Protective Agents for Male Fertility

Subjects: Reproductive Biology

Contributor: Cláudio Maia , Roberta Martins , Ana Silva

The male reproductive system is highly susceptible to noxious influences, that can induce germ cell damage, alterations in spermatogenesis and male fertility. For this reason, it is of major importance to investigate possible ways to protect the male reproductive system. For centuries, natural products have been used by humans in folk medicine as therapeutic agents, and because of their beneficial properties for human health, plenty of them have been introduced to the pharmaceutical market as supplementary therapies.

male infertility natural products oxidative stress spermatogenesis

1. Introduction

In mammals, adult testicles participate in the biosynthesis and secretion of sex steroid hormones and the production of testicular fluid and spermatozoa. These endocrine and exocrine functions are crucial for male fertility [1]. The production of male gametes is a complex, dynamic, and continuous process that occurs inside the seminiferous tubules (SeT), the functional unit of the testis. Spermatogenesis encompasses three different sequential processes: (i) mitotic division of spermatogonia (spermatocytogenesis); (ii) meiosis; and (iii) spermiogenesis, the differentiation of spermatids into spermatozoa, which are released in the lumen of the SeT (spermiation) [1][2].

Several factors have been shown to affect the normal progression of spermatogenesis, which may lead to a significant decrease in the production and/or quality of spermatozoa, causing infertility. Oxidative stress is one of the most harmful factors and a major cause of male infertility, with relevant damaging effects on the development of germ cells and sperm function [3]. The endogenous cellular antioxidant defense system protects the cells against reactive oxygen species (ROS), which can be generated via endogenous processes or in response to exogenous agents. When ROS production exceeds the capacity of the endogenous cellular antioxidant defense system, oxidative stress occurs [4]. ROS can damage biological macromolecules such as proteins, lipids, and nucleic acids. These ROS actions will disturb the structure and function of the sperm membrane and DNA, declining the normal sperm parameters (e.g., motility, counts and viability) as well as the capacity to fertilize the oocyte [5][6]. Even with poor intratesticular vascularization and low oxygen tension, spermatogenesis and steroidogenesis are very susceptible to damage due to the high levels of ROS production in the testis [7]. In addition, it is well established that increased levels of ROS are associated with an inflammatory response, which may be triggered by several conditions, such as varicocele, tobacco, alcohol, and metabolic syndromes [8]. Finally, the testis is very sensitive to exogenous agents, such as several pharmacological, treatments that can induce adverse effects on spermatogenesis, sperm parameters, and sexual function [9].

For centuries, humans have used natural products in folk medicine as therapeutic agents and drugs. However, the use of these natural products has increased in recent decades and have been gradually introduced into the pharmaceutical market [10]. Using laboratory animals, several studies have demonstrated that certain natural products and derivatives might play a protective role against the damaging effects associated with oxidative stress, inflammation, and drugs side effects [11][12]. Moreover, many natural products have already been described as being useful for the treatment of male disorders such as sexual impotence [13][14].

2. Bioactive Compounds

2.1. Curcumin

Curcumin or [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadi-ene-3,5-dione] (chemical structure in the Supplementary Materials) is a bioactive substance that is present in the rhizome of the turmeric plant (*Curcuma longa*) and is the major constituent of turmeric powder [15][16][17]. It has been used in Asian folk medicine for several purposes and is also described in Hindu texts [18]. The most important properties of curcumin rely on its therapeutic benefits, which have been described in the treatment of several diseases, with the absence of toxic side effects [19][20][21].

It presents a wide range of pharmacological and biological activities [22], such as neuroprotective, anti-ageing [23], anti-microbial [24], anti-inflammatory [25][26], anti-tumor [27][28], and antioxidant [29][30] properties. The phenolic-OH group present in curcumin and β diketone derivatives can react with ROS and are powerful radical scavengers [31][32]. ROS can include hydroxyl radicals, nitrogen dioxide radicals, and superoxide radicals [33]. Curcumin can also reduce lipid peroxidation and oxidative DNA damage and regulates glutathione (GSH) levels [32][33].

In the testis, it has been shown that curcumin acts as a protective factor against oxidative stress-inducers such as cadmium. Curcumin prevents the histopathological damage caused by the presence of cadmium chloride [32][34], reversing the effects on the mean diameter of the SeT and lumen [32]. Additionally, curcumin increases the levels of GSH, glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) [32][34]; testosterone levels, transcription factor NF-E2-related factor 2 (*Nrf2*), and γ-glutamylcysteine synthetase [34]; catalase (CAT) and total thiols levels [32]; and decreased malondialdehyde (MDA) and hydrogen peroxide content [32][34]. Considering sperm parameters, the coadministration of curcumin with cadmium chloride increased sperm motility and concentration and decreased the morphologic defects of sperm compared to cadmium chloride alone [34].

Several drugs, such as cisplatin and artesunate, can induce damage in the male reproductive system. Cisplatin is a highly effective anti-neoplastic drug used in several types of solid tumors, and artesunate is used in the treatment of malaria; both induce severe damage to the reproductive system. Curcumin cotreatment with cisplatin or artesunate (low and high-dose) showed beneficial effects, preventing histopathologic changes [31][33][35] by increasing the mean SeT diameter and germ cell layer number [35] and by presenting a slight expression of nuclear factor kappa B (NF-kB) [31][35], iNOS, p38-MAPK [35], caspase-3, and 8-deoxyguanosine (8-OHdG) [31]. Additionally, in the group treated with cisplatin plus curcumin, it was observed that the SeT displayed myoepithelial,

spermatogonia, and spermatocytes cells with normal morphology [31]. Curcumin coadministration with one of these drugs increased GSH, GSH-Px [33][35], testicular weight, testosterone levels [35], SOD, and glutathione reductase (GSH-Rx) levels [33] and decreased MDA levels [33][35], glutathione-S-transferase (GST) [33], and nitric oxide (NO) levels [35].

