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Review Article

Ingredient Dosing within Dietary Supplements: Are You Getting Enough?

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Abstract

The use of dietary supplements is commonplace for many adults living within industrialized nations. While not a guarantee, the adoption of current Good Manufacturing Practices (cGMPs) has helped to ensure that the products being produced and sold include ingredients as claimed on the product label, at the stated dosages. However, the dosing of ingredients can vary considerably across products, with some products containing dosages that are lower than the research efficacious dose. Consumers need to understand that discrepancies in dosing between products are common and learn how to identify products that contain the correct dosage based on the cited research studies. This article focuses on the often-expressed concern over varied dosing within dietary supplements. A review of selected ingredients is included, as well as the authors' viewpoint on how this issue can be addressed by consumers.

Keywords: Ingredient; Dosing; Dietary Supplements

Introduction

Although whole food and calorie-containing beverages have long been thought to provide adequate nutrients, many adults living within the industrialized world consume one or more dietary supplements each day. While the most commonly known product may be a multi-vitamin/mineral supplement, other novel supplements are used for a wide variety of purposes, including sport performance and recovery [1], weight loss [2], assistance with sleep and increased "energy" levels [3], general wellness [4], and disease prevention and management [5].

A dietary supplement is defined by the Dietary Supplement Health and Education Act (DSHEA) of 1994 as, "a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid or a dietary substance for use by man to supplement the diet by increasing the total dietary intake or a concentrate, metabolite, constituent, extract or combination of the above ingredients".

Of course, the above description provides latitude for a wide variety of products to be produced and sold. Moreover, there is no specific guidance regarding the dosage of ingredients that need to be included within a given formula. Therefore, in some cases, companies prey on the lack of consumer knowledge and include popular and "in demand" ingredients within their products but do so at relatively low dosages. This may be due in part to the often-higher costs of novel ingredients and the unwillingness of companies to include the correct dosage based on the economic downside of doing so. The consumer ends up with a product that is inferior based on the low dosage of ingredients included; a product that will unlikely deliver the desired result based on the advertised claims.

Research to Support Dietary Supplements

Over the past several years, there has been an effort to increase the number of pre-clinical and clinical studies focused on dietary supplements, with studies including outcomes specific to both safety and efficacy. The National Institutes of Health have an office exclusively for the purpose of reviewing and supporting proposals in this area (https://ods.od.nih.gov). Moreover, many contract research organizations and university research laboratories now conduct studies of dietary supplements, rather than simply pharmaceutical agents, as has been traditionally done. This has been largely fueled by consumer interest in dietary supplements and the demand for scientifically validated products. Additionally, many governing agencies such as the European Food and Safety

Authority (EFSA) and the US Food and Drug Administration (FDA) either require or strongly encourage that clinical studies are available to support the health claims that companies make specific to the product of sale. Collectively, this has increased companies' interest and willingness to fund research studies to support the safety and efficacy of their products.

Research Supported Dosage vs. Product Dosage

It should be understood that in many cases, actual finished products of sale are not investigated. Rather, the individual ingredients contained within the product of sale may be the focus of the research studies. In this way, data specific to the dosage of the ingredient needed to produce the desired effect can be determined. While this is helpful, the companies who produce the ingredient then typically sell the ingredient to other companies for inclusion within their product of sale. This is where problems may arise. Specifically, concerns exist pertaining to the use of less than optimal dosages of the ingredient being included within the finished product of sale.

