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| RESEARCH ARTICLE

Muscle Support Supplement by APOC, Medical Food EP1 (Cacao Advanced®): Systematic Review and Meta-Analysis Exploring the Supplement's Main Ingredient, the Cacao Flavanol l-Epicatechin and its Relationship Between the Follistatin to Myostatin Ratio

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| ABSTRACT

Several scientific papers refer to the cacao flavanol l-epicatechin (EPI) as the first and only discovered dietary source of myostatin (MTSN) inhibition. However, although pre-clinical models strongly support this, there is a lack of high-quality human studies; to examine the response association between the consumption of EPI in humans and the effect on MSTN and follistatin (FST). By systematically reviewing the literature and qualitatively meta-analyzing with statistical methods, it becomes possible to quantify a conclusion from several lower quality human studies instead of a few high-quality studies. Two investigators searched Scopus® for the relevant human studies, which were pooled and meta-analyzed. Heterogeneity in the findings was explored with various subgroup analyses. Nine published articles with 11 intervention arms met the inclusion criteria. A significant improvement of the FST: MSTN ratio was observed in participants who ingested EPI, with a Common Language Effect Size (CLES) for Cohen's *d* of 0.92 (95% CI: 0.74 to 0.99). Strong evidence of an association between EPI consumption and FST induction was noted, with weaker evidence for MSTN inhibition. Respectively, 0.98 (95% CI: 0.88 to 1.00) and 0.71 (95% CI: 0.50 to 0.88). This meta-analysis provides evidence that EPI ingestion significantly improves the FST:MSTN ratio in humans by inducing FST and inhibiting MSTN. However, there was substantial variation in the results that could not be explained by the characteristics that were explored, and there were significant risk-of-bias concerns, with a large majority of the studies being small populations and not blinded. Nevertheless, considering the heterogeneity of children and the elderly and the lack of exercise intervention or alternatively high-quality exercise regime interventions. EPI consumption is the only feasible explanation for the drastic FST:MSTN ratio improvement.

| KEYWORDS

l-Epicatechin, EPI, follistatin, myostatin, EP1, APOC, Cacao Advanced, muscle growth

| ARTICLE INFORMATION

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1. Introduction

EP1 (Cacao Advanced®) is a medical food formulated with EPI, designed for the dietary support of muscle growth in both children and adults and the dietary management of muscular degeneration. This meta-analysis and systematic review will investigate the claim that APOC medical food supports the FST:MSTN ratio. EPI comes from a family of protein activating steroid hormones called peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α) activating steroid hormones [McDonald et al. 2018]. EPI is a molecule that is found in small amounts in chocolate. EPI is commonly called a MSTN inhibitor in the dietary and sports supplement industry. MSTN is an enzyme that limits muscle growth. When MSTN is inhibited, deficient, or genetically modified, the inhibition greatly increases muscle mass without the major side effects associated with administering Anabolic Androgenic Steroids (AAS).

MSTN is a biomarker of muscle growth and regulation detrimental to ageing. As humans age, it becomes harder to build and maintain muscle mass [Volpi et al. 2004]. A cause of age-related muscle growth difficulty is caused by insufficient biomarkers of muscle growth [Cruz-Jentoft et al. 2010]. Age-related muscle difficulty can begin as early as 18 years of age [Mitchell et al. 2012]. Past the age of 30, 3-8% of muscle mass is lost every decade [Cruz-Jentoft et al. 2010]. This degeneration is called sarcopenia, increasing in rate after 60. Two important biomarkers of muscle growth are FST and MSTN [Baczek et al., 2020]. FST is a protein that helps muscles grow, while MSTN is a protein that tells muscles to stop growing. These proteins are called myokines. Blood levels of MSTN begin to increase during the 20s [Szulc et al., 2020]. Sarcopenia begins in some individuals between the ages of 18-20, which is the same ages where the FST:MSTN ratio starts declining.

EPI, a bioactive component of ordinary food, is the only discovered dietary FST inducer and MSTN inhibitor [McDonald, 2018]. EPI is found in foods including beans [de Pascual-Teresa et al., 2000], peaches, green tea [Ding et al. 1999], barley [Yin, 2022], Açaí [Xavier, 2021], vinegar [Natera, 2003], but most notably Cacao beans [Payne et al. 2010]. EPI increases markers of muscle growth [McDonald et al. 2018], muscular regeneration, energy stores, strength [Gutierrez-Salmean, 2014], and the FST to MSTN ratio.

