



# A systematic review and evidence-based analysis of ingredients in popular male testosterone and erectile dysfunction supplements

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## Abstract

The objective was to study available evidence for ingredients of popular over-the-counter testosterone and erectile dysfunction (ED) supplements. The top 16 male testosterone and 16 ED supplements in the USA were identified from the most popular online retailers: A1 Supplements, Amazon, Vitamin Shoppe, and Walmart. In total, 37 ingredients were identified and PUBMED online database was reviewed for randomized-controlled trials (RCT) studying their efficacy. Ingredients were categorized based on evidence quantity using an adapted version of the American Heart Association scoring system. In total, 16 ingredients from testosterone supplements and 21 from ED supplements were identified. *Tribulus*, *Eurycoma longifolia*, Zinc, L-arginine, Aspartate, Horny goat weed, and Yohimbine were most common. In all, 105 RCTs studying the identified ingredients were found. No whole supplement products have published RCT evidence. 19% of ingredients received an A grade for strong positive evidence with net positive evidence in two or more RCTs. In total, 68% received C or D grades for contradicting, negative, or lacking evidence. Overall, 69% of ingredients in testosterone supplements and 52% of ingredients in ED supplements have published RCT evidence. Many male supplements claim to improve testosterone or ED parameters; however, there is limited evidence, which should be considered when counseling patients.

## Introduction

The prevalence of use of dietary supplements has dramatically increased. It is reported that ~52% of Americans have described using a supplement product in the prior 30 days [1]. The use of these supplements is for a variety of purported health benefits, which have limited research backing their efficacy or safety up to this point. More recently, the use of supplements for low testosterone and erectile dysfunction (ED) has garnered interest [2, 3]. Another issue is

that the rapid supplement market growth has outpaced the availability and capacity of methods and trained personnel to effectively study them all. Currently, the United States market contains more than 85,000 supplement products and there are concerns about safety, quality assurance, and ingredient misidentification [4]. The evidence behind these supplements is also often conflicting and employ diverse research supports and types of evidence [4–6]. The estimated prevalence of hypogonadism in men aged 45 years and older in America is 39% [7]. For patients with male hypogonadism, testosterone replacement therapy has often been considered in order to improve symptoms of low testosterone and well-being [7, 8].

On the other hand, ED affects more than 12 million men in the USA [9]. There is a wide variety of clinical therapeutic options which include, psychotherapy, lifestyle modification, phosphodiesterase 5 inhibitors, intracavernosal injections, vacuum erection devices, and implantable penile prostheses [9, 10]. While these methods have demonstrated strong results, patients still have been on the lookout for self-treatment options. Accordingly, there has been increased interest in over-the-counter (OTC) therapies to treat male hypogonadism and ED, pushing patients to

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**Table 1** Most commonly used male testosterone and erectile dysfunction supplements.

Erectile dysfunction supplements	Testosterone supplements
Ageless male tonight no booster	Alpha King
Ecklonia cava extract	CBD + T up full-spectrum hemp extract plus T
Horny goat weed herbal complex extract	Cellucor P6 PM sleep aid T support
KAL DHEA 10 mg	Competitive edge labs M-test
Libido max for men	Extra strength L-arginine
Male libido	Extra strength T booster
Max strength male drive	MD certified T booster
Nutrachamps Korean red <i>Panax ginseng</i>	Natural T booster
Nutrakey arginine	Premium L-arginine 1500 no supplement
Olympus labs	Premium T booster for men & women
Psycho pharma sextosterone boost	Primeval labs mega test
Solaray Fo-Ti 610 mg	Progene T supplement
Steel libido for men	Redcon1 boom stick
Vialus—male T and performance booster	Six star pro nutrition T box
Vigor Labs Black Snake	<i>Tribulus terrestris</i> extract
Zyrexin world strongest sexual enhancer	Ultimate T for men

seek out supplements as an alternative solution. At this time, there is unclear evidence behind many supplement products due to minimal oversight and regulation, thus there lies uncertainty in the effectiveness of these product and subdued confidence in their use.

To our knowledge, we could not find a study that analyzed the level of evidence of the ingredients in the most popular testosterone and ED supplements. Numerous prior studies have demonstrated positive effects of OTC supplements in various male fertility issues, however, many also describe a lack of efficacy in addition to potential adverse effects [11]. We aimed to investigate the level of evidence for specific ingredients in popular OTC supplements that claim to ameliorate signs and symptoms of low testosterone as well as ED.

