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Review

Risks associated with fat burners: A toxicological perspective

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ABSTRACT

Dietary supplements "fat burners", freely available on the market, are intended to promote weight loss and reduce fat accumulation, either via stimulation of lipolysis or by inhibition of lipogenesis. Proponents claim that fat burners can increase fat metabolism, although their usefulness remains controversial. Fat burners are usually claimed to be of natural origin and viewed as being inherently safe. This review focuses on the most common ingredients of natural origin usually found in the fat burners, their molecular mechanisms of action and the toxicological profiles of these compounds in order to gain an insight into their safety.

1. Introduction

The proportion of overweight or obese adults has already surpassed 70% in the US; and 50% in Europe (Fujioka, 2015). Obesity is a complex metabolic behavioral disorder that disrupts the physiological regulation of body weight. Where lifestyle changes have not yielded results and, due to the risks associated with this condition, some cases have been treated by using a pharmacological or an operative approach, or by using dietary supplements. The hypothalamus partially regulates the intake of nutrients and metabolism, along with many signaling pathways including the leptin-melanocortin axis, the adrenergic, canabinoid, dopaminergic, opioid systems and the glucagon-like peptide 1 (GLP-1) systems. In Europe, only three approved drugs are presently available for regulating or reducing body weight: orlistat (a reversible gastric and pancreatic lipase inhibitor), naltrexone/bupropion (a combination of opioid receptor antagonist, and catecholamine uptake inhibitor) and liraglutide (GLP-1 analog). In the US, phentermine (sympathomimetic amphetamine), phentermine/topiramate (a combination of sympathomimetic and antiepileptic drugs) and lorcaserin (a 5-HT_{2C} receptor agonist) are additonally available (Arch, 2015; Fujioka, 2015). Pharmacological approaches have been "approved for human use" but adverse effects have been reported. Sibutramine (noradrenaline and serotonin uptake inhibitor) and fenfluramine (5-HT_{2C} and 5-HT_{2B} receptor agonist) were withdrawn from the market due to cardiovascular complications (Connolly et al., 1997; James et al., 2010). Similarly, rimonabant (CB1 cannabinoid receptor antagonist) was also withdrawn due to its association with depression and suicide (Arch, 2015; Fujioka, 2015). Safety concerns are further complicated by the fact that individuals trying to lose weight often resort to inappropriate and dangerous substances, such as nicotine, laxatives, diuretics as well as illicit substances including amphetamines, metamphetamine, cocaine, and 2,4-dinitrophenol, and weight-loss supplements categorized as "fat burners". The latter have been gaining popularity in recent years, especially among people between 18 and 24 years of age, due to advertisements promoting them as a simple, effective, safe and fast weight reduction method. According to Rios-Hoyo and Gutiérrez-Salmeán (2016), dietary supplements represent $ 37 billion annually in the US (Rios-Hoyo and Gutiérrez-Salmeán, 2016). Weight-loss products constitute the fastest growing segment of the food supplements industry; increasing annually by 10–20% (Rogovik and Goldman, 2009). This review is therefore focused on the most common ingredients of fat burners, their reported molecular mechanisms of action, and their

Abbreviations: ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; ATGL, adipose triglyceride lipase; cAMP, cyclic adenosine monophosphate; C/EBPα, CCAAT receptor expression/amplification-binding protein type α; CLA, conjugated linoleic acids; COMT, catechol *O*-methyl transferase enzyme; CPT, carnitine palmitoyltransferase; *N*,α-DEPEA, *N*,α-diethylphenylethylamine; DMAA, 3-dimethylamylamine; DNP, 2,4-dinitrophenol; EFSA, European Food Safety Authority; EGCG, epigallocatechin-3-galate; FDA, US Food and Drug Administration; FAS, fatty acid synthase; FEEDAP, The Panel on Additives and Products or Substances used in Animal Feed; FEMA, The Flavor and Extract Manufacturers Association of the United States; GIT, gastrointestinal tract; GLP-1, glucagon-like peptide 1; GRAS, generally recognized as safe; HCA, hydroxycytric acid; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; LXRα, liver X receptor α; β-MPA, β-methylphenethylamine; NMUR2, neuromedin U2 receptor; OTC, over-the-counter; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; PKA, protein kinase A; PPAR, peroxisome proliferator activating receptor; PTP-1B, protein tyrosine phosphatase 1B; RASFF, Rapid Alert System for Food and Feed; RK, raspberry ketone; SCD, steaoryl-CoA desaturase; SNS, sympathetic nervous system; TRPV1, transient receptor potential cation channel subfamily V member 1; UCP, uncoupling protein

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toxicological profiles in order to provide an insight into their safety.

2. Definition of »fat burners« and the relevant legislation (legal framework)

The term fat burner (also known as “fat blockers” or “weight loss pills”) is used for dietary supplements, which claim increased fat metabolism or increased energy consumption, reduced fat absorption, facilitated weight loss, increased fat oxidation during exercise or in any other way cause long-term adaptations that stimulate fat metabolism (Jeukendrup and Randell, 2011). Such supplements often contain many ingredients, each with unique mechanisms of action, to which additive effects may be attributed (Sharpe et al., 2006). Dietary supplement efficacy evaluation is a challenging process, since the regulation of these products differs from pharmaceuticals. In the US, for instance, the manufacturers of dietary supplements are not required to demonstrate the efficacy of their products, while there are requirements regarding their safety and quality (Brown, 2017a). Nevertheless, dietary supplements are widely available to the general population as over-the-counter (OTC) products. People often perceive them as natural, and therefore safer than, prescription drugs. An additional problem is the fact that, on average, such products contain several different ingredients, many of which can interact with one another (Jeukendrup and Randell, 2011). This means that, even if an individual ingredient has been proven to be safe, this might not hold true for the end product.

However, for all these products, many of which are now available online, it is important to take into consideration that profound differences exist in legislation between different countries. For example, in the European Union, legislation varies from country to country. Namely, each member state can classify the products themselves as a category of medicines, as dietary supplements or as borderline products. In the US, since 1994 dietary supplements are considered as food rather than medicines. This makes the legislation more vague, since manufacturers are not obliged to submit data on efficacy. Although, it would also be highly unlikely to expect the same level of efficacy as required for drugs. They are also not obliged to notify or register their product with the US Food and Drug Administration (FDA), let alone to have it approved before launching the product on the market, unless it contains a new dietary ingredient (Brown, 2017a). It was not until 2011 that the Food Safety Modernization Act was tightened, which gave the FDA more power to take appropriate action when needed, including withdrawing any dietary supplement for which reasonable doubt exists that it is adulterated or misbranded (Brown, 2017a). The manner by which the public is informed about potential safety issues differs considerably between the EU and the US. For example, in the EU, any unwanted effects reported by users are communicated to the Rapid Alert System for Food and Feed (RASFF), while in US they mostly rely on the Medwatch database, which is somewhat incomplete according to da Justa Neves (da Justa Neves and Caldas, 2015) and other sources, including CFSAN Adverse Event Reporting System, National Electronic Injury Surveillance System and the National Poison Data System (Brown, 2017a). An additional problem is posed by the fact that information on adverse reactions does not flow freely between poison centers and the FDA (Cohen, 2014).

3. The mechanism of action and safety of typical representatives of fat burners of natural origin (compounds, extracts, mixtures)

A large number of dietary supplements, which are intended for weight reduction or for reducing fat accumulation, act by stimulating lipolysis and inhibiting lipogenesis (Kim et al., 2016b). Despite the fact that scientific evidence suggests that certain dietary supplements can actually increase fat metabolism, the usefulness of such preparations as ergogenic agents remains controversial. Certain manufacturers also claim that their dietary supplements are predominantly of natural origin and therefore nontoxic. The problem lies in the fact that companies can refer to ingredients in their product as “generally recognized as safe” (GRAS) provided they are on the GRAS list. This designation allows for the addition of ingredients without the need for FDA approval. The GRAS Notice status is pending during which independent evaluations are conducted ultimately resulting in the publication of the final rule. On the one hand, this status can be rejected following an in-depth evaluation, following which the FDA informs the company/applicant of its safety concerns and makes the concerns public. On the other hand, the company/applicant has the possibility to prematurely withdraw their request, thus leaving the public in the dark. The focus here is primarily on organic ingredients of natural origin whose presumed molecular mechanisms of action are reviewed (Table 1). In addition, we have critically evaluated the accessible safety studies. Of note, according to the NDI Draft Guidance (2016) published by the FDA, synthetic forms of substances that occur naturally cannot be used in dietary supplements in the US.

3.1. Chromium salts

Chromium is a trace element that has also been used as an inorganic weight-loss agent. In the dietary supplement market, chromium predominantly appears in two major forms, chromium (III) picolinate (see Fig. 1) and chromium (III) chloride, while it is also present as chromium (III) nicotinate, although to a minor extent.

Mechanism of action: The molecular mechanisms by which chromium exerts its anti-obesity effects have not been fully elucidated. Chromium acts indirectly through increased insulin activity, which then affects the metabolism of carbohydrates and fats (Bai et al., 2015). Specifically, research suggests that the potential *in vivo* effect of chromium picolinate on insulin action in human skeletal muscle may occur by binding to an oligopeptide, in turn increasing insulin-dependent tyrosine kinase activity (e.g. the activation of Akt phosphorylation that facilitates the uptake of glucose into cells) (Vincent, 2000; Lamson and Plaza, 2002). This is in agreement with the results obtained in a study on insulin resistant animals, which have shown that chromium enhances the actions of insulin via an increase in kinase activity of insulin receptor, in turn amplifying the insulin signaling pathway (mediated by pI3-kinase and Akt). It also dampens the negative-regulators of insulin signaling (e.g. protein tyrosine phosphatase 1B (PTP-1B)) and upregulates AMPK-activated glucose uptake (Hua et al., 2012).

Safety: An *in vitro* study in Chinese hamster ovary cells revealed that it accumulates in cells causing chromosomal damage (Stearns et al., 1995a,b). Further, it has also been associated with a few cases of rhabdomyolysis and renal failure in humans, so that extra caution is warranted when using such preparations (Cerulli et al., 1998; Rogovik and Goldman, 2009). *In vitro* and *in vivo* studies in rats have revealed that chromium picolinate has the capacity to cause oxidative damage of biological macromolecules and is potentially mutagenic. Strikingly, *in vitro* studies indicated that other forms of chromium used as nutritional supplements (e.g. chromium chloride), are unlikely to generate this type of oxidative damage, hence the use of such compounds, rather than picolinate, might be advantageous (Stearns et al., 1995a,b; Speetjens et al., 1999; Vincent, 2003). The GRAS Notice status of chromium (III) picolinate has been withdrawn, while its analog chromium (III) nicotinate (niacin-bound chromium) still holds this status in the US. Of note, in human studies absorption levels of 2–3% have been observed for dietary chromium in the form of organic complexes, however various dietary factors can significantly affect chromium absorption (Lamson and Plaza, 2002). In spite of equivocal evidence regarding the toxicity of chromium picolinate obtained from short- and long-term studies, in 2010 EFSA approved its use reaching a final conclusion that its presence in supplements is of no concern, provided that the amount of total chromium does not exceed 250 μg/day (EFSA Panel, 2010a).

Table 1
Presumed mechanisms of action of fat burner ingredients.