Aflatoxins are toxic fungal metabolites that are produced by *Aspergillus flavus* and *Aspergillus parasiticus,* which contaminate human food. Mathuria et al. showed that the effects of curcumin on minimizing aflatoxins damage were dose-dependent, with the maximum amelioration of a decrease in the thiobarbituric acid reactive substance (TBARS) levels in mice testis being observed at 200 mg/mL [36]. Additionally, curcumin treatment plus aflatoxins (low- and high-dose) increased DNA, RNA, protein, and the activity of the 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD), both of which are enzymes involved in steroidogenesis, and decreased cholesterol. These effects were more effective when low doses of aflatoxins were used [37].

Other events/incidents inducing testicular damage may include chronic variable stress, scrotal heat stress, ischemia–reperfusion injury, and ageing. Curcumin also seems to improve histopathological testicular changes in these situations [15][16][38] by increasing the Johnson's Testicular Score [15][17], germinal epithelium height [15], the number of germ cell layers, and the mean of the SeT diameter [17]. Additionally, curcumin seems to decrease the number of apoptotic cells in the SeT [16] and oxidative stress, as indicated by the diminished MDA levels [17][38].

Chronic variable stress is a major problem that can lead to changes in endocrine and reproductive functions. When chronic variable stress was induced, curcumin treatment increased testosterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) levels compared to the non-treated group [16].

Testicular temperature is of significant importance to maintain the optimum environment for normal spermatogenesis, and consequently, scrotal heat stress is a primary factor associated with male infertility [38]. The different doses of curcumin in all of the experimental groups showed that this bioactive compound increased testis weight, testosterone levels, SOD activity, cytoplasmic copper/zinc SOD, mitochondrial manganese SOD, 3β-HSD, and phospholipid hydroperoxide glutathione peroxidase in a dose-dependent manner. Curcumin treatment increased the expression of the anti-apoptotic protein, B-cell lymphoma-extra large while decreasing expression of the apoptosis marker, caspase-3, which is indicative of its anti-apoptotic effect. Finally, heat shock protein factor 1, a major regulator of the stress-inducible response (anti-apoptotic), showed increased levels, whereas the levels of transforming growth factor-β1, a secreted protein involved in many cellular functions (e.g., cell growth, proliferation, differentiation, and apoptosis), were decreased in all of the curcumin-treated groups, indicating the anti-apoptotic effects of this bioactive compound once again [38].

Testicular torsion is a urologic emergency that leads to a surgical detorsion of the spermatic cord. The primary effect of testicular torsion–detorsion is an ischemia–reperfusion injury that increases the production of ROS. Curcumin administration repairs the noxious effects of testicular torsion by increasing heme oxygenase-1 (HO-1) protein expression levels and by decreasing xanthine oxidase (XO) activity when compared to the control and torsion–distortion groups [17].

Ageing is associated with infertility caused by decreased steroidogenesis, spermatogenesis, and sexual dysfunction. The mechanism is not totally understood, but oxidative stress and apoptosis seem to be the two significant factors that play an essential role in the ageing process. In aged testicular tissue, curcumin treatment resulted in increased GSH levels compared to the aged control group [15]. Despite the notorious beneficial effects in male reproduction in animal models, some studies claim that curcumin is not a therapeutic compound for male reproduction and other diseases [39][40]. They consider that curcumin has a PAINS (pan-assay interference compounds) and could be an IMPS (invalid metabolic panaceas) candidate.

In **Table 1**, it is summarized the beneficial effects in male reproductive system.

Table 1. Bioactive compounds with beneficial effects in male reproductive system.

Natural Product	Dosage of Natural Product	Toxic Stimulus	Dosage of Toxic Stimulus	Exposure Time	Animal Model	Reference
Curcumin	30 mg/kg/day in dimethyl sulfoxide (4% DMSO + PBS), intraperitoneally	Aging	-	21 days	Male Wistar albino rats	[15]
	100 mg/kg/day dissolved in 0.5 mL of olive oil, given orally	Chronic variable stress	-	15 days	Male Sprague Dawley rats	[16]
	200 mg/kg, intraperitoneally	Testicular torsion	-	4 h/90 days	Male Sprague Dawley rats	[17]
	100 mg/kg/day dissolved in dimethyl sulfoxide (DMSO), given orally	Cisplatin	5 mg/kg, intraperitoneally	7 days	Male Sprague Dawley rats	[31]
	100 mg/kg, intraperitoneally	Cadmium chloride	5 mg/kg, subcutaneously	24 h	Male NMRI mice	[32]
	300 mg/kg/day	Artesunate	150 mg/kg/day (low dose) 300 mg/kg/day (high-dose) dissolved in double-distilled water, given orally	45 days	Male Swiss albino mice (*Mus musculus*)	[33]