## Materials and methods

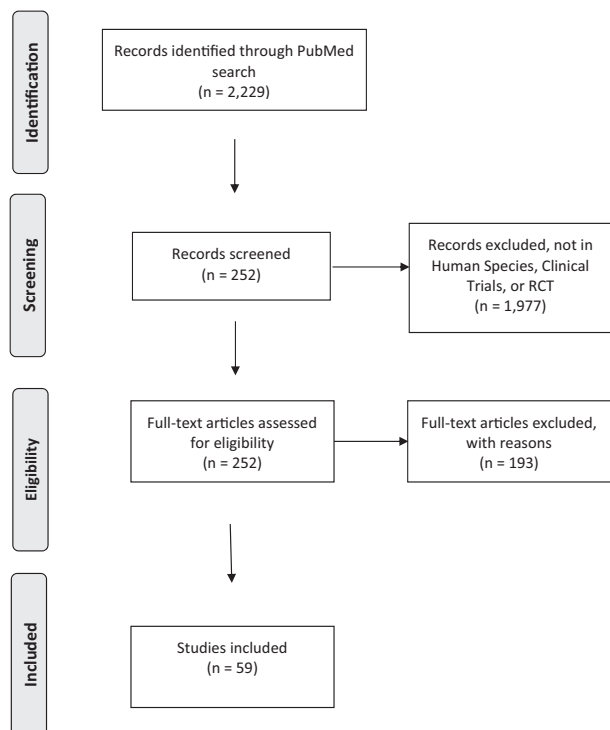
In line with the Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) guidelines, a systematic and qualitative review was performed [12]. The data used was obtained from 105 previously published randomized-controlled studies, and consequently institutional review board approval was not required.

## Search and selection strategy

The analysis was performed according to the PRISMA Statement (Supplementary). Google search identified AI Supplements, Amazon, Vitamin Shoppe, and Walmart as recognized online retailers for low testosterone/ED supplements with the most consumers. Catalogs were searched using the following phrases: terms “low testosterone supplement” and “male testosterone supplement.” to identify low testosterone supplements from these retailers. The same process was used for y ED supplements using the following phrases: “erectile dysfunction supplement” and “male erectile dysfunction supplement.” The top three search results (if there were more than three returned) for each search phrase from each retailer were distinguished as popular search results, and the “sponsored” products on the sites were screened out due to bias. The top three results are the same for anyone making a similar search and would be the ones that are most likely to be purchased. The sponsored results are subject to geography and an individual’s user’s search history. Each search query was cross-analyzed with the results from the same retailer using the different search phrases to ensure that the results were unique. If not all results were unique, results further down from the first three were used until all of the results were unique. The popular supplements products which were obtained from this search can be reviewed in Table 1.

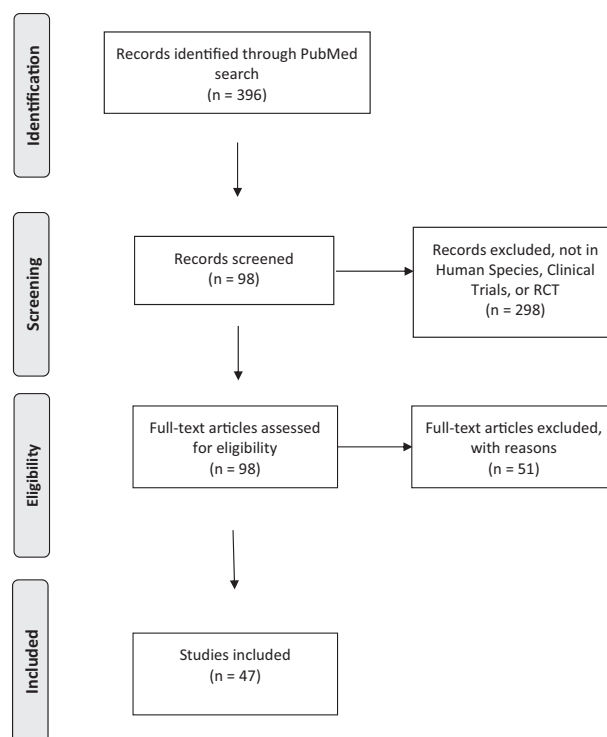
The supplement products were analyzed and their individual ingredients were identified. Ingredients utilized in more than one supplement product were included in this study for analysis. Successively, a systematic literature search was conducted for ingredients with studies identified by searching PubMed electronic database (January 1980 to September 2019). The results were limited to peer reviewed, English language, and human studies. The search strategy for studies reviewing ingredients in low testosterone supplements used the name of the ingredient followed by “testosterone” or “low testosterone.” Search for studies reviewing ingredients in ED supplements used the name of the ingredient followed by “erectile dysfunction,” “ED,” and “male erectile dysfunction.” For example, to search vitamin E, the search terms, “Vitamin E testosterone,” “Vitamin E low testosterone,” “Vitamin E erectile dysfunction,” “Vitamin E ED,” and “Vitamin E male erectile dysfunction” were used. Two reviewers (YS and JYL) independently screened published abstracts and full texts. For eligibility of inclusion, a consensus between the two authors was required. We included data from studies which were randomized and analyzed the effect of ingredients on total testosterone, free testosterone, or reported subjective patient-reported improvements for low testosterone supplements. Impact on sexual desire, sexual performance, sexual satisfaction, and International Index of Erectile

