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Review

Effectiveness of Silymarin, Sulforaphane, Lycopene, Green Tea, Tryptophan, Glutathione, and Escin on Human Health: A Narrative Review

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Abstract: Background: Recently, the role of nutraceutical compounds in the prevention of human diseases has been rapidly increasing. Here, we aim to evaluate the beneficial effect of dietary supplementation with seven active principles, i.e., lycopene, sulforaphane, silymarin, glutathione, escin, tryptophan, and green tea catechins, on human health. Methods: An extensive search of PubMed and Medline database was performed with the following keywords: "silymarin", "sulforaphane", "lycopene", "green tea catechins", "tryptophan", "glutathione" and "escin" accompanied by the keywords "supplement", "supplementation", and "nutraceutics". All preclinical and clinical trials were considered for this review. Results: One hundred and eighteen full-text articles were eligible for inclusion in this review. The papers examined presented considerable variability due to the wide heterogeneity of dosages administered, population involved, and outcomes pursued. Conclusion: Nutritional supplementation with lycopene, sulforaphane, silymarin, glutathione, escin, tryptophan, and green tea catechins appears to exert a wide range of benefits on human health, ranging from mood and cognition to cardiovascular health, fertility, metabolism, antioxidant, and anti-inflammatory capabilities, as well as potential anticancer effects. Further studies are required to better define the potential synergic effect, optimal dosage, mechanism of action, and tolerability profiles of these substances.

Keywords: sulphoraphane; silymarin; lycopene; glutathione; escin; tryptophan; green tea; men health; prevention

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1. Introduction

Nowadays, dietary supplementation is a widespread practice which involves not only patients affected by actual diseases, but also healthy populations. Over 50% of adults in the USA regularly include some form of supplement intake in their daily routine [1]. Reasons for supplementation may range from a general intention to "stay healthy" and prevent diseases—cancer in particular—to addressing specific needs tied to known medical conditions or deficits [2]. Furthermore, the user almost always chooses the supplement as a "self-prescription", rarely consulting a doctor before purchase [3].

There is an enormous amount of substances and actives of natural origin that are known for their purported health benefits. The aim of this review is to narratively summarize the properties of seven particular principles which commonly recur in commercially available supplements and present some interest in the fields of not only urology and andrology, but also general well-being and prevention of oxidative-stress damage as a result of exposure to environmental pollutants.

The chosen substances are sulforaphane, lycopene, escin, silymarin, glutathione, green tea, and tryptophan. There are multiple reasons for the choice of these seven particular substances. Firstly, they all have the common trait of having systemic wellness effects that could be useful for almost any patient regardless of age and comorbidity. Moreover, when used as supplements with adequate dosage, they have not shown relevant side effects. Finally, their combined use in a single tablet could be possible due to their non-competitive and potentially synergistic mechanisms of action.

Research Question

We put forth this research query:

Is dietary supplementation with silymarin, sulforaphane, lycopene, green tea catechins, tryptophan, glutathione, and escin able to protect human health, increase fertility, and prevent aging disease?

In order to respond to this research question, we performed a narrative review of all available studies performed with the aim to evaluate the efficacy of dietary supplementation with silymarin, sulforaphane, lycopene, green tea catechins, tryptophan, glutathione, and escin with respect to human health benefits.

2. Materials and Methods

Research Strategy and Literature Search

From January to March 2023, three independent reviewers (C.d.A., F.S., and C.V.) performed this research in the PubMed database, Cochrane CENTRAL, and Scopus. All disagreements between the two reviewers were resolved by three experienced supervisors (F.P., T.C., and A.P.). All references cited in relevant articles were also reviewed and analyzed. Considering the extent of the literature published on the subject in general and on each of the active substances in particular, the authors saw fit to present the results of this review in a narrative fashion. A systematic or meta-analytical comparison of heterogeneous outcomes in measurements, population, and methodology is beyond the scope of this work. The research strategy included the following keywords: "silymarin", "sulforaphane", "lycopene", "green tea catechins", "tryptophan", "glutathione", and "escin", accompanied by the words "supplement", "supplementation", and "nutraceutics". Only papers in English language were included. Randomized controlled trials (RCTs), quasi-RCTs, and non-randomized trials were included as a priority, whereas prospective and retrospective cohort studies, as well as case-control studies were included in cases of significant results or population numbers. Case reports and case series were excluded. Preclinical and in vitro evidence was examined and presented in the case of lack of significant clinical evidence for certain substances.

3. Results

A total of 98 papers were included in this review: 7 papers for silymarin, 21 papers for sulforaphane, 9 papers for lycopene, 33 papers for green tea catechins, 12 papers for tryptophan, 4 papers for glutathione, and 12 papers for escin. Of these, 39 papers were preclinical evidence papers and the remaining 59 papers were clinical trials. Amongst the clinical trial papers, 50 papers were RCTs, 7 papers were non-RCTs, and 2 papers were case-control studies (Figure 1).

