

# Military Effectiveness of Five Dietary Supplements Purported to Aid Cognitive and Physical Performance

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## Abstract

**Background:** The effectiveness of dietary supplements in sustaining physical and/or cognitive performance is of interest to the military. *Rhodiola rosea*, long-chain omega-3 fatty acids (LC omega-3), beetroot juice, arginine and beta-alanine have recently been claimed to enhance cognitive and/or physical performance when taken as supplements.

**Purpose:** To narratively review recent research on the military effectiveness and safety of five dietary supplements – *Rhodiola rosea*, long-chain omega-3 fatty acids (LC omega-3), beetroot juice, arginine and beta-alanine.

**Materials and Methods:** The Academy of Nutrition and Dietetics Quality Criteria Checklists were used to assign quality ratings of positive, neutral and negative to reviewed studies.

**Results:** Of the five substances reviewed, only LC omega-3 (commonly known as ‘fish oils’) is considered safe and applicable as a potential supplement for use during both fresh and field feeding. This applies to military members who do not consume the recommended intake of oily fish, whether by choice or because oily fish are not available (e.g. when feeding is with combat rations).

**Conclusions:** Conclusions are drawn on the quality of evidence for beneficial effects on health and/or military performance in the context of sustained arduous training and operations. Although health benefits may result from supplementation with LC omega-3, the available evidence suggests that such supplementation is unlikely to enhance either cognitive or physical performance. A lack of evidence for efficacy and/or possible adverse health outcomes suggest that supplemental use of the other substances reviewed here is not appropriate for military members.

## Introduction

Dietary supplements (abbreviated to ‘supplements’ in the remainder of this report) can be defined as nutrients and other substances that occur naturally in foods and herbs. Military members, particularly soldiers, show interest in many supplements that have been claimed to be effective in sustaining physical and/or cognitive performance. However, such claims are not always based on sound scientific evidence.

Research in this area is relevant not only in guiding the optimal provision of foods in barracks and combat feeding, but also in the potential provision of foods and/or supplements to sustain health and military performance in the long term. In addition, the use of some supplements by military personnel should be cautioned, due to potential risks to health, military performance and/or lack of efficacy.

Various supplements are described by researchers and the supplement industry as ‘adaptogens’ for their purported ability to help the body adapt to stress and aid cognitive performance, or ‘ergogenic aids’ for their purported ability to enhance physical performance. Yet others are claimed to be ‘nootropics’ (boost cognitive performance). Caffeine is an example of a well-understood nootropic that is useful to military members to help sustain alertness during operations<sup>1</sup>. However, few other supplements are currently recommended for military use.

Due to their highly demanding roles, military personnel—Infantry and Special Forces in particular—are often tempted to use dietary supplements to try to enhance their job performance.<sup>2</sup> The self-reported use of supplements of any kind by military personnel in the United States and United Kingdom is in the range 55–61% for males and 65–71% for females<sup>2</sup>. Anecdotal evidence also indicates that dietary use is

highly prevalent in military personnel in Australia. In 2010, The Guide to Herbs and Supplements section of the (US) Warfighter Nutrition Guide cautioned against the use of many dietary supplements claimed to enhance physical and cognitive performance, due to their adverse side effects and/or lack of efficacy<sup>3</sup>.

More recently, substances that have shown potential in the literature to increase physical and/or cognitive performance, including in the military context, include beetroot juice, extract from the herb *Rhodiola rosea*, long-chain omega-3 fatty acids from fish oil, and the amino acids arginine and beta-alanine. Many of these substances have also been claimed to enhance human performance during military-specific activities, thus, their effectiveness is of interest to the military. In many cases, the physiological processes by which these five substances may act as either ergogenic and/or cognitive aids have not been fully elucidated.

However, as with many dietary supplements, recent research relating to the effectiveness is contradictory. This paper reviews recent research (experimental and evaluative) on these five supplements, and discusses the quality of the evidence for their efficacy in the context of sustained military training and operations. The potential harmful effects of each supplement are also discussed.

### Quality Assessment

The quality of studies reviewed was assessed using the Academy of Nutrition and Dietetics Quality Criteria Checklists (Primary Research and Review Article)<sup>4, 5</sup>. Each of these checklists contains four *relevance* questions and ten *validity* questions that assess scientific rigor. They were used to assign a quality rating of *negative* (i.e. mostly weak methodological design), *neutral* (i.e. some strengths and weaknesses in the methodological design) or *positive* (i.e. mostly strengths in the methodological design) to the research used to assess the effectiveness of each supplement. The strongest quality evidence identified in this review is summarised for each supplement in Table 1.

### *Rhodiola rosea*

#### Is *Rhodiola rosea* Extract a Cognitive Aid?

*Rhodiola rosea* is a plant that grows in cold and high-altitude regions of the Arctic. An extract of *Rhodiola rosea*, which contains a substance known as salidroside, has gained the attention of the military due to its claimed ability to enhance cognitive performance by reducing the effects of fatigue in stressful situations<sup>6-8</sup>. The physiological

process by which salidroside may act as a cognitive aid has not been elucidated, however advertisements for *Rhodiola rosea* extract have suggested the supplement is useful for military personnel during operations, especially when fatigued, such as during times of sleep deprivation. Supplementation with *Rhodiola rosea* extract has also been reported to have a beneficial effect on stress related to fatigue<sup>9, 10</sup>.

Of particular relevance to the military, supplementation has been shown to reduce levels of fatigue during stressors such as night duty<sup>6</sup>, and night duty while performing military-related tasks<sup>8</sup>. In total, there is evidence from four studies that support these claimed benefits against fatigue in healthy individuals without a diagnosed mental illness.<sup>6-8, 11</sup> According to the Academy of Nutrition and Dietetics Quality Criteria, these findings arise from studies of positive<sup>6, 8</sup>, and neutral quality<sup>7, 11</sup>.

Two recent review articles (both of positive quality) assessed the bias/quality of the available research on the effects of *Rhodiola rosea* extract on cognitive performance in healthy individuals, and concluded that there is no convincing evidence of benefits<sup>12, 13</sup>. An earlier review study (of neutral quality) concluded that 'a single dose of *Rhodiola rosea* extract prior to acute stress produces favourable results'<sup>14</sup>. However, two of the three authors of this review were employees of a company which sells *Rhodiola rosea* extract, indicating a conflict of interest and hence the potential for bias. Until the reported benefits of *Rhodiola rosea* extract supplementation are replicated by independent researchers, the body of evidence remains unconvincing<sup>12, 13</sup>.