For starters, the ingredient may be too costly, and the company may decide that it is not economical to include the ingredient at the needed dosage. Therefore, a decision is made to include the ingredient within the product but often at a much lower dosage than what may be needed. This allows for the ingredient to be listed on the product label, which aids in marketing. However, at the much lower dosage, the actual finished product may not deliver nearly the results as what was noted in the clinical studies when using the higher dosage. In addition, due to the limits on how much of the actual ingredient (e.g. powder) can be included within dietary supplement capsules or tablets, manufacturers may decide to lower the dosage in order to accommodate typical consumer interest in ingesting a certain number of capsules/tablets per day. For example, if the required dosage of an ingredient is 5000 mg, the consumer may need to ingest six or more capsules in order to obtain that amount, not considering other ingredients that may need to be included within the product. This means that a 30-days supply would require 180 capsules per bottle, which is rare. Companies understand that most consumers want to purchase bottles of 60 or 90 capsules and ingest 2 or 3 capsules per day maximum. Considering this, decisions may be made to limit the dosage of said ingredient. The above scenarios need to be considered by consumers when selecting dietary supplements for use. Care must be taken to screen products for dosing based on the scientific evidence for effectiveness. The examples below highlight the variance that can be seen when comparing different products containing the same ingredient.

Example Dosing in Dietary Supplements

To better highlight the range in dosing between selected products being sold on the market today, we present a sample of ingredients which are included as "stand-alone" products, as well as imbedded within finished dietary supplements. The particular example ingredients in this discussion were selected because they are popular at the present time, are of interest to many consumers for a variety of reasons and are often included in many commercially available products. Included in our discussion are popular vitamins and minerals, ingredients marketed to promote general health, and those ingredients targeted more towards exercise/sport-specific purposes. A brief overview of each ingredient is included, as well as a synopsis of our findings pertaining to the dosage shown through research studies to be efficacious and the dosage commonly used within products sold on the market today.

Products were investigated through various online and retail vitamin/supplement stores within the local Memphis, TN area. The dosage for each ingredient was determined based on the information provided within the products' nutrition label. However, it should be noted that for novel ingredients, companies sometimes include these as part of "proprietary blends" and therefore, exact dosing is unknown. The sample size of the products observed range from 4 - 15, with 15 being the desired and maximum sample size. Mean and standard deviation values were calculated for the dosage of each ingredient. Table 1 presents a summary of our findings for each ingredient.

Ingredient	Stand Alone Sample Size†	Stand Alone Mean	Stand Alone SD	Blended Sample Size†	Blended Mean	Blended SD	RDI Male	RDI Female	RDI Pregnant or Breast Feeding	Research Dosage (units)
Vitamin C	14	1156	1091	14	1091	100	> 18 years: 90 mg	> 18 years: 75 mg	120 mg	1 - 3 (grams)
Vitamin D_3	15	2860	2416	15	2287	1792	> 18 years: 600 - 700 IU	>18 years: 600 - 800 IU	600 IU	600 - 2000 (IU)
Vitamin E	7	571	355	5	409	229	> 18 years: 15 mg	> 18 years: 15 mg	19 mg	400 - 1000 (IU)
Calcium	5	1040	89	12	949	310	> 18 years: 1g	> 18 years: 1g	1.3 g	500 - 2000 (mg)

DHA and EPA	N/A**	N/A**	N/A**	15	1126	724	N/A (250 mg)	N/A (250 mg)	N/A	1 - 4 (grams)
Garcinia Cambogia	4	888	429	12	904	268	N/A	N/A	N/A	1586 mg/ kg/bw*
EGCG	6	339	210	8	133	77	N/A	N/A	N/A	200 - 300 (mg)
Resveratol	6	333	189	9	330	397	N/A	N/A	N/A	1 - 5 (grams)
CoQ10	14	204	175	11	120	74	N/A	N/A	N/A	300 (mg)
L - Carnitine	8	806	312	5	701	540	N/A	N/A	N/A	2 - 4 (grams)
Methylsulfonyl - methane	15	1147	424	12	875	811	N/A	N/A	N/A	2 - 4 (grams)
Ornithine Alpha - Keto-glutarate	6	1300	1000	15	1132	1265	N/A	N/A	N/A	5 - 20 (grams)
Creatine Hydrochloride	15	1234	816	15	1615	609	N/A	N/A	N/A	N/A
Betaine	15	1585	983	15	2152	635	N/A	N/A	N/A	2.5 - 6 (grams)
Beta - Hydroxy Beta - methyl-butyric	15	2650	885	9	2367	1257	N/A	N/A	N/A	3 (grams)
D Aspartic Acid	15	3023	47	15	2241	1105	N/A	N/A	N/A	2 - 4 (grams)
Glucosamine	15	1291	411	15	1400	338	N/A	N/A	N/A	1000 (mg)

Table 1: Dosages of popular ingredients included within dietary supplements.