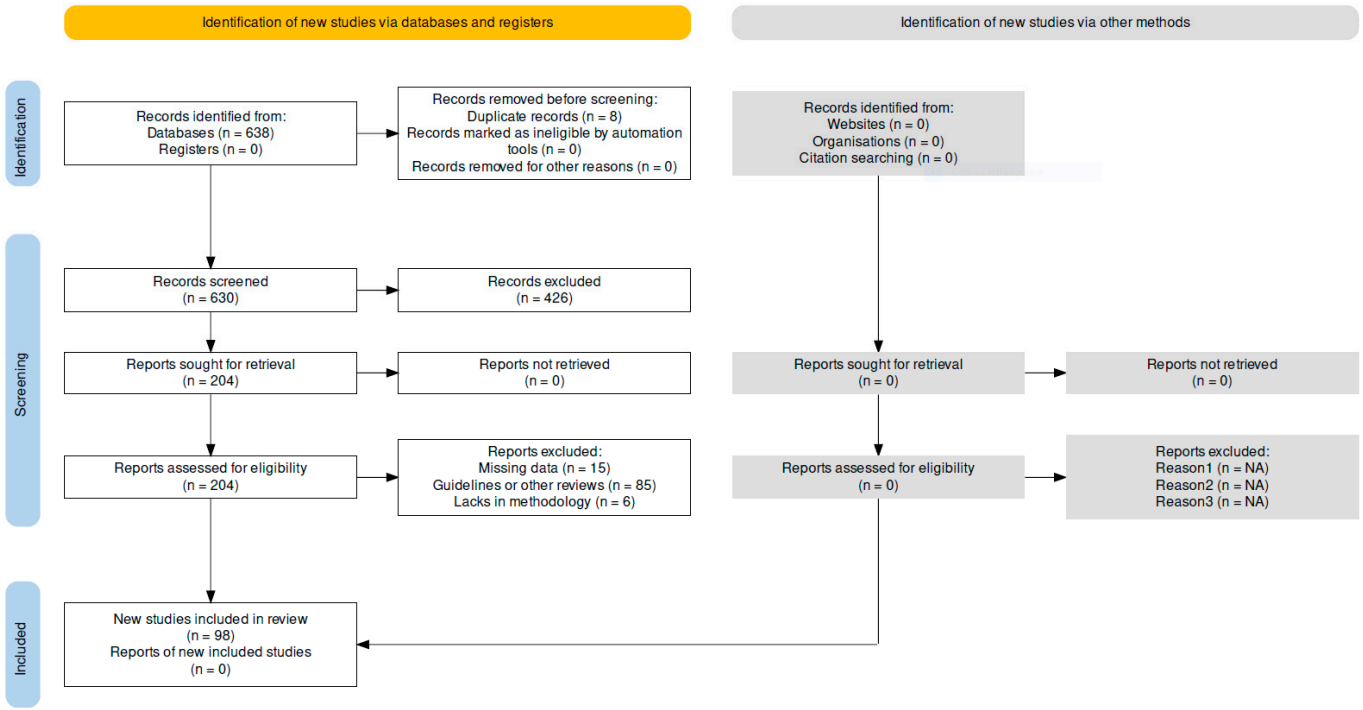

Figure 1. Schematic of this paper's selection process according to PRISMA recommendations.

4. Discussion

4.1. Silymarin

Silymarin is a flavonolignan complex derived from the seeds of milk thistle (Silybum marianum). It has been shown to have antioxidant, anti-inflammatory, anticancer, cancer protective, and also hypocholesterolemic and hepatoprotective properties [4]. In a study on prostate cancer (PCa) cells, silymarin was able to inhibit cell growth and induce differentiation of these cells [5]. In different studies, silymarin has been shown to have anticancer effects particularly in preventing the growth of PCa cells [6–8]. In addition, silymarin may delay progression after a radical treatment for PCa [9,10].

In a randomized, double-blind, placebo-controlled crossover study, 49 patients were enrolled with a history of prostate cancer and rising PSA levels after radical prostatectomy (n = 34) or radiotherapy (n = 15). After 10 weeks of supplementation, a four-week washout period followed. Baseline parameters were homogeneous among the two groups.

The results showed that the slope of the PSA concentrations improved with the supplement. The median total PSA doubling time for the supplement periods was 1150 days and 445 days for the placebo periods [9].

In another RCT, 37 patients treated with radical prostatectomy were randomly allocated into a supplementation group (n = 19) or a placebo group (n = 18) for six months; both groups were homogenous. Physical examination, quality of life score, hematology, basic clinical chemistry and oxidative stress markers, testosterone levels, and antioxidant status were evaluated at baseline and after 3 and 6 months. Statistically significant reductions of low-density lipoproteins and cholesterol were found. The authors concluded that the supplementation might be effective as these two markers are associated with PCa progression [10].

In addition, silymarin could be useful to treat BPH. In an RCT, fifty-five patients were randomly allocated to a treatment group (n = 26) or a placebo group (n = 29); both groups were treated for 6 months. The following data were collected at baseline and after 6 months: the International Prostate Symptom Score (IPSS), bladder volume (BV), urinary flow rate, ultrasound estimated postvoid residual urine volume (PVR), serum PSA, testosterone, clinical biochemistry, hematology, and oxidative stress parameters. The

authors demonstrated statistically significant differences ($p < 0.05$) between the treatment and placebo groups for the following parameters: IPSS score, maximal rate of urine flow (Qmax), average flow (Qave), BV, PVR, and total PSA value [11].

The most common adverse effects that have been reported are gastrointestinal symptoms. The frequency ranged from 2% to 10% in controlled trials and it was comparable to those of placebos. Other adverse effects that have been reported are dermatological symptoms and headache, which are similar in frequency to a placebo [12].

4.2. Sulforaphane

Sulforaphane is a sulfur-containing compound found in cruciferous vegetables such as broccoli, brussels sprouts, and cabbage. Sulforaphane has several health benefits, including antioxidant and anti-inflammatory effects, as well as the ability to inhibit the growth of cancer cells [13–35]. Different studies have shown a protective effect on different targets in both in vitro [13–17] and in vivo models associated with oxidative stress damages [13,18–21].

Several studies have highlighted the antiproliferative features of sulforaphane in bladder [22–25], prostate [26,27], and kidney cancer [28].

In a double-blinded, randomized, placebo-controlled multicenter trial, 78 patients with rising PSA levels after radical prostatectomy were allocated to a treatment group or a control group, and received daily oral administration of 60 mg of sulforaphane or placebo, respectively. The study was conducted for 6 months followed by 2 months without treatment. The primary endpoint was the PSA slope. The secondary endpoints were the differences in adverse effects, PSA progression, and the number of men with stabilized or increased PSA after 6 months. The primary endpoint was not reached, while regarding the secondary endpoints, the median PSA slopes were consistently lower in treated men, mean changes in PSA levels between the first and sixth month were significantly lower in the treatment group ($+0.099 \pm 0.341$ ng/mL) as compared with the placebo ($+0.620 \pm 1.417$ ng/mL, $p = 0.0433$), PSA doubling time was 86% longer in the SF than in the placebo group (28.9 and 15.5 months, respectively), and PSA increases >20% after six months were significantly greater in the placebo group (71.8%) than in the treatment group (44.4%) [29].

A similar study was conducted on 98 men scheduled for prostate biopsy. Patients were allocated into either a supplementation or a placebo group in a double-blind, randomized controlled trial. The effects of supplementation on histone deacetylase activity, immunohistochemical biomarkers, and prostate biopsy gene expression were evaluated. A significant difference in gene expression was observed among some genes that are related to PCa development [30].