In summary, it is concluded that supplementation with *Rhodiola rosea* extract is unlikely to be of value as a cognitive aid in the military context, and its use should be cautioned due to lack of efficacy. There is no evidence that substantiates a mode of action of the purportedly active substance, salidroside.

### *Rhodiola rosea* Extract and Exercise Performance

Evidence on the effects of *Rhodiola rosea* extract on exercise performance is limited, and findings vary among studies. One recent study (neutral quality) found no benefits to delayed onset of muscle soreness (DOMS) or vertical jump performance<sup>15</sup>. Another recent study (also neutral quality) demonstrated a benefit to performance in a time trial (TT, a measure of endurance performance)<sup>7</sup>. Benefits to time-to-exhaustion (TTE, a measure of endurance capacity) were reported in 2004<sup>16</sup>, but to our knowledge, have not been replicated.

Overall, there is some convincing evidence from a small number of neutral quality studies that *Rhodiola rosea* is effective in sustaining exercise performance. Further research, conducted in a manner that reduces potential for bias, is required.

### Long Chain Omega-3 Fatty Acids

#### What are LC Omega-3 Fatty Acids?

All dietary fats contain a mixture of three types of 'fatty acids'—polyunsaturated (abbreviated to PUFA), monounsaturated and saturated. Omega-3 fatty acids are one form of PUFA, and they are essential in the diet (together with the other major form of PUFA, omega-6 fatty acids). Of special importance to health are the long-chain (LC) omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). These are derived mainly from marine food sources, particularly dark-fleshed fish, so are commonly known as 'fish oils'.

#### How much LC omega-3 do humans need?

In Australia, the Suggested Dietary Target (SDT)—i.e. the daily intake recommended for the prevention of chronic disease based on the available evidence—for LC omega-3 fatty acids is 610 mg for men and 430 mg for women<sup>17</sup>. The mean intake of LC omega-3 in the general Australian population has been estimated at only 189 mg per day<sup>18</sup>. Although military fresh feeding combat rations contain some fish meals, LC omega-3 intakes in military populations have not been estimated. Military members who do not consume the recommended serves of oily fish or an LC omega-3 supplement may therefore have intakes even less than the general population. Low LC omega-3 levels may have deleterious effects, particularly on mood, as discussed in the next subsection.

#### LC Omega-3 and Enhancement of Cognitive Performance

Omega-3 PUFAs are abundant in the brain, and their concentration in brain cells wholly depends on how much is consumed in the diet<sup>19</sup>. LC omega-3 in the brain is an important factor in facilitating many brain processes, including neurotransmission<sup>19</sup>.

LC omega-3 supplementation, with the aim to increase the level of LC omega-3 in the brain, has been investigated for its effects on cognitive performance. However, based on the findings of two recent articles, including one of positive<sup>20</sup>, and one of neutral quality<sup>21</sup>, daily supplementation for between 12 weeks and 3 years does not enhance

cognitive performance/functioning or prevent a decline in cognitive functioning in cognitively healthy older adults<sup>20, 21</sup>. However, some researchers have acknowledged that longer term studies are required in this area<sup>19, 22</sup>.

A small number of studies have investigated the effects of LC omega-3 on cognitive function and mood in younger populations. These studies are of greater relevance to the military population than those discussed above involving older adult populations. A recent review article (neutral quality) found that the available data from randomised controlled trials (RCTs) revealed 'neither robust benefits nor a clear lack of efficacy' and described the evidence as weak and preliminary<sup>23</sup>. Further investigation is warranted and indeed is continuing<sup>23</sup>.

#### Effects of LC Omega-3 on Cognitive Function and Brain Health

Recent research has placed an emphasis on dietary or supplementary intake of LC omega-3 throughout life for general health and to sustain normal cognitive function and brain health in ageing. Researchers Luchtman & Song reviewed studies involving both animals and humans and found that supplementation with LC omega-3 is consistently shown to have protective effects throughout life on neurodegeneration, cognitive impairment and long-term potentiation (the strength of signals in the brain). Thus, further research is required in this area to explain the way in which LC omega-3 exerts these protective effects<sup>22</sup>. Reviews of human studies have emphasised the importance of an adequate dietary intake of LC omega-3<sup>20, 24, 25</sup>.

The effects of LC omega-3 intake—from both supplementation and diet—on various other aspects of cognition have been widely investigated<sup>26-29</sup>. There is strong evidence of a benefit of LC omega-3 supplementation on symptoms of depression in people without a diagnosis of major depressive disorder<sup>27</sup>. Mental health-related benefits of LC omega-3 are of interest in the context of sustained cognitive performance, because negative thoughts may be linked to increased cognitive load and errors in judgement<sup>30</sup>. There is also convincing evidence that a higher intake of LC omega-3 in the diet (and possibly supplementary LC omega-3) are effective in the prevention and treatment of depression<sup>28, 29</sup>.

#### LC Omega-3 and Military Mental Health

The military's interest in the optimal intake of LC omega-3 by military personnel has increased in recent years. Researchers in the U.S. found that male US military personnel on active duty with the

lowest levels of DHA (docosahexaenoic acid) were at a 62% greater risk of suicide than counterparts with higher levels<sup>31</sup>. This and other similar findings led to a recommendation to the U.S. Department of Defense for 'a comprehensive, coordinated research program to evaluate the multiple uses of omega-3 fatty acids'<sup>32</sup>. However, subsequent research involving military service members found no effect of relatively short term (60 days) supplementation on psychological health or cognitive function<sup>33</sup>, and another study found no association between blood LC omega-3 level and levels of depression<sup>34</sup>.

### **LC Omega-3, Inflammation and Physical Performance**

The effect of LC omega-3 supplementation on inflammation has been widely investigated. However, a recent review article (positive quality) found there is a 'lack of evidence' to support the 'use of omega-3 supplementation to reduce inflammatory biomarkers' in healthy individuals<sup>35</sup>. This finding is consistent with a previous review of the evidence<sup>36</sup>.

The effect of LC omega-3 supplementation on physical performance and recovery in the military context was recently reviewed (neutral quality)<sup>37</sup>. It was found that studies reporting positive results for reduced muscle damage and inflammation after physical activity outnumbered those finding no effect. However, it was concluded that there is currently insufficient human data to support the use of LC omega-3 to mitigate the inflammatory and immunologic response to exercise and thus possibly enhance subsequent performance. This is attributed partly to the limited ability to compare findings due to the differing methodologies and dosage protocols used. The use of a single exercise bout to investigate the effect of LC omega-3 on physical performance and recovery has been described as a major limitation in the relevance of the current evidence to the military. Troops are likely to engage in multiple bouts of exercise per day, so the effect may not be strong enough to confer benefits in the military context<sup>37</sup>. Future research involving military personnel should be designed to produce findings which are more applicable to the military. Such experimental designs might include, for example, military personnel engaged in sustained operations in the field, with repeated TTE performance tests throughout.