†The sample size is the number of products evaluated and used for computing the mean and SD values.

* Research is conflicting on this specific supplement and the majority of work has been conducted on rats; however, this is the average of mmol/IU/mg per kg used in research experiments.

** DHA and EPA indicated as N/A because no "stand-alone" products currently exist for either supplement. They are combined together as a collective product, with a combined dosage of approximately 1 gram for most products.

Ingredients Investigated

Vitamin C: Vitamin C, also known as ascorbic acid, is one of the most widely used dietary supplements in history. It has multiple proposed benefits including enhanced immunity and support of exercise recovery. Vitamin C is found in high quantities within red peppers, oranges and orange juice, grapefruit, and many other fruits and vegetables. Due to its status as a vitamin, it contains a Reference Daily Intake (RDI) value of 75 mg for women and 90 mg for men over the age of 18. The upper intake level (UL) for both women and men is 2000 mg, as well as for women who are pregnant or lactating. However, vitamin C toxicity is rare and consumption of vitamin C in high doses is not believed to cause serious side effects. Diarrhea and gastrointestinal disturbances caused by the osmotic effect of the unabsorbed vitamin C are the most commonly reported side effects from high-dose vitamin C consumption [6].

Research dosages of vitamin C vary considerably depending on the outcome measure of interest; however, common dosing is between 1 - 3 grams daily. Most multi-vitamin/mineral preparations contain vitamin C at or slightly above the RDI. Stand-alone products of vitamin C can be found in much higher quantities, from 500 - 5000 mg. In our review, the mean value from the observed vitamin C stand-alone products was 1156 mg. Vitamin C is often blended within finished dietary supplements, with mean values that are similar to the stand-alone products (i.e. 1091 mg). For this vitamin, it appears that consumers are being sold products that contain a dosage which can be expected to deliver favorable outcomes. This may be due to the relatively low cost of vitamin C, in addition to the consumers' awareness of this vitamin and expected dosing.

Vitamin D_3: Vitamin D is well known for its role in calcium metabolism, bone development, and muscle function. In recent years, vitamin D has been attributed to having a role in non-skeletal diseases such as autoimmune diseases, cancer, cardiovascular disease, and diabetes [7-10]. Furthermore, a potential role of vitamin D on glucose tolerance and insulin resistance has recently been well described [11]. Vitamin D is found in high quantities in the following food sources: fatty fish, fortified milk, egg yolks, and cheese. Despite its importance and accessibility, vitamin D deficiency is highly prevalent worldwide. Several observational studies have shown a positive association between vitamin D status and supplementation on metabolic status [9,12-14]. Despite the supplementation dose often being much higher than the RDI (600 - 800 IU), a safe increase in serum 25(OH)D250HD has been observed without causing any substantial toxic effects. It should be noted that typical research dosages of 600 - 2000 [15] IU are common throughout this field. In our review, a mean of 2860 IU was observed in the stand-alone vitamin D supplements, with a mean of 2287 IU in blended products. Based on these observations, it appears that products contain vitamin D at adequate dosages to achieve optimal benefits. The UL for women and men over the age of 18, adult pregnant women, and adult lactating women is 4000 IU. Although vitamin D toxicity is rare, extreme levels exceeding 25,000 IU/day are associated with hypercalcemia and hyperphosphatemia [16].

