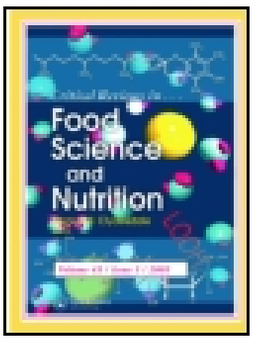

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Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: L. Melguizo Rodríguez , R. Illescas-Montes , V. J. Costela-Ruiz & O. García-Martínez (2020): Stimulation of brown adipose tissue by polyphenols in extra virgin olive oil, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1799930

To link to this article: https://doi.org/10.1080/10408398.2020.1799930

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1799930

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REVIEW

Stimulation of brown adipose tissue by polyphenols in extra virgin olive oil

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ABSTRACT

Obesity is one of the main public health problems of the 21st century resulting from an imbalance between calorie intake and energy expenditure. Currently, the search for new treatments against this pathology has become a priority. One of the therapeutic strategies against obesity could be the activation of brown adipose tissue through different molecules such as the phenolic compounds of extra virgin olive oil (EVOO). The objective of this review was to provide an update of scientific knowledge on the relationship between EVOO phenolic compounds and brown adipose tissue.

According to this review, it has been demonstrated that extra virgin olive oil phenolic compounds can have beneficial effects on obesity by activating brown adipose tissue and enhance thermogenesis through different signaling pathways mediated by molecules such as AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α) or sirtuin 1 (Sirt1).

KEYWORDS

brown adipose tissue; extra virgin olive oil; phenolic compounds; obesity

Introduction

Obesity is a chronic disease resulting from an imbalance between calorie intake and energy expenditure (Engin 2017). It is one of the main public health problems of the 21st century, affecting up to 35% of men and 40% of women in the USA (Flegal et al. 2016). It has been related to an increased risk of type 2 diabetes mellitus (Dandona, Aljada, and Bandyopadhyay 2004), metabolic syndrome (Grundy 2004), and atherosclerosis (Ritchie and Connell 2007), among other diseases. The search for measures to combat this epidemic has become a top priority. Interest has recently grown in the potential of brown adipose tissue (BAT) to prevent obesity and adverse metabolic events (Wang et al. 2015b; Mulya and Kirwan 2016; Rui 2017).

BAT, one of the main constituents of adipose tissue alongside white adipose tissue, is present in the interscapular, subscapular, axillary, perirenal, and periaortic regions of mammals, especially rodents (Zhang and Bi 2015). In humans, it is largely localized in cervical, supraclavicular, axillary, subscapular, pectoral, paravertebral, mediastinal, and perirenal regions (Harms and Seale 2013; Aldiss et al. 2017). BAT is formed by brown adipocytes, smaller than white adipocytes, with polygonal shape, multilocular lipid droplets, multiple mitochondria, and a central nucleus. It is a highly vascularized tissue innervated by the sympathetic nervous system (Betz and Enerbäck 2015; Bargut, Aguila, and Mandarim-de-Lacerda 2016). It is related to heat production and body temperature maintenance, i.e., adaptive thermogenesis (Cannon and Nedergaard 2004). However, this function is not exclusive to BAT, given that white adipocytes, especially those located in subcutaneous fat depots, can differentiate to beige adipocytes after exposure to various stimuli (Sharp et al. 2012). These include prolonged exposure to cold (Loncar, Afzelius, and Cannon 1988), β-adrenergic receptor stimulation (Cousin et al. 1992), or endocrine factors such as thyroid hormone (Solmonson and Mills 2016), fibroblast growth factor 21 (FGF21) (Fisher et al. 2012), or morphogenetic proteins (Whittle et al. 2012; Okla et al. 2015). This process has been designated adipose tissue browning (Wu, Cohen, and Spiegelman 2013; Montanari, Pošćić, and Colitti 2017).

