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REVIEWS: CURRENT TOPICS

# Modulation of adipose tissue inflammation by bioactive food compounds

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**Abstract**

Adipose tissue has an important endocrine function in the regulation of whole-body metabolism. Obesity leads to a chronic low-grade inflammation of the adipose tissue, which disrupts this endocrine function and results in metabolic derangements, such as type-2 diabetes. Dietary bioactive compounds, such as polyphenols and certain fatty acids, are known to suppress both systemic and adipose tissue inflammation and have the potential to improve these obesity-associated metabolic disorders. Mechanistically, polyphenolic compounds including non-flavonoids, such as curcumin and resveratrol, and flavonoids, such as catechins (tea-polyphenols), quercetin and isoflavones, suppress nuclear factor-κB (NF-κB) and mitogen-activated protein (MAP) kinases (MAPK) pathways while activating the 5′ adenosine monophosphate-activated protein kinase (AMPK) pathway in adipose tissue. Dietary polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), conjugated linoleic acid (CLA) and monounsaturated fatty acids (MUFA), such as oleic acid, also impart anti-inflammatory effects through several mechanisms. These include activation of AMPK and peroxisome proliferator-activated receptor gamma (PPAR-γ), as well as suppression of toll-like receptors (TLRs) and NF-κB pathway. This review discusses the major molecular mechanisms of dietary polyphenols and fatty acids, alone or in combination, which are responsible for adipose tissue-associated anti-inflammatory effects.


*Keywords:* Obesity; Adipose tissue; Inflammation; Phytochemicals; Polyunsaturated fatty acids; Monounsaturated fatty acids; Curcumin; Resveratrol; Quercetin; Tea polyphenols

## 1. Introduction

Obesity has reached epidemic proportions in the US and worldwide and is a significant economic burden [1,2]. There are multiple health consequences of obesity including type-2 diabetes, heart disease, hypertension and several forms of cancer [3,4]. While obesity and other obesity-associated co-morbid conditions are due to high caloric intake and/or reduced energy expenditure over time, their causes can be complex varying from genetic alterations, environmental factors and/or gene-environment interactions. Sedentary lifestyle and excess caloric intake due to obesigenic environmental changes coupled with genetic susceptibility likely contributed to the recent escalation of obesity rates [4,5].

Fat mass expansion in obesity occurs via adipocyte hypertrophy (increased size of adipocytes) and/or adipocyte hyperplasia (increased adipocyte number). Adipocyte hyperplasia primarily results from proliferation and subsequent differentiation of pre-adipocytes and adipose stem cells, while adipocyte hypertrophy results from excessive lipid storage within adipocytes. The latter is frequently seen in obese adipose tissue and is often associated with adipose tissue remodeling and inflammation which contributes to metabolic derangements both locally within adipose tissue and systemically [6–8]. Adipose tissue cellularity, inflammatory and metabolic functions also exhibit regional differences [9,10].

This review discusses the major molecular mechanisms of dietary polyphenols and fatty acids alone or in combination that are responsible for adipose tissue-associated anti-inflammatory effects.

## 2. Endocrine and inflammatory function of the adipose tissue

Adipose tissue is not simply an energy reservoir, thermal regulator, or protective padding for important organs but also a metabolically active endocrine organ. This latter endocrine function of adipose tissue contributes significantly toward overall energy homeostasis and systemic insulin sensitivity by secreting adipokines and cytokines [7,11]. In addition to adipocytes and preadipocytes, adipose tissue also contains immune cells such as macrophages and

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lymphocytes which help maintain the normal metabolic functions of the adipose tissue.

Adipose tissue from lean individuals contains small, insulin-sensitive adipocytes and predominantly alternatively activated macrophages (M2), while adipose tissue from obese individuals is characterized by large insulin-resistant adipocytes accompanied by the presence of classically activated macrophages (M1) as shown in Fig. 1 [12,13]. Adipocyte hypertrophy in obesity, coupled with adipocyte death, adipose tissue hypoxia and changes in immune cell populations alters adipokine secretory patterns [7,11]. This shift in adipokine secretory patterns from a less inflammatory environment to a predominantly pro-inflammatory profile is in part responsible for the development of insulin resistance [7]. In addition, adipose tissue produces other inflammatory hormones such as angiotensin II, steroid hormones, and chemokines that are known to play major roles in metabolic and chronic diseases [14]. Common pro-inflammatory adipo/cytokines produced by adipose tissue include tumor necrosis factor-α (TNF-α), interleukin-1 beta (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1) and resistin [14,15]. In contrast, adipose tissue can also produce anti-inflammatory cytokines such as adiponectin and interleukin-10 (IL-10) [15]. Toll-like receptors (TLRs) and nuclear factor-κB (NF-κB)-associated mechanisms have been proposed as primary molecular mechanisms mediating adipose tissue inflammation [16,17]. Adipose tissue TLRs (TLR1, 2 and 4) are cell surface receptors that are activated by several dietary stimulants including saturated fatty acids. The TLRs activate NF-κB [16], a transcription factor and potent inducer of gene transcription of several pro-inflammatory cytokines such as IL-6 and TNF-α. In addition, adipocyte differentiation increased by the phosphorylation of mitogen-activated protein kinases (MAPKs) [18] can further increase the secretion of pro-inflammatory cytokines. Recent evidence also suggests that reduced AMP-activated protein kinase (AMPK) activity is associated with adipose tissue inflammation [19]. Additionally, peroxisome proliferator–activated receptor-α (PPARα), a nuclear receptor primarily expressed in the liver, and a potent inducer of fat oxidizing genes, has also been reported to reduce adipose tissue inflammation [20].

Thus, obesity is characterized by a chronic low-grade inflammation, primarily due to an imbalance between production/secretion of pro-inflammatory cytokines vs. anti-inflammatory cytokines [21]. Such an imbalance has been associated with several metabolic disorders including type-2 diabetes and cardiovascular disease risk factors [22,23]. This imbalance can be restored, at least in part, through weight loss, energy restriction and nutrient dense diets [24,25]. Moreover, both human and animal studies provide evidence to support the assertion that the use of dietary bioactive compounds can increase thermogenesis and energy expenditure, providing additional benefits in preventing/limiting obesity.