Vitamin E: Vitamin E (α-tocopherol) is a lipid-soluble antioxidant found in plasma, red blood cells, and tissues. Antioxidants protect cells from the damaging effects of reactive oxygen species (ROS), which can promote the development of a variety of diseases. In addition to its activities as an antioxidant, vitamin E is involved in aiding immune function, cell signaling, regulation of gene expression, and other metabolic processes [17]. Vitamin E is found in high quantities in a variety of food sources, such as sunflower seeds, almonds, spinach, pumpkin, and asparagus. It has an established RDI of 15 mg (22.4 IU) daily for adults over the age of 18 and 19 mg (28.4 IU) for breastfeeding women. Research verified dosages of vitamin E often range from 400-1000 IU per day or higher. The UL of vitamin E is 1000 mg for adult men and women, adult pregnant women, and adult lactating women. An UL for infants has not been established. Long-term consumption of vitamin E above the UL has been associated with increased risk in adverse health effects [6]. Of the products we observed, stand-alone products averaged 571 IU per serving, with blended formulas containing approximately 409 IU. That said, these dosages remain much higher than the RDI and close to the dosages supported by research studies.

Calcium: Calcium is required for vascular contraction and vasodilation, muscle function, nerve transmission, intracellular signaling, and hormonal secretion, though less than 1% of total body calcium is needed to support these critical metabolic functions. The remaining 99% of the body's calcium supply is stored in the bones and teeth, where it supports their structure and function [18]. Milk, yogurt, and cheese are rich natural sources of calcium. Non-dairy sources include vegetables, such as Chinese cabbage, kale, and broccoli. Calcium has an established RDI of 1300 mg for all populations 9 - 18 years old, 1000 mg for all populations 19 - 50 years old, 1000 mg for men 51 - 70 years old, 1200 mg for women 51 - 70, and 1200 mg for all populations over the age of 70 [18]. The UL for calcium varies among populations. For women and men ages 19 - 50 the UL is 2500 mg, while adults over the age of 50 the UL decreases to 2000 mg. The UL for adult pregnant and lactating women the UL is 2500 mg. The main side effect of excess calcium intake is constipation. There is also some association with a decreased ability to absorb iron and zinc, but more research is needed to support this claim. In research studies, calcium is generally used at the RDI with success, although some studies have used higher dosages. The average stand-alone dose of calcium found in dietary supplements is 1,040 mg per serving, while blended formulas averaged 949 mg per serving. Based on these findings for calcium, dosages are similar to or just slightly less than both the RDI and research dosages for this mineral.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA): With such a high prevalence of cardiovascular disease (CVD) in adults living within the industrialized world, coupled with the science supporting the use of fish oil to combat CVD, it is not surprising that the expectation for fish oil sales is to reach 1.7 billion dollars globally by 2018 [19]. Omega-3 fatty acids, a unique group of polyunsaturated fats found in fatty fish, flaxseed, walnuts, soy, and canola oil, consist of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Both of these fatty acids are sold as dietary supplements and widely utilized for purposes of CVD reduction and related outcomes [20,21]. No clear RDI has been established for EPA and DHA but suggested dosages include 250 - 2000 mg per day of combined EPA + DHA [22,23]. Additionally, no UL of EPA or DHA has been established. However, it has been noted by the Institute of Medicine that high doses (900 mg/day EPA plus 600 mg/day DHA) might cause an immunosuppressive response, and levels greater than 2g may cause increased bleeding time [24]. Research dosages are sometimes even higher, with doses of 3 to 4 g/day of fish oil for 4 to 16 weeks proving useful in controlled studies. Dietary supplements typically contain a combination of EPA and DHA, often used at a dosage of approximately 1 gram (Table 1). While not as high as the amount used in many research studies, it may be adequate when taken in conjunction with a well-balanced diet consisting of omega-3 fatty acids.

Garcinia Cambogia: Garcinia cambogia is a fruit that contains hydoxycitric acid (HCA) within its rind. HCA is extracted and used as the active ingredient within dietary supplements promoted primarily as fat blockers and appetite suppressants, to assist with weight loss. There is no established RDI for this nutrient. Research in humans has resulted in conflicting results and the overall effects of the supplement are not convincing [25,26]. Of the stand-alone garcinia cambogia products observed (N = 4), the average dosage was 887 mg. Multiple blended products are available, but the quantity of garcinia cambogia is not disclosed. Rather, these products contain a proprietary blend, which includes the HCA. The mean in these blends was 904 mg. There is no way to know the precise quantity of HCA contained within these products, but it is reasonable to consider that the dosage is far lower than what has been used in research studies, as the blends typically contain multiple ingredients and these ingredients must contribute to the noted mean of 904 mg.

