

Review

Nutrition Supplements to Stimulate Lipolysis: A Review in Relation to Endurance Exercise Capacity

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Summary Athletes make great efforts to increase their endurance capacity in many ways. Using nutrition supplements for stimulating lipolysis is one such strategy to improve endurance performance. These supplements contain certain ingredients that affect fat metabolism; furthermore, in combination with endurance training, they tend to have additive effects. A large body of scientific evidence shows that nutrition supplements increase fat metabolism; however, the usefulness of lipolytic supplements as ergogenic functional foods remains controversial. The present review will describe the effectiveness of lipolytic supplements in fat metabolism and as an ergogenic aid for increasing endurance exercise capacity. There are a number of lipolytic supplements available on the market, but this review focuses on natural ingredients such as caffeine, green tea extract, L-carnitine, *Garcinia cambogia* (hydroxycitric acid), capsaicin, ginseng, taurine, silk peptides and octacosanol, all of which have shown scientific evidence of enhancing fat metabolism associated with improving endurance performance. We excluded some other supplements owing to lack of data on fat metabolism or endurance capacity. Based on the data in this review, we suggest that a caffeine and green tea extract improves endurance performance and enhances fat oxidation. Regarding other supplements, the data on their practical implications needs to be gathered, especially for athletes.

Key Words lipolytic supplements, ergogenic aid, fat metabolism, endurance exercise capacity

Carbohydrates and fats are oxidized as a mixture and are the predominant fuels that influence various aspects of exercise, including the intensity and duration. In particular, skeletal muscle demands chemical energy, which results in an increase in both fat and carbohydrate oxidation during exercise. During low-intensity, long-term exercise, the proportion of fat oxidized and used in the muscle gradually increases and that of carbohydrate decreases (1). Conversely, carbohydrate oxidation becomes more pronounced than fat oxidation with increasing exercise intensity (2). Compared with the limited storage of glycogen in human muscle and liver, endogenous fat deposits are large and can be utilized as an unlimited source of fuel during exercise. Athletes have been looking for ways to increase endurance capacity by increasing fat utilization during exercise. There are a number of supplements which possess the effects of the reduction of body weight or fat accumulation which can be achieved by stimulation of lipolysis and/or inhibition of lipogenesis. However, the usefulness of the lipolytic supplements as an ergogenic

functional food remains controversial. There are a number of lipolytic supplements available on the market, but this review focuses not on artificial ingredients but on natural ingredients, such as caffeine, green tea extract, L-carnitine, *Garcinia cambogia* (hydroxycitric acid), capsaicin, ginseng, taurine, silk peptides and octacosanol, all of which have shown scientific evidence of enhancing fat metabolism associated with improving endurance performance. Of them, silk peptides and octacosanol may inhibit lipogenesis rather than stimulating lipolysis but we include them in this review because there was evidence of enhancing endurance exercise capacity by increasing fat oxidation in human studies. In order to systematically review the association between supplement ingestion and endurance exercise capacity, we identified relevant studies through a database of Pubmed without any publication year restriction until December 31, 2015.

Caffeine

The effect of caffeine on fat metabolism

Caffeine (1,3,7-trimethylxanthine) is a major component of some of the most widely consumed psychoactive ingredients and beverages, such as coffee, tea, and

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Table 1. A summary of studies that examined the effects of caffeine on endurance performance.

Reference	Participants	Dose	Protocol	Timing	Key results	Endurance performance
Costill et al. (14)	F: 2, M: 7	330 mg	80% max to exh	1 h before exercise	Increased running time because of stimulating lipolysis.	↑
Graham & Spriet (13)	Athletes: 7 (runners)	9 mg/kg	85% max to exh	1 h before exercise	Increased running times.	↑
Erickson et al. (18)	Athletes: 5 (cyclists)	5 mg/kg	Consisted of 90 min of cycling at 65 to 75% max	1 h before exercise	Decreased muscle glycogen utilization.	↑
Spriet et al. (19)	Athletes: 8	9 mg/kg	80% max to exh	1 h before exercise	Decreased muscle glycogen utilization.	↑
Cruz et al. (20)	M: 8	6 mg/kg	1 W/kg/bw and increase 0.5 W/kg/bw until exhaustion	1 h before exercise	Improved maximal lactate steady state (22.7% vs con) and increased fat oxidation.	↑
Bruce et al. (15)	Athletes: 8 (rowers)	6 or 9 mg/kg	2,000-m rowing test on an air-braked ergometer	1 h before exercise	Decreased RQ and time (s): 411 (6 mg/kg), 412 (9 mg/kg), 416 (placebo).	↑
Kovacs et al. (16)	M: 15	0, 2.1, 3.2, 4.5 mg/kg	Complete a work output estimated to take 1 h	1 h before exercise	Reduced exercise time and increased fat oxidation.	↑
Graham & Spriet (17)	Athletes: 8 (runners)	3, 6 or 9 mg/kg	85% max to exh	1 h before exercise	Endurance was enhanced with 3 and 6 mg/kg of caffeine. Increased FFA, glycerol, catecholamines in plasma.	↑
Pasman et al. (30)	Athletes: 9 (cyclists)	0, 5, 9, 13 mg/kg	Cycle at 80% max to exh	1 h before exercise	Increased running times (min): 53.4, 67.8, 73.4, 57.9.	↑
Wells et al. (21)	Athletes: 10 (marathon runners)	5 mg/kg	Ran 20 miles (32.18 km)	1 h before exercise	No difference in plasma FFA or RQ.	↓
Perkins & Williams (22)	F: 14	0, 4, 7 mg/kg	Progressive workload (300 kpm add 100 every min) to exh	1 h before exercise	No difference in maximal endurance time, RHR, SHR or MHR.	↓
Butts & Crowell (31)	F: 15	300 mg	75% max to exh	1 h before exercise	No difference in endurance time.	↓

F: female, M: male, exh: exhaustion, W: watt, con: control group, RHR: resting heart rate, SHR: submaximal heart rate, MHR: maximal heart rate, RQ: respiratory quotient, FFA: free fatty acid.

colas, which contain approximately 60 to 150 mg, 40 to 60 mg, and 40 to 50 mg of caffeine per cup, respectively (3, 4). Caffeine is absorbed by the stomach and small intestine in 45 min, reaches its peak plasma concentration in 30–90 min, and has a half-life of approximately 4–6 h (5, 6).

A previous study reported that consumption of caffeine increases lipolysis by inhibiting cyclic nucleotide phosphodiesterase (7). In an in vitro study, caffeine was found to inhibit phosphodiesterase, the enzyme responsible for degrading cyclic adenosine monophosphate (cAMP) (8). Phosphodiesterase usually hydrolyses cyclic cAMP to AMP, but after consumption of caffeine, the cAMP concentration rises and the sympathetic nervous system (SNS) is activated, resulting in the promotion of lipolysis (7, 9). Caffeine ingestion increases the level of circulating adrenaline, thereby enhancing the availability of fatty acids for oxidation (10). We previously showed that one dose of caffeine (10 mg and 50 mg/kg) significantly decreased the respiratory quotient (RQ),

i.e., increased fat oxidation, 2 h after ingestion in an animal model (11). In addition, Kim et al. (12) reported that caffeine (0.1, 0.5, 1, 2 and 5 mM) suppressed 3T3-L1 adipocyte differentiation and inhibited the expression of CCAAT/enhancer binding protein (C/EBP α) and proliferator-activated receptor (PPAR γ), two main adipogenic transcription factors.

Taken together, the caffeine ingestion may reduce adipose tissue by stimulating both lipolysis and the inhibition of lipogenesis.

Caffeine and endurance performance

Caffeine has attracted the attention of many competitive and noncompetitive athletes as a legal ergogenic aid (see Table 1). Graham and Spriet (13) clearly demonstrated that caffeine ingestion improved endurance performance. Seven trained competitive runners completed 4 randomized and double-blind exercise trials at approximately 85% $\dot{V}O_2$ max: 2 trials of running to exhaustion and 2 trials of cycling to exhaustion. The subjects consumed either a placebo (9 mg/kg dextrose) or caffeine

(9 mg/kg) 1 h before exercise. The group that consumed caffeine showed an increase in endurance time for both running and cycling. In a similar study, Costill et al. (14) reported that caffeine ingestion increased running time. Two women and seven men conducted exercise trials at approximately 80% $\dot{V}O_2$ max. The subjects consumed caffeine (300 mg) 1 h before exercise. As a result, the caffeine consumption group increased running time (90.2 min vs 75.5 min) compared with control groups because of stimulating lipolysis. Moreover, Bruce et al. (15) reported the effect of caffeine ingestion on short-term endurance performance in competitive rowers. Eight rowers performed three familiarization trials of a 2,000-m rowing test on an air-braked ergometer, each 1 h after ingesting caffeine (6 or 9 mg/kg). As a result, the plasma free fatty acid (FFA) concentration before exercise was higher after caffeine ingestion than for the placebo group. RQ was also more greatly decreased in the caffeine group (0.93 ± 0.06) than in the placebo group (0.98 ± 0.12). Similarly, Kovacs et al. (16) found that, when caffeine (150, 225, 320 mg) was ingested, doses of 225 mg/kg and 320 mg/kg had a greater ergogenic effect. Graham and Spriet (17) also reported improvements with 3 different doses of caffeine (3, 6, 9 mg/kg).

