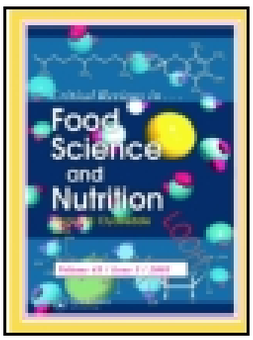

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Dan Li, Tian Zhang, Jinjian Lu, Cheng Peng & Ligen Lin (2020): Natural constituents from food sources as therapeutic agents for obesity and metabolic diseases targeting adipose tissue inflammation, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1768044

To link to this article: https://doi.org/10.1080/10408398.2020.1768044

Published online: 28 May 2020.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1768044

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REVIEW

Natural constituents from food sources as therapeutic agents for obesity and metabolic diseases targeting adipose tissue inflammation

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ABSTRACT

Adipose tissue, an endocrine and paracrine organ, plays critical roles in the regulation of whole-body metabolic homeostasis. Obesity is accompanied with a chronic low-grade inflammation status in adipose tissue, which disrupts its endocrine function and results in metabolic derangements, such as type 2 diabetes. Dietary bioactive components, such as flavonoids, polyphenols and unsaturated fatty acids from fruits and vegetables, have been widely revealed to alleviate both systemic and adipose tissue inflammation, and improve metabolic disorders. Remarkably, some dietary bioactive components mitigate the inflammatory response in adipocytes, macrophages, and other immune cells, and modulate the crosstalk between adipocytes and macrophages or other immune cells, in adipose tissue. Epidemiological and preclinical studies related to these substances have indicated beneficial effects on adipose tissue inflammation. The main purpose of this review is to provide a comprehensive and up-to-date state of knowledge on dietary components targeting adipose tissue inflammation and their underlying mechanisms. These natural products have great potential to be developed as functional food or lead compounds for treating and/or preventing metabolic disorders.

KEYWORDS

Adipose tissue inflammation; metabolic disease; macrophages; adipocytes; crosstalk; dietary bioactive nutrients

Introduction

For both children and adults, the prevalence of overweight and obesity has been increasing at an alarming rate in the past several decades worldwide (Jaacks et al. 2019). The incidence of obesity-related complications, such as type 2 diabetes (T2D) (Donmez and Guarente 2010), atherosclerosis (Karakelides et al. 2010), and several forms of cancer (Evans and Goldfine 2013), has also increased to new historically high levels. Obesity is characterized as fat mass expansion, occurred via adipocytes hyperplasia (increased number of adipocytes) and/or hypertrophy (increased size of adipocytes). Under positive energy conditions, pre-adipocytes proliferate and differentiate into adipocytes (hyperplasia), and excessive lipid accumulates within adipocytes in the form of triglycerides (TG, hypertrophy). Adipocytes hypertrophy is more often observed in adipose tissue from both obese human and animals, and is highly related to increased angiogenesis (Gealekman et al. 2008), production of extracellular matrix components (Henegar et al. 2008), activated endothelial cells, macrophage infiltration (Bourlier et al. 2008; Lumeng, Bodzin and Saltiel 2007), and production of inflammatory mediators (Barzilai et al. 2012; Mueller et al. 2017), which are termed as adipose tissue remodeling.

The low-grade chronic inflammation plays a key role linking obesity to insulin resistance (IR) and metabolic syndrome, and is a common feature of these complications that appears to emanate from adipose tissue (Barzilai et al. 2012). Under lean status, adipose tissue-resident immune cells actively secrete pro- and anti-inflammatory cytokines and maintain insulin sensitivity (Chawla, Nguyen and Goh 2011; Huh et al. 2014). Under positive energy status, adipose tissue secretes more pro-inflammatory cytokines, which lead to IR and stimulate lipolysis in adipocytes, resulting in lipotoxicity in other tissues (Chawla, Nguyen and Goh 2011). Inflammatory responses are primarily initiated in adipose tissues and chronic inflammation of adipose tissues subsequently induces systemic inflammation in other metabolic organs, such as the liver, skeletal muscle, and pancreas (Lee et al. 2011). Therefore, adipose tissue inflammation is a causal factor for widespread obesity-related metabolic syndrome, and amelioration of adipose tissue inflammation is a potential therapeutic strategy for the treatment of obesity and related metabolic diseases.

Adipose tissue contributes to endocrine regulation and inflammatory responses

Adipose tissue is not only a passive reservoir to store and release energy when nutrient overflow or deficiency, but also an endocrine organ to produce and secrete a variety of

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adipokines and cytokines (Kershaw and Flier 2004). Adipokines are polypeptides secreted from the adipose tissue, including adiponectin, leptin, resistin, adipsin, acylation stimulating protein (ASP), plasminogen activator inhibitor-1 (PAI-1) and proteins of the renin angiotensin system, which coordinately contribute toward energy metabolism, immune responses and vascular homeostasis, as well as inflammatory responses (Kershaw and Flier 2004). Thus, regulation of adipokines is a potential way to treat autoimmune diseases, obesity, IR, and adipose tissue inflammation (Shoelson, Lee and Goldfine 2006).

Besides adipocytes and preadipocytes, adipose tissue contains connective tissue matrix, nerve tissue, and stromal vascular fraction (SVF), all of which maintain the integrity of adipose tissue (Frayn et al. 2003). Macrophages, the major immune cells in adipose tissue, have various functions including scavenging cellular debris derived from apoptotic adipocytes, regulating angiogenesis, and remodeling the extracellular matrix (Chawla, Nguyen and Goh 2011). The proportion of macrophages increases from 10–15% of SVF in visceral adipose tissue of lean subjects to 40–50% of SVF in the corresponding fat pad from obese objects (Weisberg et al. 2003). More and more evidence has suggested that adipose tissue macrophages (ATMs) are a major pathogenic factor for metabolic diseases (Lumeng et al. 2007; Wellen and Hotamisligil 2003; Xu et al. 2003). ATMs consist of two subsets: pro-inflammatory M1 type (classically activated macrophages) and anti-inflammatory M2 type (alternatively activated macrophages). In the lean subjects, M2 macrophages are the predominant ATMs, which express high levels of the mannose receptor (CD206), arginase-1 (Arg-1) and CD301, and secrete anti-inflammatory cytokines including interleukin-10 (IL-10) and IL-1 receptor antagonist (IL-1Ra) (Lumeng, Bodzin and Saltiel 2007). On the contrary, M1 macrophages are increased in adipose tissue from obese subjects, which highly express CD11c and secrete pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), IL-1β, IL-6, IL-12, and monocyte chemotactic protein-1 (MCP-1). Therefore, the imbalance of pro-inflammatory and anti-inflammatory macrophages, as well as cytokines levels, is potentially associated with IR and dyslipidemia in obesity (Lumeng, Bodzin and Saltiel 2007). The major population of M1 macrophages in adipose tissue is derived from circulating monocytes (Lumeng, Bodzin and Saltiel 2007), and the proliferation of local macrophages also contributes to increased adipose tissue inflammation (Amano et al. 2014). Thus, ATMs have central roles in the inflammatory and immune responses in adipose tissue.

The adipokines and cytokines secreted from adipocytes and macrophages activate cell surface receptors including TNF receptor (TNFR), IL-1 receptor (IL-1R), toll like receptor (TLR), and receptor for advanced glycation end products (RAGE), which subsequently activate mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) pathways (Akira, Uematsu and Takeuchi 2006). In addition, cellular stresses, including endoplasmic reticulum (ER) and oxidative stress, activate inflammatory signaling in adipose tissue (Keaney et al. 2003). These molecular mechanisms responsible for adipose tissue inflammation might be therapeutic targets in combating obesity and metabolic disorders.

Lots of constituents from foods have therapeutic effects toward adipose tissue inflammation. A variety of food derived compounds and extracts exhibit potential for treating obesity and metabolic diseases. To organize this review, the relevant compounds and extracts were classified into four groups, including regulators of interaction between macrophages and adipocytes, regulators of interaction between adipocytes and other immune cells, blockers of pattern recognition receptors, and intracellular stresses releasers. This review summarized the recent research progresses in dietary constituents targeting adipose tissue inflammation, and speculated their potential as therapeutic agents for the treatment of obesity and related metabolic diseases.

Regulators of interaction between adipocytes and macrophages

Overnutrition initiates the inflammatory cascade and induces adipose tissue to secrete various adipokines and cytokines (Pacifico et al. 2006). Visceral and subcutaneous adipose tissues produce unique profiles of adipokines and cytokines to mediate inflammatory responses and IR in obese rodents and humans (Kwon and Pessin 2013). The pro-inflammatory adipokines and cytokines produced by adipose tissue include leptin, resistin, IL-1β, IL-2, IL-6, IL-8, IL-18, TNF-α, MCP-1 and PAI-1 (Ouchi et al. 2011). Some of these molecules are produced by adipocytes such as leptin, resistin, and PAI-1, while pro-inflammatory M1 macrophages and other components of SVF contribute to the expression of other inflammatory cytokines such as IL-6, TNF-α, and MCP-1 (Kwon and Pessin 2013). Lean adipose tissue preferentially secretes anti-inflammatory adipokines and cytokines such as adiponectin, transforming growth factor β (TGF-β), secreted frizzled-related protein 5 (SFRP5), visceral adipose tissue-derived serine protease inhibitor (VASPIN), omentin-1, apelin, IL-1Ra, IL-10, IL-4 and IL-13 (Fantuzzi 2005; Kwon and Pessin 2013; Makki, Froguel and Wolowczuk 2013). In obese rodents and humans, the levels of pro-inflammatory adipokines are increased (Kwon and Pessin 2013). However, this phenotypic switching model is under debate because of the recent two papers on the role of IL-10 and TGF-β derived from M2 macrophages, showing deletion of IL-10 and TGF-β, respectively, in M2 macrophages resulted in increased insulin sensitivity (Nawaz et al. 2017; Rajbhandari et al. 2018).

The secretion pattern of these molecules in expanded adipose tissue plays the detrimental role on the course of obesity and the related complications (Wu et al. 2007). Cytokines and chemokines influence local as well as systemic inflammation and are therefore critical contributors to the pathogenesis of T2D. Cytokines that modulate inflammatory responses are emerging as potential targets for intervention and treatment of the metabolic consequences of obesity (Ballak et al. 2015). Therefore, suppressors of the pro-inflammatory cytokines and inducers of the anti-inflammatory cytokines are potential therapeutic agents for

improving adipose tissue inflammation and combating obesity.

Macrophages are innate immune cells resident in every tissue in the body, where they participate in a variety of homeostatic functions in addition to host defense. The adipose tissue is a site of low-grade chronic inflammation in obese subjects, evidenced by immune cells accumulation, mainly macrophages, which constituting almost 50% of total immune cells (Weisberg et al. 2003), and polarization toward pro-inflammatory phenotype. The macrophages in adipose tissue are bone marrow-derived and their number is strongly correlated with body weight, body mass index and total body fat. The infiltration of macrophages in the adipose tissue precede the development of IR in animal models and obese patients, suggesting that they are crucial for the inflammatory changes of adipose tissue (Itoh et al. 2011). Pro-inflammatory factors produced by macrophages alter adipocytes biology and contribute to the severity of metabolic complications, including IR (Lumeng, Bodzin and Saltiel 2007). Investigating the role of macrophages in adipose tissue biology and the mechanisms involved in their recruitment and activation in obesity will provide useful insights for developing therapeutic approaches to treating obesity-induced complications. The intervention of reducing macrophage accumulation and pro-inflammatory polarization may improve IR and obesity-related metabolic disorders.