Natural Product	Dosage of Natural Product	Toxic Stimulus	Dosage of Toxic Stimulus	Exposure Time	Animal Model	Reference
	50 mg/kg/day, intraperitoneally	Cadmium chloride	2 mg/kg/day, intraperitoneally	10 days	Male Kunming mice	[34]
	200 mg/kg/day dissolved in corn oil, given orally	Cisplatin	7 mg/kg, intraperitoneally	10 days	Male Wistar albino rats	[35]
	25–200 mg/mL	Aflatoxins	2–10 mg/mL	-	Male Swiss albino mice (*Mus musculus)*	[36]
	2 mg dissolved in 0.2 mL of olive oil, given orally daily	Aflatoxins	25 mg (low dose) and 50 mg (high dose)/0.2 mL olive oil, given orally daily	45 days	Male Swiss albino mice (*Mus musculus)*	[37]
	20, 40 and 80 mg/kg/day dissolved in olive oil, given by intragastric intubation	Scrotal heat stress	-	14 days	Male ICR mice	[38]
Ellagic acid	10 mg/kg/day dissolved in alkaline solution (0.01 N NaOH), subcutaneous	Cyclosporine A	15 mg/kg/day dissolved in 1 mL olive, given orally	30 days	Male albino rats(*Rattus norvegicus*)	[41]
	10 mg/kg/day dissolved in olive oil, given orally	Cisplatin	7 mg/kg, intraperitoneally	10 days	Male Sprague Dawley rats	[42]
	10 mg/kg, given orally from the 21st week to 26th week	Cisplatin	5 mg/kg once a week in normal saline, intraperitoneally from the 23rd to 26th week	26 weeks	Male laca mice	[43]
	2 mg/kg/day dissolved in carboxy methyl	Phthalates	500 mg/kg/day dissolved in carboxy methyl	4 weeks	Male Wistar Albino rats	[44]

Natural Product	Dosage of Natural Product	Toxic Stimulus	Dosage of Toxic Stimulus	Exposure Time	Animal Model	Reference
	cellulose, given orally		cellulose, intraperitoneally			
	50 mg/kg/day dissolved in saline water (0.9% NaCl), given orally	Sodium arsenate	200 ppm/day dissolved in saline water (0.9% NaCl), given orally	40 days	Male Swiss albino mice	[45]
	2 mg/kg/every other day dissolved in alkaline solution (0.01 N NaOH), given orally	Polychlorinated biphenyl (Aroclor 1254)	2 mg/kg/day, intraperitoneally	8 weeks	Male Sprague Dawley rats	[46]
	20 mg/kg/day dissolved in 1% DMSO, given orally	Monosodium glutamate	17.5 mg/kg/day (low dose) or 60 mg/kg/day (high dose) dissolved in 1% DMSO, given orally	30 days	Male albino rats	[47]
Vitamin C	100 mg/day diluted in water, given orally	Ethanol	2 g/kg/day (25% *v*/*v*), given orally	63 days	Male Wistar rats	[48]
	5 mg/kg/day, given orally	Aluminum chloride	100 mg/kg/day dissolved in 1 mL water, given orally	4 weeks	Male Wistar rats	[49]
	200 mg/kg/day, given orally	Mercuric chloride	0.15 mg/kg/day dissolved in distilled water, intraperitoneally	30 days	Male Sprague Dawley rats	[50]
	250 mg/kg/day, given orally	Carbon tetrachloride	2 mL/kg/day dissolved in olive oil, given orally	10 weeks	Male Wistar albino rats	[51]
	100 mg/kg/day, given orally	Lead	25 mg/kg/daydissolved in distilled water, given orally	90 days	Male Wistar albino rats	[52]
	50 mg/kg/day, gastric gavage	Tetracycline	30 mg/kg/day, gastric gavage	28 days	Male Sprague	[53]

Natural Product	Dosage of Natural Product	Toxic Stimulus	Dosage of Toxic Stimulus	Exposure Time	Animal Model	Reference
					Dawley rats	
	200 mg/kg/day, given orally	Tetracycline	28.6 mg/kg/day dissolved in saline, given orally	14 days	Male Wistar rats	[54]
	50 mg/kg/day, given orally	Cisplatin	8 mg/kg, intraperitoneally	14 days	Sprague Dawley rats	[55]
	100 mg/kg, intraperitoneally	Testicular torsion	-	4 h	Male Sprague Dawley rats	[56]
	100 mg/kg/day, given orally	Sodium arsenite	8 mg/kg/day, given orally	8 weeks	Male Wistar rats	[57]
	100 mg/kg/day dissolved in corn oil, given orally	Para-nonylphenol	250 mg/kg/day dissolved in corn oil, given orally	Day 7 of pregnancy to day 21 of postnatal/90 days	Wistar rats	[58]
	20 mg/kg/day, given orally	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	1, 10 or 100 ng/kg/day dissolved in olive oil and acetone (19:1), given orally	45 days	Male Wistar rats	[59]
	200 mg/kg, given orally	Diazinon	60 mg/kg dissolved in olive oil, intraperitoneally	6 weeks	Male Wistar rats	[60]
	20 mg/kg/day, given orally	Carbendazim	25 mg/kg/day dissolved in corn oil, given orally	48 days	Male Wistar albino rats (*Rattus norvegicus*)	[61]
	250 mg/kg/day, intraperitoneally	Methotrexate	20 mg/kg on days 3 and 10, intraperitoneally	17 days	Male Wistar albino rats	[62]