Erickson et al. (18) examined the effect of caffeine ingestion (5 mg/kg) before exercise (at 65 to 75% $\dot{V}O_2$ max for 90 min) on muscle glycogen utilization in 5 competitive cyclists. They found that caffeine ingestion decreased muscle glycogen utilization. Spriet et al. (19) also showed that for eight cyclists after ingestion of caffeine (9 mg/kg) muscle glycogenolysis had decreased by approximately 55% over the first 15 min of cycling exercise at approximately 80% $\dot{V}O_2$ max. Recently, Cruz et al. (20) found that for eight active males using from two to four constant-load tests of 30 min., caffeine ingestion (6 mg/kg) approximately 1 h before cycle exercise increased whole-body fat oxidation during a cycling test.

However, Wells et al. (21) reported that caffeine ingestion exerted no significant effect on endurance performance. Ten male marathon runners ran 20 miles (32.18 km); caffeine (6 mg/kg) ingestion occurred 1 h before and during the run. However, caffeine ingestion resulted in no differences in FFA, glucose in plasma or RQ. In addition, Perkins and Williams (22) did not find any ergogenic benefit of any caffeine dose (4, 7 and 10 mg/kg), but their protocol led to a very rapid fatigue.

Meanwhile, Graham et al. (23) reported in their review that caffeine ingestion of 5 to 9 mg/kg increased citrate levels in resting muscle and cAMP during exercise (70 or 85% $\dot{V}O_2$ max). To date, many investigators have found that caffeine increases endurance performance (24–26). This positive effect of caffeine is believed to promote fat oxidation and inhibit carbohydrate oxidation in active muscle and liver (27–29). There can be no doubt that caffeine enhances endurance performance in these situations, (13–20, 23–26, 30) while only rarely has no effect been found (21, 22, 31). Some review articles recently reported that caffeine, at a dose ranging from 2 mg/kg to 13 mg/kg at 1 h before exercise, may

have an ergogenic effect on endurance performance (24, 32, 33). Of note, caffeine is included in the 2015 monitoring program of the World Anti-doping Agency (WADA) though not considered a prohibited substance (34). Although the dose of caffeine was not within the range of doping, athletes should be cautious of ingesting too much caffeine (35).

Green tea extract

The effect of green tea extract on fat metabolism

Green tea is made of *Camellia sinensis* leaves that have undergone minimal oxidation during processing (36). The predominant constituents of green tea, accounting for up to 35% of its dry weight, are polyphenols, namely flavanols, flavones, and flavan-3-ols (37). Further, flavan-3-ols, commonly known as catechins, account for 60–80% of the total proportion of polyphenols in green tea (37). Epigallocatechin-3-gallate (EGCG) is the most abundant catechin in green tea and is also considered the most bioactive component of green tea (38, 39). The remaining components of green tea include theanine, theaflavins, thearubigins, quercetin, other phenolics, and caffeine.

The effect of EGCG on adipogenic differentiation *in vitro* has been previously examined (40). Increasing concentrations of low-dose EGCG were administered for 8 d to differentiating 3T3 adipocytes, either at days 0–8 (early stage) or at days 8–16 (late stage). In both the early and late stages, the accumulation of fat was significantly reduced by the addition of EGCG at concentrations of ≥ 50 nM. Furthermore, EGCG reduced fat accumulation at concentrations of 5–10 nM during the early stage of adipocyte differentiation. Treatment of cells with EGCG (0, 50, 100, and 150 μ M) dose dependently increased the level of adenosine monophosphate-activated protein kinase- α (AMPK α) and acetyl-CoA carboxylase (ACC) phosphorylation. EGCG also stimulated AMPK α and ACC phosphorylation in a dose- (0, 50, 100, and 150 μ M) and time-dependent (0–180 min) manner in rat myotube L6 cells. In addition, orally administered EGCG (200 mg/kg) increased fat oxidation in the entire body with the upregulation of AMPK α involving phosphorylation and AMPK α activity in liver and skeletal muscle (41). In a recent study, treatment with green tea catechins (2.3, 11.5, and 23 μ M) was found to increase glycerol and free fatty acid (FFA) levels with hormone-sensitive lipase (HSL) phosphorylation in the 3T3-L1 adipocytes by regulating the PKA-dependent pathway (42). PKA activation is a classical pathway for lipolysis regulation. Norepinephrine increases cAMP production, which results in cAMP-dependent PKA activation and leads to HSL phosphorylation (43). In animal studies, Murase et al. (44) investigated the effect of oral ingestion of tea catechins for 1 mo on the development of obesity in mice. The results showed that supplementation with tea catechins resulted in a significant reduction in high-fat diet-induced visceral and liver fat accumulation. The reduction of fat accumulation may be due to increased β -oxidation activity in the liver and increased acyl-CoA oxidase and medium-chain acyl-CoA dehydrogenase

Table 2. A summary of studies that examined the effects of green tea extract on endurance performance.

Reference	Subjects	Dose	Protocol	Timing	Key results	Endurance performance
Murase et al. (44)	Male mice: 32	Meal with 0.2 or 0.5% (wt/wt)	Exh exercise on treadmill	With meal	Increased running times: fed 0.2 and 0.5% GTE were 21 and 30% longer vs con. Decreased RQ and malonyl-CoA content, higher muscle β -oxidation.	↑
Murase et al. (47)	Male mice: 32	Meal with 0.2 or 0.5% (wt/wt)	Exh swimming exercise	With meal	Increased running times and fat oxidation in whole body. FAT/CD36 mRNA in the muscle was higher in GTE fed in mice.	↑
Ota et al. (57)	M: 7, F: 7	570 mg with caffeine (40 mg)	Engaged in treadmill exercise at a pace of 5 km/h for 30 min 3 times a week	1 h before exercise for 2 mo	Improved endurance performance through fat utilization.	↑
Ichinose et al. (49)	M: 12	572.8 mg	60 W every 3 min until 180 W and, above this intensity, by 30 W energy 2 min until 240 W and then by 15 W every 2 min until exh	At least 24 h after exercise for 10 wk	Moderate-intensity exercise with GTE, increased fat oxidation on whole body energy expenditure.	↑
Dean et al. (52)	Athletes: 8 (cyclists)	270 mg	60 min of cycling at 60% max and then a self-paced 40 km cycling time trial	1 h before exercise for 6 d	A little fat oxidation and endurance performance.	↗
Venables et al. (58)	M: 12	890±13 mg/d catechins containing 366±5 mg/d EGCG	30 min cycling exercise at 60% of maximal oxygen consumption	In the morning, at lunch and at dinner	Improved endurance performance through fat oxidation.	↑
Kuo et al. (50)	M: 40	250 mg/d	Exh swimming exercise	4 wk training with either GTE with breakfast	No difference in endurance capacity. But, increased antioxidant capacity.	↓
Eichenberger et al. (51)	M:10	160 mg/d	Exercise for 2 h at 50% W (max) in cycling exercise	Before and after exercise for 3 wk	No difference in endurance capacity.	↓

F: female, M: male, exh: exhaustion/exhaustive, W: watt, RQ: respiratory quotient, GTE: green tea extract, con: control.

mRNA expression. In another study involving mice with high-fat-induced obesity, high-fat diets supplemented with 0.2 or 0.5% EGCG (w/w) for 8 wk significantly increased the mRNA levels of carnitine palmitoyltransferase I (CPT-I) and uncoupling protein 2 as well as lipolytic genes such as hormone-sensitive lipase and adipose triglyceride lipase (45). In a cross-sectional survey of 1,210 epidemiologically sampled adults, tea drinkers for more than 10 y showed a 19.6% reduction in percentage body fat and a 2.1% reduction in waist-to-hip ratio as compared to non-habitual tea drinkers (46). Thus, the effect of green tea extract on fat oxidation seem to be cumulative over time.

Green tea extract and endurance performance

Murase et al. (47) examined the effects of GTE on running endurance in mice. The total catechin content

was 81% (the sum of each catechin) and the epigallocatechin gallate content was 41% (caffeine, 0.1%). A 10-wk-intervention with dietary GTE (0.2% and 0.5% GTE) in combination with endurance running exercise markedly improved endurance levels in association with an increase in lipid utilization during exercise. They also investigated the effect of GTE (epigallocatechin gallate content, 41%) diet on the swimming endurance capacity of mice over a 10-wk period (48). The result showed that the swimming time to exhaustion for mice fed 0.2–0.5% (wt/wt) GTE increased by 8–24%. In addition, the β -oxidation activity and the level of fatty acid translocase/CD36 mRNA in the muscle was higher in the GTE-fed mice than in the control mice.