### **LC Omega-3 Summary**

The effects of LC omega-3 intake on sustained brain and cognitive health are continually being investigated. Currently, the body of research

presents various potential cognition-related benefits of an optimal intake of LC omega-3 by military members, particularly during times of deployment (e.g. cognition related to mental health). While it may be premature to recommend supplementation for cognitive enhancement, it is clear that optimal dietary intake of LC omega-3 is important for brain structure and function throughout life.

Current review evidence indicates that there is insufficient consistent and high-quality evidence to recommend supplementation to reduce physical activity-induced inflammation and soreness in the military context.

It is concluded that all military members who do not eat oily fish may obtain health benefits, but probably not performance benefits, from supplementing with LC omega-3 in the range of the NHMRC SDTs (610 mg for men and 430 mg for women) to 3000 mg per day. This applies to military personnel when they are relying on either fresh foods or combat rations.

### **Beetroot Juice (Inorganic Nitrate)**

Inorganic nitrate, the substance of interest in beetroot juice, is abundant in a healthy diet. Various leafy green and root vegetables are good sources. Beetroot juice has been widely investigated for its ability to increase plasma levels of nitrate ( $\text{NO}_3^-$ ), nitrite ( $\text{NO}_2^-$ ), and nitric oxide (NO)<sup>38, 39</sup>. These compounds are involved in activating vasodilation<sup>40</sup>. Thus, increased plasma levels as a result of drinking beetroot juice may beneficially augment blood flow, oxygen uptake and muscle oxygenation during exercise, leading to performance enhancement<sup>39, 40</sup>.

The use of beetroot juice as an ergogenic supplement has recently been reviewed numerous times (in studies of neutral quality)<sup>39, 41-43</sup>. However, further research was considered necessary in all of these reviews, and one researcher concluded that there are promising findings for '... enhancing aspects of the physiological response to exercise, such as muscle efficiency and oxygenation, which might augment performance'<sup>39</sup>.

### **Beetroot Juice Supplementation, Endurance Performance and the Military**

Military personnel often undertake prolonged physical activity during both training and operations, so substances which are claimed to enhance endurance performance are of military interest. Time-trial (TT) performance—a measure of endurance performance in well-trained individuals—has been used to study the effectiveness of beetroot juice. In a recent review

(neutral quality) of beetroot juice supplementation and TT performance, a meta-analysis of nine studies found an overall 0.9% improvement in TT performance among predominantly well-trained subjects<sup>43</sup>. However, this did not constitute a statistically significant improvement<sup>43</sup>. Even if this is a 'real' effect, it is likely to be valuable only to elite athletes<sup>39</sup>, for whom very small enhancements can mean substantial differences in race results. Such a low level of potential benefit is unlikely to have substantial effect on military performance. Furthermore, TT performance is a more accurate measurement of athletic performance than of military performance, as TT performance is measured in controlled environments over set distances—experimental conditions which aren't characteristic of 'real world' military operations.

### **Beetroot Juice Supplementation and Sustained High-Intensity Exercise Capacity (Endurance Capacity)**

Time to exhaustion (TTE) is a measure of the duration over which an individual can sustain high-intensity exercise, and is a more relevant measure of performance in the military context than TT. Hoon et al. (neutral quality)<sup>43</sup> combined the findings of three studies and showed a significant improvement in TTE at a fixed high-intensity work rate in normoxia (i.e. normal levels of oxygen available at sea level)<sup>43</sup>. These studies all involved supplementation with beetroot juice for six days, providing nitrate in the range 316–384 mg daily. Based on the average weight of participants, this corresponds to approximately 3.9–5.5 mg nitrate / kg of body mass per day<sup>44-46</sup>. However, these researchers instructed participants to exclude foods high in nitrate from their diets. This may have resulted in an overestimation of the physiological effects of nitrate supplementation if participants habitually consumed average or high levels of nitrate from eating vegetables<sup>47</sup>. Furthermore, these studies did not estimate dietary nitrate intakes<sup>44-46</sup>. Dietary intakes are likely to have been variable and therefore the reliability of findings is reduced. In the military context, a lower intake of foods high in dietary nitrate may occur during times of combat feeding.

Importantly, one of the TTE studies that was analysed in the Hoon et al. study involved recreationally active participants<sup>43, 44</sup>—a population subgroup that may not be comparable to Infantry and Special Forces soldiers, who are required to have fitness levels above that of the typical recreationally active civilian. For this reason the findings of the Hoon et al. study have limited applicability to the military. A longer supplementation period and/or higher dose—as suggested for elite athletes—may be required to demonstrate any benefits to soldiers. However,

concerns remain over taking large doses due to the poorly-understood risks to health<sup>39</sup>.

### **Sustaining Endurance Performance with Beetroot Juice in Hypoxic Conditions**

Two studies have found promising effects on endurance performance in hypoxic (low oxygen) conditions through measuring high-intensity exercise capacity<sup>48, 49</sup>. In the first, in which a benefit to TTE was found, the participants were 'young and healthy' and had a mean  $\text{VO}_2$  peak of  $61.7 \pm 2.1$  ml/kg/min, and therefore had fitness levels at or above the fitness level of highly trained military personnel such as Infantry and Special Forces soldiers<sup>48</sup>. In the second, a benefit to high intensity, resistance exercise tolerance was found in participants who were 'moderately trained in recreational sport'<sup>49</sup>. In both of these studies participants were instructed to avoid nitrate-rich foods<sup>48, 49</sup>.

However, there are differing findings in regards to an improvement in endurance performance through TT tests in hypoxic conditions in two papers so far published on this subject. Both of these studies recruited participants who were competitive athletes and had fitness levels similar to or above those of elite military personnel<sup>50, 51</sup>. The first found no benefit to TT performance during hypoxia from six weeks of supplementation at a rate of 4.3 mg / kg Body Mass (BM) / day<sup>50</sup>. In contrast, the second reported a benefit of a single dose of 310 mg of nitrate taken three hours before commencement of the TT<sup>51</sup>. Aside from differences in their dosage protocols, another methodological difference in these studies is that the first instructed participants to avoid nitrate-rich foods for the duration of the study, whereas the second did not. Neither study estimated total dietary nitrate intakes, indicating the possibility of variable intakes between studies<sup>50, 51</sup>. Further investigation of the effect of dietary nitrate intake on endurance exercise performance in hypoxic conditions is warranted.