EGCG: Epigallocatechin gallate (EGCG) is a polyphenol found in green tea. A single cup of green tea contains about 50 - 150 mg of polyphenols, but only a small percentage is EGCG. Oral administration of EGCG has been studied, with the dosing typically ranging from 200 - 300 mg a day, with some demonstrated metabolic benefits. No RDI currently exists for EGCG. Many of the stand-alone products are labeled as "green tea extract" without definitively stating the EGCG quantity. Of the stand-alone supplements observed, the estimated mean EGCG content was 339 mg. More proprietary blends contain EGCG as a main ingredient and are marketed as weight loss enhancers and fat burners. Of the products reviewed, the mean EGCG value was 132 mg, slightly less than the research dosages.

Resveratrol: Resveratrol is a polyphenol found in grapes, a variety of berries, peanuts, and medicinal plants, such as Japanese knotweed [27]. It has received considerable attention as either a potential therapy or as a preventive agent for numerous diseases, with authors suggesting that resveratrol has anti-aging, anti-carcinogenic, anti-inflammatory, and anti-oxidant properties that might be relevant to chronic diseases and/or longevity in humans [28]. The limited number of human clinical trials that are available have largely described various aspects of resveratrol's safety and bioavailability, reaching a consensus that it is generally well-tolerated, but has poor bioavailability [29]. No RDI currently exists for resveratrol. There is no clear indication for what the optimal dose for resveratrol is; however, clinical trials suggest the tolerable dose range is between one to five grams daily [30]. In contrast to this, stand-alone products and blended formulas contain far less of this agent. For example, both stand-alone products and blended products averaged approximately 330 mg per serving. It is unknown what this relatively low dosage of resveratrol would provide in terms of health benefits.

CoEnzyme Q10: The antioxidant Coenzyme Q10 (CoQ10) is found within organ meats, beef, mackerel, and sardines. It is used by the body's cells for basic cell function and this nutrient has been used for purposes of improved cardiac function, exercise performance, and neuromuscular performance. CoQ10 levels begin to decrease as we age or when diseases such as cancer, diabetes, and cardiovascular disease develop [31]. No RDI currently exists for CoQ10. Research with supplementation of CoQ10 at 1200 mg per day in humans has been shown to slow the gradual depreciation of function in Parkinson's disease patients [32]. In healthy individuals, research dosing typically falls within 200 - 400 mg daily. Of the stand-alone supplements observed, the mean dosage was 203 mg. The blended products observed included a mean dosage of 119 mg.

L-carnitine: L-carnitine plays a critical role in energy production [33]. It transports long-chain fatty acids into the mitochondria for oxidation to produce energy [34]. L-carnitine also transports the toxic compounds generated out of this cellular organelle to prevent their accumulation. Carnitine is concentrated in tissues such as skeletal and cardiac muscle that utilize fatty acids as dietary fuel. Animal products like meat, fish, poultry, and milk are the best sources for L-carnitine. Dairy products contain carnitine primarily in the whey fraction. Healthy children and adults do not need to consume carnitine from food or supplements, as the liver and kidneys produce sufficient amounts from the amino acids lysine and methionine to meet daily needs [33]. The use of supplemental L-carnitine by athletes has become rather widespread over the years. Literature suggests the most commonly alleged benefits of L-carnitine supplementation include: an increase lipid turnover in working muscles leading to glycogen sparing and as a consequence, longer performances for heavy workloads [35]. There is contention whether L-carnitine contributes to the homeostasis of free and esterified L-carnitine in plasma and muscle, the allegation being that the levels of one or more of these compounds may decrease in the course of heavy repetitive exercise [34]. No RDI currently exists for carnitine. The proposed dosage of L-carnitine varies depending on the intended purpose of use but has been approximated at 2000 - 4000 mg daily based on a variety of published studies. In comparison to the dosage of L-carnitine used in research studies, the actual amount provided in most dietary supplements is inferior. For example, stand-alone products averaged 806 mg daily, while blended formulas averaged 701 mg daily.

