# Polyphenols in Metabolic Diseases

Subjects: Nutrition & Dietetics
Contributor: Amin Gasmi , Pavan Kumar Mujawdiya , Sadaf Noor , Roman Lysiuk , Roman Darmohray , Salva Piscopo , Larysa Lenchyk , Halyna Antonyak , Kateryna Dehtiarova , Mariia Shanaida , Alexandr Polishchuk , Volodymyr Shanaida , Massimiliano Peana , Geir Bjørklund

Polyphenols (PPs) are a large group of phytochemicals containing phenolic rings with two or more hydroxyl groups. They possess powerful antioxidant properties, multiple therapeutic effects, and possible health benefits in vivo and in vitro, as well as reported clinical studies. Considering their free-radical scavenging and anti-inflammatory properties, these substances can be used to treat different kinds of conditions associated with metabolic disorders. Many symptoms of metabolic syndrome (MtS), including obesity, dyslipidemia, atherosclerosis, elevated blood sugar, accelerating aging, liver intoxication, hypertension, as well as cancer and neurodegenerative disorders, are substantially relieved by dietary PPs.

phenolic compounds natural sources metabolic syndrome bioprotective property

## 1. Introduction

Metabolic diseases such as hyperglycemia, obesity, dyslipidemia, and hypertension are now considered global problems of the world population [1][2]. Their occurrence increases yearly, and nowadays, they are considered a significant danger for human beings as the most prevalent disorders worldwide [3].

Metabolic syndrome (MtS) is a complex coexisting diagnosis including abdominal obesity, increased blood pressure, elevated fasting glucose, reduced high-density lipoprotein-cholesterol levels, and elevated triglyceride levels [4]. MtS increases the risk factors of cardiovascular diseases (CVD), which puts huge pressure on the healthcare economy of the whole society [4]. Therefore, it is an urgent challenge for researchers to determine active pharmaceutical ingredients to improve MtS and its complications.

Mts have a complex etiology, including several pathophysiological mechanisms and factors that may cause the development of MtS, such as genetics, lifestyle, diet, and gut microbiome state [5]. The molecular changes result from the interaction between environmental and genetic factors, and oxidative stress and systemic inflammation significantly contribute to MtS pathogenesis [1]. Thus, an effective method of combating MtS comprises not only appropriate diet and physical activity but also consuming drugs and/or food supplementation. Therefore, discovering new natural substances that could reduce the symptoms of MtS through antioxidant and anti-inflammatory effects and the ability to normalize lipid and carbohydrate metabolism are very important issues for researchers and clinicians [1].

Oxidative stress and inflammation are common pathophysiology keys involved in the development and progression of metabolic disorders [6]. Thus, finding appropriate natural compounds to mitigate metabolic disorder's symptoms and prevent related diseases' progression is necessary.

In recent years, polyphenols (PPs) have been considered the key plant-based bioactive compounds against various diseases, including metabolic diseases, cardiovascular and neurodegenerative disorders, and some varieties of cancer [7][8]. PPs are getting much attention in the medical industry to treat different metabolic diseases due to their intrinsic antioxidant and anti-inflammatory properties [9][10].

About eight thousand polyphenolic compounds have been recognized nowadays [11][12]. PPs are naturally occurring complexes in various plants, including herbs, tea, fruits, and vegetables. In plants, these compounds play a key role in pigmentation, growth, ultraviolet rays protection, and against pathogens. PPs are also an essential part of various chemical industries for producing commodity chemicals, food additives, cosmetics, and paints [13]. Generally, PPs are known as plant secondary metabolites and can be categorized by the presence of several phenolic groups [14]. These compounds are classified based on the chemical complexity of their respective phenolic structure (flavonoids and non-flavonoids, **Figure 1**) [15].