In human studies, Ichinose et al. (49) reported the effect of GTE on whole-body fat utilization during exer-

cise in healthy male subjects (peak oxygen consumption ($\dot{V}O_2$ peak), 50.7 ± 1.3 (SE) mL/kg/min). The subjects performed a cycle ergometer exercise at 60% of $\dot{V}O_2$ peak for 60 min/d, 3 d/wk, and daily ingested 572.8 or 0 mg tea catechins in the exercise with the GTE or placebo group, respectively, for 10 wk. The results showed that the RQ was lowered, i.e., increase in whole-body fat utilization, in the GTE group during endurance exercise, but this effect was not seen in the placebo group. Recently, Kuo et al. (50) showed the effect of GTE on endurance performance where a 4-wk-intervention with GTE (breakfast with 250 mg/d) in combination with endurance training improved exhaustive run time (14.3%) in untrained men. EGCG accounted for 48.2% of the GTE (total tea catechins=82.8%). However, this positive effect of GTE (containing about 160 mg/d total catechins, of which about 70 mg/d comprised EGCG) on endurance performance was not seen in the study conducted by Eichenberger et al. (51) in endurance-trained men. They suggest that a lower dose of GTE, as compared to that noted in previous studies, does not affect fat oxidation during exercise especially in highly trained athletes. Dean et al. (52) reported that eight male cyclists were studied in a 3-way crossover experiment. All participants received 3 different supplements—a placebo (glucose; 270 mg), caffeine (3 mg/kg), or green tea extract (270 mg)—1 h before exercise for 6 d. Then, each participant engaged in exercise consisting of 60 min of cycling at 60% maximum oxygen uptake immediately followed by a self-paced 40-km cycling time trial. That study found little benefit in consuming green tea extract on fat oxidation or endurance performance; unlike caffeine, GTE did not benefit endurance performance.

As mentioned above, caffeine has been shown to enhance the availability of fatty acids for oxidation (10), and its ingestion prior to an exercise bout showed elevated fat oxidation rates as well as performance (53). In a meta-analysis, catechin-caffeine mixtures increased fat oxidation as compared with a placebo or caffeine-only mixtures (54). Green tea catechins (375 mg+150 mg caffeine) decreased RQ by 3.4% as compared with a caffeine-free placebo, and there was no effect of caffeine alone (150 mg) in healthy young men with body fat ratings ranging from lean to mildly obese (8–30% body fat) (55). A similar effect was seen with the acute administration of 300 mg EGCG for 2 d in obese men (56). These results suggest that catechin-caffeine mixtures may increase fat oxidation even though exercise is not performed along with ingestion. Another well-designed study by Ota et al. (57) involved untrained young Japanese men consuming catechins and caffeine-rich tea (570 mg+40 mg caffeine) 1 h before exercise during an 8-wk intervention program. During the study period, they engaged in a treadmill exercise at a pace of 5 km/h for 30 min 3 times a week. Fat oxidation was found to have increased with catechin- and caffeine-rich tea administration in both the exercise and sedentary groups as compared to placebo administration. In addition, Venables et al. (58) reported on

the effect of acute GTE intake on fat oxidation rate during exercise. Twelve healthy men performed a 30-min cycling exercise at 60% of maximal oxygen consumption before and after GTE (890 ± 13 mg/d catechins containing 366 ± 5 mg/d EGCG; 3 capsules were ingested) consumption. As a result, fat oxidation rates were 17% higher after ingestion of GTE than after ingestion of a placebo (0.41 ± 0.04 and 0.35 ± 0.03 g/min).

Taken together, GTE supplementation, at a dose ranging from about 200 mg/kg to 800 mg/kg and long-term intake can improve endurance performance with increased fat oxidation, and the effect may be augmented in combination with exercise (see Table 2).

L-Carnitine

The effect of carnitine on fat metabolism

Carnitine (L-trimethyl-3-hydroxy-ammonio-butanoate) is an endogenous compound that plays a significant role in cellular biochemistry and is a vitamin-like and amino acid-like substance (59, 60). L-Carnitine is normally present in plasma in the form of free carnitine at concentrations of approximately 40 μ mol/L to 50 μ mol/L in healthy adult men (61). Dietary sources of L-carnitine primarily include animal products, particularly red meat and dairy products (61).

Synthetic carnitine occurs as both D & L isomers; however, only L-carnitine is physiologically active. L-Carnitine is mostly stored in muscle, and its most well-documented function is the translocation of long-chain fatty acids from the cytosol into the mitochondrial matrix for subsequent β -oxidation (62–64). Fatty acids must be changed into acyl-CoA prior to β -oxidation because fatty acids cannot cross the mitochondrial membrane. Acyl-CoA is converted to acylcarnitine by the malonyl-CoA-sensitive CPT-I on the mitochondrial outer membrane. Next, acylcarnitine is transported across the mitochondrial inner membrane by carnitine acylcarnitine translocase (65). In the matrix, acylcarnitine acts as a substrate for carnitine palmitoyltransferase II (CPT-II) by which acylcarnitines are converted to the respective acyl-CoAs (66). Acyl-CoA then enters the fatty acid β -oxidation pathway. Without carnitine, most dietary lipids cannot be used as energy sources. The effect of carnitine on adipogenic differentiation in vitro has been previously examined (67). In one study, when 3T3-L1 cell differentiation was induced, carnitine was also exogenously added to the cells. As a result, the exogenously added carnitine (1 nM and 10 nM) inhibited an increase in triglyceride and total lipid levels. These results suggest that carnitine plays an inhibitory role in the early stage of 3T3-L1 cell differentiation (67). In an animal study, mice were fed a normal diet (ND), high-fat diet (HD), or carnitine-supplemented (at 0.5% w/w) high-fat diet (HDC) for 12 wk. The results showed that the HDC group had lower body weight and this effect may be due to increased lipolysis by enhancing CPT-I mRNA expression compared to that of the other groups (68).

L-Carnitine and endurance performance

Several animal studies have attempted to determine the underlying mechanism by which L-carnitine

Table 3. A summary of studies that examined the effects of L-carnitine on endurance performance.

Reference	Subjects	Dose	Protocol	Timing	Key results	Endurance performance
Kim et al. (69)	Male rats: 32	Meal with 0.5% (wt/wt)	Treadmill for 60 min/d, 10 incline, 20 m/min	With meal for 8 wk	Increased CPT-1 activities and endurance times.	↑
Pandareesh et al. (70)	Male rats: 90	L-carnitine (0.15, 0.3, and 0.5%) and fat content (5, 10, and 15%) diet	Constant loads (tagged to the tail base) corresponding to 5% of their body weight	With meal for 2 wk	Increased swimming time until exh (2 and 1.5-fold) and spared liver and muscle glycogen levels.	↑
Kim et al. (71)	Male mice: 30	150 mg/kg	Speed was increased by 1 m/min up to 25 m/min until exh	Before exercise, once daily for 3 wk	Increased running time (average 25%) until exh. Fatty acid transport proteins (FAT/CD36, FABP3, CTP1) increased in skeletal muscle.	↑
Marconi et al. (72)	Athletes: 6 (competitive walkers)	4 g	For 120 min walk at about 65% max	1 g in 10 mL syrup every 6 h over a period of 2 wk	LC loading slightly increased performance.	↗
Gorostiaga et al. (73)	M: 10	2 g	45 min of cycling at 66% max	2 g/d for 28 d	RQ was significantly low during exercise.	↑
Vecchiet et al. (74)	Athletes: 10 (moderately trained)	2 g	Increased by 50 W (cycle ergometer) increments every 3 min until exh	1 h before exercise	Increased maximal oxygen uptake but, not affecting the RQ.	↗
Cha et al. (75)	Athletes: 5 (rugby players)	Caffeine (5 mg/kg)+L-carnitine (15 g), L-carnitine (15 g), and caffeine (5 mg/kg)	Cycle ergometer at 60% $\dot{V}O_2$ max for 45 min and increased at 80 $\dot{V}O_2$ max until exh	2 h before exercise	Increased endurance time compared with caffeine and control groups through stimulated fat oxidation.	↑
Orer and Guzel (76)	Athletes: 26 (footballers)	3 or 4 g	Running speed of 8 km/h and then continued at 10 km/h, and increased 1 km/h every 3 min until exh	1 h before exercise	Increased running speed and decreased lactate. LC ingestion increased physical exercise prolonged to exh.	↑
Broad et al. (77)	Athletes: 15 (runners)	3 g	90 min stationary cycling	Once a day, at any time	No difference during 90 min cycling test.	↓
Lee et al. (78)	M: 28	4 g	Trained for 40 min on a bicycle ergometer at 60% max, five times per week for 6 wk	1 h before exercise for 6 wk	Beta-HAD and FABPc expression increased by 54% compared with control. LC consumption enhanced exercise performance.	↑

M: male, exh: exhaustion, W: watt, RQ: respiratory quotient, LC: L-carnitine.

increases exercise performance (see Table 3). Kim et al. (69) reported on L-carnitine (0.5%/diet) supplementation with exercise (treadmill for 60 min/d, 10% incline, 20 m/min for 8 wk) in an animal model. They evaluated the effect of L-carnitine supplementation and antioxidants on lipids, carnitine concentration, and exercise endurance time in both trained and untrained supplemented or non-supplemented rats. CPT-I mRNA levels were higher in both supplemented and exercise trained rats. Pandareesh and Anand (70) explored the synergistic effects of dietary L-carnitine and fat content on

physical fatigue in rats. In all, 90 male Wistar rats were supplemented with different concentrations of L-carnitine (0.15, 0.3, and 0.5%) and fat content (5, 10, and 15%) through diet in different combinations. The swimming time until exhaustion was increased ~2–1.5-fold in rats fed with 10% and 15% fat diets containing L-carnitine (0.5%). Lipid peroxidation, lactic acid, and lactate dehydrogenase levels were significantly reduced in various tissues in the L-carnitine-supplemented rats as compared to the control group. Kim et al. (71) showed that L-carnitine administration promotes fat oxidation and

mitochondrial biogenesis during prolonged exercise, resulting in enhanced endurance capacity in male mice. In their study, male mice were divided into 2 groups of sedentary and exercise groups. They were orally administered L-carnitine (150 mg/kg) or a vehicle with a high-fat diet daily for 3 wk. During the experimental period, all animals were trained 3 times a week on a motorized treadmill, and the total running time until exhaustion was used as the index of endurance capacity. It was found that L-carnitine administration significantly increased the maximum running time when the mice were subjected to exercise training. Importantly, L-carnitine administration enhanced the expression of fatty acid uptake-related genes and increased mitochondrial biogenesis.