Compound/extract	Presumed mechanism of action	GRAS status[a]	Daily dose[b]	Reference
Chromium salts	Binds to an oligopeptide, in turn increasing insulin-dependent tyrosine kinase activity. Increase in kinase activity of insulin receptor → amplifies the insulin signaling pathway (mediated by pI3-kinase and Akt); dampens the negative-regulators of insulin signaling (e.g. PTP-1B) and upregulates AMPK activity glucose uptake.	Cr (III) nicotinate GRAS status withdrawn for picolinate	400–2000 μg	Vincent 2000 Lamson and Plaza 2002 Hua et al., 2012 Bai et al., 2015
Caffeine	Antagonism of adenosine receptors, Stimulation of SNS. Type IV phosphodiesterase inhibition → increase in [cAMP] → HSL-driven lipolysis, increased expression of UCP. Inhibition of adipocyte differentiation and inhibition of C/EBPα and PPARγ expression → inhibition of lipogenesis.	GRAS	200 mg	Acheson et al., 1980 Fredholm 1995 Greenberg et al., 2001 Ribeiro and Sebastiao 2010 Kim et al., 2016a Kim et al., 2016b
Green tea extract (EGCG)	COMT inhibition → increased catecholamine concentration and increased SNS activity (via cAMP and PKA) → HSL-driven lipolysis. Long-term effects – inhibitory effect on expression of PPARγ and PGC-1α → increased expression of genes involved in β-oxidation of fatty acids. Appetite suppression (β-adrenergic agonists are known to reduce food intake). Reduction of glucose absorption by inhibiting relevant GIT enzymes involved in digestion.	GRAS Notice withdrawn	400–500 mg of EGCG (GTE usually contains 50% EGCG)	Chen et al., 2005 Westerterp-Plantenga et al., 2006 Rains et al., 2011 Hodgson et al., 2013 Chen et al., 2015 Kim et al., 2016b
Green coffee beans extract (chlorogenic acid)	AMPK activation → (i) inhibition of fatty acid synthase, acyl-CoA:cholesterol acyltransferase and acetyl CoA carboxylase; (ii) increased fatty acid β-oxidation and PPARα, CPT-1, ATGL and HSL expression in the liver. Elevated plasma adiponectin levels (adipose tissue lipolysis hormone). Down-regulation of transcription factors (C/EBPα, PPARγ).	/	120–300 mg of CGA	Cho et al., 2010 Ong et al., 2013 Choi et al., 2016
L-Carnitine	Conversion of fatty acids to acylcarnitine and transfer in the mitochondrial matrix; facilitates uptake of fatty acids into muscles and increases oxidation.	GRAS Notice withdrawn	500–2000 mg	Bremer 1983 Constantin-Teodosiu et al., 1991 Cha et al., 2003 Cha, 2008
Capsaicin	TRPV1 agonism → enhanced secretion of catecholamines → ↑ SNS activity. Inhibition of lipogenesis via reduced expression of PPARγ, C/EBPα and leptin; increased expression of adiponectin. Increase in PPARα and PGC-1α expression → enhanced fatty acid oxidation. Agonism of PPARα receptor (regulation of glucose/lipid metabolism). Regulation of neuronal circuits → suppression of appetite and increase in satiety.	/(*Capsicum frutescens* and *Capsicum anuum* are GRAS)	Few mg	Diepvens et al., 2007 Hsu and Yen 2007 Kang et al., 2010b Leung 2014 Lee et al., 2015
Taurine	Stimulation of adenylate cyclase → increased [cAMP] → increased SNS activity → HSL-driven lipolysis. PPARα activation → increased CPT-I activity and improved uptake of fatty acids into muscles → increased β-oxidation. Increased expression of energy-expenditure related genes (PPARα, PPARγ and PGC-1α). Up-regulated expression of lipoprotein lipase, acyl-CoA oxidase and acyl-CoA synthase. Agonism of LXRα receptor → improved metabolism of lipids and carbohydrates. Increase in plasma insulin levels via its action on calcium homeostasis.	GRAS Notice	500–2000 mg	Chen et al., 2004 Tsuboyama-Kasaoka et al., 2006 L'Amoreaux et al., 2010 Hoang et al., 2012 You et al., 2013 Murakami 2017
Conjugated linoleic acid	PPARα activation → increased activity CPT-I and improved uptake of fatty acids into muscles → increased β-oxidation. Reduced neuropeptide Y expression → reduction of food intake. Increased UCP2 and CPT-I expression. Attenuates several transcription factors, including PPARγ and C/EBPα. Decrease in activity of proteins involved in *de novo* lipogenesis (LPL, ACC, FAS and SCD).	GRAS Notice	3200–6400 mg	West et al., 2000 Cao et al., 2007 Kennedy et al., 2010

(*continued on next page*)

Table 1 (*continued*)

Compound/extract	Presumed mechanism of action	GRAS status[a]	Daily dose[b]	Reference
Fucoxanthin	Increased expression of UCP1 → ↑energy consumption. Promotes expression of β3-adrenergic receptor PPARγ and C/EBPα inhibition → increased expression of genes involved in β-oxidation of fatty acids and decreased differentiation of adipocytes. Decreased expression of acetyl-CoA carboxylase → decreased malonyl CoA concentration. Decreased expression of fatty acid synthase → decreased synthesis of long-chain fatty acids. Decreased plasma leptin levels.	/	2.4–8 mg (240–800 mg of seaweed extract)	Maeda et al., 2005 Maeda et al., 2006 Miyashita 2009 Kang et al., 2011 Yim et al., 2011 Park et al., 2011 Beppu et al., 2013
Forskolin	Activation of adenylate cyclase → increase in [cAMP] → increased SNS activity → HSL-driven lipolysis.	*Coleus forskohlii* (GRAS herbs)	50 mg of forskolin (500 mg of 10% extract)	Ho and Shi 1982 Litosch et al., 1982 Burns et al., 1987 Insel and Ostrom 2003
***Garcinia cambogia* extract (HCA)**	ATP citrate liase inhibition → decreased malonyl CoA concentration → increased activity of CPT-I and improved uptake of fatty acids into muscles; → increased β-oxidation. Inhibition of PPARγ, C/EBPα and adipocyte protein aP2 expression → suppressed the adipocyte differentiation and intracellular lipid accumulation. Reduced plasma leptin and insulin levels. Enhances the release of serotonin – a key regulator of appetite.	Citrin K (K salt of HCA) held GRAS Notice	Up to 1500 mg	Lowenstein 1971 Ohia et al., 2001 Ohia et al., 2002 Kim et al., 2004 Preuss et al., 2005 Kim et al., 2008a Kim et al., 2008b Kang et al., 2013 Kim et al., 2013
Glucomannan	Water absorption in the GIT → gel formation → increased satiety sensation and decreased protein and fat absorption from GIT.	GRAS Notice	2000–4000 mg	Keithley and Swanson 2005
Ginseng	AMPK activation in several tissues, including liver (decrease of triglyceride synthesis and reduced cholesterogenesis and gluconeogenesis via suppressed expression of enzymes, involved in *de novo* lipogenesis), adipose tissue (inhibit triglyceride synthesis) and skeletal muscles (increased glucose uptake and fatty acid oxidation, resulting in augmented energy expenditure). PPARγ inhibition → increased expression of genes involved in β-oxidation of fatty acids (AMPK, CPT-I and UCP2) and decreased differentiation of adipocytes. Activates PPARα → enhanced oxidation and export of fatty acids. Decreased expression of transcription factors PPARγ and C/EBPα. Increases the secretion of adiponectin, leptin and neuropeptide Y.	GRAS Notice withdrawn	200–400 mg of extract (contains 2–3% ginsenosides)	Hwang et al., 2007 Li and Ji 2018
***Citrus aurantium* extract (synephrine)**	Activates β3-adrenergic receptors present in the adipose tissue → stimulates lipolysis. Modulates hypothalamic NMUR2 → suppression of appetite in humans.	FEMA GRAS (natural flavoring)	30–60 mg of synephrine	Carpéné et al., 1999 Ma et al., 2010 Mercader et al., 2011 Zheng et al., 2014 Kaats and Stohs 2017
»Raspberry« ketone	Decreased expression of genes and transcription factors involved in the process of adipogenesis (*i.e.* PPARγ, C/EBPα, acetyl-CoA carboxylase, fatty acid synthase, stearoyl-CoA desaturase 1). Increased expression of genes involved in fatty acid oxidation (HSL, CPT, triglycerid lipase). Increased secretion of adiponectin. Enhanced norepinephrine-induced lipolysis via increased translocation of HSL from cytosol to lipid droplets in white fat cells.	FEMA GRAS (natural flavoring)	100–200 mg	Morimoto et al., 2005 Park, 2010 Park, 2015
***Irvingia gabonensis* extract**	Decreased expression of PPARγ and leptin and increased expression of adiponectin. Water-soluble fibres act as "bulk-forming" laxatives and are also expected to delay stomach emptying → gradual absorption of dietary sugar.	/	150–3200 mg	Ngondi et al., 2005 Oben et al., 2008 Ngondi et al., 2009

ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; ATGL, adipose triglyceride lipase; cAMP, cyclic adenosine monophosphate; C/EBPα, CCAAT receptor expression/amplification-binding protein type α; CLA, conjugated linoleic acids; COMT, catechol O-methyl transferase enzyme; CPT, carnitine palmitoyltransferase; EGCG, epigallocatechin-3-galate; FAS, fatty acid synthase; FEMA, The Flavor and Extract Manufacturers Association of the United States; GIT, gastrointestinal tract; GRAS, generally recognized as safe; HCA, hydroxycytric acid; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; LXRα, liver X receptor α; NMUR2, neuromedin U2 receptor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; PKA, protein kinase A; PPAR, peroxisome proliferator activating receptor; PTP-1B, protein tyrosine phosphatase 1B; SCD, steaoryl-CoA desaturase; SNS, sympathetic nervous system; TRPV1, transient receptor potential cation channel subfamily V member 1; UCP, uncoupling protein.

[a] source of information: https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/default.htm

[b] source of information: https://examine.com/supplements/

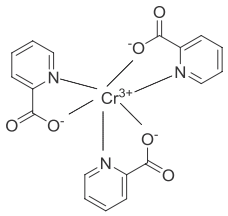


Fig. 1. Structure of chromium (III) picolinate.

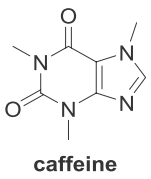


Fig. 2. Structure of caffeine.

3.2. Caffeine

Caffeine, or 1,3,7-trimethylxanthine (see Fig. 2), is an alkaloid and represents an important ingredient in many popular beverages such as coffee, tea and cola, which contain between 40 and 150 mg of caffeine per cup (Jeukendrup and Randell, 2011). A great deal of interest was sparked by research in the '70s when it was found that consuming caffeine before exercise would increase fat metabolism (Essig et al., 1980; Jeukendrup and Randell, 2011).

Mechanism of action: Caffeine works through several different mechanisms (Acheson et al., 1980; Kim et al., 2016b; Leijten and van Breemen, 1984). First and foremost, caffeine is a nonselective antagonist of adenosine A_1 and A_{2A} receptors (Gurley et al., 2015). The antagonism of the inhibitory effects of adenosine on lipolysis is the most commonly recognized mechanism of action for caffeine at non-supraphysiologic concentrations (Fredholm, 1995; Ribeiro and Sebastião, 2010). Incidentally, adenosine antagonism results in the enhanced release of several neurotransmitters, including noradrenaline, serotonin and dopamine, which account for several indirect pharmacodynamic effects (Gurley et al., 2015). Phosphodiesterase inhibition, its alternative mechanism of action, only contributes to caffeine pharmacodynamics at much higher concentrations (> 25 μg/mL) (Gurley et al., 2015). The inhibition of phosphodiesterase enzyme results in an elevated concentration of cAMP in cells, leading to activation of protein kinase A (PKA) and thus the sympathetic nervous system (Greenberg et al., 2001). The latter regulates the level of basal metabolism, which is a key component of daily energy consumption. An increase in noradrenaline concentrations also results in higher activity and higher energy consumption. PKA activation stimulates the activity of hormone-sensitive lipase (HSL) (Greenberg et al., 2001) and increases the expression of uncoupling proteins (UCP), which leads to increased heat generation due to reduced mitochondrial oxidation (Westerterp-Plantenga, 2010). In this manner, caffeine increases the concentration of adrenaline in the circulation, which then acts on β-adrenoceptors and increases energy consumption and fat oxidation, releasing fatty acids from adipose and intramuscular stores, thereby facilitating their accessibility to oxidation and stimulating lipolysis. In addition to inhibiting phosphodiesterase, caffeine also stimulates various substrate cycles, such as Cori and the triglyceride cycle (Acheson et al., 2004; Graham et al., 2008; Westerterp-Plantenga et al., 2005). Other possible mechanisms of action include inhibition of adipocyte differentiation and inhibition of CCAAT receptor expression/amplification-binding protein type alpha (C/EBPα) and peroxisome gamma-type activating receptors (PPARγ), which consequently leads to inhibition of lipogenesis (Kim et al., 2016a). Finally, it should be noted that the results of short-term human *in vivo* studies have demonstrated that caffeine ingestion results in higher basal metabolic activity, in turn increasing energy consumption, as opposed to the findings of long-term studies, most probably due to the development of tolerance (Cornelis et al., 2007; Westerterp-Plantenga, 2010). The latter is known to occur within a few days of regular daily intake of caffeine. An individual's response therefore highly depends on the dose, dosing regimen and the pharmacokinetic profile (Shi et al., 1990).