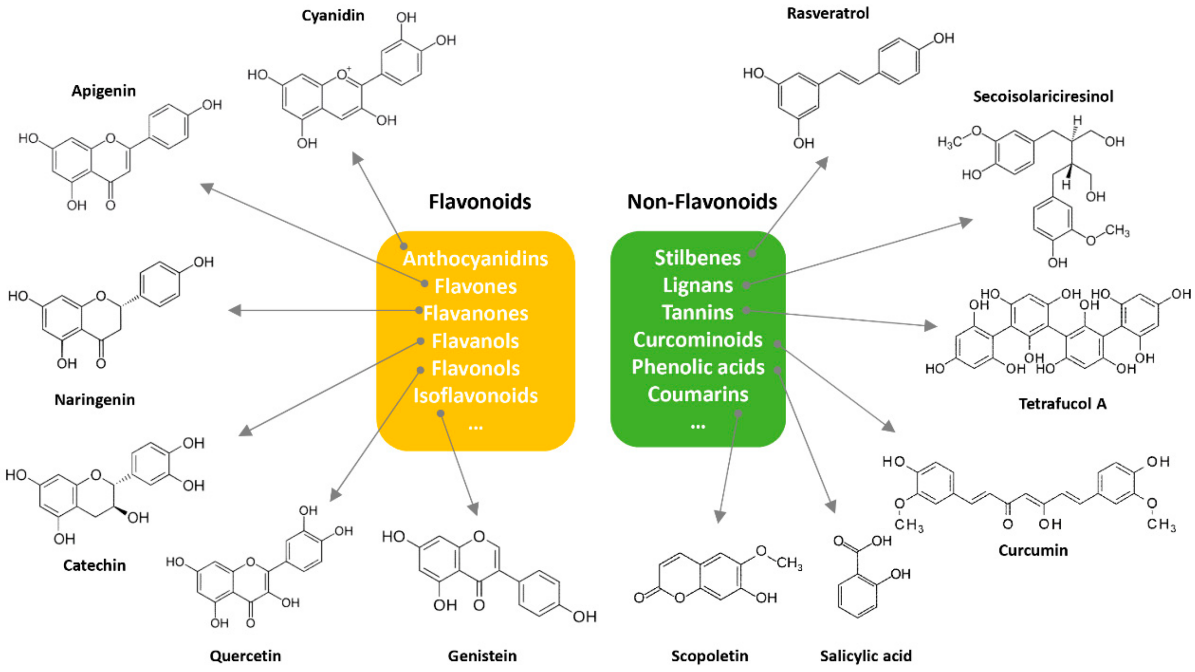



**Figure 1.** Classification of PPs with some representative examples.

It is interesting to note that polyphenolic compounds share a similar chemical structure. The structure of naturally occurring PPs varies from simple molecules (phenolic acid) to complex molecules (tannins) depending on the length of the chain attached [16]. PPs occur primarily in conjugated form, with one or more sugar residues attached to hydroxyl groups, although direct linkages to an aromatic carbon atom can be found [17][18]. PPs can also be found in associations with other compounds, such as amines, carboxylic and organic acids, and lipids; also common are their linkages with other phenols [18].

As PPs are found abundantly in the plant kingdom, their consumption in the human diet is not much surprising. These compounds are found in almost every balanced diet, especially where fruits and vegetables are mostly consumed [19]. However, quantitative information on PPs for various foods is unavailable because of their diverse nature and other factors responsible for altering their concentration in the diet. PPs possess similar properties, but their complex linkage with other compounds makes their separation challenging. Ample research has been done on different samples from various sources (foods, beverages, and plants). Thus, a deep understanding of these naturally occurring compounds and their associated biosynthesis will open new avenues to design special dietary plans enriched with PPs that ultimately strengthen respective health benefits. Considering the antioxidant and anti-inflammatory features of PPs, these compounds can be employed to treat various diseases associated with metabolic disorders [1].

Treatments of MtS may involve the design of natural drugs and special food products enriched with high-quality PPs or by the controlled drug and/or supplement delivery system, which can lead to the health improvement of the human population. Besides this, Siroma et al. supposed that scientific studies regarding ingestion of PPs and other natural nutrients could improve global food education in different countries to help schools, families, and businesses to reduce obesity, hyperglycemia, and other metabolic diseases [20].

# 2. Polyphenols in the Prevention and Treatment of Different Metabolic Disorders

## 2.1. Oxidative Stress and Inflammation

Oxidative stress is one of the health conditions which occurs due to an imbalance of free radicals (oxygen or nitrogen species) and the defensive ability of the body to respond to reactive species to heal the respective disorder [21]. The production of significant reactive oxygen (ROS) and nitrogen species is one of the consequences of the normal functioning of alive intracellular structures [22]. The structural damage of various proteins, cell tissues, permeable membranes, and nucleic acids is due to exposure to highly reactive oxygen-based species such as hydrogen peroxide and superoxide anions [23]. To counter this oxidative stress, body cells continuously express several species, such as enzymes, to detoxify the resulting reactive species and ultimately heal the damage in the respective region. Species released by the body cells to encounter oxidative stress may come from enzymes, bacterial cells, mammalian cells, and PPs. In oxidative stress, the mechanism of cell damage occurs due to the different chemical actions of oxygen-based free radicals [24]. These reactive species may come from various sources by the abnormal metabolic system (aerobic metabolism) that may generate undesirable reactive species and cause cell death. It is found that the intake of antibiotics is also a source of generating these species [25][26].