### **The Safe Intake of Inorganic Nitrate**

The Acceptable Daily Intake (ADI) of nitrate in Europe is up to 3.7 mg / kg BM / day<sup>52, 53</sup>. Doses used in some TTE studies described previously have been above this level, raising questions about the long-term safety of repeated high dosing. Three studies which found beneficial effects of supplementation on TTE in normoxia instructed participants to exclude foods high in nitrate from their diets<sup>44-46</sup>. Consuming the recommended daily intake of 1–2 serves of leafy green vegetables (such as broccoli or spinach) and one 75 g serve of root vegetables such as carrots would constitute a safe level of nitrate intake<sup>54, 55</sup>.

A recent review (neutral quality) concluded that the level of nitrate that has produced beneficial effects can be 'readily consumed within a normal diet', and that there is no evidence that providing supplementation above this level provides greater benefits<sup>39</sup>. Studies typically provide a single dose containing the amount of nitrate that is usually consumed throughout an entire day, and the safety of this manner of nitrate intake has not been demonstrated. A proportion of dietary nitrate is converted into carcinogenic compounds in the stomach<sup>56</sup>. There are opposing findings in the literature regarding the risk of stomach cancer. In addition, although increased risk of other gastrointestinal cancers has not been consistently associated with dietary nitrate intake<sup>38, 56</sup>, concerns do remain.

### **Beetroot Juice and Inorganic Nitrate Summary**

The current evidence in support of a significant improvement to TTE and non-significant improvement to TT performance is characterised by neutral quality evidence, indicating somewhat limited reliability in findings. If nitrate supplementation is studied in the military context—such as during times of field feeding when intake of nitrate-rich vegetables is low—it should be conducted in a manner that mimics the usual Australian dietary intake of nitrate-rich vegetables, and total nitrate intake should not exceed 3.7 mg / kg BM / day. Alongside this, it would be worthwhile to investigate the average nitrate intake of personnel engaged in field training. The potential of beetroot juice (inorganic nitrate) supplementation to enhance military physical performance has not been directly investigated, but current evidence suggests this to be unlikely.

### **Arginine**

Amino acids are the building blocks of protein, and there are 20 amino acids which are used by the human body. In recent years, supplementation with various forms of the amino acid arginine has been trialled for ergogenic effects. To researchers and the supplement industry alike, these are known as: L-arginine; L-arginine hydrochloride; products containing L-arginine combined with other ingredients such as glycine-arginine- $\alpha$ -ketoisocaproic acid (GAKIC); and arginine  $\alpha$ -ketoglutarate (AAKG). The Warfighter Nutrition Guide cautions against the use of products containing a combination of these ingredients, as they are potentially dangerous and their safety is often unknown<sup>3</sup>.

In 2011, a review (neutral quality) concluded that it is premature to recommend the use of L-arginine as an ergogenic aid for healthy and physically active individuals<sup>57</sup>. To our knowledge, convincing evidence

does not exist for an ergogenic effect of L-arginine in highly trained individuals such as Infantry soldiers and Special Forces troops. In 2012, the Human Performance Resource Center—a U.S. Department of Defense initiative responsible for providing evidence-based information on dietary supplements to the U.S. military—estimated that L-arginine has a low-to-moderate potential for ergogenic benefit and that there is a moderate safety concern associated with its use<sup>58</sup>.

### **Arginine's Claimed Mode of Action**

Intake of L-arginine increases the level of nitric oxide in the bloodstream<sup>59</sup>. In theory, supplementation with L-arginine may enhance performance through increasing the availability of nitric oxide, which is involved in activating vasodilation. This occurs during physical activity to increase the delivery of blood and oxygen to the working muscles<sup>40</sup>. One recent article reported that supplementation reduces the amount of oxygen required to undertake moderate intensity exercise<sup>60</sup>, a beneficial result that is inconsistent with the findings of four other studies<sup>61-64</sup>. A common methodological weakness in these studies is that dietary intake of L-arginine by participants was not controlled or estimated, indicating that intakes may have varied between the trials, thereby reducing the reliability of findings.

### **Recent Evidence on Arginine Supplementation and Sustained Physical Performance**

Several studies published between 2010 and 2014 found no significant benefits to physical performance from supplementation with differing forms and dosages of arginine, including arginine<sup>65</sup>, L-arginine<sup>62, 67</sup>, L-arginine hydrochloride<sup>66</sup>, GAKIC<sup>68, 69</sup>, and AAKG<sup>70, 71</sup>. The fitness levels of participants and physical testing protocols varied greatly among these studies. Three involved participants who were either resistance-trained or had previous resistance training experience<sup>66, 69, 71</sup>; one used trained and untrained participants in separate groups<sup>70</sup>; one used 'trained cyclists' as participants<sup>68</sup>; and the remaining three studies involved either 'recreationally' or 'physically' active participants<sup>62, 65, 67</sup>. Thus, the results from these studies have limited applicability to troops with high levels of fitness, such as the Infantry and Special Forces.

### **Arginine Supplementation and Strength Performance**

Two recent studies reported significant benefits to sustained resistance exercise performance in response to an acute dose of GAKIC relative to placebo in resistance trained individuals. These

included an increase in the total work performed during lower body resistance training<sup>72</sup>, and a higher total resistance load<sup>73</sup>. In contrast, four studies that also involved participants with previous resistance training found no significant benefits to resistance exercise performance following differing forms of acute arginine supplementation versus placebo<sup>66, 69-71</sup>. The quality of these studies could not be assessed, due to high variation in methodological design, including differing dosage forms and protocols, and disparate use of dietary controls.

To our knowledge, only three studies have investigated the effects of acute GAKIC supplementation on resistance exercise<sup>69, 72, 73</sup>. These investigations are yet to be replicated by any other research group.

### Arginine Summary

In summary, the use of an acute dose of GAKIC warrants further investigation in resistance exercise in dietary-controlled and monitored conditions to confirm the reported beneficial effects. Six grams of L-arginine (the dose administered in various studies showing benefits) could be readily consumed in a diet including foods high in L-arginine. Such foods include red and white meats, fish, eggs, soy foods including tofu, lentils, legumes, and nuts<sup>74</sup>.

The current scientific evidence is not convincing that enhanced exercise performance results from taking supplements containing arginine. Further investigation is warranted into the effect of acute GAKIC supplementation on strength performance.