The diet derived regulators of interaction between adipocytes and macrophages were summarized in Table 1.

Flavonoids and polyphenols

Luteolin (3′,4′,5′,7′-tetrahydroxyflavone, Figure 1) is a flavone widely distributed in a variety of vegetables, fruits and herbs, such as tea (Theaceae), cabbage (Brassicaceae), apple (Rosaceae), carrot (Apiaceae), artichoke (Asteraceae) and celery (Apiaceae). Lots of basic and clinical studies have strongly suggested the anti-inflammatory property of luteolin (Aziz, Kim and Cho 2018). Luteolin supplementation results in a decrease of $CD11c^{+}$ macrophages in gonadal adipose tissue, as well as a trend of decreased macrophage infiltration and decreased mRNA expression of M1 macrophage markers such as MCP-1, CD11c, TNF-α, and IL-6, to protect mice from high fat diet (HFD)-induced IR (Baek et al. 2019). It suggested that luteolin alleviates adipose tissue inflammation under positive energy status.

Naringenin (Figure 1) is a naturally occurring citrus flavanone predominantly found in grape (Vitaceae), orange (Rutaceae) and tomato (Solanaceae). Naringenin reduces Mac-2 positive cells and suppresses MCP-1 expression in adipose tissue from short-term (14 days) HFD feeding mice, which is partly mediated through inhibiting c-Jun N-terminal kinases (JNK) pathway (Yoshida et al. 2014). Moreover, naringenin inhibits MCP-1 expression in adipocytes, macrophages, and co-culture of adipocytes and macrophages (Yoshida et al. 2014). In ovariectomy-associated metabolic disturbance mice, naringenin treatment reduces intraabdominal and subcutaneous adiposity, decreases the fasting plasma leptin level and the mRNA expression of leptin, MCP-1 and IL-6 in perigonadal adipose tissue, and suppresses the leptin gene expression in subcutaneous adipose tissue (Ke et al. 2015). In another study, naringenin was reported to reduce inflammatory cytokines, including MCP-1 and IL-6, in mammary and perigonadal adipose tissues from HFD-fed ovariectomized mice (Ke et al. 2017). Hesperetin and naringenin are flavanones derived from *Citrus aurantium* L. The co-treatment of these two compounds suppresses the transcription of IL-6 through inhibiting NF-κB pathway in TNF-α-stimulated 3T3-L1 adipocytes (Yoshida et al. 2010). These two compounds were also reported to enhance the mRNA expression of adiponectin and peroxisome proliferator-activated receptor γ (PPARγ) in mature adipocytes (Liu et al. 2008). Thus, naringenin, as well as its analogue hesperetin, might regulate the interaction of adipocytes and macrophages to attenuate inflammatory responses in obese objects.

Quercetin is widely distributed in plants with abundant amount, such as apple, berry, grape, onion, shallot, tomato and tea (Figure 1). Quercetin is also found in many herbal medicines and is responsible for their therapeutic effects. The anti-inflammatory potential of quercetin has been proved in both animal and human models (Li, Yao, et al. 2016). Quercetin was found to decrease the release of macrophage inflammatory protein-1α (MIP-1α) from adipocytes, macrophages, and co-cultured adipocytes and macrophages; intriguingly, quercetin mitigates MIP-1α-induced macrophage infiltration and activation, through the downregulation of C-C motif receptor 1 (CCR1)/CCR5, and the inactivation of JNK, p38 and IKK (Noh et al. 2014). Catechin and quercetin are flavonoids existing in tea, red wine, and cocoa. Dietary supplementation with catechin, quercetin or the combination improves adipose tissue inflammation by attenuating the cytokines expression (TNF-α, MCP-1 and resistin), which is partly associated with its capacity to inactivate MAPKs, upregulate PPARγ expression and increase the adiponectin expression in epididymal white adipose tissue (eWAT) from high fructose fed rats (Prieto et al. 2015). The catechin, quercetin or the combination promotes adiponectin secretion and decreases pro-inflammatory cytokine expression (MCP-1 and resistin) in TNF-α-induced 3T3-L1 adipocytes (Prieto et al. 2015). In HFD-fed mice, the treatment with quercetin, hesperetin and anthocyanins reduces the serum leptin level (Hoek-van den Hil et al. 2015). Quercetin is a safe and effective dietary supplement based on previous studies. However, further evaluation, especially clinical trials, is needed to verify its role in ameliorating adipose tissue inflammation.

The flavan-3-ol (–)-epicatechin (EC, Figure 1) is widely present in the human diets, particularly in berries, grape, cocoa and tea. In palmitic acid-treated 3T3-L1 adipocytes, EC reduces the levels of TNF-α, IL-6 and MCP-1, and increases adiponectin production (Bettaieb et al. 2016). EC supplementation mitigates the expression of macrophage markers F4/80, TNF-α, and MCP-1 in visceral white adipose tissue (vWAT) from HFD-fed mice, through suppressing NF-κB pathway (Bettaieb et al. 2016). In another study, EC

Table 1. Regulators of interaction between adipocytes and macrophages.

compound	Dosage	Model	Index	Ref
Luteolin	0.005% in HFD	gonadal adipose tissue from HFD-fed ovariectomized C57BL/6 mice	↓$CD11c^+$ macrophages, ↓mRNA of MCP-1, CD11c, TNF-α and IL-6	(Baek et al. 2019)
Naringenin	100 mg/kg; 10 or 50 μM	adipose tissue from HFD-fed mice; adipocytes, macrophages, co-culture of adipocytes and macrophages	↓Mac-2 positive cells, ↓JNK; ↓MCP-1	(Yoshida et al. 2014)
	3% in control diet	perigonadal and subcutaneous WATs from ovariectomy-associated metabolic disturbance mice	↓leptin, ↓MCP-1, ↓IL-6	(Ke et al. 2015)
	1% or 3% in HFD	mammary and perigonadal WATs from obese ovariectomized mice	↓MCP-1, ↓IL-6	(Ke et al. 2017)
Hesperetin and naringenin	100 μM	TNF-α-stimulated 3T3-L1 adipocytes	↓IL-6, ↓NF-κB	(Yoshida et al. 2010)
	80 μM	mature adipocytes	↑adiponectin, ↑PPARγ	(Liu et al. 2008)
Quercetin	2 or 10 μM	adipocytes, macrophages and co-cultured adipocytes/ macrophages	↓MIP-1α, ↓CCR1/CCR5, ↓JNK, p38 and IKK	(Noh et al. 2014)
Catechin and quercetin	20 mg/kg; 1 or 10 μM	eWAT from fructose-fed rats; TNF-α-induced 3T3-L1 adipocytes	↓TNF-α, ↓MCP-1, ↓resistin, ↓MAPKs, ↓PPARγ, ↑adiponectin; ↓MCP-1, ↓resistin	(Prieto et al. 2015)
Quercetin, hesperetin and anthocyanins	0.33% quercetin, 0.33% hesperetin, 0.5% anthocyanins in HFD	serum from HFD-fed mice	↓leptin	(Hoek-van den Hil et al. 2015)
EC	0.1, 1 μM; 20 mg/kg	palmitate induced 3T3-L1 adipocytes; vWAT from HFD-fed mice	↓TNF-α, ↓IL-6, ↓MCP-1, ↑adiponectin; ↓F4/80, ↓TNF-α, ↓MCP-1, ↓NF-κB	(Bettaieb et al. 2016)
	50 μM; 200 mg/kg	adipocytes co-cultured with LPS-induced macrophages; WAT from HFD-fed mice	↓IL-6, ↓CCL19, ↓Rantes, ↓Ip-10, ↓Saa3, ↓Lbp, ↓Socs3; ↓TNF-α, ↓IL-6, ↓MCP-1, ↓Saa3;	(Sano et al. 2017)
GC-(4−>8)-GCG	10, 20 μg/ml; 40 or 80 mg/kg/day	TNF-α induced adipocytes; serum and eWAT from HFD-fed mice	↓IL-6, ↓COX-2; ↓MCP-1, ↓IL-6, ↓TNF-α, ↓F4/80, ↓CD11b, ↓NF-κB, ↓JAK, ↓STAT3, ↓MAPKs	(Peng et al. 2019)
Isoliquiritigenin,	1, 3 or 10 μM	palmitic acid-induced macrophages; TNF-α-induced adipocytes; LPS plus IFNγ-stimulated BMDMs	↓TNF-α, ↓JNK; ↓MCP-1, ↓IκBα; ↓iNOS, ↓TNF-α	(Watanabe et al. 2016)
	0.05% in HFD	eWAT from HFD-fed mice	↓TNF-α, ↓IL-6, ↓MCP-1, ↓$F4/80^+$ macrophages, ↓$F4/80^+/CD11c^+$ macrophages, ↓$F4/80^+/CD206^+$ macrophages	(Honda et al. 2014)
Butein	3, 10 or 30 μM	TLI-treated adipocytes	↓iNOS, ↓IL-6, ↓MCP-1, ↓Cxcl1, ↓Cxcl10; ↓MCP-1, ↓IL-6	(Wang et al. 2014)
	10 mg/kg	eWAT from HFD-fed mice	↓TNF-α, ↓IL-6, ↓MCP-1, ↑HO-1	(Wang et al. 2017)
Phlorizin	0.02% in HFD	serum and WAT from HFD-fed mice	↓MCP-1, ↓TNF-α, ↓IL-6, ↓IL-1β, ↓F4/80, ↓CD11c, ↑CD206	(Tian et al. 2017)
Resveratrol	50 μM	hypoxia-induced human adipocytes	↓IL8, ↓IL6, ↓leptin	(Cullberg et al. 2013)
	10, 50, 100 μM	human inflamed adipose tissue	↓PAI-1	(Zagotta et al. 2013)
	0.01% in drinking water	visceral fat from sleep-fragmentation-induced mice	↓leptin, ↓TNF-α, ↓M1 macrophages, ↑M2 macrophages	(Carreras et al. 2015)
	480 mg/kg/day	eWAT from HFD-fed mice	↓TNF-α, ↓IL-1β	(Lv et al. 2015)
	80 and 480 mg/day for the first and second year, respectively	vWAT from HFHS-fed rhesus monkeys	↑SIRT1, ↓NF-κB	(Jimenez-Gomez et al. 2013)
Curcumin	2.5, 5, 10, 20 μM; 1% in HFD	LPS/IFNγ-induced RAW264.7 macrophages; adipocytes from HFD-fed rats	↓iNOS, ↓MCP-1, ↓IL-6, ↓TNF-α, ↓IL-1β, ↑KFL4, ↑PPARγ, ↑Arg-1, ↑IL-4	(Song et al. 2018)
Gingerenone A	10, 20, 40 μM; 10 or 50 mg/kg	co-culture of 3T3-L1 adipocytes and RAW264.7 macrophages; eWAT from HFD-fed mice	↓CCL2, ↓TNF-α; ↓CD68, ↓ITGAX, ↑MRC1	(Suk et al. 2017)
1,3,6,7-tetrahydroxy-8-prenylxanthone	5, 10, 20 μM; 20 mg/kg	LPS-induced macrophages; eWAT from LPS-induced mice	↓IL-6, ↓MCP-1, ↓IL-1β, ↓TNF-α, ↓iNOS, ↓COX2, ↓MIP-1α, ↓Cxcl10, ↓CCL11, ↓Cx3cl1, ↓F4/80, ↓CD11b, ↓CD11c	(Li et al. 2018)
α-Mangostin	10 mg/kg; 25 or 50 mg/kg	eWAT from LPS-induced mice; eWAT from aged mice	↓IL-6, ↓MCP-1, ↓IL-1β, ↓TNF-α, ↓MAPKs, ↓NF-κB, ↑SIRT3, ↓F4/80, ↓M1 macrophages	(Li et al. 2019)
Corosolic acid	10 mg/kg	adipose tissue from HFD-fed mice	↓IL-6, ↓MCP-1, ↓TNF-α, ↓CLSs, ↓Fizz1	(Yang et al. 2016)
Chikusetsu saponin IVa	50 or100 mg/kg			(Yuan et al. 2017)