## 3. Dietary interventions to reduce adipose tissue inflammation and insulin resistance

In addition to total energy intake, the composition of a diet can also affect the metabolic and endocrine functions and overall energy balance [11,26]. Indeed, most health recommendations emphasize diets rich in fruits and vegetables, which have higher nutrient density and lower caloric density, for prevention of chronic diseases [26]. Such diets would provide significant amounts of bioactive components, with known beneficial effects due in part to their anti-inflammatory properties [27].

Since adipose tissue inflammation is causally linked to the pathogenesis of insulin resistance and several chronic diseases, dietary interventions targeted at improving adipose tissue inflammation could be a useful strategy for improving the overall metabolic profile.

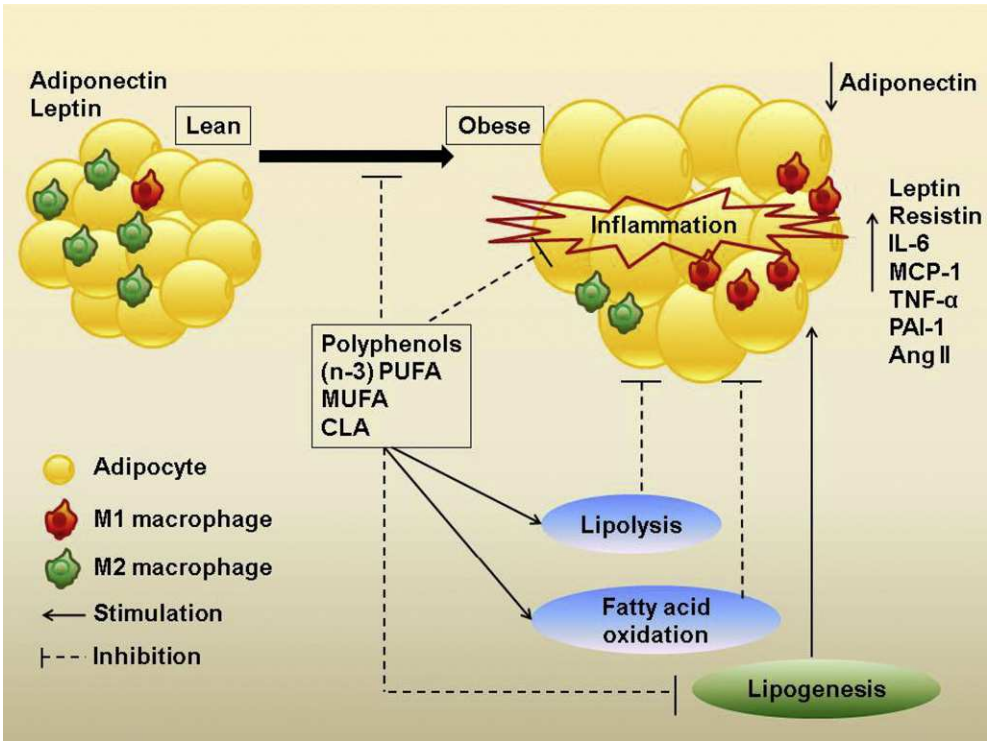


Fig. 1. Effects of polyphenols, (n-3) PUFA, MUFA and CLA on adipose tissue function. Obesity leads to adipocyte hypertrophy and increased secretion of pro-inflammatory adipokines and reduced secretion of anti-inflammatory adipokines from the adipose tissue, giving rise to a chronic low-grade inflammation. This is also characterized by an increase in M1:M2 macrophage ratio. Polyphenols, (n-3) PUFA — mainly EPA and DHA, MUFA and CLA promote loss of adiposity via increasing lipolysis and fatty acid oxidation and inhibiting lipogenesis. EPA, DHA, MUFA and *cis*-9,*trans*-11-CLA also exhibit anti-inflammatory properties.

Energy restriction is a successful weight loss strategy that can improve and/or reverse metabolic derangements in obesity. Indeed, energy restriction reduces adipose tissue mass and adipocyte size (cell hypotrophy), which leads to improvements in insulin sensitivity. This is also accompanied by improvements in adipose tissue inflammation and systemic insulin resistance [28,29]. Besides energy restriction, consumption of dietary bioactive compounds in the form of fruits and vegetables is also known to improve metabolic profile and reduce the risk of chronic diseases. There is also emerging evidence that dietary bioactive compounds in the form of supplements can also provide similar benefits. Esfahan et al. recently reviewed literature of 18 human trials with 1363 adult individuals related to mixed fruit and vegetable supplements and showed that fruit and vegetable concentrates significantly increase serum levels of antioxidant pro-vitamins and vitamins (β-carotene, vitamins C and E) as well as folate. In addition, the supplements were shown to reduce homocysteine and markers of oxidative stress [30]. Also, the Dietary Guidelines for Americans recommends a diet rich in plant food sources for long term health benefits [31].

Dietary bioactive compounds impart anti-inflammatory effects on the adipose tissue by several mechanisms. While some bioactive compounds suppress the pro-inflammatory adipokine production, some bioactive compounds are known to increase the production of anti-inflammatory adipokines such as adiponectin. Although some controversy exists regarding adiponectin expression/levels under different conditions, adiponectin is known as an anti-inflammatory adipokine and its circulating levels tend to decrease with increasing visceral obesity. In addition, adiponectin levels are shown to be lower in patients with type-2 diabetes, and cardiovascular disease compared with controls matched by body mass index [32]. Décordé et al. showed that chronic consumption of grape phenolics reduced obesity development and related metabolic pathways including increased adiponectin secretion [33]. Understanding of these mechanisms might provide further insight into the pathogenesis of obesity-induced adipose tissue inflammation and help to uncover molecular targets for the development of treatment strategies for chronic diseases such as type-2 diabetes. In this review, we discuss important mechanisms that mediate the effects of selected food bioactives, namely common polyphenolic compounds and unsaturated fatty acids (dietary omega-3 polyunsaturated fatty acids (n-3 PUFAs), monounsaturated fatty acids, and conjugated linoleic acid), on adipose tissue inflammation.

