Heliyon 7 (2021) e07695

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

A review of the lipolytic effects and the reduction of abdominal fat from bioactive compounds and moro orange extracts

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HIGHLIGHTS

- First comprehensive review of pharmacological and molecular mechanisms involving *Citrus sinensis*.
- Anthocyanins upregulate the target genes of β-oxidation and downregulate the main components of adipogenic pathways.
- Synephrine regulates thermogenesis and browning of adipose tissue and.
- Flavonoids inhibited the activation of the NF-kB and JNK pathways.

ARTICLE INFO

Keywords:
Lipolytic effects
Thermogenic effects
Fat reduction
Citrus sinensis
Moro orange

ABSTRACT

Dietary supplementation containing *Citrus sinensis* extract is being widely used for weight loss due to its anti-adipogenic and antioxidant effects that regulate the metabolism of fatty acids. Bioactive compounds upregulate PPARα in the liver tissue, increasing oxidation of fatty acids and improving insulin sensitivity in addition to decreasing the expression of genes involved in the synthesis of fatty acids, such as LXRα and FAS. Studies on synephrine demonstrated their ability to stimulate the development of beige adipose tissue through greater expression of UCP1 and mtTFA, contributing to an increase in thermogenesis and mitochondrial biogenesis. However, despite its widespread use to reduce abdominal fat, few scientific studies have consensually proven the effectiveness of Moro orange extract for weight loss. This literature review summarizes the current information on the pharmacological and molecular mechanisms involved in the modulation of lipid metabolism by the bioactive compounds present in Moro orange extract.

1. Introduction

Citrus sinensis (L.) Osbeck (*Citrus aurantium dulcis*) is a variety of pigmented sweet oranges belonging to the Rutaceae family, typically grown in the area around Mount Etna in eastern Sicily (Italy) (Cardile et al., 2015; Tamokou et al., 2017). These oranges, known as Moro orange or red orange, are popularly commercialized as functional foods or as dry extract in dietary supplementation in order to promote maintenance of body weight and prevention of obesity (Farag et al., 2020; Russo et al., 2019).

Moro orange has a reddish coloration and a distinctive appearance due to the presence of pigments called anthocyanins that act as potent antioxidants and are not normally found in other citrus fruits. In addition, Moro oranges have greater concentration of vitamin C and phenolic bioactive compounds compared to yellow oranges (Cardile et al., 2015; Kaneko and Shirakawa, 2018).

The bioactive compounds in Moro red orange extract include anthocyanins, especially Cyanidin-3-O-β-glucoside (C3G); phenolic compounds, mainly Naringenin and Hesperetin; alkaloids, such as Synephrine; Ascorbic acid; and Hydroxycinnamic acids, such as Ferulic acid (Figure 1A-F). The combination of these compounds seems to act synergistically, potentiating its effect when associated with other weight loss protocols (Sousa et al., 2019).

Recently, much attention has been focused on these compounds in order to develop new strategies devised to ameliorate hyperglycemia and insulin sensitivity.

Many previous studies support that anthocyanins have a role in the regulation of adipocytokine gene expression, including adiponectin and

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https://doi.org/10.1016/j.heliyon.2021.e07695
Received 8 May 2021; Received in revised form 23 June 2021; Accepted 28 July 2021

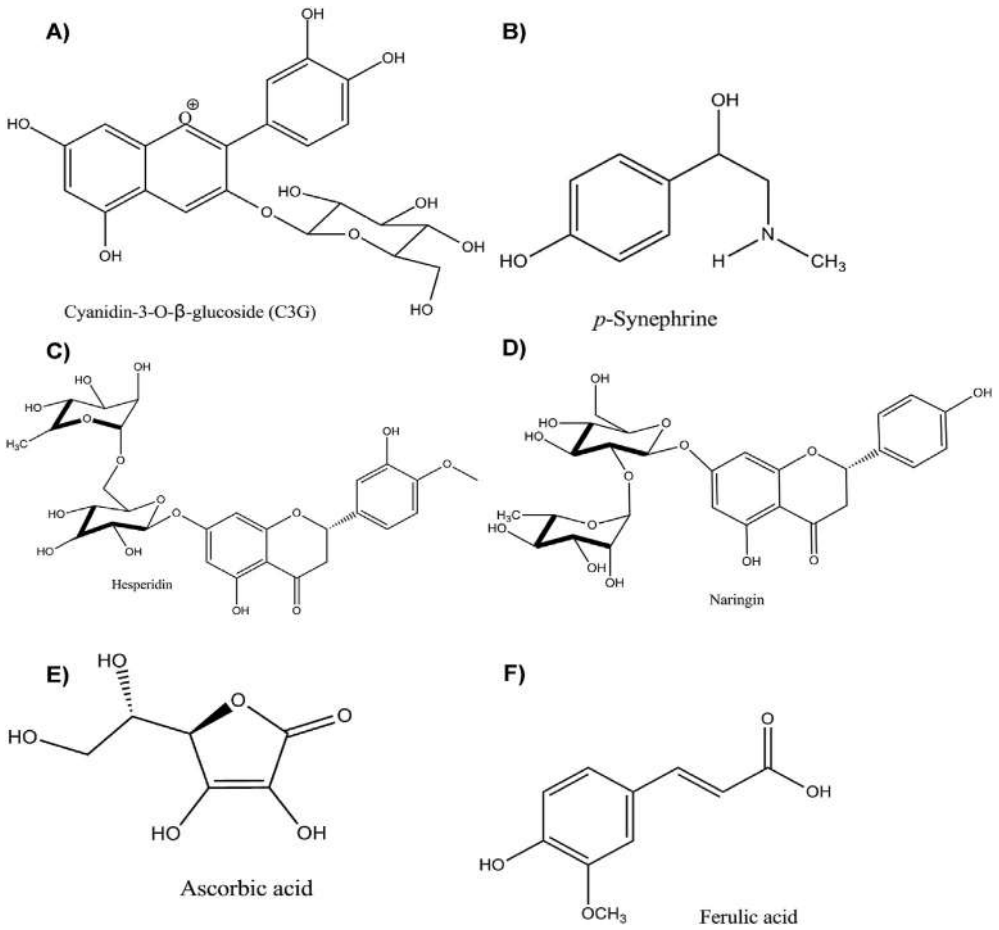

Figure 1. Basic chemical structure of bioactive compounds. A: Cyanidin-3-O-β-glucoside (C3G); B: *p*-Synephrine; C: Hesperidin; D: Naringin; E: Ascorbic acid; F: Ferulic acid.

leptin, improving insulin sensitivity (Tsuda et al., 2006; Tsuda, 2008); the downregulation of Plasminogen Activator Inhibitor-1 (PAI-1) and Interleukin 6 (IL-6), which are associated with the development of diabetes mellitus type 2 and obesity (Tsuda et al., 2006; Tsuda, 2008); the reduced intracellular production of reactive oxygen species; the attenuation of insulin resistance through inhibition of the JNK pathway (Guo et al., 2008); the modulation of genes related to lipid metabolism, such as Uncoupling Protein 2 (UCP2), acyl-CoA oxidase 1 and perilipin (Tsuda et al., 2006); as well as the regulation of hepatic fatty acid metabolism through AMPK-ACC-malonyl CoA-CPT1 pathway (Guo et al., 2012a,b).

In fact, studies also corroborate that flavonoids like naringenin may induce fatty acid oxidation through the activation of PPAR target genes, such as Cytochrome P450 Family 4 Subfamily A Member 11 (CYP4A11), Peroxisomal Acylcoenzyme A Oxidase (ACOX), Uncoupling Protein 1 (UCP1) and Apolipoprotein A-I (ApoAI), while inhibiting the adipogenic pathway by downregulating target genes of LXRα, such as Fatty Acid Synthase (FAS), Phospholipid-transporting ATPase ABCA1 (ABCA1), ATP Binding Cassette Subfamily G Member 1 (ABCG1), and 3-Hydroxy-3-methylglutaryl-CoA Reductase (HMGR) (Goldwasser et al., 2010a).

Furthermore, Moro orange has been reported to exhibit antioxidant, anti-inflammatory, anti-diabetic, anti-obesity, antitumor, anti-neuroinflammatory, immunomodulatory and cardiovascular protective properties (Dosoky and Setzer, 2018; Gandhi et al., 2020; Lv et al., 2015; Montalbano et al., 2019). Moreover, numerous studies support other varied properties of the essential oils of *Citrus sinenesis*, which include liver, pancreatic, vascular and renal protection. As well as antibacterial, antifungal, antiviral, antihelmintic, larvicidal, insecticidal, anxiolytic, relaxing, pain relief and acne treatment (Dosoky and Setzer, 2018). In addition, the dried extract of Moro orange is marketed as a new therapeutic approach to reduce abdominal and waist fat (Silva and Lima Filho, 2020).

Indeed, there are many pharmacological mechanisms of bioactive agents in the regulation of lipid metabolism; however, they are still unknown in the literature. The results of clinical research still seem to be divergent and insufficient to prove the effectiveness of Moro orange extract in the management and weight loss (Feng and Wang, 2018).

Therefore, this literature review focuses on the biological activities and molecular mechanisms of Moro orange extract's bioactive compounds in the context of obesity prevention and regulation of metabolic syndrome.

2. Materials and methods

2.1. Search strategy

This study is a literature review conducted in databases Web of Science, PubMed and Science Direct on the use of the herbal medicine "*Citrus sinensis*" for the treatment of metabolic disorders and weight loss. The keywords used in the research were: "anthocyanins", "cyanidin-3-glucoside", "*citrus sinensis* lipolysis", "*citrus sinensis* flavonoids", "orange moro weight loss" and "synephrine". Articles would become eligible if they comprised the period from 2015 to March 2021. Additionally,

articles written in languages other than English, Portuguese or Spanish were excluded. Due to our inclusion and exclusion criteria, the duplicate articles were eliminated.

2.2. Study selection criteria

Studies were selected for inclusion in the review process it they met the following criteria (see Figure 2):

(i) basic research on the effects of the main bioactive components of Moro orange extract mainly in experimental murine models and human adipocyte cell culture.
(ii) information on the association of natural bioactive compounds with inflammatory biomarkers.
(iii) studies on the mechanisms of pharmacological action, molecular modulation and the gene expression profile of the phytochemical.
(iv) clinical research on the effects of Moro orange extract on men and women.
(v) clinical research on the effects on body weight, waist circumference, lipid profile and physical activity.
(vi) research on the synergistic action of bioactives with other compounds.

3. Results

3.1. Moro orange extract gene regulation and pharmacological mechanisms

Scientific studies demonstrate the role of Moro orange extract in preventing metabolic disorders, obesity, insulin resistance, liver steatosis and cardiovascular diseases (Rupasinghe et al., 2016). This therapeutic action is due to the synergistic mechanism between the bioactive compounds promoting weight management, reduction of triglycerides and total cholesterols (Sousa et al., 2019).

These compounds upregulate the expression of lipolytic genes in the liver by regulating enzymes involved in β-oxidation such as peroxisome proliferator activated receptor (PPAR) α and acyl-CoA oxidase while inhibiting the expression of lipogenic genes such as Liver X Receptor (LXR) and Fatty Acid Synthase (FAS) substantially improving fat accumulation in liver and the reduction of blood levels of triacylglycerols (Figure 3) (Nakajima, 2016).