(*continued*)

Table 1. Continued.

compound	Dosage	Model	Index	Ref
		eWAT from HFD-fed mice; *ex vivo* cultured adipocytes from eWAT	↓TNF-α, ↓MCP-1, ↓IL-6, ↓CCL-5, ↓Cxcl1, ↓Saa3, ↓IL-1β, ↓Caspase-1, ↓NLRP3, ↓NF-κB	
Lycopene	0.5, 1, 2 μM	LPS-mediated macrophages; macrophage CM-induced 3T3-L1 adipocytes	↓TNF-α; ↓IL-6, ↓IL-1β, ↓MCP-1, ↓Rantes, ↓Cxcl1, ↓Cxcl10, ↓JNK, ↓NF-κB	(Marcotorchino et al. 2012)
	10 mg/kg	eWAT from HFD-fed rats	↓leptin, ↓resistin, ↓IL-6, ↓MCP-1	(Luvizotto et al. 2013)
AX	0.02% in HFD	eWAT from HFD-fed mice	↓IL-6, ↓IL-1β, ↓TNF-α, ↓CD11c, ↓NLRP3	(Nishida et al. 2020)
Catalpol	100 mg/kg	eWAT from HFD-fed mice	↓TNF-α, ↓IL-6, ↓IL-1β, ↓MCP-1, ↓iNOS, ↓JNK, ↓NF-κB, ↑Arg-1, ↑Ym-1, ↑IL-10, ↑MGL1, ↑Clec7a, ↓F4/80, ↓CLSs	(Zhou et al. 2015)
Abscisic acid	12.5, 25, 50 μM; 100 mg/kg	3T3-L1 pre-adipocytes; WAT from HFD-fed *db/db* mice	↑PPARγ; ↑PPARγ, ↑adiponectin, ↑aP2, ↑CD36, ↓TNF-α	(Guri et al. 2007)
	100 mg/kg	WAT from HFD-fed *db/db* mice	↓MCP-1, ↓$CCR2^{+}$ $F4/80^{hi}$ ATMs	(Guri et al. 2008)
Stevioside	10 mg/kg, twice a day	WAT from HFD-fed mice	↓TNF-α, ↓IL6, ↓IL1β, ↓MIP-1α, ↓NF-κB, ↓CD11b, ↓CD14, ↓F4/80, ↓CD11b	(Wang et al. 2012)
Vitamin D	25(OH)D_3 (150 nM) or 1,25(OH)$_2$$D_3$ (1 nM)	LPS-induced fresh omental adipose tissue from women	↓TNF-α, ↓IL-6	(Roy et al. 2015)
	25000 IU/kg in diet	eWAT from HFD-fed mice	↓MCP-1, ↓Rantes, ↓IL-6, ↓IL-1β	(Park et al. 2019)
Berberine	100 mg/kg/d	vWAT from HFD-fed mice	↓IL-1β, ↓TNF-α, ↓JNK1, ↑adiponectin, ↓M1 macrophages	(Guo et al. 2016)
Caffeine	0.5, 5 or 50 μg/mL	human subcutaneous adipose tissue	↓TNF-α, ↓IL-6	(Dray et al. 2007)
Niacin	200 mg/kg/day for the first four weeks, 360 mg/kg/day for the fifth week	serum and eWAT from HFD-fed mice	↓MCP-1, ↓IL-1β, ↑adiponectin, ↓CD11c	(Wanders et al. 2013)
Capsaicin	0.015% in HFD	vWAT from HFD-fed KKAy mice	↑adiponectin, ↓MCP-1, ↓IL-6, ↓macrophages	(Kang et al. 2011)
	0.015% in HFD	WAT from HFD-fed mice	↑adiponectin	(Kang et al. 2010)
	0.075% in HFD	mesenteric WAT from HFD-fed mice	↑PPARα, ↑PPARγ, ↑visfatin, ↑adipsin, ↓TNF-α, ↓IL-6	(Lee et al. 2013b)
Methyl 2-(4′-methoxy-4′-oxobutanamide) benzoate	1, 10 μg/mL	LPS-induced RAW264.7 cells; 3T3-L1 adipocytes incubated with macrophage-CM	↓IL-1β, ↓IL-6, ↓TNF-α; ↓TNF-α, ↓IL-6, ↓IL-1β, ↓MCP-1, ↓Rantes	(Jung et al. 2016)
Indole-3-carbinol	40 mg/kg/day	eWAT from alcohol-induced mice	↓IL6, ↓MCP1, ↓CD11c	(Choi, Abdelmegeed and Song 2018)
Ononitol monohydrate	3.2 μM	3T3-L1 adipocytes	↓leptin, ↓C/EBPα, ↓LTB4R, ↑adiponectin	(Subash-Babu and Alshatwi 2018)
malaxinic acid	40 mg/kg	WAT from HFD-fed mice	↓F4/80, ↓CD68, ↓TNF-α, ↓ITGAX, ↓MCP-1, ↓IL-6	(Truong et al. 2019)
ALA-rich flaxseed oil	an ALA-rich flaxseed oil diet	adipose tissue from *fa/fa* Zucker rats	↓MCP-1, ↓TNF-α	(Baranowski et al. 2012)
DHA	50 μM	co-culture of macrophages and adipocytes	↑IL-10	(Oliver et al. 2012)
	4 mg/g	WAT from HFD-fed mice	↑IL-10, ↑Arg1, ↑CD206, ↑Ym1, ↑RELMα	(Titos et al. 2011)
17-HDHA	50 ng/g	gonadal adipose tissue from HFD-fed mice	↑adiponectin	(Neuhofer et al. 2013)
EPA	5% in HFHS diet	SVF and adipose tissue from HFHS-fed mice	↓IL-6, ↓TNF-α, ↓MCP-1, ↓CLSs, ↓CD11c, ↑CD206	(Yamada et al. 2017)
	EPA 36 g/kg HFD	eWAT from HFD-fed mice	↓adipocyte size, ↓galactin-3 positive cells	(LeMieux et al. 2015)
n − 3 PUFA	3.36 g/d	sWAT, vWAT and serum from severe obese non-diabetic patients	↓CCL2, ↓CCL3, ↓IL-6, ↑eicosanoids, ↓CD40	(Itariu et al. 2012)

was found to suppress the gene expression of inflammatory cytokines, including IL-6, CCL19, Rantes, Ip-10, Saa3, Lbp, and Socs3, in adipocytes co-cultured with lipopolysaccharides (LPS)-induced macrophages, and decrease the levels of TNF-α, IL-6, MCP-1, and Saa3 in adipose tissue from HFD-fed mice (Sano et al. 2017). Thus, EC shows great potential to attenuate adipose tissue inflammation.

Gallocatechin-(4→8)-gallocatechin-3-*O*-gallate [GC-(4→8)-GCG, Figure 1], is a proanthocyanidin dimer from *Camellia ptilophylla*. In TNF-α induced adipocytes, GC-(4→8)-GCG decreases the production of pro-inflammatory cytokines including IL-6 and COX-2. Moreover, GC-(4→8)-GCG reduces the levels of MCP-1, IL-6 and TNF-α in both serum and eWAT, and decreases the mRNA levels of F4/80 and CD11b in eWAT from HFD-fed mice, through inhibiting the activation of NF-κB, Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) and MAPK signaling pathways (Peng et al. 2019). Thus, GC-(4→8)-GCG possesses the ability to attenuate adipose tissue inflammation and reduce adiposity in HFD-fed mice.

Isoliquiritigenin (Figure 1), a chalcone derived from *Glycyrrhiza uralensis*, has emerged as a potential anti-

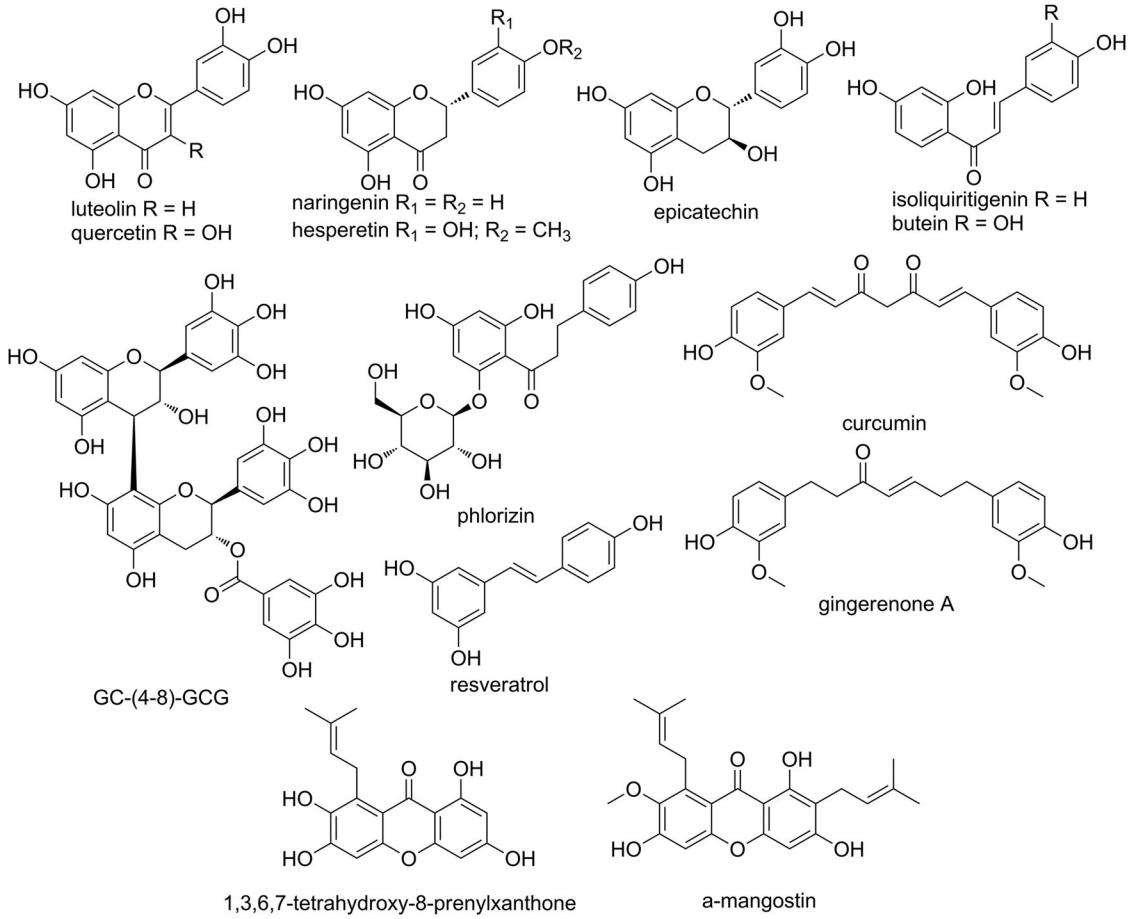

Figure 1. Structures of flavonoids and polyphenols that regulating the interaction between adipocytes and macrophages.