## 4. Polyphenols and adipose tissue inflammation

Polyphenols are compounds naturally present in plants with a wide range of biological functions. In addition to their well-documented anti-oxidant properties, dietary polyphenols are reported to exert a variety of valuable bioactivities including anti-inflammatory, anti-cancer, anti-obesity and anti-aging properties [34,35]. As shown in the Table 1, dietary polyphenols impart their beneficial effects on adipose tissue inflammation via numerous mechanisms. Because adipose tissue inflammation is closely interconnected with adiposity and systemic insulin resistance, the reported effects of these polyphenols on these disorders are also indicated in Table 1. Signaling pathways associated with polyphenol-mediated improvements in adipose tissue inflammation include AMPK, MAPK, NF-κB, PPARα/γ and TLR2/4 (Fig. 2). In the following section, we review several important and representative polyphenolic compounds, which impact adipose tissue inflammation, obesity and insulin resistance.

## 5. Curcumin

Due to its many promising health benefits, curcumin has become one of the most intensively investigated bioactive non-flavonoids extracted from turmeric. Comprising 2–8% of most turmeric

Table 1
Major dietary polyphenols: their sources and effects on adipose tissue inflammation, adiposity, systemic insulin resistance and associated molecular mechanisms

| Polyphenol | Source | Effects on adipose tissue | | Systemic effects | Mechanisms/signaling pathways associated with activities |
|---|---|---|---|---|---|
| | | Inflammation | Adiposity | Insulin resistance/diabetes | |
| Non-flavonoids | | | | | |
| Curcumin | Turmeric | ↓[36,46] | ↓[43] | ↓[36,45] | ↓NF-κB [36,46]<br>↓ MAPK phosphorylation [39]<br>↑ Wnt[43] |
| Resveratrol, | Wine, grapes, berries | ↓[52] | ↓[155] | ↓[155] | ↑Sirt1[52], ↓TLR2/4 & NF-κB [53] |
| Flavonoids | | | | | |
| Anthocyanin/anthocyanidins | | | | | |
| Cyanidin 3-glucoside | Red berries | ↓[156] | ↓[157] | | ↑pAMPK [157] |
| Flavanols | | | | | |
| Catechin | Green tea | | ↓[66,67] | | |
| Epigallocatechin gallate | Green tea | | ↓[60,64] | ↓[158–160] | ↓pERK1/2[62]<br>↑AMPK [158] |
| Theaflavins | Black tea | | | ↓[59] | |
| Flavanones | | | | | |
| Hesperetin | Citrus fruits | ↓[161,162] | ↑[163] | | ↓NF-κB [162] |
| Naringenin | Citrus fruits | ↓[161,162] | ↑[163] | | |
| Flavonols | | | | | |
| Quercetin | Apple, vine | ↓[71] | ↓[68] | ↓[71] | ↓NF-κB, JNK[71] |
| Fisetin | Strawberries | | | ↓[59] | |
| Kaempferol | Spinach, turnip green, blueberries, black tea | | ↓[164] | ↓[59] | |
| Isorhamnetin/myricetin | Berries, fruits, herbs | | ↓[165] | ↓[166] | |
| Flavones | | | | | |
| Apigenin | Parsley, onions, | | | ↓[59] | |
| Luteolin | Parsley, artichoke, basil | | | ↓[59,167] | ↑PPARγ [167] |
| Isoflavones | | | | | |
| Daidzein | Soy products | | ↓[83,168] | | |
| Genistein | Soy products | | ↓[60,83,84,169] ↑[170] | ↓[163] | ↑AMPK [60]<br>↑ Wnt signaling [83]<br>↑PPARα [171] |

In the table, ↑indicates increased activation/levels; ↓ indicates decreased activation/levels.
Blank areas in the table indicate no data found/reported.

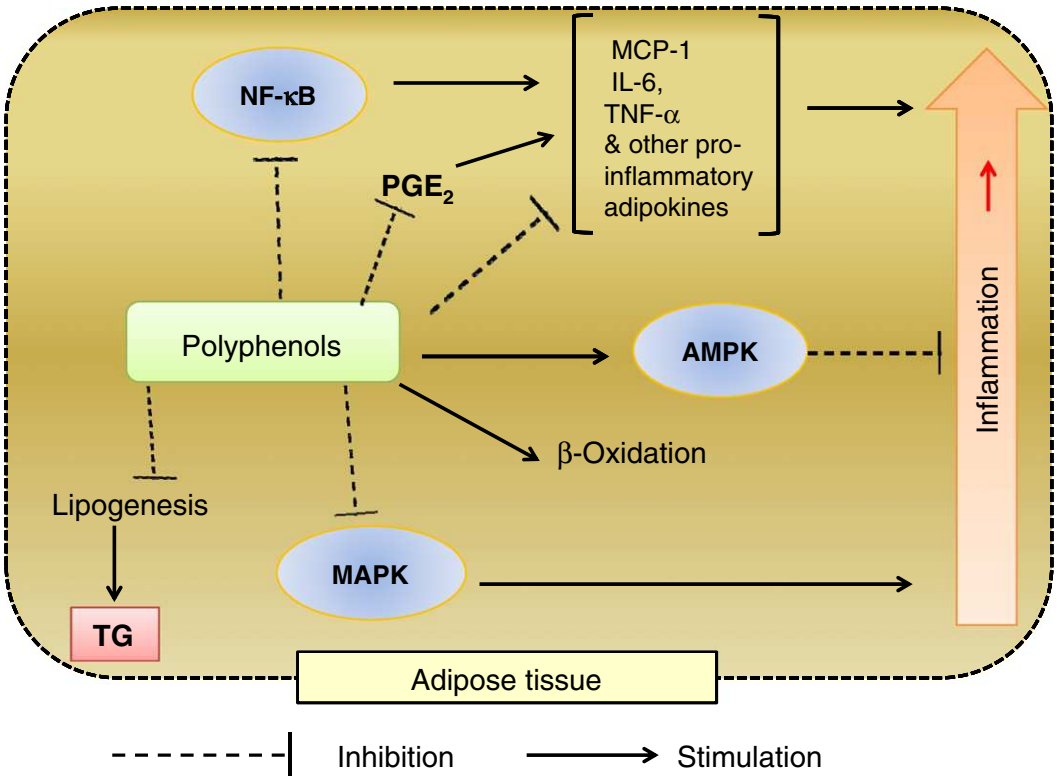


Fig. 2. Anti-inflammatory effects of polyphenols on the obese adipose tissue. Obesity leads to activation of the NF-κB and MAPK signaling pathways and suppression of AMPK signaling pathway in the adipose tissue. Polyphenols are known to suppress the pro-inflammatory mediators associated with NF-κB, MAPK and AMPK pathways. Also, polyphenols are known to increase lipid oxidation and suppress lipogenesis, both of which can lead to reductions in adiposity.

