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What Else Is in Your Supplement? A Review of the Effectiveness of the Supportive Ingredients in Multi-ingredient Performance Supplements to Improve Strength, Power, and Recovery

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ABSTRACT

THIS REVIEW SUMMARIZES THE EMPIRICAL RESEARCH OF THE EFFECTIVENESS, SAFETY, AND DOSAGES OF THE LESSER-KNOWN, BUT COMMONLY ADDED, SUPPORTIVE INGREDIENTS IN MULTI-INGREDIENT PERFORMANCE SUPPLEMENTS (MIPS). PRIMARY INGREDIENTS THAT ARE WELL KNOWN AND PREVIOUSLY REVIEWED (I.E., CAFFEINE, CREATINE, BETA-ALANINE) ARE EXCLUDED FROM THIS REVIEW. THE IMPROVEMENTS REPORTED ARE COMMONLY MEDIATED BY SECONDARY MECHANISMS SUCH AS IMPROVED BLOOD FLOW, PROTEIN BALANCE, METABOLISM, AND ANTIOXIDANT STATUS. OVERWHELMING EVIDENCE EXISTS SUGGESTING THAT THE SUPPORTIVE INGREDIENTS IN MIPS ARE SAFE TO USE; HOWEVER, THE AMOUNT PRESENT IN MOST MIPS IS LIKELY TOO SMALL TO ELICIT STRENGTH, POWER, OR RECOVERY RESPONSES.

INTRODUCTION

Because of the increased stringency of substance-banning agencies and the decreasing margin of victory between winning and losing, coaches and athletes continue to search for new ways to gain a performance advantage. As such, nutritional and pharmacological ergogenic aids and cocktails are commonly used by athletes as certain products have been shown to improve strength and power performance when combined with resistance training (28). These cocktails of assorted ergogenic aids have been coined as multi-ingredient performance supplements (MIPS) because of their inclusion of a vast

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array of ingredients purported to help with performance outcomes. In fact, regular use of ergogenic nutritional supplements, including MIPS, has increased by 64% in young athletes since 2010 (29). Despite the increase in commercially available MIPS and the use of these products by athletes, the efficacy for improved strength and/or power performance is most commonly attributed to just 4 primary ingredients: creatine monohydrate (85), beta-alanine (BA) (28), caffeine (9), and branched-chain amino acids (BCAAs) (55). Foremost, creatine monohydrate exerts the strongest influence on enhancements of resistance training adaptations among multiple populations, such as athletes (14), sedentary females (82), and neurological disease patients (4). For instance, creatine supplementation in 0.1 g/kg body weight (BW) doses, when combined with 8 weeks of in-season practice, in union rugby players has been shown to significantly increase the number of repetitions of bench press and leg press when compared with a placebo (14). Furthermore, BA supplementation is known to increase muscle carnosine levels (38), potentiating improvements in hydrogen ion buffering capacity during high-intensity exercise. Attenuation of hydrogen ions may lead to an increase in training volume and a reduction in fatigue (28). Additionally, BCAA supplementation aids in maintenance of power and muscular strength and preservation of muscle mass and promotion of muscle recovery through alterations in muscle protein balance during caloric restriction in elite wrestlers (55). Finally, 6 mg/kg BW of acute caffeine supplementation has been shown to significantly increase power output and the number of lifting repetitions in athletes and resistance-trained men (31,74). These primary ingredients are also known to work synergistically to elicit improvements in muscular strength and power in resistance-trained (58) and untrained men (68) with few associated side effects (68). Of interest, MIPS also include many additional supportive ingredients purported to increase strength and power or improve recovery despite limited empirical evidence of their efficacy and safety.

To further educate athletes, coaches, and sports nutrition practitioners about the diverse extraneous ingredients found in MIPS, we reviewed the most current scientific literature related to strength and power performance outcomes from the supportive ingredients most commonly found in MIPS, as well as associated adverse effects. Therefore, the purpose of this review is to (a) briefly outline the physiological changes induced by exercise for which many supplement marketing strategies are designed, (b) classify the most common supportive ingredients in MIPS, and (c) review the supportive ingredients purported to improve strength, power, and recovery (outside the most common primary ingredients).

EXERCISE AND MUSCLE PERFORMANCE

Exercise results in numerous physiological changes that may impact performance. Four primary exercise-induced physiological outcomes that are targeted by MIPS include increased blood and nutrient demand during exercise, mechanical muscle damage, decreased energy supply and stores, and production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Exercise initiates significant blood redistribution because of vasodilation of the active muscles and vasoconstriction of the inactive muscles, and it is reflected in an approximately 4-fold (20–22 L/min) increase in cardiac output (a product of heart rate and stroke volume) in sedentary individuals and up to an 8-fold (35–40 L/min) increase in elite athletes (20). Likewise, the muscle damage associated with high-intensity eccentric resistance exercise (10 sets of 10 repetitions at a mean torque 84 ± 5% of peak concentric torque) may also reduce muscle cell insulin sensitivity resulting in increased insulin resistance (40). Insulin is important to postexercise recovery because it promotes the restoration of muscle glycogen stores (which can be considerably lowered during exercise) by moving glucose from circulation into the muscle cells. The inability to restore muscle glycogen levels after exercise may result in decrements in subsequent strength performance (49). Exercise also mechanically produces microtears in the muscle fibers (15), particularly after exercise incorporating eccentric contractions. This damage affects subsequent muscular performance because of loss of the capacity of muscular force production or a voluntary reduction of effort (6). Exercise at high intensity or for prolonged periods of time results in a potential overproduction of ROS and RNS, which are highly reactive atoms or molecules that possess one or more unpaired electrons (24). Overproduction of ROS/RNS and inadequate endogenous production of antioxidants (molecules that scavenge ROS/RNS) results in significant oxidative damage to the proteins and lipids of the contracting muscle cells (56). As a result, contractile dysfunction may ensue, resulting in muscular weakness and fatigue (62). These physiological responses are greatly exacerbated by daily high-volume training often experienced by athletes and can significantly affect muscle power, strength, and recovery. Therefore, ergogenic and recovery aids such as MIPS may provide a mechanism to reduce some of the deleterious effects of intense exercise.

