Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Nutrition and Physical Activity in Aging, Obesity, and Cancer*

Inflammation-mediated obesity and insulin resistance as targets for nutraceuticals

Myung-Sunny Kim,[1] Myeong Soo Lee,[2] and Dae Young Kown[1]

[1]Korea Food Research Institute, Gyongki-do, Republic of Korea. [2]Korea Institute of Oriental Medicine, Daejeon, Republic of Korea

Address for correspondence: Myung-Sunny Kim, Ph.D., Korea Food Research Institute, Baekhyon-dong 516, Bundang-ku, Songnam, Gyongki-do, 463-746, Republic of Korea. truka@kfri.re.kr

Obesity-induced inflammation plays an important role in the development of insulin resistance, type 2 diabetes (T2D), and metabolic dysfunctions. Chronic activation of proinflammatory pathways within insulin target cells can lead to obesity-related insulin resistance. The inflammatory mediators consist of immune cells, cytokines, adipokines, and inflammatory signaling molecules. Targeting obesity-associated inflammation has been shown to protect experimental animals and human subjects from obesity-induced insulin resistance. Modulation of the inflammatory responses associated with obesity may help prevent or improve obesity-induced metabolic dysfunctions. In this review, we introduce the beneficial effects of nutraceuticals for targeting inflammation in the treatment of obesity-induced insulin resistance and metabolic dysfunctions.

Keywords: inflammation; obesity; metabolic disease; nutraceuticals

Introduction

The growing prevalence of obesity and the pathologies associated with it has become a major threat to public health. The chronic inflammation observed in obesity appears to be a critical factor in the development of pathological disturbances such as insulin resistance, type 2 diabetes, cardiovascular disease, and other metabolic diseases. The obesity-induced alteration of biological conditions in target tissues results in systemic insulin resistance and inflammation.[1–3]

Modulating inflammatory responses in obese patients may be useful for preventing or ameliorating obesity-related pathologies. This review summarizes the molecular pathways that link inflammation and metabolic dysfunctions, and we also review evidence for the modulation of obesity-induced inflammation by various nutraceuticals.

Inflammation and insulin resistance

Many studies have shown that adipose tissue is an important initiator of the inflammatory response to obesity. The inflammation characterized by infiltration of macrophages and other immune cells into obese white adipose tissue can cause systemic insulin resistance.[4,5]

Adipose tissue macrophages (ATMs) are a major source of proinflammatory cytokines, which can function in a paracrine and potentially an endocrine fashion to decrease insulin sensitivity. Activation of these tissue macrophages leads to the release of a variety of chemokines, which in turn recruit additional macrophages. Recent studies have detected various subsets of T lymphocytes in obese adipose tissue of humans and mice.[6–8] In obese subjects, adipose tissue T_H1 lymphocytes may help to recruit macrophages into adipose tissue; the macrophages then stimulate inflammation, leading to insulin resistance. Although the role of immune cells in adipose tissue has not been fully elucidated, it seems probable that the inflammatory response mediated by AT immune cells plays a key pathogenic role in the development of obesity-induced insulin resistance.

The proinflammatory cytokine tumor necrosis factor (TNF)-α was identified as the first molecular link between obesity, diabetes, and inflammation.[9,10] TNF-α was found to be overexpressed in

doi: 10.1111/j.1749-6632.2011.06098.x

Ann. N.Y. Acad. Sci. 1229 (2011) 140–146

the adipose and muscle tissues of obese mice and humans.[11–13] In experimental models, neutralization of TNF-α improved insulin sensitivity in obese *fa/fa* rats,[9,11] and the TNF-α–deficient obese mice were protected from obesity-induced insulin resistance.[14] Since these findings, obesity has been characterized by the presence of many inflammatory mediators in adipose tissue. These include leptin, resistin, plasminogen activator inhibitor type-1 (PAI-1), adiponectin, visfatin, monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-6, IL-1, serum amyloid A (SAA), retinol binding protein-4 (RBP-4), and macrophage inflammatory protein (MIP).[1–3] These play a central role in regulating energy and vascular system homeostasis by influencing various metabolic processes. There is also evidence of macrophage infiltration in the other metabolic organs, the liver, and skeletal muscle.[1] Kupffer cells, the resident macrophages of the liver, contribute to the production of inflammatory mediators that promote insulin resistance in hepatocytes.