Recently studies have documented that the role of anthocyanins such as Cyanidin-3-glucoside (C3G) or Cyanidin (CYN) contributes to increase the secretion of adipocytokines (adiponectin and leptin) and to positively regulate a specific gene expression of adipocytes without PPARγ

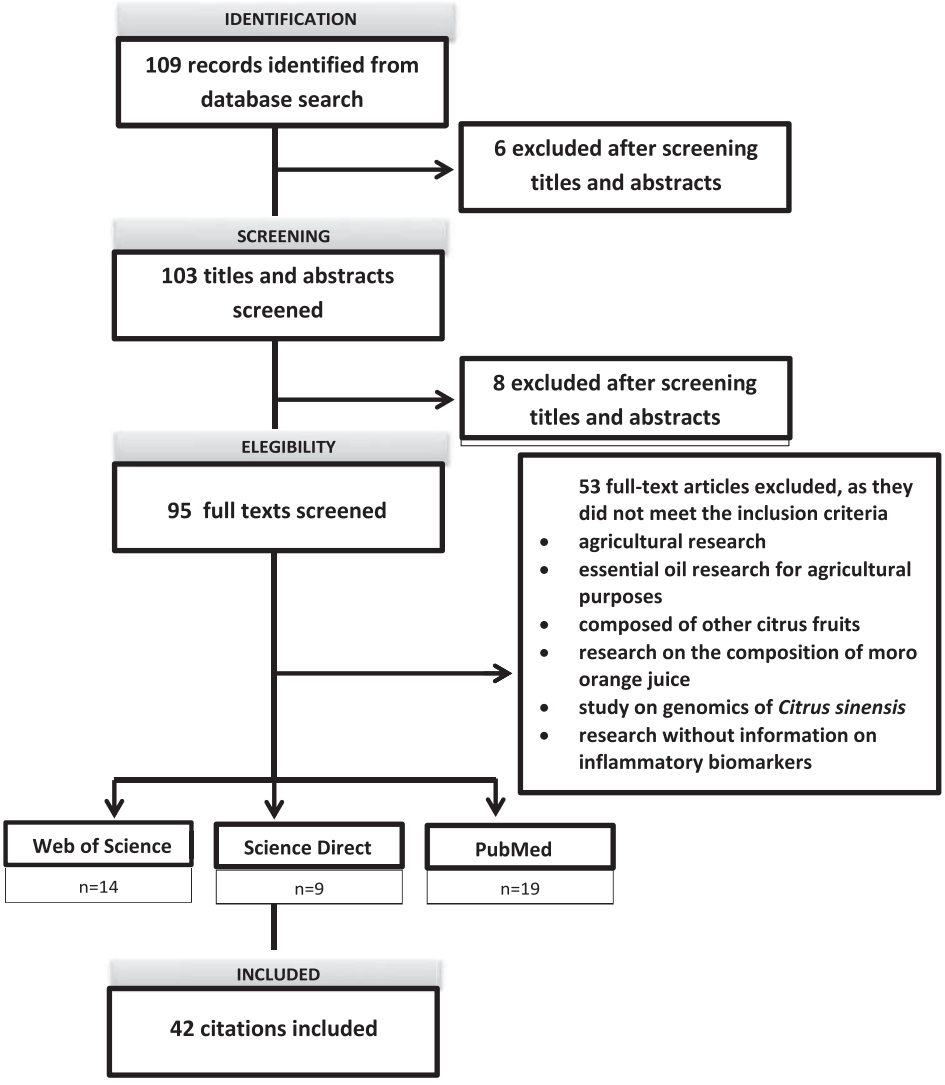

Figure 2. Flow diagram of the literature review.

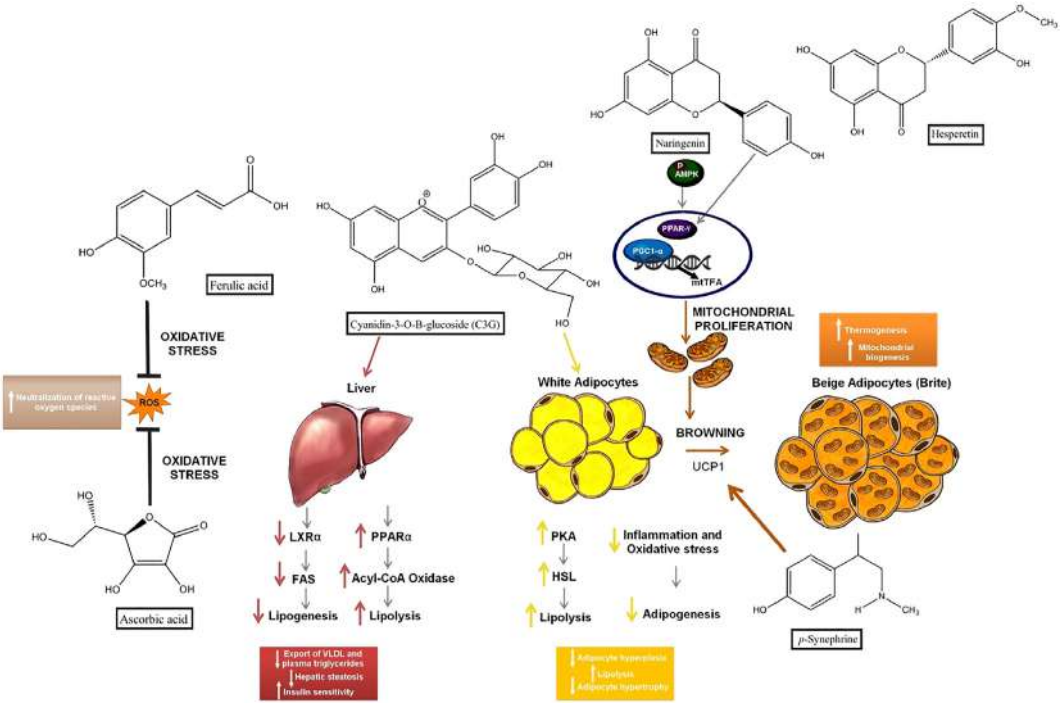

Figure 3. Schematic model of the pharmacological action mechanisms of *Citrus sinensis* (Adapted from Jia et al., 2020; Wang et al., 2019). Ferulic acid and Ascorbic acid act mainly by neutralizing reactive oxygen species. Anthocyanin C3G downregulates adipogenic genes in the liver such as Liver X Alpha Receptor (LXRα) and Fatty Acid Synthase (FAS) reducing lipogenesis, while upregulating genes involved in lipid β-oxidation such as Peroxisome Proliferator-activated Receptor Alpha (PPARα) and Acyl- coA Oxidase. C3G-mediated activation also induces the hydrolysis of triglycerides through the activation of lipases such as Hormone-sensitive Lipase (HSL) resulting in the process of lipolysis. Furthermore, C3G reduces inflammatory markers and oxidative stress, attenuating stimuli to the adipogenic pathway. Naringenin and Hesperitin act as important anti-inflammatory bioactive agents; in addition, naringenin increases AMP-activated protein kinase (AMPK) and Peroxisome Proliferator-activated Receptor Gamma (PPARγ). PPARγ and PGC-1α interact by binding to DNA, promoting the expression of Mitochondrial transcription factor A (mtTFA) and resulting in the modulation of mitochondrial biogenesis. *p*-Synephrine stimulates the transdifferentiation of white adipose tissue (WAT) into beige adipose tissue (Brites) by increasing the expression of Uncoupling Protein 1 (UCP-1).
Abbreviations: ROS: Reactive oxygen species; LXRα: Liver X receptor alpha; FAS: Fatty acid synthase; PPARα: Peroxisome proliferator-activated receptor alpha; PKA: Protein kinase A; HSL: Hormone-sensitive lipase; AMPK: AMP-activated protein kinase; PPARγ: Peroxisome proliferator-activated receptor gamma; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1 alpha; mtTFA: Mitochondrial transcription factor A; UCP1: Uncoupling Protein 1; VLDL: Very low-density lipoprotein.

activation, this activity of adipocytokines is an important mechanism in improving the insulin sensitivity and metabolic regulation (Sivamaruthi et al., 2020).

In addition, citrus polyphenols such as Naringenin and Hesperetin act to inhibit the ERK and NFκB pathways, contributing to the reduction of free fatty acids (FFA), and inhibiting pro-inflammatory markers, and consequently, further improving insulin sensitivity (Figure 5B) (Nakajima, 2016; Pereira, 2015).

Interestingly, another bioactive compound in Moro orange extract is the alkaloid known as Synephrine which acts as a β3 adrenergic agonist promoting an increase in thermogenesis leading to β-oxidation by brown adipose tissue (BAT) (Figure 3). Furthermore, it promotes the activation of hallmarks of the browning adipose tissue, in which it induces thermogenesis and the proliferation of mitochondria in white adipocytes (WAT) (Hu et al., 2020).

3.2. Anthocyanins regulate target genes involved in fatty acid oxidation and inhibit key mechanisms of the adipogenic transcriptional pathway

Anthocyanidins and their glycosides, anthocyanins, are essential water-soluble pigments that contribute to the coloring of various flowers, seeds, fruits and plants. They are phytochemicals belonging to a class of flavonoids that have recently demonstrated several promising biological activities in human health including prevents dyslipidaemia, type 2 diabetes, neurodegeneration, cardiovascular disease, liver diseases and cancer (Jia et al., 2020; Lv et al., 2015; Rupasinghe et al., 2016). Anthocyanins are found naturally in a variety of dark-colored foods such as apple, apricot, blackberry, blackcurrant, blueberry, cranberry, grape, purple carrot, raspberry, strawberry and some other citrus fruits (Zhang et al., 2019; Sivamaruthi et al., 2020).

Cyanidin-3-glucoside (C3G) is a major flavonoid anthocyanin found in plant-based foods and its daily intake has suggested attenuating adipose tissue inflammation and improving mitochondrial biogenesis (Zhang and de Mejia, 2020).

Interestingly, C3G is a molecular structure more stable than its aglycone cyanidin (CYN) form in aqueous solution; therefore, C3G is more bioavailable and more active than the cyanidin (CYN) form in human tissues. However, the mechanisms of action and the target genes of C3G still remain unclear (Jia et al., 2020).

A study by using human HepG2 hepatocytes treated with Cyanidin-3-O-β-glucoside suggested substantially induced AMPK downstream target acetyl CoA carboxylase (ACC) phosphorylation and inactivation accompanied by a decrease in malonyl CoA contents via the allosteric regulation of CPT-1 (Rupasinghe et al., 2016). Demonstrating the important role in the downregulation of genes involved in the adipogenic transcriptional network (Figure 3).

Consistently, supplementation with Moro orange extract significantly decreased the activation of both ACC and FAS enzymes, probably due to the suppression of PPARγ and C/EBPα adipogenic markers (Tomasello et al., 2019).