## 2.2. Insulin Resistance/Hyperglycemia

Insulin resistance is the most common MtS in which body cells (fat, liver, and respective muscles) cannot provide an effective response to insulin and cannot consume glucose from the blood to produce energy [27]. Insulin resistance leads to the destruction of insulin-producing pancreatic *B*-cells.

This MtS can further complicate the health problems such as a rise in blood pressure, obesity, unbalanced cholesterol levels, and diabetes problems [28]. This type of syndrome can easily be identified by regular glucose checkups and other corresponding analyses to check the glucose tolerance level in the human body. The origin of this MtS may come from various sources such as the family history of the disease, dietary habits, smoking, age, and others [29]. In addition to a high blood sugar level, diabetes mellitus often has manifestations of metabolic disorders such as obesity, dyslipidemia, and hypertension, which increase the risk of cardiovascular and cerebrovascular diseases and increase mortality [30].

## 2.3. Obesity

Obesity, or a body having a higher weight than normal (as per BMI index), is one of the major problems in the new generation and society [31]. Over 1/3 of the world's population is obese [1]. Obesity is closely linked with several health disorders, such as adipocyte hypertrophy, insulin resistance, diabetes mellitus, systematic inflammation, non-alcoholic fatty liver disorder, coronary heart diseases, cardiovascular diseases, and cancer [20][32][33].

## 2.4. Liver Intoxication

The liver is one of the vital internal organs of the body responsible for regulating more than 500 functions occurring in the human body. The liver's most important function is to detoxify and neutralize the toxins coming into the body to avoid further health complications [34]. When it comes to liver cleansing, there are several home or market-wide methods available. However, many of these methods are not even tested on a clinical basis or are not regularized by the national drug authorities [35]. Liver detoxification is also associated with the metabolic system.

## 2.5. Aging

The idea of extension in life and a beautiful appearance is necessary for every human body to reverse the effects of aging. This effect can be achieved in several ways, either by using different medicines and supplements or by the dramatic physical changes in the body. Thus far, no such dramatic changes have been clinically observed that can prove effective for the subject. In this concern, various remedies are available over the counter, such as home remedies or allopathic medicines. In the medical industry, antiaging products and their corresponding cosmetic sector have promising contributions within the industry [36]. The consumption of these products is in demand worldwide. Consumers continually desire not only the long-term effects of these agents but also require a response after application to the target. Many cosmetic industries have introduced soft focus and lifting effect concepts considering consumer demand.

In the first one, results are observed in long-term applications, while in the lifting effect, an immediate effect of the proposed cosmetics is offered [37]. In various cosmetics, many naturally occurring compounds are used as skin mediators and healing agents. In these naturally occurring compounds, phenolic-based compounds have a very promising demand as antiaging and for other skin diseases such as skin cancer [38][39]. The antioxidative features of phenolic compounds enable extensive usage of these substances in the cosmetic industry as antiaging agents. Many phenolic compounds have been extracted from various sources, such as potato peels, apples, papaya,

rosemary, *Crataegus* spp., and *Ginkgo biloba,* and their applications have been investigated for antiaging purposes [40].

Aging is associated with an increased risk of developing diabetes mellitus, neurodegeneration, cardiovascular diseases, osteoarthritis, or cancer [41]. Natural antioxidants might prevent aging-related pathologies via different signaling systems involving ROS and nitrogen species scavenging, with the Nrf2/Keap1-ARE system and the pathway mTOR/Foxo/SIRT1 [42]. However, to enhance the antiaging effect of PPs, various intermediates (ethanol and weak acids) are used to achieve maximum benefits [43]. In the cosmetic industry, the most used PPs are anthocyanins, phenolic acids, and flavonoids because of their excellent antioxidant activity. Anthocyanins are mostly found in colored vegetables and fruits, while flavonoids and phenolic acids are mostly found in various seed sources. Although the use of these compounds is much broader, their extraction and separation are key challenges in commercializing these compounds in medical research [44][45].

## 2.6. Carcinogenesis

Carcinogenesis or oncogenesis is the formation of various cancer types involving a multistep and complex process of normal cell division to malignant ones (cancer cells). Different biological alterations generally identify these processes at genetic, internal cellular, and epigenetic levels. These further cause cell division in dead cells and can occur in almost all body tissues under several circumstances [46]. The general theory of carcinogenesis suggests that DNA mutation is a major cause of developing cancer cells. However, only a few mutations can cause cancer cells while others cannot [47]. Carcinogenesis occurs due to human exposure to carcinogens, which can be chemical, biological, radiative, or viral substances. During the process of carcinogenesis, it is observed that the imbalance response of cytokines and their growth in the normal human body also plays a key role in the formation of cancer cells and their further progress by altering the cell cycle proteins [48]. The anticancer effects of natural phytochemicals, such as PPs, relevant to the modulation of cytokine signaling pathways in various cancer cells are evident from many reports.