inflammatory agent. Isoliquiritigenin decreases bovine serum albumin (BSA)-palmitic acid-induced TNF-α mRNA expression and secretion in RAW264.7 macrophages through inhibiting JNK phosphorylation, suppresses TNF-α-induced MCP-1 mRNA expression and secretion from 3T3-L1 adipocytes, and inhibits TNF-α and MCP-1 mRNA levels in the co-culture of adipocytes and macrophages through inhibiting the phosphorylation of IκBα (Watanabe et al. 2016). Moreover, isoliquiritigenin strongly suppresses the expression of M1 macrophage markers, including inducible nitric oxide synthase (iNOS) and TNF-α, in LPS plus IFNγ-stimulated bone marrow-derived macrophages (BMDMs) (Watanabe et al. 2016). In another study, isoliquiritigenin treatment reverses the elevated gene expression of TNF-α, IL-6, and MCP-1 in eWAT from HFD-fed mice, and inhibits IL-1β production in *ex vivo* cultured adipocytes from HFD-fed mice (Honda et al. 2014). Additionally, the numbers of F4/80$^+$, F4/80$^+$/CD11c$^+$ (M1 macrophages) and F4/80$^+$/CD206$^+$ (M2 macrophages) in eWAT were reduced in isoliquiritigenin treated HFD-fed mice (Honda et al. 2014). These evidence indicates that isoliquiritigenin has great potential to alleviate adipose tissue inflammation.

Butein (Figure 1), a chalcone widely distributed in plants, inhibits mRNA expression of pro-inflammatory cytokines (iNOS and IL-6) and chemokines (MCP-1, Cxcl1, and Cxcl10) in adipocytes stimulated with TNF-α, LPS and IFNγ (TLI) or conditioned medium (CM) from RAW264.7 macrophages treated with LPS, and decreases the secretion of IL-6 and MCP-1 from TLI induced adipocytes through suppressing NF-κB and MAPKs signaling pathways (Wang et al. 2014). Interestingly, macrophages treated with butein exhibit a reduced migration ability toward adipocytes (Wang et al. 2014). In HFD-fed mice, butein treatment decreases the expression of TNF-α, IL-6, and MCP-1 in eWAT through activating heme oxygenase-1 (HO-1) expression (Wang et al. 2017).

Phlorizin (Figure 1) is a glucoside of phloretin, which is found primarily in unripe apple, and in strawberry with trace amounts. Dietary supplement of phlorizin reduces the pro-inflammation cytokines (MCP-1, TNF-α, IL-6, and IL-1β) in serum and adipose tissue from HFD-fed mice, through inhibiting JNK and NF-κB pathways (Tian et al. 2017). Short-term treatment with phlorizin suppresses the protein expression of macrophage maker F4/80 and M1 macrophage marker CD11c, while enhances the protein expression of M2 macrophage marker CD206 in adipose tissue from HFD-fed mice (Tian et al. 2017). Phlorizin might be a potential therapeutic agent for treating metabolic diseases associated with adipose tissue inflammation.

Resveratrol (Figure 1), a polyphenol widely distributed in red wine, peanuts and mulberries, exerts potent anti-inflammatory property. Resveratrol attenuates adipose tissue inflammation via inhibition of NF-κB and MAPKs pathways as well as activation of SIRT1 (Zhu et al. 2011). Resveratrol

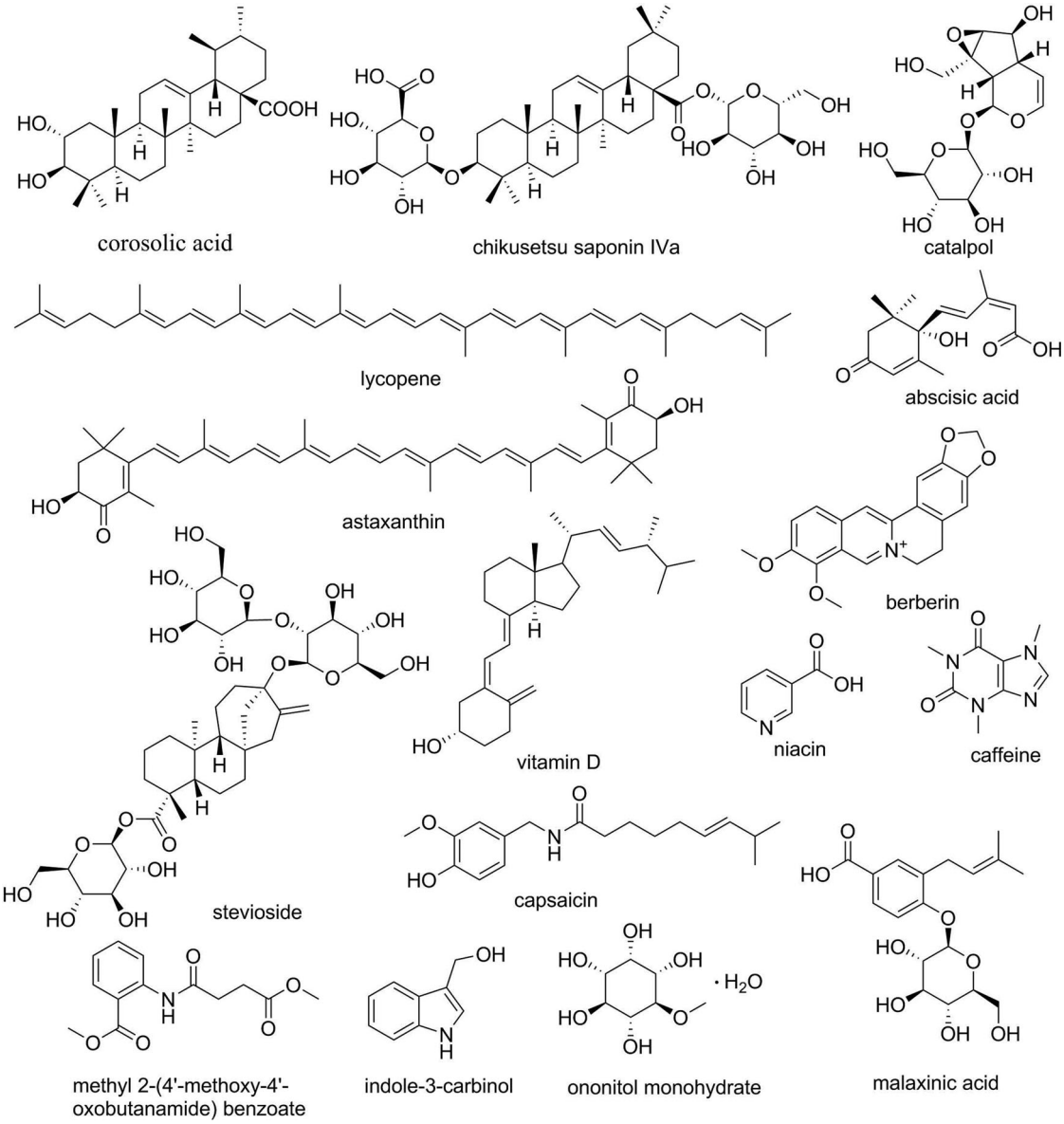

Figure 2. Structures of terpenoids, alkaloids and others that regulating the interaction between adipocytes and macrophages.

inhibits the expression of IL-8, IL-6 and leptin in hypoxia-induced human adipocytes (Cullberg et al. 2013). Resveratrol reduces PAI-1 mRNA expression in a model of human inflamed adipose tissue (Zagotta et al. 2013), decreases plasma leptin level and reduces the TNF-α release in macrophages isolated from visceral fat (Carreras et al. 2015), and decreases TNF-α and IL-1β mRNA levels in eWAT from HFD-fed mice (Lv et al. 2015), thereby providing a potential treatment option of vWAT inflammation. Administration of resveratrol decreases the pro-inflammatory M1 phenotype ($CD11c^+$) and increases M2 polarity ($CD206^+$) in vWAT from sleep apnea mice (Carreras et al. 2015). Resveratrol supplementation decreases adipocyte size, increases SIRT1 expression, decreases NF-κB activation, and improves insulin sensitivity in visceral, but not subcutaneous, WAT from high fat, high sugar (HFHS) diet-fed rhesus monkeys (Jimenez-Gomez et al. 2013). Resveratrol shows great potential to treat metabolic disease targeting adipose tissue inflammation.

Curcumin (Figure 1) is a diarylheptanoid from plants of the family Zingiberaceae, which is widely used as food flavoring, cosmetics ingredient and herbal supplement. Tons of evidence has indicated that curcumin inhibits a number of different molecules involving in inflammation, including phospholipase, lipooxygenase, COX2, MCP-1, TNF-α, and IL-12. Curcumin has been reported to reduce iNOS, MCP-1 and IL-6 expression in LPS/IFNγ-induced RAW264.7 macrophages and decrease MCP-1, IL-6, TNF-α and IL-1β expression in rat-derived adipocytes (Song et al. 2018). Interestingly, curcumin increases M2-like subtype macrophage markers (KFL4, PPARγ, and Arg-1), as well as the expression of anti-inflammatory cytokine IL-4 in LPS/IFNγ-induced RAW264.7 macrophages (Song et al. 2018). The role of curcumin in ameliorating adipose tissue inflammation might mediate its broad range of bioactivities.