Table 1. l-Epicatechin content in solid food

Food	mg EPI per 100 g of food	Percent of EPI in food	Reference
Cacao powder	158.30	0.158%	[14]
Dark chocolate	70.36	0.07%	[14]
Broad been pod, raw	37.55	0.038%	[7]
Broad been seeds, raw	22.51	0.023%	[15]
Blackberry, fresh	18.08	0.018%	[15]
Milk chocolate	12.61	0.013%	[15]
Black grapes, fresh	8.64	0.009%	[15]
Red raspberry, fresh	8.26	0.008%	[15]
Fresh green bean, raw	6.06	0.006%	[16]
Apricot, raw	6.06	0.006%	[15]
Sweet cherries	5.45	0.005%	[7]
Plum, fresh	4.45	0.00445%	[7]
Peach, raw	4.35	0.00435%	[7]
Cranberry, fresh	4.20	0.0042%	[15]
Pear, fresh	3.70	0.0037%	[15]
Nectarine, raw	2.39 *	0.0024%	[17]
Blueberry, fresh	1.11	0.0011%	[15]
Green grapes, fresh	1.02	0.001%	[15]
Cashew nut, raw	0.90	0.0009%	[18]
Pistachio, raw	0.80	0.0008%	[18]
Pecan nut, raw	0.80	0.0008%	[18]
Cloudberry, fresh	0.80	0.0008%	[19]
Avocado, raw	0.56	0.00056%	[15]
Rhubarb	0.51	0.00051%	[15]
Blackcurrant, fresh	0.47	0.00047%	[15]
Kiwi fruit	0.45	0.00045%	[15]
Lentils, raw	0.41	0.00041%	[7]
Almond, raw	0.30	0.0003%	[18]
Banana, raw	0.20	0.0002%	[18]
Redcurrant, fresh	0.19	0.00019%	[7]
Common bean, raw	0.14	0.00014%	[7]
Pomegranate	0.08	0.00008%	[7]
Fig, fresh	0.05	0.00005%	[7]
Strawberry, fresh	0.02	0.00002%	[7]
Fresh peas, raw	0.01	0.00001%	[7]

2. Pharmacology of l-epicatechin

2.1 Pharmacokinetics

2.1.1 Absorption

EPI has a bioavailability of as low as 16% [Zhu, 2000; Baba, 2000]. The bioavailability of EPI is increased with the inclusion of a cyclodextrin complex [Lopez-Miranda, 2006].

2.1.2 Distribution

After administration of EPI from chocolate, peak plasma levels of EPI are noted at 2-3 hours [Richelle et al. 1999]. However, when administrating pure EPI, peak plasma levels are noted between 1-2 hours after ingestion [Barnett, 2015].

2.1.3 Metabolism

EPI is quickly and vastly metabolised into sulfate, methyl sulfate, and glucuronide metabolites [Barnett, 2015].

2.1.4 Elimination

EPI has an elimination half-life of approximately 1.9-2.3 hours [Richelle, 1999].

2.2 Pharmacodynamics

2.2.1 l-Epicatechin biomechanic, receptor, and enzyme essay

EPI targets essential proteins involved in muscle development, growth, and regeneration: MSTN, FST, dystrophin, utrophin, and dysferlin [Gutierrez-Salmean, 2014; McDonald, 2021]. These proteins work synergistically through gene transcription. Transcription is the first step in gene expression where deoxyribonucleic acid (DNA) is copied as ribonucleic acid (RNA) and sent by mRNA (messenger RNA) to ultimately create new cells [Livingstone, 2010]. These proteins are paramount in muscle growth – known as biomarkers for muscle regulation – and are currently being researched as targets for muscle wasting diseases, such as dystrophy [Tsuchida, 2008] [Schuelke, 2004].