Low Testosterone Supplement Ingredients Search Strategy



**Fig. 1** Flow diagram: Algorithm for identification of studies evaluating ingredients in low testosterone supplements in the systematic review (PRISMA format).

Erectile Dysfunction Supplement Ingredients Search Strategy



**Fig. 2** Flow diagram: Algorithm for identification of studies evaluating ingredients in ED supplements in the systematic review (PRISMA format).

Function (IIEF) scores were considered for ED supplements. Trials were excluded if they analyzed compounded ingredients because individual effects of ingredients would not be able to be elucidated. Flowcharts for the study selection for low testosterone and ED ingredients can be seen in Figs. 1 and 2, respectively. The data were extracted independently by two reviewers (YS and JYL) and disparities were verbally communicated and discussed with the other co-authors. The discussion would take place in a meeting with all the co-authors and the analysis would be conducted together to prevent any differences in methods.

## Data analysis

An adapted version of the scoring system which The American Heart Association has developed for analyzing scientific evidence from clinical trial was used to evaluate the supplement ingredients [13]. The scoring system assigns a grade (A, B, C, or D) to ingredients based on the demonstrated level of published evidence. An ingredient was designated evidence level A if it had demonstrated net positive impact in multiple randomized-controlled trials (RCTs). Level B was assigned if a net positive impact is demonstrated in just one RCT. Level C was assigned if multiple RCTs show the opposing results, resulting in an

indeterminate outcome or no effect, and level D was designated for ingredients showing negative impacts or a lack of evidence.

## Results

### Low testosterone supplements

After review, 16 ingredients were identified from the top 16 listed male testosterone supplements. The most commonly used ingredients were Aspartate, *Eurycoma longifolia*, Fenugreek, L-arginine, *Tribulus*, and Zinc. A search of PubMed online database returned 59 trials studying the efficacy of the identified ingredients. Of the 59 studies, 24 (40.7%) reported on total testosterone, and 22 (37.3%) reported on free testosterone. Some studies either reported one or both metrics. For studies that did not explicitly report either metric, a general blanket term such as, serum testosterone or bioavailable testosterone was typically used. Six out of the 16 ingredients we identified in the popular testosterone supplements had no published data at all. The most studied ingredients were *Tribulus*, Zinc, and Fenugreek, with each having five or more RCTs of published data. None of the whole supplement products had any

**Table 2** Level of evidence for ingredients in popular male testosterone supplements.

Ingredient	Level of evidence	Articles of evidence (PMID)
<i>Eurycoma longifolia</i> (tongkat ali)	A	30790614, 28259255, 24386995, 21671978, 23754792, 24386995, 23705671, 23754792
<i>Tribulus</i>	A	30790614, 29172782, 27760089, 24630840, 23173697, 17530942, 15994038, 14559928, 11725694, 11601567, 10997957
<i>Mucuna pruriens</i> (velvet bean)	B	30790614, 18973898
Fenugreek ( <i>Trigonella</i> )	C	30790614, 21312304, 30863446, 29623697, 29018642, 28138310, 30356905, 26791805, 25914334
Aspartate	C	15895316, 28841667, 24074738, 19860889
Boron	C	8508192, 7889885, 9197924, 30143848
L-arginine	C	29544063, 21789887, 21618639, 20300016, 15895316
L-citrulline	C	29057836
Maca root ( <i>Lepidium meyenii</i> )	C	12525260, 30790614
Zinc	C	8875519, 23356505, 20446777, 17984944, 17882141, 1609752, 2515494, 6350404, 7051913, 6786094, 6107409, 72240
Cayenne pepper	D	
Diindolylmethane (DIM)	D	
Magnesium	D	20352370
Nettle leaf	D	
Sarsaparilla extract	D	
Vitamin B6	D	

published evidence of their use in an RCT. Grading for the ingredients with level of evidence is summarized in Table 2. Overall, an A, B, C, or D grade was designated to 2 (12.5%), 1 (6.3%), 7 (44.8%), and 6 (37.5%) ingredients, respectively. While, 13% of ingredients in this study were given A grades, meaning they had strong positive evidence supporting their use, 81% of ingredients received grades that determined their evidence was indeterminate (C grade) or completely lacking/negative (D grade). Overall, our results showed that 69% of ingredients in testosterone supplements have published evidence of their use in RCTs.