Vitamin E

Several studies have used ellagic acid as a protective factor against several compounds that induce-reproductive damage, such as phthalates, arsenic, and polychlorinated biphenyl (Aroclor 1254), which are environmental pollutants that are present in a wide variety of daily products. Quite a few studies have shown that ellagic acid avoids histopathologic damage [44][45][46], preventing the decrease of SeT diameter, germinal cell layer thickness [44][46], and the Johnsen's testicular score [46]. Additionally, it increases the levels of antioxidant defense, GSH [44][45][46], SOD [44][46], and CAT [45][46], total antioxidant capacity (TAC) [45], and GSH-Px [46] and decreased TBARS levels

[44][46] as well as MDA and protein carbonyl (PC) content [45]. Ellagic acid improves sperm parameters [45][46], functional membrane integrity, mitochondrial membrane potential, and sperm kinematics (progressive motility, rapid and fast progressive motility) [45]. Additionally, arsenic up-regulates the *Ppargc1a* (peroxisome proliferative activated receptor, gamma, coactivator 1 alpha) gene and down-regulates the *Nrf2* and *StAR* (steroidogenic acute regulatory protein) genes [45]. *Ppargc1a* is a gene that is related to energy metabolism and mitochondrial biogenesis, which is upregulated in response to cell stress. *Nrf2* is a regulator of the antioxidant defense system, and low expression of this gene is related to decreased TAC in the testes and increased sperm abnormalities. *StAR* is a gene that regulates steroid hormone synthesis, and low *StAR* expression of is linked with low testosterone production and sperm quality [45]. These variations were prevented with ellagic acid treatment, demonstrating the protective effect of ellagic acid against the toxic effects of arsenic-induced toxicity [45].

Ellagic acid also seems to protect against monosodium glutamate, a food additive and flavor enhancer. The presence of low and high doses of monosodium glutamate ellagic acid improved histopathological findings, increased the antioxidant enzymes SOD, CAT, and GSH-Rx as well as thiol, testosterone, and inhibin B levels and decreased myeloperoxidase (MPO) XO, PC, 8-OHDG, MDA, and GSH-Px levels [47].

In **Table 1**, it is summarized the beneficial effects in male reproductive system.

2.3. Vitamin C

Vitamin C or ascorbic acid (chemical structure at Supplementary File) is a water-soluble vitamin found in berries, citrus fruits, green leafy vegetables, tomatoes, and potatoes [75]. Vitamin C can only be obtained from the diet and is mainly absorbed by the intestine and is then distributed throughout the body [76]. It functions as an enzymatic cofactor in the biosynthesis of collagen, carnitine, and catecholamines; enzyme complement; co-substrate; and a potent antioxidant [75][76]. The antioxidant properties of Vitamin C are due to its ability to scavenge reactive oxygen and nitrogen species and its ability to regenerate other small antioxidant molecules such as α-tocopherol (Vitamin E), GSH, urate, and β-carotene [77].

Vitamin C plays an important role in the male reproductive system, protecting spermatogenesis, preventing sperm agglutination, and increasing testosterone synthesis [48][78]. Several studies have shown the beneficial effects of vitamin C administration against the reproductive toxicity of environmental pollutants such as aluminum, mercury, carbon tetrachloride, and lead. The effects of vitamin C against aluminum chloride toxicity include ameliorated histopathological and sperm parameters, namely counts, concentration, morphology, and motility (increased fast progressive motility and decreased slow progressive motility). Additionally, vitamin C increased SOD activity while decreasing NO activity [49]. Vitamin C co-administration against mercuric chloride toxicity improved histopathological findings, daily sperm production parameters, and final body weight compared to the group treated for mercuric chloride only. Moreover, it increased the total protein, high-density lipoprotein (HDL) cholesterol, testosterone and the antioxidant enzymes peroxidase, and GST. On the other hand, decreased levels of low-density lipoprotein (LDL) cholesterol and lipid peroxidation (ROS and TBARS levels) were observed [50]. Additionally, vitamin C treatment against carbon tetrachloride toxicity improved the histopathological findings in testis sperm parameters (motility, counts and morphology). It increased FSH and LH hormone levels and the

expression of antioxidant enzymes, CAT, and SOD. Additionally, vitamin C decreased GSH-Px expression and TBARS levels compared to the carbon tetrachloride group [51]. Finally, vitamin C treatment can recover histopathological parameters to the control levels [52].

Vitamin C co-treatment against ethanol toxicity ameliorated testicular histopathological analysis, decreasing (i) abnormal tubules, (ii) immature germ cells in the lumen, (iii) acidophilic cells, and (iv) vacuolization. The sperm number in the testis and daily sperm production showed an increase, and MDA levels decreased [48].

Some drugs can also induce reproductive toxicity in males, such as the antibiotic tetracycline or cisplatin. Vitamin C co-administration with these drugs restored histopathological changes [53][55], sperm parameters (counts, viability, motility, and morphology) [53][55][54] and increased the weight of the testis and accessory sex organs [55][54], FSH, LH [53][55], testosterone [53][55][54], SOD, GSH, GST, and glucose-6-phosphate dehydrogenase (G6PD) levels [54] and decreased MDA levels [55][54].