MIPS: EVIDENCE FOR SUPPORTING INGREDIENTS

Products containing certain proprietary blends focusing on performance enhancement through increased strength, increased power, or improved recovery time are common. However, it is extremely important to note that many of these proprietary blends do not report the amounts of the included ingredients; rather, they simply report their presence. For this reason, it is difficult or impossible to know the exact amount of the given ingredients, leading to speculation that many of these ingredients only appear in trace amounts. Importantly, this makes it difficult to draw any definitive conclusions regarding mechanisms for performance changes.

Because of extensive existing research regarding the effectiveness of creatine, caffeine, BA, BCAA, and essential amino acids on strength and power (Figure 1) (7,28,42,85), these ingredients are not discussed in this review. In addition, because of the plethora of supportive ingredients commonly listed on MIPS supplement facts labels, we discuss ingredients that compose >5% of commonly used MIPS (Figure 2). All current MIPS marketed on bodybuilding.com, amazon.com, and google.com were searched (November 2014) for ingredients and dosing and were subsequently summarized. Many of the commonly used supportive ingredients in MIPS have modest or no empirical data to suggest their effects on strength (Table 1), power (Table 2), or recovery (Table 3). For instance, although present in 11% of the MIPS analyzed, because Huperzine A supplementation is known to enhance memory and learning in patients with Alzheimer's disease (18), it is commonly added to MIPS for mental acuity despite the lack of evidence for improving performance. Similarly, dimethylaminoethanol, capsicum, and hawthorn extract are also added because of their supposed effects on mental acuity but have no direct evidence for improving strength, power, or recovery. Other ingredients added to MIPS, such as *Rhodiola rosea* (1,12,37) and glycerol (65), have been shown to aid in endurance performance but, again, have sparse or no empirical evidence suggesting direct effects of improving strength, power, or recovery. Specifically, although *Rhodiola rosea* is classified as an adaptogen, defined as a plant, compound, or herb in which administration results in promotion of homeostasis through the stabilization of physiological properties, there is inconsistent evidence suggesting its efficacy for improving recovery and/or recovery time after exercise (67,87). The other supportive ingredients, excluding the aforementioned ones, may not be directly associated with improvements in performance; however, they are added to MIPS likely because of their theoretical mechanistic properties: (a) increased blood flow to facilitate increased blood and nutrient demand (19,22), (b) promotion of protein balance or protection against protein breakdown to counteract mechanical muscle damage (5,44), (c) promotion of metabolism to counter decreased energy supply and stores (12,77), and (d) protection against oxidative stress to combat ROS/RNS production (46,60). Because of the high amount of overlap with the mechanistic properties of each ingredient, protection against oxidative stress is not discussed in considerable depth in its own section; rather, it will act supplementary to the other mechanisms.

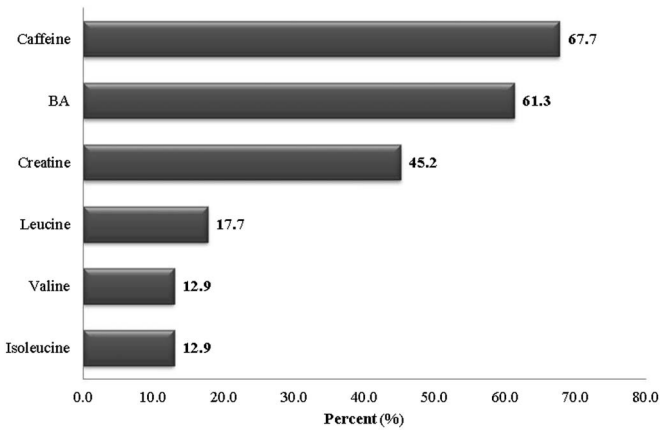

Figure 1. Percentage of the total MIPS analyzed that contain the primary ingredients, caffeine, beta-alanine, creatine, and the branch-chain amino acids. BA, beta-alanine.

BLOOD FLOW

Approximately 60% of the MIPS analyzed contain a proprietary blend designed to improve blood flow with common marketing titles such as "maximal pump/vascularity" or "nitric oxide blend." Of the most common ingredients purported to enhance vasodilatory properties and subsequent blood flow, beetroot extract, grape seed extract (GSE), and agmatine have the most supportive evidence (19,22,64,71). An important point to make clear is the lack of direct association between increases in blood flow and improvements in muscle strength, power, and recovery (2), yet these outcomes continue to be heavily marketed. The mechanism for increased blood flow with supplementation of many of these supportive ingredients centers mostly on increasing nitric oxide (NO; potent vasodilator) production through nitric oxide synthase (NOS), an enzyme that catalyzes the production of NO from molecules such as nitrates and arginine. Enhanced NO production (64) as a result of supplementation with these ingredients and especially during exercise is documented to (a) promote increased muscle cell perfusion; (b) optimize glucose, oxygen, and nutrient transportation; (c) stabilize muscle glucose concentrations; (d) prolong the onset of fatigue during exercise; and (e) augment muscle protein synthesis and recovery in healthy physically active individuals (3). The major supportive ingredients that are purported to potentiate increases in blood flow are discussed.

Nitrates and nitrites. Primary effects

Nitrates (NO_3^-) and nitrites (NO_2^-), found in products such as beetroot juice (BRJ) and pomegranate juice (PJ), are reduced to form NO through the enzyme nitrate reductase during hypoxic (low oxygen) situations (19,51). Thus, although the decrease in oxygen availability with increasing exercise intensity results in lower levels