Safety: Pharmacokinetic studies in humans have demonstrated that caffeine absorption from the gastrointestinal tract, especially in the small intestine, is rapid and complete with the bioavailability of 99–100% after oral administration (Blanchard and Sawers, 1982; Bonati et al., 1982). A single oral dose of caffeine (100 mg) resulted in the average plasma levels of 1.5–1.8 μg/mL (Kamimori et al., 2002). The time to reach peak plasma concentration was 0.5–1.5 h, while the elimination half-life was about 4–6 h (Jeukendrup and Randell, 2011). In general, caffeine has an excellent safety profile when consumed in moderation. Caffeine exerts its CNS stimulatory effects in humans at approximately 3 mg per kg body weight and a caffeine intake of < 400 mg/day is deemed tolerable. Acute clinical toxic effects begin at 1000 mg, while going above this level (> 2000 mg) reaches the toxic effects of high doses of caffeine, which manifest as nausea, vomiting, tachycardia, seizures and cerebral edema, and can also lead to electrolyte disorders (Yen and Ewald, 2012; Gurley et al., 2015; Brown, 2017c). Nevertheless, it should be pointed out that individuals sensitive to caffeine may exhibit such adverse events at lower doses (Gurley et al., 2015). This sensitivity has been partly attributed to their genetic makeup (e.g. COMT, CYP1A2 gene polymorphisms) (Yang et al., 2010; Gurley et al., 2015). Caffeine has recently been shown to increase the activity of cardiomyocytes *in vitro* to the same extent as ephedrine (Calvert et al., 2015). Ingesting very high caffeine doses can therefore lead to serious cardiotoxic effects which can prove to be fatal, usually as a result of ventricular arrhythmia (Brown, 2017c). Of note, the acute human fatal dose of caffeine was reported to be over 170 mg per kg (Brown, 2017c). Nevertheless, EFSA concluded that its use is of no concern, provided that the amount of caffeine does not exceed 3 mg/kg/day (EFSA Panel, 2015).

3.3. Green tea extract

Green tea is obtained from the minimally oxidised processed leaves of *Camellia sinensis*. The content of polyphenols in green tea, in particular flavonols, flavones and flavan-3-ols, amounts to 35% dry weight of leaves, with flavan-3-ols or catechins representing 60–80% of all polyphenols. Epigallocatechin-3-galate (EGCG) (see Fig. 3) is considered to be the most biologically active component of green tea extract, and constitutes 50–80% of the total catechin content (Kim et al., 2016b). One cup (250 mL) of green tea contains approximately 100–300 mg catechins and 50–90 mg caffeine.

Mechanism of action: In recent years, studies of EGCG have raised considerable interest. Inhibition of the catechol *O*-methyl transferase enzyme (COMT) is often indicated as a possible mechanism of action,

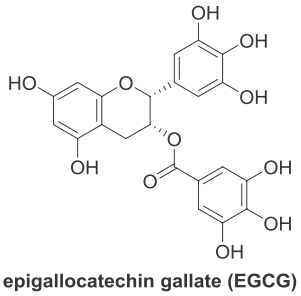


Fig. 3. Structure of epigallocatechin gallate.

which in theory leads to elevated catecholamine concentrations and hence stimulation of the sympathetic nervous system and increased energy consumption (Borchardt and Huber, 1975; Lu et al., 2003; Chen et al., 2005). This proposed mechanism, however, has not yet been confirmed *in vivo* and, since most of the catechins in circulation are conjugated, it is highly unlikely to be correct because glucuronidated forms lose the ability to inhibit COMT (Hodgson et al., 2013). By inhibiting COMT, EGCG increases the concentration of noradrenaline in the circulation, which in turn increases energy consumption and fat oxidation (Westerterp-Plantenga et al., 2006). Noradrenaline, as expected, also stimulates lipolysis in peripheral tissues (fat, liver and skeletal muscles), thereby releasing fatty acids into the circulation (Rains et al., 2011). *In vitro* studies have revealed that EGCG reduces fat accumulation in adipocytes, as well as increasing the concentration of glycerol and free fatty acids through the action of hormone-sensitive lipases (Chen et al., 2015). Long-term effects are probably induced by PPARγ-mediated increased expression of genes coding for enzymes that metabolize fat as well as the reduced expression of genes involved in adipogenesis in the liver (Hodgson et al., 2013). Moreover, it also increases the level of phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (Kim et al., 2016b; Sakurai et al., 2009). An *in vivo* study in mice showed that EGCG reduced fat accumulation as a result of increased β-oxidation in the liver and increased expression of acyl-CoA oxidase and medium-chain acyl CoA dehydrogenase. A similar study showed that EGCG increased the expression of carnitine palmitoyltransferase I (CPT-I), UCP2 and various lipases (Chen et al., 2009a; Lee et al., 2009). The findings of *in vivo* oral studies conducted in mice, in most cases revealed increased fat oxidation throughout the body, while an increased AMPK activity has only been observed in the liver and skeletal muscles (Murase et al., 2009). As a third possible mechanism of action, appetite suppression has been suggested, since substances that increase liver oxidation of fats, such as β-adrenergic agonists, are known to reduce food intake (Rains et al., 2011). Finally, certain *in vitro* studies have even found that EGCG can reduce glucose absorption by inhibiting relevant GIT (gastrointestinal tract) enzymes involved in nutrient digestion (Rains et al., 2011).

Safety: Pharmacokinetic studies in humans have shown that most of the ingested GTE (98%) undergoes extensive conjugation in the liver (glucuronidation, methylation, and sulfonation) and degradation by gut microbiota, thus demonstrating a very poor bioavailability of green tea catechins (< 2%) which only reach plasma at the micromolar level after 1–2 h (Ullmann et al., 2003; Lambert et al., 2007; Yashin et al., 2012; Clifford et al., 2013). Green tea extract principally possesses a favourable safety profile, although it has been linked to numerous harmful effects on the liver (Mazzanti et al., 2009; Bunchorntavakul and Reddy, 2013; Isomura et al., 2016; Brown, 2017b). The underlying mechanism of hepatotoxicity has been suggested to involve the formation of reactive oxygen species induced by the catechins, which in turn affect the mitochondrial membrane potential (Han et al., 2004; Schmidt et al., 2005). Of all the tested catechins, EGCG proved to be the most cytotoxic catechin in rat hepatocytes (EFSA Panel, 2018). Nevertheless, the animal studies indicated that GTE taken with food produced no overt hepatotoxicity. The latter was only observed when GTE was administered in a fasted state. It should also be noted that most hepatotoxicity case reports have been linked to ethanolic extracts. The extraction procedure may also have led to the presence of impurities such as pyrrolizidine alkaloids in the extracts, which are known to form hepatotoxic metabolites (EFSA Panel, 2018). Due to these concerns, EFSA has assessed the safety of green tea catechins from dietary sources and reached a conclusion that catechin intake with beverages, such as green tea infusions is normally safe, given the extremely low number of cases compared to the large number of consumers. However, long-term catechin supplementation at doses above 800 mg/day may pose health concerns given the fact it has been associated with an increase of serum transaminases, known biomarkers of liver toxicity (EFSA Panel, 2018). Nevertheless, it should also be noted that catechins, in particular EGCG, can exacerbate the pharmacologic effects of caffeine due to COMT inhibition (Dulloo et al., 2000). Moreover, catechins have been shown to inhibit cardiac ion channels, particularly hERG potassium channel, which may lead to QT interval prolongation thus increasing the risk of cardiotoxicity (Kelemen et al., 2007; Kang et al., 2010a).

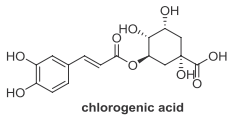


Fig. 4. Structure of chlorogenic acid.

3.4. Green coffee bean extract

Green coffee bean extract is present in green or raw coffee as well as in roasted coffee, although to a minor extent. Its main ingredient is chlorogenic acid (also known as 5-*O*-cafeoylquinic acid) (see Fig. 4).

Mechanism of action: In HepG2 hepatocytes chlorogenic acid affects lipid metabolism by activation of AMPK, which results in the suppression of fatty acid synthesis (Ong et al., 2013). AMPK regulates cellular metabolism and is a key mediator that converts adipocytes from anabolizing to catabolizing lipids. An *in vivo* study in mice fed with a high-fat diet revealed that ingestion of chlorogenic acid improved lipid metabolism by inhibiting fatty acid synthase, 3-hydroxy-3-methylglutaryl CoA reductase and acyl-CoA:cholesterol acyltransferase activities thus down-regulating fatty acid and cholesterol biosynthesis. At the same time it induced fatty acid β-oxidation and PPARα receptor expression in the liver. Of note, chlorogenic acid also elevated the plasma levels of adiponectin, an adipose tissue lipolysis hormone (Cho et al., 2010). Similar results were obtained from a study conducted in green coffee bean extract-treated obese mice treated, wherein the observed decreased body weight, liver weight and white adipose tissue weight have also been attributed to the up-regulation of adiponectin (Choi et al., 2016). In addition, PPARα, CPT-1, adiponectin, adipose triglyceride lipase (ATGL) and HSL expression were up-regulated in the liver in a dose-dependent manner as well as adipose tissue. Conversely, the transcription factors that regulate adipocyte differentiation, such as C/EBPα and PPARγ, were down-regulated (Choi et al., 2016).

Safety: Most polyphenols exhibit poor bioavailability following ingestion. Pharmacokinetic studies in rats showed only traces of metabolites, the conjugates of caffeic and ferulic acids, were detected in plasma after chlorogenic acid administration indicating the latter is not well absorbed from the digestive tract (Azuma et al., 2000). Recent studies investigating plasma appearance of chlorogenic acids after ingestion of coffee in healthy volunteers revealed they appear in plasma reaching peak concentration in 1 h but were present only in low quantities (Cmax < 100 nM) (Renouf et al., 2011). A systematic review of studies assessing the safety of green coffee been extract revealed a favourable profile since no major side effects have been reported (Onakpoya et al., 2011; Watanabe et al., 2006). However, although these results might seem promising, it has to be kept in mind that the studies were all of poor methodological quality and many were industry sponsored. Hence, more thorough studies are needed to evaluate the safety of green coffee been extract.

3.5. L-carnitine

L-Carnitine (see Fig. 5) is an endogenous substance, synthesized in the liver and kidneys, that plays an important role in physiological cell processes, and is mostly stored in skeletal muscle (98%), but also present in plasma of healthy people (40–60 μM). Of note, its isomer D-carnitine is completely devoid of any physiological activity and is even toxic (Spasov and Ilezhitsa, 2005).

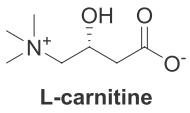


Fig. 5. Structure of L-carnitine.

Mechanism of action: The central role of L-carnitine in fat metabolism is to facilitate the transmission of long-chain fatty acids from the cytosol to the mitochondrial matrix (Jeukendrup and Randell, 2011; Kim et al., 2016b). This process begins with the conversion of fatty acids to acyl-CoA, which CPT-I subsequently converts to acylcarnitine. It is then transported via the mitochondrial membrane by carnitine-acylcarnitine translocase. In the matrix, acylcarnitine is converted back to the corresponding acyl-CoA by CPT-II, and finally enters the β-oxidation process (Fritz and Marquis, 1965; Bremer, 1983). Without carnitine, most dietary lipids cannot serve as a source of energy. Carnitine also maintains the ratio of mitochondrial acetyl-CoA/CoASH, that regulates flux through the pyruvate dehydrogenase complex and thus carbohydrate metabolism (Constantin-Teodosiu et al., 1991). *In vitro* studies have shown that carnitine inhibits adipocyte differentiation (Cha et al., 2003), while the *in vivo* study conducted in mice revealed carnitine reduced body weight through increased lipolysis, the latter being a direct result of increased CPT-I expression (Cha, 2008). Carnitine is often advertised as a compound that improves fat metabolism and reduces body fat and is, therefore, commonly used among athletes. This is based on the assumption that daily oral ingestion of carnitine increases its concentration in muscle (a fact: that is very difficult to achieve due to the already high concentration in muscles at 4–5 mM). A further assumption is that an increased concentration in muscle increases fat oxidation and consequently leads to weight reduction. However, consumption of 6 g of carnitine per day for several weeks did not lead to an increase in its concentration in muscles (Barnett et al., 1994; Vukovich et al., 1994). Human muscles contain enough carnitine to ensure maximum activity of CPT-I. Previous claims are therefore not only unfounded but theoretically impossible. However, recent studies have shown that carnitine concentration can be increased in muscles, by simultaneous ingestion of carbohydrates or by an injection of insulin, which would theoretically mean that this provides a possible way of affecting the metabolism of fats (Stephens et al., 2007, 2006). Nevertheless, there is currently not enough evidence to support this theory.