Several human studies on the effect of carnitine supplementation on endurance capacity have been conducted since the 1980s. Marconi et al. (72) examined the effect of carnitine supplementation (1 g in 10 mL syrup every 6 h over a period of 2 wk) on the aerobic performance of 6 long-distance athletes and reported that the $\dot{V}O_2$ max in the carnitine supplementation group increased by 6%. Gorostiaga et al. (73) investigated the effect of L-carnitine addition (2 g/d for 4 wk) to the diet of endurance-trained humans on RQ changes during submaximal exercise. After 4 wk, the subjects performed a submaximal exercise test consisting of 45 min of cycling at 66% of $\dot{V}O_2$ max. Each subject performed the test under the condition of placebo or L-carnitine treatment (double-blind, crossover design). The RQ was significantly low during exercise, i.e., increased fat oxidation, for the subjects treated with L-carnitine. Vecchiet et al. (74) also showed that the acute dose of 2 g L-carnitine increased the work capacity with increased $\dot{V}O_2$ max in moderately trained young men, although not affecting the RQ. Cha et al. (75) showed that acute carnitine ingestion (15 g in 250 mL) 1 h before endurance exercise could promote fat oxidation, presumably resulting in increased exercise time until exhaustion in rugby athletes. Ozer and Guzel (76) demonstrated the positive effect of acute L-carnitine loading (3 g or 4 g) on the endurance performance of footballers. They used a lower dose of L-carnitine than the dose (15 g of acute carnitine ingestion) used by Cha et al. (75). The athletes were given a glass of fruit juice 1 h before administering L-carnitine (3 g or 4 g) with the double-blind method. The athletes began the exercise test at a running speed of 8 km/h and then continued at 10 km/h. The result showed that 3 g or 4 g of L-carnitine taken before physical exercise prolonged the time to exhaustion. Although L-carnitine may contribute to improved endurance exercise performance, no effect of L-carnitine on fat metabolism has been reported in any animal or human study (76, 77). Broad et al. (77) reported that L-carnitine plus L-tartrate supplementation (3 g/d for 4 wk) had no effect on fat oxidation or endurance performance in trained males. In a human study using the muscle biopsy method, L-carnitine supplementation was considered unlikely to be associated with enhanced exercise performance in untrained males (78). Although

they did not conduct any exercise performance test, they concluded that the combination of exercise training and L-carnitine supplementation does not augment the fatty acid-binding protein (FABPC), an indicator of the capacity for fatty acid oxidation, and the activity of β -hydroxyacyl-CoA dehydrogenase in the human skeletal muscle of untrained healthy males. Of note, L-carnitine is basically an endogenous substance, production of which usually satisfies the requirements but it should be taken especially by athletes loaded by higher volume of exercise. Overall, L-carnitine at a dose ranging from about 2–4 g consumption may improve endurance performance but the data on the practical implications of L-carnitine supplementation need to be further accumulated, especially for athletes.

Garcinia cambogia (Hydroxycitric Acid)

The effect of hydroxycitric acid on fat metabolism

Garcinia has been used for centuries in Asian countries for culinary purposes as a condiment and flavoring agent in place of tamarind or lemon and to make meals more filling (79). Garcinia or, more specifically, *G. cambogia*, *G. atroviridis*, and *G. indica* have been found to contain large amounts of hydroxycitric acid (HCA) (80). It is widely used in anti-obesity herbal supplements around world (81, 82).

HCA ingestion might have an effect on fat oxidation because extramitochondrial cleavage of citrate is the penultimate step in the conversion of glucose into malonyl-CoA, suggesting that HCA could reduce cytosolic malonyl-CoA concentration and increase fatty acid oxidation (83, 84). It is well known that malonyl-CoA is an inhibitor of CPT-I that controls fatty acid by regulating its transfer into the mitochondria (85–87). Therefore, malonyl-CoA not only serves as a substrate for lipogenesis but also inhibits CPT-I allosterically, thereby suppressing fatty acid oxidation (87, 88). HCA is believed to be a powerful inhibitor of the enzyme ATP-citrate lyase (89). In in vitro studies, Garcinia extract (1 mg/mL) treatment inhibited lipid droplet accumulation in 3T3-L1 preadipocytes (90). Similarly, Garcinia extract was found to inhibit cytoplasmic lipid accumulation as well as adipogenic differentiation of preadipocytes (91, 92).

Some studies have shown that HCA consumption promotes fat metabolism in animals and humans. Shara et al. (93) reported the dose-and-time-dependent effects of HCA on body and organ weight over a period of 90 d in rats. They observed a significant reduction in body weight and adipose tissue in the HCA group as compared to the control group. Kim et al. (94) showed that *G. cambogia* (soy peptide and L-carnitine) with a high-fat diet decreased body fat and improved insulin resistance in rats, and down-regulation of leptin, TNF- α , SREBP1c, and PPAR γ 2 gene expression in the epididymal adipose tissue. Similarly, in a study by Leonhardt et al. (95) involving rats fed a high-carbohydrate diet with 3% HCA for 6 d, the 3% HCA diet was found to suppress lipogenesis, and the fat oxidation of the HCA group was significantly higher than that of the control group. Similar results were seen in human studies where HCA

Table 4. A summary of studies that examined the effects of HCA on endurance performance.

Reference	Subjects	Dose	Protocol	Timing	Key results	Endurance performance
Ishihara et al. (100)	Male mice: 54	10, 30 mg	Swimming exercise until exh and treadmill exercise at 15 m/min for 1 h	Oral administration every day after swimming (at 17:00 h)	FFA levels and glycogen concentration levels were higher in the HCA group. Decreased RQ both resting and exercise.	↑
Lim et al. (102)	F: 6	250 mg	Ergometer exercise for 60 min at 40% $\dot{V}O_2$ max. And then, 60% $\dot{V}O_2$ max exercise until exh	2 h before exercise with meal for 5 d	Decreased RQ and CO for 1 h of exercise. Increased running time until exh.	↑
Lim et al. (103)	Athletes: 6 (male)	250 mg	Ergometer exercise for 60 min at 60% $\dot{V}O_2$ max. And then, $\dot{V}O_2$ 80% $\dot{V}O_2$ max until exh	2 h before exercise with meal for 5 d	HCA ingestion decreased RQ and increased fat oxidation.	↑
Cheng et al. (105)	M: 8	500 mg	60 min cycling exercise at 70–75% $\dot{V}O_2$ max	With meal for 7 d	HCA ingestion lowered post-meal insulin response with similar glucose levels compared to placebo. Glycogen synthesis was about one-fold higher. FAT/CD36 mRNA increased in skeletal muscle.	↑
Tomita et al. (104)	M: 6	500 mg	Ergometer exercise at 40% $\dot{V}O_2$ max, and then 60% $\dot{V}O_2$ max until exh	With meal for 5 d	FFA levels increased and RQ decreased by HCA.	↑
Kriketos et al. (101)	M: 10	3.0 g	Treadmill exercise on 30 min of exercise at 40% $\dot{V}O_2$ max, and then 15 min of exercise at 60% $\dot{V}O_2$ max, and a final 30 min of RMR	Each subject consumed 15 tablets (200 mg) for 4 d	No difference in RQ on resting or during exercise. HCA did not affect endurance performance in a post-absorptive state.	↓

F: female, M: male, exh: exhaustion, CO: carbohydrate oxidation, FFA: free fatty acid, RMR: resting metabolic rate, HCA: hydroxycitric acid, RQ: respiratory quotient.

(300 mg) ingestion for 2 wk reduced body weight in randomized crossover trials in men and women (96). Kovacs and Westerterp-Plantenga (97) also reported that HCA (500 mg/d for 3 d or 8 wk) reduced de novo lipogenesis during overfeeding with carbohydrates. HCA can also decrease circulating cholesterol and triglyceride concentrations in overweight humans (98). Taken together, the HCA ingestion may reduce body weight and adipose tissue by both the stimulation of lipolysis and the inhibition of lipogenesis.