In a three-arm parallel randomized double-blinded intervention study, forty-nine men on active surveillance were treated with a supplementation of broccoli soup for 12 months. The primary outcome was gene expression of prostate tissue obtained by transperineal biopsy before and after a dietary intervention, while the secondary outcome was changes in metabolites. The three groups were supplemented, weekly, with 300 mL of soup made from a standard broccoli (control group) or from one of two experimental broccoli genotypes with enhanced concentrations of glucoraphanin, delivering three and seven times that of the control, respectively. The authors observed that changes in gene expression and associated oncogenic pathways were attenuated in men on the glucoraphanin-rich broccoli soup in a dose-dependent trend [31].

Since sulforaphane is able to change the gene expression in prostatic tissue [30–32], this mechanism may explain the reduction in cancer risk progression [29].

4.3. Lycopene

Lycopene is a natural compound that belongs to the carotenoid family of phytochemicals, which are found in various fruits and vegetables. It is a bright red pigment that gives tomatoes their distinct color [33]. Lycopene has been extensively studied over the past few decades for its ability to attenuate inflammation and oxidative stress [34].

In vitro and in vivo models have also highlighted its suppressive ability against cancer cells growth [35,36].

Research suggests that it may have a large number of potential health benefits, particularly in the field of cancer prevention [37–39] and cardiovascular health promotion [33]. In a phase II clinical study, 41 patients diagnosed with localized prostate cancer were enrolled and supplemented with 10 mg lycopene tablets per day. Among these patients, 37 patients completed the study. On the one hand, regression slopes of (log) PSA against time decreased in 26/37 (70%, 95% CI 53–84%) and in eight cases (21%) the post-treatment slope was negative. On the other hand, analysis of the PSA doubling time (pre- vs. post-treatment PSA) showed a median increase after supplementation of 174 days; however, this was not statistically significant ($p = 0.18$) [36].

In a study on men with prostate cancer, 79 patients with prostate cancer were randomized to a nutritional intervention with either (1) tomato products containing 30 mg lycopene per day; (2) tomato products plus selenium, omega-3 fatty acids, soy isoflavones, grape/pomegranate juice, and green/black tea (tomato-plus); or (3) a control diet for 3 weeks. Among patients with intermediate risk ($n = 41$) based on tumor classification and Gleason score after surgery, it was revealed that the median PSA decreased significantly in the tomato group as compared to the controls (−2.9% and +6.5% respectively, $p = 0.016$) [40].

In another study, a total of 40 patients diagnosed with HGPIN were randomized into two groups: Group A ($n = 20$) received 4 mg lycopene twice a day for one year, and Group B ($n = 20$) was periodically followed up. The serum PSA level in the treated Group A decreased for a mean level of 6.07–3.5 ng/mL, while in the control Group B, it increased from a mean value of 6.55 to 8.06 ng/mL [38].

Lycopene's anti-inflammatory and antioxidant properties are believed to contribute to its potential protective effects against prostate cancer [41].

In addition, lycopene may be a novel approach for the treatment of benign prostatic hyperplasia [42].

4.4. Green Tea

Green tea is a well-known common beverage obtained with the infusion of camellia sinensis leaves and buds, the daily consumption of which is particularly widespread in eastern countries. Its purported health benefits have been attributed to its rich content in plant polyphenols, especially epigallocatechin-3-gallate (EGCG), which is the most represented catechin in green tea and the most investigated one [43]. Experimental evidence on humans exists on a wide range of beneficial effects by either consumption of green tea as a beverage or as supplementation with green tea extracts in the form or EGCG capsules or powder. The most reported health benefit of green tea polyphenols is, by far, its antioxidant activity. There are numerous studies that have investigated the mechanism and magnitude of this effect in human subjects. One such study investigated the antioxidant activity of tea polyphenols by attempting to measure their capacity to protect against the toxicity of probable human carcinogens such as acrylamide, which is commonly present in carbohydrate-rich heat-processed food. In a randomized single-blind trial, 78 adults were randomly assigned to receive corn starch capsules containing either a placebo or 50 mg, 100, or 200 mg tea polyphenols after ingesting a bag of potato chips containing an estimated level of acrylamide. Blood samples were taken before, after 2 days, and after 10 days, which showed that tea polyphenol supplementation with the highest dose (200 mg) significantly increased the excretion of acrylamide via its oxidative metabolism pathway [44]. More commonly, the antioxidant activity of green tea has been investigated by measuring variations in the blood levels of cells or enzymes involved in antioxidant status. For instance, in a recent study, leukocyte activity and total plasma antioxidant status were measured by chemiluminescence methods measuring the capacity of plasma to scavenge superoxide. Volunteers were asked to take 300 mg of green tea extract daily for 14 days; whole blood samples from participants were stimulated with a bacterial peptide. The intervention caused a slight but irrelevant decrease in circulating leukocytes count, but

the total antioxidant status significantly increased ($p = 0.05$) [45]. Antioxidant activity of green tea was also observed in a study on 16 subjects who ingested either a single dose of green tea, 7 days of 2-cups-per-day green tea, or water as a control treatment. The single-dose and 7-day groups both showed significant increases ($p < 0.0005$) in the activity of human oxoguanine glycosylase 1 (hOGG1), a DNA repair enzyme, and in the activity of heme oxygenase-1, a protein with antioxidant and anti-inflammatory effects. Lymphocytic DNA damage was also significantly lower ($p < 0.001$) in the intervention groups [46]. Furthermore, a trial in which 18 healthy male volunteers ingested green tea extract (254 mg of catechins) highlighted that plasma phosphatidylcholine hydroperoxide (PCOOH) levels decreased with an inverse correlation with the increase in epigallocatechin plasma levels, suggesting an effective antioxidant capability of the substance [47]. Supplementation of 4 cups per day of green tea, or two capsules per day of green tea extract, compared to a placebo, were also associated with a reduction in the level of serum amyloid alpha (SAA), an inflammation marker, in 35 obese subjects with metabolic syndrome during the course of an 8-week study [48]. Finally, a 4-month phase II randomized controlled three-arm trial studied the effect of drinking 4 cups daily of either green or black tea or water on oxidative DNA damage among a population of 133 heavy smokers by measurement of urinary 8-hydroxydeoxyguanosine (8-OHdG). This marker decreased significantly in green tea consumers after 4 months of the intervention in subjects with mutated genotypes of glutathione-S-transferase which are associated with many different types of tumors [49].