Adaptive thermogenesis starts with the sympathetic nervous system-stimulated release of noradrenaline, which then interacts with β-adrenergic receptors (especially adrenergic receptor beta 3 [AR-beta3]) (Jimenez et al. 2002). The adrenergic receptor couples with a G protein of the Gs subtype, stimulating adenylyl cyclase (Granneman 1988) and consequently increasing cAMP (Zhao, Cannon, and Nedergaard 1997; Hoffmann et al. 2015). This molecule in turn acts by activating protein kinase A (PKA) (Fredriksson et al. 2001; Cao et al. 2001; Hoffmann et al. 2015), which induces the phosphorylation of nuclear-related proteins and cytosolic proteins. This PKA stimulation is responsible for inducing lipolysis *via* two different pathways: activation of both hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL); and perilipin phosphorylation (Holm et al. 1987; Chaudhry and Granneman 1999). This process mobilizes reserves of triglycerides, which degrade in the

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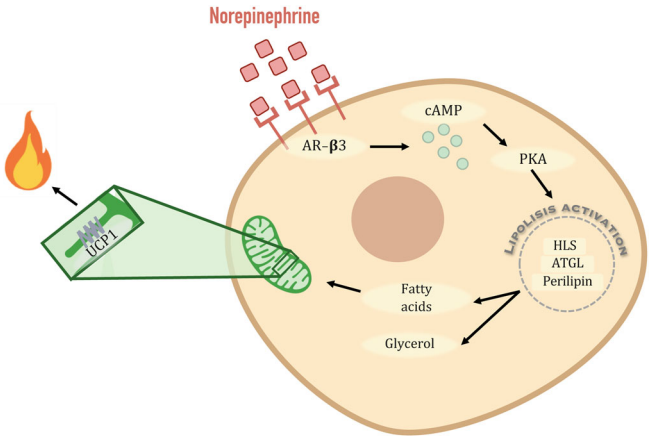

Figure 1. Adaptive thermogenesis process.

form of glycerol and fatty acids (Figure 1). The general activation/carnitine shuttle system transfers these fatty acids into the mitochondria, where they serve as substrate for *β*-oxidation and act on uncoupling protein one (UCP1), considered a specific BAT marker. This protein is located in the inner mitochondrial membrane and allows protons to filter into the mitochondrial matrix and dissipate the energy generated in the form of heat (Nicholls and Locke 1984; Matthias et al. 2000; Rial and González-Barroso 2001; Cannon and Nedergaard 2004). The mechanisms of interaction between fatty acids and UCP1 have not been elucidated, although there are three possible pathways: allosteric interaction, cofactor theory, and shuttling theory (Rial, Poustie, and Nicholls 1983; Winkler and Klingenberg 1994; Garlid et al. 2000; Jabůrek et al. 2001).

The downstream activation of p38 mitogen-activated protein kinase (MAPK) is one of the pathways stimulated by cAMP/PKA signaling. AMP-activated protein kinase (AMPK) is activated directly by AMP/ADP or through the phosphorylation of threonine residue 172 by upstream kinases, liver kinase B1 (LKB1), or Ca2+/calmodium-dependent protein kinases. AMPK phosphorylates and inhibits acetyl-CoA carboxylase and promotes fatty acid oxidation, reducing adipose tissue accumulation (Jäger et al. 2007; O'Neill, Holloway, and Steinberg 2013; Fullerton et al. 2013).

Over the past few years, some new factors have been proposed as possible BAT activators, including physical activity (Ruiz et al. 2015a, 2015b; Acosta et al. 2019) and certain nutritional factors, e.g., capsaicin (Baskaran et al. 2016), carotenoids (Murholm et al. 2013; Bonet et al. 2015), long chain (poly)unsaturated fatty acids (Fleckenstein-Elsen et al. 2016; Shen and McIntosh 2016), and polyphenols (Wang et al. 2015a; Mu et al. 2015; Lone et al. 2016; Choi et al. 2017). Recent studies have demonstrated the potential of olive oil and its phenolic compounds as thermogenesis inducers, either by increasing UCP1, UCP2, and UCP3 levels or by acting locally on BAT and skeletal muscle through the positive regulation of UCP mRNA expression (Rodríguez et al. 2002; Oi-Kano et al. 2007; Castro-Barquero et al. 2018).

Due to the high interest that the impact of phenolic compounds on health is generating in the scientific community, further study of the mechanism of action of EVOO phenolic compounds on the activation of brown adipose tissue is a new and important field of research based on the possible therapeutic potential of this tissue against obesity and related medical problems.

The objective of this review was to provide an update of scientific knowledge on the relationship between olive oil phenolic compounds and BAT.

Brown adipose tissue and olive oil phenolic compounds

Extra virgin olive oil (EVOO) contains five main phenolic compounds groups: flavonoids, lignans, phenolic acids, phenolic alcohols, and secoiridoids. Their presence can vary in quantity (150–700 mg/L) and quality according to the olive variety, degree of maturation, soil composition, climate, harvesting technique, processing, and storage (Uceda et al. 1999; Martínez Nieto, Hodaifa, and Lozano Peña 2010; Inglese et al. 2011).

