Front. Biol. 2012, 7(1): 40–47
DOI 10.1007/s11515-011-1174-y

REVIEW

# Estrogens, inflammation and obesity: an overview

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**Abstract Emerging research has suggested that inflammatory stress may play a role in the development of obesity. Both the leptin and insulin receptor are sensitive to intracellular inflammatory signaling that can be stimulated through toll-like receptor 4 activation by saturated fat. Pharmacological intervention within this cascade often protects animals from becoming obese, thus highlighting inflammatory pathways as a possible site of study in the prevention of pathologic weight gain. It has been well established in animal models that females display a marked reduction in the susceptibility to weight gain on high-fat diets compared to males. In addition, it has been widely accepted that females are partially protected from inflammatory-related diseases. At the molecular level, this reduction in disease susceptibility has been suggested to be due to the anti-inflammatory properties of 17 β-estradiol. Through direct free radical scavenging, transcriptional regulation, and protein interactions, chronic exposure to estradiol can reduce systemic inflammatory stress. As the knowledge base continues to grow on the etiology of obesity, further research is needed on the precise molecular pathways that can be inhibited by estradiol. Understanding of such pathways may provide a basis for the future use of estrogen and its related compounds (daidzein, genistein, resveratrol) to prevent weight gain in peri- and post-menopausal females.**

**Keywords** inflammation, obesity, sex differences, estrogen, high fat diets, phytoestrogens

## Introduction

Obesity is commonly recognized as a disorder characterized by a chronic inflammatory status (Kahn and Flier, 2000; Wellen and Hotamisligil, 2003; Wellen and Hotamisligil, 2005). This systemic inflammation renders those affected susceptible to developing co-morbidities such as the metabolic syndrome, cardiovascular disease, cancer, osteoporosis, and neurodegenerative diseases (Lehrke and Lazar, 2004; Hotamisligil, 2006). While the development of the related diseases has been linked to obesity-initiated inflammation, emerging research is beginning to suggest that obesity in itself may also share its etiology in inflammatory stress. Several animal studies have shown that the supplementation of anti-inflammatories to a high-fat diet can effectively defend against excess weight gain (Jayaprakasam et al., 2006; Charradi, et al. 2011). However, because of the complexity of human obesity, how large of a role inflammation plays in the development of obesity is contested. Regardless of the conflict, the following review will summarize the inflammatory pathways that may lead to the development of obesity with specific interest in leptin and insulin resistance.

It is well accepted that females experience lower rates of inflammatory diseases and this significant difference in the inflammatory response of women compared to men has been suggested to be due to the anti-inflammatory properties of 17 β-estradiol. As research is ever increasing suggesting inflammatory signaling plays an important role in increasing the susceptibility to excess weight gain, the anti-inflammatory properties of estrogens emerge as a potential modulator of these cascades. In the following sections we will provide potential explanations behind the anti-obesity effects of estrogen in regards to inflammatory stress. Also, we will review phytoestrogens that have anti-obesity effects in part due to their anti-inflammatory properties.

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Received July 25, 2011; accepted August 29, 2011

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## The role of leptin and insulin resistance in obesity

Two hormones have been identified as potent regulators of appetite suppression, leptin and insulin. Both hormones are released in relation to adiposity providing the brain with the status of the body's long-term energy storage (fat). Leptin is released directly from adipocytes in relation to the amount of subcutaneous adipose tissue (Clegg and Woods, 2004; Shi and Clegg, 2009). While insulin has a primary role in managing blood glucose levels, it is also released in proportion to visceral adipose mass and can inform the brain of the body's energy status over the long-term. If fat stores are high due to a positive energy balance, signaling will result to reduce food intake and increase activity, while the opposite occurs when fat stores are low. Another common characterization of obesity is the development of central leptin and insulin resistance (Berthoud and Morrison, 2008). Hyperleptinemia under obese conditions fails to suppress appetite or increase energy expenditure since the circulating leptin fails to reach the brain or leptin signaling is disrupted leading to a condition called leptin resistance (Enriori, Evans et al., 2006). Similarly, hyperinsulinemia, most commonly seen in obese patients, is manifested by decreased insulin-stimulated glucose transport resulting in part from impaired insulin signaling and from downregulation of glucose transporter, GLUT4 (Reaven, 1995). Development of central leptin and insulin resistance may only propagate the malfunctions in energy balance, leading to even more weight gain and further fat deposition.