Safety: Very little information is available on the toxicology of L-carnitine and L-carnitine L-tartrate with the exception that they are not irritant to skin and eyes nor are they skin sensitisers (EFSA Panel, 2012). Previous studies on humans have provided no conclusive evidence to justify the consumption of carnitine in order to increase fat oxidation or to decrease body mass, despite the fact that it proved to be safe when multi-gram quantities were consumed. It is also worth noting that the bioavailability of L-carnitine has been shown to decrease with increasing L-carnitine concentrations. For example, in humans it drops to about 16% and 5% following oral administration of a single dose of 2 or 6 g L-carnitine (Evans and Fornasini, 2003; EFSA Panel, 2012). Taking all information into account, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) concluded that the use of L-carnitine and L-carnitine L-tartrate are well tolerated by humans and all animal species, and can be deemed safe as additives in animal nutrition for the consumer. Although much higher doses (e.g. 6 g/day for a period of 1 year) have been tested in humans without noticeable adverse effects and may be safe, the recently reported risk assessment indicates that chronic supplementation of L-carnitine is safe at intakes up to 2 g/day. There were no major adverse effects of L-carnitine except for an unpleasant fishy body odor, which has been ascribed to its metabolite trimethylamine (Hathcock and Shao, 2006).

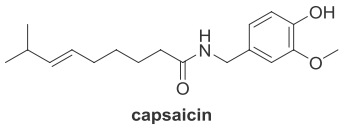


Fig. 6. Structure of capsaicin.

3.6. Capsaicin

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) (see Fig. 6) is the major pungent and irritating capsaicinoid present in the fruits of plants from the genus *Capsicum*, including chili, cayenne and red peppers. The capsaicinoids present in the *Capsicum* fruit are composed predominantly of capsaicin and dihydrocapsaicin, making up 80–90%.

Mechanism of action: Several potential mechanisms of action underlying the anti-obesity effects of capsaicin have been suggested (Leung, 2014). A neural pathway also modulates the regulation of fat metabolism via transient receptor potential vanilloid-1 (TRPV1)-sensitive sensory nerves since it enables activation of sympathetic nerve activity in brown adipose tissue (Leung, 2014). Capsaicin has been suggested to increase fat oxidation primarily by binding to and in turn activating the vaniloid TRPV1 receptor, which is expressed in many neurons (Westerterp-Plantenga et al., 2006). This results in increased secretion of adrenaline from the adrenal glands (Kawada et al., 1986; Watanabe et al., 1988; Diepvens et al., 2007). Capsaicin thus leads to increased lipolysis via β-adrenergic stimulation. Interestingly, recent *in vitro* studies have shown it also has an important role in adipogenesis by inhibiting lipogenesis through reduced expression of certain proteins (PPARγ, C/EBPα, leptin) and increased expression of adiponectin (Hsu and Yen, 2007). These actions induced apoptosis and inhibited adipogenesis in 3T3-L1 preadipocytes and adipocytes *in vitro*. A similar observation has also been reported by Zhang et al. (2007), who suggested it was a direct result of TPRV1 activation. These observations are in line with the findings from studies in obese mice fed a high-fat diet receiving a 0.015% capsaicin supplement, which revealed decreased leptin concentrations, enhanced expression of adiponectin in the adipose tissue and increased peroxisome proliferator-activated receptor α (PPARα) and peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) expression in the liver, ultimately resulting in augmented fatty acid oxidation (Kang et al., 2010b). PPARα is a nuclear hormone receptor which regulates glucose and lipid metabolism. Its agonists have been shown to protect against hepatic steatosis. Kang et al. revealed capsaicin not only increases PPARα expression but also acts as its ligand/agonist. The observed effects have therefore been linked to its dual action on PPARα and TRPV1 activation (Kang et al., 2010b). Finally, capsaicin has the potential to suppress appetite and increase satiety via regulation of neuronal circuits in the hypothalamus (Lee et al., 2015). Numerous preclinical studies reported anti-obesity effects of capsaicin (Zheng et al., 2017). Moreover, a recent clinical study in healthy subjects indicated that ingestion of 9 mg of capsaicin for 8 weeks increases brown adipose tissue activity thus increasing thermogenesis (Nirengi et al., 2016). Increased lipolysis has also been observed in several studies in humans who ingested 30–135 mg of capsaicin daily, which led to increased energy consumption and increased fat oxidation (Lejeune et al., 2003; Westerterp-Plantenga et al., 2006; Yoshioka et al., 1995).

Safety: Pharmacokinetic studies in rats have revealed that a single oral dose of capsaicin is absorbed within 1 h after ingestion (Kawada et al., 1986; Kim et al., 2016b). From a toxicological perspective, capsaicin is a powerful irritant, at low concentrations causing burns and pain to the skin and mucous membranes. In its concentrated form, a large dose of capsaicin could be toxic upon ingestion, causing difficulty in breathing and leading to convulsions (Johnson, 2007). However, the quantity usually found in hot peppers is so minuscule that there is practically no risk of harm from these toxic effects on consumption of

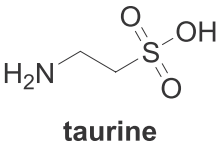


Fig. 7. Structure of taurine.

capsaicin itself. Nevertheless, several studies have linked capsaicin to neurological problems and possibly even tumor formation following topical application in mice in the presence of a tumor promotor such as sunlight (Bode and Dong, 2011).

3.7. Taurine

Taurine (2-aminoethanesulfonic acid) (see Fig. 7) is a sulfur-containing amino acid that is normally present in the body but has also found use as a component of commercialized energy drinks. It has also become increasingly popular as an ingredient in dietary supplements and functional foods.

Mechanism of action: Taurine has been shown to exert its anti-obesity effect via multiple points of action, including white adipose tissue, liver, muscle and the central nervous system (Murakami, 2017). In particular, the white adipose tissue being the major source of taurine in the body, and the fact that obesity development correlates with reduced taurine blood concentration as well as reduced synthesis in the adipose tissue have been highlighted (Murakami, 2017). Taurine supplementation in mice has been shown to increase the expression of energy-expenditure related genes, such as PPARα, PPARγ and PGC-1α in white adipose tissue, while it did not produce those effects in brown adipose tissue. Additionally, it up-regulated the expression of lipoprotein lipase, acyl-coenzyme A oxidase and acyl-CoA synthase (Tsuboyama-Kasaoka et al., 2006). Taurine also proved to be an agonist of the liver X receptor α (LXRα), a nuclear receptor that plays a major role in lipid and glucose homeostasis, thereby affecting the metabolism of lipids and carbohydrates in the adipose tissue (Hoang et al., 2012). An *in vivo* study in rats fed a high-fat diet revealed another possible mechanism of action underlying the anti-obesity action of taurine, since it increased the serum adiponectin level (You et al., 2013). Similar results were obtained in another study in rats, which revealed elevated hepatic expression of adiponectin (Chen et al., 2009b). An *in vitro* study on pancreatic beta cells has shown that taurine is capable of increasing plasma insulin levels via its action on calcium homeostasis (L'Amoreaux et al., 2010). Besides playing an important role in the regulation of metabolic pathways, adiponectin has also shown beneficial effects on suppression of adipose tissue inflammation (Murakami, 2017). Numerous *in vitro* studies have led to the suggestion that taurine has the capacity to increase cAMP production, either directly via stimulation of adenylate cyclase or through increased secretion of catecholamines (Chen et al., 2004). A study in rats has shown that the use of taurine increases liver oxidation of fatty acids (Fukuda et al., 2011) while it has also been shown to increase the expression of PPARγ and, consequently, increased lipid oxidation through augmented activity of CPT-I (Bonfleur et al., 2015). Increase in fat oxidation has also been confirmed by a recent study in humans. It was suggested that the observed effects can be ascribed to the activation of adenylate cyclase, increased cAMP concentration and, consequently, increased lipolysis and fat oxidation (Rutherford et al., 2010). Of note, earlier studies with taurine did not reveal similar findings, however, in those studies subjects ingested taurine and carbohydrates which may have masked the effect (Galloway et al., 2008).

Safety: Pharmacokinetic studies in humans have shown that the ingestion of supplemental oral doses of taurine (4 g) resulted in the average plasma levels of 86 μg/mL. The time to reach peak plasma concentration was 1.5 h, while the elimination half-life was about 1 h (Ghandforoush-Sattari et al., 2010). Overall, the literature demonstrates an extensive level of safety for supplemental taurine, given the fact no major adverse effects have been reported in any of the reviewed studies, in spite of using doses reaching as high as 10 g per day in a 6-month human clinical trial (Durelli et al., 1983; Shao and Hathcock, 2008). In fact, only minor gastrointestinal disturbances have been reported in a single study (Jeejeebhoy et al., 2002). Nevertheless, although higher doses have been tested in humans without noticeable adverse effects, the recently reported risk assessment based on the available published human clinical trial data indicates that long-term supplementation of taurine is safe at intakes up to 3000 mg/day (Shao and Hathcock, 2008). It should however be noted that taurine has been shown to potentiate certain pharmacodynamic effects of caffeine related to cardiotoxicity (Steele et al., 1990).

3.8. Conjugated linoleic acids

Conjugated linoleic acids (CLA) (see Fig. 8) comprise a group of positional and geometric isomers of the omega-6 essential fatty acid, linoleic acid. The *cis*-9, *trans*-11 isomer is the predominant form in food, while dietary supplements contain the same amounts of *cis*-9, *trans*-11 (also named 9c, 11t) and *trans*-10, *cis*-12 (also named 10t, 12c) isomers (most commercial preparations contain approximately 40% of *cis*-9, *trans*-11 and 44% of the *trans*-10, *cis*-12 isomer). It has been argued that CLA can reduce energy intake and lipogenesis and increase energy consumption, lipolysis and fat oxidation (Jeukendrup and Randell, 2011). On the basis of preliminary results, it was suggested that, of the two isomers the *trans*-10, *cis*-12 form possessed a stronger biological activity (Jeukendrup and Randell, 2011).

Mechanism of action: CLA affects the expression of certain hypothalamic appetite-regulating genes, for example it reduces neuropeptide Y expression, in turn reducing food intake (Cao et al., 2007). In addition, the influence on increased UCP expression was also suggested to be one of the possible mechanisms of action (West et al., 2000). Specifically, its anti-obesity effects are a result of its upregulation of uncoupling proteins, in particular UCP2, the most highly expressed UCP. CLA also augmented the expression of the mitochondrial enzyme CPT-I. Studies in rodents have corroborated that CLA-induced fat oxidation is associated with increased activity of CPT and with lipolysis in brown fat tissue, skeletal muscle and liver (Park et al., 1997; Rahman et al., 2001; West et al., 2000). Further, there is a significant amount of evidence indicating that CLA has the capacity to suppress the conversion of preadipocytes to adipocytes. This process is highly dependent on activation of several transcription factors, including PPARγ and C/EBPα. In agreement with this line of reasoning, CLA has been shown to attenuate these transcription factors (Kennedy et al., 2010). In addition, CLA is able to antagonize PPARγ indirectly via other pathways and not only at the transcription level (Kennedy et al., 2010). Another potential mechanism of CLA involves a decrease in activity of proteins that are involved in *de novo* lipogenesis, such as lipoprotein lipase (LPL), acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) and stearoyl-CoA desaturase (SCD) (Kennedy et al., 2010). Finally, increased lipolysis or

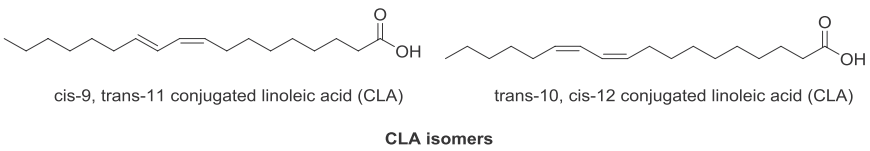
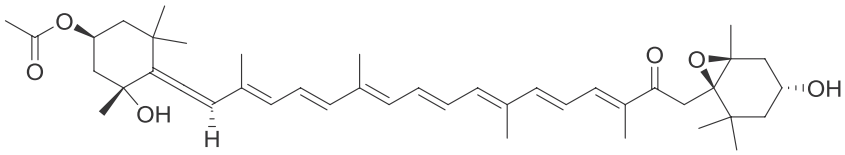


Fig. 8. Structures of conjugated linoleic acid isomers.



fucoxanthin

Fig. 9. Structure of fucoxanthin.

delipidation in adipocytes have also been proposed to be underlying the anti-obesity properties of CLA, while its (pre)adipocyte apoptosis-inducing capacity via an increase in endoplasmatic reticulum stress can also not be disregarded (Kennedy et al., 2010).