## 2.7. Cardiovascular Diseases

The past few years have witnessed an extreme transformation in habits, pushing modern populations away from a natural diet and toward unhealthy foods and a sedentary lifestyle. The risk of developing CVDs has increased due to the integration of the modern lifestyle with a persistent intake of harmful intoxicants, including tobacco and misuse of drugs [49].

CVDs are a group of several heart-related complications, such as hypertension, heart failure, hyperlipidemia, acute coronary syndrome, peripheral artery disease, and stroke. Inflammation, atherosclerosis, immune responses, and any physical damage are the most common causes linked to the pathogenesis of heart stroke and failure. Furthermore, increased ROS generation results in altered molecular pathways and endothelial dysfunction; both play a significant role in the etiology of CVDs [50]. Several chemical-based drugs, such as antiplatelet drugs and

cholesterol-lowering agents, are extensively utilized for CVDs treatment. However, these drugs pose several harmful effects.

Consequently, the use of herbal products is expanding rapidly in the 21st century [51]. Most plant species have remarkable safety records, making them a unique candidate for treating heart-related diseases [52]. PPs are the most promising plant compounds which showed significant cardioprotective properties due to their antioxidant potential. Recently, several research studies have evaluated their anti-atherosclerotic and immunomodulatory properties through pre-clinical and clinical trials. These studies highlight the importance of polyphenolic compounds as a natural way of reducing the risk of developing CVDs [53][54][55].

## 2.8. Other Health Problems

In the fourth century B.C., Hippocrates emphasized the importance of diet in health and disease, saying, “death sits in the bowels” [56]. Many in vivo studies and human trials suggest that gut microbiota dysbiosis is involved in gastrointestinal diseases and obesity, diabetes, and other MtS [57]. Recent data have revealed the ability of foods rich in polyphenols to modulate intestinal dysbiosis present in various diseases by reducing the number of potential pathobionts [57].

**Table 1** summarizes the current state of the Mts treatments with PPs from clinical studies.

**Table 1.** The current state of the Mts treatments with polyphenols from clinical studies.

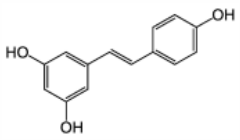
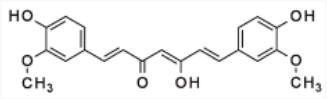
| PPs Type and Main Features of Treatment | Pathologies and Mechanism of Action | Refs. |
|---|---|---|
| **Oxidative Stress and Inflammation** | | |
| **Oleuropein, hydroxytyrosol, curcumin, resveratrol, epigallocathechin** | Cell protection (redox homeostasis) through the activation of vitagene signaling pathways | [58] [59] |
| **Grape products containing PPs (resveratrol, proanthocyanidin, quercetin, etc.)** | Significant increase in the levels of total antioxidant capacity and oxygen radical absorbance capacity as well as improving various enzymatic systems such as superoxide dismutase or glutathione peroxidase (dependently on the dosage) | [60] |
| **Genistein, silymarin caffeic acid, chlorogenic acid, ellagic acid** | Healing chronic inflammation is the key pathomechanism of obesity-related metabolic disorders (insulin resistance, type 2 diabetes, and cardiovascular diseases) | [61] |
| **PPs from cocoa, fruits, and vegetables** | Alleviating the oxidative damage and inflammation parameters | [6][7] [10] [62] |
| **Diabetes** | | |