Vitamin C treatment along testicular torsion induction prevented alterations in spermatogenesis and the SeT diameter and decreased serum MDA levels compared to non-treated rats [56]. Although vitamin C has recently been receiving attention from the scientific community due to its beneficial effects in several systems, some studies have shown contradictory effects regarding its action or have even shown no effects [79][80]. Additionally, it is not clear what the recommended dose of vitamin C required in humans could be to be able to have results that are similar to those obtained in animal models [81].

2.4. Vitamin E

Vitamin E is a lipo-soluble vitamin that is obtained exclusively through the diet [82] and is widely present in olive and sunflower oils, avocados, green leafy vegetables, nuts, soybeans, and wheat [83]. Vitamin E presents eight different isoforms that include alpha, beta, gamma, and delta-tocopherol and alpha, beta, gamma, and delta-tocotrienol [83].

The main biological activity of vitamin E is its antioxidant properties [84], protecting cell membrane components such as polyunsaturated fatty acids (PUFA) and LDL from oxidative damage mediated by free radicals [82]. It has been described that vitamin E deficiency is associated with defects in spermatogenesis, decreased testosterone production [85], and testicular degeneration [86]. Several studies that have used vitamin E supplementation against environmental pollutants such as arsenic, para-nonylphenol, and 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) have shown the beneficial effects of vitamin E, mainly in terms of several histological parameters [57][58]. Vitamin E also increases the epididymal sperm number [57], the number of spermatogonia A, spermatogonia B, spermatocytes, spermatids and Sertoli cells [58], and daily sperm production [59]. Vitamin E treatment has been used against TCDD-induced toxicity; has been shown to increase body, testis, epididymis, seminal vesicles, and ventral prostate weights; antioxidant enzymes (SOD, CAT, GSH-Rx and GSH-Px); and has been shown to decrease hydrogen peroxide generation and TBARS levels [59].

Vitamin E also seems to have a protective effect against agricultural products that induce reproductive toxicity, such as diazinon (or o,o-diethyl-o-[2-isopropyl-6-methyl-4-pyrimidinyl] phosphorothioate), an organophosphate

pesticide. In the presence of this pesticide, vitamin E increased GSH levels and decreased MDA levels [60]. Additionally, vitamin E seems to have a protective effect against carbendazim [61] (or methyl-2-benzimidazole carbamate), which is a fungicide that is often used as a pesticide and herbicide. Vitamin E co-administration ameliorated histopathological changes by increasing the SeT diameter and the SeT lumen diameter and decreased the carbendazim concentration in the testis and in serum [61].

Moreover, vitamin E seems capable of improving the effect of some drugs that can induce reproductive toxicity in males. Vitamin E counteracted the damage associated with methotrexate, improving histopathological parameters, increasing SOD levels, and decreasing MDA levels [62]. Increasing evidence of the beneficial actions of vitamin E against several diseases prompted have its use as a dietary supplement. However, it should be taken into account that excessive doses of vitamin E supplementation induce toxicity and can lead to hazardous complications, such as bleeding, thyroid problems, weakness, emotional disorders, and gastrointestinal derangement, among others [87].

In **Table 1**, it is summarized the beneficial effects in male reproductive system.

3. Natural Products with Bioactive Compounds

3.1. Garlic

Garlic has been used as a therapeutic and medicinal agent in several cultures for centuries, specifically in Egyptian Cordex Ebers and in ancient Greece, Rome, India, China, and Japan [88][89]. Garlic is mainly constituted by water, but it also contains carbohydrates, sulfur compounds, proteins, fibers, and free amino acids. In addition, it contains high levels of saponins, phosphorus, potassium, sulfur, zinc; moderate levels of selenium and vitamins A and C; and low levels of calcium, magnesium, sodium, iron, manganese, and B-complex vitamins [90]. Furthermore, a substantial amount of evidence has shown that some of the compounds present in garlic have antioxidant properties with radical-scavenging functions and antioxidant enzyme modulation [91][92].

Several garlic preparations, such as raw garlic homogenate, garlic powder, aged garlic extract, and garlic oil have been used in scientific studies to determine the effects of garlic. These may explain the diversity of the results concerning the effect of garlic in the male reproductive system. For example, Oi et al. used garlic powder to evaluate its effect on testosterone production in rats on a casein-based diet, a high protein level diet [93]. After 28 days of supplementation, the testosterone levels were increased in the rats fed 40 and 25% casein diets, indicating that garlic enhanced testosterone production in high protein level diets [93].

On the other hand, the effect of garlic extract on sperm characteristics and testicular oxidative damage after cadmium exposure showed that garlic extract improved epididymal sperm parameters (concentration, motility and counts) and reduced the number of abnormal sperm. It increased GSH, SOD, CAT, and alkaline phosphate (ALP) and decreased MDA and GST levels, improving antioxidant status after cadmium exposure [94]. Concerning other environmental contaminants, Furan is a contaminant found in a wide variety of foods that have been heat-treated

via thermal degradation that can induce damage in the testis. Garlic oil has been shown to ameliorate the effect of furan on histopathological alterations and the reduction of testosterone levels. Garlic oil also increased SOD, CAT, and GSH levels and decreased the MDA, CYP2E1, and caspase-3 levels [95].