So far, according to research, the possible mechanisms of genetic modulation of anthocyanins indicate an induction of fatty acid oxidation

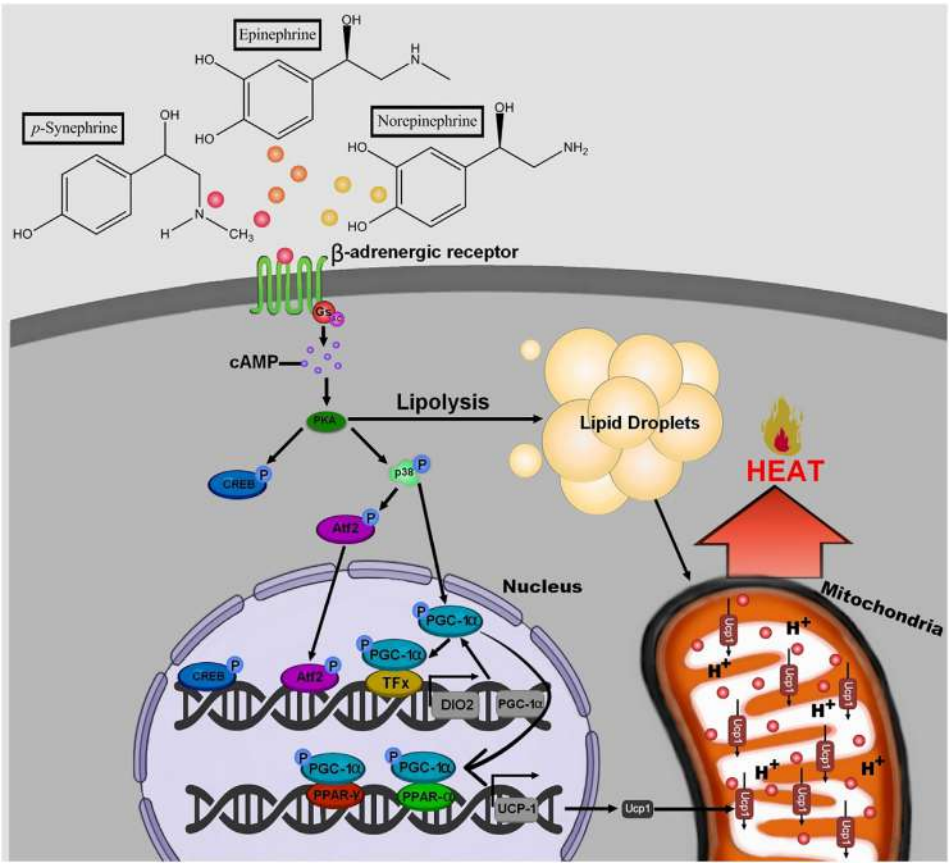

Figure 4. Proposed scheme for the transcriptional regulation of thermogenesis in adipocytes by activating β-adrenergic receptors (Adapted from Wang et al., 2019). The catecholamines Epinephrine, Norepinephrine and the alkaloid *p*-Synephrine (orange, yellow and red circles, respectively), bind to β-adrenoreceptors through the G subunit (GS), leading to the activation of adenylyl cyclase (Ac), promoting an increase in cyclic AMP levels (cAMP) (purple circles) and improving Protein kinase A activity (PKA). PKA induces the hydrolysis of triglycerides to free fatty acids (FFA) through the activation of lipases. These FFA activate mitochondrial uncoupling protein 1 (UCP1) (red rectangles) located in the inner mitochondrial membrane, which enhances proton leak (H^+) and, consequently, thermogenesis. On the other hand, PKA still activates cAMP response element-binding protein (CREB) (dark blue circles), p38 mitogen-activated protein kinases (p38 MAPK) (aquamarine shape), Atf2 and PGC-1α. PPGC-1α (light blue circles) interacts with the thyroid receptor (TFx) (yellow circles), PPARα (light green circles) and PPARγ (dark red circles) when it binds to DNA, thus inducing transcriptional effects in the nucleus for the synthesis of UCP1.
Abbreviations: Gs: G protein subunit; AC: Adenylyl cyclase; cAMP: Cyclic adenosine monophosphate; PKA: Protein kinase A; CREB: cAMP response element-binding protein; p38 MAPK: p38 mitogen-activated protein kinases; ATF2: activating transcription factor 2; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1 alpha; TFx: thyroid receptor; DIO2: type II deiodinase; PPARα: peroxisome proliferator-activated receptors alpha; PPARγ: peroxisome proliferator-activated receptors gamma; UCP1: Uncoupling Protein 1.

via AMPK while simultaneously inhibiting key mechanisms of fatty acid synthesis (Figure 3) (Rupasinghe et al., 2016).

In fact, the evidence still supports the ability of anthocyanins to differentially regulate genes such as PPAR-α, PPAR-δ, UCP-2, UCP-3 and mitochondrial transcription factor A (mtTFA) that also participate in the modulation of lipid metabolism (Rupasinghe et al., 2016).

Additionally, other studies indicate that anthocyanin supplementation (Cyanidin or C3G) improves the secretion of adiponectin and leptin in rat adipocytes independently of PPARγ. Specifically, cyanidin increases leptin secretion while C3G does not appear to significantly affect the secretion of adipocytokines (Sivamaruthi et al., 2020).

And more recently, studies show that C3G is a possibility for new approaches to treatment and prevention of obesity due to the potential for increased BAT activation and beige cell formation in WAT through greater proliferation and mitochondrial activity. In summary, this activity appears to be modulated mainly by better expression of genes like PGC1α, mtTFA, NRF1/2 and UCP1 in both BAT and WAT tissues (Kang et al., 2018; You et al., 2018).

Finally, all of these target mechanisms seem promising in the regulation of the systemic energy balance through the improvement of thermogenic capacity.

3.3. Synephrine in regulating non-shivering thermogenesis and browning of adipose tissue

Synephrine is a bioactive alkaloid compound found naturally in *Citrus sinensis* and in another *Citrus* spp such as *Citrus aurantium*, *C. reticulata*, *C. deliciosa*, *C. limon*, *C. limonia* and *C. unshiu* (Alves, 2018).

This alkaloid modulates a sympathomimetic action due to its structural similarity to the adrenergic amines ephedrine and catecholamines (Stohs, 2017).

Synephrine is found in its forms of *p*-synephrine isomers which have a hydroxyl group located in the *para* position of the benzene ring as opposed to *m*-synephrine (phenylephrine) which is in the *meta* position and a third isoform called *o*-synephrine, in which, the benzene ring is in the ortho position, the latter isomer not found in nature and not even used as a pharmacological agent (Fagundes, 2016). This is important because the two structures have different pharmacological effects due to their respective affinities to adrenoreceptors. In addition, *m*-synephrine isn't found naturally in citrus species (Ruiz-Moreno et al., 2021).

The *p*-synephrine has properties of α-adrenergic and β-adrenergic agonists and acts more similarly to norepinephrine (Figure 3). Despite this, studies on binding to the receptor have shown that the natural forms of the L-enantiomer of *p*-synephrine bound to the β-1 and β-2 adrenergic receptors 40,000 times less readily than norepinephrine. In addition, the binding activities of the L-forms of *p*-synephrine to α1 and α2 adrenergic receptors were also examined, demonstrating that they were approximately 10,000 times less active in binding to both adrenoreceptors (Ruiz-Moreno et al., 2021). Based on these study results, the L-form of *p*-synephrine demonstrated very low binding affinity for α-1 and α-2 as well as β-1 and β-2 adrenoreceptors compared to norepinephrine, epinephrine, ephedrine and *m*-synephrine, indicating that it would exhibit very little cardiovascular activity. In more recent studies it has been suggested that *p*-synephrine may act as a rather antagonist of the pre-synaptic adrenoreceptor subtypes α2a and α2c-adrenoreceptors (Ruiz-Moreno et al., 2021; Stohs, 2017).

Most importantly, several studies reinforce that *p*-synephrine promotes the activation of β3-adrenergic receptors that modulate the mechanism of action of thermogenesis and, consequently, stimulate weight loss (Figure 4) (Takagi et al., 2018). Interestingly, BAT and WAT browning are currently potential targets for emerging therapeutic strategies such as forms of treatment for obesity and factors associated with metabolic disorders (Herz and Kiefer, 2019).

In fact, recent research shows that synephrine can induce the differentiation of these thermogenic adipocytes, called beige adipocytes. These beige adipocytes are white adipocytes that altered gene expression via β3-adrenoceptor activation and started to share multilocular morphological characteristics, increased mitochondrial density and UCP1 expression similar to brown adipocytes. And they hypothesize that this promotion of thermogenesis depends on activation of specific gene programs such as ATF2, PGC-1α, C/EBP and PPARγ that lead to the expression of the thermogenic gene, as well as to the generation of heat (Figure 4) (Takagi et al., 2018; Wang et al., 2019).

All of these mechanisms of action together would stimulate lipolytic effects and weight loss.

3.4. Effects of naringenin and hesperetin on inflammation and regulation of several adipogenic key pathways

Flavonoids are a class of polyphenols found in plants as secondary metabolites, in which they confer innate functions of photoprotection, defense against invading insects and parasitic microorganisms, as well as being responsible for pigmentation and some organoleptic characteristics of these plants (Nakajima, 2016). These phenolic compounds are considered important for human consumption due to various biological activities previously described in the literature, such as antioxidant, antitumor, antiviral, antibacterial, improve immunity, repair DNA damage, anti-inflammatory, antiadipogenic and cardioprotective effects (Salehi et al., 2019).

Naringenin and Hesperetin belong to a subclass called flavanone. In citrus fruits flavonoids are widely found including Naringenin, Hesperidin, Rutin, Quercetin and several Polymethoxylated flavones (Nakajima, 2016; Gandhi et al., 2020).

The important thing to consider is that these citrus flavonoids are found especially in their glycosylated forms (Naringin and Hesperidin) or in their aglycon form (Naringenin and Hesperetin). And studies have already shown that the structure of polyphenol can modify its bioavailability for the body, since its aglycone form has better absorption compared to glycosylates in both murine and human models (Nakajima, 2016).

To date, a variety of studies have shown in the literature that the combined use of these flavonoids or isolates can suppress adipogenic and adipocyte differentiation markers through especially the modulation of PPARγ, C/EBPα, C/EBPβ, SREBP-1 and even stimulating thermogenesis through the expression of UCP-2 (Rufino et al., 2021).

Interestingly, naringenin supplementation reduced adipose tissue weight gain and triacylglycerol content in rats by increasing the expression PPARα, CPT-1, and UCP-2 in the liver which are target genes for fatty acid oxidation. Further in vitro investigations have revealed that 3T3-L1 preadipocytes treated with the flavonoid aglycosides naringenin and hesperetin inhibited adipogenesis by suppressing transcription factors including C/EBPα, PPARγ and SREBP-1c, in addition, to inducing lipolysis mechanisms in these adipocytes. Additionally, in another study also carried out on 3T3-L1 preadipocytes treated with naringenin inhibited adipogenesis through the molecular markers PPARγ, *a*P2, adiponutrin (ADPN) and STAT5s (Rufino et al., 2021).