Hydroxycitric acid and endurance performance

Some studies have shown that HCA supplementation improved endurance capacity in animals and humans (see Table 4). HCA is considered an ergogenic aid because its ability to increase fatty acid oxidative capacity can help limit the utilization of muscle and liver glycogen during aerobic exercise (99). Ishihara et al. (100) showed that acute HCA (10 mg) administration increased serum FFA levels in mice, but the level of RQ was not different between the HCA and control group. On the other hand, on the 26th day of HCA administration, the RQ was significantly lower in the HCA group

than in the control group during both resting and exercising conditions. They suggested that chronic administration of HCA promoted lipid oxidation and spared carbohydrate utilization at rest and during running.

On the other hand, Kriketos et al. (101) reported that high-dose HCA (3 g/d) ingestion led to significantly different RQ or energy expenditure in the fasted state either during rest or during moderate (40–60% $\dot{V}O_2$ max) exercise. These results are explained by the fact that HCA treatment was not sufficiently long-term (3 d), high-dose, and or administered during a fasted state. On the other hand, we confirmed the opposite results: an effect of short-term HCA ingestion on fat oxidation during exercise in untrained animals and humans (102). In 2 experiments designed as a double-blind crossover test, untrained women ingested breakfast with 250 mg of HCA or a placebo equal amount of dextrin) via capsule for 5 d and then participated in a cycle ergometer exercise. They cycled at 40% $\dot{V}O_2$ max for 1 h; then, the exercise intensity was increased to 60% $\dot{V}O_2$ max until exhaustion on day 5 of each experiment. HCA tended to decrease the RQ during 1 h of exercise and significantly

Table 5. A summary of studies that examined the effects of capsaicin on endurance performance.

Reference	Subjects	Dose	Protocol	Timing	Key results	Endurance performance
Kim et al. (110)	Male mice: 24	3, 6, 10, and 15 mg/kg	Swimming exercise until exh	1, 2, and 3 h before exercise	Increased swimming time in a dose-dependent manner, only 2 h before swimming. Increased adrenaline and muscle glycogen concentration in the CAP group.	↑
Oh et al. (122)	Male rats: 49	6, 10, and 15 mg/kg	3% body weight attached to the tail, swimming exercise until exh	2 h before exercise	Highest dose (15 mg/kg) increased endurance performance time, FFA and muscle glycogen concentration by circulating catecholamine.	↑
Luo et al. (123)	Male mice: 12	Meal with 0.01%	The endurance test regimen was 10 m/min for the first 60 min followed by 1 m/min increment increases at 15-min intervals	With meal for 12 mo	Up-regulated PGC-1 α in skeletal muscle by TRPV1 activation. Improved endurance performance through fat oxidation.	↑
Shin and Moritani (124)	M: 10	150 mg	5-min rest and 30 min exercise at 50% of maximal ventilatory threshold (50% VT max)	1 h before exercise	Decreased RQ (0.92 vs. 0.94) and higher fat oxidation (0.17 vs. 0.12 g/min) during exercise in the capsaicin ingestion group than in the control group.	↑
Hwang et al. (125)	F: 6	0.5 mg/kg	Rest of 60 min, exercise for 40 min	With meal	Increased post-exercise fat oxidation and FFA levels.	↑
Oh and Ohta (120)	Male rats: 24	6, 10, and 15 mg/kg	Swimming exercise until exhaustion (3% BW attached to the tail)	2 h before exercise	Enhanced the endurance performance time (219%↑), epinephrine, norepinephrine and FFA. Liver and muscle glycogen concentration was higher in the capsaicin (15 mg/kg) group.	↑
Matsuo et al. (121)	Male rats: 20	Meal with 0.014%	For 60 min at 24 m/min up an 8° incline	With meal for 7 d	No difference in liver or muscle glycogen contents.	↓

F: female, M: male, exh: exhaustion, RQ: respiratory quotient, FFA: free fatty acid, CAP: capsaicin, TRPV1: transient receptor potential vanilloid 1, BW: body weight, PGC-1 α : peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

increase the exercise time to exhaustion. Similar results were seen in another study involving athletes who were orally administered HCA (250 mg after breakfast or lunch) for a short period (103, 104). For ergogenic purposes, a dose of HCA ranging from 250 to 500 mg or/and a low dose for a long term may be effective in increasing endurance exercise capacity. It has recently been reported that oral HCA ingestion enhances glycogen synthesis in exercised human skeletal muscle. Eight healthy males conducted a 60-min cycling exercise at 70–75% $\dot{V}O_2$ max and a crossover design repeated after a 7-d washout. Volunteers were served a high-carbohydrate meal (2 g/kg, 80% carbohydrate, 8% fat, 12% protein) with 500 mg HCA. As a result, HCA ingestion increased glycogen synthesis and up-regulated FAT/CD36 mRNA in exercised human skeletal muscle (105).

However, to the best of our knowledge, no study has examined whether HCA ingestion improves the endurance exercise performance of athletes except for the study by Lim et al. (103). Therefore, more studies should look at the effect of HCA ingestion on the endurance performance of athletes.

Capsaicin

The effect of capsaicin on fat metabolism

Capsaicin is the major pungent element in red pepper. It is used in food products as a spice worldwide, especially in Asia. Capsaicin is passively absorbed, with approximately 20% absorbed in the stomach and 80% in the small intestine within 1 h after ingestion (106, 107). Capsaicin is believed to increase fat oxidation in a dose-dependent manner by enhancing adrenal medullary catecholamine secretion (108–111). Specific capsaicin-sensitive neurons are thought to be involved in this process (112). The stimulatory effect of pungent elements in spices on oxygen consumption is likely due to the involvement of transient receptor potential vanilloid receptor 1 (TRPV1), which is linked to the thermogenic mechanism and increased fat oxidation (113). TRPV1 is expressed in the sensory neurons, brain, and various non-neuronal tissues; it is activated in the putative pain neural circuit. Increase in lipolysis induced by capsaicin is probably caused by β -adrenergic stimulation. In an in vitro study, Hsu and Yen (114) studied the effects of capsaicin (0–250 μ M) on the induction of apoptosis

and inhibition of lipid accumulation in 3T3-L1 preadipocytes and adipocytes. The results showed that capsaicin inhibited cell population growth of 3T3-L1 preadipocytes. Moreover, capsaicin significantly decreased the amount of intracellular triglycerides and glycerol-3-phosphate dehydrogenase (GPDH) activity in 3T3-L1 adipocytes. Capsaicin also inhibited the expression of PPAR γ , C/EBP α , and leptin but induced upregulation of adiponectin at the protein level. Therefore, the capsaicin ingestion may reduce adipose tissue by both stimulating lipolysis and inhibiting lipogenesis.

Most studies show that capsaicin intake induces lipolysis in humans. Yoshioka et al. (115) reported that red pepper (10 g; capsaicin: 30 mg), which releases catecholamine, causes an increase in energy expenditure (approximately 30%). In another experiment, red pepper (10 g; capsaicin: 30 mg) added to the meal (high-fat and high-carbohydrate) increased energy expenditure and fat oxidation over 210 min in Japanese females (116). Similarly, a mixed-diet and red pepper (6 g; capsaicin: 18 mg) ingestion led to an increase in SNS activity (117). In addition, Lejeune et al. (118) found that 4 wk of capsaicin (135 mg/capsaicin/d) consumption increased fat oxidation in male and female subjects. These results are similar to those obtained in animal studies. Kawada et al. (106) reported that capsaicin intake (0.6 mg/kg) improved lipolysis by enhancing the function of the adrenal medulla through sympathetic activation of the central nervous system. In addition, capsaicin receptor agonist reduced the body fat in obese rats. Moreover, capsaicin (200 μ g/kg) has been reported to increase lipolysis in a dose-dependent manner, thereby enhancing catecholamine secretion from the adrenal medulla in rats (119). Thus, capsaicin stimulates catecholamine production by the TRPV1 receptor, resulting in enhanced fat oxidation through an increase in SNS activity.

Capsaicin and endurance performance

It is well known that catecholamine secretion stimulates adipose tissue lipolysis and intramuscular triglyceride breakdown. This process promotes fat oxidation and prevents muscle glycogen depletion, thereby enhancing exercise capacity (see Table 5). Many studies have reported that the physiological effect of capsaicin is similar to that of caffeine in increasing plasma catecholamine levels (120). Kim et al. (110) showed that oral administration of capsaicin (10 mg/kg) 2 h before exercise increased the swimming endurance capacity of mice. After 30 min of swimming, the muscle glycogen concentration was higher in the capsaicin group than in the control group. This increase was the result of increased fat oxidation due to capsaicin-induced adrenal catecholamine secretion. However, Matsuo et al. (121) reported that meal with capsaicin (0.014%) consumption does not affect glycogen contents in the liver or skeletal muscle of rats ($n=20$) before or after exercise. They did not find any studies that supported their findings at that time. Nevertheless, there can be no doubt that capsaicin enhances endurance performance.