The antibiotic Adriamycin has been shown to induce reproductive toxicity. Aged garlic extract attenuates the toxic effects of Adriamycin, improving all sperm parameters (count, motility, viability and morphology) as well as the histological, biochemical, and ultrastructural findings in testicular sections. Moreover, it increases the levels of antioxidant defenses (GSH, GSH-Px, CAT, and SOD) and decreased MDA levels [96]. Although garlic has several beneficial effects and is considered safe, care should be taken in terms of its therapeutic use, as some studies have shown its potential toxicity in the male reproductive system [88][97]. In addition, a study showed that garlic might cause gastric irritation, nausea, vomiting, flushing, tachycardia, headache, insomnia, sweating, and dizziness, among other symptoms [97].

In **Table 2**, it is summarized the beneficial effects in male reproductive system.

Table 2. Bioactive compounds present in natural products with beneficial effects in male reproductive system.

Natural Product	Dosage of Natural Product	Toxic Stimulus	Dosage of Toxic Stimulus	Exposure Time	Animal Model	Reference
Garlic	0.8 g/100 g/day, given orally	Casein-based diet (High Protein Diet)	40, 25 or 10 g/100 g/day, given orally	28 days	Male Sprague Dawley rats	[93]
	1.0 mL/100 g/day, given orally	Cadmium	1.5 mg/100 g/day, given orally	4 weeks	Male albino Wistar rats	[94]
	80 mg/kg/day for 5 days per week, given orally	Furan	4 mg/kg/day for 5 days per week dissolved in corn oil, given orally	90 days	Male Sprague Dawley rats	[95]
	250 mg/kg/day given orally	Adriamycin	10 mg/kg, intraperitoneally	14 days	Male Wistar rats	[96]
Ginger	100 mg/kg/day, given orally	Gentamicin	50 mg/kg, intraperitoneally	30 days	Male Wistar rats	[98]
	250 mg/kg/day (hydro-alcoholic extract of ginger), given orally	Carbon tetrachloride	1 mL/kg dissolved in olive oil, intraperitoneally	14 days	Male Wistar rats	[99]
	1 g/kg/day, given orally	Ethanol	4 g/kg/day, given orally	28 days	Male Sprague	[100]

Natural Product	Dosage of Natural Product	Toxic Stimulus	Dosage of Toxic Stimulus	Exposure Time	Animal Model	Reference
					Dawley rats	
	500 mg/kg/day, given orally	Sulfite salts (sodium metabisulfite)	260 mg/kg/day dissolved in distilled water, given orally	28 days	Male Wistar rats	[101]
	1 g/kg/day, given orally	Ethanol	4 g/kg/day, given orally	28 days	Male Sprague Dawley rats	[102]
	50, 100 and 150 mg/kg/day, given orally	Busulfan	5mg/kg, intraperitoneally	48 days	Male Sprague Dawley rats	[103]
	300 mg/kg/day or 600 mg/kg/days, given orally	Cyclophosphamide	100 mg/kg, intraperitoneally	6 weeks	Male Wistar albino rats	[104]
	1 g/kg/day, given orally	Cisplatin	10 mg/kg dissolved in normal saline, intraperitoneally	26 days	Male Wistar albino rats	[105]
	500 mg/kg/day, given orally	Fructose	Fed a diet containing 60% fructose	8 weeks	Male Sprague Dawley rats	[106]
	500 mg/kg/day, given orally	Diabetes	60 mg/kg of STZ dissolved in 0.01 M sodium citrate buffer, intraperitoneally	6 weeks	Male Sprague Dawley rats	[107]
	fed a diet supplemented with ginger roots at 3%	Diabetes	120 mg/kg of alloxan saline solution, intraperitoneally	30 days	Male Wistar rats	[108]
Grape	75 mg/kg/day, given orally	Ethanol	10 mL/kg/day ate 25% *v*/*v*, given orally	10 weeks	Male albino rats	[109]
	100 mg/kg/day, given orally 6 days a week	Plant growth regulators	75 ppm/L or 100 ppm/L	60 days	Male albino rats (*Rattus*	[110]

Natural Product	Dosage of Natural Product	Toxic Stimulus	Dosage of Toxic Stimulus	Exposure Time	Animal Model	Reference
			dissolved in drinking water, given orally 6 days a week		*rattus*)	
	2 g/kg/day, given orally	Cadmium chlorine	1.2 mg/kg diluted in 0.5 mL of distilled water, intraperitoneally	86 days	Male Wistar rats	[111]
	100 mg/kg/day dissolved in normal saline, given orally	Cadmium chloride	5 mg/kg/day dissolved in normal saline, given orally	30 days	Male albino rats	[112]
	120 mg/kg, given orally	Cadmium chlorine	5 mg/kg in saline, given orally	4 weaks	Wistar albino male rats	[113]
	400 mg/kg/day dissolved in water, given orally	Cadmium chlorine	5 mg/kg/day dissolved in water, given orally	90 days	Male Wistar rats	[114]
	100 mg/kg/day, given orally	Cadmium	2.5 mg/kg, intraperitoneally	10 days	Male Wistar rats	[115]
	1.8 g/kg/day or 2.36 g/kg/day, given orally	Cadmium chlorine	1.2 mg/kg, intraperitoneally	56 days	Male Wistar rats	[116]
	2 g/kg/day, given orally	Cadmium chlorine	1.2 mg/kg diluted in 0.5 mL of distilled water, intraperitoneally	30 days	Male Wistar rats	[117]
	200 or 400 mg/kg three times per week, given orally	Dexamethasone	0.1 mg/kg three times per week, subcutaneously	30 days	Male Wistar rats	[118]
	250 mg/kg/day, given orally	Varicocele	-	8 weeks	Male Wistar rats	[119]
	100 mg/kg/day dissolved in saline, given orally	Testicular torsion	-	7 days	Male Wistar albino rats	[120]
	20 mg/kg/day of *trans*-resveratrol dissolved in	-	-	90 days	Male Sprague	[121]