preparations, curcumin is generally regarded as its most active component, and has potent anti-oxidant, obesity-associated anti-inflammatory and anti-diabetic properties [36–38]. Curcumin is known to be well-tolerated by humans without significant side effects, even at high dosages up to 8 g/day [36]. Early studies in humans showed that curcumin at a dose of 3.6 g/day was sufficient to decrease pro-inflammatory prostaglandin E2 ($PGE_2$) levels in plasma [40]. According to a recent review published by Vermorken et al., the average intake of turmeric in the adult Indian population is estimated at 2 g/day (containing up to 200 mg curcumin) [41]. Curcumin is poorly absorbed from the gastrointestinal tract; however the co-ingestion of curcumin with other natural phytochemicals, such as piperine has been shown to dramatically increase its absorption and bioavailability [42].

Curcumin was shown to inhibit adipogenic differentiation in vitro as well as adipose tissue angiogenesis and obesity in C57/BL mice [43,44]. Furthermore, curcumin exhibited potent anti-inflammatory and blood glucose reducing effects in mice with type 2 diabetes [41,42]. Potential mechanisms by which curcumin mediates anti-adipogenic and anti-inflammatory activities include activation of Wnt/β-catenin signaling and suppression of MAPK and NF-κB activation pathways [43,36]. Anti-inflammatory and anti-diabetic effects of curcumin were also reported in genetic obesity (ob/ob mice) and diet-induced obesity models in which mechanisms that reduced macrophage infiltration into adipose tissue, increased adiponectin production, and decreased hepatic NF-κB activation were observed [36]. The latter was related to curcumin's suppression of IκB degradation and subsequently suppression of NF-κB activation, resulting in reduced TNFα, IL-1β, IL-6 and cyclooxygenase-2 (COX-2) gene expression in differentiated adipocytes [46]. The above documented anti-adipogenic and anti-inflammatory activities of curcumin in adipose tissue suggest that curcumin is a potential dietary polyphenolic source to effectively control adipose tissue expansion and inflammation.

## 6. Resveratrol (RSV)

Resveratrol (RSV) is a non-flavonoid polyphenol found in wine, grapes (mostly grape skin), peanuts, and many berries including blueberries and cranberries. RSV in red wine comes from the skin of grapes used to produce wine. Because red wine is fermented with grape skins longer than white wine, red wine contains more RSV [47]. In red wine, the concentrations of RSV generally ranges between 2 and 12.6 mg/L [48]. In addition, simply eating grapes (0.24–1.25mg/cup/160 g), or drinking grape juice (1.14–8.69 mg/L) has been suggested for getting sufficient RSV without alcohol intake. RSV supplements are also available in the U.S. and contain 10–50 mg of RSV. Although RSV appears to be well-absorbed by humans when taken orally, its bioavailability is relatively low due to its rapid metabolism and elimination [49]. The serum concentration of total RSV (resveratrol and metabolites) 30 min after oral administration of RSV (25 mg/70 kg men) ranged from 416 to 471 μg/L, depending on whether RSV was administered in wine, vegetable juice, or grape juice [50]. A recent study reported that bioavailability of RSV from red wine did not differ when the wine was consumed with a meal (low- or high-fat) versus on an empty stomach [51].

RSV is a potent anti-inflammatory compound which can reduce adipose tissue inflammation [46]. These anti-inflammatory effects led to reduced adipose tissue inflammation particularly via suppression of NF-κB and extracellular signal-regulated kinase (ERK) activation as well as activation of sirtuin-1 (silent mating type information regulation 2 homolog, Sirt1) [46,52]. In agreement with these RSV's anti-inflammatory effects in vitro, RSV also significantly attenuated high-fat (HF) diet-induced production of TNFα, interferon α (IFNα),

IFNβ, and IL-6 and their upstream signaling molecules including TLR 2/4, myeloid differentiation primary response gene 88 (MyD88), toll-interleukin 1 receptor (TIR) domain containing adaptor protein (TIRAP), TIR-domain-containing adapter-inducing interferon (TRIF), TNF receptor associated factor 6 (TRAF6), interferon regulatory factor 5 (IRF5), p-IRF3, and NF-κB in mouse adipose tissue [53]. Overall, RSV actions in obesity may be linked to the ability of this compound to direct adipose tissue metabolism towards increased oxidative capacity and reduced lipogenesis. On the other hand, RSV effects on insulin resistance and inflammation are in part mediated by down-regulation of pro-inflammatory adipokines such as resistin and retinol-binding protein 4 (RBP4) [54].

In human adipocytes, RSV increases adiponectin levels via a SIRT1-dependent mechanism [52]. However, in mouse 3T3-L1 adipocytes, RSV enhances adiponectin multimerization via a Sirt1-independent mechanism [55]. This in vitro study also demonstrated that a recently identified adiponectin-interactive protein (disulfide-bond A oxidoreductase-like protein, DsbA-L) was a major player in RSV-mediated adiponectin multimerization and regulation of cellular levels. Other recently proposed mechanisms for improved insulin sensitivity by RSV in humans include decreased oxidative stress and activation of Akt-mediated insulin signaling [56]. Taken together, RSV is a promising dietary bioactive compound that can be easily incorporated in the diet to control adipose tissue inflammation and obesity-associated metabolic disorders.

## 7. Tea polyphenols

All teas (white, green and black tea) are derived from the leaves of *Camellia sinensis*, but different processing methods produce different types of tea. Fresh tea leaves are rich in catechins. When tea leaves are intentionally broken or rolled during processing, contact with the enzyme polyphenol oxidase causes catechins to join together forming dimers and polymers known as theaflavins and thearubigins. The tea leaves which are allowed to oxidize completely before drying (most black teas) are rich in theaflavins and thearubigins, but are relatively low in monomeric catechins, such as epigallocatechin gallate (EGCG, found mostly in green and white teas) [57].