### Beta-Alanine

#### Beta-Alanine and Exercise performance

Soldiers undertake resistance training programs to develop the strength required in their Army roles, and may be tempted to use supplements marketed at improving resistance training ability, such as the amino acid beta-alanine. The military's interest in the effectiveness of beta-alanine supplementation in enhancing exercise performance has increased in recent years, particularly in the U.S. This is consistent with the widespread and continuing investigation of beta-alanine's effect on exercise performance, especially in bouts of exercise lasting up to four minutes, and for resistance exercise<sup>75, 76</sup>. Supplementation has been reported to increase the carnosine content in muscle cells, thereby improving the buffering capacity of the muscle during exercise and possibly leading to performance enhancement<sup>76</sup>.

The U.S. Department of Defense recently sponsored an 'evidence-based evaluation of potential benefits

and safety of beta-alanine supplementation for military personnel'. This study (positive quality) concluded that the limited available evidence 'did not support the use of beta-alanine supplementation alone or in combination [with other] products for enhancement of athletic performance or improved recovery from exhaustion in active adults'<sup>77</sup>. The quality of the evidence reviewed varied greatly and many studies were poorly documented, indicating the possibility of bias in the findings. Another recent review (positive quality), found that benefits to exercise performance are characterised by moderate-to-high quality evidence<sup>76</sup>. However, both these reviews found no studies investigating the effect of long-term supplementation on exercise performance<sup>76, 77</sup>. The first review indicated that the lack of long-term studies conducted over several months as a limiting factor in the assessment of benefits<sup>77</sup>, while the second recommended that until long-term studies are conducted to confirm its safety and long-term efficacy, those considering using beta-alanine to enhance physical performance should err on the side of caution<sup>76</sup>.

Reported benefits relevant in the military context include improvements in the number of shots on target, target engagement speed, and jump power<sup>78</sup>. However, these benefits have not been replicated.

Military members should also be aware of the issue of safety—harmful effects of acute use of beta-alanine may include paraesthesia (a tingling sensation) in hands and fingers<sup>76, 77</sup>. This would likely have a detrimental effect on military performance (e.g. shooting accuracy), therefore the use of beta-alanine as a dietary supplement is not recommended.

The use of supplementary beta-alanine, either alone or in combination with other supplements, is not appropriate due to lack of efficacy and the potential for detrimental side effects.

### Limitations

It is beyond the scope of this study to capture the entire breadth of research that has been conducted on each of the supplements reviewed. However the findings provide an update on recent research relating to the military effectiveness of each dietary supplement in enhancing physical and cognitive performance.

### Conclusions

In summary, of the five substances reviewed here, only LC omega-3 is considered safe and applicable for supplementation—to SDT levels—in fresh and

combat feeding of military members who do not consume the recommended intake of oily fish. Recent neutral–positive quality evidence suggests that cognitive and physical enhancement from this is unlikely; however, there is mounting evidence for benefits to sustaining brain function and mental health throughout life.

No other substances reviewed here currently show potential for cognitive and/or physical sustainment or enhancement. L-arginine, beetroot juice (inorganic nitrate), and beta-alanine appear to

be already present in the diet of military members in adequate quantities for optimal physical and cognitive performance. Military members should not expect benefits to cognitive or physical performance from supplements containing these substances. There are chronic safety concerns associated with the use of beetroot juice and acute safety concerns associated with the use of beta-alanine supplements. Accordingly, health professionals should caution the use of L-arginine, beetroot juice (inorganic nitrate) and beta-alanine by military personnel for lack of efficacy and/or deleterious side effects.

Table 1. Summary of Findings

Supplement Name	Effectiveness	Potential Harmful Effects	Strength of Evidence	Dose / time course & administration method	Potential applicability to the Military
<b>Rhodiola rosea Extract</b>	<i>Rhodiola rosea</i> has not been demonstrated to be an effective cognitive or ergogenic aid.	Infrequent potential side effects include minor and severe headaches, hypersalivation, and insomnia. The vast majority of people appear to experience no side effects <sup>12</sup> .	Two recent positive quality review studies do not support effectiveness as a cognitive aid <sup>12, 13</sup> .	Oral dose, such as 170 mg daily, containing approximately 4.5 mg of the (purportedly active) ingredient salidroside.	Not applicable.
<b>LC (Long Chain) Omega-3</b>	As a cognitive aid: ineffective in enhancing cognitive performance in older adults when taken for between three months and three years and in younger adults when taken between four and twenty-six weeks <sup>20, 21, 23</sup> .  There is good evidence for LC omega-3 reducing depressive symptomatology <sup>28, 29</sup> .  As an ergogenic aid:  There is no convincing evidence to support a reduction in the inflammatory or immunologic response to exercise and thus increasing the speed of recovery and enhancing subsequent performance <sup>37</sup> .	No known harmful effects in dosages up to 3 g per day. No risk of increased bleeding from injury at this level.	As a cognitive aid: one positive quality review study and two neutral quality review studies do not support the use of LC omega-3 to enhance cognitive performance <sup>20, 21, 23</sup> .  As an ergogenic aid: not conclusively shown to reduce inflammation (delayed onset of muscle soreness) and enhance subsequent exercise performance in one positive quality and one neutral quality review study <sup>35, 37</sup> .	Oral doses in the range 550–2400 mg of combined EPA and docosahexaenoic acid (DHA) daily <sup>23</sup> .  Good dietary sources include dark-fleshed fish.	Increased inclusion in fresh and combat feeding would be appropriate. This should be aimed at achieving the Suggested Dietary Target (610 mg for men and 430 mg for women) <sup>17</sup> .  Omega-3 is an essential nutrient that is currently likely to be consumed at sub-optimal levels in the military for general health (e.g. for cardiovascular, mental, and possibly brain and cognitive health).