Natural Product	Dosage of Natural Product	Toxic Stimulus	Dosage of Toxic Stimulus	Exposure Time	Animal Model	Reference
	10 g/L of carboxymethylcellulose				Dawley rats	
Green tea	150 mg/kg/day, given orally	Deltamethrin	0.6 mg/kg/day dissolved in corn oil, given orally	28 days	Male mice	[122]
	2% or 5% dally, given orally	-	-	52 days	Male Wistar rats	[123]
	200 mg/kg/day dissolved in water, given orally	Para-nonylphenol	200 mg/kg/day dissolved in corn oil, given orally	56 days	Male Wistar rats	[124]
	1.5% *w/v* dally, given orally	Cadmium chloride	1.5 mg/kg dissolved in water, intraperitoneally	13, 25 and 49 days	Male Wistar rats	[125]
	70 mg/kg/day, given orally	Cadmium chloride	3 mg/kg/day, given orally	63 days	Male Wistar rats	[126]
	2% *w/v* dally, given orally	Nicotine	1 mg/kg/day dissolved in water, intraperitoneally	60 days	Male Wistar rats	[127]
	200 mg/kg/day or 500 mg/kg/day, given orally	Doxorubicin	0.15 mg/kg, intraperitoneally 2 days per week for 5 weeks	14 weeks	Male ICR mice	[128]
Microalgae/algae	50 mg/kg/day, dissolved in 1 mL saline given orally	Deltamethrin	3 mg/kg/day dissolved in 1 mL saline, given orally	8 weeks	Male albino rats	[129]
	70 mg/kg/day, dissolved in 0.9% sodium chloride given orally	Sodium nitrite	80 mg/kg/day dissolved in distilled water, given orally	90 days	Male Wistar Albino rats	[130]
	150 mg/kg/day, in drinking weather given orally	Cadmium chloride	2 mg/kg/day, subcutaneously	10 days/30 days	Male Sprague–Dawley rats	[131]

Natural Product	Dosage of Natural Product	Toxic Stimulus	Dosage of Toxic Stimulus	Exposure Time	Animal Model	Reference
	300 mg/kg/day, via gastric tube	Furan	16 mg/kg/day, given orally	4 weeks	Male Sprague–Dawley rats	[132]
	300 mg/kg/day, given orally	Mercuric chloride	5 mg/kg dissolved in water, subcutaneously 3 days per week	60 days	Male Wistar albino rats (*Rattus norvegicus*)	[133]
	300 mg/kg/day, given orally	Bifenthrin	5 mg/kg/day, given orally	35 days	Male white Swiss mice	[134]
	300 mg/kg, given orally	Lead acetate	30 mg/kg, given orally	8 weeks	Male Wistar rats	[135]
	200 mg/kg/day, given orally	Diabetes	50 mg/kg of STZ dissolved in 0.1 M citrate buffer, intraperitoneally	28 days	Male Wistar rats	[136]
	200 mg/kg, 400 mg/kg, 800 mg/kg, given by gastric intubation	Benzo[alpha]pyrene	125 mg/kg/day dissolved in corn oil, intraperitoneally	3 weeks	CF1 mice	[137]
	200 mg/kg, 400 mg/kg, 800 mg/kg, given orally	Cyclophosphamide	40 mg/kg dissolved in 0.9% saline, intraperitoneally	3 weeks	CF1 mice	[138]
	900 mg/kg/day, given orally	Cadmium chloride	2.0 mg/kg/day, given orally	21 days	BALB/c mice	[139]
	13 mg/kg, 26 mg/kg or 65 mg/kg, given orally	Diabetes	65 mg/kg of STZ and 230 mg/kg of NA, intraperitoneally	4 weeks	Male Sprague Dawley rats	[140]
	100 mg/kg/day, 200 mg/kg/day, 500 mg/kg/day dissolved in olive oil, given orally [99]	Cisplatin [98]	7 mg/kg, intraperitoneally	5 days	Male Syrian hamsters [150]	[141]
Propolis	100 mg/kg/day dissolved in [151] ethanol	Copper sulphate	128 mg/kg/day dissolved in	21 days	Male Sprague	[142]

cooking
t to treat
nausea,
Persia,
effective
l erectile

dysfunction [152]. Additionally, hot ginger remedies are used to increase sexual energy and semen volume [150].