Table 2. EPI pharmacodynamic essay

Biomechanism	Action	Description	Reference
FST	Induce	See Table 3	[13]
MSTN	Inhibit	See Table 4	[29]
Dystrophin	Induce	Protein that supports muscle fibre plasma membranes	[25]
Utrophin	Induce	Protein involved in muscular contraction	[25]
Dysferlin	Induce	Repairs sarcolemma when damage occurs due to muscle strain	[25]
Myogenin	Induce	Transcription factor involved in myogenesis	[13; 25]
Myogenic factor-5 (Myf5)	Induce	Protein regulating myokine differentiation and myogenesis	[13; 25]
MyoD	Induce	Protein regulating myokine differentiation	[13; 25]
Myosin	Induce	ATP-dependant muscle protein involved in muscle contraction	[25]
Skeletal muscle actin alpha-1	Induce	Protein involved in myocyte structure and integrity	[25]
PPAR-y	Agonise	Receptor involved in fatty oxidation	[25]
AMPK	Induce	Pathway involved in ATP production	[25]
Mitofilin	Induce	Inner mitochondrial protein	[25]
VO_2.max	Decrease	Maximal oxygen consumption during exercise	[25]
Lactic acid	Decrease	Chemical byproduct of anaerobic respiration	[25]
Heart Rate (HR)	Decrease	Number of heartbeats per minute	[13; 30]
Monoamine Oxidase-B (MAO-B)	Reversible inhibition	Enzyme involved in breaking down phenylethylamine and dopamine, as well as other xenobiotic amines	[31]

2.2.2 PGC1-α activating steroids

EPI is a PGC1-α activating steroid hormone – through nuclear receptor ligand affinity [McDonald, 2018]. PGC1-α steroid hormones promote mitochondrial growth and induce skeletal muscle regeneration [Rius-Perez, 2020]. These steroid hormones are known as the 'master regulators' of mitochondrial biogenesis. PGC1-α is a transcriptional coactivator that regulates energy metabolism in myocytes. It does this through the nuclear receptor peroxisome proliferator-activated receptor-gamma (PPAR-γ). PPAR is heavily involved in ketosis and fat oxidation [Wang, 2010].

2.2.3 Follistatin

Table 3. FST pharmacodynamic essay

Biomechanism	Action	Description	Reference
MSTN	Inhibit	MSTN is a myokine that inhibits muscle growth	[29]
Follicle-stimulating hormone (FSH)	Inhibit	FSH is a sexual reproductive hormone	[34]
Activin	Inhibit	Activin is a paracrine hormone involved in cellular proliferation	[35]
Transforming growth factor-beta (TGF-β) superfamily	Inhibit	TGF-β are growth factor peptides	[35]

2.2.4 Myostatin

EPI has a positive expression on FST. FST binds to MSTN, inhibiting MSTN via antagonism [Rodino-Klapac, 2009]. MSTN is a secreted growth differentiation factor (GDF), specifically GDF-8 [Carnac, 2006] [Joulia-Ekaza, 2007]. MSTN plays a crucial role in muscle regulation. MSTN regulates the limitation and inhibition of muscle development [Saunders, 2006]. As such, MSTN is a major target for drug discovery involved in muscular degradation conditions such as dystrophy, sarcopenia, and ataxia [Tsuchida, 2008] [Schuelke, 2004].

Table 4. MSTN pharmacodynamic essay

Biomechanism	Action	Description	Reference
Protein kinase-B (Akt)	Inhibit	Akt is a kinase involved in muscle hypertrophy	[39]
Protein synthesis	Inhibit	Akt-induced protein synthesis	[39]
Myocyte proliferation	Inhibit	Muscle cell growth division	[40]
Myocyte quiescence	Induce	Muscle cell deactivation	[40]

3. Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were followed for the systematic review and meta-analysis [Sterne, 2001]. Furthermore, the Cochrane Handbook for Systematic Reviews of Interventions [Begg, 1994] and the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care [Egger, 1997] guidelines were subsequently followed.

3.1 Search strategy

Two investigators independently performed a literature search by means of the Scopus® database (Elsevier BV, Amsterdam, The Netherlands) to identify clinical trials published up to May 2022. The clinical trials investigated the effects of daily consumption of EPI-rich Cacao products or pure EPI on FST and MSTN. Keywords used in the search criteria were:

("Myostatin" OR "follistatin" OR biomarkers) AND (Cacao* OR chocolate OR cacao OR *catechin) AND (clinical AND trial OR trial OR human OR "double blind*" OR "single blind*"). In addition, reference lists of published trials and reviews were checked for relevant studies.

3.2 Literature selection

A flow diagram for study selection is presented in Figure 1. Clinical trials were included in the meta-analysis and systematic review if they met the following inclusion criteria:

1. The primary or secondary outcome of the study was both FST and MSTN; and
2. The intervention lasted for at least five days (this is due to the effective half-life of EPI); and
3. The intervention was an EPI-containing Cacao or chocolate food or pure EPI; and
4. The last measurement of FST and MSTN was performed after the intervention period.