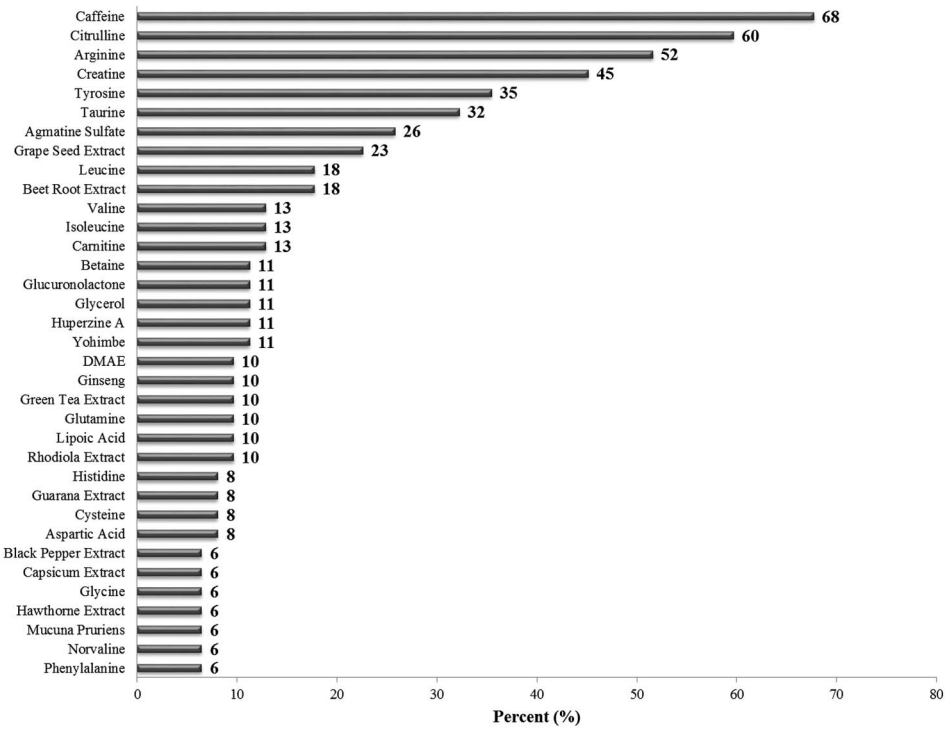

Figure 2. Percentage of the total MIPS analyzed that contain all supportive ingredients.

of NO production through NOS, NO production through the nitrate-nitrite-NO pathway is accelerated (51).

Secondary effects

In addition to its effects on NO, the rate of adenosine triphosphate (ATP) turnover, or the amount of energy being used, can be reduced in contracting muscle cells with 500 mL/d of BRJ containing at least 5.1 mmol of NO_3^- (8). This conservation of energy may potentiate improved exercise tolerance during high-intensity endurance exercise (8). Likewise, in a review by our group, it was concluded that NO_3^- in 1,500 mg/L doses from BRJ attenuates the decline of phosphocreatine stores and enhances oxidative phosphorylation efficiency necessary for explosive energy, thereby promoting improvements in anaerobic capacity (57).

Although the performance effects of NO_3^- supplementation in the form of BRJ are consistent, when NO_3 are provided in the form of PJ, the evidence of direct strength benefits of its combination with resistance training are contradictory (79,80). However, there is extensive evidence supporting the muscular recovery benefits (79,80) by postexercise attenuation of subjective muscle soreness immediately after exercise (80). It is noteworthy that this effect will diminish with increasing time because levels of muscle soreness have been shown to normalize between placebo and NO_3^- groups 24 hours after exercise (79). PJ also seems to attenuate the reduction in strength typically reported after intense bouts of eccentric exercise (79). Overall, an overarching consensus for performance enhancement due to NO_3^- supplementation may be difficult to conclude because there are many other active substances that may influence these responses, such as betalain, betaine (BET), betanin, betacyanin, and betaxanthin in BRJ (57), and tannins, anthocyanins, and ellagic acids in PJ (80). Thus, although 1,500 mg/L of dietary NO_3^- in the form of BRJ may yield performance benefits (57), comparisons of effective levels of supplemental nitrates through PJ would be difficult to conclude because of the lack of reported amounts of NO_3^-. Interestingly, the benefits of NO_3^- supplementation seem most effective in low-to-moderately trained, but not elite, athletes (57).

Some nitrogenous foods are classified as phenolic compounds, which are a type of antioxidant shown to protect cardiovascular and muscle tissues (48,52,79). Even so, the performance benefits of these ingredients are inconsistent (37,46,60,79,80). Ellagitannin, a polyphenol in PJ, exerts positive effects on recovery from eccentric exercise (79). After being subjected to 2 sets of maximal eccentric elbow flexion exercises, subjects who supplemented with PJ (95% ellagitannin) showed marked postexercise strength recovery compared with a placebo (79), which was confirmed by a later study (52). However, it is important to note that PJ extract contains many active ingredients with similar antioxidant properties, such as vitamin C and vitamin E. Despite the findings of improved strength recovery, PJ supplementation does not seem to effect blood markers

Table 1
Changes in muscular strength associated with supportive ingredients in MIPS

	Study	Design	*N*, population	Supp/exercise intervention	Timing prior	Testing protocol	Results	Strength performance
BET								
	Hoffman et al. (26)	R, DB	24 young, active M	15 d; 1,250 mg BET/PL; NoEx	None	S and BP reps to failure (75% 1RM)	↑S reps, ↑S reps at 90% or greater of PP; ↔in reps to exhaustion	↑
	Kraemer et al. (41)	R, DB, B, CO	12 young, RT M	14 d; 1,500 mg BET/PL; NoEx	None	Max iso S and BP, 10 min BLT	↑max iso S and performance in BLT; ↔iso BP	↑/↔
	Trepanowski et al. (78)	R, DB, CO	13 young, RT M	14 d; 2,500 mg BET/PL; NoEx	30 min before	LBS and UBS on leg press and BP	↔	↔
Carnitine								
	Ho et al. (25)	R, DB, PC, B, CO	Active middle-aged M (n = 9) and W (n = 9)	21 d; 2,000 mg Carn/PL; NoEx	3 h before	4 × 15 of S/leg press at 50% estimated 1RM, HG, perceived muscle soreness	↔	↔
P. ginseng								
	McNaughton et al. (54)	R, DB, PC, CO	15 M, 15 W	42 d; 100 mg ginseng root powder/PL; NoEx	?	?	↑pectoral strength (27%)/quadriceps strength (18%), ↔in HG	↑
Nitrates								
	Trombold et al. (80)	R, DB, CB, PC, CO	17 young, RT M	15 d; 250 mL of PJ/PL; Ecc EF to produce DOMS	Imm after exercise	Max iso EF/KE	↑EF strength at all time frames, ↔KE strength	↑/↔
	Trombold et al. (79)	R, PC, CO	17 healthy, recreationally active young M	9 d; 500 mL of PJ/PL; Ecc EF to produce DOMS	Imm after exercise	Max iso EF, subjective soreness rating, blood draw	↔b/t groups in strength at 2/24 h after ecc; ↑strength after 48 h	↑
Yohimbine								