Furthermore, it has been shown in Huh7 hepatic cells human treated with naringenin that these bioactive agents promote significant increased target genes that control fatty acid oxidation, such as CYP4A11, ACOX, ApoAI and UCP1 while concurrently, inhibiting LXRα-regulated lipogenesis genes, such FAS, ABCA1, ABCG1, and HMG CoA reductase (HMGR) (Rufino et al., 2021).

And to better elucidate the underlying mechanism by which naringenin modulates the transcriptional regulation of fat metabolism and mitochondrial biogenesis, Alam et al., (2013) proposed a model in which PPARγ promotes increased thermogenesis through greater expression of UCP-1, mtTFA and components of the respiratory chain complex via AMPK-PGC-1α–mediated pathway and, as a result, increased cellular respiration and mitochondrial proliferation (Figure 5A) (August, 2016; Ma et al., 2020).

Consistently, naringenin has also been shown to be useful in improving inflammatory changes in obese adipose tissue because it supposedly acts by inhibiting tissue-derived adipose MCP-1, which is a chemotactic factor that triggers the infiltration of macrophages in adipose tissue and which subsequently, it activates pro-inflammatory mediators such as TNF-α, thus hypothesizing that naringenin could suppress the inflammatory state by inhibiting the synthesis of TNF-α and MCP-1 (Abbasi-Parizad et al., 2020).

Previous studies also indicated that naringin exhibited pharmaceutical activities such as anti-inflammatory and increase insulin sensitivity, therefore, have proposed that hesperetin and naringenin could directly inhibit the secretion of pro-inflammatory cytokines as tumor necrosis factor-alpha (TNF-α) which is responsible by the NF-κB activation pathway which suppresses the transcription of IL-6 resulting in the reduction of the secretion of free fatty acids in an autocrine manner and therefore ameliorating the resistance to FFA-induced insulin. Furthermore, it suggests that inhibition of the ERK activation pathway prevents the TNF-alpha downregulation of the expression of antilipolytic genes such as phosphodiesterase-3B (PDE3B) and perilipin (Figure 5B). Thus, a greater expression of PDE3B promotes an increase in the hydrolysis of cAMP activated by insulin signaling, which results in the reduction of protein kinase A (PKA) activity and, consequently, the reduction of FFA while the reduction of perilipin phosphorylation decreases the activity of the hormone sensitive lipase (HSL) resulting in the final decrease in the hydrolysis of triglycerides in FFA and glycerol, therefore, decreasing insulin resistance induced by FFA (Nakajima, 2016).

In addition, some authors report that hesperidin has been shown to be a potent bioactive due to the anti-inflammatory and antioxidant pharmacological activity that occurs by some varied mechanisms, such as: (i) the inhibition of monocyte adhesion to endothelial cells by suppression of the intercellular adhesion molecule -1 (ICAM-1); (ii) suppression of pro-inflammatory cytokine genes that include TNF-α, IL-1β, IL-6; (iii) potent antioxidant activity by the positive regulation factor 2 related to NF-E2 (NRF2) which is a modulator of the enzymes glutathione S-transferase (GST) and quinine reductase (QR); (iv) inhibition of the formation of reactive oxygen species (ROS) and reduction of DNA damage (Fernández-Bedmar et al., 2017; Rocha, 2016).

3.5. The influence of moro orange extract bioactives on weight maintenance and loss of abdominal measurement

In experimental models, the nutritional intervention with Moro orange juice was able to reverse most of the metabolic abnormalities related to obese rats, including reduced body mass and improved biochemical profile (decreased triacylglycerol (21.35%), total cholesterol (14.0%) and LDL-cholesterol (16.2%) and increase in HDL-cholesterol) (Magalhães et al., 2020).

Another study in rats demonstrated that red orange extract and swimming practice have a synergistic action, reducing the cardiac deleterious effects caused by the high calorie diet. And it was reported that only supplementation with red orange extract was not efficient in reducing abdominal fat in rats treated with a high-calorie diet, therefore there being a need to associate regular exercise and a balanced diet to provide less abdominal adiposity (Rodrigues et al., 2020).

Other results report that oral administration of C3G in mice with high calorie diet reduced levels of plasma and liver triglycerides, adiposity and improved glucose sensitivity (Jia et al., 2020).

These findings can be reinforced by another study that demonstrated in 3T3-L1 preadipocytes treated with Moro orange extract the promotion

of anti-adipogenic and anti-oxidant effects, being useful in the neutralization and prevention of excess weight as a way to prevent severe conditions of obesity (Tomasello et al., 2019).

When it comes to human clinical studies, a recent randomized controlled trial study was conducted with 60 subjects taking the supplement containing *Citrus sinensis* extract and assessed after 12 weeks of dietary administration compared to the placebo group. The present results suggested that daily ingestion was able to reduce all parameters evaluated including body weight, BMI, waist and hip circumference (Kaneko and Shirakawa, 2018).

In another clinical study, they evaluated the effect of supplementation with *Citrus sinensis* extract (400 mg/day) for 12 weeks in healthy overweight human volunteers. And the results not only demonstrated that *Citrus sinensis* extract was able to induce a significant reduction in body mass index (BMI) after 4 weeks of treatment, but also presented clinical parameters such as body weight, BMI, waist and hip circumference significantly different from the placebo group (Cardile et al., 2015).

Contrasting these results, another study carried out with 11 obese women evaluating parameters associated with obesity, such as antioxidant status, lipid and metabolic profile and inflammatory biomarkers over a period of 12 weeks with daily administration of 500mL in two doses (250 mL) of commercial red orange juice. And the results show that the daily intake of red orange juice did not have significant effects on body weight, but indicated a decrease in the values of total cholesterol and LDL cholesterol (Azzini et al., 2017). In association, the study that investigated the influence of sweet orange juice consumption in healthy subjects revealed that there was no change in the participant's anthropometric parameters, but reduced some risk factors related to metabolic syndrome such as total cholesterol levels, LDL-C, C-reactive protein (PCR) and blood pressure, in addition to increasing antioxidant activity and normalizing the insulin resistance index (HOMA-IR) in some patients (Silveira et al., 2015).

In combination, another randomized clinical trial with 78 obese patients with a combination of a low calorie diet and the intake of 500 mL of orange juice analyzed over the 12-week period compared to the control group reported that the administration of orange juice contributed to weight loss, improved insulin sensitivity, lipid profile or inflammatory state and did not even contribute nutritionally to the quality of the diet (Ribeiro et al., 2017).

And finally, an integrative review evaluated the effects of phytochemicals present in orange juice on abdominal fat, and showed that

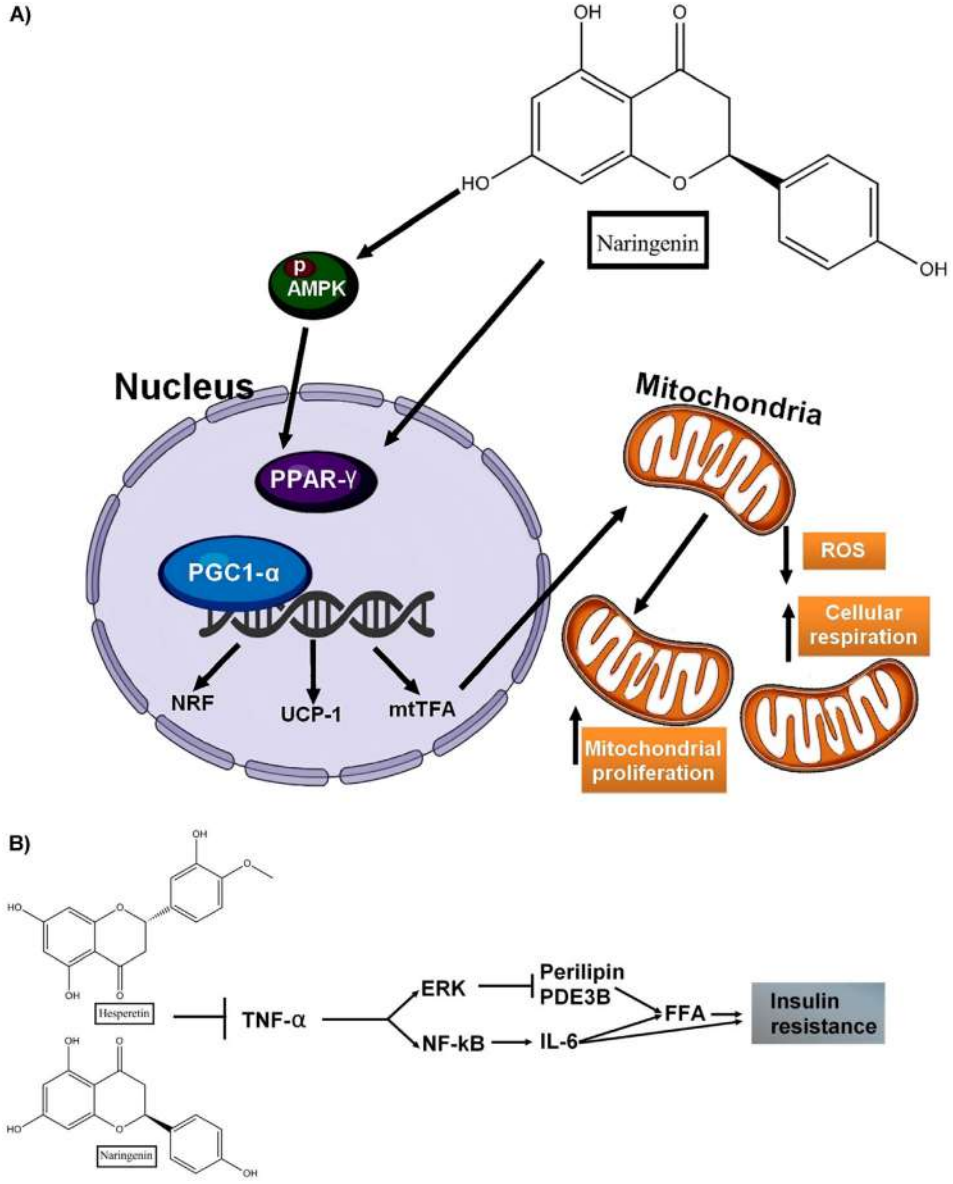

Figure 5. Proposed scheme for the transcriptional regulation of lipid metabolism, mitochondrial biogenesis and insulin sensitization (Adapted from Alam et al., 2013; Nakajima, 2016). A: Naringenin increases AMPK (dark green circle) which activates PPARγ (purple circle). PPARγ interacts with PGC-1α (blue circle) by regulating the expression of genes such as NRF, UCP-1, mtTFA and the components of the respiratory chain complex. The mtTFA factor is translocated to the mitochondria, promoting gene expression and mitochondrial replication. B: Inhibition of ERK and NFκB pathways through naringenin and hesperetin, culminating in the decrease of FFA secretion and attenuating insulin resistance.
Abbreviations: AMPK: AMP-activated protein kinase; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PPARγ: peroxisome proliferator-activated receptors gamma; NRF: nuclear respiratory factor; mtTFA: mitochondrial transcription factor A; UCP1: Uncoupling Protein 1; TNF-α: Tumor necrosis factor alpha; ERK: Extracellular signal-regulated kinase; NF-kB: Factor nuclear kappa B; IL-6: Interleukin 6; PDE3B: Phosphodiesterase 3B; FFA: Free fatty acids.

some studies have shown the ineffectiveness of the compound for this purpose and others have shown that the compound is capable of actually decreasing abdominal measurements. Therefore demonstrating that the scientific results are still controversial about the use of orange extract to decrease abdominal fat (Silva and Lima Filho, 2020).