Abundant experimental evidence exists in the literature on the purported effects of green tea catechins on metabolism and cardiovascular health. The general consensus seems to be that regular intake of green tea and/or green tea extracts produces positive effects on body weight control, lipid and general hormonal metabolism, glucose level control, and blood pressure control; however, the results have not always reached statistical significance. The main issue with evaluating this body of work comes from the extreme heterogeneity of outcomes investigated and the methods used to express those outcomes. For instance, green tea consumption has been observed to either be protective against weight gain or be associated with body weight reduction, in studies mostly conducted on overweight or obese individuals, even if some of these results were significant only when compared against the baseline and not against the placebo arm in some cases [50–52]. In some studies, lipid metabolism has been shown to be positively impacted by long-term green tea supplementation (12 to 14 weeks) in terms of lowering LDL cholesterol [53,54], while one other study showed no acute benefit on total or LDL cholesterol after a single assumption of a high-dose EGCG supplement, even if a significant attenuation of postprandial triglycerides was observed [43]. Findings on blood glucose level control, insulin, and insulin resistance are mostly inconsistent between the various studies, with some showing positive effects, and others concluding either limited or no benefit [43,52,54–60]. In terms of blood pressure control, green tea supplementation has been associated with a positive lowering effect, but the results were significant against a placebo only in a single study on 88 overweight or obese males, while another study showed only a within-group significance when comparing to baseline levels [52,60].

Green tea integration has also been investigated in terms of possible benefits on physical performance in the context of regular physical exercise or training programs. Improvements in muscle mass have been observed in sarcopenic elderly adults supplemented with green tea extract and essential amino acids during the course of 24 weeks [61]. Positive modifications in enzymes involved in physical endurance capacity have been found in previously untrained men and overweight women [62–64].

Green tea has a long history of having been associated with anticancer or at least chemopreventive properties. While this seems to have been confirmed by human experimentation on supplementation in relation to certain tumors, such as relapsing colorectal adenoma [65] or the incidence of de novo myelodysplastic syndromes [66], the evidence has not been as solid for neoplasms of uro-andrological interest and no clear conclusions on safety have been drawn [67–71]. Evidence for a clear benefit of green tea supplementation in human gynecologic neoplasms is not totally conclusive either, despite very strong

basic science, animal and human epidemiological evidence. EGCG supplementation for 12 months has been linked to a reduction in mammographic density (MD)—a measurement linked with breast cancer risk—in 1075 post-menopausal women, but only in the very selective group of women aged 50 to 55 years old [72]. Moreover, in a phase II clinical trial on ovarian cancer recurrence, less than one third of women treated with green tea supplementation presented absence of recurrence at 18 months [73–75]. The findings on cervical intraepithelial neoplasia (CIN) and vulvar usual type of intraepithelial neoplasia (uVIN) have been more encouraging, with significant benefits on clinical response or absence of progression in treatment arms. Of note, some of these studies included the application of catechin ointments with or without oral green tea supplements tested against placebos [73,76–81].

With regards to safety of green tea consumption, adverse effects ranging from gastrointestinal symptoms to liver toxicity have been reported with very high doses, but to date, no real consensus on a recommended upper level of intake has been reached [78].

4.5. Tryptophan

Tryptophan (TRP) is an essential amino acid; thus, it cannot be synthesized by humans and must be obtained through dietary intake, usually by means of plant- and animal-based proteins and most commonly in the quantity of 3.5–5.0 mg per kilogram of body weight, or more, depending on nutritional habits. Dietary supplementation with TRP has a long history because of the purported benefits on mood and nervous system health; it is a precursor of the neurotransmitter serotonin or 5-hydroxytryptamine (5HT) which itself strongly modulates mood and sleep functions [79]. The effects of TRP on mood and nervous system health have been widely examined in interventional trials. Most commonly, improvements were found in depressive symptoms, stress management, sleep patterns, social-cognitive and emotional processing, attention, and chronic pain. For instance, notable improvements in depression symptoms, mood, and sleep patterns were highlighted in depressed young adults, healthy adult women undergoing a series of cognitive and emotional tests, and elderly individuals with depression and sleep disorders when supplemented with TRP [80–82]. Increased recognition of positive emotions and consequent improvements in social interaction have been observed in healthy middle-aged and older adults who underwent supplementation with TRP, suggesting a potential role of the substance in preventing age-related decline in social-cognitive processes [83]. Behavior can be positively influenced by TRP supplementation, as a shift towards inclination to charity, improvement in response patterns to negative words, and emotion- and task-related impulsivity have been observed in several studies [84–87]. Chronic pain also seems to be positively influenced by TRP supplementation, as observed in 60 females with fibromyalgia syndrome supplemented with a multi-nutraceutical compound [88]. There is also limited clinical evidence of TRP supplementation on gastrointestinal health, although in a few selected medical conditions. In particular, TRP, glutamine, leucine, and micronutrient supplementation improved environmental enteropathy in affected Zambian adults [89] and a nutraceutical formulation with TRP and other actives significantly improved gastrointestinal symptoms in subjects with irritable bowel syndrome [90]. Another scarcely explored possible health benefit of TRP seems to pertain to physical exercise and performance. In fact, TRP supplementation has been observed to improve physical performance in aerobic exercise with supramaximal intercalated anaerobic bouts in 20 young healthy men, possibly because of serotoninergic modifications in neural drive [91]. When it comes to the safety of TRP supplementation, there are a few considerations to make. Unfortunately, in late 1989, a new syndrome appeared, named eosinophilia myalgia syndrome (EMS), and presented with muscle pain and a high eosinophil blood count, which was initially linked with inordinate or excessive intake of TRP supplements. Later investigation concluded that this syndrome was not TRP itself but the presence of contaminants in some of the supplements available. In fact, the incidence of EMS gradually returned to zero after the ban of certain products. Only excessive TRP consumption may actually induce side effects when taken at very

high doses (generally estimated in upwards of 70–200 mg/kg) which consist of tremor, nausea, and dizziness. Of course, special caution must be exercised in individuals who are chronically treated with 5HT reuptake inhibitors, as TRP interactions with such drugs may cause serotonin syndrome, which manifests with delirium, seizure, fever, and rarely coma. Although large-scale dose-related assessment remain to be found, it is nonetheless not likely that modest supplementation with TRP may cause more than mild and occasional side effects [79].