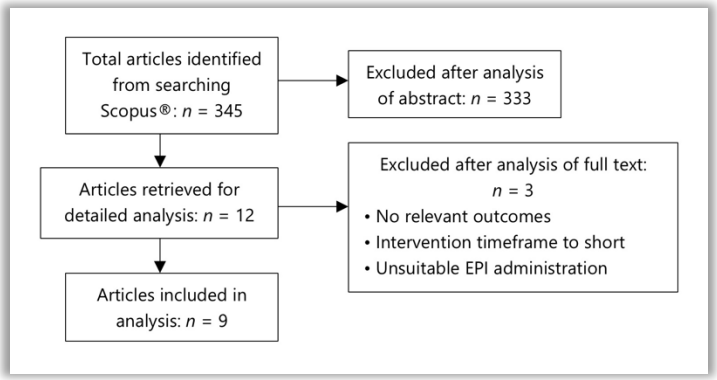
3.3 Data extraction

Following the literature search, the investigators reviewed the study titles and abstracts, followed by the full-text articles for eligibility. Discrepancies were resolved by discussion and agreement. Data was extracted following the inclusion criteria. Studies were also excluded if there was no FST and MSTN measurement, did not include EPI-rich Cacao or chocolate extract or pure EPI, or when acute intervention was performed. Data on means and standard deviations (SD) at the end of the intervention was extracted. If FST or MSTN data was not available in the text, they were estimated from the plots. Estimations were extrapolated by the following methods. If SDs were not reported, they were calculated or estimated from:

- Standard errors (SEs); or
- Confidence intervals (CIs); or
- *p*-values for difference in means; or
- Pooled correlation coefficients between baseline and final measurements from trials reporting sufficient information.

Multiple comparison arms sharing the same control group were separated to create double counting and correlated comparisons. If more than one flavanol dose level was tested, a separate intervention was included in the main meta-analysis; if more than one treatment time was described in the intervention (i.e., 80 or 150 days), multiple intervention time was considered for the main meta-analysis.

Figure 1. Search strategy



3.4 Risk-of-bias assessment

Two investigators independently assessed the risk-of-bias by performing a risk-of-bias assessment using the Cochrane Collaboration's tool [Higgins, 2011]. The criteria used in the risk-of-bias assessment were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, or selective reporting. Overall risk-of-bias was assigned to interventions, and the risk-of-bias was defined as:

Table 5. Risk-of-bias factors

Risk factor	Conditions for risk
Low	When 4–6 of the above criteria scored low risk, and 0–2 criteria scored unclear risk
Moderate	When unclear risk was scored in 3–4 of the criteria, low risk in 2–3 criteria, and moderate risk in 0–1 criteria
High	When high risk was scored in any of the criteria

3.5 Statistical analysis

All statistical analyses for the meta-analysis were performed using the open-source statistical online calculator Psychometrica [Lenhard, 2015]. The meta-analysis was performed using the calculator function – '*2. Comparison of groups with different sample sizes (Cohen's d, Hedges' g)*' – within the package meta, which produces both Cohen's *d* and CLES statistical values from pre and post-intervention mean, SD, and sample size *n*. Considering the large between-study heterogeneity in most cases, results from the random-effects model were presented.

Weighted scatterplot smoothing function was calculated with Microsoft Excel. 95% confidence interval Cohen's *d* values were calculated and used since the number *n* of each intervention was below 50. Inverse Log's were calculated and applied to find a mean and SD of CLES.

Potential heterogeneity sources were investigated according to various study characteristics priori defined as: study design, subject characteristics, type of intervention, duration of intervention, risk-of-bias, and funding body.

CLES was used to assess the statistical significance of the strata differences. The meta-regression considered characteristics from residual heterogeneity. The robustness of the meta-analysis was assessed using sensitivity analysis by removing the studies one at a time. Visual inspection of Egger's *p*-value test was assessed for publication bias [Egger, 1997].

4. Literature Review

The following literature resources were of significant value to the current research contribution in the meta-analysis and systematic review.