3.6. Toxicity

Moro orange extract is widely used in dietary supplements marketed for weight loss and loss of abdominal measurements. Despite this, there is a concern about *Citrus sinensis* extract producing significant adverse effects when combined with other stimulating compounds such as caffeine or when accompanied by exercise. And clinical investigations attribute this potential cardiovascular effect mainly to the synephrine compound.

Unfortunately, there are few clinical studies on the safety and toxicological profile of synephrine in humans. Some research has shown that synephrine has low oral bioavailability in humans. And that after ingesting 46.9 mg of synephrine, it took 1–2 h to reach its maximum plasma concentration of 3 ng/mL, while the elimination half-life was about 3 h. In addition, they evaluated the extract of *Citrus aurantium* that contains synephrine in its composition and it showed low acute oral toxicity in rats (LD50 $>$ 5000 mg/kg) (Jakopin, 2019). In a study with mice treated with dry extract of *C. aurantium* standardized for 2.5% of *p*-synephrine (doses 300–5000 mg/kg) observed a reduction in the locomotor activity of these animals. And animals treated with *p*-synephrine (doses 150–2000 mg/kg) observed that in addition to the decrease in locomotor activity, they also presented symptoms of piloerection, salivation and exophthalmos, suggesting transient acute toxicity with effects that persisted for only 3–4 h (Fagundes, 2016; Kharchoufa et al., 2018; López-Gil et al., 2017).

As reported by Stohs (2017) previously reviewed 22 US FDA adverse event reports (AERs) from April 2004 through October 2009, which analyzed the involvement of products containing bitter orange (*C. aurantium*), in addition to 10 clinical case reports on the possible involvement in adverse events of products containing bitter orange (*p*-synephrine) that were published during this same period. In all these case reports, the authors suggest the extract of *C. aurantium* and/or p-synephrine as the probable agents that cause adverse events, despite the fact that these products consumed are poly-herbal, poly-alkaloids and poly-protoalkaloid. Among the adverse events included acute lateral-wall myocardial infarction, exercise-induced syncope associated with QT prolongation, vasospasm and stroke, ischemic stroke, ventricular fibrillation, variant angina, ischemic colitis, coronary spasm and thrombosis, and ST segment-elevation myocardial infarction (Stohs, 2017).

Despite the importance of these events, there are several factors that weren't taken into account in these case reports such as heart murmur, preexisting heart disease, hypertriglyceridemia, obesity, a history of smoking, gastroesophageal disease, sedentary lifestyle, sickle cell trait, dehydration, pneumonia, possible use of anabolic steroids and/or performance-enhancing drugs, high caffeine intake, and high alcohol consumption. Sometimes these products were neither considered recommended nor was it even clear whether these patients were taking other unreported dietary supplements and/or drugs (Stohs, 2017).

In fact, many cases of adverse reactions to products containing synephrine have reported a cardiotoxic potential and altered blood pressure. In spite of the importance of these case reports of assuming synephrine as a probable causative agent, many times these products were not even ingested by the daily dose recommendation and also many of these products were composed of different additional herbs, as well, it is not clear whether these patients made simultaneous use of other supplements or drugs (Jakopin, 2019).

In addition, there is a concern regarding the labeled content and doses of active compounds, as some research reports that many natural supplement products have a very different characteristic from the constitution between suppliers or even between their batches. These commercialized dietary products sometimes had very high synephrine concentrations, much lower or even nonexistent than what had been labeled (Pawar et al., 2020).

In contrast to these case reports, more recently a literature review revealed that no serious adverse events were directly attributed to bitter orange extract, *p*-synephrine or any form of a variety of juices and jellies consumed by millions daily. This is reinforced by a 2-month, double-blind, placebo-controlled study in healthy volunteer subjects who received 98 mg of synephrine daily and did not demonstrate adverse effects related particularly to heart rate and blood pressure. This study is considered to be the longest that has ever existed and although it used the highest dose to date, this study gives significant credibility to the safety of synephrine administration (Jakopin, 2019).

On the other hand, another concern would be about the ability of possible cardiotoxic effects to be increased by other stimulating compounds, in particular caffeine, which is often formulated together in dietary supplements.

For this reason, more recently, a risk assessment was carried out in Canada on the isolated or combined use of *p*-synephrine. The Intertek-Cantox Report indicated that the following specified dosage limits that include 70 mg of *p*-synephrine alone or 40 mg in combination with 320 mg of caffeine aren't likely to cause adverse effects. Even doses of 100 mg of p-synephrine alone or 70 mg of *p*-synephrine in combination with 400 mg of caffeine taken in divided doses and spaced out over the course of the day is unlikely to be associated with adverse effects on human health (Stohs, 2017).

In summary, despite the relative safety of these compounds, there are some concerns related to the counterfeiting of these products, the association between other stimulants and that should only be administered to healthy people.

4. Discussion

In recent years, functional and nutraceutical foods have received attention for their varied biological benefits for human health. And the properties of *Citrus Sinensis* (L.) Osbeck are becoming popular on the market as a dietary supplement due to the synergistic action between their bioactive compounds in the reduction of inflammation and in the control of body weight.

In fact, many studies demonstrate the effects of Moro orange extract on the marked reduction in the size of adipocytes and on the accumulation of lipids through the suppression of inflammatory markers, attenuation of oxidative stress, modulation of the secretion of adipocytokines, and mainly, the positive regulation in expression of lipolytic genes, inhibition of adipogenic pathways and increased thermogenesis. And all of these events seem to be enhanced by the synergistic action of these bioactive compounds on important allosteric active sites. Which makes *Citrus sinensis* extract supplementation an interesting auxiliary approach for the treatment and prevention of obesity and cardiovascular diseases. However, these biochemical effects seem to act more pronounced in animal models when related to humans, which reflects contradictory and divergent effects in clinical studies when treated with Moro orange extract.

Thus, our study brought to light new discoveries in the debate about the possible mechanism of action and the potential contribution of these compounds to the health of the population.

So far, the data suggest that most of these effects of Moro red orange on metabolic regulation are mediated by anthocyanins (especially C3G) and their metabolites through the induction of lipolysis via PPAR-α and inhibition of lipogenesis by suppression of LXRα and associated with synephrine that acts in browning adipose tissue by increasing the expression of UCP1 activated by β3-adrenergic agonist action. In addition, it is known that these compounds also have their effect amplified by other bioactive agents such as Naringenin and Hesperetin, which have a great antioxidant and anti-inflammatory effect, mainly by inhibiting the ERK and NF-kB pathways that improve insulin sensitivity, as well as,

Table 1. Presumed mechanisms of action and properties of phytochemicals present in *Citrus sinensis*.

Extract/compound	Experimental model	Daily dose	Duration	Extraction	Targets and Effects	Ref.
Flavonoids (especially cyanidin, hesperidin, naringenin or naringin)	I. In vivo, HFD-obese C57BL/6N mice	I. 50,100 and 200 mg/kg	I. 8 weeks	I. Cyanidin-3-O-Galactoside-Enriched *Aronia melanocarpa* Extract (AM-Ex)	I. Reduces food intake and the weight of WAT → Reduced serum levels of leptin. Inhibits adipogenesis → decrease of C/EBP-α, PPARγ, SREBP-1c, PAGC-1α, FAS, and aP2 mRNA expression (Lim et al., 2019).	[(Rufino et al., 2021)]
	II. In vitro, Adipocytes derived from human MSCs	II. 1, 10 and 25 μM	II. 8 days	II. Hesperidin	II. Reduces TGs content → Inhibited genes (C/EBPβ, SREBP-1c, and perilipin) involved in the three phases of adipogenesis (Gómez-Zorita et al., 2017).	
	III. In vivo, Male Long-Evans hooded rats	III. 0.003, 0.006, and 0.012% (g/100 g diet)	III. 6 weeks	III. Naringenin	III. Reduces BW and TGs contents in adipose tissue in rats → Increased PPARα, CPT-1, and UCP-2 expression in the liver (Cho et al., 2011).	
	IV. In vitro, 3T3-L1 preadipocytes	IV. 1–100 μM	IV. 12–48 h	IV. Naringenin	IV. Inhibits proliferation of preadipocytes → Decreased expression of PPARγ and MCE inhibition (Harmon and Harp, 2001).	
	V. In vitro, Huh7 hepatic cells	V.0–400 μM	V. 24 hours	V. Naringenin	V. Increases fatty acid oxidation → Induction of expression of PPARα coactivator (PGC1α) → induction of PPAR-regulated fatty acid oxidation genes, including CYP4A11, ACOX, UCP-1 and ApoAI (Goldwasser et al., 2010b).	
	VI. In vivo, Ovariectomized C57BL/6J mice	VI. diet supplemen-ted with 3%	VI. 11 weeks	VI. Naringenin	VI. Inhibits adipogenesis, increases lipolysis and fatty acid oxidation → Decreased leptin and leptin mRNA levels on lipid depot and decreased MCP-1 and IL-6 levels (Ke et al., 2015).	
	VII. In vitro, E0771 mouse mammary cancer cell line	VII. 50, 100, and 200 μM	VII. 24–48 h	VII. Naringenin	VII. Decreases BW, and adiposity (adipose mass, adipocyte size) → Increased phosphorylation of AMPK and regulation of energy expenditure (Ke et al., 2017).	
	VIII. In vitro, 3T3-L1 preadipocytes	VIII. 0.5 mg/mL; 0.5–1.5 mg/mL	VIII. 1–10 days	VIII. Naringenin-Enriched *Citrus unshiu* peel extract; Sinetroll	VIII. Inhibits adipogenesis and induces lipolysis → Suppression of mRNA and protein levels of C/EBPα, PPARγ and SREBP-1c (Lim et al., 2015).	
	IX. In vitro, 3T3-L1 preadipocytes	IX. 6–50 μg/mL	IX. 24–72 h	IX. Naringenin	IX. Inhibits adipogenesis → Inhibition of PPARγ, aP2, adiponutrin, and STAT5s (Richard et al., 2013).	
	X. In vivo, Ldlr−/− mice fed a high-fat, cholesterol- containing (HFHC) diet	X. diet supplemen-ted with 3%	X.12 weeks	X. Naringenin	X. Decreases adipocyte size and number → Reduced expression of TNF-α. Enhances energy expenditure and increases hepatic fatty acid oxidation → enhanced liver mRNA expressions of CPT-1a and PGC1a; reduced SREBP-1c mRNA expression. Decrease TC and TGs → decreased plasma VLDL and LDL (Burke et al., 2018).	
	XI. In vivo, High-fat/high-carbohydrate -fed Wistar rats	XI. 100 mg/kg	XI. 8 weeks	XI. Naringin	XI. Lowers abdominal fat deposition (Alam et al., 2013).	
	XII. In vivo, HFD-C57BL/6J mice	XII. 25, 50 or 100 mg/kg	XII. 8 weeks	XII. Naringin	XII. Reduces BW → Activation of AMPK, resulting in altered expression of SREBPs, PCSK9, and LDLR (Sui et al., 2018).	
	XIII. In vivo, HFD-C57BL/6J mice	XIII. 0.2 g/kg diet	XIII. 4 weeks	XIII. Naringin	XIII. Increases fatty acid oxidation → Activation of AMPK (Pu et al., 2012).	
p-Synephrine	-	-	-	*p*-synephrine	Acute intake of *p*-synephrine didn't modify running sprint performance, jumping capacity, or aerobic capacity. Acute ingestion of *p*-synephrine at a dose of 2–3 mg/kg enhanced the rate of fat oxidation during incremental and continuous exercise (30%–80% VO2peak). In exercise of increasing intensity the intake of *p*-synephrine increases the maximal rate of fat oxidation without affecting the workload at which Fatmax is obtained. *p*-Synephrine increases fat utilization during exercise at low-to-moderate intensities. In aerobic, anaerobic or resistance-based exercises, acute intake of p-synephrine produces little or none ergonomic benefit.	[(Ruiz-Moreno et al., 2021)]
Anthocyanins (C3G)	In vitro, HepG2 cells and HEK293 cells; In vivo, Male mice C57BL/6 J and PPARα-deficient	1, 10 and 50 μM; 50 mg/kg	24 h; 8 weeks	C3G	C3G is a direct agonist ligand of PPARs, having greater affinity for the PPARα subtype. Up-regulated expression of PPARα and PPARγ. PPARα activation → increased the oxidation of hepatic fatty acids and reduced fatty acid synthesis. PPARα activation → reduction of plasma and hepatic TG concentrations. PDH inhibition via PDK4 → stimulates ketogenesis and reduces hepatic citrate levels (stimulating fatty acid oxidation) while suppressing production of acetyl CoA from pyruvate and glycolysis → reducing fat accumulation in extra-adipose tissue, ameliorating lipotoxicity, and improving insulin resistance.	[(Jia et al., 2020)]