Oh et al. (122) also confirmed the effects of low and

high (5, 10, and 15 mg) oral doses of capsaicin on the endurance capacity of rats. These results indicate that high doses (15 mg/kg) 2 h prior to exercise enhance endurance performance and induce the glycogen-saving effect. Luo et al. (123) showed the long-term (4 mo) effect of dietary 0.01% capsaicin in mice. They showed that TRPV1 activation by dietary capsaicin improves energy metabolism and exercise endurance, which are likely to be driven by TRPV1-mediated Ca²⁺-dependent upregulation of PGC-1 α and its target genes involved in mitochondrial respiration and fatty acid oxidation in the skeletal muscle. Importantly, these effects of capsaicin were absent in TRPV1-deficient mice (123).

In human studies, Shin and Moritani (124) reported that capsaicin (150 mg) ingestion 1 h before aerobic exercise among untrained males led to significantly lower RQ (0.92 vs. 0.94) and higher fat oxidation (0.17 vs. 0.12 g/min) during exercise in the capsaicin ingestion group than in the control group. We also previously demonstrated that a standard meal plus red pepper with 200 mL water (10 g; capsaicin: 0.5 mg/kg) induced post-exercise fat oxidation and increased plasma FFA level in young untrained women (125). Ingestion of capsinoids, which are capsaicin-like compounds in a non-pungent type of red pepper derived from the CH-19 sweet pepper (107, 112, 126), has been found to enhance fat metabolism in humans (127, 128). Josse et al. (129) examined how ingestion of capsinoids (10 mg) affected energy expenditure, lipid oxidation, and blood metabolites at rest and during moderate intensity exercise in untrained men. The subjects had ingested the capsinoid capsules 30 min prior to exercise. It was found that ingestion of 10 mg of capsinoid increased adrenergic activity and energy expenditure and resulted in a shift in substrate utilization toward lipid at rest. However, the effect was not shown during exercise. Although many researchers are interested in the effect of capsaicin or capsinoids on thermogenesis, to date, very little research has been conducted on their effect on the endurance performance of athletes. Thus, further studies are needed to clarify the dose and timing of capsaicin ingestion before exercise for effectively improving the endurance performance of athletes.

Ginseng

Effect of ginseng on fat metabolism

Ginseng, the root of *Panax ginseng* CA Meyer, has been traditionally used for thousands of years in Asian countries such as Korea, Japan, and China (130). Panax means "all treat" in Greek, and the Chinese characters for ginseng were derived from the human-like shape of the ginseng root (131). Many reports have shown that ginseng has many pharmacological effects on the CNS, immunomodulatory, neuroprotective, anti-oxidative, antitumor, and cardiovascular systems (132–137). These beneficial effects are attributed to ginsenosides (Rg1, Rb1, and Rg2) and saponin. In particular, ginsenosides have been shown to constitute a large proportion of "red ginseng." Red ginseng is produced by steaming and drying ginseng. During this heat process, ginsen-

Table 6. A summary of studies that examined the effects of ginseng on endurance performance.

Reference	Subjects	Dose	Protocol	Timing	Key results	Endurance performance
Avakian et al. (148)	Male rats: 30	2 mg/100 g	Swimming exercise for 90 min	1 h before exercise via i.p. injections	Increased plasma glucose levels and fatty oxidation in skeletal muscle.	↑
Tang et al. (149)	Male mice: 120	Low-dose (0.05 mg/kg), intermediate-dose (0.1 mg/kg), high-dose (0.5 mg/kg)	Swimming exercise until exh using weight-loaded method	Before exercise for 2 wk	Evaluated biochemical parameter related to fatigue, such as SUN, LDH, SOD, MDA, LA and liver glycogen. Increased exercise time.	↑
Hwang et al. (152)	Male mice: 42	1 g/kg (19.64 mg ginsenosides/g RG extract)	Treadmill exercise at 25 m/min, slope at 8° for 1 h (65–70% $\dot{V}O_2$ max) using the whole body chamber	1 h before exercise for 2 wk	Promoted fat oxidation (initial 20 min of the 1 h exercise) and a glycogen-sparing effect during exercise.	↑
Kim et al. (154)	M: 7	2 g	Treadmill was started at 2.74 km/h (1.7 mph) and at a gradient (or incline) of 10%. At 3 min intervals the incline of the treadmill increased by 2%	3 times a day for 8 wk	Increased exercise duration until exhaustion by 1.5 min. Elevated MDA, CAT, and SOD.	↑
Liang et al. (156)	M: 15, F: 14	1,350 mg/d (450 mg/capsule \times 3 times)	Ergometer exercise until exh (30 W every 5 min)	With meal for 30 d	Improved maximal MBP (from 113 ± 12 to 109 ± 14 mmHg) and endurance time by >7 min.	↑
Biondo et al. (153)	M: 10	1,125 mg (375 mg \times 3 capsules/d)	Ergometer exercise at 6 min of warm-up at 1.5 kp and 50 r/min, followed by 15 min at 80% VT, and then 15 min at 100% VT (60 to 70 r/min)	With meal for 5 wk	No difference in total white WBC counts, lactate, insulin, cortisol or growth hormone.	↓
Wang et al. (150)	Male mice: 24	40, 50, 100, 160, and 200 mg/kg	Swimming exercise until exh	1 h before exercise	Improved the physiological markers (GPx, CK, LDH, and MDA) for fatigue.	↑
Wang and Lee (151)	Male rats	10 and 20 mg/kg	Treadmill exercise until exh	Before exercise	Increased running time and FFA in plasma levels. Liver and muscle glycogen concentration was higher.	↑

F: female, M: male, exh: exhaustion, SUN: serum urea nitrogen, LDH: lactic dehydrogenase, SOD: superoxide dismutase, MDA: malondialdehyde, LA: blood lactic, CAT: catalase, MBP: mean blood pressure, WBC: white blood cell, GPx: glutathione peroxidase, CK: creatine phosphokinase, LDH: lactic dehydrogenase, MDA: malondialdehyde, FFA: free fatty acid.

osides undergo chemical changes resulting in a compound with the potential to induce specific physiologic activities. Ginseng is absorbed in the intestines (the absorption rate is as low as 1 to 3.7%). Most ginsenosides are metabolized in the stomach (acid hydrolysis) and in the intestine (bacterial hydrolysis) or transformed to other ginsenosides (138).

Hwang et al. (139) showed that the ginsenosides Rh2 and Rh3 effectively inhibited adipocyte differentiation via PPAR γ inhibition in a dose-dependent manner (0, 20, and 40 μ m). The ginsenoside Rh2 stimulated acti-

vated protein kinase (AMPK) in 3T3-L1 adipocytes. In addition, the ginsenoside Rh2 activated CPT-I and UCP-2, and this activation was halted by AMPK inhibitor treatment. AMPK and PPAR are the major proteins involved in the regulation of adipocyte differentiation (140). These results suggest that the action of ginseng in increasing fat metabolism involves the AMPK signaling pathway and PPAR γ inhibition (140–142).

Many studies have reported that ginseng intake has an anti-obesity effect via fat metabolism. Intraperitoneal injection of ginseng extract for 10 d (5 mg) not only

inhibited mRNA levels of acyl-CoA oxidase, a rate-limiting enzyme for PPAR α -mediated peroxisomal fatty acid β -oxidation, but also inhibited the induction of PPAR α target genes in mice (143). Song et al. (144) found a relationship between the anti-obesity effects of Korean red ginseng extract and hepatic gene expression profiles in mice fed a high-fat diet for the long term. Levels of leptin, adiponectin, and insulin, which carry out critical functions in energy and lipid metabolism, were impaired profoundly by the high-fat diet. However, Korean red ginseng extract treatment brought these levels back to normal. This result is supported by Lee et al. (145), who showed the effect of Korean red ginseng (0.5–5%) in mice fed a high-fat diet for 8 wk. They found that as compared with the untreated group, obese mice with high-fat-diet-induced obesity fed with ginseng showed reduced adipose tissue mass (49–60%) and adipocyte size. Li et al. (146) showed that consumption of ginseng (0.5 g/kg) with a high-fat diet for 14 wk reduced body fat mass and improved glucose tolerance and insulin sensitivity. In addition, the expression of several transcription factors associated with adipogenesis (C/EBP- α and PPAR γ) had decreased the adipose tissue. In a human study, Park et al. (147) reported that long-term consumption (3–5 y) of red ginseng (about 1,600 mg) had a positive effect on obesity and levels of blood lipids. The results also showed that the long-term red ginseng consumption group had lower obesity ratio (%), TG concentration, triglyceride levels, and systolic blood pressure than the non-consumption group. Taken together, the ginseng ingestion may reduce body weight and adipose tissue by both stimulating lipolysis and inhibiting lipogenesis.

