic agents. *RSC Adv.* **2015**, *5*, 48822–48834. [[CrossRef](#)]
251. Jiang, C.S.; Liang, L.F.; Guo, Y.W. Natural products possessing protein tyrosine phosphatase 1B (PTP1B) inhibitory activity found in the last decades. *Acta Pharmacol. Sin.* **2012**, *33*, 1217–1245. [[CrossRef](#)] [[PubMed](#)]
252. Heiss, E.H.; Baumgartner, L.; Schwaiger, S.; Heredia, R.J.; Atanasov, A.G.; Rollinger, J.M.; Stuppner, H.; Dirsch, V.M. Ratanhiaphenol III from *Ratanhia radix* is a PTP1B inhibitor. *Planta Med.* **2012**, *78*, 678–681. [[CrossRef](#)] [[PubMed](#)]
253. Feng, Y.; Carroll, A.R.; Addepalli, R.; Fechner, G.A.; Avery, V.M.; Quinn, R.J. Vanillic acid derivatives from the green algae *Cladophora socialis* as potent protein tyrosine phosphatase 1B inhibitors. *J. Nat. Prod.* **2007**, *70*, 1790–1792. [[CrossRef](#)] [[PubMed](#)]
254. Yoon, G.; Lee, W.; Kim, S.N.; Cheon, S.H. Inhibitory effect of chalcones and their derivatives from *Glycyrrhiza inflata* on protein tyrosine phosphatase 1B. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5155–5157. [[CrossRef](#)] [[PubMed](#)]
255. Werz, O. Inhibition of 5-lipoxygenase product synthesis by natural compounds of plant origin. *Planta Med.* **2007**, *73*, 1331–1357. [[CrossRef](#)] [[PubMed](#)]
256. Oettl, S.K.; Gerstmeier, J.; Khan, S.Y.; Wiechmann, K.; Bauer, J.; Atanasov, A.G.; Malainer, C.; Awad, E.M.; Uhrin, P.; Heiss, E.H.; *et al.* Imbricarinic acid and perlatolic acid: Multi-targeting anti-inflammatory depsides from *Cetrelia monachorum*. *PLoS ONE* **2013**, *8*, e76929. [[CrossRef](#)] [[PubMed](#)]
257. De la Puerta, R.; Ruiz Gutierrez, V.; Hoult, J.R. Inhibition of leukocyte 5-lipoxygenase by phenolics from virgin olive oil. *Biochem. Pharmacol.* **1999**, *57*, 445–449. [[CrossRef](#)]
258. Winekenstädde, D.; Angelis, A.; Waltenberger, B.; Schwaiger, S.; Tchoumtchoua, J.; König, S.; Werz, O.; Aligiannis, N.; Skaltsounis, A.-L.; Stuppner, H. Phytochemical profile of the aerial parts of *Sedum sediforme* and anti-inflammatory activity of myricitrin. *Nat. Prod. Commun.* **2015**, *10*, 83–88. [[PubMed](#)]
259. Endo, A. A historical perspective on the discovery of statins. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* **2010**, *86*, 484–493. [[CrossRef](#)] [[PubMed](#)]
260. Tanzawa, K.; Kuroda, M.; Endo, A. Time-dependent, irreversible inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase by the antibiotic citrinin. *Biochim. Biophys. Acta* **1977**, *488*, 97–101. [[PubMed](#)]
261. Endo, A.; Kuroda, M. Citrinin, an inhibitor of cholesterol synthesis. *J. Antibiot. Tokyo* **1976**, *29*, 841–843. [[CrossRef](#)] [[PubMed](#)]
262. Endo, A.; Kuroda, M.; Tsujita, Y. ML-236A, ML-236B, and ML-236C, new inhibitors of cholesterol synthesis produced by *Penicillium citrinum*. *J. Antibiot. Tokyo* **1976**, *29*, 1346–1348. [[CrossRef](#)] [[PubMed](#)]
263. Endo, A.; Kuroda, M.; Tanzawa, K. Competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by ML-236A and ML-236B fungal metabolites, having hypocholesterolemic activity. *FEBS Lett.* **1976**, *72*, 323–326. [[CrossRef](#)]

264. Endo, A.; Tsujita, Y.; Kuroda, M.; Tanzawa, K. Inhibition of cholesterol synthesis *in vitro* and *in vivo* by ML-236A and ML-236B, competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. *Eur. J. Biochem.* **1977**, *77*, 31–36. [[CrossRef](#)] [[PubMed](#)]
265. Alberts, A.W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; *et al.* Mevinolin: A highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 3957–3961. [[CrossRef](#)] [[PubMed](#)]
266. Endo, A. Monacolin K, a new hypocholesterolemic agent produced by a *Monascus* species. *J. Antibiot. Tokyo* **1979**, *32*, 852–854. [[CrossRef](#)] [[PubMed](#)]
267. Endo, A. A gift from nature: The birth of the statins. *Nat. Med.* **2008**, *14*, 1050–1052. [[CrossRef](#)] [[PubMed](#)]
268. Grundy, S.M. Dyslipidaemia in 2015: Advances in treatment of dyslipidaemia. *Nat. Rev. Cardiol.* **2016**, *13*, 74–75. [[CrossRef](#)] [[PubMed](#)]
269. Bailey, C.; Day, C. Metformin: Its botanical background. *Pract. Diab. Int.* **2004**, *21*, 115–117. [[CrossRef](#)]
270. Müller, H.; Reinwein, H. Pharmacology of galegin. *Arch. Exp. Pathol. Pharmacol.* **1927**, *125*, 212–228. [[CrossRef](#)]
271. Tanret, G. An alkaloid extracted from *Galega officinalis*. *Compt. Rend.* **1914**, *158*, 1182–1184.
272. Barger, G.; White, F.D. The constitution of galegine. *Biochem. J.* **1923**, *17*, 827–835. [[CrossRef](#)] [[PubMed](#)]
273. Watanabe, C.K. Studies in the metabolic changes induced by administration of guanidine bases. I. The influence of injected guanidine hydrochloride upon blood sugar content. *J. Biol. Chem.* **1918**, *33*, 253–265.
274. Bailey, C.; Campbell, I.; Chan, J.; Davidson, J.; Howlett, H.; Ritz, P. *Metformin: The Gold Standard. A Scientific Handbook*; Wiley: Chichester, UK, 2007.
275. Cusi, K.; DeFronzo, R.A. Metformin: A review of its metabolic effects. *Diabetes Rev.* **1998**, *6*, 89–131.



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