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Table 1 (*continued*)

Extract/compound	Experimental model	Daily dose	Duration	Extraction	Targets and Effects	Ref.
					C3G suppressed fatty acid synthesis, increased catabolic pathways and partially increased lipolysis in white adipose tissues, C3G increased levels of branched amino acids → improving protection against hepatic steatosis and NAFLD. C3G improved glucose tolerance and insulin sensitivity. Activation of the PPARα-PGC-1α-UCP1 → increased oxygen consumption and energy expenditure in BAT and reduced adiposity.	
Citrus sinensis (C3G)	In vivo, Wistar obese and diabetic rats	200 mL	28 days	Pure Moro orange juice	Decreased lipid uptake and hypertrophy of the adipocytes → increased expression of PPARγ. Increased expression of energy-expenditure related genes (AdipoQ (adiponectin) and Lep (leptin)). Increased expression of UCP2 and Acyl-CoA synthase → ↑energy consumption. Decreased blood glucose levels → increases phosphorylation Akt and FoxO1 leading to a downregulation of G6Pase and PEPCK. Reduction of hepatic cholesterol content, cholesterol esterification and increase the activity of LDL receptors (decreases the plasma concentrations of remaining chylomicrons and LDL).	[(Magalhães et al., 2020)]
Citrus sinensis	Human	250 mL–700 mL or 400 mg	Approximately 12 weeks	Orange juice or dry extract of Moro orange juice	Few evidences and non-significant results associated with anthropometric measurements. Improvement of the biochemical profile. Improvement of endocrine-metabolic conditions associated with glucose modulation. Attenuates inflammatory biomarkers, enhanced anti-oxidant effects and modulates immunological biomarkers.	[(Silva and Lima Filho, 2020)]
Citrus sinensis	In vivo, male Wistar rats	7 mg/kg	84 days	Dry extract of Moro orange juice	Swimming practice and Moro orange extract have synergistic action reducing the deleterious effects of the high calorie diet → ↑cardiac chambers thickness and ↑number of cardiomyocytes.	[(Rodrigues et al., 2020)]
Citrus flavonoids	-	-	-	*Citrus* species (Naringenin, hesperidin, ascorbic acid and polymethoxylated flavones)	Hesperidin has antioxidant and anti-inflammatory properties. Hesperidin decreased the expression of COX-2. Hesperidin inhibits tumor growth by increasing anti-oxidant defense system → induces apoptosis in cancer cells, decreasing cytokines and inflammatory enzymes, inhibits angiogenesis and metastasis. Hesperidin has antidiabetic effects → reduces levels of HbA1c and serum glucose. Hesperidin reduces levels of LDL, total cholesterol and triglycerides, while increasing HDL. Naringenina ameliorate the neurobehavioral defects induced by physical and chemical stimuli. Naringin restored the levels of all oxidative stress markers such as oxidative, nitrosative, enzymes, and mitochondrial complexes. Naringin has shown beneficial effects on obesity, diabetes, hypertension and metabolic syndrome. PMFs have greater metabolic stability and permeability, so they are more easily absorbed and have greater bioavailability. Nobiletin PMFs reduces the secretion of VLDL triglycerides, attenuating dyslipidemia. PMFs Nobiletin has reported anti-dementia activity. Nobiletin PMFs increase PKA in PC12D cells and rat hippocampal neurons. Nobiletin PMFs improves memory effects on various animal models (Alzheimer disease, oxidative stress, cholinergic neurodegeneration, and dysfunction of synaptic plasticity-related signaling). l-Ascorbic acid (AsA) prevents scurvy disease. AsA stimulates the formation of collagen, improves iron absorption, immune function and prevents cardiovascular disease and age-related macular degeneration. AsA reduces risks to lung, breast, stomach and esophageal cancers. Ingestion of AsA prevents oxidative damage in smokers and non-smokers who have been exposed to secondhand smoke.	[(Ma et al., 2020)]

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Table 1 (*continued*)

Extract/compound	Experimental model	Daily dose	Duration	Extraction	Targets and Effects	Ref.
Citrus Flavonoids (especially naringenin, naringin, hesperidin, hesperetin and Neohesperidin)	I. RAW264 cells and 3T3-L1 adipocytes; C57BL/6J Mice	I. 0, 10, and 50 μM; 100 mg/kg	I. 3 hours; 14 days	I. Naringenin	I. Inhibited MCP-1 expression and secretion in adipocytes. Also inhibited the production of MCP-1 induced by adipocyte-macrophage interaction. Suppressed the infiltration of macrophages in adipose tissues. Inhibition of the JNK pathway → downregulated MCP-1 (Yoshida et al., 2014).	[(Gandhi et al., 2020)]
	II. Wistar Rats	II. 10 mg/kg (intraperitoneal)	II.35 days	II. Naringenin	II. Naringenin ameliorated aortic reactivity dysfunction in diabetic rats → modulation of nitric acid-dependent pathway → attenuate lipid peroxidation and oxidative damage (Fallahi et al., 2012).	
	III. Wistar Rats	III. 20, 50, and 100 mg/kg	III. 56 days	III. Naringenin	III. Reversed hyperglycemia and down-regulated superoxide dismutase activity. Prevented diabetic neuropathy → reversed chemical and thermal hyperalgesia in diabetic rats (Hasanein and Fazeli, 2014).	
	IV. Sprague-Dawley Rats	IV. 100 mg/kg	IV. 28 days	IV. Naringin	IV. Reduced blood glucose, total cholesterol, triglycerides and LDL. Modulated fructose-induced and endothelial metabolic changes. Dysfunction → restored vasorelaxation mediated by acetylcholine. Improved NOx, eNOS and the expression of p-eNOS. Preserved endothelium-dependent relaxation in the aortae (Malakul et al., 2018).	
	V. C57BL/6J Mice	V. 100 mg/kg	V. 14 days	V. Naringenin	V. Inhibited the infiltration of neutrophils in adipose tissues → reduced the expression of several chemokines MCP -1 and MCP-3, in the adipose tissues (Tsuhako et al., 2020).	
	VI. Pancreatic islets and Wistar Rats	VI. 0.25, 0.5, 1, and 2 mg/mL and 50 mg/kg	VI. 1 and 24 h and 30 days	VI. Hesperidin and naringin	VI. The two compounds increased the production and release of insulin and decreased intestinal glucose absorption. Reduced the glucose level, improved the expression of GLUT4 and restored the altered parameters of glucose metabolism (A. M. Mahmoud et al., 2015).	
	VII. Wistar Rats	VII. 50 mg/kg	VII. 28 and 30 days	VII. Hesperidin and naringin	VII. Normalized altered blood glucose and antioxidant parameters in the liver → reduced inflammatory markers such as TNF-α and IL-6 and enhanced antioxidant defenses (A. M. Mahmoud et al., 2012).	
	VIII. Rat liver cells	VIII. 40, 80, 120, 160, and 200 μM	VIII. 24 hours	VIII. Hesperidin and hesperetin	VIII. Prevents metabolic disorders and diabetes → inhibited the activities of gluconeogenesis enzymes like ALT and AST (Zareei et al., 2017).	
	IX. Wistar Rats	IX. 100 mg/kg	IX. 15 days	IX. Hesperidin and quercetin	IX. The two compounds demonstrated beneficial effects on insulin metabolism → restored the level of glutathione (GSH) and reduced levels of triglycerides, MDA, IL-6, and TNFα (Dokumacioglu et al., 2018).	
	X. KK-Ay and C57BL/6 Mices	X. 50 mg/kg	X. 42 days	X. Neohesperidin	X. Attenuated fasting blood glucose and insulin resistance. Decreased levels of total cholesterol, triglycerides and leptins while increasing AMPK and its target genes. Decreased epididymis size adipocytes in diabetic mice (Jia et al., 2015).	
	XI. RGC-5 cells	XI. 12.5, 25, and 50 μmol/L	XI. 6 hours	XI. Hesperidin	XI. Protected against a high level of glucose-induced cell apoptosis → downregulated caspase-3and 9, and Bax/Bcl-2. Inhibited the phosphorylation of JNK and activated p38 MAPK (Liu et al., 2017).	
	XII. Wistar Rats	XII. 25, 50, or 100 mg/kg	XII. 21 days	XII. Hesperidin	XII. Modulated neurogenesis in diabetic rats → increased neurotrophic factor BDNF, monoamines in the brain and reduced hyperglycemia, decreased levels of MDA and IL-6 (El-Marasy et al., 2014).	
	XIII. Sprague-Dawley Rats	XIII. 25, 50, and 100 mg/kg	XIII. 28 days	XIII.Hesperidin	XIII. Reduced hyperglycemia and pro-inflammatory markers. Increased insulin levels, the nociceptive threshold, motor nerve conduction velocity, sensory nerve conduction velocity and (ATP)ase activity (Visnagri et al., 2014).	
	XIV. Sprague-Dawley Rats	XIV. 25, 50, and 100 mg/kg	XIV. 21 days	XIV. Hesperidin	XIV. Ameliorated the increased levels of blood glucose, serum insulin, food intake, and water intake. Demonstrated protective effect on the wound architecture → upregulated the expression of VEGF-c, Ang-1/Tie-2, TGF-β and Smad-2/3 → accelerated angiogenesis and vasculogenesis (Li et al., 2018).	
	XV. Wistar Rats	XV. 40 mg/kg (intragastric)	XV. 45 days	XV. Hesperetin	XV. Restored the change in hepatic glucose metabolic enzymes, lipid profiles and serum biomarkers.	