Molecular mechanisms of inflammation and insulin resistance

Previous studies focusing on the intracellular pathways activated by inflammation have provided key insight into obesity-induced insulin resistance. Increased inflammatory stimuli in obese subjects, including cytokines and Toll-like receptor (TLR) stimulation, can activate the inhibitor of κB kinase-β/nuclear factor κB (IKKβ/NF-κB) axis and c-Jun N-terminal kinase (JNK).[15–17] The activation of these kinases in obesity highlights the overlap between metabolic and immune pathways, the latter of which are activated during the innate immune response by TLR signaling in response to lipopolysacharide (LPS), peptidoglycan, fatty acids, and other microbial products.[18] Genetic disruption of IKKβ and pharmacological inhibition of IKKβ with salicylates in obese mice have been shown to improve insulin resistance.[17] In addition, JNK1 knockout (KO) mice are protected against diet-induced insulin resistance, and inhibitors of JNK also appear to improve insulin sensitivity in models of insulin resistance.[16,19] Additionally, cellular stresses such as reactive oxygen species (ROS), endoplasmic reticulum (ER) stress, and ceramide can activate the NF-κB and JNK inflammatory pathways.[20]

Peroxisome proliferator-activated receptor (PPARγ) is a major molecular target for all insulin-sensitizing thiazolidinediones (TZD).[21] In normal adipose tissue, PPARγ senses fatty acids and regulates the expression of many genes involved in glucose metabolism and adipocyte differentiation. Although it is most highly expressed in adipocytes, PPARγ is also expressed in macrophages, where it can negatively regulate a large set of inflammatory genes.[22–25] Recently, it was demonstrated that macrophage-specific PPARγ KO mice on normal and high-fat diets showed inflammatory pathway activation, glucose intolerance, and insulin resistance.[26,27] In terms of glucose homeostasis, TZD treatment was much less effective in macrophage-specific PPARγ KO mice compared with controls, suggesting an essential role of macrophage PPARγ in the maintenance of systemic insulin activity.[26] IL-1 and TNF-α also suppress the ligand-induced transactivation of PPARγ, which is mediated through NF-κB and is activated by the TAK1/TAB1/NF-κB-inducing kinase (NIK) cascade downstream of IL-1 and TNF-α signaling.[28]

However, the immunological dysfunctions associated with obesity are not restricted to local metabolic tissues. It has been suggested that obesity alters the functions of circulating immune cells.[29–31] Circulating mononuclear cells from obese subjects are in a constitutive proinflammatory state and show an increase in intranuclear NF-κB binding and elevated transcript levels of proinflammatory genes such as IL-6, TNF-α, and migration inhibition factor, which are regulated by NF-κB.[29] Obesity has also been linked to elevated circulating leukocyte and lymphocyte subset counts, increased granulocyte phagocytosis, and higher levels of oxidative burst.[31]

Targeting inflammation by nutraceuticals in obesity and insulin resistance

There is a considerable need for safe therapeutic agents that can reduce the risk of obesity-induced metabolic dysfunctions, and the range of nutraceutical compounds with potential benefits for obese patients continues to expand. The reported anti-inflammatory properties of food-derived nutraceuticals may be crucial for the treatment of such diseases.

Curcumin

Curcumin, a yellow pigment of curry powder, has been shown to downregulate the expression of various NF-κB–regulated proinflammatory adipokines, including chemokines (MCP-1, MCP-4, and eotaxin)[32] and interleukins (IL-1, IL-6, and IL-8)[33] *in vitro*. Curcumin was also shown to suppress the expression of PAI-1 by inhibiting the transcription factor early growth response (Egr-1),[34] which has been closely linked with insulin resistance and obesity.