### Erectile dysfunction supplements

Upon data extraction, 21 ingredients were identified from the top 16 listed ED supplements. The most commonly used ingredients were Horny goat weed, Yohimbine, *Tribulus*, *E. longifolia*, and L-arginine. A search of PubMed online database returned 46 trials studying the efficacy of the identified ingredients. Of the 46 studies, 33 (71.7%) reported on sexual desire, 11 (23.4%) reported on sexual performance, 28 (60.9%) reported on sexual satisfaction, and 23 (50.0%) reported on IIEF scores. These metrics were not mutually exclusive, and some studies reported at least one or all four metrics. For studies that did not report these, they used other metrics or questionnaires such as nocturnal penile tumescence and rigidity test, Aging Males' Symptom scale, Erection Hardness Score, etc., to assess changes in erectile function. Of the 21 ingredients, 48% identified in

the popular ED supplements had no published data evaluating their efficacy in any RCT. Similar to testosterone supplements, none of the whole supplement products had any published evidence of their use in an RCT. Grading for the ingredients with level of evidence are summarized in Table 3. Overall, an A, B, C, or D grades were designated to 5 (23.8%), 4 (19%), 2 (9.5%), and 10 (47.6%) ingredients, respectively. While, 24% of ingredients in this study were given A grades, as determined by having strong positive evidence supporting their use, 57% of ingredients received grades that determined their evidence was indeterminate (C grade) or completely lacking/negative (D grade). Overall, our results showed that 52% of ingredients in ED supplements have published evidence of their use in RCTs.

### Discussion

We identified ingredients contained in the most popular male testosterone and ED supplements. In total, 16 ingredients were identified in testosterone supplements and 21 ingredients were identified for ED supplements. As expected, evidence for efficacy was limited and available in RCTs for only 59% of the ingredients in popular testosterone and ED supplements. Along with this, 68% of all the testosterone and ED ingredients received C or D grades as they were determined to have contradicting, negative, or lacking evidence. On the contrary, 19% of ingredients in both low testosterone and ED supplements received an A grade by

**Table 3** Level of evidence for ingredients in popular male erectile dysfunction supplements.

Ingredient	Level of evidence	Articles of evidence (PMID)
<i>Eurycoma longifolia</i> (tongkat ali)	A	24550993, 21671978, 23243445
Horny goat weed ( <i>Epimedium sagittatum</i> )	A	24844765, 24146455
L-arginine	A	21618639, 20184576, 17703218, 25664962, 23413135, 10743698, 10233492, 19624286, 12851125
<i>Panax ginseng</i> (Korean red ginseng)	A	23254461, 19234482, 16855773, 12394711, 8750052
Yohimbine	A	12074777, 11896474, 11890513, 9315493, 9123711, 9015579, 8714425, 7490815, 7974947, 1439854, 1564046, 2370671, 2657105, 2887726, 3295302, 3021082
<i>Butea superba</i>	B	12937809
Fenugreek ( <i>Trigonella</i> )	B	21312304
<i>Kaempferia parviflora</i>	B	29880257
Maca root ( <i>Lepidium meyenii</i> )	B	19260845
Saw palmetto ( <i>Serenoa repens</i> )	C	24399119, 12887481
<i>Tribulus</i>	C	24630840, 23173697, 29901295, 28364864, 25136552
Ashwagandha powder	D	
<i>Cnidium monnieri</i>	D	
Dimethylglycine (DMG)	D	
Fo-ti ( <i>Polygonum multiflorum</i> )	D	
<i>Mucuna pruriens</i> (velvet bean)	D	
Muira puama ( <i>Ptychopetalum olacoides</i> )	D	
NADH	D	
<i>Polypodium vulgare</i>	D	
Sarsaparilla ( <i>Hemidesmus indicus</i> )	D	
<i>Xanthoparmelia scabrosa</i>	D	

determination that they had strong positive evidence behind their use. To the best of our knowledge, there are no published results from an RCT for any whole supplement product.