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Table 1 (*continued*)

Extract/compound	Experimental model	Daily dose	Duration	Extraction	Targets and Effects	Ref.
					Protected the liver, kidneys, and pancreatic cells of STZ-induced functional changes. Reduced the level of glucose in the blood and increased the plasmatic insulin and the hepatic glycogen levels (Jayaraman et al., 2018).	
	XVI. Wistar Rats	XVI. 50 mg/kg	XVI. 46 days	XVI. Hesperetin	XVI. Reduced serum glucose level, improved serum level testosterone level, increased testicular antioxidant enzymes, reduced testicular inflammatory markers, such as TNF and IL-17 and prevent damage to seminiferous tubules (Samie et al., 2018).	
Anthocyanins (especially cyanidin or C3G)	I. In vivo, KK-Ay mice	I. 1 g/kg	I. 12 weeks	I. Cyanidin-3-O-β-D-glucoside (C3G)	I. Induced the lipoprotein lipase activity. Reduced BW, liver and visceral adipose tissue weight. Stimulated the pAMPK in skeletal muscle and visceral adipose. Reduced the plasma and hepatic TG, and steatosis score (Wei et al., 2011).	[(Sivamaruthi et al., 2020)]
	II. In vivo, Obese mice	II. 2 g/kg in the diet	II. 12 weeks	II. C3G-rich purple corn color	II. Normalized the expression of TNF-α, suppressed fatty acid and triacylglycerol synthesis, reduced the weight of adipose tissue and weight gain (Tsuda et al., 2003).	
	III. In vivo, Male obese C57BLKS/J-(db/db) mice	III. 1 mg/mL	III. 16 weeks	III. C3G	III. Decreased weight gain and the weight of EWAT and SWAT. Increased energy expenditure, retained glucose homeostasis, normalized hepatic steatosis and enhanced cold tolerance. Induced the formation of brown-like adipocytes in SWAT. Increased mitochondrial biogenesis in BAT and body temperature. Influenced the expression of uncoupling protein 1 (UCP1) (You et al., 2017).	
	IV. In vivo, High fructose and high fat diet induced obese mice	IV. 6.4 g/kg or 0.02 g/kg	IV. 8 weeks	IV. Blueberry or C3G	IV. Reduced body weight, body fat, and blood pressure. Improved glucose tolerance (Shi et al., 2019).	
	V. In vitro, Rat adipocytes	V. 100 μM	V. 24 hours	V. Cyanidin or Cyanidin 3-O-β-D- glucoside (C3G)	V. Increased the secretion of adiponectin and leptin and expression of adipocyte-specific genes (Tsuda et al., 2004).	
	VI. In vitro, 3T3-L1 adipocytes	VI. 10– 100 μM	VI. –	VI. Cyanidin or C3G	VI. Suppressed the release and activation of MCP-1 and MRP-2 (Choe et al., 2007).	
	VII. In vitro, 3T3-L1 adipocytes	VII. 20– 100 μM	VII. 24 hours	VII. C3G	VII. Increased AMP-activated protein kinase activity and suppressed the FFAs and glycerol release. Decreased Glutamine (fructose 6-phosphate aminotransferase activity) and suppressed expression of adipose triglyceride lipase (Guo et al., 2012a,b).	
	VIII. Fluorometric method	VIII. -	VIII. -	VIII. Cyanidin and C3G	VIII. Inhibits pancreatic lipase activity (Vijayaraj et al., 2019).	
C3G, PCA and FA	In vitro, Murine RAW264.7 MΦ and 3T3-L1 preadipocytes	12.5, 25.0, and 50.0 μM	24 h	C3G, PCA and FA	Suppressed the production of pro-inflammatory cytokines TNF-α and IL-6. Increased secretion of adiponectin → improves insulin sensitizing. Decrease in the MCP-1 factor → decreases recruitment of pro-inflammatory cells in adipose tissue. Down-regulation of the NF-κB and JNK/MAPK pathways → inhibition of phosphorylation of IκBα and JNK. Neutralization of oxidative stress and enhanced ΔΨm → elimination of ROS and mitochondrial superoxide. Up-regulated expression of PGC-1α e UCP-1 induced by PCA and FA → regulation of mtTFA and mtDNA expression, modulation of mitochondrial replication and UCP1 transcription. PCA increases protein expression of mitochondrial CI → restoring bioenergetic capacity and preventing mitochondrial cell death. PCA stimulates the activation of LKB1, CAMKII and adiponectin-ADIPOR1 signaling → increasing the phosphorylation status of AMPK. Activation of AMPK → inhibit NF-κB through SIRT1. The activation of AMPK also indirectly inhibits the activity of NF-κB and the oxidative response through phosphorylation of P53 and FoxO. Stimulation of Akt activation → improved insulin sensitivity. PCA potentially attenuates inflammatory processes and modulates energy metabolism via AMPK and Akt.	[(Zhang and de Mejia, 2020)]

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Table 1 (*continued*)

Extract/compound	Experimental model	Daily dose	Duration	Extraction	Targets and Effects	Ref.
Flavonoids, Anthocyanins, hydroxycinnamic acids and ascorbic acid	-	-	-	Dry extract *Citrus Sinensis*	It has a synergistic mechanism between total polyphenols, providing a reduction in triglycerides and total cholesterol and is used to manage body weight.	[(Sousa et al., 2019)]
Citrus aurantium extract (synephrine)	I. In vitro, rat, hamster, canine, guinea-pig and human adipocytes cells	I. 30–60 mg	I. -	I. Synephrine	I. Activates β3-adrenergic receptors located in adipose tissue → induces lipolysis (Carpéné et al., 1999).	[(Jakopin, 2019)]
	II. In vitro, HEK293 cells	II. 1, 10, and 100 μM	II. 4 hours	II. Synephrine	II. Modulates hypothalamic NMUR2 → suppression of appetite in humans (Ma et al., 2010).	
Flavonoids	In vivo, male zebrafish	5 mL	5 weeks	Flavonoid-Rich Extract from *Citrus sinensis* Juice	Modulated genes involved in obesity including leptin A, ghrelin, orexin, pro-opiomelanocortin (POMC) and neuropeptide Y (NPY), in both the intestines and the brain. Significantly decreased body weight, BMI and visceral adipose tissue in obese animals. Decreases the size and number of adipocytes in both the visceral and subcutaneous adipose tissues of healthy and obese groups.	[(Montalbano et al., 2019)]
Naringenin	Different methodologies in vivo, in vitro and clinical trials	varied doses	varied duration	Naringenin	Naringenin demonstrated effects such as antioxidant, antitumor, antiviral, antibacterial, antiaging, anti-Alzheimer's, antiasthma, antidiabetic, anticonvulsant, anti-inflammatory, antiadipogenic, immunomodulatory, kidneyprotective, hepatoprotective and cardioprotective.	[(Salehi et al., 2019)]
Varied compounds (especially *Citrus sinensis and Citrus aurantium*)	I. In vitro, 3T3-L1 and HIB1B preadipocytes	I. 100μM	I. 6–8 day	I. (*Citrus sinensis and Citrus depressa*) Nobiletin	I. AMPK → PKA mediated AMPK activation → Induced brown adipocyte-like phenotype (PGC-1a, PRDM16,UCP1, and FGF21). Enhanced lipolysis by HSL expression (Lone et al., 2018).	[(Wang et al., 2019)]
	II. In vivo, C57BL/6J mice	II. 3.12–50 μM	II. 6, 12 h and 20 days	II. (*Citrus aurantium*) *p*-Synephrine	II. Brownlike morphological changes in WAT by increasing UCP-1 (Takagi et al., 2018).	
Anthocyanins (C3G, (P3G) and (Pr3G)	RAW264.7 macrophages and 3T3-L1 preadipocytes	0.25, 0.50, 1.0 mg/mL; 25, 50, 100 μM	4, 8, and 24 h	Extract (PMW) and (RMW)	PMW and RMW reduced production of pro-inflammatory cytokines such as TNF-α and MCP-1. PMW, RMW, C3G and Pr3G inhibited the activation of NF-κB and JNK pathways.	[(Zhang et al., 2019)]
Anthocyanins	In vitro, 3T3-L1 pre-adipocytes	2.5, 5, 10 and 25 μM	7 days	Extract of *Citrus sinensis*	Inhibited adipocyte differentiation → downregulation of all genes involved in the adipogenic transcriptional network such PPARγ C/EBPα and SREBP-1c. Inhibited enzymes-involved adipogenesis like ACC and FAS. Decreased activity of citrate synthase → decreased adipocyte differentiation. Decreased adiponectin overexpression during differentiation → decreasing lipid storage and adipogenesis. Increased leptin expression during adipocyte differentiation → decreases lipogenesis.	[(Tomasello et al., 2019)]
p-Synephrine	In vitro SVF cells (C57BL/6J mice and *db/m* mice)	12.5 μM	12 h - 20 days	Extract of the peel of *Citrus unshiu*	Activation of β3 adrenoreceptors → upregulation of genes like UCP1 and CIDEA → differentiation of adipocytes from beige.	[(Takagi et al., 2018)]
Citrus sinensis	Human	400 mg	12 weeks	Extract of *Citrus sinensis*	Reduced body weight, BMI, waist and hip circumference.	[(Kaneko and Shirakawa, 2018)]
C3G	In vivo, male C57BL/6J mice	1 mg/mL in water	15 weeks	C3G	Increased heat production in BAT and iWAT, biogenesis and mitochondrial function. Increased BAT marker genes such as UCP1, Cidea, PRDM16, PGC1α, PGC1β, CPT1α, MCAD, PPARα, ATGL and HSL. Increased expression of UCP1 and other thermogenic genes in iWAT. Enhanced mitochondrial proliferation in BAT and iWAT. Modulated proteins like OXPHOS. Increased energy expenditure and thermogenic capacity in BAT.	[(You et al., 2018)]
Flavonoids (especially hesperidin and C3G)	I. In vitro, 3T3-L1 cells	I. 12.5 and 50 μg/mL	I. 24 hours	I. *Gelidium elegans* (Hesperidin)	I. Upregulation of genes like UCP1 and PRDM16 (Choi et al., 2016).	[(Kang et al., 2018)]
	II. In vitro, C3H10T1/2 cells	II. ME and MWE (10 μg/mL) of C3G (1–100 μM)	II. 6 days	II. Mulberry extract (ME), mulberry wine extract	II. ME and MWE upregulated genes UCP1, Ucp1, Pgc1a, Cpt1a, and Prdm16. C3G upregulated genes UCP1, Ucp1, Pgc1α, Pgc1β, Prdm16, Nrf1, mitochondrial	