Methylsulfonylmethane: Methylsulfonylmethane (MSM) is a naturally occurring nutrient composed of sulfur, oxygen, and methyl groups found in a wide range of human foods including fruits, vegetables, grains, and beverages [36]. MSM is often used in conjunction with glucosamine and chondroitin sulfate intended to promote healthy joints, reduce inflammation and oxidative stress, and to treat arthritic and rheumatic pain [37]. Having been studied extensively, MSM has received attention as a dietary supplement shown to be effective in treating various conditions, including alleviating exercise-induced muscle soreness and associated variables

[38,39]. Furthermore, MSM (100, 200, and 400 mg/kg/day) for 10 days before monocrotaline injection (n = 48) and continued until week 4 after monocrotaline injection has been shown to reduce hemodynamic functions and oxidative stress in rats with monocrotaline induced pulmonary arterial hypertension [40]. The discrepancy between dosing used in research studies as compared to that used in products of sale is large. On average, consumers are getting approximately 875 and 1146 mg of MSM in stand-alone and blended products, respectively. The amount used in controlled studies is at minimum 2-fold higher, with an average dosing of 2422 mg.

Ornithine Alpha-Ketoglutarate: When two molecules of the amino acid ornithine and one of alpha-ketoglutarate are combined, the salt ornithine alpha-ketoglutarate (OKG) is formed [41]. Food sources of ornithine (non-essential amino acid) are meat, poultry, fish, eggs, and soybeans [42,43]. These sources contain complete protein that include all nine essential amino acids. The supplement is marketed as a muscle builder in the sports nutrition market. Both experimental and clinical data have shown that OKG can partly prevent muscle glutamine depletion [44] and reduce wound healing time, as well as improve nitrogen balance in severe burn patients [45]. Because of its ability to improve nitrogen balance, it has been suggested to provide some value for athletes engaged in intense training. However, this belief is based on human studies in a population completely different than what the supplement has been generalized towards. There is currently no RDI for OKG. Dosages upwards of 25g were used via parenteral feeding in post-operative and burn patients and 5 - 20 grams have been used by humans for oral consumption [46]. In comparison to recommendations provided by supplement manufacturers (Table 1), there exists a very large difference between the dosages used in a controlled research environment compared to manufacturer recommendations.

Creatine Hydrochloride: One of the most effective and widely researched sports supplement on the market is creatine monohydrate. This well-known supplement can increase high intensity exercise capacity, as well as body mass and/or muscle mass as a result of training [47,48]. Due to the ergogenic properties of creatine, a variety of creatine containing formulations now saturate the sport supplement market, often with unsubstantiated claims. One such formulation is creatine hydrochloride (HCL). Although the oral bioavailability of creatine monohydrate is very good [49], this variant is marketed as a better variety, with claims of enhanced oral bioavailability in two ways: 1) by increasing aqueous solubility and 2) by increasing cellular permeability [50]. Due to its claimed improved bioavailability, creatine HCL is typically available in a micro-dosing. The recommended dose per the manufacturer is 750 mg for every 100 pounds of bodyweight, which is far lower than for creatine monohydrate. There currently exists no RDI for this nutrient.

To our knowledge, very little if any studies have been conducted with regards to the use of creatine HCL. Nonetheless, a case report was published citing the "first use of creatine hydrochloride in premanifest Huntington disease" [51]. During this study, 12 grams of creatine HCL was consumed daily over a period of approximately two years by a patient with Huntington disease, with the dosage being well-tolerated without any associated side-effects. It should be noted that this case report lacked vital information in regard to pharmacokinetic profile of creatine hydrochloride, absorption and distribution, therapeutic usage, and dosing, which are used collectively to show the efficacy of a dietary supplement. The dosages in available products are on average 1234 mg/day for stand-alone products and 1615 mg/day for blended products. With no controlled studies to use as a reference or guideline for proper dosage, it is difficult to determine how much is needed. Clearly, additional studies on proper dosages are needed to further elucidate the role and potential benefits of creatine HCL.