The hypothalamus is the target destination for such hormones, and serves as the master satiety switch by decreasing or increasing energy consumption and output. Injury to this area, seen often from tumor growth or lesions, results in rapid weight gain caused by an insatiable appetite (Hetherington and Ranson, 1940; Anand and Brobeck, 1951; York and Hansen, 1998; Berthoud and Morrison, 2008; Vinchon et al., 2009). This thereby strongly supports the idea that interference with hormonal signaling in the hypothalamus can in itself cause obesity. Research has previously demonstrated that dietary saturated fat promotes central leptin and insulin resistance (Milanski et al., 2009). How and when this hormonal resistance is developed during the timeline of obesity development is still a major issue under investigation, however several studies have discovered that systemic leptin and insulin resistance can occur in as little as 72 h after rodents are switched to a high-fat diet (Wang et al., 2001; Morgan et al., 2004; Boghossian et al., 2009; Clegg et al., 2011).

## Malfunctions in leptin signaling

The leptin receptor is a transmembrane receptor that falls within the cytokine receptor family. Upon ligand binding, the receptor undergoes a conformational change resulting in its autophosphorylation by the protein janus kinase (JAK) and subsequent activation of signal transducers and activation of transcription protein (STAT) (Wauman and Tavernier 2011 paper for a more descriptive view of leptin receptor signaling). Activated STAT serves as a transcription factor and stimulates expression of proteins that result in the inhibition of appetite inducing neurons [neuropeptide Y (NPY) and agouti-related protein (AgRP)], enhancing activity of appetite suppressing neurons [proopiomelanocortin (POMC)], and increasing intracellular levels of suppressor of cytokine signaling 3 protein (SOCS3) (Gong et al., 2008).

Many cytokine receptors are thought to be auto-inhibitory due to their ability to increase SOCS3 protein levels (Fig. 1.1). SOCS3 binds directly to these receptors, including the leptin receptor, rendering JAK inactive and preventing phosphorylation of STAT (Fig. 1.2). Therefore increased cellular concentrations of the SOCS3 protein can lead to a reduction in leptin signaling. While SOCS3 becomes elevated through normal leptin receptor activation, as described above, levels of the protein are also increased during inflammatory stress, again through activation of cytokine receptors such as toll-like receptor 4 (TLR-4) (Fig. 1.3) (Zhang et al., 2008; Milanski et al., 2009). Through this pathway, it is thereby possible for inflammatory signaling to inhibit the leptin receptor without the presence of obesity, hyperleptinemia, and over-activation of the leptin receptor (Yang and Hotamisligil, 2008).

## Malfunctions in insulin signaling

The insulin receptor is a transmembrane tyrosine kinase receptor that activates its intracellular substrate, insulin receptor substrate 1 (IRS-1), through phosphorylation on its tyrosine residues. Within the hypothalamus, IRS-1 triggers activation of mitogen-activated protein kinase (MAPK) signaling and transcription. Much like the leptin receptor, activation of the insulin receptor results in the inhibition of NPY/AgRP signaling, activation of POMC signaling, thereby resulting in a pro-anorexic state (Schwartz et al., 1992).

Another trait that the insulin receptor shares with the leptin receptor is its sensitivity to increased intracellular SOCS3 concentrations. SOCS3 binds directly to the IRS-1 marking it for ubitiquin-mediated degradation, reducing its active concentrations, and thereby blunting insulin-stimulated signaling and its downstream effects (Fig. 1.4) (Rui et al., 2002; Uekio et al., 2004). To be expected, cross-talk between these two receptors is mediated by SOCS3. Because intracellular SOCS3 is elevated through normal leptin signaling, the increase can result in IRS-1 degradation and reductions in insulin sensitivity. Because of the connection between these receptors, changes in leptin signaling will also impact the insulin receptor as well.