Safety: Pharmacokinetic studies in rats assessing the oral absorption and plasma kinetics of the two main isomers contained in commercial CLA-rich oil (3 g) have shown rapid oral absorption reaching maximum plasma concentrations of 7.9 mg/mL 2 h after ingestion (Rodríguez-Alcalá et al., 2017). A 36-week study of toxicity of CLA has been conducted in rats fed with a diet supplemented with 1.5% CLA. The obtained results of autopsy and haematological analysis of collected cardiac blood indicated no treatment-related effects (Scimeca, 1998).

A randomized double-blind placebo-controlled study in overweight male volunteers was conducted to investigate the short-term safety of dietary CLA. The subjects received 3.4–6.8 g of CLA (contained as equal proportion of 9c,11t- and 10t, 12c-isomers) daily for 12 weeks. Although the occurrence of adverse events tended to be higher in the high dose CLA group (compared to placebo group), these events were mild to moderate, within normal ranges, and temporary. Serum aspartate aminotransferase activity was only slightly increased from the baseline as opposed to serum alanine aminotransferase activity, which was significantly higher in the high CLA group than in the placebo group after 12 weeks. Given the fact that no clinically significant changes in vital signs were observed, CLA at a dose of 3.4 g/day has been suggested as a safe dietary level in healthy populations (Iwata et al., 2007). Unfortunately, in humans, the long-term application of CLA has been suggested to be potentially hepatotoxic (Larsen et al., 2003). Also, dietary CLA enhanced the growth of transplanted rat hepatoma dRLh-84 cells *in vivo* (Yamasaki et al., 2002). In spite of these concerns, it is worth mentioning that Clarinol®, a CLA-rich oil, consisting of approximately 80% of the two CLA isomers c9,t11:t10,c12 (1:1) has been recently assessed by EFSA. The reported animal studies did not indicate a risk for genotoxicity, reproductive toxicity, carcinogenicity or allergenicity. A large number of available human studies provided an even better insight into the safety of CLA (Pariza, 2004). While the long-term effects of CLA intake have not been properly addressed, CLA consumption for up to 6 months does not appear to have adverse effects on insulin sensitivity, blood glucose control or liver function, and that observed effects on blood lipids are unlikely to have an impact on cardiovascular risk. Hence, the safe dose of Clarinol® has been established at 3.75 g per day (corresponding to 3 g CLA), for up to six months (EFSA Panel, 2010b).

3.9. Fucoxanthin

Fucoxanthin (see Fig. 9) is a carotenoid isolated from the edible brown seaweed *Undaria pinnatifida* with a unique structure featuring an unusual allenic moiety, an epoxide and 9 conjugated double bonds. It has recently caught much attention since it displayed many interesting biological activities including anti-obesity effects.

Mechanism of action: Different mechanisms of action have been proposed. In particular, studies have shown that fucoxanthin affects thermogenesis by inducing UCP1 in abdominal white adipose tissue and muscles, in turn leading to fatty acid oxidation and heat production (Maeda et al., 2005; Miyashita, 2009; Gammone and D'Orazio, 2015). It also promotes the expresssion of β3-adrenergic receptor, responsible for both lipolysis and thermogenesis. Further, it has been shown to decrease the expression of enzymes involved in lipid synthesis, such as FAS and ACC. While FAS catalyzes the synthesis of palmitate from acetyl-CoA and malonyl-CoA, ACC functions as an upregulator of fatty acid metabolism by producing a vital building block, malonyl-CoA. It also reduces the expression of acetyl-CoA carboxylase, which leads to a decrease in the concentration of malonyl-CoA and fatty acid synthase, ultimately leading to a diminished production of long-chain fatty acids (Rios-Hoyo and Gutiérrez-Salmeán, 2016). Fucoxanthin and its metabolites have also been reported to cause inhibition of glycerol-3-phosphate dehydrogenase and a decrease in the expression of PPARγ and C/EBPα, which hinder adipocyte differentiation and accumulation of lipids (Maeda et al., 2006, 2005; Kang et al., 2011; Yim et al., 2011). Interestingly, an ethanolic extract of brown seaweed has also been found to decrease leptin plasma levels in mice (Park et al., 2011). Fucoxanthin also suppresses the SCD1 activity and alters fatty composition of the liver thus contributing to the prevention of obesity via leptin-dependent signaling (Beppu et al., 2013). A recent long-term Russian study in humans showed that the consumption of fucoxanthin increased the energy consumption and reduced the percentage of body and liver fat (Abidov et al., 2010). These encouraging results, however, should be taken *cum grano salis*, since at least one of the authors of that study is in a situation of a conflict of interest.

Safety: In general, there is limited information available regarding the toxicity of fucoxanthin. Firstly, fucoxanthin pharmacokinetics have been shown to be species-dependent. Human studies revealed fucoxanthinol to be the primary active metabolite as opposed to the metabolite profile observed in mice (fucoxanthinol and amarouciaxanthin A). Also, bioavailability of fucoxanthinol in humans was significantly higher than in mice (Hashimoto et al., 2012). Nevertheless, a 28-day oral toxicity study in rats showed no obvious toxicity. It should, however, be noted that significant increases in total cholesterol blood levels were observed at doses of 10 mg/kg/day or higher (Kadekaru et al., 2008). Similar observations have been reported in a repeated dose study in mice conducted by Beppu et al. (2009a) at doses of 500 and 1000 mg/kg. To confirm its safety, the underlying mechanism by which fucoxanthin induces hypercholesterolemia in rodents should be elucidated (Beppu et al., 2009a). Further, the *in vitro* mutagenicity assay of fucoxanthinol, the major metabolite of fucoxanthin, revealed no cause for concern. The ensuing *in vivo* micronucleus test in mice fed with fucoxanthin at doses of 500, 1000 and 2000 mg/kg was also found to be negative at all tested doses (Beppu et al., 2009b). Based on the obtained data it has been presumed that orally administered fucoxanthin is a safe compound in terms of mutagenicity (Peng et al., 2011). Finally, it should be noted that EFSA has not yet conducted a safety assessment of fucoxanthin.

3.10. Forskolin

Forskolin (see Fig. 10) is a diterpene compound isolated from a plant belonging to the mint family, *Coleus forskohlii*. It has already found traditional use in Ayurveda medicine for treating diverse disorders (Rios-Hoyo and Gutiérrez-Salmeán, 2016).

Mechanism of action: *In vitro* cell studies indicate forskolin acts directly on adenylate cyclase, which in turn causes an increase in cAMP (Burns et al., 1987; Insel and Ostrom, 2003). If this effect were

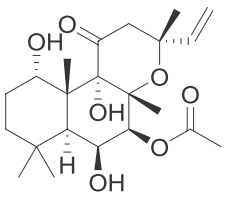


Fig. 10. Structure of forskolin.

reproduced in an *in vivo* setting, it could also affect fat metabolism, since cAMP activates HSL, thereby releasing fatty acids from fat tissue. A study in rats has shown that forskolin increases lipolysis in adipose tissue (Ho and Shi, 1982; Litosch et al., 1982). Similar effects were observed in obese men who had ingested forskolin for 12 weeks (Godard et al., 2005).

Safety: Pharmacokinetic studies in rats, investigating the absorption of dissolved forskolin after oral administration, showed it is absorbed well in all segments of the intestine. Based on the obtained results, the absorbed fraction of dissolved forskolin after oral administration in humans was estimated to be 100%. However, the low aqueous solubility of forskolin is a crucial factor underlying its poor oral bioavailability (Liu et al., 2012). In general, there is limited information available regarding toxicity of *Coleus forskohlii* extract and forskolin with the exception of the reported embryo-related toxicity and the traditional use of *Coleus forskohlii* extract in folk medicine to interrupt pregnancy. Although this extract did exhibit dose-dependent hepatotoxicity in mice, purified forskolin was devoid of these effects (Virgona et al., 2013). The safety study of *Coleus forskohlii* extract has also been conducted in healthy volunteers at doses ranging from 250 to 1000 mg over a 4-week period. No major adverse events were reported. In fact, only minor dose-related gastrointestinal events such as soft stool and diarrhoea, were observed. *Coleus forskohlii* thus appears to be well tolerated in daily oral doses up to 1000 mg (Kamohara et al., 2015). A subsequent study of *Coleus forskohlii* (containing 10% forskolin) also showed no signs of toxicity in the repeated dose 28-day oral toxicity study and in chronic 6-month oral toxicity study. Furthermore, the extract was also negative in the *in vitro* mutagenicity assay up to 5000 μg/plate, thus it was concluded that it was not mutagenic (Majeed et al., 2015). It should however be noted that forskolin has been shown to exacerbate the teratogenicity of methylxanthines in an embryonic heart model (Nishikawa et al., 1995). Finally, it is worth mentioning that EFSA has not yet conducted a safety assessment of forskolin.

3.11. Hydroxycitric acid (Garcinia cambogia)

Extracts of *Garcinia cambogia* often appear in a range of dietary supplements for weight-loss application, which have received considerable attention recently. The proposed main bioactive ingredient of this extract, accounting for 20–60% of its total mass, is hydroxycitric acid (HCA) as a free acid or in the lactone form (see Fig. 11). HCA is an α,β-dihydroxy tricarboxylic acid, which is also available commercially as a free acid or in the form of different salts (Chuah et al., 2013; Semwal et al., 2015).

Mechanism of action: HCA inhibits ATP-citrate lyase enzyme, resulting in reduced concentrations of malonyl-CoA, thus diminishing fatty acid synthesis as well as increasing fat oxidation. Malonyl-CoA serves not only as a substrate for lipogenesis but also as an allosteric inhibitor of the CPT-I enzyme, thus reducing the oxidation of fats (Loweinstein, 1971; Watson and Lowenstein, 1970). Interestingly, although four isomeric forms of HCA exist, only (−)−HCA, the prevalent isomer found in the fruit also known as (2*S*, 3*S*)−HCA, was shown to potently inhibit ATP citrate lyase (Stallings et al., 1979). *In vitro* studies have shown that HCA reduces adipocyte differentiation (Kim et al., 2004). Similarly, treatment of 3T3-L1 cell line with *G. cambogia* extract containing 60% HCA suppressed adipocyte differentiation and intracellular lipid accumulation by inhibiting PPARγ, C/EBPα and adipocyte protein aP2 expression (Kang et al., 2013). Ensuing *in vivo* studies corroborated the findings obtained in *in vitro* studies by detecting reduced fat levels caused by inhibition of lipogenesis and increased fat oxidation (Leonhardt et al., 2004; Kim et al., 2008). Specifically, *G. cambogia* extract administration to obese mice resulted in decreased visceral fat accumulation and reduced plasma leptin and insulin levels (Kim et al., 2008a). Human studies using HCA or *G. cambogia* extract also revealed their capacity to reduce the accumulation of visceral fat (Hayamizu et al., 2003; Kim et al., 2013). This effect has been partly attributed to the observed increased gene expression and activity of enzymes involved in fatty acid oxidation (Kim et al., 2013). Finally, the anti-obesity effects of HCA could also be mediated via the suppression of food intake sinceseveral studies demonstrated the capacity of HCA to enhance the release of serotonin, a key regulator of appetite in animals (Ohia et al., 2001, 2002) and humans (Preuss et al., 2005).

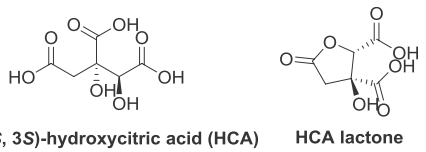


Fig. 11. Structures of (2*S*, 3*S*)-hydroxycitric acid and its lactone form.