EGCG from green tea and theaflavins of black tea are the most studied bioactive compounds from tea. EGCG is the main polyphenolic compound in green tea and is claimed to have variety of bioactivities including anti-cancer, anti-obesity, anti-diabetic and anti-inflammatory activities [58,59]. Several mechanisms have been proposed to mediate EGCG's anti-adipogenic effects including activation of AMPK [60], and inactivation of forkhead box protein O1 (FoxO1) and sterol regulatory element-binding protein 1c (SREBP1c) [61]. Anti-inflammatory effects of EGCG such as suppression of resistin secretion from adipocytes are mediated via the ERK-dependant parthway [62]. The catechin-enhanced expression and secretion of adiponectin is mediated in part via suppression of Krüppel-like factor 7 (KLF7) protein, which inhibits the expression of adiponectin and other adipogenesis-related genes, including leptin, PPARγ, CCAAT/enhancer-binding protein α (C/EBPα), and adipocyte fatty acid-binding protein (aP2) in adipocytes [63].

Short-term EGCG treatment reverses pre-existing HF-induced metabolic pathologies in obese mice [64] and leads to reductions in body weight, plasma triglyceride and liver lipid content in HF diet-induced obesity [65]. Also, it has been reported that a green tea–caffeine mixture could improve weight maintenance through enhanced thermogenesis, fat oxidation, and sparing of fat free mass [66]. Further, Wang et al. reported that high level of catechin (886 mg/day) could improve the body composition by reducing abdominal fatness in moderately overweight human subjects [67].

Theaflavins are the major bioactive compounds in black tea which are produced by the postharvest fermentation of tea leaf catechins. Theaflavins are also claimed to have numerous health benefits including lipid and cholesterol lowering, as well as anti-cancer, anti-diabetic, and anti-inflammatory effects [54]. Theaflavins were also reported to suppress insulin-induced glucose uptake in MC3T3-G2/PA6 adipocytes [59]. Direct evidence, however, is missing with regard to potential anti-inflammatory in vivo effects of theaflavins in adipose tissue inflammation and insulin resistance, thereby meriting further investigation in this area.

## 8. Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is one of the most widely available dietary flavonoids found in apples, grapes, berries, onions, teas, red wines, citrus, garlic, parsley and many other foods; and thus can be easily incorporated with diet. It is a multifunctional, natural compound with diverse biological functions such as anti-obesity, anti-inflammatory, anti-atherogenic, hypolipidemic, anti-diabetic, anti-cancer, anti-hypertensive, anti-histamine and anti-oxidant activities [68,69].

Quercetin is readily bioavailable and it was reported that consumption of 100 g/day of berries (black currants, lingonberries and bilberries) for 8 weeks can increase the quercetin serum concentration by 32–51% as compared to the control group that consumed only habitual diets [70]. The serum concentrations of quercetin ranged between 21.4 and 25.3 μg/L in the berry group. Daily administration of quercetin reduced insulin resistance, dyslipidemia, and hypertension in rats [68]. Anti-inflammatory effects of quercetin are also reported for both adipocytes and macrophages and these activities are mediated by NF-κB associated mechanisms [71]. In particular, Overman et al. reported that quercetin may lower inflammation in adipose tissue by reducing the infiltration of macrophages and preventing infiltrated macrophage-mediated inflammation and insulin resistance in human adipocytes [71]. This study also showed that these effects were associated with quercetin-dependent suppression of NF-κB activation. Quercetin is known to decrease TNF-α-induced NF-κB transcriptional activity in primary human adipocytes and further attenuates the TNF-α-mediated suppression of PPARγ activity and PPARγ target genes [72]. Preliminary data from our laboratory also support anti-lipogenic and anti-inflammatory effects of quercetin in human pre-adipocytes. This is in-line with studies by Ahn et al. showing that quercetin can activate the AMPK signaling pathway in 3T3-L1 preadipocytes [73]. This study also reported that quercetin may limit fat accumulation by inducing apoptosis in mature adipocytes via ERK and c-jun-N-terminal kinase (JNK) pathways. Overall, the above studies support multiple beneficial effects of quercetin in improving obesity-associated inflammation and other related conditions.

## 9. Isoflavones

Isoflavones (ISO) are plant-derived phytochemicals also called “phytoestrogens”, which are a group of diphenolic compounds with estrogenic and antioxidant properties. Soy beans and soy products are well-known sources of isoflavones. In particular, genistein, daidzen and glycetin are three major soy ISOs, with genistein being the most abundant and most studied phytoestrogen in soy [74,75]. A number of factors affect the flavonoid content of foods, including agricultural practices, environmental factors, ripening, processing, storing, and cooking [76]. The amount of total isoflavones in 100g of variously processed soy products showed that soy drinks (7 mg), unsalted immature, soybeans immature, cooked, boiled, and drained (14 mg), iced soymilk (4 mg), soy sauce made from hydrolyzed vegetable protein (0.1 mg), and soybean chips (50 mg) had much lower amounts of isoflavones content as compared to soy flour (130–200 mg) and defatted raw soy meal (130 mg) [77].

Several lines of evidence point to beneficial roles of soy in health promotion and disease prevention, including hypocholesterolemic and hypotriglyceridemic effects, lowering of adiposity, insulin resistance and incidence of certain cancers and protective effects against symptoms of menopause and osteoporosis [74,75]. In 1999, FDA approved the claim that 25 g of soy protein per day (approx. 50 mg/d of ISO) may reduce the risk of heart disease. A cross-sectional study reported a significant inverse relation between genistein consumption and markers of the metabolic syndrome including weight, body mass index, waist circumference, and total body fat in human subjects consuming Western diets [78]. Further, several animal studies reported that soy ISOs and proteins, independent of food intake, improved the lipid and metabolic profile, decreased insulin secretion and prevented insulin resistance despite an 18-week-long HF diet feeding [79]. Similarly, Zhang et al. reported that doses of 150 mg and 450 mg/kg per day of ISO fed to obese rats significantly decreased adiposity and serum pro-inflammatory adipokine (IL-6, TNF-α, and resistin) levels, and increased anti-inflammatory adipokine (adiponectin) levels, suggesting that dietary soy ISOs improve insulin sensitivity and suppress adipose tissue inflammation [80,81]. Many studies report that soy improves inflammation in a variety of conditions. With regard to mechanisms for the metabolic effects of ISOs, estrogen and estrogen-like receptors (ERs) are obvious candidates because of the structural similarities between ISOs and steroid hormones. Estrogen receptors can also exhibit bidirectional crosstalk with PPARγ, a receptor intertwined with adipose development and function as well as insulin sensitivity [79,82]. Different potential mechanisms were proposed to explain anti-adipogenic effects of genistein including activation of Wnt signalling via ERs-dependent pathway [83], and inhibition of adipocyte differentiation leading to apoptosis of mature adipocytes via AMPK activation [60]. Anti-lipogenic effects of genistein supplementation include limiting adipocyte hypertrophy via up-regulation of genes involved in fatty acid β-oxidation, such as PPARα, AMPK and very long-chain acyl CoA dehydrogenase (VLCAD), as well as through the down-regulation of genes associated with adipogenesis or lipogenesis, including liver X receptor-α, SREBP1c, PPARγ, retinoid X receptor-α and acetyl CoA carboxylase (ACC) [84]. Therefore, isoflavones are a promising group of flavonoids that can reduce adipose tissue inflammation and thereby impart multiple benefits to human health.