Table 6. Meta-analysis study inclusions

Study	Intervention #	Population	Age	*n*	EPI (mg)	Days	Training	Reference
Seo et al. 2021	Intervention 1	Korean's	60≥	72	130-204	80	Nil	[46]
Qureshi et al. 2020	Intervention 2	Friedreich's ataxia	10-22	10	75	144	Nil	[47]
	Intervention 3			10	150	144	Nil	[47]
Mafi et al. 2019	Intervention 4	Sarcopenic elderly	66-71	17	75	151	Nil	[48]
	Intervention 5			15	75	151	Resistance	[48]
Garcia-Merino et al. 2020	Intervention 6	Athletes	n.d.	14	100	151	Nil	[49]
McDonald et al. 2021	Intervention 7	BMD	18-60	7	40	70	Endurance	[25]
Taub et al., 2013	Intervention 8	HF, T2D	47-71	5	100	90	Nil	[50]
Gutierrez-Salmeannet al. 2014	Intervention 9	Healthy	36-46	6	50	7	Nil	[13]
Barnett et al. 2015	Intervention 10	Healthy	n.d.	8	50-200	5	Nil	[24]
Schwarz et al., 2018	Intervention 11	Athletes	18-30	20	200	28	Endurance	[51]

BMD Becker muscular dystrophy
HF Heart failure
n.d. Not disclosed
T2D Type-2 Diabetes

5. Results

Nine published articles with 11 intervention arms met the inclusion criteria. A significant improvement of the FST:MSTN ratio was observed in participants who ingested EPI, with a CLES for Cohen's *d* of 0.92 (95% CI: 0.74 to 0.99). Strong evidence of an association between EPI consumption and FST induction was noted, with weaker evidence for MSTN inhibition. Respectively, 0.98 (95% CI: 0.88 to 1.00) and 0.71 (95% CI: 0.50 to 0.88). The most significant marker observed during EPI interventions was the significant increase in FST. This leads to a natural inhibition of MSTN and, by default, a favourite FST:MSTN. Ratio towards FST.

Figure 2. Meta-analysis forest plot of FST:MSTN ratio

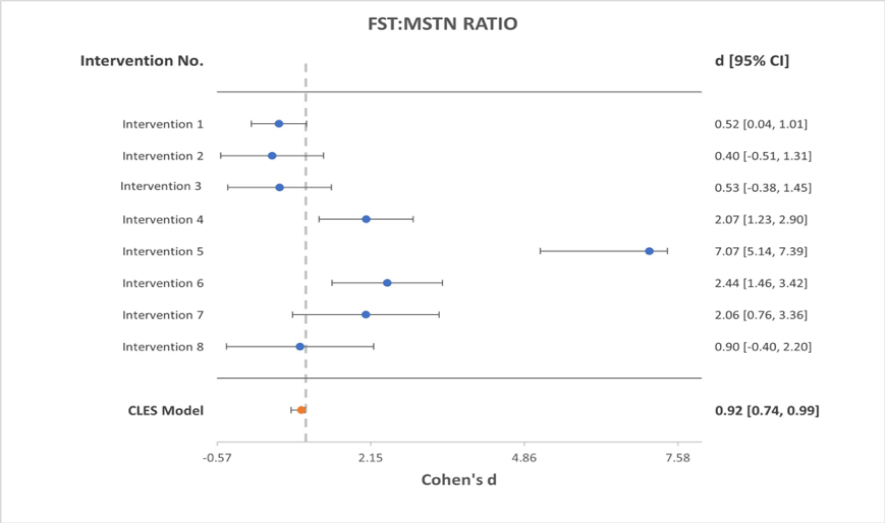


Figure 3. Meta-analysis forest plot of FST on right and MSTN on left

6. Discussion

6.1 Effects of l-epicatechin administration on follistatin and myostatin

It is evident that EPI has a significant impact on the ratio of FST:MSTN. Whether EPI interventions used different training regimes (i.e., endurance, resistance) or involved different populations, from young to elderly and healthy, sick, to athletic, a positive trend was always observed in the FST:MSTN ratio. This trend cannot be explained by the usual means of increasing FST and decreasing MSTN, such as training, age, or illness. However, within interventions, there were different levels of inhibition and induction. One explanation for this could be digestion and metabolism related. A plausibility in muscle biomarker efficacy could be explained by poor absorption of EPI, P450 isozyme levels based on diet, or enzymatic metabolism and microflora fermentation in the gastrointestinal tract. A method to bypass these transitional factors is by utilization of cyclodextrin-inclusion complexes. A cyclodextrin-inclusion complex causes the lipophilic EPI molecule to become water soluble. This, in turn, increases stability (i.e., gastrointestinal tract metabolism and fermentation) also absorption through hydrophilic juices in the small intestine.