Table 1 (continued)

	Ostojic (59)	R, DB, PC	20 young, M soccer athletes	21 d; 20 mg of Y/PL; normal soccer conditioning	None	BP max reps (100% BW), leg press max reps (200% BW)	↔	↔
Citrulline								
	Pérez-Guisado and Jakeman (61)	R, DB, CO	40 RT M	Single dose 8 g CM/PL	1 h before	4 sets of BP reps to fatigue at 80% 1RM	↑reps to fatigue with CM	↑

B = balanced; BET = betaine; BLT = box lift test; BP = bench press; BW = body weight; b/t = between; carn, L-carnitine L-tartrate; CB = counter-balanced; CM = citrulline malate; CO = crossover; DB = double-blind; DOMS = delayed-onset muscle soreness; ecc = eccentric exercise; EF = elbow flexion; HG = maximal handgrip testing; imm = immediately; iso = isometric; KE = knee extension; LBS = maximal lower-body isometric force; M = men; max = maximum; NoEx = no exercise intervention; PC = placebo-controlled; PL = placebo; PJ = pomegranate juice; PP = peak power; R = randomized; 1RM = 1-repetition maximum; reps = repetitions; RT = resistance-trained; S = squat; supp = supplementation; UBS = maximal upper-body isometric force; ? = unknown; W = women; Y = yohimbine; ↔ = no change/does not improve; ↑ = increases/improves; ↓ = decreases/worsens.

of muscle damage or inflammation (79,80).

Grape seed extract. ***Primary effects***

GSE has largely been used clinically in diseased populations as a blood pressure regulator at rest (71). This is due to its effects on vasodilation through high concentrations of phenolic compounds (71). However, its effects in combination with resistance training are unknown and purely anecdotal.

Secondary effects

In addition to its effects on vasodilation, GSE is also an antioxidant and may help improve performance through reductions in oxidative stress. Physical performance and explosive power were significantly increased in elite male handball players with 4 weeks of 400 mg/d of GSE, possibly because of decreased creatine kinase (CK) and increased hemoglobin (Hb) (46). CK is associated with muscle cell permeability (13), which is compromised after induced oxidative stress resulting from high-intensity exercise (33), and Hb concentration (oxygen-carrying capacity of blood) is significantly reduced after intense exercise (66). However, findings are not consistent and, in small sample sizes, the previously reported benefits of GSE were not reported in basketball (n = 5), sprint (n = 4), or volleyball (n = 1) athletes (46). Overall, beneficial changes may occur with doses of 400 mg/d or more (46); therefore, the average amount of GSE in MIPS (Table 4; 225 mg; range: 150–300 mg) is likely unable to elicit any performance advantage.

Citrulline. ***Primary effects***

Interestingly, 60% of the MIPS supplements analyzed contained a form of citrulline, primarily as a part of a vasodilatory blend. L-citrulline may be more effective for postexercise recovery rather than performance by enhancing delivery of nutrients, hormones, and oxygen, as well as eliminating waste products such as ammonia (75), which is shown to be produced

Table 2
Changes in muscular power associated with ingredients in MIPS

	Study	Design	*N*, population	Supp/exercise intervention	Timing before	Testing protocol	Results	Power performance
BET								
	Hoffman et al. (26)	R, DB	24 young, active M	15 d; 1,250 mg BET/PL; NoEx	None	VJP, BPT; two 30-s W	↔	↔
	Trepanowski et al. (78)	R, DB, CO	13 RT M	14 d; 2,500 mg BET/PL; NoEx	30 min before	VJ, BPT	↔	↔
	Pryor et al. (63)	R, DB, CO	Active M (n = 9) and W (n = 7)	7 d; 2,500 mg BET/PL; NoEx	Morning of the test day (testing at night)	Four 12-s W 5.5% BW	↑average PP, max PP, and max mean power; ↑average and max peak and mean power from baseline to end point-in BET and not PL	↑
	Kraemer et al. (41)	R, DB, B, CO	12 young, RT M	14 d; 1,500 mg BET/PL; NoEx	None	10 max VJ	↔	↔
Carnitine								
	Ho et al. (25)	DB, PC, B, CO	Active middle-aged M (n = 9) and W (n = 9)	21 d; 2,000 mg Carn/PL; NoEx	3 h before	10 max VJ	↔	↔
Grape extract								
	Lafay et al. (46)	R, DB, PC, CO	20 elite sportsmen (HB = 10; BB = 5; sprint = 4; VB = 1)	28 d; 400 mg GE/PL; normal sports conditioning	None	PhyP, EP	↑PhyP and EP in the handball players; ↔in the other sports	↑/↔
Nitrates								
	Bailey et al. (8)	R, DB, CO	7 young M	6 d; 500 mL BRJ (5.1 mmol NO_3^-)/PL; NoEx	Before testing	Blood sample, incremental 2-legged KE test (peak work rate)	↓amplitudes of PCr and $\dot{V}O_2$ slow components and improved time to exhaustion, ↓total ATP turnover rate	↑
Yohimbine								

Table 2 (continued)

Ostojic (59)	R, DB, PC	20 young, M soccer athletes	21 d; 20 mg Y/PL; normal soccer conditioning	None	VJ height, SP	↔	↔

ATP = adenosine triphosphate; B = balanced; BB = basketball; BET = betaine; BPT = bench press throw; BRT = beet root juice; BW = body weight; Carn = L-carnitine, L-tartrate; CO = crossover; DB = double-blind; d = days; EP = explosive power; GE = grape extract; HB = handball; KE = knee extensors/extension; M = men; max = maximum; NO_3^- = nitrate; NoEx = no exercise intervention; PC = placebo-controlled; PCr = phosphocreatine; PhyP = physical performance; PhysP = total physical performance; PL = placebo; PP = peak power; R = randomized; RT = resistance-trained; SP = sprint-power test; supp = supplementation; VB = volleyball; VJ = vertical jump; VJP = vertical jump power; $\dot{V}O_2$ = oxygen consumption; W = wingate test; W = women; Y = yohimbine; ↔ = no change/does not improve; ↑ = increases/improves; ↓ = decreases/worsens.

during intense anaerobic exercise (23,61).