Lastly, saturated fat is able to induce the activation of

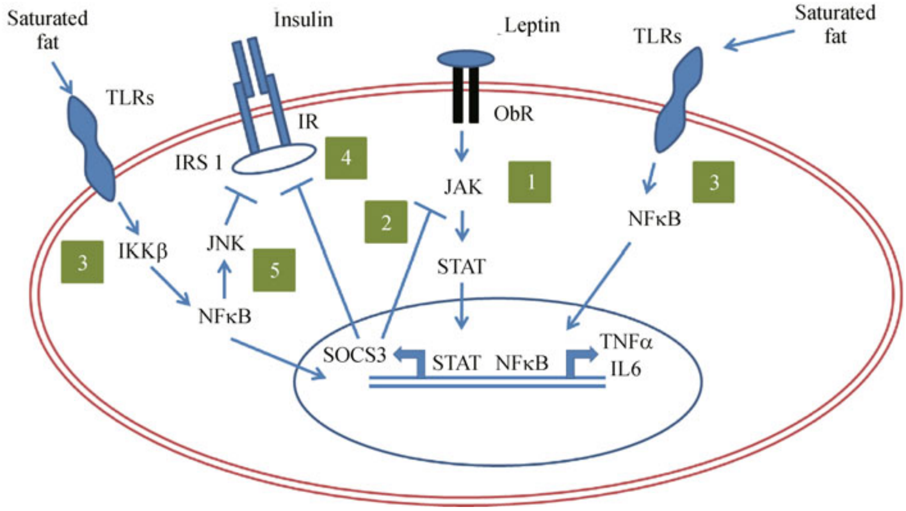


**Figure 1** Chronic inflammation disrupts hypothalamic leptin and insulin signaling. Leptin receptor results in SOCS3 gene expression (1), resulting in inhibition of JAK-STAT signaling (2). Leptin receptor is also inhibited through saturated fat-induced activation of NFκB, and downstream increases in SOCS3 (3). Insulin receptor is sensitive to SOCS3 (4), as well as JNK (5), both a consequence of saturated fat-induced NFκB activation. Abbreviations: toll-like receptor (TLR), inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ), nuclear factor kappa B (NFκB), c-jun N-terminal kinase (JNK), insulin receptor substrate 1 (IRS 1), insulin receptor (IR), suppressor of cytokine signaling 3 (SOCS3), leptin receptor (ObR), janus kinase (JAK), signal transducers and activators of transcription (STAT), tumor necrosis factor alpha (TNFα), interleukin 6 (IL6)

nuclear factor kappa-B (NFκB) through direct stimulation of TLR-4 (Milanski et al., 2009). This also results in the activation of JNK, which phosphorylates IRS-1 on its inhibitory serine residues, preventing its activation when insulin receptor is stimulated (Fig. 1.5) (De Souza et al., 2005; Yang and Hotamisligil, 2008).

## Hypothalamic inflammatory signaling and obesity

In a hallmark study by Zhang et al. 2009, it was determined that inflammatory signaling caused by saturated fat directly results in obesity in rats. Chronic inflammation activates NFκB signaling in the hypothalamus resulting in resistance to insulin and leptin. In contrast, suppression of inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) in the medial basal hypothalamus, or in hypothalamic AgRP neurons, reverses diet-induced obesity (Zhang et al., 2008; Kleinridders et al., 2009). The molecular mechanisms involved in these processes include SOCS3, suppression of NFκB, and inhibition of insulin and leptin signaling. Signaling by the IKKβ/NFκB pathway in the hypothalamus represents an important factor in obesity, and it has been proposed that suppression of hypothalamic NFκB signaling may inhibit obesity and related diseases (Zhang et al., 2008; Kleinridders et al., 2009). Additionally, obliteration of TLR-4, the receptor target of saturated fat, protects rodents from diet-induced obesity (Tsukumo et al., 2007; Davis et al., 2008). This is due to a direct reduction of activated IKKβ complex and maintenance of central insulin sensitivity. Pharmacological inhibition of NFκB also produces the same results; reduction of food intake due to restoration of insulin sensitivity previously blunted by high-fat diet (Posey et al., 2009).

There are changes in energy balance that precede the onset of obesity when animals are fed a HF diet. A possible causal factor is that inflammation leads to leptin and insulin resistance (De Souza et al., 2005; Zhang et al., 2008). De Souza et al. found inhibiting inflammatory signaling by blocking JNK activation reduces food intake and bodyweight in rats fed a high-fat diet compared to controls. The authors suggested this is due to the restored insulin signaling that occurs when inflammation is reduced (De Souza et al., 2005). Additionally, when inflammatory cytokines are delivered into the hypothalamus during high-fat feeding, a robust excess amount of weight is gained (Oh-I et al. 2010). This may be attributed to cytokine-induced activation of NFκB because the use of IKKβ inhibitor PS1145 in Oh et al.'s study prevented additional weight gain.