## 10. Modulation of adipose tissue function by dietary fats

The amount and type of dietary fat in the diet are important factors influencing adipose tissue function as well as whole-body metabolism, with important health ramifications. Fatty acids are classified into three different groups based on their structure: viz. saturated, monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids. PUFAs are further classified into omega-3 and omega-6 groups, based on the position of the first double bond from the methyl end of the fatty acid. The structural dissimilarities of these fatty acids also give rise to functional differences, in terms of their effects on metabolism and inflammation. For example, saturated fatty acid intake is associated with increased cardiovascular disease risk, partly due to the pro-inflammatory actions of these fats. In contrast, omega-3 PUFAs have anti-inflammatory properties, and their intake is associated with reductions in cardiovascular disease risk. We and others have also shown that dietary fatty acids are important in modulating adipose tissue function and glucose-insulin homeostasis [85]. High saturated-fat intake induces obesity and adipose tissue inflammation in mice, while these effects can be partially reduced when these HF diets are energy-restricted [86]. Conversely, we have shown that dietary eicosapentaenoic acid [20:5 (n-3) – EPA] supplementation improves adipose tissue inflammation, independent of adipose tissue mass [85]. Taken together, this highlights the importance of fatty acids in modulating adipose tissue function.

In general, saturated fatty acids contribute to adipose tissue inflammation, possibly due to activation of TLR-2 and TLR-4, as well as activation of downstream pro-inflammatory signaling pathways including the NF-κB pathway [87]. In contrast, (n-3) PUFA, mainly EPA and docosahexaenoic acid [22:6 (n-3) – DHA] alleviate adipose tissue inflammation in several animal models of obesity [11]. Compared to n-6 PUFA such as arachidonic acid (AA), n-3 PUFA produce less inflammatory eicosanoids. Also, n-3 PUFA competitively reduce AA-mediated inflammatory eicosanoid (PGE2) formation. There is also evidence for anti-inflammatory actions of MUFA and *cis*-9,*trans*-11 conjugated linoleic acid (CLA), which will be reviewed in detail here (Fig. 1). Taken together, dietary sources that provide healthy fats at higher levels and replace unhealthy fats including saturated fats and n-6 PUFA may impart both long and short term health benefits.

## 11. (n-3) polyunsaturated fatty acids

Long-chain (n-3) PUFA of marine origin, namely EPA and DHA, have adiposity- dependent and independent effects on adipose tissue inflammation. The most common sources of EPA and DHA are fish oil supplements and fish such as anchovies, bluefish, herring, mackerel, mullet, sardines, salmon, sturgeon, tuna and trout. EPA and DHA consistently prevent high fat diet-induced excessive weight gain and adiposity in rodents [88]. Some human studies have also shown similar effects of EPA and DHA on improving adiposity [89]. Since loss of adipose mass leads to improvements in adipose tissue function, (n-3) PUFA-mediated improvements in adipose tissue inflammation can be partially attributed to its effects on reducing adiposity.

(n-3) PUFA reduce adiposity by several mechanisms. First, EPA and DHA activate AMPK, which in turn promotes fatty acid β-oxidation in adipose tissue [90] (Fig. 3). EPA and DHA are also known to promote mitochondrial biogenesis [85], which potentially contributes to increased energy metabolism. In addition to the adipose tissue, EPA and DHA also increase fatty acid oxidation in the liver [91] and small intestine in rodents in vivo [92]. In vitro studies also support these findings. Finally, EPA and DHA inhibit hepatic lipogenesis in a PPARα and AMPK-dependent manner [93]. These EPA- and DHA-mediated increases in fatty acid oxidation and reduction in lipogenesis could be responsible for their anti-obesity effects.

In addition to EPA and DHA's adiposity-dependent effects on improving adipose tissue function, these fatty acids also have direct anti-inflammatory effects. We have shown that EPA reduces insulin resistance and ameliorates adipose tissue inflammation (even when body and fat mass are not changed in HF diet-induced obese mice) [85]. These improvements in adipokine profile are characterized by increases in anti-inflammatory adipokines such as adiponectin and decreases in proinflammatory cytokines such as TNFα, IL-6, MCP-1 and PAI-1. EPA and DHA's effect on normalizing plasma adiponectin levels appears to be largely responsible for their insulin sensitizing effect. This favorable effect on adiponectin secretion seems to be PPARγ-dependent, because fish oil fails to increase plasma adiponectin in PPARγ-null mice [94] (Fig. 3).

There are several other contributing mechanisms by which EPA and DHA impart anti-inflammatory actions on adipose tissue. These include activation of PPARγ and G-protein coupled receptor (GPR)-120, secretion of resolvins and protectins and inhibition of AA-mediated increases of pro-inflammatory eicosanoids (Fig. 3). EPA and DHA act as ligands for GPR120 and 40. In macrophages, activation of GPR120 leads to inhibition of the NF-κB pathway [95]. More specifically, activation of the NF-κB and JNK are dependent upon activation of TGF-β activated kinase (TAK)-1, which in turn is activated by its association with TAK-1 binding protein (TAB)-1. EPA and DHA bind to GPR120, which leads to internalization of the