4.6. Glutathione

Glutathione (GSH) is a tripeptide present in most tissues, especially in the liver, which plays an extremely important role in the protection of cells from damage caused by free radicals and from endogenous and exogenous toxicity [92]. Glutathione is known to have strong antioxidant power which is expressed because of its intrinsic ability to alternate a reduced form (GSH), predominant and higher than 98%, with an oxidized form (GSSG), lower than 1%. It is distributed primarily in the cytosol and, to a lesser extent, in organelles such as the mitochondrion, nucleus, and endoplasmic reticulum, where it participates in many cellular metabolic activities including ROS removal, DNA and protein synthesis, and signal transduction [93]. Antioxidant activity is its main distinctive character; glutathione has seen wide preclinical and clinical experimentation mainly in the fields of oxidation-reduction balance, cancer prevention, and male infertility. It is known that reactive oxygen species (ROS) are essential for cellular metabolism and for various biochemical processes, but in excess, they can generate oxidative stress that can cause cell death. This is why cells possess several enzymes capable of maintaining a healthy balance between the synthesis and transformation of ROS into non-reactive forms. Glutathione is an essential part of a class of antioxidant enzymes called glutathione peroxidase. Glutathione peroxidase converts hydrogen peroxide (H_2O_2) into water with a mechanism that can be represented as follows:

$$2\ \text{G-SH} + \text{ROOH} \rightarrow \text{GSSG} + \text{ROH} + H_2O$$

In this process, the reduced glutathione (GSH) is oxidized to GSSG by glutathione peroxidase, and then regains its antioxidant capacity through the activity of another enzyme, glutathione reductase, which converts the macromolecule back into the reduced form with a NADPH-dependent process [92]. Glutathione has been investigated, mostly in the preclinical setting, because of its theorized anticancer activity. Cancer cells require high concentrations of ROS, higher than normal cells, and therefore need an equally effective antioxidant system to stem the resulting oxidative stress [92]. In fact, a reduction in GSH is implicated in the induction of various mechanisms of cell death (apoptosis, necrosis, and autophagy) which the tumor cell inhibits, to the point that, in many cancerous forms, an increase in the level of GSH has been associated with resistance to chemotherapy [94]. Therefore, it is legitimate to hypothesize that the modulation of GSH concentration in the tumor population could be a valid therapeutic target to induce cell death by directly interfering with GSH synthesis, by inhibition of glutamate cysteine ligase (GCL) [95], or by exploiting the affinity that GSH shows towards various substrates such as isothiocyanates [94]. The latter are phytochemicals that are well represented in plant foods such as cruciferous vegetables and which avidly bind the sulfhydryl group of the cysteine residue of GSH, demonstrating that they can play an important role in the prevention of tumors such as prostate cancer [96]. Glutathione has also been of interest in the field of male infertility. The antioxidant property of reduced glutathione is essential for the development and protection of the germinal epithelium from ROS damage. In particular, reduced glutathione reacts with lipid peroxides which, if left active, can induce alterations in membrane permeability and potential, undermining the integrity of spermatozoa, whose cell membrane is rich in polyunsaturated fatty acids [97,98]. As evidence of this, a reduction in GSH, induced or pathological, can generate oxidative stress such as to activate the autophagy mechanism in germ cells as an adaptive response [99]. From this, it can be deduced that adequate levels of GSH can promote the survival and well-being of germ cells. Nonetheless, antioxidant

therapy is commonly included as a means of treatment for male infertility. Spermatozoa are aerobic cells and, as such, are equipped with a wealth of different antioxidant enzymes for the various types of ROS to be modulated [100]. Indeed, ROS are natural products of sperm metabolism and are not always harmful. At low concentrations and carefully regulated, they lead to the genesis of the signals necessary for the fertilization processes. Conversely, at high concentrations, they trigger oxidative stress to which spermatozoa are particularly sensitive and which can cause damage to the DNA and the lipid and protein content of the cell [100]. Despite the high risk of incurring injury due to oxidative stress, spermatozoa have a very low concentration (−0.3 mM) of reduced glutathione compared to somatic cells (10 mM), probably due to their inability to synthesize new proteins [100]. Yet, in various studies, it has been found that glutathione plays an important role in the reactivation of some antioxidant enzymes. In particular, in a study conducted on 112 patients between 28 and 38 years of age, it was possible to compare the concentration of phospholipid-hydroperoxide glutathione peroxidase, a selenoprotein belonging to the glutathione peroxidase family, both in a group of 75 men with infertility of various types (varicocele, unilateral orchidopexy, orchitis, testicular trauma, unknown) and in a group of 37 healthy donor men. The results showed that, in the infertility group, the enzyme activity (93.2 ± 60.1 mU/mg) was much lower than in the control group (187.5 ± 55.3 mU/mg), resulting in a decrease in sperm count ($p < 0.01$) and percentage increases in morphological ($p < 0.001$) and motility ($p < 0.001$) changes [101]. There is also experimental evidence of the utility of glutathione for the treatment of other pathological conditions linked to male infertility. Leukocytospermia and varicocele represent two different pathological conditions that are both associated with oxidative stress resulting from inflammation [97]. Specifically, varicocele increases oxidant levels and decreases antioxidant levels [102]. In a study conducted on 53 patients, the concentrations of various antioxidant substances were evaluated, including GSH/GSSG ratio in three different groups: one group represented by patients with leukocytospermia, the second group including patients with varicocele, and a third group was a control with healthy patients. At the end of the study, it was possible to determine that the GSH/GSSH ratio was significantly higher in the control group than in the leukocytospermia group ($p < 0.05$) and in the varicocele group ($p < 0.001$) and, among the latter, it was higher in the leukocytospermia as compared with the varicocele group ($p < 0.05$). Sperm concentration ($p < 0.001$), sperm motility ($p < 0.001$), and the percentage of sperm cells with normal morphology ($p < 0.001$) were also positively correlated with the GSH/GSSG ratio [97].