| PPs Type and Main Features of Treatment | Pathologies and Mechanism of Action | Refs. |
|---|---|---|
| ***Aloe Vera*** **extract (enriched with PPs), PPs from grapes,and cinnamon** | Control of insulin resistance | [63] [64] [65] |
| **Quercetin, resveratrol and epigallocatechin-3-gallate** | Enhancing glucose uptake in the adipocytes and muscles in type 2diabetes by the activation of the AMP-activated protein kinase pathway | [66] |
| **Resveratrol** | Reducing blood glucose levels | [30] |
| **PPs from fruits and vegetables** | Protecting pancreatic β-cells and activating glucose/lipid metabolism pathways, affecting glucose absorption and uptake | [62] [66] |
| | **Obesity** | |
| **Epigallocatechin gallate** | Increasing energy consumption and weight loss due to a higher rate of fat oxidation | [67] |
| **The total PP content (measured in urine samples using the Folin–Ciocalteu method)** | Long-term intake of PPs led to significant loss of weight | [68] |
| **Curcumin and resveratrol** | Anti-obesity effect to avoid associated metabolic disorders | [69] |
| **Brown seaweed PPs** | Effective regulation of metabolic disorders via correction of fat function (transforming white adipose tissue into “brown” and enhancing energy consumption) | [70] |
| **PPs from fruits and vegetables** | Reducing lipid accumulation and regulating intestinal microflora | [62] |
| | **Liver Intoxication** | |
| **Silymarin/Silybin** | Hepatoprotection, preventing and treatment of chronic liver disease | [35] |
| **Flavonoids (anthocyanins, flavonols, flavanones and isoflavones)** | Detoxifying and oxidative stress preventive abilities of flavonoids through regulation of the autophagy and apoptosis pathways as well as by impact on mitochondria-ER stress-proteasome | [71] [72] [73] [74] [75] |
| **Foods’ PPs (whole-foods approach)** | It affects the activity of detoxification pathways, including Nrf2 signaling, phase I cytochrome P450 enzymes, phase II conjugation enzymes, and metallothionein | [76] |
| | **Aging** | |

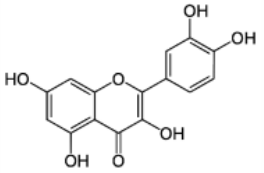
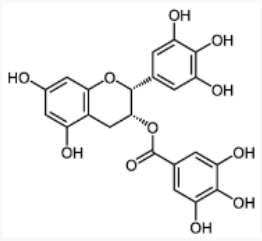
| PPs Type and Main Features of Treatment | Pathologies and Mechanism of Action | Refs. |
|---|---|---|
| **Resveratrol** | Vascular dysfunction in aging | [66] |
| **Resveratrol, quercetin, curcumin and catechins** | Modulation of some of the evolutionarily conserved hallmarks of aging, such as oxidative damage, cell senescence, and autophagy | [38] |
| **Flavonoids, curcumin and resveratrol** | Disruption of age-associated deterioration in physiological function | [44] |
| **Isoflavones from soybean** | Anti-arteriosclerotic effect | [77] |
| **Flavonoids and tannins** | Modulating genes associated with stress defense, drug-metabolizing enzymes, detoxification, and transporter proteins | [78] |
| **Carcinogenesis** | | |
| **Epigallocatechin and other tea PPs** | Chemopreventive effects on colorectal cancer | [79] |
| **Pomegranate fruit extract, green tea PPs, grape seed proanthocyanidins, resveratrol, genistein, silymarin, and delphinidin** | Inhibition of photocarcinogenesis (melanoma, squamous cell carcinoma, basal cell carcinoma) | [80] [81] |
| **Isoflavones from soybean** | Prevention of prostate and breast cancer | [82] [83] |
| **Cardiovascular Diseases** | | |
| **Resveratrol** | Increasing total plasminogen activator inhibitor and circulating vascular cell adhesion molecules | [84] |
| **Green tea PPs** | Prevention the coronary heart disease | [85] |
| **Cocoa flavanols** | Improving the levels of biomarkers for cardiometabolic disorders | [86] [87] |
| **Lignans, flavonoids, and hydroxybenzoic acids** | Diminishing risk of major cardiovascular disorders (ischemia, myocardial infarction, stroke) | [9] |
| **Rheumatoid Arthritis** [89] | | |
| **Curcumin** | Improving metabolic parameters and inflammatory factors in women with rheumatoid arthritis | [88] |

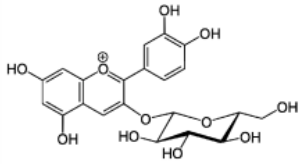
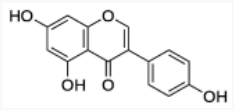
. Several potential: nes (e.g., etin, rutin, that exist s [90]. The nocyanins in plants [90][91].

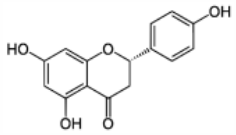
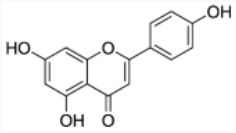
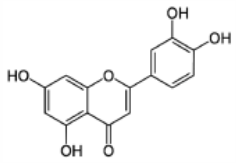
**Table 2.** The main polyphenols and underlying mechanisms of their pharmacological activity in MtS treatment and prevention.