Secondary effects

However, recently, citrulline malate has been shown to improve strength performance (Table 1) (61). A single 8 g dose of citrulline malate significantly increased the number of repetitions performed in the flat barbell bench press in young men (61). The average amount of citrulline in MIPS is 1.5 g, which is considerably lower than the 8 g dose in the study by Pérez-Guisado and Jakeman, albeit an acute dose (61).

Agmatine and norvaline. In addition to NO_3^- and GSE, agmatine, a byproduct of arginine metabolism, and norvaline, an isomer of valine (a BCAA) are known to enhance NO production in animal models (64). However, performance benefits in humans mediated by increased blood flow with agmatine or norvaline supplementation have not been examined despite the appearance of these ingredients in many commercially available MIPS. Therefore, no effective comparisons of the average amount of agmatine (435 mg; range: 250–500 mg) or norvaline (100 mg) in MIPS (Table 4) can be made.

Mechanistically, agmatine, provided in acute 4-μg dose to rats, is known to stimulate pituitary release of growth hormone (GH) (35), which increases the speed and size of muscle tissue growth and muscular strength (5,35). However, although hormone level changes may be apparent with supplementation, there are no clear associations with subsequent changes in performance and recovery. Therefore, further research is warranted to compare the effectiveness of the average amounts of agmatine (Table 4; 435 mg; range: 250–500 mg) in MIPS.

MUSCLE PROTEIN BALANCE

Because of microtears in muscle tissue associated with intense exercise, numerous ingredients in MIPS target muscle protein balance (synthesis and breakdown). Interestingly, only approximately 20% of MIPS contain these ingredients or market enhancement of muscle protein balance, with labeled proprietary blends such as "muscle building and repair system" and "explosive muscle building matrix." There are multiple potential mechanisms through which protein balance may be maintained with certain supportive ingredients, including direct maintenance and protection of structural proteins of muscle fibers. Therefore, the primary promoters of muscle protein balance, carnitine, BET, *Mucuna pruriens*, alpha lipoic acid (ALA), and *Panax ginseng* are discussed.

Carnitine. *Primary effects*

L-carnitine L-tartrate (LCLT) is known to improve muscle protein balance through many purported mechanisms. Foremost, LCLT attenuates muscle soreness and reduces metabolite damage after resistance training–induced hypoxia (25,43,44,86), promoting increased recovery time as well as muscle tissue repair and remodeling in normally active and weight-trained men and women (25,43,44,86). LCLT supplementation (2 g/d) for 3 weeks was shown to attenuate muscle tissue disruption and lower blood markers of purine metabolism (hypoxanthine, xanthine oxidase, and serum uric acid) after exercise-induced hypoxia (5 sets, 15–20 repetitions of squats) (25,86). Catabolism of purines occurs in response to intense exercise. Therefore, LCLT supplementation may enhance oxygen delivery, thereby reducing the magnitude of hypoxia and thus attenuating subsequent purine catabolism and ATP breakdown (preservation of energy) (86). Although markers of muscle tissue disruption (myoglobin and CK) and self-reported muscle soreness were reduced, neither handgrip strength nor vertical jump improved (25). Additionally, 2 g/d of LCLT for 21 days has been shown to upregulate androgen receptor content in resistance-trained men, which may contribute to increased uptake of testosterone and subsequent improvements in recovery after resistance training (45). Thus, the benefits of LCLT supplementation when added

Table 3
Changes in muscular recovery associated with ingredients in MIPS

	Study	Design	*N*, population	Supp/exercise intervention	Timing before	Testing protocol	Results	Recovery
P. ginseng								
	McNaughton et al. 1989	R, DB, PC, CO	15 M, 15 W	6 wk; 100 mg ginseng root powder/PL; NoEx	?	?	↑postexercise recovery	↑
Carnitine	Ho et al. (25)	DB, PC, B, CO	Active middle-aged M (n = 9) and W (n = 9)	3 wk; 2,000 mg Carn/PL; NoEx	3 h before	Perceived muscle soreness, blood samples	↓levels of muscle soreness, attenuated blood markers of purine catabolism, free radical formation, and muscle tissue damage	↑
Nitrates								
	Trombold et al. (80)	R, DB, CB, PC, CO	17 RT M	15 d; 250 mL PJ/PL; Ecc EF/KE exercise to produce DOMS	Imm after exercise	Perceived muscle soreness	↓soreness during all time points with EF, ↔ with KE	↑/↔
	Trombold et al. (79)	R, PC, CO	17 active M	9 d; 500 mL PJ/PL; Ecc EF to produce DOMS	Imm after exercise	Perceived muscle soreness, blood draw	↓perceived muscle soreness at 2 h after, but not 24 or 48 h; more rapid strength recovery at after 48 h; ↔ in blood markers	↑

B = balanced; Carn = L-carnitine, L-tartrate; CB = counter-balanced; CO = crossover; DB = double-blind; DOMS = delayed-onset muscle soreness; ecc = eccentric exercise; EF = elbow flexor; imm = immediately; KE = knee extensor; M = men; mg = milligrams; mL = milliliters; NoEx = no exercise intervention; PC = placebo-controlled; PJ = pomegranate juice; PL = placebo; R = randomized; RT = resistance-trained; supp = supplementation; W = women; ↔ = no change/does not improve; ↑ = increases/improves; ↓ = decreases/worsens; ? = unknown; ? = data not provided.

to resistance exercise training seem to be mediated by improvements in recovery.

Secondary effects

In addition to its effects on muscle protein balance, L-carnitine (2 g/d for 3 weeks) has also been shown to display antioxidant effects by attenuating blood makers of free radical formation (malondialdehyde and xanthine oxidase) (25,86). Although evidence suggests that 2 g/d of L-carnitine elicits muscle protein balance and antioxidant responses, the average MIPS supplement contains on average <800 mg (range: 333–1,250 mg) per serving (Table 4), which is likely inefficient in providing beneficial responses.