It has been demonstrated that EVOO polyphenols can have beneficial effects on health and act against cardiovascular and neurodegenerative diseases, cancer, and osteoporosis, among other conditions (Berrougui, Ikhlef, and Khalil 2015; Casamenti and Stefani 2017; Melguizo-Rodríguez et al. 2018a, 2018b; Melguizo-Rodríguez et al. 2019).

Secoiridoids

Oleuropein

Oleuropein is a secondary metabolite of olive oil and belongs to the secoiridoid group (Alagna et al. 2016), which is responsible for endowing the oil with organoleptic properties such as acidity and bitterness (Servili and Montedoro 2002). Various studies have demonstrated the capacity of this phenolic compound to act on BAT. Thus, Oi-Kano et al. (2007) suggested that the oleuropein fraction, which includes oleuropein, and its absorbed form (oleuropein aglycone), can increase the secretion of adrenalin and noradrenalin, which are directly involved in BAT activation. An in vivo study (Oi-Kano et al. 2008) examined the effect of oleuropein on thermogenesis and the secretion of adrenalin and noradrenalin in rats fed with a high-fat diet supplemented with this phenolic compound. The researchers found that UCP1 concentrations and adrenalin and noradrenalin levels in urine and plasma were significantly higher in the animals fed with the oleuropein-supplemented diet than in controls. In 2017, the same authors studied the mechanisms of action of this molecule and of oleuropein aglycone on BAT, indicating that BAT can act on transient receptor potential ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1), related to weight maintenance, hormone secretion, thermogenesis and neuronal function, increasing the expression of UCP1 and reducing visceral fat (Oi-Kano et al. 2017).

Flavonoids

Luteolin

Luteolin is a phenolic compound of the flavonoid group and is present in a wide variety of foods, including olive oil, pepper, celery, and rosemary (López-Lázaro 2009). Luteolin has important functions in the organism, acting as a potent antioxidant and anti-inflammatory, and it has been found to exert a protective effect against neurological disease and cancer (Theoharides et al. 2015; Nabavi et al. 2015; Tuorkey 2016). This phenolic compound has been reported to prevent obesity development and inhibit adipocyte differentiation and lipid accumulation (Xu et al. 2014). Some authors have proposed that the mechanism of action underlying this protective effect against obesity may be related to adipose tissue browning, because luteolin can stimulate BAT and enhance thermogenesis *via* the AMPK/peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α) signaling pathway (Xiao et al. 2014; Zhang et al. 2016), which plays a key role in metabolism regulation.

Rutin

The flavonoid rutin or rutoside is characteristic of citruses, but a large amount is also present in olive oil (Oliveras-López et al. 2007). In a model of obese mice, Yuan et al. (2017) demonstrated that rutin induces BAT and beige adipose tissue by activating the sirtuin 1 (Sirt1)/PGC1α/mitochondrial transcription factor (Tfam) pathway and by increasing mitochondrial and UCP1 activation. Another mouse study described the potential of rutin to improve polycystic ovary syndrome by BAT activation, reducing insulin sensitivity, hyperandrogenism, acyclicity, and infertility, among other symptoms of this disease (Hu et al. 2017).

Quercetin

Quercetin is the most abundant flavonoid in the human diet and the most widespread in fruit and vegetables (Anand David, Arulmoli, and Parasuraman 2016). It is exceptional for its anti-inflammatory, antihypertensive, and vasodilator effects and for its antihypercholesterolemic, antiatherosclerotic, and anti-obesity properties (Boots, Haenen, and Bast 2008; Sultana and Anwar 2008; Salvamani et al. 2014). With regard to its anti-obesogenic effects, UCP1 expression and thermogenesis were increased in mice receiving a quercetin-enriched diet, and these effects appeared to be related to the AMPK/Sirt1 signaling pathway (Dong et al. 2014). Lee, Parks, and Kang (2017). observed white adipose tissue transdifferentiation after administering this phenolic compound in in vivo and in vitro studies, and they demonstrated the thermogenic potential of this molecule, finding that the highest dose administered (100 μM) enhanced the gene expression of markers closely related to this process, including Prdm 16, PGC1α, Ucp1, Fgf21, and Cidea. These results and the in vivo findings of Kuipers et al. (2018) in C57Bl/6 J mice suggest that quercetin may act by browning white adipose tissue.