| The Common Name of Polyphenolic Compound | Structural Formula and IUPAC Name | Class of Phenolic Compounds | Main Sources | Main Targets of Action (Metabolic Diseases and States) | Refs. |
|---|---|---|---|---|---|
| Resveratrol |  <br>3,5,4'-trihydroxystilbene | Stilbenes | Grapes, raspberries, mulberries, blueberries, apples, plums, and peanuts | - Antioxidant, antidiabetic, anti-obesity, antinociceptive, anticancer, hepatoprotective effects<br>- Modulation of cytokines and suppression of inflammatory disease<br>- Enhancing glucose uptake in the adipocytes and muscles in people with diabetes (by the activation of the amp-activated protein kinase pathway)<br>- Maintenance of genome stability<br>- Autophagy inducers in aging research | [92] [93] [94] [30] [66] [69] [95] [96] [97] [98] [99] |
| Curcumin |  <br>(1*E*,6*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione | Curcuminoids (diarylheptanoid) | Turmeric (*Curcuma longa*) rhizome | - Antioxidant, anti-inflammatory, anti-obesity, hepatoprotective, anti- | [94] [66] [69] [100] [101] [102] [88] |

| The Common Name of Polyphenolic Compound | Structural Formula and IUPAC Name | Class of Phenolic Compounds | Main Sources | Main Targets of Action (Metabolic Diseases and States) | Refs. |
|---|---|---|---|---|---|
| | | | | atherosclerotic, and anti-diabetic properties<br>- It can effectively suppress inflammatory mediators such as cyclooxygenase<br>- Inhibiting the inflammation and apoptosis signaling for the treatment of endotoxemia (liver failure)<br>- Improving gut health, glycemic index, lipid profile, and obesity values<br>- Treatment of chronic diseases (diabetes, gastrointestinal, neurological, cardiovascular, several types of cancer) | [103] [104] |

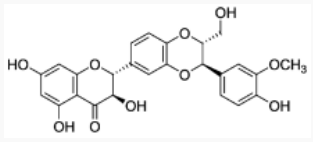
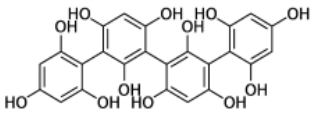
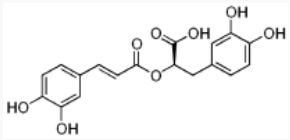
| The Common Name of Polyphenolic Compound | Structural Formula and IUPAC Name | Class of Phenolic Compounds | Main Sources | Main Targets of Action (Metabolic Diseases and States) | Refs. |
|---|---|---|---|---|---|
| Quercetin |  3,3′,4′,5,7-Pentahydroxyflavone | Flavonoids (flavonols) | Fruits and vegetables (mainly of yellow or orange color) | - Capability to suppress oxidative stress and severe inflammation,<br>- Enhancing glucose uptake in the muscles and adipocytes, inducing autophagy<br>- Improving gut health<br>- Suppressing colon carcinogenesis through its anti-inflammatory effects | [105] [106] [72] [73] [41] [107] [102] [99] [108] [109] [110] |
| Epigallo-catechin gallate |  (2*R*,3*R*)-3′,4′,5,5′,7-Pentahydroxyflavan-3-yl 3,4,5-trihydroxybenzoate | Flavonoids (catechins) | Green tea | - Strong antioxidant and anti-inflammatory properties<br>- Modulating sensitivity towards insulin in case of type 2 diabetes<br>- Improving the dyslipidemia state<br>- Anti-obesity influence | [27] [111] [66] [41] [112] [113] [114] [102] |

| The Common Name of Polyphenolic Compound | Structural Formula and IUPAC Name | Class of Phenolic Compounds | Main Sources | Main Targets of Action (Metabolic Diseases and States) | Refs. |
|---|---|---|---|---|---|
| | | | | (stimulating weight loss)<br>- Inhibiting carcinogenesis, inducing autophagy | |
| Anthocyanins |  <br>(2S,3R,4S,5S,6R)-2-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromenylium-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol chloride<br>(Cyanidin-3-glucoside) | Flavonoids (anthocyanins) | Berries and flower corollas (in red, blue, or purple colors) | - Management of various metabolic disorders, including diabetes, obesity, high blood pressure, and neurodegeneration<br>- Preventing free radical production<br>- Protecting $\beta$-cells | [90] [115] [116] |
| Genistein |  <br>4′,5,7-Trihydroxyisoflavone | Flavonoids (isoflavone) | Mainly *Fabaceae* plants (soy-beans in particular) | - Suppression of free radicals<br>- Inhibition of inflammation<br>- Promotion of apoptosis<br>- Prevention of hormone-dependent tumors through modulation of steroidal hormone receptors | [75] [77] [117] |