Gingerenone A (Figure 1), a polyphenol present in ginger, is an analogue of curcumin. Gingerenone A treatment suppresses CCL2 and TNF-α expression in the co-culture

system of 3T3-L1 adipocytes and RAW264.7 macrophages (Suk et al. 2017). Gingerenone A inhibits the migration of macrophages toward adipocyte-CM, suppresses HFD-induced increases of $CD68^+$ cell recruitment and CD68 gene expression, decreases the expression of integrin subunit α X (ITGAX, M1 marker), and increases mannose receptor C type 1 (MRC1, M2 marker) in eWAT from HFD-fed mice, suggesting gingerenone A suppresses monocyte/macrophage infiltration and promotes an M2 macrophage polarization in eWAT (Suk et al. 2017).

Xanthones are the main components of mangosteen (*Garcinia mangostana*, Clusiaceae), with potential anti-inflammatory properties (Feng et al. 2020; Liu et al. 2016). 1,3,6,7-tetrahydroxy-8-prenylxanthone (TPX, Figure 1) was reported to ameliorate LPS-induced inflammatory responses in RAW264.7 macrophages, and TNF-α mediated inflammation in 3T3-L1 adipocytes, through inhibiting MAPKs and NF-κB activation; TPX blocks macrophages migration toward adipocytes in co-culture system. Furthermore, TPX alleviates LPS-induced adipose tissue inflammation in mice by reducing pro-inflammatory cytokines and preventing pro-inflammatory polarization of macrophages. These results implicate that TPX orchestrates the inflammatory responses between macrophages and adipocytes, and attenuates adipose tissue inflammation (Li et al. 2018). α-Mangostin (Figure 1), the main xanthone in mangosteen, has been widely reported with anti-inflammatory property (Choi et al. 2015; Franceschelli et al. 2016; Tsai et al. 2016). α-Mangostin inhibits p65 acetylation and reduces COX-2 and iNOS gene expression via activating SIRT1 in LPS-treated human monocytes (Franceschelli et al. 2016). α-Mangostin suppresses adipocyte differentiation and reduces adiposity in HFD-fed mice (Choi et al. 2015; Tsai et al. 2016). In a recent study, α-mangostin was found to alleviate adipose tissue inflammation, resulting in improved adiposity, insulin sensitivity, lipid profile and liver injury in aged mice (Li et al. 2019).

Terpenoids

Corosolic acid (Figure 2), a naturally occurring triterpenoid, is well known as "phyto-insulin" due to its insulin-like activity. Administration of corosolic acid reduces the gene expression of pro-inflammatory cytokines, including IL-6, MCP-1 and TNF-α, in adipose tissue from HFD-fed mice, through suppressing IKKβ phosphorylation (Yang et al. 2016). Corosolic acid treatment reduces the number of crown-like structures (CLSs) in adipose tissue, suggesting less macrophages population, and also suppresses the gene expression of Fizz1 (the M2 macrophage marker) in adipose tissue from HFD-fed mice (Yang et al. 2016).

Ginseng has been used as both medicine and food in Eastern Asia. Chikusetsu saponin IVa (CS, Figure 2) is one of the major triterpenoid saponins from ginseng (*Panax japonicas*) rhizome. CS was found to decrease the mRNA expression levels of inflammation related genes in eWAT, inhibit the accumulation of ATMs, shift their polarization from M1 to M2, and suppress HFD-induced expression of NLRP3 inflammasome component genes, as well as IL-1β and caspase-1 production in mice (Yuan et al. 2017). The levels of TNF-α, MCP-1, IL-1β and caspase-1 are decreased by CS treatment in *ex vivo* cultured adipocytes isolated from eWAT of HFD-fed mice. Moreover, CS treatment inhibits the activation of NLRP3 inflammasome in BMDMs, and effectively suppresses HFD-induced inflammation in eWAT from mice through inhibiting both NLRP3 inflammasome activation and NF-κB signaling (Yuan et al. 2017). Thus, CS could serve as a potential therapeutic drug in the prevention and treatment of adipose tissue inflammation.

Lycopene (Figure 2) is a bright red tetraterpene found in red and pink fruits and vegetables, such as tomato, watermelon, carrot and asparagus. Lycopene is able to attenuate TNF-α expression in LPS-mediated RAW264.7 macrophages, decrease macrophages CM-induced pro-inflammatory cytokines (IL-6, IL-1β, MCP-1, and Rantes) and chemokines (Cxcl1 and Cxcl10) mRNA expression in 3T3-L1 adipocytes, through modulating JNK and NF-κB signaling pathways (Marcotorchino et al. 2012). The anti-inflammatory effect of lycopene on macrophages is accompanied by a decrease in LPS-stimulated macrophage migration (Marcotorchino et al. 2012). Lycopene decreases leptin, resistin and IL-6 gene expression and reduces MCP-1 level in eWAT from HFD-fed rats (Luvizotto et al. 2013). Due to its safety and effectiveness, lycopene could be further developed as food supplements for attenuating adipose tissue inflammation.

Carotenoids are widely known for their antioxidant activities, and it has been shown that astaxanthin (AX, Figure 2), a xanthophyll carotenoid, possesses a particularly high antioxidant capacity, as it has more conjugated double bonds than many other carotenoids (Shibata et al. 2001). AX has also been demonstrated to ameliorate hepatic IR in obese animals and to partially improve metabolic parameters in obese humans (Hussein et al. 2007; Preuss et al. 2011; Uchiyama et al. 2002). A recent report showed that AX exerts anti-inflammatory effects via its antioxidant activity in adipose tissue (Nishida et al. 2020).

Catalpol (Figure 2), a bioactive component from the root of *Rehmannia glutinosa*, decreases the pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, MCP-1, and iNOS, in eWAT from HFD-fed mice, through interfering with the JNK and NF-κB signaling pathways (Zhou et al. 2015). Treatment of catalpol increases the anti-inflammatory genes expression, including Arg-1, Ym-1, IL-10, macrophage galactose-type lectin-1 (MGL1), and C-type lectin domain family 7 member A (Clec7a) in eWAT from HFD-fed mice (Zhou et al. 2015). Additionally, catalpol reduces CLS formation and the gene expression of macrophage marker F4/80 in eWAT from obese mice (Zhou et al. 2015).

Abscisic acid (Figure 2) is a natural phytohormone with structural similarity to thiazolidinediones, which improves insulin sensitivity and glucose homeostasis (Guri et al. 2010). Abscisic acid induces transactivation of PPARγ in 3T3-L1 pre-adipocytes. Dietary abscisic acid-supplementation decreases the fasting blood glucose, ameliorates glucose tolerance, and increases the mRNA expression of PPARγ and its responsive genes adiponectin, aP2, and CD36 in

WAT. The adipocyte hypertrophy, TNF-α expression, and macrophage infiltration in WAT are attenuated in abscisic acid treated HFD-fed *db/db* mice (Guri et al. 2007). F4/80^{hi} ATMs express greater concentrations of CCR2 and CCR5 compared to F4/80^{lo} ATMs. Abscisic acid decreases CCR2^{+} F4/80^{hi} infiltration into WAT and suppresses MCP-1 expression in WAT and plasma. Furthermore, the deficiency of PPARγ in immune cells, including macrophages, impairs the ability of abscisic acid to suppress the infiltration of F4/80^{hi} ATMs into WAT, to repress MCP-1 expression in WAT and improve glucose tolerance (Guri et al. 2008). This evidence demonstrates that abscisic acid improves IR and adipose tissue inflammation by inhibiting MCP-1 expression and F4/80^{hi} ATM infiltration through a PPARγ-dependent mechanism.

Stevioside (Figure 2) is a diterpenoid glycoside derived from the stevia plant, which is used as a sweetener for centuries. Interestingly, oral administration of stevioside reduces the mRNA expression levels of TNF-α, IL-6, IL-1β and MIP-1α in adipose tissue from HFD-fed mice by inactivating the NF-κB pathway (Wang et al. 2012). Stevioside reduces the mRNA levels of CD11b and CD14 in adipose tissue from HFD-fed mice and reduces the expression of macrophage membrane-specific markers F4/80 and CD11b and chemotactic factor MIP-1α in the SVF, which indicates reduced infiltration of macrophages into the adipose tissue (Wang et al. 2012).

Vitamin D (Figure 2) is a hormone mainly described for its role as a regulator of phosphate and calcium homeostasis, and can be obtained through animal (VD_3, cholecalciferol) or plant (VD_2, ergocalciferol) diets (Landrier et al. 2016). Vitamin D ($25(OH)D_3$ and $1,25(OH)_2D_3$) inhibits the secretion of TNF-α and IL-6 in omental adipose tissue, but not subcutaneous adipose tissue from women (Roy et al. 2015). The mRNA levels of MCP-1, Rantes, Il-6 and Il-1β are higher in eWAT from HFD-fed mice and their overall expression levels are down-regulated by vitamin D supplementation (Park et al. 2019). Vitamin D insufficiency exacerbates adipocyte size, the gene expression of PPARγ, proinflammatory cytokines IL-6 and TNFα and ATMs infiltration in eWAT from HFD-fed rats through reducing AMPK/SIRT1 activities (Chang and Kim 2017). Consistently, vitamin D restriction enhances periovarian adipose tissue inflammation in a model of menopause (Borges et al. 2020). These results suggested that vitamin D plays a beneficial role in adipose tissue inflammation and obesity progression.

Alkaloids

Berberine (Figure 2) is an isoquinoline alkaloid found in numerous herb plants (Meng et al. 2018). Many animal studies and clinical trials have indicated berberine with powerful anti-hyperglycemic and anti-dyslipidemic effects (Lee et al. 2006; Yan et al. 2015; Yin et al. 2008). Treatment with berberine decreases the mRNA levels of IL-1β and TNF-α in adipose tissue through reducing the phosphorylation of JNK1, and increases the mRNA level of adiponectin in adipose tissue from HFD-fed mice (Guo et al. 2016). In response to berberine treatment, the percentage of M1 macrophages (F4/80^{+}CD11b^{+}CD11c^{+}CD206^{-}) in adipose tissue of HFD-fed mice is decreased in relative to those of HFD-fed mice while the percentage of anti-inflammatory M2 macrophages (F4/80^{+}CD11b^{+}CD11c^{-}CD206^{+}) is not altered (Guo et al. 2016). Its effect in regulating adipose tissue inflammation is still unconvinced.

Caffeine (Figure 2) is a methylxanthine alkaloid, which is found in the seeds, nuts, or leaves of a number of plants native to Africa, East Asia and South America. In a previous study, caffeine was found to reduce the TNF-α gene expression in human subcutaneous adipose tissue explants from healthy, drug free non-obese women and the SVF, whereas IL-6 was only down-regulated in the SVF (Dray et al. 2007). More studies are needed to further elucidate the effectiveness and mechanism of caffeine in modulating adipose tissue inflammation.

Niacin (Figure 2), also known as nicotinic acid, is a form of vitamin B3, an essential human nutrient. Niacin reduces MCP-1 and IL-1β expression in the adipose tissue from HFD-fed mice (Wanders et al. 2013). Niacin increases the serum level of adiponectin and its gene and protein expression in eWAT from HFD-fed mice (Wanders et al. 2013). Niacin treatment reduces CD11c expression in the fat of HFD-fed mice (Wanders et al. 2013). These results indicated that niacin may promote a shift in macrophage polarization toward M2 phenotype rather than alter the amount of macrophages in the adipose tissue.