Betaine: Betaine, also known as trimethylglycine (TMG), is isolated from sugar beets and is sold for a multitude of uses [52]. As an organic osmolyte, betaine protects cells under stress, such as dehydration [53,54]. It is also a methyl group donor, lowering homocysteine levels and acting as a potential vasodilator of endothelial tissue via nitrate production. Betaine, therefore, plays an important role in several aspects of human health and nutrition [53]. In addition to improving health, betaine may also improve sport performance. In fact, acute ingestion of betaine has been shown to increase average peak power, maximum peak power, and bench press repetitions [55,56]. These findings have led to supplement companies marketing betaine as a potential ergogenic aid.

However, there appears to be a discrepancy in regard to dosing used in controlled studies compared to what is available on today's market. Dosages used in controlled studies range from 2.5 - 6 grams of betaine ingested over a 14-days period [57]. It should be noted that 2.5 grams of betaine increased maximum peak power, average peak power, and maximum peak power compared to placebo over 14-days [55]. Stand-alone or blended supplements on average contained 1.5 grams. There currently exists no RDI for this nutrient.

β-hydroxy β-methylbutyrate (β-HMB): Leucine and metabolites of leucine such as β-hydroxy β-methylbutyrate (β-HMB) have been reported to inhibit protein degradation particularly during periods of increased proteolysis [58]. In addition, an increase in muscle mass and strength have been noted. Due to the anti-catabolic and potential ergogenic effect of this supplement, β-HMB has been marketed to bodybuilders and athletes spanning various sports. However, the results are not impressive as pertaining to well-trained individuals when ingesting the typically used dosage of 1.5 to 3 g/day-a similar dosage as used in most stand-alone and blended products. There is currently no RDI for this nutrient and while marketing efforts have been made to promote the use of HMB for enhancing muscle mass, there is little to no evidence in otherwise healthy individuals to support this claim.

D Aspartic Acid: D-aspartic acid is an endogenous amino acid, which has been found in the neuroendocrine tissues of both invertebrates and vertebrates [59]. Several studies have demonstrated that D-aspartic acid is concentrated in the endocrine gland, particularly in the pineal gland, the pituitary gland, and the testis [60]. D-aspartic acid supplementation in rats is capable of eliciting the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, the luteinizing hormone (LH) and the growth hormone (GH) from the pituitary gland, and testosterone from the testes [60]. Supplement companies produce products that contain an average of approximately 3 grams of DAA per serving and this amount is similar to the range of 2.76 - 3.51 grams used in human studies [60-65].

Glucosamine: Glucosamine is a nutritional supplement amongst many others used for 'joint health' to prevent or treat cartilage disorders, including osteoarthritis [63]. Among these, glucosamine inhibits the degradation and stimulates synthesis of glycosaminoglycan polysaccharide chains of proteoglycans. Furthermore, glucosamine suppresses the expression of collagen-degrading enzymes, such as matrix metalloproteinases (MMPs), whereas it increases the expression of type II collagen in chondrocytes. Based on these observations, it has been hypothesized that glucosamine exerts a chondroprotective effect on cartilage disorders by keeping proteoglycans and type II collagen in the articular cartilage. Therefore, glucosamine may be used to treat osteoarthritis in humans. Although no RDI exists for glucosamine, research studies generally use a dosage of 500 - 2000 mg daily. These amounts are generally similar to what is provided in stand-alone and blended products-1291 and 1400 mg of glucosamine, respectively.