| The Common Name of Polyphenolic Compound | Structural Formula and IUPAC Name | Class of Phenolic Compounds | Main Sources | Main Targets of Action (Metabolic Diseases and States) | Refs. |
|---|---|---|---|---|---|
| Naringenin |  (2*S*)-4′,5,7-Trihydroxyflavan-4-one | Flavonoids (flavanone) | Citrus fruits (oranges, lemons, grapefruits, etc.) | - Strong anti-inflammatory and antioxidant effects,<br>- Treatment of diabetes, obesity, hypertension, and other manifestation of MtS<br>- Improving lipid metabolism | [118] [119] |
| Apigenin |  4′,5,7-Trihydroxyflavone | Flavonoids (flavone) | Celery, parsley, *Lamiaceae* plants | - Effectiveness against cardiometabolic diseases due to the antioxidant and anti-inflammatory properties<br>- Inducing autophagy,<br>- Anticancer effect | [41] [120] [121] [122] |
| Luteolin |  3′,4′,5,7-Tetrahydroxyflavone | Flavonoids (flavone) | Celery, carrot, parsley, broccoli, oranges, chamomile tea, and *Lamiaceae* plants (thyme, oregano, rosemary, etc.) | - Prominent antioxidant and anti-inflammatory effects<br>- Treatment of glycolipid | [123] [89] [124] |

Berry-derived PPs are mainly obtained from the fleshy fruits of strawberry, blueberry, mulberry, currant, raspberry, blackberry, barberry, rosehip, and gooseberry [91]. Berries are rich sources of pigments, particularly anthocyanins (up to 5 g/kg), which are responsible for their red, blue, or purple colors. They also contain flavonols, phenolic acids, tannins, etc. Due to their ability to cross the blood-brain barrier, PPs with low molecular weight have beneficial antioxidant effects.

The potential benefits of PPs on human health make them the best micronutrients obtained from plant foods. These active principles possess excellent antioxidant and anti-inflammatory properties that ultimately favor the metabolic system of the human body and can avoid various chronic diseases (**Figure 2** and **Figure 3**). Epidemiologic and related case studies on mouse and human diets demonstrate that daily intake of PPs can easily

| The Common Name of Polyphenolic Compound | Structural Formula and IUPAC Name | Class of Phenolic Compounds | Main Sources | Main Targets of Action (Metabolic Diseases and States) | Refs. |
|---|---|---|---|---|---|
| | | | | metabolism disorders (in case of obesity and diabetes) | |
| Silybin |  Silybin A (2*R*,3*R*)-3,5,7-Trihydroxy-2-[(2*R*,3*R*)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,3-dihydro-4H-chromen-4-one | Flavonolignan (silymarin group) | Milk thistle (*Silybum marianum*) fruits. Silymarin is a flavonoid mixture in which silybin is the major one. | - Antioxidative, anti-inflammatory, antiapoptotic, hepatoprotective properties,<br>- Preventing and treatment of chronic liver disease | [61] [125] [126] |
| Phlorotannins |  Tetrafucol A, [$1^1$,$2^1$:$2^3$,$3^1$:$3^3$,$4^1$-Quaterphenyl]-$1^2$,$1^4$,$1^6$,$2^2$,$2^4$,$2^6$,$3^2$,$3^4$,$3^6$,$4^2$,$4^4$,$4^6$-dodecol | Oligomer of phloroglucinols (a fucol-type phlorotannin) | Brown seaweeds | - Counteracting high free radicals production<br>- Ability to activate the transformation of white adipose tissue to “brown”<br>- Tackling neurodegeneration | [127] [70] [128] |
| Rosmarinic acid |  (2*R*)-3-(3,4-Dihydroxyphenyl)-2-{[(2*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy}182propanoic acid | Hydroxycinnamic acids | Mainly *Lamiaceae* plants (especially from the *Nepetoideae* subfamily) | - Antioxidant and anti-inflammatory actions,<br>- Ability to decrease the blood glucose, triglyceride, and | [129] [130] [131] |

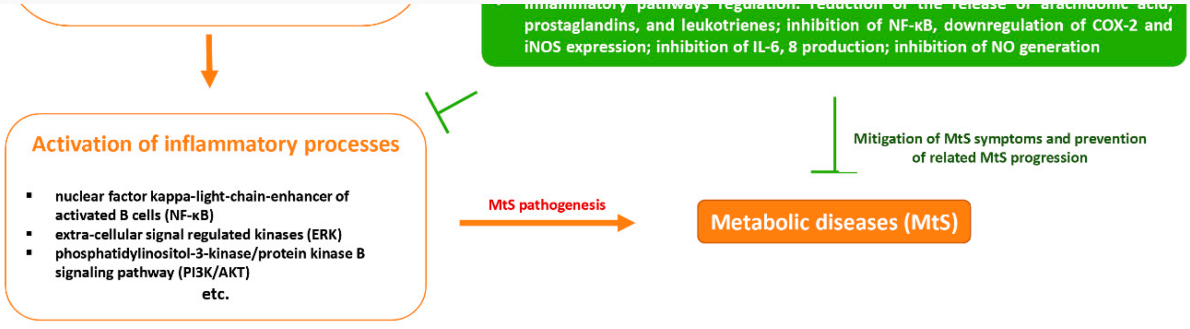
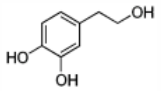
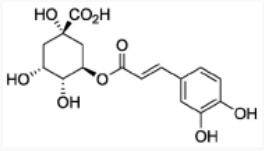
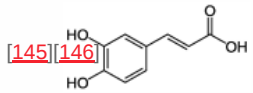