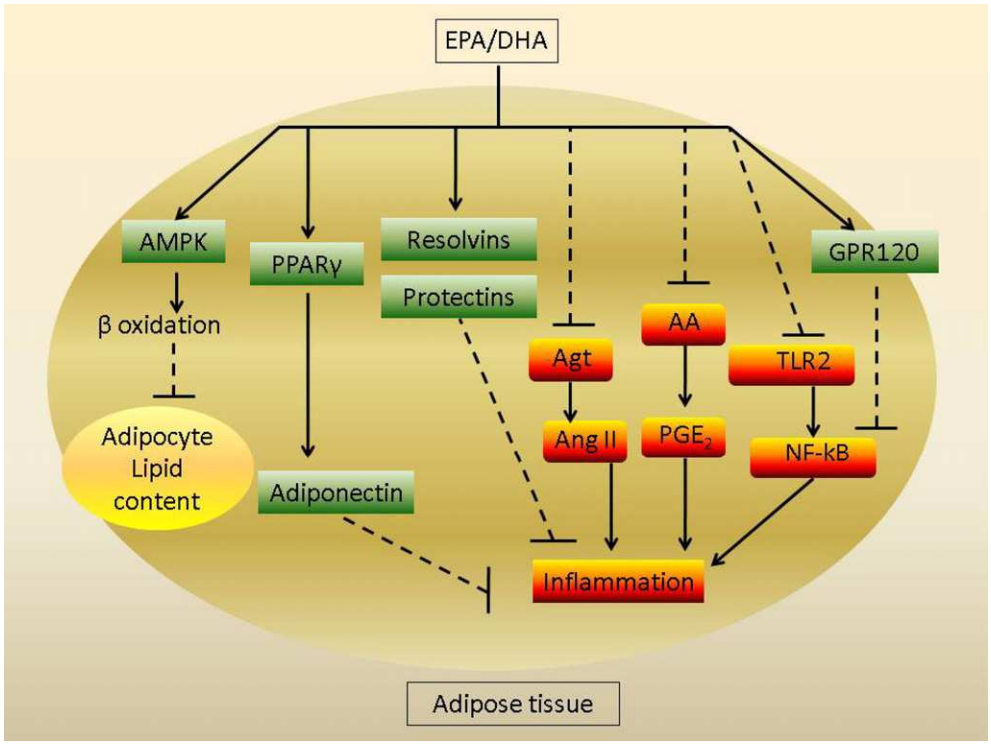


Fig. 3. Mechanisms by which EPA and DHA alleviate adipose tissue inflammation. EPA/DHA increase fatty acid oxidation in an AMPK-dependent manner, leading to adipocyte hypotrophy. Other mechanisms include PPARγ-mediated increases in adiponectin production, resolvin and protectin-mediated resolution of inflammation, antagonism of AA-dependent increases in pro-inflammatory eicosanoids production and GPR120-mediated inhibition of the NF-κB pathway.

receptor-ligand complex along with β-arrestin2. This prevents TAB-1 from associating with TAK-1; thereby preventing the latter's activation and subsequent stimulation of the NF-κB and JNK signaling cascades. The importance of GPR120 in mediating EPA and DHA's anti-inflammatory effects are highlighted by the finding that these fatty acids' beneficial effects on insulin sensitivity and adipose tissue function are absent in mice lacking GPR120 [95]. Other than in macrophages, EPA and EDA also inhibit the NF-κB pathway in other adipose tissue cell types such as adipose stem cells [96].

Adipocytes secrete eicosanoids such as prostaglandins, which have pro-inflammatory actions. AA-derived eicosanoids such as $PGE_2$ and thromboxane A2 have a higher inflammatory activity than EPA-derived ones. Since EPA competes with AA for incorporation into cell membranes, it is possible that increased dietary EPA intake reduces production of AA-derived eicosanoids. Indeed, we have previously shown that EPA prevents AA-induced secretion of $PGE_2$ from 3T3-L1 adipocytes in vitro [97]. This is potentially another mechanism by which EPA alleviates adipose tissue inflammation.

While the onset and progression of inflammation is dependent upon immune cells and pro-inflammatory mediators, current evidence suggests that resolution of inflammation is a similarly active process. EPA and DHA-derived resolvins and protectins are key examples of such inflammation resolution agonists [98]. Studies involving treatment with resolvins or transgenic restoration of protectins prevented adipose tissue macrophage infiltration and improved insulin resistance in rodents [99,100]. Production of these mediators could be another mechanism by which EPA and DHA improve adipose tissue inflammation (Fig. 3).

## 12. Monounsaturated fatty acids

While the most popular MUFA source is olive oil, several fruits and nuts, specially avocados, almond, cashews, peanuts, pecans and dark chocolate, are also rich sources. Several clinical studies have shown that MUFAs, mainly oleic acid [18:1 (n-9)], favorably affect adiposity and improve insulin sensitivity in obese, insulin resistant individuals [101,102]. In rodents, MUFAs prevent HF diet-induced excessive adiposity, compared to high-(n-6) PUFA diets [103]. MUFA also prevent the HF diet-induced adipose tissue infiltration of M1 macrophages and CD8(+) T cells in rodents [103]. Moreover, MUFAs reduce secretion of proinflammatory cytokines from adipocytes. For example, adipocytes isolated from rats fed a high-MUFA diet exhibit lower IL-6 secretion compared to high saturated or PUFA-fed ones [104]. Oleic acid also decreases resistin gene expression while increasing the adiponectin gene expression in 3T3-L1 adipocytes [105].

While there appears to be direct anti-inflammatory actions of MUFAs, the major benefit of these fatty acids appear to be due to their replacement of saturated fatty acids from the diet. Indeed, diets high in MUFA with a high PUFA to saturated fatty acid (P/S) ratio prevent excessive adiposity in rodents compared to diets low in MUFA with a low P/S ratio [106]. Moreover, in individuals with abdominal obesity, adipose tissue inflammation is induced by high-saturated, but not high-MUFA diets [107]. In post-menopausal women with type-2 diabetes, supplementation with safflower oil (high MUFA), induces truncal fat loss and improvements in blood glucose and adiponectin levels [108]. Since high MUFA diets reduce expression of lipoprotein lipase (LPL) and increase phosphorylation of hormone-sensitive lipase (HSL), the mechanism of MUFA-mediated anti-obesity effects appear to be related to decreasing lipid storage and increasing lipolysis in the adipose tissue [106,109,110]. MUFA also suppress the lipogenic transcription factor SREBP1c in adipose tissue [111].

While there is strong evidence to support the beneficial effects of MUFA on adipose tissue function and insulin sensitivity, the exact mechanisms responsible for these effects have not been explored in detail and warrants further study.