<p><b>Beetroot Juice / Dietary (inorganic) Nitrate Supplements</b></p>	<p>Effectiveness in sustaining physical performance in the military context has not been directly investigated.</p> <p>One report of increased time-to-exhaustion (TTE, i.e. endurance capacity) has little relevance to troops due to the low fitness level of individuals in whom benefits have been observed<sup>44</sup>, whilst two other reports of increased TTE have involved individuals with fitness levels of greater relevance to troops<sup>45, 46</sup>.</p>	<p>Caution is necessary due to potential for long-term harmful effects. The Acceptable Daily Intake (ADI) in Europe is 0.0–3.7 mg per kg of body weight per day<sup>47, 52</sup>.</p>	<p>Not strong. The meta-analysis reporting significant benefit to TTE from pooled analysis of three studies is characterised by neutral quality<sup>43</sup>.</p>	<p>Chronic supplementation: single oral dose in the 24 h before exercise, or daily for six weeks<sup>50</sup>.</p> <p>Acute supplementation: single oral dose 1–3 h before exercise.</p> <p>For both acute and chronic protocols, 300–380 mg or 3.9–5.5 mg of nitrate per kg of body mass per day is commonly used.</p>	<p>Potential to enhance military physical performance has not been directly investigated, but current evidence suggests this to be unlikely.</p> <p>Supplementation is not applicable and military members should adhere to the ADI.</p>
<p><b>L-arginine, L-Arginine Hydrochloride and glycine-arginine-ketoisocaproic acid (GAKIC)</b></p>	<p>Not effective in enhancing aerobic exercise performance. Inconclusive evidence.</p>	<p>L-arginine: acute doses are well tolerated, with side effects rarely reported<sup>57</sup>.</p> <p>GAKIC: no side effects have been reported from acute GAKIC supplementation<sup>69</sup>; however, confirmatory studies need to be conducted regarding safety.</p>	<p>There are differing methodologies and inconsistent demonstration of significant benefits in the literature on strength performance. Overall, the evidence in support of benefits is weak.</p>	<p>Acute doses: taken orally 40–80 minutes before exercise.</p> <p>Oral L-arginine doses studied are in the range 500–750 mg per kg of body weight or 2–6 g total.</p> <p>Oral glycine-arginine- ketoisocaproic acid (GAKIC) doses studied are in the range 10.2–11.2 g.</p>	<p>Supplementation is not applicable.</p>
<p><b>Beta-Alanine</b></p>	<p>As an ergogenic aid: ineffective in enhancing exercise performance in trained individuals<sup>77</sup>.</p> <p>As a cognitive aid: there is some evidence to support the claimed decrease in subjective feelings of fatigue and perceived exhaustion<sup>76</sup>, however this is unconvincing.</p>	<p>Harmful effects of acute use may include paraesthesia (a tingling sensation) in hands and fingers<sup>76, 77</sup>. This would likely have a detrimental effect on troops in their military roles, therefore use is cautioned against.</p>	<p>Recent positive quality review evidence does not support the use of beta-alanine to enhance exercise performance or recovery<sup>77</sup>.</p>	<p>Oral dosages vary between 800 and 1600 mg 2–4 times / day (a total of 1.6 to 6.4 g / day)<sup>77</sup>.</p>	<p>Supplementation is not applicable; however research appears to be continuing.</p>

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### References

1. Caldwell, J & Caldwell, JL. Fatigue in military aviation: an overview of US military-approved pharmacological countermeasures. *Aviat Space Environ Med.* 2005; 76(1):39-51.
2. Knapik, JJ, Steelman, RA, Hoedebecke, S et al. A systematic review and meta-analysis on the prevalence of dietary supplement use by military personnel. *BMC Complement Altern Med.* 2014;14(1):143.
3. Deuster, PA, Thomasos, CJ, and Minnick C. Warfighter Nutrition Guide, USU Consortium for Health and Military Performance; Undated [cited 2014 September 24]. Available from: <http://www.usuhs.mil/mem/chnutrition.html>
4. American Dietetic Association (now Academy of Nutrition and Dietetics). *ADA Evidence Analysis Manual: Scientific Affairs and Research*, Chicago; 2005.
5. Academy of Nutrition and Dietetics. *Evidence Analysis Manual: Steps in the Academy Evidence Analysis Process: Scientific Affairs and Research*, Chicago; 2012.
6. Darbinyan, V, Kteyan, A, Panossian, A et al. Rhodiola rosea in stress induced fatigue—a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. *Phytomedicine*; 2000;7(5):365-371.
7. Noreen, EE, Buckley, JG, Lewis, SL et al. The effects of an acute dose of Rhodiola rosea on endurance exercise performance. *J Strength Cond Res.* 2013;27(3):839-847.
8. Shevtsov, V, Zholus, B, Shervarly, V et al. A randomized trial of two different doses of a SHR-5 Rhodiola rosea extract versus placebo and control of capacity for mental work. *Phytomedicine.* 2003;10(2):95-105.
9. Olsson, EM, von Schéele, B, and Panossian, AG. A randomised, double-blind, placebo-controlled, parallel-group study of the standardised extract shr-5 of the roots of Rhodiola rosea in the treatment of subjects with stress-related fatigue. *Planta Med.* 2009;75(2): 105-112.
10. Ross, SM. Rhodiola rosea (SHR-5), part I: a proprietary root extract of Rhodiola rosea is found to be effective in the treatment of stress-related fatigue. *Holist Nurs Pract*, 2014;28(2): 149-154.
11. Edwards, D, Heufelder, A, and Zimmermann, A. Therapeutic Effects and Safety of Rhodiola rosea Extract WS® 1375 in Subjects with Life stress Symptoms—Results of an Open label Study. *Phytother Res.* 2012;26(8):1220-1225.
12. Ishaque, S, Shamseer, L, Bukutu, C et al. Rhodiola rosea for physical and mental fatigue: a systematic review. *BMC Complement Altern Med.* 2012 [cited 2014 August 26];12(1). Available from: <http://www.biomedcentral.com/1472-6882/12/70>
13. Hung, SK, Perry, R, and Ernst, E. The effectiveness and efficacy of Rhodiola rosea L.: a systematic review of randomized clinical trials. *Phytomedicine*, 2011;18(4):235-244.
14. Panossian, A, Wikman, G, and Sarris, J. Rosenroot (Rhodiola rosea): traditional use, chemical composition, pharmacology and clinical efficacy. *Phytomedicine.* 2010;17(7): 481-493.
15. Shanely, RA, Nieman, DC, Zwetsloot, KA et al. Evaluation of Rhodiola rosea supplementation on skeletal muscle damage and inflammation in runners following a competitive marathon. *Brain Behav Immun.* 2014;39:204-210.
16. De Bock, K, Eijnde, BO, Ramaekers, M et al. Acute Rhodiola rosea intake can improve endurance exercise performance. *Int J of Sport Nutr Exerc Metab.* 2004;14(3):298-307.
17. Australian Government. *Nutrient Reference Values for Australia and New Zealand*. Department of Health and Ageing; National Health and Medical Research Council (NHMRC). Canberra: Australian Government; 2006.
18. Meyer, BJ, Mann, NJ, Lewis, JL et al. Dietary intakes and food sources of omega-6 and omega-3 polyunsaturated fatty acids. *Lipids.* 2003;38(4): 391-398.