Animal studies have shown that curcumin administration ameliorated diabetes in obese and leptin-deficient *ob/ob* C57BL6/J mice, as indicated by glucose- and insulin-tolerance testing and the percentage glycosylated hemoglobin.[35] Curcumin also reduced macrophage infiltration in WAT, increased adipose tissue adiponectin production, decreased hepatic NF-κB activity, and reduced the expression of hepatic inflammation markers, including TNF-α, IL-1β, suppressor of cytokine signaling 3, MCP-1, and C-C motif receptor-2. Jain *et al.*[36] reported that curcumin supplementation lowered the high glucose-mediated monocyte production of inflammatory cytokines, including TNF-α, IL-6, IL-8, and MCP-1. This same study also showed that blood levels of TNF-α, MCP-1, glucose, and glycosylated hemoglobin were decreased in diabetic rats on a curcumin diet. Taken together, these data suggest that curcumin may be a useful phytochemical for attenuating obesity-induced inflammation and obesity-related metabolic complications.

Capsaicin

Capsaicin, a biologically active compound found in red pepper, has anti-inflammatory activities[37–39] and shows potential benefits for treating obesity and insulin resistance in animal models and clinical studies.[40–42] Capsaicin has diverse activities in metabolic tissues. In addition to its metabolic properties that induce thermogenesis and fat oxidation, capsaicin also shows anti-inflammatory properties.[41] A proteomic analysis showed that thermogenesis- and lipid metabolism-related proteins in white adipose tissue[43] and skeletal muscle[44] were altered upon capsaicin treatment, suggesting that capsaicin has a role in regulating energy metabolism. In addition to altering thermogenic proteins, capsaicin also reduced the expression of TNF-α in adipose tissue.[43] Capsaicin affected the secretion of inflammatory adipocytokines, such as IL-6 and MCP-1, in obese adipose tissue and isolated adipocytes by modulating the proinflammatory transcription factors NF-κB and PPARγ.[40] Capsaicin also directly suppressed the macrophage inflammatory response by inhibiting NF-κB activation *in vitro*.[37,45] In addition, our group has observed that capsaicin directly increases the insulin-stimulated uptake of glucose in muscle cells (unpublished data). These results indicate that capsaicin may be useful for the treatment of obesity-related inflammatory metabolic dysfunctions. In addition, the beneficial effects of spice-derived nutraceuticals on inflammation and obesity have been reviewed.[46]

Polyunsaturated fatty acids

Fatty acids (FAs) can function as endogenous ligands that modulate inflammatory responses. Saturated FAs promote inflammation by activating Toll-like receptor 4 (TLR4) on fat cells and macrophages,[47] and unsaturated FAs are weakly proinflammatory or neutral. However, ω-3 polyunsaturated fatty acids (PUFAs) from fish oils, such as docosahexanoic acid (DHA) and eicosapentaenoic acid (EPA), are known anti-inflammatory factors.[48,49] Recently, Oh *et al.*[50] showed that the ω-3 fatty acids DHA, EPA sense G protein–coupled receptor 120 (GPR120), which is highly expressed in adipose tissue macrophages and fat cells. The activation of this receptor by DHA attenuates the proinflammatory effects of TNF-α and LPS on macrophages. Activation of GPR120 by ω-3 fatty acids induces potent insulin sensitization and other antidiabetic effects *in vivo* by repressing macrophage-induced tissue inflammation. In addition, PPARγ activation by long chain ω-3 PUFA has been implicated in the prevention of high-fat diet-induced adipose tissue inflammation and remodeling.[51,52] Meijerink *et al.*[53] also showed that docohexaenoylethanolamine (DHEA), the ethnaolamide metabolite of DHA, modulates inflammation by reducing MCP-1 and nitric oxide (NO) production in macrophages. In conclusion, fish oil supplements can alleviate metabolic disease by modulating inflammatory signaling pathways.