Betaine. ***Primary effects***

BET, which is found in BRJ, may also enhance protein balance. BET is endogenously produced during times of stress (i.e., dehydration or hypertonic state during exercise) to protect the cell. BET does this through maintenance of cellular hydration, which enhances muscle cell survival and protein synthesis (41,78,81). Ultimately, these properties of BET may help to protect muscle tissue from exercise-induced damage. However, direct enhancement of these mechanisms with BET supplementation has not thoroughly been examined. Trepanowski et al. reported significantly higher squat repetitions and lifting volume but no effects on muscular strength or power with 2.5 g/d of BET for 2 weeks in resistance-trained young men (78). However, these results were not a consequence of increased protein metabolism; rather, the authors reported that changes were likely due to an increase in oxygen saturation and an attenuation of blood lactate levels (78). These findings confirm an earlier study by Hoffman et al. (26) in active (including resistance training) college-aged men using 1.25 g/d of BET for 2 weeks. Importantly, power output was only shown to improve in recreationally active males and females, not resistance-trained individuals, supplemented with 2.5 g/d for 1 week (63).

Table 4
Supportive ingredient amounts and amount empirically known to elicit responses

	No. MIPS	No. MIPS reporting levels	Range of amount (mg)	Average amount (mg)	Amount known to elicit responses	Sufficient?
Citrulline	37	15	75–6000	1500	?	?
Agmatine	16	4	250–500	435	?	?
GSE	16	2	150–300	225	400 mg/d, for 1 mo	No
BRJ	12	3	100–500	300	50.1 mmol NO_3^-/d for 6 d	Cannot conclude
Carnitine	8	3	333–1250	778	2000 mg	No
BET	7	3	833–2500	1611	2000–3000 mg	Yes
Glucuronolactone	7	1	600	600	600 mg (acute)	Yes
Glycerol	7	3	500–2500	1033	?	?
Huperzine A	7	1	50	50	?	?
Yohimbe	7	4	2–28	23	20 mg	Yes
P. ginseng	6	2	12–100	56	6,000–60,000 mg	No
GTE	6	3	100–200	133	1256 mg total: 890 mg polyphenols and 366 mg EGCG	No
ALA	6	4	20–5000	1275	?	?
Rhodiola rosea	6	4	33–100	63	340 mg extract with 30 mg active *R. rosea*	Yes
Black pepper	4	3	1.6–5	2.9	?	?
M. Pruriens	4	0	UD	UD	?	?
Norvaline	4	1	100	100	?	?

ALA = alpha lipoic acid; BET = betaine; BRJ = beet root juice; EGCG = epigallocatechin gallate; GSE = grape seed extract; GTE = green tea extract; UD = unable to determine; ? = unknown.

Therefore, there may be a higher propensity of power improvements in untrained individuals, likely mediated by improved oxygen saturation and lactate levels.

Secondary effects

BET also acts as a methyl donor, which is highly important in the methionine cycle. In this metabolic cycle, a methyl group is transferred from BET to homocysteine by the enzyme betaine homocysteine methyltransferase, producing methionine, which is converted to S-adenosylmethionine (SAM) (16). Ultimately, SAM acts as a methyl donor during creatine synthesis (84), which is important for explosive energy; however, there has been no direct established link between performance benefits and SAM formation as a result of BET supplementation.

BET also has been shown to improve the anabolic and catabolic hormonal milieus. Two weeks of 1.25 g/d doses of BET in combination with an acute full-body resistance training protocol in weight-trained men stimulated pituitary release of GH, and, subsequently, insulin-like growth factor-1 (IGF-1) (5). This finding is supported by Kraemer et al. (41) who found that 3 g/d for 2 weeks of BET in resistance-trained young men increases the GH and IGF-1 area under the curve (AUC), contributing to increases in muscular force production. Supplementation of BET also stimulates and accelerates the anabolic signaling environment by increasing signaling proteins (i.e., Akt, p70, S6k, and AMPK) involved in protein synthesis (5). Additionally, the concentration (5) and AUC (41) of cortisol (a catabolic hormone) are shown to decrease with 1.25–3.0 g/d of BET consumed for 1–2 weeks.

In conclusion, the 1.25–3.0 g/d doses of BET for 1–2 weeks that produce modest performance benefits in the literature may be higher than the average dose (1.6 g per serving) of BET in MIPS (Table 4; range: 0.83–2.5 g). Therefore, amounts in MIPS are likely ineffective in producing performance results but may improve the anabolic and catabolic hormonal milieus, and subsequently augment hormonal

responses to exercise. However, it is important to note that recent evidence suggests that resistance training–induced increases in anabolic hormones are not always associated with concomitant increases in muscle protein synthesis (88); thus, changes in extraneous variables such as changes in the receptor number and/or subject responsiveness also likely contribute to outcomes and should be considered upon analysis.

Mucuna pruriens. Independent of exercise, *M. pruriens* stimulates the release of testosterone (69), however, only in hypogonadal young and middle-aged men who were supplemented for 12 weeks with 5.0 g/d of *M. pruriens* combined with milk (69). Although testosterone changes may be apparent with supplementation of *M. pruriens*, these changes have not been associated with improvements in performance, supporting the recent evidence that improvements in the hormonal milieu do not necessarily translate into changes in strength (88). Therefore, further research is warranted to compare the effectiveness of the average amounts of *M. pruriens* (present, but no doses reported) in MIPS.

Alpha lipoic acid. ***Primary effects***

Insulin sensitivity is also important to consider in regard to postexercise glycogen refueling and subsequent muscle protein metabolism. In obese Zucker rats, an animal model of insulin resistance, hyperinsulinemia, and dyslipidemia, treatment (10 days) of ALA (100 mg/kg BW for 1 hour) without exercise enhances insulin-stimulated glucose transport and metabolism (73). However, there have been no reported effects of ALA on glucose kinetics after exercise in humans, and therefore more research is warranted.