6.2 Application of cyclodextrins in supplements

The gastrointestinal tract typically has a poor absorption rate of plant extracts and isolated plant compounds, also known as phytonutrients – that are used as ingredients in supplements. Phytonutrients have many health benefits; however, they generally suffer from poor absorption rates and low bioavailability. Most notably, this is a result of the lipophilicity of phytonutrients. The lipophilicity results in poor dissolution in gastric juices and general instability. This instability is factored in either by acid-sensitivity, enzymatic metabolism, and/or microflora fermentation.

Cyclodextrin-inclusion complexes have been developed to optimize the bioavailability of phytonutrients and bypass instability factors. On the market, a number of supplements have been released that include cyclodextrin as an ingredient in their products. This is based on research suggesting cyclodextrins increase the rate of absorption and bioavailability of phytonutrients. Nonetheless, these new-era supplements simply add and mix cyclodextrin with a phytonutrient in a capsule instead of creating an inclusion complex. The data, however, shows that inclusion complexes using cyclodextrin are pre-synthesized to achieve optimal absorption and bioavailability. Pre-synthesized cyclodextrin-inclusion complexes are expensive and complicated to formulate, usually requiring some level of professional laboratory.

When simply mixing cyclodextrin and a phytonutrient in a capsule, as the new-era supplements, the digestive process, by chance, will naturally utilize part of the cyclodextrin to complex some of the phytonutrients. Multiple factors determine the amount of cyclodextrin that will form an inclusion complex during digestion. These factors include general stomach and intestine content, time taken for the capsule to break down and dissolve during digestion, the acidity of stomach acids, and whether there are other lipids in the digestive tract that will interact with the cyclodextrin. In essence, the human digestive tract is an inefficient medium for forming cyclodextrin-inclusion complexes. The literature uses pre-formed, pre-synthesized cyclodextrin-inclusion complexes so that a standardized control can be administered to research subjects without a range of different levels of complexes forming.

Ingesting a pre-complexed cyclodextrin in a liquid form removes the sporadic factors of forming inclusion complexes within the human digestive system. This creates a far superior absorption and bioavailability of the phytonutrient compared to new-era

cyclodextrin supplements. The liquid cyclodextrin complex-inclusion formula by APOC is in line with the results found within the scientific literature on effective cyclodextrin-inclusion complexes.

6.3 Ideal dosing of l-epicatechin

An important consideration of the dosing protocol is the effective half-life of a compound. This defers from a blood elimination half-life. The effective half-life is the biological effects that remain after a compound has been eliminated from the blood (i.e., a compound may initiate a process in the body that might last a day, but the compound is eliminated from the blood in a few hours). Human studies indicate that although EPI is eliminated from the blood with a half-life of approximately 2.1 hours, the effects of EPI on biomarkers take five days to cease. To further support this, dosing studies of EPI on humans found no difference in FST or MSTN levels whether EPI was dosed two or four times per day. This clinical evidence suggests that the effect of EPI on biomarkers is not cumulative by dose regularity but is a gradual biological process. This means that for the process of inducing FST and inhibiting MSTN, the number of doses per day of EPI is of insignificance.

Further to support the once-a-day dosing, the acute effects of EPI are as an inducer of nitric oxide (NO). NO is a significant contributor to athletic performance. Once a day, dosing of EPI before physical activity is most beneficial for a performance advantage induced by NO induction. FST and MSTN are unaffected and not increased by maintaining stable blood levels of EPI due to effective half-life. For practicality, ease, and performance, the author supports once daily dosing of EPI.

6.4 Dietary exposure of l-epicatechin

EPI exposure from the diet is interdependent on the social determinants of health. Exposure can depend on factors such as age, gender, location, education, socioeconomic status, culture, tradition, beliefs, disability, and health. Foods can also vary in EPI content based on harvesting location, growing conditions, and season. This means individuals can be limited or impaired to some degree in their exposure to EPI from food. Different EPI-containing food harvests constitute varying levels of EPI. A method of optimal EPI ingestion is through supplementation. EP1 (Cacao Advanced®) supplements the maximum acceptable quantity of EPI in raw Cacao beans in accordance with the European Dietary Guidelines for cacao flavanols [https://www.efsa.europa.eu/en/efsajournal/pub/2809]. Food Standards Australia New Zealand has created a legislative provision incorporating European standards under the Australian medical food category, under s11(b) of Standard 2.9.5 – Food for special medical purposes of the *Australian New Zealand Food Standards Code* [https://www.legislation.gov.au/Details/F2021C00198]. EP1 (Cacao Advanced®) further incorporates a patented food technology that delivers food-derived EPI efficiently and with maximum absorption through the human digestive tract utilizing a cyclodextrin-inclusion complex.