According to Choi, Kim, and Yu (2018) the mechanism of action underlying the effect of this phenolic compound on BAT may be related to sympathetic nervous system stimulation, revealed by an increase in norepinephrine levels and the upregulation of β-adrenergic receptor mRNA. After feeding C57BL/6 mice a fat-rich diet supplemented with 0.05% quercetin, these authors observed stimulation of AMPK and the increased expression of genetic markers such as mitochondrial transcription factor A (TFAM), nuclear respiratory factor-1 (NRF-1), PR domain containing 16 (PRDM16), Cell death activator CIDE-A (Cidea), transmembrane protein 26 (TMEM26), and UCP1. UCP1 was also increased in in vitro studies in 3T3-L1 adipocytes of murine origin.

Cyanidin 3 glucoside

The anthocyanin cyanidin 3 glucoside is widely distributed in nature and abundantly present in Turkish olive oil (Aslı Yorulmaz et al. 2012). Its action on systemic energy homeostasis was demonstrated by You et al. (2017), who found that 16 weeks of treatment with guanine nucleotide-exchanger protein (C3G) at a dose of 1 mg/mL stimulated BAT in C57BLKS/J-Leprdb/Leprdb (db/db) mice, inducing the formation of beige adipocytes. This treatment enhanced the gene expression of thermogenesis-related markers (e.g., UCP1) and activated and stimulated the mitochondrial function of BAT, a metabolically active tissue characterized by an abundance of mitochondria.

Phenolic acids

Chlorogenic acid

Chlorogenic acid is a phenolic compound present at low concentrations in olives and olive oil (Venditti et al. 2015). This simple phenol can also be found in other foods, including green coffee beans (Farah et al. 2008). This molecule has been found to act synergistically with leucine and its metabolite β-hydroxy-β-methylbutyrate as a natural thermogenic agent capable of stimulating AMPK and Sirt1, favoring fatty acid oxidation (Bruckbauer and Zemel 2014).

Vanillic acid

Olive oil is also an important source of vanillic acid, which acts as a potent aromatizing agent (Juturu 2014). This polyphenol has beneficial health effects and has demonstrated cardioprotective (Radmanesh et al. 2017), chemopreventive (Vinoth and Kowsalya 2018), and anti-obesogenic (Jung et al. 2018) properties. Han et al. (2018) reported that its protective effect against obesity may be mediated by its action on BAT; in their study of C57BL/6J mice fed with a high-fat and high-fructose diet supplemented with vanillic acid, they found that this polyphenol can stimulate thermogenesis, BAT mitochondrial activity, and inguinal white adipose tissue browning. Jung et al. (2018) postulated that the action mechanism underlying this upregulation of thermogenesis may be related to activation of the AMPK signaling

Table 1. Mechanism of action of EVOO phenolic compounds.