Secondary effects

In addition, ALA is an important component of metabolism and antioxidant systems. In response to muscle-damaging isometric and isokinetic exercise in resistance-trained and untrained men, ALA supplementation (600 mg/d for 8 days) was shown to display antioxidant properties by diminishing oxidative damage and modulating the antioxidant response (89). Because of the paucity of mechanistic evidence suggesting the effectiveness of ALA supplementation on improving antioxidant status and metabolism after acute exercise, there has been no direct assessment of chronic improvements in performance, and therefore, effective comparisons of the average amount of ALA (Table 4; 1,275 mg; range: 20–5,000 mg) in MIPS cannot be made.

Panax ginseng. ***Primary effects***

The adaptogenic properties of *P. ginseng* (17) (4 g/d over 8 weeks) protect active muscle tissue against exercise-induced oxidative stress in response to acute exhaustive treadmill exercise in men (39). Likewise, *P. ginseng* effectively promotes reductions in exercise-induced muscle damage and inflammatory responses in dosage ranges of 4 g/d for 8 weeks to 20 g/d for 1 week in healthy men (34,39). Importantly, each of these studies used aerobic exercise and not resistance training as an exercise perturbation. Albeit a different form of ginseng, 100 mg of Chinese ginseng root powder provided over 42 days has been shown to increase pectoral and quadriceps strength in recreationally active men and women (54).

Secondary effects

Improvements in insulin sensitivity are also the result of the adaptogenic properties of *P. ginseng* (47). Insulin sensitivity seems to improve in an insulin-resistant rat model with injections of 1 mg/kg, 3 times per day for 3 days of ginsenoside Rh2, an active ingredient in *P. ginseng* root, independent of the addition of an exercise perturbation (47). The average 0.56-g dose in MIPS products (Table 4; range: 0.12–1.0 g) is extremely small compared with the high ranges of doses (4–20 g) that are shown to be effective in performance enhancement.

METABOLISM

Over 66% of the supplements analyzed contain metabolism-enhancing ingredients that aim to boost metabolism and also promote fat loss in labeled blends such as "shredded complex," "metabolism booster," or "energy-enhancer." The primary metabolism enhancers, green tea/green tea extract (GT/GTE), glucuronolactone, taurine, black pepper, and yohimbine are discussed.

Green tea and green tea extract. ***Primary effects***

Although beyond the scope of this review, the primary effect of GT/GTE supplementation is the metabolism of fat in overweight and obese men and women. For example, when supplemented with 625 mg of catechins from GT and 39 mg caffeine for 12 weeks, while concomitantly encouraged to perform ≥180 minutes of moderate exercise per week, total fat and body composition improved in overweight and obese men and women (53). Another study reported that fat oxidation is increased by 17% after 30 minutes of cycling at 60% of maximal oxygen consumption with supplementation of GTE (1256 mg total: 890 mg polyphenols and 366 mg epigallocatechin gallate [EGCG]) in recreationally active young men when compared with a corn-flour placebo (83). However, 400 mg/d for 12 weeks of GTE showed no effects on body mass or waist/hip measurements in obese women (30). Thus, the fat metabolism properties of GT/GTE differ in doses and populations.

Secondary effects

GT has also been shown to improve insulin sensitivity. In recreationally active young men, GTE (1256 mg total: 890 mg polyphenols and 366 mg EGCG) ingested twice on the day before laboratory testing significantly lowered serum insulin concentrations and insulin AUC during a 2-hour oral glucose tolerance test (75 g of glucose administered intravenously) (83). These results equate to a 13% increase in insulin sensitivity and a 15% reduction in insulin response to a glucose load, thus indicating improvements in glycemic control (83). In addition to its effects on insulin sensitivity, 2 g of GT leaves in 200 mL of

hot water, thrice a day for 1 week has been shown to offer protection against oxidative damage after resistance training in young healthy recreationally weight-trained males (60). Although beneficial to glucose metabolism, insulin sensitivity, and exercise-induced oxidant production, the combination of GT/GTE supplementation and exercise interventions still warrants further research. Likewise, it seems as though the method of administration (i.e., capsule, beverage, extract) does not affect performance outcomes, because both GTE and GT leaves produce positive results. However, MIPS commonly use GTE (Table 4; 133 mg; range: 100–200 mg), and not GT; therefore, it is difficult to make comparisons with limited evidence of the performance effects of GTE.

Glucuronolactone. Glucuronolactone is claimed to boost detoxification, or glucuronidation; however, this effect is not supported in the literature. As a result of these claimed effects, it is purported that glucuronolactone may promote improvements in fatigue through clearance of waste products produced during exercise (77). Most research regarding glucuronolactone supplementation exists vicariously through supplementation with energy drinks, in which this ingredient is found in high doses (600 mg in 1 serving of Red Bull energy drink). In resistance-trained males, total lifting repetitions and volume of repetitions (27) were enhanced with acute supplementation of an energy drink containing 350 mg of glucuronolactone, which was also associated with increased anabolic hormone status (GH and insulin) (27). Importantly, because these energy drinks contain multiple ingredients such as caffeine, amino acids, B-vitamins, and taurine, exact comparisons of performance effects of individual ingredients and certain doses are difficult to ascertain. However, glucuronolactone seems to exert ergogenic effects when combined with other supportive ingredients. Therefore, research regarding individual supplementation is required to most efficiently compare the effects of the average amount of glucuronolactone (Table 4; 600 mg) in MIPS.

Taurine. Approximately 1 in 3 MIPS contain the amino acid taurine (Figure 2) for purported improvements in mental acuity and energy levels. When combined with other ingredients in energy supplements, taurine in acute 1.5 g doses has been shown to increase the number of lifting repetitions performed and training volume in resistance-trained males (27). Additionally, reported strength levels were increased and muscle soreness levels were decreased with 2 weeks of 15 mg/kg BW/d (1.1 g taurine/d for a 70 kg man) of taurine supplementation, compared with a placebo in response to elbow extensor eccentric exercises at 80% 1RM in 3 sets to failure (70). Blood concentrations of lactate dehydrogenase, CK, and markers of oxidative damage (xylenol and protein carbonyl) were also significantly decreased with taurine supplementation (70). However, antioxidant activity and inflammatory markers were not altered (70). It seems that taurine supplementation is beneficial; however, more research is needed in conjunction with resistance training. The 1,043-mg average (range, 500–1,500 mg; Table 5) amount of taurine in MIPS seems to be sufficient in providing performance benefits.