Resveratrol and stillbenes

Resveratrol, a polyphenolic compound found in the skin of grapes and related food products, has been shown to prevent a number of diverse pathologic

processes, including cardiovascular disease (CVD), cancer, oxidative stress, and inflammation.[54–56] Although the majority of research on metabolic dysfunctions has focused on its ability to enhance the effects of sirtuin SIRT1 in preventing cellular damage associated with aging and chronic illness,[57] there have been many reports detailing its anti-inflammatory and antiadipogenic effects.[58–60] A recent study reported that resveratrol has an anti-inflammatory effect on TNF-α–induced MCP-1 expression by inhibiting NF-κB transcriptional activity in adipocytes.[60] In animal models, resveratrol repressed TLR2- and TLR4-mediated proinflammatory signaling cascades in adipose tissue[58] and inhibited NF-κB signaling in the sciatic nerves of rats with streptozotocin-induced diabetes.[61] In human retinal epithelial cells, resveratrol showed an inhibitory effect on hyperglycemia-induced inflammation.[62] It has also shown the potential for preventing CVD by inhibiting inflammatory markers, the cyclooygenase (COX)-1 enzyme, and polyphosphoinositide metabolism in platelets.[63] In rats, resveratrol administration prevented the decrease in vascular NO induced by inflammatory mediators, and it decreased the expression of TNF-α.[64] In addition, previous studies have shown that Vitisin A, a resveratrol tetramer purified from the skin of grape trees, has anti-inflammatory,[65,66] antiadipogenic, [67] and anticholestrolemic activities.[68] Vitisin A reduces the expression of LPS-stimulated proinflammatory markers in macrophages and decreases adipocyte differentiation by inhibiting PPARγ activation. Inhibition of cellular 3-hydroxy-3-methylgluctaryl coenzyme A (HMG CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis, can lower the levels of circulating cholesterol and several proinflammatory cytokines products of NF-κB target genes. These mechanisms demonstrate a potential for resveratrol and its tetramer in the control of obesity and metabolic disorders.

Ginger-derived components

The two major pungent compounds of ginger, 6-gingerol and 6-shogaol, have potent anti-inflammatory activities and can improve diabetes and insulin resistance.[69–71] Both molecules attenuate the effects on TNF-α–induced downregulation of adiponectin expression by different mechanisms in adipocytes; 6-shogaol functions as a potent agonist of PPARγ, but 6-gingerol does not, although it is structurally similar to 6-gingerol. In addition, 6-shogaol inhibits the TNF-α–mediated downregulation of adiponectin expression via PPARγ transactivation. In contrast, 6-gingerol inhibits JNK signaling pathways in TNF-α–stimulated adipocytes without affecting PPARγ transactivation.[72] In addition, 6-gingerol is also a potent inhibitor of COX-2 expression and acts by blocking the activation of p38 MAPK and NF-κB[73] along with enhancing adipocyte differentiation.[71] Zingerone, a component of ginger, also suppresses the secretion of MCP-1 from adipose tissue of obese mice and inhibits macrophage inflammatory action such as migration and activation.[32] In animals, the ethanol extract of ginger protects against egg albumin–induced acute inflammation and hypoglycemia in models of diabetes.[70] Thus, these studies suggest that ginger has the potential to prevent inflammation and inflammation-linked metabolic dysfunction.

Flavonoids

Flavonoids are a polyphenol subclass widely distributed in plants and in the diet, and they exhibit a variety of health benefits. The anti-inflammatory properties of flavonoids have been extensively studied to establish and characterize their potential utility as therapeutic agents in the treatment of inflammatory diseases.[74] Antocyanins are found in red fruits and vegetables and have been shown to have anti-inflammatory activity in obese adipose tissues, which is mediated by PPARγ-dependent mechanisms.[75,76] Cyanidin 3-glucoside (C3G), a typical anthocyanin, downregulates the expression of RBP-4, which is known to contribute to insulin resistance in adipose tissue of diabetic mice,[77] and this improvement is associated with the inhibition of inflammatory mediators and stimulation of AMPK activity in adipocytes.[75] (–)-epigallocatechin-3-gallate (EGCG), a major green tea polyphenol, provides beneficial effects for metabolic syndrome. Long-term EGCG treatment impairs the development of obesity and decreases the expression of inflammatory markers, such as MCP-1, in obese mice, suggesting that EGCG-mediated reductions in mesenteric and retroperitoneal adipose tissue weight may have a beneficial impact on high fat–induced inflammation and the development of metabolic syndrome.[78] In humans, green tea consumption has been

inversely correlated with liver damage and with the levels of inflammation markers.[79,80]