Capsaicin (Figure 2), a major constituent of hot pepper, enhances energy metabolism through its β-adrenergic action, and it also elicits anti-inflammatory activities (Liu, Wang and Lin 2019; Manjunatha and Srinivasan 2006; Park et al. 2004). In male KKAy mice fed an HFD for 2 weeks, dietary capsaicin reduces the expression of MCP-1 and IL-6 in adipose tissue, increases the level of adiponectin in plasma and its gene expression in adipose tissue, and decreases CD11b^{+}F4/80^{+} macrophages in SVF from vWAT (Kang et al. 2011). Interestingly, dietary capsaicin shows the similar results in HFD-fed mice, through enhancing the expression of adiponectin and its receptor (Kang et al. 2010). Capsaicin increases the expression of adiponectin, PPARα, PPARγ, visfatin, and adipsin, and reduces the expression of TNF-α and IL-6 in mesenteric adipose tissues (Lee, Shin, et al. 2013). These findings suggested that capsaicin may be useful as a dietary factor for treating obesity-related metabolic disorders.

Methyl 2-(4′-methoxy-4′-oxobutanamide) benzoate (Figure 2) from Jerusalem Artichoke (*Helianthus tuberosus*) suppresses the inflammatory response in LPS-treated RAW264.7 cells by decreasing the secretion of IL-1β, IL-6 and TNF-α. Moreover, the mRNA expression of TNF-α, IL-6, IL-1β, MCP-1 and Rantes was decreased by methyl 2-(4′-methoxy-4′-26 oxobutanamide) benzoate in 3T3-L1 adipocytes incubated with macrophage-CM, through inhibiting the activation MAPK pathway (Jung et al. 2016).

Indole-3-carbinol (I3C, Figure 2), found in Brassica family vegetables, exhibits antioxidant, anti-inflammatory, and anti-cancerous properties. I3C treatment decreases the

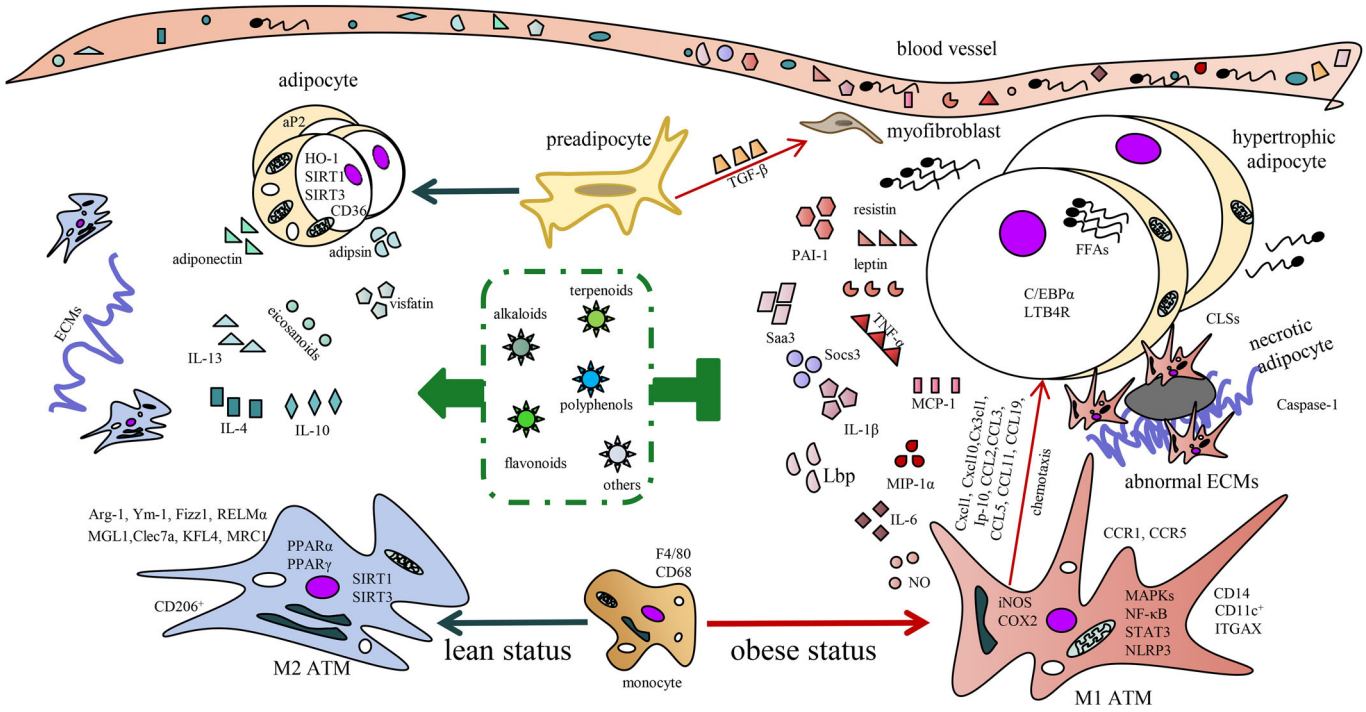

Figure 3. Dietary bioactive compounds modulate the crosstalk between adipocytes and macrophages.

mRNA transcripts of IL-6, MCP1 and CD11c in eWAT from alcohol-treated mice (Choi, Abdelmegeed and Song 2018).

Others

Ononitol monohydrate (OMH, Figure 2), a glycoside, is originally isolated from *Cassia tora* Linn. Leptin, C/EBPα and leukotriene B4 receptor (LTB4R) are down regulated by OMH treatment in mature adipocytes, and the protein expression level of adiponectin is increased by OMH treatment in mature adipocytes (Subash-Babu and Alshatwi 2018).

Malaxinic acid (Figure 2) is identified as an active component from pears (*Pyrus spp.*), which is responsible for its anti-obesity effect. Malaxinic acid decreases the expression of F4/80, CD68, TNF-α, ITGAX, MCP-1, and IL-6 in WAT from HFD-fed mice (Truong et al. 2019).

Oxylipins are metabolized from dietary ω3 and ω6 polyunsaturated fatty acids (PUFA) and are involved in an inflammatory response. ω3-PUFA enriched diet induces the synthesis of oxylipins in non-obesogenic non-inflammatory conditions, which is involved in an anti-inflammatory response and enhancement of the M2 macrophage molecular signature, without affecting inflammatory cytokines secretion (Colson et al. 2019). Dietary intervention with ω3 fatty acid α-linolenic acid (ALA)-rich flaxseed oil reduces MCP-1 and TNF-α protein levels in adipose tissue from *fa/fa* Zucker rats (Baranowski et al. 2012). Long-chain (n-3) PUFA, namely EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), alleviate adipose tissue inflammation and IR in HFD-fed mice (Kalupahana, Claycombe and Moustaid-Moussa 2011). DHA has been reported to increase IL-10 secretion from co-culture of macrophages and adipocytes (Oliver et al. 2012), and alleviate inflammation by increasing the expression of IL-10 in adipose tissue from HFD-fed mice (Titos et al. 2011). Its analogue 17-OHDHA (17-hydroxydocosahexaenoic acid) enhances adiponectin expression in gonadal adipose tissue from obese mice (Neuhofer et al. 2013). DHA and 17-OHDHA reduce the ratio of $CD11c^+$ to $CD206^+$ ATMs in obese mice (Neuhofer et al. 2013). DHA also up-regulates the expression of recognized established markers of macrophage polarization toward M2 phenotype, including Arg1, CD206, Ym1, RELMα and IL-10 in adipose tissue from HFD-induced obese mice (Titos et al. 2011). EPA supplementation suppresses the inflammatory cytokines expression, including IL-6, TNF-α, MCP-1, in the SVF and adipose tissue from HFHS-induced mice (Yamada et al. 2017). EPA supplementation suppresses HFHS-induced CLS formation in eWAT of mice and alters macrophage phenotypes from M1 (CD11c) to M2 (CD206) in the SVF through attenuating p-JNK and NF-κB p-p65 levels (Yamada et al. 2017). EPA ameliorates adipocyte size and galactin-3 positive cells in eWAT from HFD-fed mice, which are independent of body weight or adiposity (LeMieux et al. 2015). ω3 FUFAs ameliorate adipose tissue inflammation in morbidly obese patients. In comparison with control subjects who received butterfat, the circulating IL-6 is decreased in the long-chain n-3 PUFAs group. Treatment with long-chain n-3 PUFAs decreases the gene expression of inflammatory genes CCL2, CCL3, IL-6, and CD40 in subcutaneous adipose tissue and increases the production of anti-inflammatory eicosanoids in vWAT and subcutaneous adipose tissue (Itariu et al. 2012).

There are forceful results from supplementation of commonly consumed food, showing beneficial effects on the production of pro-inflammatory and anti-inflammatory cytokines and adipokines, inhibition of macrophage

Table 2. Modulators of interaction between adipocytes and other immune cells.

Object	Dosage	Model	Target	Ref
PEE, kaempferol	PEE 100 μg/mL, PEE 100 mg/kg, kaempferol, 1 or 10 mg/kg	macrophage-like cell line J774.1; peritoneal macrophages, eWAT from HFD-fed mice or *ob/ob* mice	↑Ly6g, ↑IL-10, ↑Gr-1$^+$ MDSCs, ↑CD11b$^+$ MDSCs	(Kitamura et al. 2018)
Isoliquiritigenin	0.5% in HFD	eWAT from HFD-fed mice	↓CD3$^+$ cells	(Honda et al. 2014)
Resveratrol	0.01% in drinking water	SVF of vWAT from sleep apnea mice	↓CD8$^+$ lymphocytes, ↑Treg lymphocytes	(Carreras et al. 2015)
ALA-rich flaxseed oil	an ALA-rich flaxseed oil diet	adipose tissue from *fa/fa* Zucker rats	↓CD3	(Baranowski et al. 2012)
Vitamin D	15000 IU/kg	eWAT from HFD-fed mice	↓CD3	(Karkeni et al. 2015)
Ononitol monohydrate	3.2 μM	T-lymphocytes treated with adipocyte CM	↑IL-4/STAT6, ↓TNF-α, ↓LTB4	(Subash-Babu and Alshatwi 2018)

infiltration, and reversion of M2 to M1 phenotypic polarization, resulting in improvement of paracrine loop between adipocytes and macrophages (Figure 3). Manipulation of interaction between macrophages and adipocytes with constituents from dietary plants is a potential strategy for improvement of adipose tissue inflammation and treatment of obesity and metabolic disorders. Large clinical trials are needed to confirm the role of consumed food and the bioactive components in treatment of adipose tissue inflammation.