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Table 1 (*continued*)

Extract/compound	Experimental model	Daily dose	Duration	Extraction	Targets and Effects	Ref.
				(MWE) and cyanidin-3-glucoside (C3G)	activity and proliferation. ME increased phosphorylation of p38 MAPK (You et al., 2015).	
	III. In vitro, 3T3-L1 cells	III. 50 or 100 μM	III. 30 min	III. C3G	III. Increased cAMP levels and AMPK phosphorylation. Upregulation of genes like FABP4, UCP1, PGC1α. Increased mitochondrial biogenesis. Upregulation of C/*ebpb*, Tbx1 and Cited 1 (Matsukawa et al., 2017).	
	IV. In vivo, Male ICR mice	IV. 50, 200 mg/kg	IV. 7 weeks	IV. Extract of *Gelidium Elegans* (hesperidin rich)	IV. Decreased body weight, fat mass, plasma insulin, and TG level. Increased AMPK phosphorylation in BAT and BAT activity (Choi et al., 2017).	
	V. In vivo, Male Wistar rats	V. 60 mg	V. acute oral administration	V. G-hesperidin	V. Stimulate activation of the BAT-sympathetic nerve and cutaneous sympathetic nerve activity. Increased body temperature (Shen et al., 2009).	
Citrus sinensis	Different methodologies	varied doses	varied duration	Essential oil of sweet orange (*Citrus sinensis*)	Demonstrated effects anticarcinogenic, relaxant, anxiolytic, pain relief, hepatocarcinogenesis suppressant, anti-tumor, antioxidant, food preservative, acne treatment (with sweet basil oil), antibacterial, antifungal, anti-aflatoxigenic (at 500 ppm), larvicidal, insecticidal, anthelmintic, growth promoter (in Tilapia).	[(Dosoky and Setzer, 2018)]
Citrus sinensis	Human	500 mL	12 weeks	Juice of *Citrus sinensis L. Osbeck*, var. Pera-Rio	The combination of a low calorie diet and orange juice intake didn't contribute to weight loss, improvement in insulin sensitivity, lipid profile, inflammatory state and not even for nutritional quality of the diet.	[(Ribeiro et al., 2017)]
Citrus sinensis	Human	500 mL	12 weeks	Red orange juice	Didn't demonstrate significant effects on body weight, insulin resistance and/or inflammatory state. Showed beneficial effects on the lipid profile, such as the decrease in total cholesterol and LDL cholesterol levels.	[(Azzini et al., 2017)]
Herb products (especially *Citrus aurantium*)	-	-	-	*p*-synephrine and limonin	Promotes weight loss. Potentially improves sports performance. Demonstrates anti-inflammatory effects. Reduces oxidative stress. Mortality due to cardiovascular toxicity. Alteration of carbohydrate metabolism and oxygen consumption.	[(López-Gil et al., 2017)]
Naringenin	In vivo, female Wistar rats	50 mg/kg	Throughout pregnancy	Naringenin	Increased antioxidant agents in offspring. Increased mitochondrial biogenesis → increased the activity of the electron transport chain. Inhibited the activity of the citric acid cycle dehydrogenases → interfering with the NAD^+ binding site. The cerebellum is the brain structure most susceptible to the effects of naringenin.	[(August, 2016)]
Biotransformed citrus extract	RAW264.7 and 3T3-L1 cells	0.01 mg/mL – 1.00 mg/mL	24 h	Dry residue and citrus peel (flavedo and albedo)	Promoted reduction in adipocyte differentiation, lipid content in the cell and also influenced programmed cell death.	[(Nakajima, 2016)]
Orange juice	Human	500 mL	4 weeks	Orange juice	The meal with a high content of saturated fatty acids accompanied whether or not orange juice intake showed a more pro-inflammatory profile. The consumption of high content of saturated fatty acids demonstrated a compensation mechanism in which the body seeks to limit post-prandial subclinical inflammation through IL-10. The meal accompanied by orange juice reduced postprandial inflammation induced by the high content of saturated fatty acids through IL-17A. Suggests that postprandial phase induces a physiological inflammatory response associated with nutrient availability.	[(Rocha, 2016)]
Polyphenols and alkaloids	-	-	-	I. Naringin	I. Increased CPT-1α expression.	[(Rupasinghe et al., 2016)]
	-	-	-	II. Synephrine (Bitter orange)	II. β-Adrenergic action agonist.	
	-	-	-	III. Anthocyanins (Purple corn, blueberry, strawberry, bitter orange pomegrant)	III. Increased CPT-1α expression and increased AMPK.	

(*continued on next page*)

Table 1 (*continued*)

Extract/compound	Experimental model	Daily dose	Duration	Extraction	Targets and Effects	Ref.
Citrus sinensis	Human	400 mg	12 weeks	Extract of *Citrus sinensis*	Induced a significant reduction body mass index (BMI). Reduced body weight, waist and hip circumference.	[(Cardile et al., 2015)]
Citrus sinensis	Human	750 mL	8 weeks	Red orange juice (*Citrus sinensis*, var. Mombuca)	There was no change in the anthropometric parameters. Decreases total cholesterol, LDL-C, blood pressure and also C-reactive protein. Increased antioxidant activity. Reversed HOMA-IR levels from above the threshold suggesting enhanced insulin sensitivity.	[(Silveira et al., 2015)]
Citrus flavonoids	I. Human	I. 210 mL	-	I. Orange juice	I. Decreased body mass index, cholesterol and LDL levels. 21% less chance of developing obesity, men showed a 36% reduction in risk for metabolic syndrome (O'Neil et al., 2012).	[(Pereira, 2015)]
	II. Human	II. Orange juice in combination with a 900-kcal HFHC meal	II. 1, 3, and 5 h	II. Orange juice	II. Individuals who consumed OJ didn't show an increase in the expression of the NADPH oxidase subunit p47phox, p38 MAPK, SOCS3, (MMP)-9 in mononuclear cells, plasma concentrations of endotoxin, TLR2 and TLR4. Prevented meal-induced oxidative and inflammatory stress (Ghanim et al., 2011).	
	III. Human	III. 500 mL	III. 4 weeks	III. Orange juice (*Citrus aurantium)* or hesperidin	III. Promoted low recruitment and infiltration of cells in the vascular wall and low accumulation of lipids → altered the expression of 3422 genes associated with chemotaxis, adhesion, infiltration, lipid transport. Downregulated LDL receptor (LDLR) on macrophages and the ACAT enzyme - responsible for the formation of lipid droplets (Milenkovic et al., 2011).	
	IV. In vitro, 3T3-L1 pre-adipocytes	IV. 0,10 or 0,50 μg/mL	IV. 4 or 6 days	IV. Extract of *Citrus aurantium* (hesperidin, naringenin and nobiletine)	IV. Suppressed the accumulation of lipids, stimulated lipolysis and inhibited the differentiation of pre-adipocytes downregulated C/EBPβ, C/EBPα and PPARγ genes during adipocyte differentiation. Decreased aP2, FAS and AKT which modulates adipocyte differentiation (Kim et al., 2012).	
	V. Human	V. 1,4 g	V. 4 or 12 weeks	V. *Citrus paradisi*, *Citrus sinensis* and *Paullinia cupana*	V. Demonstrated the lipolytic activity in a range of 6 fold greater than the control. Reduced 5.5% of the fat percentage and reduced 2.2 kg of body weight (4 weeks). Reduced 15.6% of the fat percentage and reduced 5.2 kg of body weight (12 weeks) (Dallas et al., 2008).	
	VI. Human	VI. 900 mg	VI. 12 weeks	VI. *Citrus paradisi*, *Citrus sinensis* and *Paullinia cupana*	VI. Reduced waist circumference by 5.71%. Decreased hip circumference by 4.71%. Decreased body fat by 9.73%. Decreased inflammatory markers such as CRP by 22.87%. Increased the level of antioxidant enzymes in the plasma, such as superoxide dismutase (17.38%) and glutathione peroxidase (4.63%) (Dallas et al., 2014).	
	VII. In vivo, Male C57BL/6J mice	VII. 0.5% lemon polyphenols supplemented HFD	VII. 12 weeks	VII. Eriocitrin, hesperidin, naringenin and diosmina	VII. Reduced weight gain and fat accumulation. Suppressed the development of hyperlipidemia, hyperglycemia and insulin resistance. Increased peroxisomal β-oxidation of lipids → increased PPARα (Fukuchi et al., 2008).	
	VIII. In vitro and in vivo, Obese C57BL/6 mice and mature 3T3-L1 adipocytes	VIII. 150 mg/kg and 200 μg/mL	VIII. 70 days and 2, 6, 12, and 24 h	VIII. Extract from the peel of *Citrus sunki* (rutin, hesperidi,sinensetin, nobiletine and tangeretine)	VIII. Increased β-oxidation → Increased AMPKC and ACC levels. Increased lipolysis → Increased PKA and HSL levels. Decreased weight gain, adipose tissue mass, total cholesterol and triglycerides (Kang et al., 2012).	

reduce the migration of inflammatory cells in adipose tissue. And more recently, these flavonoids have shown an important role in increasing biogenesis and mitochondrial activity.

As for the toxicological profile of supplementing plant extracts, the potential cardiotoxic effects are often attributed to products containing synephrine in their composition. However, so far, research has revealed the safety of these nutraceuticals, showing little toxicity and low drug interactions. What seems to be important in many case reports are that these patients often make indiscriminate use of several stimulants simultaneously as well as administration of dosages above the daily recommendation. And another important factor is the discovery of many adulterated products on the market, with higher or nonexistent concentrations in relation to the labeled values. In addition, some still have a discrepancy in concentrations between different batches of the same product. And all of this makes it difficult to attribute these rare adverse effects especially and solely to the synephrine compound (see Table 1).

5. Conclusion

The present study provides more data on the pharmacological mechanisms and genetic modulation by which Moro orange extract (*Citrus sinensis*) promotes the control of lipid metabolism and stimulates the oxidation of fatty acids. The results demonstrate several phytochemicals present in the composition of Moro orange extract that can potentially contribute in a complementary way to other treatments in the regulation of lipid metabolism and in weight management. The biological effects of Moro orange extract are due to the combination of bioactive compounds that possibly act synergistically in allosteric sites, enabling its potential pharmacological action. These scientific findings are supposed to reveal its important role as a nutraceutical in the prevention of obesity, insulin resistance, liver steatosis and cardiovascular diseases. On the other hand, many of these mechanisms aren't yet established in the literature and due to the scarcity of clinical research, further studies are needed to prove the effectiveness of Moro orange extract supplementation, especially in weight management and in the treatment of obesity. In addition, further studies are also needed to evaluate some specific properties of these phytochemicals that include: toxicological profile, pharmacological interactions, affinities with receptors, gene regulation and their supposed selectivity for fats located on the flanks and inner thighs. However, these discoveries about these mechanisms of action provide a new insight into the future therapeutic implications in several diseases related to inflammation and metabolic disorders.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

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

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

We thank Faculdade Ana Carolina Puga (FAPUGA) for the partnership.

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