Conclusions

The evidence implicating inflammation in the pathogenesis of insulin resistance and type 2 diabetes suggests the possibility of targeting inflammation with pharmacological and dietary interventions. While pharmacological approaches that alter the inflammatory process are undoubtedly of great clinical importance dietary, nutraceuticals with anti-inflammatory activities can improve insulin sensitivity. These approaches may provide clinical benefits to the vast number of patients affected by the obesity epidemic and the metabolic disorders. However, preserving other innate immune functions should be considered in this approach.

Acknowledgments

This work was supported by research grants from Korea Food Research Institute and the Biofood Research Program from the National Research Foundation, Korea.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Schenk, S., M. Saberi & J.M. Olefsky. 2008. Insulin sensitivity: modulation by nutrients and inflammation. *J. Clin. Invest.* **118:** 2992–3002.
2. Stumvoll, M., B. J. Goldstein & T.W. van Haeften. 2005. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* **365:** 1333–1346.
3. Shoelson, S.E., J. Lee & A.B. Goldfine. 2006. Inflammation and insulin resistance. *J. Clin. Invest.* **116:** 1793–1801.
4. Weisberg, S.P. *et al*. 2003. Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Invest.* **112:** 1796–1808.
5. Xu, H. *et al*. 2003. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Invest.* **112:** 1821–1830.
6. Feuerer, M. *et al*. 2009. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat. Med*. **15:** 930–939.
7. Nishimura, S. *et al*. 2009. CD8 +effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med*. **15:** 914–920.
8. Winer, S. *et al*. 2009. Normalization of obesity-associated insulin resistance through immunotherapy. *Nat. Med.* **15:** 921–929.
9. Hotamisligil, G.S., N.S. Shargill & B.M. Spiegelman. 1993. Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance. *Science* **259:** 87–91.
10. Sethi, J.K. & G.S. Hotamisligil. 1999. The role of TNF α in adipocyte metabolism. *Semin. Cell. Dev. Biol*. **10:** 19–29.
11. Hotamisligil, G.S. *et al*. 1995. Increased adipose tissue expression of tumor necrosis factor-α in human obesity and insulin resistance. *J. Clin. Invest.* **95:** 2409–2415.
12. Kern, P.A. *et al.* (1995. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. *J. Clin. Invest.* **95:** 2111–2119.
13. Saghizadeh, M., *et al.* 1996. The expression of TNF α by human muscle. Relationship to insulin resistance. *J. Clin. Invest.* **97:** 1111–1116.
14. Uysal, K.T. *et al*. 1997. Protection from obesity-induced insulin resistance in mice lacking TNF-α function. *Nature* **389:** 610–614.
15. Aguirre, V. *et al*. 2000. The c-Jun NH(2)-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser (307). *J. Biol. Chem*. **275:** 9047–9054.
16. Hirosumi, J. *et al*. 2002. A central role for JNK in obesity and insulin resistance. *Nature* **420:** 333–336.
17. Yuan, M. *et al.* 2001. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkβ. *Science* **293:** 1673–1677.
18. Lee, J.Y. *et al*. 2001. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. *J. Biol. Chem.* **276:** 16683–16689.
19. Vallerie, S. N. & G.S. Hotamisligil. 2010. The role of JNK proteins in metabolism. *Sci. Transl. Med.* **2:** 60rv65.
20. Summers, S. A. 2006. Ceramides in insulin resistance and lipotoxicity. *Prog. Lipid Res.* **45:** 42–72.
21. Forman, B.M. *et al*. 1995. 15-Deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR γ. *Cell* **83:** 803–812.
22. Jiang, C., A. T. Ting & B. Seed. 1998. PPAR-γ agonists inhibit production of monocyte inflammatory cytokines. *Nature* **391:** 82–86.
23. Marx, N. *et al*. 1998. Macrophages in human atheroma contain PPARγ: differentiation-dependent peroxisomal proliferator-activated receptor γ (PPARγ) expression and reduction of MMP-9 activity through PPARγ activation in mononuclear phagocytes *in vitro*. *Am. J. Pathol*. **153:** 17–23.
24. Ricote, M. *et al*. 1998. Expression of the peroxisome proliferator-activated receptor γ (PPARγ) in human atherosclerosis and regulation in macrophages by colony stimulating factors and oxidized low density lipoprotein. *Proc. Natl. Acad. Sci. USA* **95:** 7614–7619.
25. Ricote, M. *et al*. 1998. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. *Nature* **391:** 79–82.
26. Hevener, A.L. *et al*. 2007. Macrophage PPAR γ is required for normal skeletal muscle and hepatic insulin sensitivity and full antidiabetic effects of thiazolidinediones. *J. Clin. Invest.* **117:** 1658–1669.
27. Odegaard, J.I. *et al*. 2007. Macrophage-specific PPARγ controls alternative activation and improves insulin resistance. *Nature* **447:** 1116–1120.