19. Haag, M. Essential fatty acids and the brain. *Can J Psychiatry*. 2003;48(3):195-203.
20. Sydenham, E, Dangour, AD, and Lim, W-S. Omega 3 fatty acid for the prevention of cognitive decline and dementia. *The Cochrane Database of Systematic Reviews*. 2012;6(CD005379).
21. Mazereeuw, G, Lanctôt, KL, Chau, SA et al. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. *Neurobiol Aging*. 2012;33(7):1482.
22. Luchtman, DW and Song, C. Cognitive enhancement by omega-3 fatty acids from child-hood to old age: findings from animal and clinical studies. *Neuropharmacology*. 2013;64:550-565.
23. Muldoon, MF, Ryan, CM, Yao, JK et al. Long-chain omega-3 fatty acids and optimization of cognitive performance. *Mil Med*. 2014;179(11S):95-105.
24. Karr, JE, Alexander, JE, and Winningham, RG. Omega-3 polyunsaturated fatty acids and cognition throughout the lifespan: a review. *Nutr Neurosci*. 2011;14(5):216-225.
25. Denis, I, Potier, B, Vancassel, S et al. Omega-3 fatty acids and brain resistance to ageing and stress: body of evidence and possible mechanisms. *Ageing Res Rev*. 2013;12(2):579-594.
26. Bauer, I, Crewther, S, Pipingas, A et al. Does omega 3 fatty acid supplementation enhance neural efficiency? A review of the literature. *Hum Psychopharmacol Clin Exp*. 2014;29(1):8-18.
27. Grosso, G, Pajak, A, Marventano, S et al. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PloS one*. 2014;9(5):1-18.
28. Hibbeln, JR, Nieminen, LR, Blasbalg, TL et al. Healthy intakes of n- 3 and n- 6 fatty acids: estimations considering worldwide diversity. *American J Clin Nutr*. 2006;83(6S):1483-1493.
29. Coulter, ID. The response of an expert panel to nutritional armor for the warfighter: can omega-3 Fatty acids enhance stress resilience, wellness, and military performance? *Mil Med*. 2014;179(11S):192-198.
30. Takano, K, Iijima, Y, Sakamoto, S et al. Exploring the cognitive load of negative thinking: A novel dual-task experiment. *J Behav Ther Exp Psychiatry*. 2014;45(4):435-440.
31. Lewis, MD, Hibbeln, JR, Johnson, JE et al. Suicide deaths of active duty US military and omega-3 fatty acid status: a case control comparison. *J Clin Psychiatry*. 2011;72(12):1585-1590.
32. Lewis, MD and Bailes, J. Neuroprotection for the warrior: dietary supplementation with omega-3 fatty acids. *Mil Med*. 2011;176(10):1120-1127.
33. Dretsch, MN, Johnston, D, Bradley, RS et al. Effects of Omega-3 Fatty Acid Supplementation on Neurocognitive Functioning and Mood in Deployed US Soldiers: A Pilot Study. *Mil Med*. 2014;179(4):396-403.
34. Johnston, DT, Deuster, PA, Harris, WS et al. Red blood cell omega-3 fatty acid levels and neurocognitive performance in deployed US Servicemembers. *Nutr Neurosci*. 2013;16(1):30-38.
35. Khorsan, R, Crawford, C, Ives, JA et al. The Effect of Omega-3 Fatty Acids on Biomarkers of Inflammation: A Rapid Evidence Assessment of the Literature. *Mil Med*. 2014;179(11S):2-60.
36. Rangel-Huerta, OD, Aguilera, CM, Mesa, MD et al. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomarkers: a systematic review of randomised clinical trials. *Br J Nutr*. 2012;107(2S):159-170.
37. Shei, R-J, Lindley, MR, and Mickleborough, TD. Omega-3 polyunsaturated fatty acids in the optimization of physical performance. *Mil Med*. 2014;179(11S):144-156.
38. Habermeyer, M, Roth, A, Guth, S gel, KH et al. Nitrate and nitrite in the diet: How to assess their benefit and risk for human health. *Mol Nutr Food Res*. 2015;59(1):106-128.
39. Jones, AM. Dietary nitrate supplementation and exercise performance. *Sports Med*. 2014a ;44(1):35-45.
40. Casey, DP, Walker, BG, Ranadive, S et al. Contribution of nitric oxide in the contraction-induced rapid vasodilation in young and older adults. *J Appl Physiol*. 2013;115(4):446-455.
41. Jones, AM. Influence of dietary nitrate on the physiological determinants of exercise performance: a critical review 1. *Appl Physiol Nutr Metab*. 2014b;39(9):1019-1028.
42. Ormsbee, MJ, Lox, J, and Arciero, PJ. Beetroot juice and exercise performance. *J Int Soc Sports Nutr*. 2013;5(S):27-35.
43. Hoon, MW, Johnson, NA, Chapman, PG et al. The effect of nitrate supplementation on exercise performance in healthy individuals: a systematic review and meta-analysis. *Int J Sport Nutr Exerc Metab*. 2013;23(5):522-532.