Other: black pepper and yohimbine. Active ingredients in black pepper and yohimbine are also purported to enhance metabolism. Piperine and capsaicin are active compounds in black pepper, which are known to increase metabolism (72,76); however, the effects of black pepper on exercise performance remain unknown. Black pepper also offers protection against oxidative damage at rest (72). Because of the lack of evidence supporting performance benefits with black pepper supplementation, it is impossible to make effective comparisons of the 2.9 mg average (Table 4; range: 1.6–5 mg) in MIPS.

In addition to black pepper, yohimbine, an extract from the yohimbe tree, is known to increase fat metabolism acutely (0.2 mg/kg BW; 14 mg for a 70 kg man) in healthy men because of its antagonist effect on alpha adrenergic receptors on adipocytes (21). Additionally, the lipid-mobilizing effects after acute yohimbine supplementation are strengthened during low-intensity aerobic exercise (30 minutes of cycling at 60% $\dot{V}O_2max$) (21); however, its effects in conjunction with resistance training are unknown. Likewise, supplementation with 20 mg/d oral tablets for 3 weeks in combination with typical sports training in professional soccer players significantly decreases fat mass; however, it does not elicit effects on strength or power performance (59). Therefore, although fat metabolism may be altered with acute and chronic yohimbine supplementation in 0.2 mg/kg BW or 20 mg/d doses, from a performance standpoint, the average 23 mg (Table 4; range: 2–28 mg) dose of yohimbine in MIPS seems to be inefficient in producing strength or power performance results.

SIDE EFFECTS

Although a small amount of the listed ingredients are known to induce complications with high to extreme doses primarily reported in case studies and without exercise perturbations (32), these side effects are extremely rare in studies examining consumption of recommended/normal levels of these ingredients in conjunction with exercise perturbations in a controlled setting (Table 5). Although not the form of ginseng discussed in this review, in a review of red ginseng used for the treatment of erectile dysfunction, Jang et al. reported gastric distress with doses from 600 to 900 mg/d, 3 times per day (32). This review also reports headaches and insomnia with red ginseng supplementation at 1,000 mg/d doses, 3 times per day (32). Yohimbine in the powder form (not yohimbe bark) in normal doses (5.4 mg) for the treatment of erectile dysfunction is known to increase nausea, nervousness, abdominal pain, and dizziness (36), as well as induce tachycardia and hypertension with higher doses (15–20 mg) (50). Side effects associated with GTE often mimic those of caffeine, such as heart arrhythmia (11),

Table 5
Anecdotal side effects and empirically reported side effects

	Anecdotal side effects	Side effects in literature
Citrulline	None	None
Agmatine sulfate	Diarrhea and nausea	None
GSE	Headache, dizziness, nausea, possible pharmacological interactions	None
BRJ	Beeturia (discoloration of the urine)	None
Carnitine	Fishy body odor, cramps, nausea	None
BET	↑cholesterol, upset stomach, diarrhea	None
Glucuronolactone	None	None
Glycerol	Anal irritation, burning sensation, diarrhea, gas, rectal bleeding, nausea, stomach cramps	None
Huperzine A	Nausea, diarrhea, vomiting, sweating, blurred vision, slurred speech, restlessness, loss of appetite, cramping, ↑saliva and urine, inability to control urination, high blood pressure, slowed heart rate	None
Yohimbe	Irregular or rapid heartbeat, kidney failure, seizure, heart attack, stomach upset, excitation, tremor, sleep problems, anxiety/agitation, high blood pressure, dizziness, stomach irritation, drooling, sinus pain, irritability, headache, frequent urination, bloating, rash, nausea, vomiting, difficulty breathing, paralysis, very low blood pressure	Nausea, nervousness, abdominal pain, dizziness
Red ginseng	High blood pressure, insomnia, restlessness, anxiety, hypoglycemia, euphoria, diarrhea, vomiting, headache, nosebleed, breast pain, vaginal bleeding	Headache, insomnia, gastric upset, constipation
GTE	Restlessness, irritability, sleeping problems, tremor, heart palpitations, loss of appetite, upset stomach, nausea, frequent urination	Nausea, constipation, abdominal discomfort, ↑blood pressure
ALA	Hunger, weakness, nausea, irritability, tremors, drowsiness, dizziness, headache, confusion, trouble concentrating, sweating, fast heart rate, upset stomach, numbness or tingly feeling, muscle cramps	None
Rhodiola rosea	Dry mouth, blood pressure changes	Jitteriness, sleep interference
Black pepper	Burning aftertaste	None
M. Pruriens	Reduction in smooth muscle contractions, hypotension, slowed heart rate	None
Norvaline	None	None

ALA = alpha lipoic acid; BET = betaine; BRJ = beet root juice; GSE = grape seed extract; GTE = green tea extract.

and can also include constipation and abdominal discomfort (30). When overweight sedentary men and women consumed a drink containing 625 mg of catechins (present in GT), there was one report of increased blood pressure that required hospitalization (53). Finally, a review of *R. rosea* revealed possible jitteriness and complications with sleep (10). Overall, these supportive ingredients in MIPS seem to be safe at the doses commonly consumed in MIPS.

CONCLUSION

The supportive ingredients in MIPS aim to provide beneficial strength and power performance effects through increased blood flow, promotion of protein balance, promotion of metabolism, and protection against oxidative stress. The existing data on these supportive ingredients indicate no major safety issues, and thus, seem to be safe to use. However, evidence regarding performance effects is largely tested with aerobic exercise perturbations and in animals. Even so, there is a small body of growing, supportive evidence substantiating the efficacy and potential potency of some of the aforementioned ingredients (i.e., nitrates, citrulline, BET, glucuronolactone, and

taurine) with a resistance exercise model. Although there are growing evidence-based dosing recommendations of many of the ingredients, this review has shown that many of the commercially available MIPS products do not meet the respective recommendations. In light of these findings, further investigation of individual products containing these supportive ingredients in combination with strength or athletic performance is warranted to better elucidate strength and power outcomes, mechanisms, synergistic effects with other ingredients, and dosing recommendations.

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