28. Suzawa, M. *et al*. 2003. Cytokines suppress adipogenesis and PPAR-γ function through the TAK1/TAB1/NIK cascade. *Nat. Cell. Biol*. **5:** 224–230.
29. Ghanim, H. *et al*. 2004. Circulating mononuclear cells in the obese are in a proinflammatory state. *Circulation* **110:** 1564–1571.
30. Mendall, M. A. *et al*. 1997. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart* **78:** 273–277.
31. Nieman, D. C. *et al*. 1999. Influence of obesity on immune function. *J. Am. Diet. Assoc.* **99:** 294–299.
32. Woo, H.M. *et al*. 2007. Active spice-derived components can inhibit inflammatory responses of adipose tissue in obesity by suppressing inflammatory actions of macrophages and release of monocyte chemoattractant protein-1 from adipocytes. *Life Sci.* **80:** 926–931.
33. Wang, S.L. *et al*. 2009. Curcumin, a potential inhibitor of up-regulation of TNF-α and IL-6 induced by palmitate in 3T3-L1 adipocytes through NF-κB and JNK pathway. *Biomed. Environ. Sci*. **22:** 32–39.
34. Pendurthi, U.R. & L.V. Rao. 2000. Suppression of transcription factor Egr-1 by curcumin. *Thromb. Res.* **97:** 179–189.
35. Weisberg, S. P., R. Leibel & D.V. Tortoriello. 2008. Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. *Endocrinology* **149:** 3549–3558.
36. Jain, S.K. *et al*. 2009. Curcumin supplementation lowers TNF-α, IL-6, IL-8, and MCP-1 secretion in high glucose-treated cultured monocytes and blood levels of TNF-α, IL-6, MCP-1, glucose, and glycosylated hemoglobin in diabetic rats. *Antioxid. Redox. Signal*. **11:** 241–249.
37. Kim, C.S. *et al*. 2003. Capsaicin exhibits anti-inflammatory property by inhibiting IkB-a degradation in LPS-stimulated peritoneal macrophages. *Cell. Signal*. **15:** 299–306.
38. Manjunatha, H. & K. Srinivasan. 2006. Protective effect of dietary curcumin and capsaicin on induced oxidation of low-density lipoprotein, iron-induced hepatotoxicity and carrageenan-induced inflammation in experimental rats. *FEBS J*. **273:** 4528–4537.
39. Park, J.Y. *et al*. 2004. Capsaicin inhibits the production of tumor necrosis factor α by LPS-stimulated murine macrophages, RAW 264.7: a PPARγ ligand-like action as a novel mechanism. *FEBS Lett*. **572:** 266–270.
40. Kang, J.H. *et al*. 2007. Capsaicin, a spicy component of hot peppers, modulates adipokine gene expression and protein release from obese-mouse adipose tissues and isolated adipocytes, and suppresses the inflammatory responses of adipose tissue macrophages. *FEBS Lett*. **581:** 4389–4396.
41. Shin, K.O. & T. Moritani. 2007. Alterations of autonomic nervous activity and energy metabolism by capsaicin ingestion during aerobic exercise in healthy men. *J. Nutr. Sci. Vitaminol*. **53:** 124–132.
42. Suri, A. & A. Szallasi. 2008. The emerging role of TRPV1 in diabetes and obesity. *Trends Pharmacol. Sci.* **29:** 29–36.
43. Joo, J.I. *et al*. 2010. Proteomic analysis for antiobesity potential of capsaicin on white adipose tissue in rats fed with a high fat diet. *J. Proteome Res.* **9:** 2977–2987.