4.7. Escin

Escin is a natural blend of triterpene saponins extracted from the seeds and the shell of the seeds of Aesculus hippocastanum. It includes various isoforms of which the most exploitable clinically is β-escin. This form, although endowed with considerable clinical efficacy, is unfortunately impaired by reduced bioavailability when administered orally; therefore, modifications are required, aimed at increasing its water solubility. Nonetheless, from a pharmacological perspective, escin has been shown to possess different and perfectly usable beneficial activities, although with not fully clarified mechanisms [103]. In fact, it is present in commercially available supplements and compounds for the management of varicose veins, hematomas, hemorrhoids, and venous congestion, and it also presents potential utility in the fields of urolithiasis, male infertility and varicocele, prostate and bladder cancer, and chronic prostatitis. The purported antiedema effect has an actual mechanistic basis. In various preclinical models, it has been found that escin can inhibit the activity of hyaluronidases, i.e., hyaluronic acid degradation enzymes, favoring the reconstitution and strengthening of one of the essential components of the extravascular matrix of the capillaries, and thus reducing the loss of plasma from the endothelium [103]. Escin may also be beneficial in protecting the endothelium from hypoxic damage. In various studies conducted on the endothelial cells of the umbilical vein incubated in hypoxic conditions, it was possible to appreciate the response of escin, capable of inhibiting the

cascade of reactions causing tissue damage. In a study by Arnould et al., it was shown that, in hypoxia, endothelial cells reduced the amount of ATP by 40% and increased the activity of phospholipase A2, an enzyme involved in the release of precursors of inflammatory mediators as well as stimulating adhesiveness to neutrophils. In this setting, administration of escin (at a dose of 100–750 ng/mL) inhibited ATP loss, reduced phospholipase A2 activity by 57–72%, and was shown to prevent increased adhesion to neutrophils [104]. To confirm this ability, in another study conducted on the same model, attention was given to the hypoxia-induced alterations in the expression of PECAM-1, a macromolecule important for the integrity of the junctions in the interendothelial adhesion sites and for the modulation of neutrophil transmigration. Escin has been shown to be able to prevent PECAM-1 alterations as well [105]. Moreover, escin has been shown to prevent hypoxia-induced reorganization of the endothelial cytoskeleton, with a consequent reduction in permeability and resolution of edema [103]. The effects of escin on vascular tone have also been investigated. In an in vitro study on a segment of the saphenous vein (obtained by saphenectomy and pretreated with norepinephrine), the administration of escin (at a dose of 5–10 µg/mL) induced an increase in venous tone which was maintained for more than 1 h after application. This increase has been shown to be suppressed by incubating the segment with indomethacin or other NSAIDs. This suggests that the effect of escin on vascular tone may be dependent on prostaglandin F2α [106,107]. As described in a recent review, escin also seems to have anti-inflammatory activity comparable to that of glucocorticoids, with the added advantage of triggering less adverse events. In fact, there are many similarities between escin and glucocorticoids, starting from the fact that the chemical structures both belong to the tetracyclic triterpenoids. Even more surprising are the similarities regarding pharmacological effects. Starting from an animal model, it would seem that escin not only can induce a downregulation of inflammatory mediators by upregulating the expression of glucocorticoid receptor (GR) but it can also inhibit the expression of NFkB and AP-1. This follows, on the one hand, the marked anti-inflammatory activity of glucocorticoids and, on the other hand, recalls their antiedema effect, with the inhibition of the proinflammatory pathways in the capillary endothelium which, by reducing permeability, solves consequently also edema. Escin, therefore, induces anti-inflammatory effects through transrepression (reduction in proinflammatory protein synthesis) and transactivation (increases in Ikb, lipocortin 1, and superoxide dismutase). Unlike glucocorticoids, however, it does not inhibit the physiological processes of tissue repair, does not increase the endogenous secretion of corticosterone, and does not induce cellular apoptosis in the spleen or thymus of mice [108].

The benefits of escin in patients suffering from urolithiasis have been observed in clinical settings. Urolithiasis is a pathological condition characterized by the presence of solid agglomerates of various types (calcium, struvite, uric acid, and cystine) present in the kidney and urinary tract. It is a very frequent pathology (it is estimated that 3 out of 20 men and 2 women out of 20 experience lithiasis at least once in their life) which can trigger even very intense symptoms with violent abdominal pain, restlessness, nausea, hematuria, and dysuria. In a prospective study, in particular, the effects of escin and prednisolone were compared on patients suffering from symptomatic ureteral calculi. A total of 360 patients were randomized into three groups: a group treated with escin, a second group treated with glucocorticoid prednisolone, and a third placebo control group. After 10 days of treatment, the reduction in pain, the decrease in the dilatation of the urinary tract, the rate of expulsion of the stones, and any adverse events that occurred during the treatment were evaluated. The group treated with escin showed better outcomes than the placebo group ($p < 0.00001$) and superior efficacy compared to the prednisolone group ($p < 0.05$). Regarding stone expulsion, significant differences were found between the treatment groups and the control group ($p < 0.05$) but not between the escin group and the prednisolone group ($p > 0.05$), while adverse events were recorded only in the group taking prednisolone [109].

A promising role of escin can be found in the field of male infertility. First, a potential mechanism might be in the antioxidant properties of this substance. It is known that reac-

tive oxygen species (ROS), although indispensable at low concentrations for fertilization processes, at high concentrations can damage the protein and lipid component and the DNA of spermatozoa [100]. In an animal model of a gastric ulcer induced by the administration of indomethacin, it was found that escin (at a dose of 0.45, 0.9, or 1.8 mg/Kg), in addition to reducing the concentrations of malondialdehyde, TNF-alpha, P -selectin, and VCAM-1, also promoted the activity of myeloperoxidases, superoxide dismutases, catalases, and glutathione peroxidases, suggesting a relevant antioxidant effect [110]. Moreover, there is evidence of the efficacy of escin in ameliorating seminal alterations linked with varicocele. In an animal model (rats), the pathological venous dilatation due to varicocele was reproduced with partial ligation of the left renal vein. After 4 weeks of daily administration of escin, the density of polymorphonuclear leukocytes, the number and motility of spermatozoa in the epididymis, and the concentrations of follicle-stimulating hormone, luteinizing hormone, and testosterone were evaluated. It was seen that, in a group of rats treated with escin, the testicular blood flow was significantly reduced, the density of polymorphonuclear leukocytes underwent a significant decrease and, conversely, the sperm count increased [111]. Findings in human subjects were also encouraging. In a randomized, placebo-controlled trial, three groups of patients with varicocele infertility were compared, including a control group, a group treated with surgery, and a group treated with orally administered escin at a dose of 60 mg/day continuously for 2 months. At the end of the treatment, compared to the control group, patients treated with surgery and escin showed an improvement both in sperm density (68.8% and 57.5%, respectively, compared to 38.5% in the control group) and in sperm motility (77.1% and 55.7%, respectively, versus 46.2% of the control group) [112].