Based on the outcome of this study, it is evident that there is still work to be done in order to clearly elucidate the efficacy of many commonly used ingredients in testosterone and ED supplements. It has previously been demonstrated that human studies evaluating the efficacy of ED supplements is limited and has not yielded definitive findings on the effects of ED [14]. The majority of ingredients in this study have poor or lacking data behind their use, however, there are several evidence-backed ingredients that have strong positive evidence backing their use; these include *E. longifolia*, Horny goat weed, L-arginine, *Panax ginseng*, Yohimbine, and *Tribulus*.

The ability to guide patients in selection may be limited. There is growing evidence that many patients seek healthcare advice on the internet from various forums and blogs which may recommend options that are not scientifically

backed [15]. E-commerce has also become one of the most popular methods for patients to obtain goods, often cutting out advice, and input from healthcare professionals [14]. The findings of this review are important as they unify the evidence behind commonly used ingredients into one place and provide a simple tool for their evaluation. Although only a minority of supplement purchases are a result of clinician recommendations, clinicians may still utilize this information to better educate and guide their patients [16].

The use of dietary supplements has been growing at a steady pace over the past several decades due to e-commerce, readily available advice, and limited regulation [1]. With the current set up of regulations in The USA, the US Food and Drug Administration does not regulate supplement products according to the Dietary Supplement Health and Education Act of 1994 [17]. Since these supplements do not have reliable or strict regulations on their efficacy, they have been recommended by healthcare providers with caution, however, this has not prevented their huge growth in use due to the fact that less than 25% of dietary

supplements used result from a healthcare visit [16]. In addition, many patients who take supplements may not actually have a diagnosable condition and instead are taking these supplements due to their own perceptions which may actually be more harmful in another health and well-nourished individual [18]. Instead, many consumers may be trapped by extravagant claims; supplement experts stand by the phrase: if it sounds too good to be true that typically means that it is. It is important to be aware of extravagant claims and help patients to not fall prey to them when they are not backed by evidence. Many terms such as all natural, antioxidant rich, clinically proven, antiaging, and other vague but tempting terms of a promised outcome should be viewed with caution since supplements are not uniformly regulated and are rarely evaluated for efficacy [19]. Lastly, it should be known that more is not always better. For example, an elevation of vitamin or antioxidant levels in the body can actually lead to an increase risk of fracture or tumors as can be seen in vitamin A and folic acid, respectively [19].

Our study has strengths and limitations. A strength of this study is that it is the first study to analyze the available evidence in the ingredients of popular male testosterone and ED supplements. It gives clear and concise grading designations with clear parameters which will aid clinicians in counseling their patients. Limitations of this study include the absence of RCTs studying the efficacy of commercially available whole supplement products as well as the quality of the RCTs. Even though RCTs constitute the best level of evidence, they could be biased due to industry funding, underpowered, and demonstrate lack of efficacy. RCTs may also be subject to publication bias with only positive results being selected to be reported. The lack of RCTs studying the whole supplement prevents the analysis of the interaction of the ingredients within each supplement product. Another limitation is the scoring system that is used which assigns an equal grade to an unstudied ingredient and an ingredient demonstrating negative benefit. The rationale for this is the fact that unstudied and unregulated supplements can cause extraordinary detriment to the patient, and the uncertainty of the ingredient should raise extreme cautiousness. Furthermore, more studies of ingredients should be conducted in the future so that all ingredients are graded on evidence, and not just uncertainty. Lastly, this study relies on the evidence of individual ingredients; however, this does not give an accurate judgment of the effectiveness of the supplement as a whole. Although it does shed light on the level of evidence backing these products and provides a motive for skepticism. With that being said, this information provides robust and structured information about the evidence available for these ingredients. Future studies should focus on effectively studying the variety of ingredients that are utilized in supplement products. It will

be essential to accurately evaluate these items for the sake of patients. In addition, whole supplement products should be studied, and their individual ingredient lists should be evaluated to designate a level of evidence for the whole product. Alongside this, effective dosages should be identified to promote better utilization of the ingredients by supplement producers.

In conclusion, the majority of ingredients in male testosterone and ED supplements are unfortunately understudied. Only 1/5th of the ingredients in testosterone and ED supplements have positive evidence that supports their use resulting in improvements. Although there are several ingredients with A level of evidence, their use should be considered with caution. The evaluation of their safety and effectiveness in conjunction with other components has not been evaluated. Moreover, it has become apparent that many patients often do not consult healthcare providers before trying these products. However, at this time there are still no published RCTs evaluating the efficacy of whole supplement products for testosterone or ED. Therefore, the use of testosterone and ED supplements should be recommended with caution due to the paucity of available research.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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