Lastly, it also important to briefly mention the role of immune cells in mediating the inflammatory response and obesity. Saturated fat has shown to stimulate immune cell infiltration in a variety of tissue types including hepatocytes and adipocytes (Kennedy et al., 2008; Csak et al., 2011). By reducing the functioning of infiltrating immune cells, this provides an additional site of potential interventions. Studies that have blunted such functioning have found a protection from excessive weight gain in animals fed a high-fat diet (Weisberg et al., 2006; Poggi et al., 2011). Most recently, transgenic mice deficient in CD40L were protected from diet-induced obesity in addition to other metabolic consequences (Poggi et al., 2011). While research is quite limited in this area, the emerging literature is building a strong case that inflammation indeed plays a significant role in the development obesity.

## Estrogens as anti-obesity agents

It has been widely documented that in diet-induced obesity models, females gain weight at a slower pace than aged-matched males (Hong et al., 2009). Hong and colleagues reported that female mice gain less after 20 weeks on a high-fat diet than males. Additionally, the bodyweight change in HF diet-fed females mimicked that of chow-fed males. Research has shown that this is due to overall reduced energy consumption and increased levels of spontaneous physical activity (Basterfield et al., 2009; Priego, et al. 2009; Shi and Clegg, 2009). In addition, females tend to store fat in the less stressing subcutaneous depot compared to the visceral depot that has been associated with increased risk of disease (Clegg et al., 2006; Shi and Clegg, 2009).

The estrogen receptors (ER) are expressed in nearly every tissue in the body, with ERα being the most widely expressed and ERβ much more sporadic and only found in the hypothalamus, lungs, and female reproductive tract (Couse et al., 1997).Their anti-obesity effects can be attributed to effects both systemically and centrally. 17β-estradiol (E2), the primary circulating female sex hormone, has shown to increase lipolytic activity of adipose, reduce levels of *de novo* lipogenesis, and regulate central leptin sensitivity by increasing leptin receptor expression, to name a few (Hewitt et al., 2003; Rocha et al., 2004; Bryzgalova et al., 2008; Shi and Clegg, 2009). For the purpose of this review however, more focus will be on estrogen's roles within the hypothalamus regulating energy balance.

## Anti-inflammatory activity of estrogens

E2 is involved in both the acute and chronic phase responses in regards to inflammation (Straub, 2007). Within the acute-phase response, E2 rapidly increases inflammatory signaling to help defend against bacterial or viral infection. Naturally, this would be a protective response and would increase the likelihood of survival during infection. However, chronic activation of pro-inflammatory environments results in an over-stressed system and deterioration of normal tissue responses. A chronic exposure to estrogen results in the blunting of inflammatory pathways, reducing the amount of damaged caused by long-term exposures to stressors such as dietary saturated fat or high glucose levels. It is by this chronic response that the female sex is protected from the development of diseases that share their etiology in inflammatory stress.

Estrogens, both biologic and environmental, bind to the estrogen receptors. (Vegeto et al., 2001; Vegeto et al., 2003; Vegeto et al., 2006). Estrogen receptor α (and in some cases ERβ) is expressed in immune and cytokine-producing cells including macrophages and microglia, and *in vitro* studies have shown E2-activated estrogen receptor α decreases pro-inflammatory cytokines (Vegeto et al., 2001; Vegeto et al., 2003). It should be noted that immune cells like macrophages that infiltrate adipose tissue are responsible for apparent increase in the production of proinflammatory mediators (Wellen and Hotamisligil, 2003). Tumor necrosis factor alpha (TNFα) is the predominant factor that mediates the crosstalk between macrophages and adipocytes, and elevated systemic TNFα levels are found in obese individuals (Suganami et al., 2005). On the other hand, leptin induces the release of TNFα from mononuclear cells in circulation, and estrogens inhibit leptin induced TNFα production (Fazeli et al., 2004). The anti-inflammatory properties of E2 can also be partially explained by the ability of estrogen receptors to act as transcriptional repressors by inhibiting the activity of NFκB through protein-protein interactions between agonist-bound estrogen receptor and a subunit of activated NFκB (Stein and Yang, 1995; Ghisletti et al., 2005; Kalaitzidis and Gilmore, 2005). E2's inhibitory action on NFκB function is still not clearly understood and may be target and gene selective (Harris et al., 2003; Chadwick et al., 2005; Kalaitzidis and Gilmore, 2005).