Of note, escin is being investigated for potential cytotoxic effect and antitumor activity. In a recent study on both in vivo and in vitro models, the response of escin on castration-resistant cells of prostate cancer was evaluated. At the end of the treatment, it was found that escin could induce a cytotoxic effect in resistant cancer cells by inducing a chain mechanism. In fact, escin has been shown to be able to stimulate cell cycle arrest in G2/M leading to a marked reduction in cyclinβ1 expression and cyclin-dependent kinase 1 activation, with concomitant induction of p21 [113]. Potential cytotoxic properties were also investigated in bladder cancer cells. In the in vitro model, the ability of escin to inhibit cell growth and induce apoptosis seemed to be mediated by modulation of the FAS receptor. Escin can also induce a cytotoxic effect by reducing the mitochondrial membrane potential and increasing the activity of cytochrome C with consequent release of ROS [114].

Escin could also be of interest in the management of chronic prostatitis (CP) and chronic pelvic pain syndrome (CPPS). CP/CPPS is a pathological clinical condition characterized by pain in the perineum, pelvis, suprapubic area and external genitalia, urinary disturbances, and ejaculation disorders, without evidence of bacterial infection. It is a condition that significantly reduces the quality of life of patients, and it has been the subject of many studies. Among these, a recent study investigated the potential and efficacy of the combined treatment of extracorporeal shock wave therapy (ESWT) and administration of bromelain and escin. A total of 100 CP/CPPS patients were randomized into two groups, one group treated with ESWT alone and another group treated with ESWT plus bromelain and escin. Pain intensity, urinary and prostatitis symptoms, and quality of life were assessed after 4, 12, and 24 weeks, showing a significant reduction and even disappearance of pain in a significantly higher percentage of patients in the treated group with combined therapy compared to the group treated with ESWT alone, as well as slight improvements that were also found with regard to prostatic and urinary symptoms [115]. This can be explained by going back to the anti-inflammatory activity of both escin and bromelain (inhibition of mediators such as NF-kB, IL-1β, IL-6, TNF-α, and PGE2), which inhibit different inflammatory pathways by cooperating with the ESWT in addressing the complex pathogenesis of CP/CPPS.

As for tolerability, escin has not yet produced drug interactions and is, in general, well tolerated. Even where it has produced adverse events, they have been mild and transient,

commonly represented by gastrointestinal disorders (constipation, diarrhea, vomiting, and nausea), headache, dizziness, hot flushes, itching, and fatigue [116,117].

Table 1 summarizes the relevant findings according to the compounds.

Table 1. The table shows all included studies characteristics.

Substance	Reference	Species	Level of Evidence	Dose and Duration	Main Conclusions	Clinical Field of Significance
Green tea	[47]	Human	RCT	50 or 100 or 200 mg , single dose	Highest dose significantly increases excretion of carcinogenic acrylamide	Antioxidant activity
	[48]	Human	Non-RCT	300 mg/day for 14 days	Slight decrease in plasma leukocyte count, significant increase in antioxidant status	
	[49]	Human	RCT	1 cup single dose or 2 cups/day for 7 days	Increase in heme oxygenase-1 activity, decrease in lymphocytic DNA damage	
	[50]	Human	Non-RCT	254 mg , single dose	Plasma PCOOH levels decreased with an inverse correlation to the increase in plasma EGCG levels	
	[51]	Human	RCT	4 cups/day or 2 capsules/day for 8 weeks	Decrease in SAA levels	
	[52]	Human	RCT	4 cups/day for 16 weeks	Decrease in urinary 8-OHdG levels in heavy smokers with mutations of glutathione-S-transferase	
	[53]	Human	RCT	800 mg/day for 6 weeks	Beneficial period x treatment interaction in terms of body weight control in overweight subjects	Metabolism and cardiovascular health
	[54]	Human	RCT	4 cups/day or 2 capsules/day for 8 weeks	Significant decrease in body weight and BMI	
	[55]	Human	RCT	456 mg/day for 8 weeks	Mild changes in insulin level	
	[56]	Human	RCT	630 mg/day for 14 weeks	Reduction in cholesterol levels	
	[57]	Human	RCT	400 mg/day or 800 mg/day for 8 weeks	Reduction in LDL cholesterol and glucose-related markers	
	[58]	Human	RCT	100 mg/day for 4 weeks	Improvements in insulin resistance	
	[59]	Human	RCT	1450 mg , single dose	Reduction in some circulating catecholamines	
	[60]	Human	RCT	1500 mg/day for 16 weeks	Within-group reduction in waist circumference, HOMA-IR index, insulin level; increase in ghrelin level	

Table 1. *Cont.*

Substance	Reference	Species	Level of Evidence	Dose and Duration	Main Conclusions	Clinical Field of Significance
	[61]	Human	RCT	456 mg/day for 8 weeks	Reduction in HbA1c levels, borderline significant reduction in blood diastolic pressure	
	[62]	Human	RCT	350 mg/day for 7 days	Reduction in insulin levels	
	[63]	Human	RCT	800 mg/day for 8 weeks	Reduction in blood diastolic pressure	
	[64]	Human	RCT	540 mg/day for 24 weeks	Improvements in skeletal muscle mass in sarcopenic subjects	Physical performance
	[65]	Human	RCT	250 mg/day for 4 weeks	No negative effects on endurance-training adaptation	
	[66]	Human	RCT	570 mg/day for 8 weeks	Improvements in aerobic capacity during training	
	[67]	Human	RCT	1500 mg/day for 10 weeks	Improvements in metabolic and antioxidant status during physical exercise	
	[68]	Human	RCT	900 mg/day for 52 weeks	Reduction in incidence of relapsing metachronous colorectal adenomas	Anticancer activity
	[69]	Human	Case-control	>2 cups/day for >20 years	Significant decrease in incidence of de novo myelodysplastic syndromes	
	[70]	Human	RCT	600 mg/day for 24 weeks	No effect in preventing PCa incidence	
	[71]	Human	RCT	600 mg/day for up to 20 weeks	No effect in preventing PCa incidence	
	[72]	Human	Non-RCT	6000 mg/day for a median of 4 weeks	No antineoplastic activity in PCa patients	
	[73]	Human	RCT	600 mg/day for 52 weeks	No effect in preventing PCa incidence in HGPIN patients	
	[74]	Human	RCT	400 mg/day for 52 weeks	No effect in preventing PCa incidence in HGPIN and ASAP patients	
	[75]	Human	RCT	843 mg/day for 52 weeks	Reduction of mammographic density in women aged 50–55	
	[78]	Human	RCT	800 mg/day for 16 weeks	Absence of recurrence in 1/3 of treated women with ovarian cancer	
	[79]	Human	RCT	800 mg/day for 16 weeks	No protective effect on CIN	
	[76]	Human	RCT	200 mg/day for up to 12 weeks	Lower recurrence of CIN	
	[80]	Human	RCT	N/A	Higher clinical response in uVIN	