Modulators of interaction between adipocytes and other immune cells

Understanding composition and functions of adipose tissue resident cells in the non-obese and obese state is significant for therapeutic purposes. Besides pre-adipocytes, adipocytes, fibroblasts, and endothelial cells, almost all immune cell types are found in adipose tissue, such as T lymphocytes, B lymphocytes, neutrophils and mast cells. These cells play important roles in adipose tissue, including removing apoptotic cells, maintaining adipocytes in healthy condition, and sustaining adipose tissue homeostasis in non-obese animal and humans (Schipper et al. 2012). Emerging evidence showed that the total numbers of immune cells are increased in adipose tissue of obese subjects, but their recruitment kinetics are different, each cell type participates in the progression of inflammation via different mechanisms (Clement et al. 2004). Therefore, immune cells may regulate metabolic parameters at different levels, ranging from appetite, adipocyte growth, and lipid metabolism, to adipose tissue inflammation. The diet derived modulators of interaction between adipocytes and other immune cells were listed in Table 2.

Brazilian propolis, mainly from *Baccharis dracunculifolia*, is rich in flavonoids and cinnamic acid derivatives, and has been widely used in preventing metabolic disorders, such as T2D and arteriosclerosis, owing to its anti-inflammatory effects. Ethanol extract of Brazilian propolis (PEE) or its major component kaempferol induces cultured M1 macrophages to transdifferentiate into Gr-1$^+$ myeloid-derived suppressor cells (MDSCs), which have strong anti-inflammatory ability. PEE increases the mRNA transcript levels of Ly6g and IL-10 in peritoneal macrophages and macrophage-like J774.1 cells. Intraperitoneal injection of PEE or kaempferol induces CD11b$^+$ MDSCs in vWAT and the peritoneal cavity of lean and obese mice (Kitamura et al. 2018). The number of CD3$^+$ cells in eWAT is reduced in isoliquiritigenin treated HFD-fed mice compared with those in HFD mice (Honda et al. 2014). Administration of resveratrol decreases the number of CD8$^+$ lymphocytes as well as increases the Treg lymphocytes in the SVF of vWAT from sleep apnea mice (Carreras et al. 2015). Dietary intervention with ω-3 fatty acid ALA-rich flaxseed oil lowers CD3 protein level in adipose tissue from *fa/fa* Zucker rats, which indicating reduced T-cell infiltration in adipose tissue (Baranowski et al. 2012). Vitamin D regulates leukocytes infiltration in adipose tissue and inhibits the mRNA expression of CD3 in eWAT from HFD-fed mice (Karkeni et al. 2015). T-lymphocytes treated with ononitol monohydrate and CM from adipocytes show increased mRNA levels of IL-4/STAT6 and decreased mRNA levels of TNF-α and LTB4 (Subash-Babu and Alshatwi 2018).

Under the situation of obesity, IR or diabetes, the increase of immune cells infiltration in adipose tissue initiates the inflammatory cascade. Interfering the local and infiltrated mast cells, T-lymphocytes and natural killer cells by dietary plants and the bioactive components displays effects on the inhibition of pro-inflammatory cytokines and elevation of anti-inflammatory cytokines, and the regulation of macrophages inflammatory phenotype, resulting in beneficial improvements for systemic and adipose tissue inflammation (Figure 4). Therefore, it would be meaningful to elucidate the effects of commonly consumed food and the bioactive components on pathophysiologic role of other immune cells in adipose tissue inflammation.

Blockers of pattern recognition receptors

During metabolic dysregulation, stimuli (cytokines and chemokines) activate the corresponding receptors, including TNFR, IL-1R, TLRs, and RAGE on the cell membrane (Shoelson, Lee and Goldfine 2006). RAGE is a multi-ligand receptor that recognizes stress and inflammatory signals, including high mobility group box 1 (HMGB1), advanced glycation end products (AGEs), S100/calgranulins, lysophosphatidic acid, phosphatidyl serine, and integrin α M (ITGAM) (Hofmann et al. 1999; Kislinger et al. 1999; Ramasamy, Yan and Schmidt 2009; Song et al. 2014; Taguchi et al. 2000). RAGE is highly expressed on monocytes and macrophages, and its expression is further

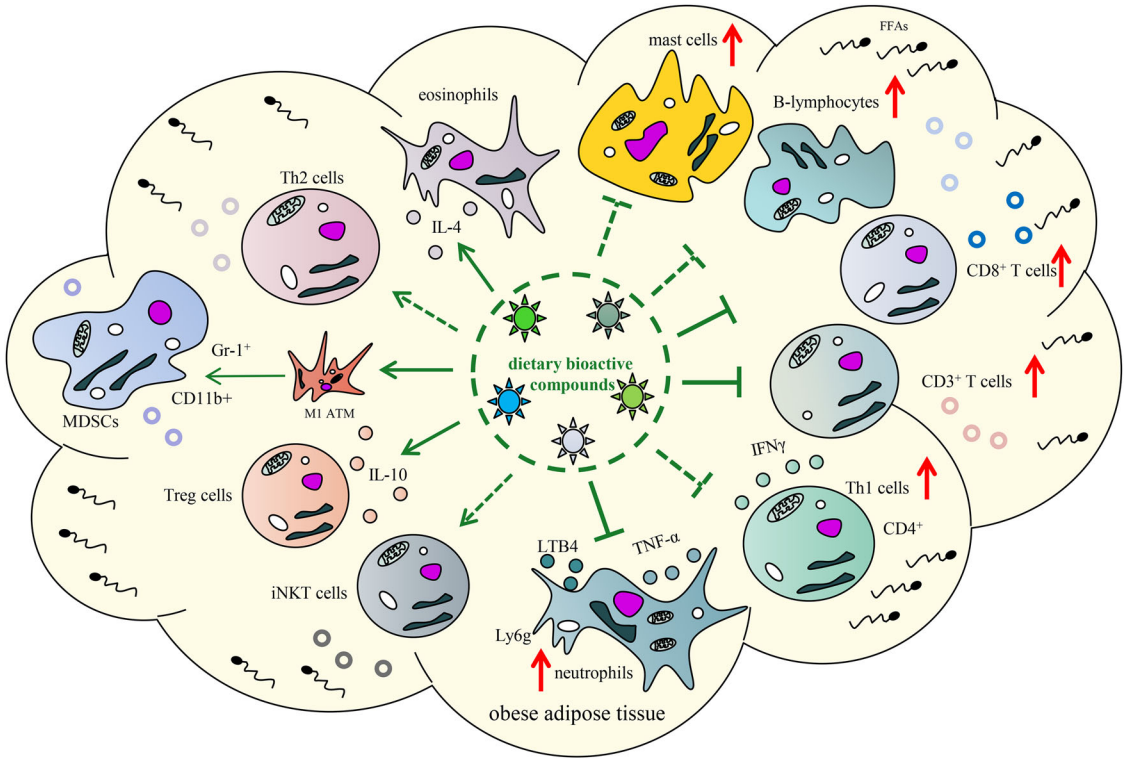

Figure 4. Dietary bioactive compounds regulate immune cells in adipose tissue.

enhanced after immune activation or infection (Miyata et al. 1996; Shanmugam et al. 2003; Xu et al. 2010). The roles for RAGE in carbohydrate excess and lipid metabolism have been investigated widely. The HFD feeding triggers the production and accumulation of RAGE ligands in adipose tissue, which consequently activate inflammatory signaling and lead to obesity and IR (Song et al. 2014). TLRs play a key role in innate immune response and their activation leads to IR in adipose tissue, liver and muscle, which consequently increase glucose and lipids level in blood. This reaction is defined as a condition of physiological IR, which provides immune processes with energetic and plastic substances (Vitseva et al. 2008). Ligands of TLRs are components of microorganisms: bacterial lipopeptides and LPS (Akira, Uematsu and Takeuchi 2006), as well as saturated fatty acids (Lee et al. 2001). Inadequate uptake of the non-saturated fatty acids in food activates TLR-4 and TLR-2, which acts as a mechanism of pathological alterations. When the innate immunity receptors are excessive activated, adipose tissue inflammation, over production of cytokines, and IR occur, which in turn promote the progress of obesity and diabetes (Jeon et al. 2014). The cytokines and chemokines activate their corresponding receptors that induce inflammatory signaling in adipose tissue (Jeon et al. 2014). Therefore, inhibition or antagonism of cell surface receptors would help to ameliorate adipose tissue inflammation. The diet derived blockers of pattern recognition receptors were listed in Table 3.

Polyphenols from *Antirhea borbonica* and caffeic acid, chlorogenic acid, and kaempferol were found to inhibit TLR2, TLR4, MyD88 and NF-κB gene expression in LPS-treated adipocytes (Le Sage, Meilhac and Gonthier 2017). Monascin, isolated from Monascus-fermented rice (red mold rice), inhibits cytokine production in S100b-treated THP-1 monocytes via up-regulation of nuclear factor-erythroid 2-related factor-2 (Nrf2) and alleviation of p47phox translocation to the membrane. Inhibitions of RAGE and p47phox by monascin (Figure 5) are confirmed by peripheral blood mononuclear cells (PBMCs) from methylglyoxal-induced rats, that indicating monascin prevents the development of T2D (Lee, Hsu, et al. 2013). Ankaflavin (Figure 5) is a water-insoluble polyketide metabolite isolated from Monascus, which was reported to suppress RAGE expression in PBMCs and decrease IL-1β and TNF-α production in LPS-stimulated PBMCs, these results are in accordance with the lower IL-1β and TNF-α levels in the kidney, liver, pancreas, and serum from methylglyoxal-induced rats (Lee et al. 2012). Isoliquiritigenin was reported to suppress palmitic acid-induced TLR4 activation in Ba/F3 macrophages (Watanabe et al. 2016). Vitamin A plays a role in glucose and lipid metabolism, and *Dunaliella* is the best known nutritional source of 9-cis β-carotene. The mRNA levels of TLR2 and TLR4 were decreased in adipose tissue from *Dunaliella*-treated *db/db* mice (Harari et al. 2013). Resveratrol was found to attenuate the mRNA levels of TLR2 and TLR4 in the adipose tissues from HFD-fed mice (Kim et al. 2011).

In general, upon receptor engagement, the inflammatory molecules activate several effector pathways, such as MAPKs and NF-κB, which is subsequently degraded by proteasome, permitting the translocation of the transcription factor AP-1 or p65 to the nucleus. Subsequently, the expression of several inflammatory-related genes is enhanced, which creates a vicious circle in adipose tissue. Hence, the suppression of

Table 3. Blockers of pattern recognition receptors.