Ginseng and endurance performance

Avakian et al. (148) examined the effect of acute ginseng extract (2 mg/100 g) administration on endurance performance in rats. During swimming exercise, the ginseng extract-treated animals were found to have higher blood glucose levels and markedly lower concentrations of circulating lactic acid than the control rats. The plasma FFA level was also lower in the ginseng extract-treated animals after 30 min of swimming. They suggested that the ginsenosides significantly alter the mechanisms involved in fuel homeostasis during prolonged exercise (148). These positive effects are similarly seen in long-term ingestion. In a study by Tang et al. (149), 2 wk after 20(R)-ginsenoside Rg3 was administered intranasally to mice at 3 different doses, the anti-fatigue effect of 20(R)-Rg3 was evaluated by a weight-loaded swimming test and biochemical parameters related to fatigue. The results showed that the intermediate dose (0.1 mg/kg) and high dose (0.5 mg/kg) significantly increased exercise time in the weight-loaded swimming test. In a similar method, 15 d of swimming exercise with isolated ginseng polysaccharide (40, 50, 100, 160, and 200 mg/kg) ingestion had anti-fatigue activity, also reflected in the effects on the physiological marker (GPx: glutathione peroxidase, CK: creatine phosphokinase, LDH: lactic dehydrogenase, MDA: malondialdehyde) for fatigue in mice (150). In addition, Wang and Lee (151)

showed a short-term (4 d) ginseng (10, 20 mg/kg/d) treatment effect in mice. These results indicate that ginseng treatment enhances exercise endurance (time) and liver and skeletal muscle glycogen contents were higher than in the control group after exhaustive exercise. Our recent study involved the use of a metabolic chamber, and administration of red ginseng (1 g/kg, including 19.64 mg ginsenosides/g red ginseng extract) treatment 1 h before exercise training. The combination of ginseng with 2 wk of endurance training (70% of $\dot{V}O_2$ max) increased fat oxidation in the initial 20-min phase in mice, and a glycogen-saving effect was observed during the 1-h running exercise (152).

In human studies, Biondo et al. (153) showed that 5 wk of meal with ginseng (1,125 mg/d; 375 mg \times capsules/d) consumption did not affect immune response (neutrophils, monocytes, or lymphocytes) or exercise-induced changes in the plasma concentration of insulin, cortisol, growth hormone or lactate in healthy men. They reported that ginseng had limited effects on the immune response to a moderate bout of acute exercise.

On the other hand, Kim et al. (154) showed that administration of 2 g of *Panax ginseng* extract 3 times a day for 8 wk led to an increase in exercise duration until exhaustion in healthy males. The lower dose of ginseng (1 g/d) than that (2 g/d) used in the study by Kim et al. also increased maximal oxygen consumption and the post-exercise recovery period (155). Liang et al. (156) also used a similar low dose of *Panax ginseng* and found that administration of 1,350 mg/d *Panax ginseng* for 30 d improved endurance exercise time to exhaustion in untrained young adults. Taken together, chronic ginseng administration may have an ergogenic effect because of enhanced fat oxidation during exercise (see Table 6). Further studies are needed to clarify the dose and timing of ginseng administration on the endurance performance of athletes.

Taurine

The effect of taurine on fat metabolism

Taurine (2-amino ethylsulfonic acid), one of the most abundant amino acid-like compounds in plasma and various tissues in mammalian species, is not used for protein synthesis (157). The intracellular concentration of taurine ranges between 5 and 20 μ mol/g wet weight in the tissues of many organs such as the brain, heart, and skeletal muscle (157, 158). The endogenous synthesis of taurine is highly variable among individuals depending on their nutritional state, the amount of protein intake, and cysteine availability in the body (159). Endogenous synthesis occurs in the liver via the cysteine sulfinic acid pathway (159). There is a body of both in vivo and in vitro studies on the physiological and pharmacological role of taurine (160). Taurine's effect on fat metabolism has gained attention only recently. Ueki and Stipanuk (161) examined whether the pathways for taurine synthesis are present in the adipocyte. They used 3T3-L1 cells undergoing adipogenic conversion and fat from rats fed diets with varied sulfur-amino

Table 7. A summary of studies that examined the effects taurine on endurance performance.

Reference	Subject	Dose	Protocol	Timing	Key results	Endurance performance
Manabe et al. (165)	Male rats: 31	400 mg	Treadmill exercise for 1 h (speed, 20 m/min)	Twice a day 09:00 and 17:00, for 4 wk	Decreased fat accumulation and blood levels of cholesterol and triglyceride. Improved insulin resistance and utilization of fat and glucose.	↑
Yatabe et al. (166)	Male rats: 50	0.5 g/kg	Treadmill exercise until exh	Every morning for 2 wk	Increased taurine concentration in skeletal muscle and running time to exh.	↑
Zhang et al. (167)	M: 11	6 g	Ergometer exercise until exh	With meal for 7 d	Increased $\dot{V}O_2$ max, exercise time to exh and maximal workload in test with taurine supplementation.	↑
Lee et al. (169)	Athletes: 24 (runners)	4 g	Ergometer exercise until exh (at 75% $\dot{V}O_2$ max)	With meal for 2 wk	Improved running time to exh. Decreased lactate and ammonia concentration.	↑
Balshaw et al. (170)	Athletes: 8 (middle distance runners)	1 g	Treadmill in 3-km time trial	2 h before exercise	Improved 3-km time trail performance (1.7% ↑).	↑
Rutherford et al. (171)	Athletes: 11 (cyclists)	1.66 g	Ergometer exercise at 15-min intervals during the 90 min	1 h before exercise	Increased total fat oxidation during submaximal cycling in endurance-trained cyclists. But acute ingestion of taurine before exercise did not enhance time-trials.	↗
Ishikura et al. (168)	Male rats: 42	3% taurine solution in drinking water	Treadmill exercise at 21.7 m/min until exh	Before exercise for 2 or 3 wk	Increased running time to exh, and reduced amino acids in skeletal muscle.	↑

M: male, exh: exhaustion.

acid content. They found that genes related to taurine synthesis increased during adipogenic differentiation of 3T3-L1 cells, meaning taurine metabolism could alter fat metabolism. Fukuda et al. (162) showed that rats fed a taurine-supplemented diet experienced enhanced hepatic fatty acid oxidation. This result is supported by Bonfleur et al. (163), who showed that drinking water supplemented with 2.5% taurine reduced liver triglyceride content and body fat in obese male rats by increasing PPAR α mRNA expression, which in turn increases lipid oxidation through CPT-1a gene expression. Similarly, another study showed that increased hepatic CPT-1a protein expression in mice fed a high-fat diet lowered hepatic triglyceride content and increased fatty acid oxidation and ATP production (164). Taken together, taurine ingestion may reduce adipose tissue by both stimulating lipolysis and inhibiting lipogenesis.

Taurine and endurance performance

Some studies have shown that taurine supplementation improved endurance capacity in animals and humans (see Table 7). In their animal study, Manabe et al. (165) showed that chronic taurine (200 mg in 2 mL water twice a day at 9:00 and 17:00) treatment in rats decreased fat accumulation and the blood level of triglycerides, resulting in improved fat utilization. In addition, after exercise, the blood concentration of lactic

acid was lower in the chronic taurine treatment group than in the control group. These results indicated that taurine treatment is useful for reducing physical fatigue. Yatabe et al. (166) also showed that taurine administration (0.5 g/kg/d for 2 wk) resulted in increased treadmill running time to exhaustion in rats. Likewise, in healthy young men, cycling time to exhaustion was found to improve with taurine supplementation at a daily dose of 6 g (2 g three times a day) (167). Similar, Ishikura et al. (168) showed the effect of taurine (3% taurine solution in drinking water) supplementation on the alterations in amino acid content in skeletal muscle with exercise in rats. As a result, taurine ingestion decreases the concentration of threonine, serine and glycine. Therefore, the reduction of the amino acids utilized for gluconeogenesis induced by taurine might be one of possible mechanisms behind the endurance performance. After supplementation, the change in taurine concentration showed a positive correlation with changes in exercise time to exhaustion and maximal workload. In trained male subjects, the running time to exhaustion has been found to improve with taurine supplementation (4 g/d for 2 wk) (169). A lower oral dose of taurine (1 g) than that used by Zhang et al. (167) and Lee et al. (169) has been also shown to improve the maximal 3-km time trial performance of trained middle-distance runners (170).

However, to date, few studies have looked at the effect of taurine ingestion on endurance performance, especially as related to increased fat metabolism. Rutherford et al. (171) examined whether acute taurine ingestion before prolonged cycling improved time-trial performance and altered whole-body fuel utilization. Eleven endurance-trained male cyclists completed 3 trials in a randomized, crossover, blinded study where the subjects consumed a non-caloric sweetened beverage with either 1.66 g of taurine or nothing added (control and placebo groups, respectively) 1 h before exercise. The participants then cycled at an average 66.5% $\dot{V}O_2$ max for 90 min, followed immediately by a time-trial performance. The taurine ingestion group showed a 16% increase in total fat oxidation over the 90-min exercise period as compared with the control and placebo groups. On the other hand, the acute ingestion of taurine before exercise did not enhance time-trial performance in endurance-trained cyclists. Of note, taurine is basically an endogenous substance, production of which usually satisfies the requirements, but it should be taken especially by athletes loaded by a higher volume of exercise. Taken together, there is insufficient evidence related to the effect of taurine on fat metabolism associated with exercise performance, and further studies are needed to elucidate the role of taurine in fat metabolism during exercise.