44. Kim, D.H. *et al*. 2010. Differential expression of skeletal muscle proteins in high-fat diet-fed rats in response to capsaicin feeding. *Proteomics* **10:** 2870–2881.
45. Singh, S., K. Natarajan & B.B. Aggarwal. 1996. Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a potent inhibitor of nuclear transcription factor-κ B activation by diverse agents. *J. Immunol*. **157:** 4412–4420.
46. Aggarwal, B.B. 2010. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. *Annu. Rev. Nutr.* **30:** 173–199.
47. Shi, H. *et al*. 2006. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J. Clin. Invest.* **116:** 3015–3025.
48. Batetta, B. *et al*. 2009. Endocannabinoids may mediate the ability of (n-3) fatty acids to reduce ectopic fat and inflammatory mediators in obese Zucker rats. *J. Nutr.* **139:** 1495–1501.
49. Lee, J.Y. *et al*. 2003. Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. *J. Lipid Res.* **44:** 479–486.
50. Oh, D.Y. *et al*. 2010. GPR120 is an ω-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* **142:** 687–698.
51. Huber, J. *et al*. 2007. Prevention of high-fat diet-induced adipose tissue remodeling in obese diabetic mice by n-3 polyunsaturated fatty acids. *Int. J. Obes.* **31:** 1004–1013.
52. Todoric, J. *et al*. 2006. Adipose tissue inflammation induced by high-fat diet in obese diabetic mice is prevented by n-3 polyunsaturated fatty acids. *Diabetologia* **49:** 2109–2119.
53. Meijerink, J. *et al*. 2011. The ethanolamide metabolite of DHA, docosahexaenoylethanolamine, shows immunomodulating effects in mouse peritoneal and RAW264.7 macrophages: evidence for a new link between fish oil and inflammation. *Br. J. Nutr*. Feb. 4: 1–10 [Epub ahead of print]
54. Baur, J.A. & D.A. Sinclair. 2006. Therapeutic potential of resveratrol: the *in vivo* evidence. *Nat. Rev. Drug Discov*. **5:** 493–506.
55. Fremont, L. 2000. Biological effects of resveratrol. *Life Sci.* **66:** 663–673.
56. Jang, M. *et al*. 1997. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* **275:** 218–220.
57. Pillarisetti, S. 2008. A review of Sirt1 and Sirt1 modulators in cardiovascular and metabolic diseases. *Recent Pat. Cardiovasc. Drug Discov*. **3:** 156–164.
58. Kim, S. *et al*. 2011. Resveratrol exerts anti-obesity effects via mechanisms involving down-regulation of adipogenic and inflammatory processes in mice. *Biochemical Pharmacol*. **81:** 1343–1351.
59. Rayalam, S. *et al*. 2008. Resveratrol induces apoptosis and inhibits adipogenesis in 3T3-L1 adipocytes. *Phytother. Res*. **22:** 1367–1371.
60. Zhu, J. *et al*. 2008. Anti-inflammatory effect of resveratrol on TNF-α-induced MCP-1 expression in adipocytes. *Biochem. Biophys. Res. Commun.* **369:** 471–477.
61. Kumar, A. & S.S. Sharma. 2010. NF-κB inhibitory action of resveratrol: a probable mechanism of neuroprotection in experimental diabetic neuropathy. *Biochem. Biophys. Res. Commun.* **394:** 360–365.