Table 1. *Cont.*

Substance	Reference	Species	Level of Evidence	Dose and Duration	Main Conclusions	Clinical Field of Significance
Sylmarin	[9]	Human	RCT	160 mg 4 tablets/day for 10 weeks	The dietary supplement utilized in this study was shown to delay PSA progression after potentially curative treatment in a significant fashion	Anticancer activity
	[10]	Human	RCT	570 mg/day for 24 weeks	The combination of this study significantly reduced two markers of lipid metabolism known to be associated with PCa progression	
	[11]	Human	RCT	570 mg daily for 24 weeks	Improvement of IPSS score, urodynamic parameters: maximal rate of urine flow (Qmax), average flow (Qave), V and RV, total PSA value	Antioxidant
Sulforaphane	[29]	Human	RCT	Two tablets containing 10 mg sulforaphane each, three times/day for 24 weeks	Median log PSA slopes were consistently lower in sulforaphane-treated men	Anticancer activity
	[30]	Human	RCT	Two 100-µmol/day taken 12 h apart. Mean intervention period was 4.4 weeks	The supplement was associated with significant interactions in gene expression among some genes that are related to PCa development	
	[31]	Human	RCT	A weekly 300 mL portion of soup made from a standard broccoli or from an experimental broccoli genotype with an enhanced concentration of glucoraphanin	Changes in gene expression and associated oncogenic pathways were attenuated in men on the glucoraphanin-rich broccoli soup in a dose-dependent manner.	
Lycopene	[36]	Human	Non-RCT	10 mg/day	A significant and maintained effect on PSA velocity over 1 year was demonstrated	Anticancer activity
	[38]	Human	RCT	4 mg twice a day for 52 weeks	Lycopene delay or prevent HGPIN from developing into occult prostate cancer	
	[40]	Human	RCT	30 mg/day for 3 weeks	Three weeks supplementation lowers PSA in patients with non-metastatic prostate cancer	
Escine	[115]	Human	RCT	10 days	Reduction in pain, decrease in the dilatation of the urinary tract, effective expulsion of the stone	Urolithiasis
	[116]	Human	RCT	60 mg/day for 2 months	Improvement in sperm density and in sperm motility	Male infertility

Table 1. *Cont.*

Substance	Reference	Species	Level of Evidence	Dose and Duration	Main Conclusions	Clinical Field of Significance
	[117]	Human	RCT	160 and 500 mg/day for 5 weeks	Decreased pain, improvements regarding prostatic and urinary symptoms	CP/CPPS
Reduced Glutathione	[102]	Human	RCT	N/A	Reduced glutathione reacts with lipid peroxides protecting germinal epithelium from ROS damage	Male infertility
	[106]	Human	Non-RCT	N/A	GSH can reactivate antioxidant enzymes stimulating an increase in sperm count and a decrease in morphological and motility changes	
Tryptophan	[83]	Human	RCT	200 mg/day for 7 days	Improvement of depressive mood in severe depression patients	Mood and cognition
	[84]		RCT	2000 or 4000 mg , single dose	Benefits on emotional function	
	[85]		Non-RCT	25 mg /kg of body weight for 12 weeks	Mental state improvement of elderly subjects with mood disorders	
	[86]		RCT	200 mg or 400 mg/day for 12 weeks	Improvements in social interaction	
	[87]		RCT	800 mg , single dose	Promotion of charitable behavior	
	[88]		RCT	1000 mg for 19 days	Benefits on emotional and social function	
	[89]		Case-control	N/A	Higher intake of tryptophan is linked to reduced emotion-related impulsivity	
	[90]		RCT	100 mg , single dose	Influence on attention-switching tasks	
	[91]		RCT	N/A	Reduced chronic pain in fibromyalgia syndrome	Chronic pain
	[92]		RCT	280 mg/day for 16 weeks	Improvement in environmental enteropathy	Gastrointestinal health
	[93]		RCT	N/A	Improvement in gastrointestinal symptoms in irritable bowel syndrome	
	[94]		Non-RCT	N/A	Decrease in fatigue perception during aerobic exercise	Physical performance

4.8. Limitations of the Study

This narrative review was limited by the extreme heterogeneity of the studies included in terms of methodology, measurements, and outcomes. Therefore, other than the classification of the effects and benefits of these substances, it was not possible to present statistical data significance. Further studies might be needed to provide confrontation between the significance of each trial performed for every single substance.

5. Conclusions

The evidence available on the substances investigated frame them as potential tools in the hands of the informed physician. Silymarin, sulforaphane, lycopene, green tea catechins, tryptophan, glutathione, and escin each demonstrated a potential benefit in offsetting the negative effects of oxidative stress and inflammation induced by environmental pollution on human health; improvements ranging from mood and cognition to cardiovascular health and metabolism have also been observed. These substances have also shown a possible promising antiaging and anticancer effect. Finally, a wide range of medical conditions, especially interesting for the urologist and andrologist, can be addressed by proper utilization of such supplements. Due to the different pathways involved in their mechanisms of action, it is also unlikely for these substances to generate negative interactions in the case of simultaneous intake. Thus, further studies are required to better define the potential synergic effect, optimal dosage, mechanisms of action, and tolerability profiles of these substances.

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