**Figure 3.** Overall mechanisms of action of PPs against oxidative stress and inflammation leading to MtS.

It could be concluded that a single source of PPs, not always and not everywhere, can fulfill an effective role. Generally, the benefits of PPs involve the mechanism of bioactive scavenger theory in which free radicals are

| The Common Name of Polyphenolic Compound | Structural Formula and IUPAC Name | Class of Phenolic Compounds | Main Sources | Main Targets of Action (Metabolic Diseases and States) | Refs. |
|---|---|---|---|---|---|
| | | | | plasma total cholesterol levels significantly | [139] |
| Hydroxytyrosol |  4-(2-Hydroxyethyl)benzene-1,2-diol | Phenylethanoid (phenolic compound) | Olive oil (in the form of oleuropein) | - Inhibiting oxidative stress and inflammation,<br>- Improving MtS parameters in case of excessive body weight, insulin resistance, and hypertension | [132] [133] [139] [140] [141] [142] |
| Chlorogenic acid |  (1*S*,3*R*,4*R*,5*R*)-3-{[(2*E*)-3-(3,4-Dihydroxyphenyl)prop-2-enoyl]oxy}-1,4,5-trihydroxycyclohexane-1-carboxylic acid | Hydroxycinnamic acids (phenolic compound) | Coffee beans, peaches, eggplant, prunes | - Anti-inflammatory, antioxidant, anticarcinogenic activities<br>- Hypoglycemic and hypolipidemic effects | [61] [134] [143] [144] |
| Caffecic acid |  3-(3,4-Dihydroxyphenyl)-2-propenoic acid3,4-Dihydroxycinnamic acid | Hydroxycinnamic acids (phenolic compound) | Coffee beans, *Lamiaceae* plants, etc. | - Antioxidant, anti-inflammatory, anticancer and antidiabetic properties,<br>- Ability to reverse insulin resistance, dyslipidemia, hyperglycemia, and oxidative | [61] [135] [136] [145] [146] [147] |

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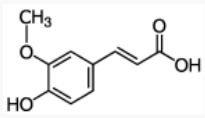
barrier [148]. In a rat model of 3-nitropropionic acid-induced Huntington's disease, it was observed that curcumin-encapsulated solid lipid nanoparticles effectively reduced mitochondrial dysfunction [149]. A remarkable research study demonstrated that solid-liquid nanoparticles functionalized with the anti-transferrin receptor (OX26) monoclonal antibody offered a reliable carrier to deliver the resveratrol and grape skin extract to target the brain and treat neurodegenerative disease [150]. Oral administration of resveratrol-loaded PLGA nanocarrier showed enhanced resveratrol bioavailability [151]. In another recent study, resveratrol oral bioavailability was enhanced in Sprague Dawley rats by binding the galactose ligand (N-oleoyl-d-galactosamine) on the surface of the resveratrol-loaded PLGA nanoparticles [152].

The literature notably documented that using polyphenol-loaded nanocarriers has increased their antioxidant and anti-inflammatory effects [153][154][155][156][157]. Therefore, although there are several types of delivery systems that have been assessed through in vitro and in vivo studies for improved bioavailability and target delivery of PPs in

| The Common Name of Polyphenolic Compound | Structural Formula and IUPAC Name | Class of Phenolic Compounds | Main Sources | Main Targets of Action (Metabolic Diseases and States) | Refs. |
|---|---|---|---|---|---|
| | | | | stress in case of MtS | |
| Ferulic acid |  (2*E*)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid | Hydroxycinnamic acids (phenolic compound) | Mainly *Apiaceae* plants (*Angelica sinensis*, genus *Ferula*, *etc.*) | - Lowering stored fat in human adipocytes,<br>- Reversing insulin resistance, dyslipidemia, hyperglycemia, inflammation, and oxidative stress | [110] [136] [137] |

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