Safety: *Garcinia* extracts have been used as a traditional diet for centuries without any major adverse events reported. Pharmacokinetic studies of the oral bioavailability of HCA in humans (single dose of 2 g) have shown that absorption is relatively fast with maximum concentrations (8.4 μg/mL) occurring 2 h after ingestion (Loe et al., 2001). Toxicity studies conducted in experimental animals have not revealed increased mortality or serious adverse events. The results of the examined cytotoxicity, genotoxicity, acute/sub-chronic toxicity studies, two-generation reproductive and teratogenicity studies as well as clinical studies of *G. cambogia* extract/HCA demonstrate its safety at high doses (1500 mg/day) (Chuah et al., 2012). Acute oral toxicity studies in animals indicate the low acute oral toxicity of HCA (Ohia et al., 2002). Further, no adverse effects have been observed in a 90-day subchronic study in rats (Soni et al., 2004). It should be noted that certain mutagenic properties have been observed in the Ames assay but the authors dismissed those effects as being not indicative of a mutagenic effect (Soni et al., 2004). A long history of use of HCA and its mechanism of action show that there are few, if any, grounds for causing reproductive or developmental effects (Soni et al., 2004). This presumption has been corroborated by the results obtained in reproductive toxicity studies, including developmental toxicity (teratogenicity) and a two-generation reproductive toxicity study, which indicate no toxicity at doses up to 1240 mg/kg/day (Deshmukh et al., 2008). On the other hand, it has been shown in subchronic animal studies, that administration of high doses of HCA can lead to testicular toxicity (i.e., testicular atrophy and impaired spermatogenesis) (Saito et al., 2005). Nevertheless, no serious adverse events have been observed in humans treated with *G. cambogia* in thorough literature reviews of clinical trials (Chuah et al., 2012; Márquez et al., 2012). Given the fact, that no adverse effects were reported in placebo-controlled, double-blind human studies at doses up to 2800 mg/day HCA (Downs et al., 2005) and the availability of sufficient qualitative and quantitative scientific evidence, it has been established that intake of gram quantities of HCA per day are safe for human consumption (Anton et al., 2011; Chuah et al., 2012; Soni et al., 2004). Remarkably, Stohs et al. (2010) demonstrated the safety of even higher doses (4667 mg/day). It is worth mentioning that in spite of the fact that most studies concluded HCA was safe, some uncertainties still exist regarding its safety, particularly when ingesting supplements containing high amounts of HCA (Bakhiya et al., 2017). HCA has been

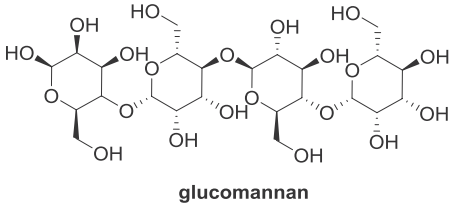


Fig. 12. Structure of glucomannan.

observed to cause severe adverse reactions, manifested mainly as hepatotoxicity. However, the formulations associated with hepatotoxicity were multicomponent (Shim and Saab, 2009), so HCA may not be the sole culprit. Moreover, a recent case study in a patient on escitalopram therapy associated the use of *Garcinia* extract-containing supplement with serotonin toxicity, although no definitve proof of cause and effect was presented (Lopez et al., 2014). Given the fact that HCA is known to increase serotonin levels upon ingestion and the fact that escitalopram acts as a selective serotonin reuptake inhibitor, serotonin toxicity could occur.

3.12. Glucomannan

Glucomannan (see Fig. 12) is a polysaccharide isolated from the root of *Amorphophallus konjac* consisting of monomers of D-mannose and D-glucose linked by β-1,4 glycosidic bonds (Keithley and Swanson, 2005).

Mechanism of action: The β-1,4 glycosidic bond renders glucomannan resistant to amylase metabolism, so that it passes the GIT unchanged. Like all fibers, glucomannan absorbs large volumes of water in the GIT (50 times its mass), thereby forming a gel, which produces a sense of satiety through the induction of gastric and cephalic phase signals, while also inhibiting the absorption of proteins and lipids, which is presumed to be the underlying mechanism of action (Keithley and Swanson, 2005). Slow absorption of nutrients reduces postprandial insulin secretion, whereas faster food passage to terminal ileum produces satiety signals and increases cholecystokinin (Keithley and Swanson, 2005).

Safety: The available toxicological data are somewhat limited. *In vivo* 90-day studies in rats and dogs showed no major adverse effects. Konjac glucomannan has also proven to be non-genotoxic. Glucomannan appears to be tolerated well at higher doses (2–4 g/day). In fact, the only side-effects were observed in a human study in healthy adults receiving a daily dosage of 3 g for 12 weeks, during which certain individuals experienced gastrointestinal discomfort including diarrhoea or constipation (Keithley et al., 2013). EFSA Panel therefore concluded that there was no safety concern for the reported use of glucomannan below 3 g/day (EFSA Panel, 2017). The most serious risk posed is actually a premature release of glucomannan from the capsule, which may cause airway obstruction (Keithley and Swanson, 2005).

3.13. Ginseng

Ginseng, the root of *Panax ginseng*, has been used in traditional medicine for many years for many indications and is also considered as one of the most popular herbal dietary supplements. Its predominant pharmacologically active components are ginsenosides (see Fig. 13), which undergo hydrolysis to their corresponding aglycones in the gastrointestinal tract. The profiles of ginsenoside content are related to the type of *Panax* species (Li and Ji, 2018).

Mechanism of action: *In vitro* studies showed that ginsenosides Rh2 and Rh3 effectively inhibit adipocyte differentiation by inhibiting PPARγ, while ginsenoside Rh2 also increased the activation of AMPK, CPT-I and UCP2 at the molecular level, which in turn led to facilitated fat oxidation (Hwang et al., 2007). The effects of ginseng on lipolysis and lipogenesis inhibition were also confirmed by animal studies (Kim et al., 2016b).

Ginseng and ginsenosides induce the AMPK pathway, which plays a major role in cell metabolism. Specifically, its activation leads to fatty acid oxidation, while it suppresses lipogenesis, triglyceride synthesis and cholesterogenesis, ultimately resulting in an increase in energy expenditure (Li and Ji, 2018). The stimulatory effect of ginseng on AMPK pathway was demonstrated in several tissues, including liver, adipose tissue and skeletal muscles (Li and Ji, 2018). In liver, it caused a decrease of triglyceride synthesis and reduced cholesterogenesis and gluconeogenesis via suppressed expression of enzymes, involved in *de novo* lipogenesis (Li and Ji, 2018). The ginseng-induced stimulation of AMPK pathway in the adipose tissue has also been shown to inhibit triglyceride synthesis. The effect of ginseng and ginsenosides in skeletal muscle is demonstrated by increased glucose uptake and fatty acid oxidation, resulting in augmented energy expenditure (Li and Ji, 2018).

Moreover, ginseng extracts activate PPARα, which allows for enhanced oxidation and export of fatty acids (Li and Ji, 2018). Thus, intraperitoneal administration of 5 mg of ginseng extract into mice led to a decrease in acyl-CoA oxidase mRNA levels, while it also resulted in inhibition of the induction of PPARα target genes (Yoon et al., 2003). Further, ginseng extract has been shown in several long-term studies in mice to possess the capacity to reduce adipose tissue mass as well as adipocyte size (Lee et al., 2009; Li et al., 2014). This inhibitory effect on adipogenesis has been attributed to ginseng-mediated decreased expression of transcription factors PPARγ and C/EBPα (Li et al., 2014; Li and Ji, 2018). For example, it has been shown that *Panax ginseng* leaf extracts exhibited an inhibitory effect on adipogenesis of 3T3-L1 adipocytes via suppression of PPARγ and C/EBPα. It should be noted that PPARγ is mostly expressed in white and brown adipose tissues and is considered as a key regulator of adipogenesis. (Lee et al., 2017).

In addition, ginseng possesses the capacity to increase the secretion of adiponectin both *in vitro* and *in vivo*. This hormone is exclusively secreted by adipose tissue, modulating fatty acid oxidation and glucose regulation (Li and Ji, 2018). Further, in mice treated with ginseng extract, plasma levels of leptin and neuropeptide Y were increased (Lee Y.S. et al., 2010), which offers a possible mechanism underlying the repressed food intake observed in several *in vivo* studies (Li and Ji, 2018).

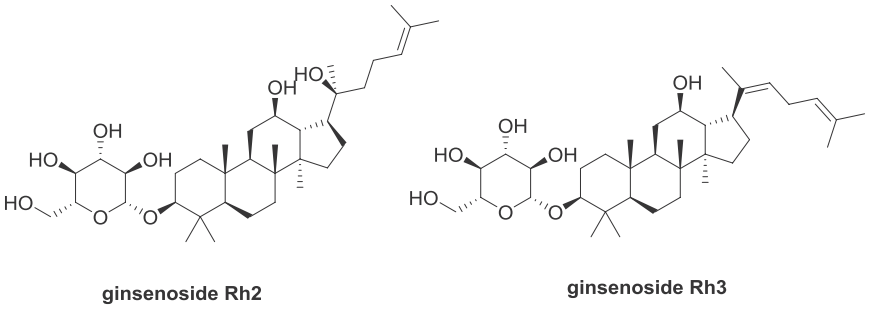


Fig. 13. Structures of representative ginsenosides.

Safety: Pharmacokinetic studies in humans have revealed that ginseng is poorly absorbed from the GIT. Its absorption rate amounts to 1–3.7% as it is extensively metabolised in the stomach and in the intestine by acid and bacterial hydrolysis, respectively (Ong et al., 2015). The available toxicology studies in rodents and larger animals indicated that ginseng is of rather low acute oral toxicity (LD50 > 5000 mg/kg for rodents, equivalent to 200 mg ginsenoside/kg) (Carabin et al., 2000), while it also proved to be non-toxic in repeated dose studies in dogs (Hess et al., 1983). Similarly, no toxicological effects were observed for ginseng in reproduction studies in rodents (Hesse et al., 1982), although an *in vitro* study of ginsenosides indicated a certain embryotoxic potential (Chan et al., 2004) nor was there any mutagenic activity in an *in vitro* mutagenicity assay (Chang et al., 1986). In humans, long-term ginseng consumption (1600 mg for 3–5 years) did not cause any adverse effects (Li and Ji, 2018; Park, H.J. et al., 2010). In a recently reported human trial, healthy volunteers were daily administered *P. ginseng* extract over a 4-week period and it proved to be safe at the highest dose tested (2000 mg/day) (Lee N.H. et al., 2012). Similarly, standardized ginseng extracts given to humans (114 μg ginsenoside/kg) for 12 weeks have not resulted in any adverse effects (Carabin et al., 2000). In fact, no adverse reactions in humans have yet been attributed either to ginseng alone in a human study or to ginseng consumption in general (Carabin et al., 2000).

3.14. Ma huang (*Ephedra sinica major*)

Ma huang is the Chinese name for the plant genus *Ephedra*, a natural source of the *Ephedra* alkaloids (i.e. ephedrin, pseudoephedrine, norephedrine, methylephedrine and norpseudoephedrine). Preparations of ma huang have a long and successul track record in traditional Chinese medicine (Gurley et al., 2015). On the other hand, in the US, this and other supplements containing *Ephedra* alkaloids were a source of controversy throughout their use and eventually banned by the FDA in 2004 due to significant cardiovascular risk (Gurley et al., 2015), although, it remains widely available on the web.

Mechanism of action: *Ephedra* alkaloids have indirect activity as α-adrenergic agonists (α1) and some direct β-adrenergic properties (β1 and β2), which together stimulate both CNS and cardiovascular systems. At this junction, a reference must also be made to “ECA stack”, a combination of ephedrine (75–150 mg), caffeine (150 mg) and acetylsalicylic acid (330 mg) (Daly et al., 1993). Until the ban on *Ephedra* alkaloids, certain bodybuilders used it for weight loss. It exploited the synergistic stimulatory effects of the ingredients on the sympathetic nervous system. Ephedrine was shown to stimulate brown adipose tissue and skeletal muscle thermogenesis in rodents and humans, respectively, via activation of β-receptors, in particular β3-adrenergic receptor (Greenway, 2001). However, ephedrine only possesses weak partial agonist activity on this receptor subtype (Vansal and Feller, 1999). Nevertheless, this ephedrine-induced thermogenesis was significantly induced by co-treatment with acetylsalicylic acid and methylxanthines (Greenway, 2001).