6.5 The application of EP1 (Cacao Advanced®) as general medical food and in sporting activities as a nutritional supplement

Utilization of the APOC medical food is in athletes, recreational sports people, and those undergoing physical rehabilitation. Apart from the utilization of dietary EPI exposure and the benefits of utilization of cyclodextrins, EPI is involved in a cellular process called membrane healing [Shay, 2015]. Membrane healing is involved in skeletal muscle repair and faster recovery time. This means that EPI, and in particular, EP1 (Cacao Advanced®), can be used in the dietary management of unhealthy muscle gain techniques used by athletes, in the gym, or for physical rehabilitation. Athletes and sports people harming their bodies for gain in performance is a growing endemic and is of such significance that the Royal Australian College of General Practitioners (RACGP) has recently included athletic-based nutrition deficiencies and manipulations as medical conditions [REF]. Included in athlete-based medical conditions is an abuse of protein intake and abuse and misuse of a World Anti-Doping Agency (WADA) prohibited compound known as YK-11, a Selective Androgen Receptor Modulator (SARM). YK-11 has *in vitro* and *in vivo* evidence of MSTN inhibition and FST induction. As such, it is commonly sold online and purported as a MSTN inhibitor for a super physiological advantage in the gym. However, YK-11 has no clinical evidence of efficacy or safety. It is an exploratory compound of interest; it is still in the animal model research phase. For persons who are inclined to potentially damage their health, EP1 (Cacao Advanced®) is a nutritional viable alternative.

A fascinating biomechanical role of flavanols is their ability to inhibit the enzyme MAO-B [Carradori, 2016]. EPI has shown pre-clinical evidence of inhibiting MAO-B [Jager, 2011]. MAO-B enzymes are involved in the degradation of phenylethylamines and the neurotransmitter dopamine – as well as other xenobiotic amines. It is theorized that MAO-B inhibition may elicit nootropic-like activity [Stancheva, 1988]. Nootropics have begun gaining popularity in the sports supplement industry, with evidence supporting the utilization of nootropics for an athletic edge.

7. Conclusion

Every clinical study exploring the effects on the FST:MSTN ratio due to EPI consumption resulted in a significant positive ratio towards FST. This meta-analysis and systematic review provide evidence that EPI ingestion significantly improves the FST:MSTN ratio in humans by inducing FST and inhibiting MSTN. However, the included studies showed a high risk-of-bias, and there was substantial variation in the results that could not be explained by the heterogeneity characteristics that were explored. The significant risk-of-bias concerns being small populations and most studies being unblinded. Nevertheless, considering the heterogeneity of children and elderly and the lack of exercise intervention or alternatively high-quality exercise regime interventions, it is difficult to purport the significant change in FST:MSTN to a reason other than EPI administration. The EPI consumption is the only feasible explanation for the drastic FST:MSTN ratio improvement.

As the reviewed studies elicited impressive results for the FST:MSTN ratio fair conclusion is that a medical food – in this case, EP1 (Cacao Advanced®) by APOC – is a supplement for nutritional support of the FST:MSTN ratio activated by the phytonutrient epicatechin from cacao. The evidence of the utilization of FST and MSTN in muscular disease supports the use of EP1 (Cacao Advanced® by APOC) in muscular structure in those who are limited or impaired in accessing EPI from ordinary food. Furthermore, EP1 (Cacao Advanced®) by APOC can be used as a healthy alternative to replace unhealthy muscle gain techniques used by athletes, in the gym, or anyone undergoing physical rehabilitation.

This meta-analysis was limited by small sample sizes, insufficient blinding, and heterogeneity. Although results are promising, it is pertinent to conduct further clinical trials with larger sample sizes and targeted populations to clinically form evidence to use EPI as a targeted therapy in pathophysiological conditions.

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Conflicts of Interest: Victor Chiruta holds a provisional patent under the company Octavian and Desmond Pty Ltd for the use of EPI in medical foods and conducts compliance advisory for APOC Pty Ltd.

Ethics declaration: The author confirms that the current meta-analysis and systematic review were conducted in accordance with the International Committee of Medical Journal Editors (ICMJE) *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* [55].

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