Object	Dosage	Model	Target	Reference
Polyphenols from *Antirhea borbonica*, caffeic acid, chlorogenic acid and kaempferol	25 μM	LPS-treated adipocytes	↓TLR2, ↓TLR4	(Le Sage, Meilhac and Gonthier 2017)
Monascin	25 μM	PBMCs from methylglyoxal-induced rats	↓RAGE	(Lee, Hsu, et al. 2013)
Ankaflavin	10 mg/kg	PBMCs from methylglyoxal-induced rats	↓RAGE	(Lee et al. 2012)
Isoliquiritigenin	1, 3 or 10 μM	palmitic acid-induced macrophages	↓TLR4	(Watanabe et al. 2016)
Dunaliella	8% powder of the alga	adipose tissue from *db/db* mice	↓TLR2, ↓TLR4	(Harari et al. 2013)
Resveratrol	0.4% in HFD	adipose tissue from HFD-fed mice	↓TLR2, ↓TLR4	(Kim et al. 2011)

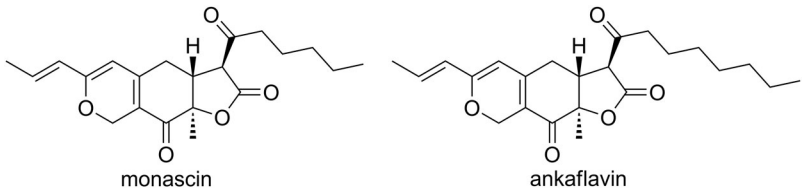

Figure 5. Structures of monascin and ankaflavin.

TNFR, IL-1R, TLR, and RAGE by nutrients and bioactive natural components reveals several advantages for adipose tissue inflammation, including decrease the pro-inflammatory cytokines production, reduce the infiltration and pro-inflammatory phenotypic polarization of macrophages, and improve the microenvironment in adipose tissue (Figure 6). More attentions should be paid on the identification of small molecular suppressors of TNFR, IL-1R, TLR, or RAGE.

Releasers of intracellular stresses

In addition to pro-inflammatory cytokines and pattern recognition receptors, intracellular stresses could activate inflammatory signaling, including reactive oxygen species (ROS), ER stress, ceramides, and various protein kinase C (PKC) isoforms. Systemic oxidative stress increases with obesity, consistent with a role for ROS in the development of IR (Keaney et al. 2003). The potential mechanism is that lipid accumulation in adipocytes increases ROS production through activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Furukawa et al. 2004), increases the production of IL-6, TNF-α and MCP-1, and decreases the production of adiponectin (Shoelson, Lee and Goldfine 2006). The ER is a key player in the cellular stress response and a membranous network that functions in the synthesis and processing of secretory and membrane proteins (Oezcan et al. 2004). Excess lipid accumulation, increased synthesis of secretory proteins, and expression of mutant or misfolded proteins can trigger ER stress, subsequently induces peripheral and central IR (Chavez and Summers 2012; Kaufman et al. 2002). Ceramides are produced under condition of cell stress. The sphingolipid ceramide is a putative intermediate linking both excess nutrients (i.e. saturated fatty acids) and inflammatory cytokines (e.g. TNF-α) to the induction of IR (Summers 2006). It acts as an inducer of pro-inflammatory cytokines through the activation of kinases (e.g. IKKβ) (de Mello et al. 2009). PKC isoforms are being elucidated as an increasingly diverse family of enzymes involved in the downstream signal transduction and cell function in various types of cells. They are grouped according to their molecular structures and mode of activation: conventional PKCs (α, βI, βII, and γ), novel PKCs (δ, ε, μ, θ, and η), and atypical PKCs (ζ and ι/λ) (Yamaguchi et al. 2006). Excessive lipid increases the activation of PKCs, which activates IKKβ and NF-κB pathways. Consequently, the reduction of intracellular stresses may attenuate the adipose tissue inflammation.

HFD consumption triggers ER stress in the visceral fat as assessed by PERK and eukaryotic initiation factor 2α (eIF2α) phosphorylation, ATF6 cleavage, JNK and IRE1α phosphorylation and the levels of X-box binding protein 1 spliced isoform (sXBP-1). Epicatechin supplementation partially or completely mitigates HFD-mediated activation of PERK and inositol-requiring enzyme 1α (IRE1α) branches, but has no effects on ATF6 cleavage. Attenuation of adipocyte ER stress by epicatechin contributes to decreased inflammation and improved visceral adipose tissue insulin sensitivity. In the HFD-fed group, the levels of BiP/Grp78 chaperone are elevated, and this increase is partially prevented by epicatechin (Bettaieb et al. 2016). Resveratrol reverses the HFD-induced up-regulation of PKCδ in eWAT from mice (Kim et al. 2011). Treatment of resveratrol inhibits ROS-associated mitochondrial fission by up-regulating dynamin-related protein (Drp1) phosphorylation (Ser 637) in an AMPK-dependent manner, and then suppresses ER stress indicated by dephosphorylation of IRE1α and eIF2α in adipose tissue from diabetic mice (Li, Li, et al. 2016). Resveratrol protects mitochondrial integrity by inhibiting Drp1 activity and prevents NLRP3 inflammasome activation by suppressing ER stress, and thereby protects adipose function from high glucose insult (Li, Zhang, et al. 2016).

These intracellular stresses occurred in adipose tissue are ameliorated by consumption of nutrients and bioactive components, which is benefit for improving inflammatory status (Figure 6). However, more clinical trials are needed to confirm the role of these substances in regulation of ROS, ER stress, ceramides, and various PKC isoforms. Manipulation

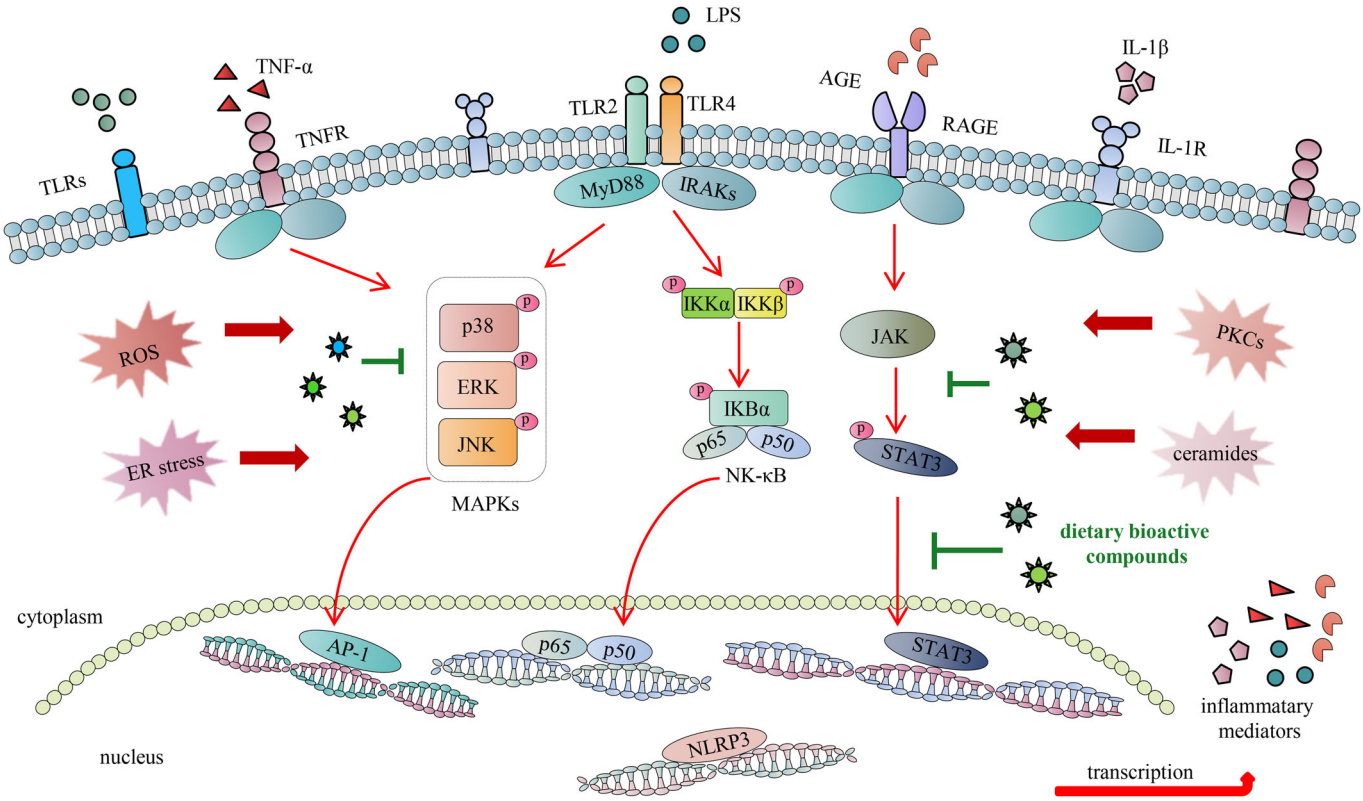

Figure 6. Dietary bioactive compounds modulate pattern receptor and intracellular stresses in adipose tissue.

of intracellular stresses with small molecules is a potential strategy for improvement of adipose tissue inflammation and treatment of obesity and metabolic disorders.

Conclusions

Adipose tissue is a vital endocrine organ that produces and secretes a wide range of mediators regulating the function of adipose tissue and other tissues, such as liver, skeletal muscle, pancreas and cardiovascular system, in an endo-/paracrine-manner. In metabolic disorder status, enlargement of adipocytes leads to adipose tissue dysfunction and a shift in the secretory profile with an increased release of pro-inflammatory adipokines and cytokines (Romacho et al. 2014). Adipose tissue inflammation is a key hallmark of metabolic disorders (Osborn and Olefsky 2012; Ouchi et al. 2011). Obviously, development of therapeutic and preventive strategies to ameliorate adipose tissue inflammation is potential for treating metabolic diseases. More and more scientists are paying attention on nutrients and bioactive natural components to solve the emergent condition on adipose tissue inflammation. Nutrients and bioactive components show many benefit effects in adipose tissue, such as decreasing pro-inflammatory cytokines production, promoting anti-inflammatory adipokines secretion, inhibiting immune cells migration toward adipocytes, suppressing pattern recognition receptors expression, and reducing intracellular stresses. According to the studies over the past decades, the natural products ameliorating adipose tissue inflammation mainly belong to vitamins, unsaturated fatty acid, polyphenols, flavonoids, alkaloids, and terpenoids. These compounds are different in chemical structures, but some of them might function on the same targets. Therefore, it is difficult to ascertain how they regulate the same target in adipose tissue inflammation. Quantitative structure–activity relationship can be applied to provide scientific evidence. Although the activities of nutrients and bioactive natural components are not as strong as those of synthetic compounds, they provide new starting points in the discovery of new dietary supplements or lead compounds for treatment of adipose tissue inflammation and its related metabolic disorders.

Author contributions

L Lin conceived the idea for this review; D Li, T Zhang, J Lu, C Peng and L Lin wrote and revised the manuscript, and have approved the final version for submission.

Disclosures statement

The authors declare no conflict of interest.

Funding

Financial support by The Science and Technology Development Fund, Macau SAR (File no. 0031/2019/A1 to L.L.), University of Macau (File no. MYRG2017-00109-ICMS and MYRG2018-00037-ICMS to L.L.), National Natural Science Foundation of China (81872754 to L.L, 81630101 and 81891012 to C.P.), the Open Research Fund of Chengdu University of Traditional Chinese Medicine Key Laboratory of Systematic Research of Distinctive Chinese Medicine Resources in Southwest China (2020GZ2011011), and China Postdoctoral Science Foundation (2019TQ0044 and 2019M663456) are gratefully acknowledged.

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