Safety: *Ephedra* alkaloids possess an excellent oral bioavailability, comparable to that of caffeine. They reach peak plasma concentrations within 2–3 h upon ingestion, and are widely distributed into highly perfused organs (Gurley et al., 1998). Of note, when ephedrine and caffeine are ingested simultaneously, they reach their maximum plasma concentrations at the same time, which likely contributes to any enhanced sympathomimetic activities and potentiates the cardiotoxic effects (Haller et al., 2002; Dunnick et al., 2007). Adrenergic effects of ephedrine can lead to acute myocardial infarction, hypertension, and cardiac arrhythmias (Gurley et al., 2015; Brown, 2017c). Ma huang has also been associated with hepatic injuries, such as hepatitis and liver failure (Bunchorntavakul and Reddy, 2013).

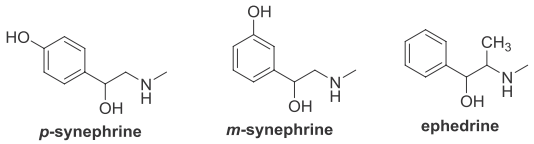


Fig. 14. Structures of *p*-synephrine, *m*-synephrine and ephedrine.

3.15. *Citrus aurantium* extract

Extract of *Citrus aurantium* (bitter orange) has long been used in traditional Chinese medicine. It contains many alkaloids, including *para*- and *meta*-synephrine (also known as phenylephrine), which are structurally similar to ephedrine and catecholamines (see Fig. 14). Currently, manufacturers often use this extract as a substitute/surrogate for banned *Ephedra* alkaloids under the moniker *Ephedra*-free supplements (Gurley et al., 2015). *Para*-synephrine (also known as 1-(4-hydroxyphenyl)-2-methylaminoethanol) comprises about 90% of protoalkaloids of *Citrus aurantium* extracts, which are usually standardized to 4–6% synephrine (Brown, 2017c; Stohs, 2017). In the citrus fruit bitter orange and other citrus fruits, (−)-synephrine is the only enantiomer possessing any significant biological activity.

Mechanism of action: Given its structural similarity to ephedrine (an indirect α-adrenergic agonist with some β-adrenergic properties), *p*-synephrine was thought to act as a typical sympathomimetic, that is by stimulating the CNS and cardiovascular system. Specifically, the structure of *p*-synephrine carries an additional hydroxyl group on the benzene ring, while ephedrine contains an additional methyl group attached to the side chain. However, it has been shown that due to these minor modifications, these compounds differ considerably in terms of their adrenergic receptor binding capacities and pharmacological properties. Its regioisomer, *m*-synephrine, however exhibits considerable sympathomimetic activity since it carries the hydroxyl group in *meta* position, which is known to promote adrenergic receptor binding (Ma et al., 2010). Therefore, the cardiovascular effects of other sympathomimetics, including those of ephedrine, cannot be simply extrapolated to *p*-synephrine. Most are namely mediated via adrenergic receptors, in particular α1-, α2-, β1-and β2-receptors (Stohs, 2017), while *p*-synephrine and its *N*-demethylated metabolite octopamine have a preference for β3-adrenergic receptors (Carpéné et al., 1999; Mercader et al., 2011) and only bind poorly to other adrenoceptors (Brown et al., 1988). Of note, β3-adrenergic receptors are present in the adipose tissue and do not influence heart rate or blood pressure. Synephrine thus stimulates lipolysis mostly via the activation of β3-and, to a smaller extent, α-adrenergic receptors, thus increasing oxidative fat metabolism (Rios-Hoyo and Gutiérrez-Salmeán, 2016). In a small experiment, synephrine has been shown in the short term to increase the basal metabolic rate, however longer studies are needed to substantiate these findings (Stohs et al., 2012). It is worth mentioning, that the extract also contained some flavonoids (hesperidin, naringin), which also could have contributed to the final effect. Finally, Kaats and Stohs (2017) have shown that *p*-synephrine also possesses the ability to suppress the appetite in humans, most likely via the modulation of hypothalamic neuromedin U2 receptor (NMUR2) (Zheng et al., 2014).

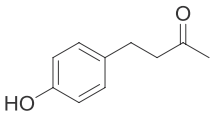
Safety: Pharmacokinetic studies of synephrine in humans have revealed its low bioavailability when taken orally. Following the ingestion of 46.9 mg, the time to reach peak plasma concentration of 3 ng/mL was 1–2 h, while the elimination half-life was about 3 h (Haller et al., 2005). *Citrus aurantium* extract showed low acute oral toxicity in rats (LD50 > 5000 mg/kg), while it also proved to be non-mutagenic in the *in vitro* Ames mutagenicity assay at doses up to 5000 μg/plate (Deshmukh et al., 2017a). Subsequent 90-day subchronic studies on rats receiving a standardized *Citrus aurantium* extract indicated no

major adverse effects at 1000 mg/kg (equals to 500 mg synephrine/kg) (Deshmukh et al., 2017b). Structurally, it is classified as a sympathomimetic amine, which are notorious for their negative effects on the cardiovascular system (e.g. hypertension, tachycardia). The research conducted by Bent and colleagues is in line with the former statement since it suggested that *Citrus aurantium* consumption leads to increased blood pressure and enhances the risk of cardiovascular events (Bent et al., 2004). Further, numerous cases of adverse reactions associated with bitter orange extract/synephrine have been reported in recent years, which attest to the potential cardiotoxicity of these agents (Brown, 2017c; Stohs, 2010). However, Stohs also indicated that although they were implicated as the probable causative agent, the products also contained numerous additional herbal ingredients. Further, these products were not always taken by the recommended regimen, as it was also not clear whether the patients were using other supplements/drugs (Stohs, 2010). Notwithstanding their extensive use, a review of the most recent literature revealed that no serious adverse events have ever been directly attributed to bitter orange extract, *p*-synephrine or any form of a variety of juices and marmalades consumed by millions on a daily basis (Shara et al., 2016; Stohs, 2017). For instance, a double-blinded, placebo-controlled 2-month study in healthy volunteers receiving 98 mg of synephrine daily demonstrated no adverse effect, in particular with regard to heart rate and blood pressure (Kaats et al., 2013). This study lends significant credibility in favor of safety of synephrine as it is considered as the longest that has ever been reported, while it also used the highest dose to date. In general, *p*-synephrine is fairly innocuous by itself, however, it should also be noted that the cardiotoxic effects of bitter orange extract can be enhanced by other stimulants, caffeine in particular, frequently formulated together in dietary supplements, thus raising the level of concern (Brown, 2017c). When establishing safety profiles of products, one should always look at the big picture. A recent risk asessment of *p*-synephrine alone and in combinations with caffeine conducted in Canada took that into account. They concluded that up to 50 mg/day of *p*-synephrine alone was not likely to cause any adverse effects. Similar claims have also been made for a combination of 40 mg of *p*-synephrine with 320 mg of caffeine daily (Stohs, 2013, 2017). Of note, these allegedly safe levels of intake are significantly higher than 6.7 and 20 mg synephrin/day, recommended by the German and French authorities, respectively (Bakhiya et al., 2017).

3.16. Raspberry ketone

Raspberry ketone (4-(4-hydroxyphenyl)-2-butanone) (see Fig. 15) is a volatile phenolic compound that gives raspberries their distinctive odor (occurring at concentration up to 4.3 mg/kg), while it is also used in the food industry as a taste enhancer/flavoring agent and as a fragrance in cosmetics (Lee, 2016). In recent years, it has gained a lot of attention as one of the latest self-proclaimed miracle weight loss agents. Although raspberry ketone may be found in limited quantities in other fruits, the vast majority present in weight-loss supplements is of synthetic origin (Lee, J., 2016).

Mechanism of action: An *in vitro study* in adipocytes showed that raspberry ketone increased the oxidation of fatty acids, inhibited lipid accumulation, and increased the secretion of adiponectin (Park, 2010). At the molecular level, the underlying mechanism for these biological effects includes decreased expression of transcription factors and genes involved in the adipogenesis process (PPARγ, C/EBPα, ACC, FAS, SCD1), and increased expression of genes involved in the oxidation of fatty acids (HSL, CPT, triglyceride lipase) (Park, K.S., 2015). Given the structural similarity between RK and synephrine, it has been speculated that RK stimulates lipolysis via the activation of β-adrenergic receptors. However, studies in rats have shown that RK significantly increases the noradrenaline-induced lipolysis, not via the HSL activation but by facilitating the translocation of HSL from the cytosol to lipid droplets in rat fat cells (Morimoto et al., 2005).



raspberry ketone

Fig. 15. Structure of raspberry ketone.

Safety: Pharmacokinetic studies of raspberry ketone in rats administered via oral gavage showed it was rapidly absorbed from the GIT. The ingested RK was predominantly excreted in urine within the first 24 h in the form of glucuronide and/or sulphate conjugates (Sporstøl and Scheline, 1982). Instead of using its chemical name 4-(4-hydroxyphenyl)-2-butanone, RK is being marketed under an innocuous sounding name including the wording “100% natural”, which can be misinterpreted as inherently safe. Bredsdorrf pointed out a potential toxicological concern with regard to the ingested recommended amounts of raspberry ketone (between 100 and 1400 mg per day), within these weight-loss products (Bredsdorff et al., 2015). The available data on toxicological properties of raspberry ketone are mostly limited to the results of acute and subchronic studies conducted in rats. However, quantitative structure-activity relationship toxicity models predicted potential cardiotoxic effects of raspberry ketone as well as its potential effects on reproduction/development (Bredsdorff et al., 2015). Incidentally, FEEDAP concluded that raspberry ketone is safe at 25 mg/kg when used as feed flavour for all examined species (EFSA Panel, 2016).

3.17. Irvingia gabonensis extract

Irvingia gabonensis, also known as the African wild mango, is a plant rich in polyphenols, including ellagic acid, mono-, di-, and tri-*O*-methyl-ellagic acid, and their related glycosides as the major constituents (Sun and Chen, 2012).

Mechanism of action: An *in vitro* study in adipocytes has shown that the extract of this plant containing a large number of flavonoids inhibits the expression of PPARγ and leptin, thus acting as an adiposity signal and regulates energy intake. At the same time, it caused an increase in the expression of adiponectin (Oben et al., 2008). These findings have been corroborated in human studies, wherein a decrease of serum leptin levels has also been observed (Ngondi et al., 2009). The water-soluble fibres of *Irvingia gabonensis* have also been suggested to act as “bulk-forming" laxatives. These fibres are also expected to delay stomach emptying, which would bring about a more gradual absorption of dietary sugar (Ngondi et al., 2005). Like other soluble fibers they should be able to bind bile acids in the gut and facilitate their excretion with faeces, which in turn would cause the body to convert more cholesterol into bile acids (Ngondi et al., 2005).

Safety: The results of a subchronic toxicity study of *I. gabonensis* extract in rats indicated no toxicity at the highest dose tested (2500 mg/kg bw/day). Subsequent genotoxicity studies (*in vitro* mutagenicity Ames assay, the *in vitro* and *in vivo* chromosomal aberration test and *in vivo* micronucleus assay) showed no signs of genotoxicity (Kothari et al., 2012). No safety concerns were reported in human studies for doses up to 3150 mg/day for 10 weeks. In fact, only minor side effects were observed, including headache, sleep difficulties and flatulence (Onakpoya et al., 2013).