It is possible that E2 may be protecting normal hypothalamic signaling and energy balance by acting as an anti-inflammatory agent in the cell. Proestrus E2 levels are associated with reduced levels of inflammatory cytokines including TNFα, interleukin 6 (IL-6), and interleukin 8 (IL-8) (Straub, 2007; Hamilton et al., 2007). In addition to changes in serum cytokines during the estrous cycle, ovariectomy is associated with increased cytokine expression that is reversible upon E2 treatment (Evans et al., 2001; Hamilton et al., 2007). E2 has also been suggested to have antioxidant capacities by regulating gene expression of γ-glutamylcysteine synthetase, the rate limiting enzyme of glutathione synthesis, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase thereby increasing the cellular capacity of free-radical scavenging and reducing formation of reactive oxygen species (ROS), respectively (Fig. 2.1) (Straub, 2007). Additionally, there is much research on the ability of E2 and estrogen receptor α to regulate NFκB activity (Stice and Knowlton, 2008). Genomically, E2 is able to increase the expression of nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha (IkBα), the inhibitory subunit of NFκB (Fig. 2.2). E2 can also reduce IkBα phosphorylation, keeping it bound to NFκB and preventing the activation of NFκB (Fig. 2.3). Estrogen receptor α has the capacity to colocalize with the p65 subunit of active NFκB, preventing its transcriptional activities, which has been observed in rodents (Fig. 2.3) (Evans et al., 2001).

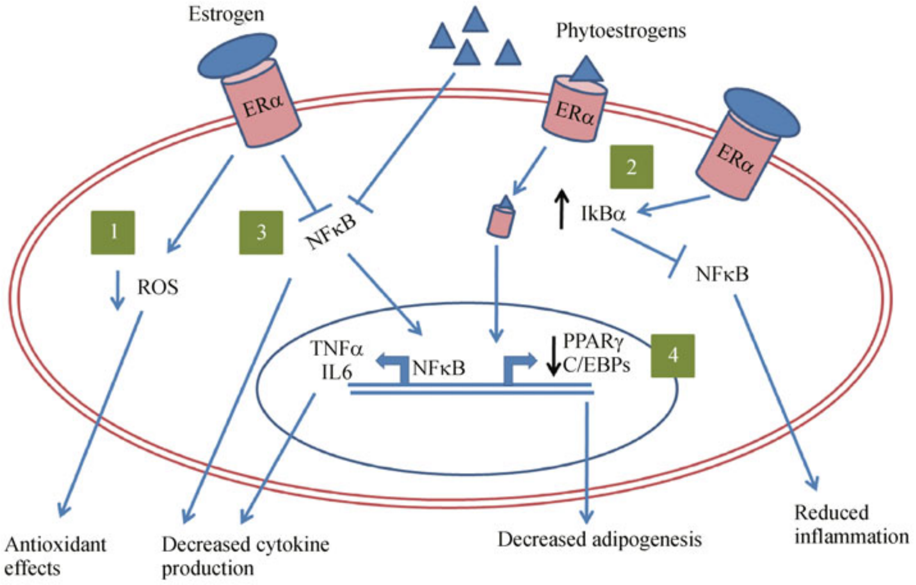


**Figure 2** Anti-inflammatory effects of estrogens and phytoestrogens. Estrogens are capable of reducing ROS concentrations through direct free radical scavenging and ERα-mediated increases in other scavenger proteins (1). Intracellular reductions of ROS would reduce cellular stress and subsequent inflammatory signaling. ERα also mediates NFκB activity through increasing the inhibitory subunit IκBα (2) and direct protein on protein interactions with the NFκB complex (3). It is also important to mention that the anti-obesity effects of estrogens are in part due to ERα-mediated suppression of adipogenic genes (4). Abbreviations: estrogen receptor alpha (ERα), reactive oxygen species (ROS), nuclear factor kappa B (NFκB), tumor necrosis factor alpha (TNFα), interleukin 6 (IL6), nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha (IkBα), peroxisome proliferator-activated receptor gamma (PPARγ), CCAAT-enhancer binding proteins (C/EBPs)