## 13. Conjugated linoleic acid

Conjugated linoleic acid (CLA) belongs to a class of dienoic derivatives of linoleic acid, which is found primarily in beef and dairy products. There are two main isomers — *cis*-9,*trans*-11-CLA and *trans*-10,*cis*-12-CLA, with divergent effects on lipid and glucose metabolism [112]. Both forms of CLA induce rapid reductions in body and fat pad weight in rodents [113,114] and pigs [115]. In humans, CLA only produces a modest degree of weight loss in both adults [116] and children [117]. Recently, conjugated nonadecadienoic acid (CNA, 19-carbon conjugated fatty acid) was shown to have better anti-obesity effects than CLA [118]. Polyethylene glycolylated CLA also has better efficacy and improves insulin resistance in HF-fed ob/ob mice [119]. While the exact mechanism of CLA's anti-obesity effects are hitherto unknown, some studies suggest that these effects may be related to increased fatty acid oxidation [120] and energy expenditure [121]. Indeed, CLA increases adipose carnitine palmitoyltransferase 1b (CPT1b), peroxisome proliferator activated receptor gamma coactivator (PGC1α) and uncoupling protein 1 (UCP1) expression in ob/ob mice [122]. Other studies showing that CLA reduces LPL expression suggests that this may be related to lower lipid deposition in adipose tissue [123]. Finally, some studies suggest that CLA increases lipolysis and apoptosis in adipocytes [124–126].

Evidence for anti-inflammatory effects of CLA is, however, inconsistent, with some studies showing beneficial effects, while others showing no change or detrimental effects despite promoting adipocyte hypotrophy [127]. It is likely that that the effects of CLA on inflammation are isomer-dependent. *cis*-9, *trans*-11-CLA reduces adipose tissue inflammation in ob/ob mice [128], whereas *trans*-10, *cis*-12-CLA reduces adiposity without improving [129] or worsening insulin resistance and adipose tissue inflammation [130] in rodents. Mixtures of CLA are also known to reduce plasma adiponectin levels, adversely affecting insulin sensitivity [131]. Moreover, the *trans*-10, *cis*-12-CLA induces IL-6 production from human adipocytes in vitro, in an NF-κB dependent manner [132].

Human studies also show that reduction in body weight with CLA, especially with the *trans*-10,*cis*-12 isomer, is associated with reduction in insulin sensitivity [133], increased inflammatory markers [134,135] and increases in low-density lipoprotein (LDL): high-density lipoprotein (HDL) cholesterol ratios [136]. This is a paradoxical finding because reductions in weight and adipose tissue mass are typically associated with improvements in insulin sensitivity. Some researchers have compared the CLA-induced loss of adiposity to lipodystrophy [126], a condition with defective adipogenesis associated with severe insulin resistance. Indeed, adipose tissue is required for storage of lipids, and the absence of it promotes deposition of fat in other organs like liver and skeletal muscle leading to insulin resistance of these organs. Even in obesity, the onset of insulin resistance is linked to an inadequate adipogenic capacity of the adipose tissue [137]. Therefore, the CLA-induced reduced adiposity is likely to lead to worsening in insulin resistance by similar mechanisms. For example, *trans*-10,*cis*-12 CLA inhibits differentiation of 3T3-L1 preadipocytes [138], reduces the expression of adipogeneic genes as well as adipocyte precursor cell numbers in subcutaneous adipose tissue, while increasing intramuscular lipid accumulation [139]. CLA rich diets also induce hepatomegaly and increase hepatic triglyceride content in rodents [140].

While there is evidence for beneficial effects of CLA on adiposity, adverse effects of this fatty acid, specially the *trans*-10,*cis*-12 isomer, on glucose homeostasis need further investigation.

## 14. Combined effects of dietary polyphenols and fatty acids

Human diet contains multiple types of bioactive compounds including different fatty acids and flavonoids. Some of those compounds are known to have synergistic affects with other dietary compounds. Therefore, when a diet is rich with potentially beneficial multifunctional bioactive compounds, the probability to have added/synergistic benefits are higher compared to diets with only few compounds. While most studies have focused on studying the effects of individual polyphenols, these phytochemicals are typically consumed simultaneously from various food sources; therefore, it is much more relevant to investigate their combined effects. However, very few studies have actually addressed how combinations of these compounds effect adipose tissue function, especially from whole foods sources [141–143]. Park et al. showed that lower concentrations of combined treatments with genistein, quercetin and resveratrol triggered adipose tissue remodeling through suppression of adipogenesis and enhanced adipocyte apoptosis [144].

Recent studies have also tested combinations of fats and polyphenols to improve the shelf life of the fatty acids as well as to increase the beneficial health effects by combined effects of fats and polyphenols [145,146]. For example, extra-virgin olive oil (olive oil not subjected to refining process) exerts health benefits, not only due to the oleic acid content but also due to its high level of naturally occurring phenolic compounds [147–149]. Human clinical studies directly suggest that olive oil with elevated levels of polyphenols enhances the health benefits [150]. Moreover, a review by Watkins et al. proposed that n-3 PUFA and flavonoids combined therapies could decrease environmental pollutant-induced inflammation [151]. Furthermore, in a study by Nakagawa et al., EPA at 210 μM combined with genistein at 93 μM was more efficient than either EPA (600 μM) or genistein (176 μM) alone [152]. Additionally, combined CLA and ISO proved beneficial for reducing adiposity, and soy protein further enhanced the body fat reducing effects of CLA, which was not observed with casein as a protein source. The synergistic effects of CLA and soy were however partially reversed in the presence of HF diets, again emphasizing the importance of promoting functional foods as part of a healthy balanced low fat diet [153,154].

Taken together, obesity-associated inflammation which can cause a variety of human diseases can be overcome by dietary polyphenolic compounds and fatty acids described above. Mechanistically, those compounds act via single or multiple mechanisms involving NF-κB, MAPK, JNK, AMPK, TLRs, PPARγ, protein kinase B (PKB/AKT) and ERK. However, in order to achieve the desired benefits, it is important to maintain optimum levels of those bioactive compounds in the body. Frequent consumption of fish, fruits and vegetables rich in those compounds as well as carefully selected supplements can fulfill these requirements. When taking medicines for certain diseases, it is important to consider proper medical advises before taking supplements or increasing certain bioactive compounds in the diet to avoid undesirable interactions.

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