Silk Peptides

The effect of silk peptides on fat metabolism

Silk peptides (SPs) have been consumed for many years in Asian countries (172). SP comprises biopolymers from the cocoons produced by silkworms for protection from the environment during metamorphosis to the mature moth stage (172). In recent years, additional applications of silk have been developed, mainly in the field of biotechnology and biomedicine. The versatility of these new implementations can be attributed to the singularity of the molecular structure of silk (173). Proteins such as fibroin and sericin are the main constituents of silk, with fibroin constituting 70–80% and sericin, 20–30% of the total cocoon weight (172, 174). SP is a natural biomolecule used in powder or extract form that does not cause any side effects (175, 176). Some recent studies have reported the benefits of SP treatment in body weight and health management (177–179). Recently, Lee et al. (180) assessed the effect of SP on adipogenesis in 3T3-L1 pre-adipocyte in vitro and its action against obesity in vivo. SP treatment (1 mg/mL + 0.2 nM insulin) increased glucose uptake ($124 \pm 2.5\%$) via up-regulation of GLUT4 and decreased fat accumulation via the up-regulation of leptin. In addition, it inhibited the differentiation of preadipocytes and adipogenesis by modulating the signal transduction pathway (PPAR γ and Acrp30) and improved high-fat diet-induced obesity by reducing lipid accumulation and the size of adipocytes ($86.1 \pm 2.5\%$). Additionally, an 8-wk-long SP (5% silk peptides + normal diet) treatment inhibited both preadipocyte differentiation and adipogenesis, and reduced the body fat weight of rats with high-fat diet-induced obesity (180). Furthermore, 4 wk of SP

(0.1–0.2 g/kg) treatment not only regulated blood glucose level and hyperlipidemia and but also decreased the levels of blood triglycerides and LDL cholesterol (181, 182). Taken together, SP ingestion may have anti-obesity effects through the inhibition of lipogenesis but the evidence for the lipolysis effect should be further confirmed through in vivo and in vitro studies.

Silk peptides and endurance performance

Using a metabolic chamber, we recently reported that SP (800 mg/kg) ingestion increased whole body resting energy expenditure, leading to fat oxidation in exercise-trained mice. In addition, fat oxidation was significantly higher in the SP ingestion group than in the control group (183). In another study, we showed that SPs with endurance training led to higher fat oxidation in the initial 20-min phase and the glycogen content was significantly higher during the recovery period in the SP ingestion group than in the control group (for 1-h recovery time) (184). Besides, Shin et al. (185) reported that SP ingestion increased physical stamina in a dose-dependent (50, 150, or 500 mg/kg) manner during maximum swimming exercise in mice. A glycogen-sparing effect and prevention of tissue damage (creatine phosphokinase, aspartate transaminase, or lactate) were observed with SP ingestion (186). Of note, SP has been recently linked to improved endurance performance. Thus, we anticipate that SP is one of the supplements that has an ergogenic aid effect. The effect of SPs on the endurance performance of athletes needs to be clarified in the near future.

Octacosanol

The effect of octacosanol on fat metabolism

Octacosanol ($\text{CH}_3(\text{CH}_2)_{26}\text{CH}_2\text{OH}$), a major component of the fatty alcohol mixture policosanol, is commonly found in the natural wax extracted from various plant parts including fruits, leaves, and barks (187). It has been suggested that octacosanol and policosanol decrease cholesterol by downregulating the cellular expression of 3-hydroxy-3-methylglutaryl-CoA reductase (188, 189). It is well known that a number of statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin) are reversible and competitive inhibitors of HMG-CoA reductase. HMG-CoA reductase catalyzes the reduction of HMG-CoA to mevalonate, which is the rate-limiting step in cholesterol synthesis (190).

Kirk (191) reported that octacosanol intake increased fat metabolism in order to prevent glycogen depletion. Kato et al. (192) showed that 20 d of an octacosanol (10 g/kg diet) supplemented high-fat diet reduced adipose tissue weight and serum triacylglycerol levels and enhanced the levels of serum fatty acid, suggesting that octacosanol suppresses lipid accumulation by increasing the total oxidation rate of fatty acid in the muscles. Zuyuan et al. (193) also showed the long-term (12 wk) effects of dietary octacosanol (0.2% [wt/wt]) on cholesterol with 1% ([wt/wt] octacosanol) in plasma lipids in apolipoprotein E-knockout mice. They observed that a long-term octacosanol diet reduced the levels of plasma

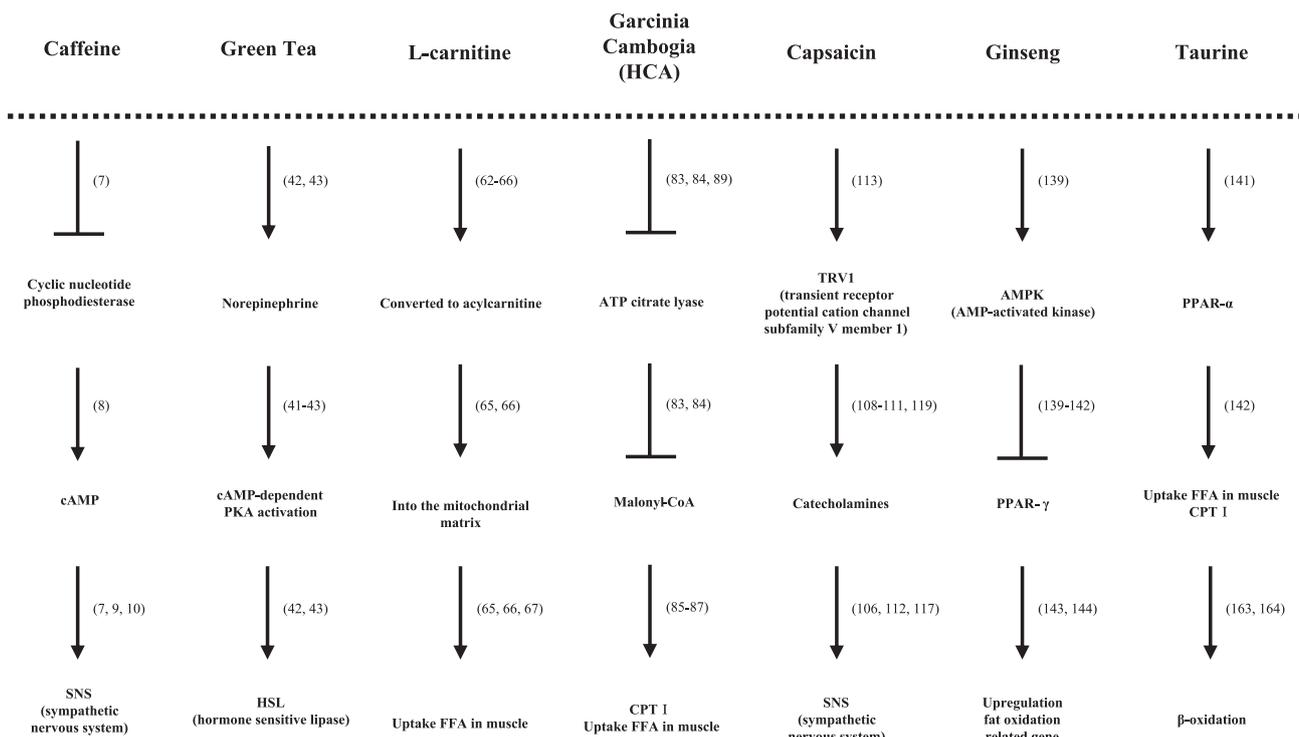


Fig. 1. Proposed lipolysis mechanisms of each supplement of caffeine, green tea, garcinia cambogia (HCA), L-carnitine, capsaicin, ginseng and taurine. Number in parentheses indicates reference.

triacylglycerol by approximately 70% by week 5 of the study, as compared with the control group. However, to date, there is very little evidence regarding the effect of octacosanol on stimulating lipolysis in in vivo or in vitro studies.

Octacosanol and endurance performance

The long-term (4 wk) effects of an octacosanol (0.75%)-supplemented diet on endurance performance and related biochemical parameters in exercise-trained rats were evaluated in one study (194). Significantly higher creatine phosphokinase activity in the plasma (approximately 44% increase) and citrate synthase activity in the muscle (approximately 16% increase) were observed in the group with dietary supplementation of octacosanol than in the sedentary control and exercise control groups. Furthermore, as compared with other groups, the exercise-with-octacosanol group showed increased running time until exhaustion and glycogen concentration at rest. They suggested that the ergogenic properties of octacosanol include the sparing of muscle glycogen stores by increasing fat oxidation. Meanwhile, these results were also found in human studies. To date, there is a lack of sufficient evidence regarding the efficacy of octacosanol on endurance performance in humans, although it possibly has an ergogenic effect.

Closing Remarks

Figure 1 proposes the lipolysis mechanisms of each supplement of caffeine, green tea, garcinia cambogia (HCA), L-carnitine, capsaicin, ginseng and taurine. Silk peptides and octacosanol may inhibit lipogenesis rather

than stimulate lipolysis. Based on the data in this review, caffeine and green tea extract improve endurance performance and enhance fat oxidation. For L-carnitine, although some studies show its potential to improve endurance performance associated with increasing fat oxidation, the data on the practical implications need to be further elucidated, especially for athletes. In future, mixed supplementations, e.g., caffeine, L-carnitine, and silk peptide, which may maximize fat utilization during exercise, could be developed for athletes.

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