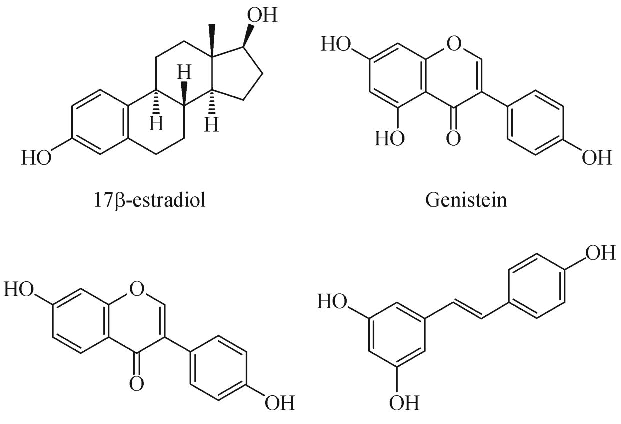
## Anti-inflammatory and anti-obesity activity of phytoestrogens

Natural products with estrogenic activity have been used for some time now as potential anti-obesity agents, including genistein and resveratrol. Much like E2, phytoestrogens are phenolic compounds capable of direct free radical scavenging thereby reducing ROS production and downstream inflammatory signaling (Fig. 3). However, unlike E2, the phytoestrogens have generally weak affinity to estrogen receptors compared to E2, in particular ERα (Kuiper et al., 1998). As mentioned previously, because the α subtype is widely expressed, many of the anti-obesity effects of these compounds may be due to estrogen receptor-independent signaling. Interestingly though, a recent study demonstrated an estrogen receptor-dependent effect of resveratrol to reduce hepatic IL-6 in a trauma-hemorrhage model (Yu et al., 2008). Additionally, both genistein and daidzein have also been shown to prevent endoplasmic reticulum stress activation in neuroblastoma cells (Park et al., 2009). As endoplasmic reticulum stress is a known activator of both NFκB and JNK, this may indicate ability for the phytoestrogens to reduce inflammatory signaling within the brain in an estrogen receptor-dependent fashion (Kaneko et al., 2003). Furthermore, in human adipocytes, anti-adipogenic effect of genistein was associated with decreased ERβ, which has an adipogenic role in adipose tissue (Park et al., 2009).

The key mediators of the inflammatory response, TNFα, IL-6, and cyclooxygenase (COX-2) are reduced by resveratrol in adipocytes (Gonzales and Orlando, 2008). It is well known that TNFα mediates its effects on adipocytes by activating the NFκB signaling and NFκB activity is elevated during adipocyte differentiation. Resveratrol is a potent inhibitor of NFκB activation indirectly influencing the adipocyte differentiation (Gonzales and Orlando, 2008). Further, in a recent *in vivo* study by Kim el al, rats fed with high-fat diet supplemented with resveratrol had lower body-weights and smaller adipose tissue depots accompanied with reduced expression of the pro-inflammatory cytokines, TNFα, interferon alpha (IFNα), interferon (IFNβ), and IL-6 in adipose tissue (Kim et al., 2011) suggesting that resveratrol, like E2, protected rats from high-fat diet-induced inflammation and obesity.

## Conclusions

As rates of overweight and obesity continue to rise, with some estimates suggesting 86% of the US population by 2030, a strong understanding behind the pathways that are affected during the development of obesity is needed (Wang et al., 2008). The increase of obesity and the diseases that make up the metabolic syndrome has resulted in a significant burden



17β-estradiol Genistein

Daidzein Resveratrol

**Figure 3** Molecular structure of estrogen and common phytoestrogens. Anti-inflammatory properties of the estrogens are in part due to the free-radical scavenging capabilities of the hydroxyl (-OH) groups in their structures. Reduction in free radicals and reactive oxygen species result in reduced cellular stress and inflammatory signaling.

that is being placed on the health care system that will only continue to become more taxing in the coming years (Clegg and Woods, 2004; Haslam and James, 2005). As inflammation emerges to be a contributing factor to the etiology of obesity, such pathways provide a potential target for pharmacological intervention.

Many observational studies support that once someone becomes obese, their likelihood of sustaining a weight-loss over time is very low. This would suggest that the optimal way of reducing obesity and its comorbidities is to prevent it instead of treating it. The anti-inflammatory properties of estrogens, both biologic and environmental, provide insight on potential sites of intervention in inflammatory pathways that may reduce the burden on the body caused by westernized diets. Further research is needed in this area.

## Acknowledgements

This review was written under the financial support of USDA ARS NC06871 and the UNCG Office of Research and Economic Development New Faculty grant.

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