44. Bailey, SJ, Winyard, P, Vanhatalo, A. et al. Dietary nitrate supplementation reduces the O<sub>2</sub> cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans. *J Appl Physiol.* 2009;107(4):1144-1155.
45. Bailey, SJ, Fulford, J, Vanhatalo, A. et al. Dietary nitrate supplementation enhances muscle contractile efficiency during knee-extensor exercise in humans. *J Appl Physiol.* 2010a;109(1):135-148.
46. Lansley, KE, Winyard, PG, Fulford, J. et al. Dietary nitrate supplementation reduces the O<sub>2</sub> cost of walking and running: a placebo-controlled study. *J Appl Physiol.* 2011;110(3):591-600.
47. Haider, G and Folland, JP. Nitrate supplementation enhances the contractile properties of human skeletal muscle. *Med Sci Sports and Exerc.* 2014;46(12):2234-2243.
48. Masschelein, E, Van Thienen, R, Wang, X. et al. Dietary nitrate improves muscle but not cerebral oxygenation status during exercise in hypoxia. *J Appl Physiol.* 2012;113(5):736-745.
49. Vanhatalo, A, Fulford, J, Bailey, SJ. et al. Dietary nitrate reduces muscle metabolic perturbation and improves exercise tolerance in hypoxia. *J Physiol.* 2011;589(22):5517-5528.
50. Puype, J, Ramaekers, M, Van Thienen, R. et al. No effect of dietary nitrate supplementation on endurance training in hypoxia. *Scand J Med Sci Sports.* 2014;25(2):234-241.
51. Muggeridge, DJ, Howe, CC, Spendiff, O. et al. A single dose of beetroot juice enhances cycling performance in simulated altitude. *Med Sci Sports Exerc.* 2014;46(1):143-50.
52. FAO/WHO (Food and Agriculture Organisation / The United Nations/World Health Organization). Nitrate (and potential endogenous formation of N-nitroso compounds). WHO Food Additive series 50 [Internet]; 2003 [cited 2015 January 5]. Available from:  
< <http://www.inchem.org/documents/jecfa/jecmono/v50je06.htm#1.0>>
53. EFSA (European Food Safety Authority). Nitrate in vegetables: scientific opinion of the panel on contaminants in the food chain. *The EFSA Journal.* 2008;689:1-79.
54. Australian Government. Australian Dietary Guidelines - Providing the scientific evidence for healthier Australian diets. Department of Health and Ageing: National Health and Medical Research Council (NHMRC). Canberra: Australian Government; 2013
55. Santamaria, P. Nitrate in vegetables: toxicity, content, intake and EC regulation. *J Sci Food Agric.* 2006;86(1):10-17.
56. Keszei, AP, Goldbohm, RA, Schouten, LJ. et al. Dietary N-nitroso compounds, endogenous nitrosation, and the risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. *Am J Clin Nutr.* 2013;97(1):135-146.
57. Alvares, TS, Meirelles, CM, Bhambhani, YN. et al. L-Arginine as a Potential Ergogenic Aid in Healthy Subjects. *Sports Med.* 2011;41(3):233-248.
58. HPRC (Human Performance Research Centre). L-Arginine [Internet], 2012 [cited 2015 Jan 5]. Available from:  
<[http://hprc-online.org/dietary-supplements/dietary-supplement-classification-system-1/class-8-supplements/copy3\\_of\\_branched-chain-amino-acids](http://hprc-online.org/dietary-supplements/dietary-supplement-classification-system-1/class-8-supplements/copy3_of_branched-chain-amino-acids)>
59. Rhodes, P, Leone, A, Francis, P. et al. The L-arginine: nitric oxide pathway is the major source of plasma nitrite in fasted humans. *Biochem Biophys Research Commun.* 1995;209(2):590-596.
60. Bailey, SJ, Winyard, PG, Vanhatalo, A. et al. Acute L-arginine supplementation reduces the O<sub>2</sub> cost of moderate-intensity exercise and enhances high-intensity exercise tolerance. *J Appl Physiol.* 2010b;109(5):1394-1403.
61. Camic, CL, Housh, TJ, Mielke, M. et al. The effects of 4 weeks of an arginine-based supplement on the gas exchange threshold and peak oxygen uptake. *Appl Physiol Nutr Metab.* 2010;35(3):286-293.
62. Vanhatalo, A, Bailey, SJ, DiMenna, FJ. et al. No effect of acute l-arginine supplementation on O<sub>2</sub> cost or exercise tolerance. *Eur J Appl Physiol.* 2013;113(7):1805-1819.
63. Forbes, SC, Harber, V, and Bell, GJ. The acute effects of L-arginine on hormonal and metabolic responses during submaximal exercise in trained cyclists. *Int J Sport Nutr Exerc Metab.* 2013;23(4):369-377.
64. Sunderland, KL, Greer, F, and Morales, J. VO<sub>2</sub>max and ventilatory threshold of trained cyclists are not affected by 28-day l-arginine supplementation. *J Strength Cond Res.* 2011;25(3):833-837.
65. Olek, R, Ziemann, E, Grzywacz, T. et al. A single oral intake of arginine does not affect performance during

- repeated Wingate anaerobic test. *J Sports Med and Phys Fitness*. 2010;50(1):52-56.
66. Álvares, TS, Conte Jr, CA, Paschoalin, VMF et al. Acute l-arginine supplementation increases muscle blood volume but not strength performance. *Appl Physiol Nutr Metab*. 2012;37(1):115-126.
67. da Silva, DVT, Conte-Junior, CA, Paschoalin, VMF et al. Hormonal response to L-arginine supplementation in physically active individuals. *Food Nutr Res*. 2014 [cited 2014 October 7];58:22569. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3967014/>
68. Beis, L, Mohammad, Y, Easton, C et al. Failure of Glycine-arginine-[alpha]-ketoisocaproic acid to improve high intensity exercise performance in trained cyclists. *Int J Sport Nutr Exerc Metab*. 2011;21(1):33-39.
69. Kavazis, AN, Wax, B, and Harris, MC. Effects of glycine-arginine- ketoisocaproic acid on muscular force and endurance. *Archives of Exercise in Health and Disease*. 2012;3(3):200-206.
70. Wax, B, Kavazis, AN, Webb, HE et al. Acute L-arginine alpha ketoglutarate supplementation fails to improve muscular performance in resistance trained and untrained men. *J Int Soc Sports Nutr*. 2012 [cited 2014 October 7];9(1). Available from: <http://www.jissn.com/content/9/1/17>  
doi: 10.1186/1550-2783-9-17
71. Greer, BK and Jones, BT. Acute arginine supplementation fails to improve muscle endurance or affect blood pressure responses to resistance training. *The Journal of Strength & Conditioning Research*. 2011;25(7):1789-1794.
72. Wax, B, Kavazis, AN, Brown, SP et al. Effects of supplemental GAKIC ingestion on resistance training performance in trained men. *Res Q Exerc Sport*. 2013a;84(2):245-251.
73. Wax, B, Hilton, L, Vickers, B et al. Effects of Glycine-Arginine- Ketoisocaproic Acid Supplementation in College-Age Trained Females during Multi-Bouts of Resistance Exercise. *J Diet Suppl*. 2013b;10(1):6-16.
74. United States Department of Agriculture Research Service. National Nutrient Database for Standard Reference Release 27, Nutrient Lists [Internet]. Undated [cited 2015 January 5], Available from: <http://ndb.nal.usda.gov/ndb/nutrients/report?nutrsort=511&max=25&offset=0&nutrient1=505&nutrient2=511&nutrient3=&measureby=m&fg=&subset=0&sort=c&totCount=5096>
75. Hobson, RM, Saunders, B, Ball, G et al. Effects of -alanine supplementation on exercise performance: a meta-analysis. *Amino Acids*. 2012;43(1):25-37.
76. Quesnele, JJ, Laframboise, MA, Wong, JJ et al. The effects of beta-alanine supplementation on performance: a systematic review of the literature. *Int J of Sport Nutr Exerc Metab*. 2014;24(1):14-27.
77. Ko, R, Dog, TL, Gorecki, DK et al. Evidence-based evaluation of potential benefits and safety of beta-alanine supplementation for military personnel. *Nutr Rev*. 2014;72(3):217-225.
78. Hoffman, JR, Landau, G, Stout, JR et al. -alanine supplementation improves tactical performance but not cognitive function in combat soldiers. *J Int Soc Sports Nutr*. 2014 [cited 2014 October 7];11(1). Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3983672/>  
doi: 10.1186/1550-2783-11-15.