EVOO phenolic compounds groupS	Phenolic compounds	MECHANISM OF ACTION	References
Flavonoids	Luteolin	Luteolin can stimulate BAT and enhance thermogenesis via the AMPK/peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α) signaling pathway	Xiao et al. 2014 Zhang et al. 2016
	Rutin	Rutin induces BAT and beige adipose tissue by activating the sirtuin 1 (Sirt1)/PGC1α/ mitochondrial transcription factor (Tfam) pathway and by increasing mitochondrial and UCP1 activation	Yuan et al. 2017
	Quercetin	1. Quercetin increase UCP1 expression and thermogenesis through AMPK/Sirt1 signaling pathway. High doses of quercetin (100 μM) enhance the expression of Prdm 16, PGC1α, Ucp1, Fgf21, and Cidea genes, closely related to thermogenesis. 2. Quercetin may stimulate sympathetic nervous system with an increase in norepinephrine levels and the upregulation of β-adrenergic receptor mRNA. This polyphenol stimulates AMPK and increase expression of genetic markers such as mitochondrial transcription factor A (TFAM), nuclear respiratory factor-1 (NRF-1), PR domain containing 16 (PRDM16), Cell death activator CIDE-A (Cidea), transmembrane protein 26 (TMEM26), and UCP1	1. Dong et al. 2014 Lee, Parks, and Kang 2017 2. Choi, Kim, and Yu 2018
	Cyanidin-3-glucoside	This polyphenol induces the formation of beige adipocytes, enhancing the gene expression of thermogenesis-related markers (e.g., UCP1) and activating and stimulating the mitochondrial function of BAT	You et al. 2017
Phenolic acids	Chlorogenic acid	This molecule act synergistically with leucine and its metabolite β-hydroxy-β-methylbutyrate as a natural thermogenic agent capable of stimulating AMPK and Sirt1, favoring fatty acid oxidation	Bruckbauer and Zemel 2014
	Vanillic acid	1. This polyphenol can stimulate thermogenesis, BAT mitochondrial activity, and inguinal white adipose tissue browning. 2. The upregulation of thermogenesis induced by vanillic acid may be related to activation of the AMPK signaling pathway with an increase in mitochondrial activity, UCP1, and PGC1α (which stimulates the secretion of aminoisobutyric acid, a specific molecule related to adipose tissue browning)	1. Jung et al. 2018 2. Roberts et al. 2014
	Gallic acid	Gallic acid can act on the AMPK/ Sirt1 / PGC1α pathway and modify the expression of BAT genetic markers responsible for thermogenesis	Doan et al. 2015
Phenolic ALCOHOLS	Hydroxytyrosol	1. This compound inhibits the oxidation of low-density lipoproteins (LDLs) 2. Hydroxytyrosol promotes BAT stimulation by increasing UCP1 and AMPK in subcutaneous white adipose tissue	1. Covas et al. 2006 Soler Cantero 2009 2. Wang et al. 2019
Secoiridoids	Oleuropein/ Oleuropein aglycone	Oleuropein increase of the secretion of adrenalin, noradrenalin and UCP1 concentration which stimulate BAT. BAT can act on transient receptor potential ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1), related to weight maintenance, hormone secretion, thermogenesis and neuronal function and reducing visceral fat	Oi-Kano et al. 2008 Oi-Kano et al. 2017

pathway. They administered vanillic acid at doses of 10, 100, and 1000 mg/kg/d to obese mice and observed increases in mitochondrial activity, UCP1, and PGC1α. PGC1α stimulates the secretion of aminoisobutyric acid, which also participates in adipose tissue browning (Roberts et al. 2014).

Gallic acid

Gallic acid is an organic acid found in free form in plant galls and can be obtained by the hydrolysis of tannins. Besides its antioxidant function, gallic acid possesses anti-carcinogenic, anti-mutagenic, anti-allergic, and anti-inflammatory properties (Cheorun Jo et al. 2006; Kahkeshani et al. 2019). In vivo studies have indicated a protective effect of gallic acid against obesity and dyslipidemia (Latha and Daisy 2011; Oi et al. 2012; Setayesh et al. 2019), although the underlying mechanisms of action have not been fully elucidated. In vitro studies of the HepG2 cell line and in vivo mouse experiments found that gallic acid can act on the AMPK/Sirt1/PGC1α pathway and modify the expression of BAT genetic markers responsible for thermogenesis,

supporting their usefulness against metabolic diseases (Doan et al. 2015).

Phenolic alcohols

Hydroxytyrosol

Hydroxytyrosol is the main phenolic alcohol in EVOO (Bonoli et al. 2004), although its concentration is generally low in fresh oils and increases during storage (Montedoro et al. 1992). Various studies have confirmed that this compound inhibits the oxidation of low-density lipoproteins (LDLs) (Covas et al. 2006; Soler Cantero 2009). However, Oi-Kano et al. (2007) reported that hydroxytyrosol has no effect on BAT, observing no difference between rats receiving a femoral dose of 10 or 30 mmol/L and those injected with vehicle alone. In contrast, a study by Wang et al. (2019) of mice exposed to fine particular matter ($\leq$2.5 μM) showed that hydroxytyrosol promoted BAT stimulation by increasing UCP1 and AMPK in subcutaneous white adipose tissue.

Conclusion

The phenolic compounds in olive oil may be useful in the management of obesity through their stimulating effect on BAT and their anti-obesogenic potential (Table 1). However, most published evidence is based on animal models, and further research is needed on the effects of EVOO phenolic compounds in animals and humans, exploring in greater depth their mechanism of action on BAT and their potential preventive role against metabolic diseases such as obesity.

Acknowledgements

This study was supported by the research group BIO277 (Junta de Andalucía) and Department of Nursing (University of Granada). The work outlined in this article has been partially funded by the Spanish Ministry of Education under FPU fellowship reference FPU16-04141.

Disclosure statement

The authors declare that they have no conflict of interest and/or competing financial interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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