Actions that consumers should take when selecting dietary supplements

As can be seen in reviewing the information above and within Table 1, variance can exist in dosing for individual ingredients being sold as stand-alone or blended dietary supplements. For the vitamin and minerals, both stand-alone products and blended formulas appear to contain dosages that can be supported by available research, which is reassuring. This may be due to the relatively low cost of these ingredients as compared to other novel ingredients also included in this review. For ingredients besides vitamins and minerals, there exists a degree of variability between products of sale, with some containing dosages that can be supported by the available research and others falling far short of this amount. As with any purchase, consumers should conduct a rather thorough investigation when considering the use of a dietary supplement.

Specifically, this process may begin by obtaining confirmation that the product is being produced using current Good Manufacturing Practices (cGMPs). This will at least ensure that the ingredients stated on the label are contained within the product. It should also help to ensure that the product does not contain adulterated ingredients and is free of contaminants. Products should contain information on the label that discloses by whom the product was manufactured. The company should have a website which provides an overview of their services and information pertaining to their adherence to cGMPs.

Going beyond standard cGMPs, some companies seek additional quality assurance. For example, some products carry the "USP" seal, which is the verification of the United States Pharmacopeia. USP verification ensures that the product contains the ingredients listed on the label and at the declared dosage, does not contain harmful contaminants, will break down and release into the body within a specified period of time, and has been manufactured following cGMPs. If sport-specific products are being purchased, products receiving certification from Informed Choice may be good options, as this organization evaluates products to ensure that they are free of banned substances.

In addition to quality control, consumers should consider asking companies for research studies that support the various claims being made for their products. These studies should be freely available on the company's website. If not on the website, consumers can conduct a simple search using the medical database PubMed, available at https://www.ncbi.nlm.nih.gov/pubmed, or Google Scholar. A search of the product or ingredients contained within the product should reveal the dosage of ingredients being used in clinical studies, as well as the expected outcome of using the ingredient and/or product of sale. It should be understood that in some cases, there exists no clinical studies to support the use of ingredients that may be contained in certain dietary supplements. In such a case, the consumer is simply taking a chance as to whether or not the product of sale will deliver results as claimed.

Once data pertaining to product manufacture following cGMPs is verified, as well as confirmation as to ingredient dosing based on scientific study of said ingredient, the consumer should feel confident that they have a reasonably high-quality product. Of course, the specific ingredients used, including the amount of active component within each ingredient, in conjunction with one another, will have a major influence on the product's overall effectiveness. Moreover, the type/form of ingredient being used is of great importance, in particular as related to bioavailability or absorption of the nutrient (e.g., co-enzyme Q 10, for which the ubiquinol form is best and not the ubiquinone form). If studies have been conducted on the finished product of sale, this is helpful. If not, the consumer is left to assume that the combination of ingredients contained within the finished product will yield a desired outcome. Only through trial and error will an individual determine what might work best for them.

Conclusion

Dietary supplements are a multi-billion dollar per year business on a global scale. Consumers are interested in using dietary supplements for a variety of purposes and will likely continue to do so in the coming years. While many products are of high quality and potency, there exists variance when considering the dosing provided. In this review, several products containing specific ingredients were evaluated and compared. Three points are apparent: 1) many ingredients are provided within dietary supplements at dosages that can be supported by the available evidence, which should be reassuring to consumers; 2) a great deal of variance exists from product to product in terms of the dosage of a specific ingredient and consumers need to pay close attention to nutrition facts labels to make certain that the product of interest contains adequate dosing of ingredients (see SD values in Table 1); 3) for some ingredients, in particular non-vitamins/minerals, the dosage contained within the finish products is far less than what has been used in the clinical research studies. With this being the case, it is unknown what benefit would be gained by using the product at the manufacturer's recommended dosage.

Consumers should understand these above facts and seek products that contain the correct dosage of the desired ingredients. A careful review of the product label, coupled with a review of the available scientific evidence for effectiveness of the ingredient, should allow consumers to make an informed choice as to which products may be best suited to their individual needs. Education is of great importance here and consumers need to take the time to carefully evaluate products before making a decision to purchase, and to ultimately use the product of sale.

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