62. Losso, J.N., R.E. Truax & G. Richard. 2010. Trans-resveratrol inhibits hyperglycemia-induced inflammation and connexin downregulation in retinal pigment epithelial cells. *J. Agric. Food Chem.* **58:** 8246–8252.
63. Szewczuk, L.M. *et al*. 2004. Resveratrol is a peroxidase-mediated inactivator of COX-1 but not COX-2: a mechanistic approach to the design of COX-1 selective agents. *J. Biol. Chem.* **279:** 22727–22737.
64. Zhang, H. *et al*. 2009. Resveratrol improves endothelial function: role of TNFα and vascular oxidative stress. *Arterioscler. Thromb. Vasc. Biol*. **29:** 1164–1171.
65. Mi Jeong, S. *et al*. 2009. Vitisin A suppresses LPS-induced NO production by inhibiting ERK, p38, and NF-κB activation in RAW 264.7 cells. *Int. Immunopharmacol*. **9:** 319–323.
66. Huang, K.S., M. Lin & G.F. Cheng. 2001. Anti-inflammatory tetramers of resveratrol from the roots of *Vitis amurensis* and the conformations of the seven-membered ring in some oligostilbenes. *Phytochemistry* **58:** 357–362.
67. Kim, S.H. *et al*. 2008. Vitisin A inhibits adipocyte differentiation through cell cycle arrest in 3T3-L1 cells. *Biochem. Biophys. Res. Commun*. **372:** 108–113.
68. Koo, M. *et al*. 2008. 3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitory effect of *Vitis vinifera*. *Fitoterapia* **79:** 204–206.
69. Levy, A.S. *et al*. 2006. 6-Shogaol reduced chronic inflammatory response in the knees of rats treated with complete Freund's adjuvant. *BMC Pharmacol.* **6:** 12.
70. Ojewole, J.A. 2006. Analgesic, antiinflammatory and hypoglycaemic effects of ethanol extract of *Zingiber officinale (Roscoe) rhizomes* (Zingiberaceae) in mice and rats. *Phytother. Res*. **20:** 764–772.
71. Sekiya, K., A. Ohtani & S. Kusano. 2004. Enhancement of insulin sensitivity in adipocytes by ginger. *Biofactors* **22:** 153–156.
72. Isa, Y. *et al*. 2008. 6-Shogaol and 6-gingerol, the pungent of ginger, inhibit TNF-α mediated downregulation of adiponectin expression via different mechanisms in 3T3-L1 adipocytes. *Biochem. Biophys. Res. Commun.* **373:** 429–434.
73. Kim, S.O. *et al*. 2005. [6]-Gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF-κB in phorbol ester-stimulated mouse skin. *Oncogene* **24:** 2558–2567.
74. Garcia-Lafuente, A. *et al*. 2009. Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. *Inflamm. Res*. **58:** 537–552.
75. Tsuda, T. 2008. Regulation of adipocyte function by anthocyanins: possibility of preventing the metabolic syndrome. *J. Agric. Food Chem*. **56:** 642–646.
76. Tsuda, T. *et al*. 2003. Dietary cyanidin 3-O-β-D-glucoside-rich purple corn color prevents obesity and ameliorates hyperglycemia in mice. *J. Nutr*. **133:** 2125–2130.
77. Sasaki, R. *et al*. 2007. Cyanidin 3-glucoside ameliorates hyperglycemia and insulin sensitivity due to downregulation of retinol binding protein 4 expression in diabetic mice. *Biochem. Pharmacol*. **74:** 1619–1627.
78. Bose, M. *et al*. 2008. The major green tea polyphenol, (-)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome, and fatty liver disease in high-fat-fed mice. *J. Nutr*. **138:** 1677–1683.
79. Imai, K. & K. Nakachi. 1995. Cross sectional study of effects of drinking green tea on cardiovascular and liver diseases. *Br. Med. J.* **310:** 693–696.
80. Steptoe, A. *et al*. 2007. The effects of chronic tea intake on platelet activation and inflammation: a double-blind placebo controlled trial. *Atherosclerosis* **193:** 277–282.