4. Hepatotoxicity of compounds of natural origin occurring in dietary supplements for weight loss

Hepatotoxic reactions to dietary supplements are considered idiosyncratic as they only occur in a small fraction of the population (Brown, 2017b). Most products are advertised as completely natural, but a few natural ingredients, including green tea extract, usnic acid,

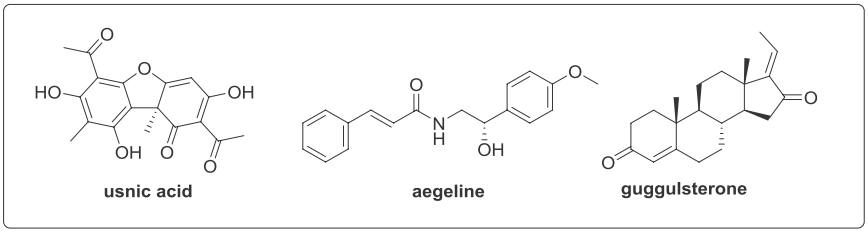


Fig. 16. Structural formulae of selected hepatotoxic ingredients present in fat burners.

aegeline, aloe vera, germander and conjugated linoleic acid, are believed to be hepatotoxic and may lead to hepatitis or even liver failure (Chitturi and Farrell, 2008; Zheng and Navarro, 2015; Brown, 2017b). In Hawaii, in 2013, several cases of hepatitis and liver failure were associated with the consumption of a product containing a naturally occurring hepatotoxic compound, aegeline (Johnston et al., 2013). However, aegeline toxicity was only reported when extremely high concentrations not found in nature were inserted into a fat burner. It is worth mentioning that a dietary supplement (OxyELITE Pro) containing aegeline, caffeine, yohimbine, and other sympathomimetics produced similar hepatotoxic effects in mice (Miousse et al., 2017). Similar adverse events occurred in consumers of fat burners containing usnic acid (no longer sold in dietary supplements). The latter is a product of the lichen of the genus *Usnea*. Its mechanism of action has been suggested to involve decoupling of oxidative phosphorylation, while the hepatotoxic effects were considered to be idiosyncratic (Durazo et al., 2004; Han et al., 2004; Araújo et al., 2015). Krishna and colleagues (2011) described a case study of a couple of young bodybuilders who frequently ingested various fat burners, which led to liver failure. Usnic acid was identified as the causative agent of hepatotoxicity, however guggulsterone, a resin from *Commiphora mukul*, which is known to cause hepatitis, also may have contributed to hepatotoxicity (Grieco et al., 2009). The chemical structures of usnic acid, aegeline and guggulsterone (shown in Fig. 16) reveal the presence of electrophilic functional groups in all three compounds, indicating the potential to form electrophilic metabolites that could contribute to the hepatotoxic potential of these compounds. Namely, such *in situ* formed metabolites can react with biological macromolecules present in hepatocytes, including proteins, membranes and DNA, thus potentially causing toxic effects. In terms of hepatotoxicity, the green tea extract, present in several products, cannot be deemed perfectly safe, since it has been linked to acute liver failure (Molinari et al., 2006; Chitturi and Farrell, 2008; Mazzanti et al., 2009; Bunchorntavakul and Reddy, 2013; Bonkovsky, 2006). The mechanism of hepatotoxicity may be the induced formation of reactive oxygen species by the catechins, which in turn affect the mitochondrial membrane potential (Han et al., 2004; Schmidt et al., 2005). Nevertheless, the animal studies indicated that GTE taken with food produced no overt hepatotoxicity. The latter was only observed when GTE was administered in a fasted state. It should also be noted that the extracts were prepared by extraction with organic solvents, which may have led to impurities such as pesticides to be present in the extracts. Even products with purely natural ingredients and extracts are not completely safe, as evidenced in numerous publications highlighting various commercially available products (Schoepfer et al., 2007; Shim and Saab, 2009; Fong et al., 2010), the use of which, in many cases, resulted in mild injuries and, in some cases, even liver failure. The multi-ingredient composition of Hydroxycut also included *Garcinia cambogia* extract and green tea catechins, which have recently been demonstrated unequivocally to have marked hepatotoxic effects. Studies in rodents have shown it to cause inflammation of the liver, fibrosis, and oxidative stress (Lunsford et al., 2016).

5. Common synthetic adulterants: their mechanisms of action and safety profiles

An increasing number of important issues concerning dietary supplements have been moving to the forefront, in particular the addition of a variety of adulterants, which pose the most significant safety concern. Adulterants are illegal and usually include unauthorized substances, mainly appetite suppressants, such as sibutramine and its active metabolites, or fenfluramine and rimonabant, as well as various old and new psychostimulants (diethylpropion, *N*,α-diethylphenylethylamine (*N*,α-DEPEA), β-methylphenethylamine, 3-dimethylamylamine (DMAA) and clenbuterol). Importantly, some of these compounds have never been studied in humans, so that their adverse affects are still unknown (Cohen, 2014). As impurities, laxatives, diuretics or even animal thyroid tissue have also been found in these products. The internet has made it very easy to sell products containing prohibited substances. Unfortunately, the consumption of such products may have serious consequences, from mild poisoning to death (Table 2) (Yen and Ewald, 2012).

2,4-Dinitrophenol (also known as DNP, Dinosan, Dnoc, Solfo Black, Nitrophen, Aldifen, Chemox), which has long been banned from the market, acts by decoupling mitochondrial oxidative phosphorylation, thereby leading to increased fat metabolism and loss of weight. During glycolysis, most energy-rich phosphate bonds are typically generated during the process of oxidative phosphorylation, in which ATP synthetase converts adenosine diphosphate to ATP by adding an inorganic phosphate group. DNP can disturb this pathway in several ways (shown in Fig. 17): (*i*) by preventing phosphate uptake into mitochondria; and

Table 2
Potential adverse effects of synthetic adulterants.

Synthetic adulterants	Toxic effects	Reference
2,4-dinitrophenol	Hyperthermia, cataracts, cardiac arrest	Grundlingh et al., 2011
Sibutramine and active metabolites	Manic/panic attacks, psychosis, myocardial infarction, cerebrovascular complications	James et al., 2010
Fenfluramine and *N*-nitrosofenfluramine)	Cardiac valve injuries, primary pulmonary hypertension	Connolly et al., 1997
Sympathomimetics (diethylpropion or amfepranone, *N*,α-DEPEA, β-MPA, DMAA, clenbuterol)	Cardiac arrhythmias, palpitations, tremor, anxiety, panic, hypertension	Yen and Ewald 2012
Laxatives (anthraquinones, phenolphtalein)	Hypoglycaemia, alterations in colonic anatomy	Yen and Ewald 2012
Diuretics (furosemide, hydrochlorothiazide, spironolactone)	Electrolyte balance disturbance	Yen and Ewald 2012
Thyroid tissue/hormones	Thyroid storm (thyrotoxic crisis), thyrotoxic periodic paralysis, cardiac arrhythmia, palpitation, tremor, anxiety, hypertension	Akinyemi et al., 2011 Chen et al., 2001 Hartung et al., 2010

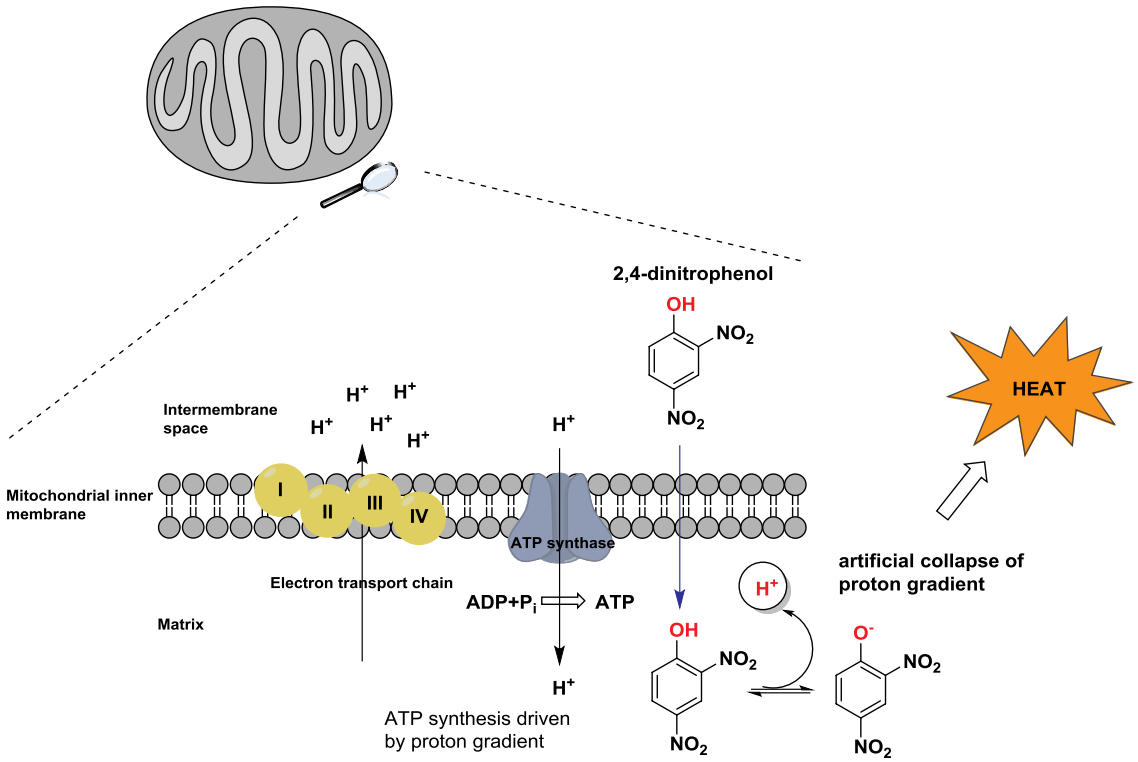


Fig. 17. 2,4-dinitrophenol and its mechanism of action/toxicity.

(*ii*) by acting as a chemical ionophore, increasing the basal leak of protons and thus inhibiting energy conversion. This shift in proton gradient prevents the excess energy from being stored as ATP but, instead, being dissipated as heat (Grundlingh et al., 2011). Collectively, these effects lead to the accumulation of pyruvate and lactate and a rise in temperature, which may result in hyperthermia, tachycardia, tachypnoea, and cardiac arrest, its use having therefore been prohibited since 1938 (Yen and Ewald, 2012). DNP has a very low therapeutic index and is extremely dangerous in overdose (3–5 g). This low-cost substance has recently been detected in a number of products, intended primarily for bodybuilders, that are accessible online, being most commonly sold as 100–200 mg capsules (Grundlingh et al., 2011). The most notorious case of its abuse arose in the 1980s, when it was marketed by a doctor in Texas as a weightlifting agent, Mitcal (Grundlingh et al., 2011).

Excessive adrenergic effects of sympathomimetics can lead to cardiotoxicity, ranging from hypertension and cardiac arrhythmias to acute myocardial infarction. Laxatives and diuretics can cause electrolyte disorders, usually hypokalemia. Thyroid hormones increase the basal metabolism by acting on the hypothalamus or through peripheral effects, leading to loss of weight. However, the use of exogenous thyroid hormones can result in thyroid storms and thyrotoxic periodic paralysis (Chen et al., 2001; Hartung et al., 2010; Akinyemi et al., 2011). Another issue often encountered with weight-loss agents is the misleading of users with inconsistent labeling of individual ingredients (da Justa Neves and Caldas, 2015; Tang et al., 2011). For example, the sympathomimetic DMAA (not allowed in US nor in EU), which is a stimulant banned in sport, often appears on the list of ingredients under various pseudonyms (2-amino-4-methylhexane, methylhexaneamine, geranamine or geranium oil) - a classic case of deception, even when using the name geranamine, since natural geranium oils have been shown not to contain this substance. The presence of DMAA could only have been a result of the subsequent addition of this synthetic chemical (Lisi et al., 2011).

6. Conclusion

Easy public access to potentially harmful fat burners, accessible as dietary supplements, has led to widespread use of these products. Dietary supplements constitute a dynamic market that, in all likelihood, can only grow in the sense of discovering new substances, and the generation of scientific evidence required to support their safety can only follow at an even slower rate. In terms of safety, of all the active ingredients and extracts examined, the safest seems to be glucomannan, given the fact that excessive consumption of caffeine and green tea extract can sometimes have serious consequences. It has also become increasingly clear that multi-component supplements may not be as innocuous as many consumers have come to believe. Namely, the contribution of each ingredient to overall pharmacologic activity is almost impossible to predict, yet only few of these products have been examined prospectively in terms of tolerability. Without a doubt, adulterated products pose the biggest safety concern of all fat burners and dietary supplements in general. Namely, these illegal adulterated products marketed as fat burners have often not been tested for efficacy or safety. In general, very few dietary supplements have demonstrated weight-loss efficacy beyond reasonable doubt, especially with long-term usage. It may be possible to lose some weight with dietary supplements, but the most important route to this end lies via healthy food and a generally healthy lifestyle.

Conflicts of interest

The author declares no competing financial interest.

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