In terms of biological activity, ginger is an antioxidant and shows [153], anti-inflammatory [154], anti-cancer [155][156] anti-microbial [157], anti-diabetic, hypolipidemic properties [158] as well as androgenic activity [159]. The compounds present in ginger include acids, choline, folic acid, inositol, pantothenic acid, resins, sesquiterpenes, vitamin B3 and B6, vitamin C compounds, volatile oils, and bio-trace elements such as calcium, magnesium, phosphor, and potassium [160]. However, the main bioactive compounds present in ginger are gingerdiol, gingerol, shogaols,

Natural Product	Dosage of Natural Product	Toxic Stimulus	Dosage of Toxic Stimulus	Exposure Time	Animal Model	Reference
	70%, given orally		water, given orally [100]		Dawley rats	
	300 mg/kg/day dissolved in distilled water, given orally	Diabetes	60 mg/kg of STZ dissolved in ice-cold saline, intraperitoneally	4 weeks	Male Sprague Dawley rats	[143][144]
	50 mg/kg/day, given orally [101]	Aluminum chloride [101]	34 mg/kg/day, given orally [101]	70 days	Male Wistar Albino rats [99][101]	[99] [145]
	50 mg/kg/day dissolved in DMSO, given orally	Cadmium [100][109]	1 mg/kg/day, intraperitoneally starting in day 8th	17 days	Male Wistar rats	[146]
	100 mg/kg/day dissolved in DMSO, given orally	Methotrexate	20 mg/kg, intraperitoneally in day 8th	15 days	Male Wistar rats	[147]
	200 mg/kg 5 days per week, given orally	Doxorubicin	3 mg/kg, intraperitoneally in day 8th, 10th, 12th, 15th, 17th and 19th	21 days	Male Wistar albino rats	[148]
	50 mg/kg/day dissolved in 1 mL distilled water, given orally	Paclitaxel	5 mg/kg diluted in 1 mL normal saline once a week, intraperitoneally	4 weeks	Male Sprague Dawley rats	[149]

s of free

ride, an
fite salts
xide that
abisulfite
nd in the
[99][101],

nption is
creasing
r, ginger
osterone
[100][102]

damage.
, a drug
ed in all
) mg/kg,
ncreased
[103] e effects

against the toxic effects of cyclophosphamide, an anti-neoplastic agent. Both doses led to histological improvement and increased germ cells counts and antioxidant levels, but only the dose of 300 mg/kg increased the epithelium thickness, and the 600 mg/kg dose increased testosterone levels [104].

The co-administration of ginger with gentamicin, an antibiotic, and cisplatin decreased the number of apoptotic cells compared to the non-treated group [12][98] and restored normal testicular morphology, spermatogenesis, and sperm parameters (counts, motility and morphology) [105]. In addition, the MDA levels decreased in response to treatment with ginger [12].

Several metabolic syndromes can induce damage in the testis, such as high-fructose diet-induced metabolic syndrome and diabetes. Fructose is a carbohydrate that is widely used as a food additive because of its sweetness. However, it is one of the main factors that is responsible for the progression to metabolic syndrome, leading to oxidative stress [106]. In rats fed with a high-fructose diet, ginger decreased the total body weight but increased testicular weight. Additionally, it improved histopathological findings, increasing the epithelial height and SeT perimeter and proliferative cell nuclear antigen (PCNA) and Beclin 1 immunoreactivity. PCNA is considered to be a proliferation marker that can be used to analyse spermatogenesis, and Becilin 1 is a protein involved in autophagic pathways and is considered to be an important regulatory mechanism in spermatogenesis and

steroidogenesis [106]. The increased immunoreactivity of PCNA and Beclin 1 indicate an improvement in spermatogenesis and steroidogenesis in the presence of ginger treatment. Ginger increased the FSH, LH, testosterone, HDL, and SOD levels and decreased the triglycerides, LDL, MDA, and serum levels of glucose, insulin as well as the subsequent diminution of the homeostasis model assessment for insulin resistance (HOMA-IR) [106].

Diabetes is a chronic metabolic disease that is associated with infertility [107]. Ginger treatment in induced diabetic rats with streptozotocin improved histopathological findings; increased the TAC, androgen receptor, and the PCNA levels; and decreased the blood glucose level and caspase-3 expression [107]. Additionally, a different study showed that in alloxan-induced diabetic rats, a ginger supplemented diet improved sperm parameters (counts and motility) and increased testis, epididymis, prostate, and seminal vesicles weights. Moreover, a ginger-supplemented diet in diabetic rats increased (i) the hormonal serum levels of testosterone, FSH and LH and (ii) the antioxidant enzymes SOD, CAT and GSH-Px levels and decreased (i) plasma glucose; (ii) the metabolic enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and ALP; and (iii) MDA levels in the testis [108].

In **Table 2**, it is summarized the beneficial effects in male reproductive system.

3.3. Grape

Grape (*Vitis vinifera*) is one of the most farmed and largely produced fruits in the world [110] and has a history of use in Europe for traditional treatments [162]. Dried grape seeds contain 35% fiber, 29% extractable components such as phenolic compounds, 11% proteins, 7% water, and 3% of minerals [163] and can be used to produce grape seed extract. The phenolic compounds found in grape include non-flavonoids such as resveratrol and flavonoids (e.g., catechin, epicatechin, quercetin, anthocyanin, and pro-anthocyanidins) [109][111].

Grape seed extract presents several biological activities, namely anti-apoptotic, anti-necrotic, cardiovascular [164], anti-cancer [165], anti-inflammatory [166], and antioxidant [167] effects. Its capacity to scavenge oxidants and free radicals is due to the presence of the phenolic compounds, especially the pro-anthocyanidins [168], which present a higher antioxidant capacity than vitamin C or E [169]. Both grape seed extract and grape seed pro-anthocyanidin extract present protective effects against male reproductive toxic inducers.

Several studies have identified grape seed extract, grape seed pro-anthocyanidin extract, and grape juice concentrate as protective factors against cadmium toxicity. Grape seed extract and grape seed pro-anthocyanidin extract improved histopathological findings [112][113][114][115], increasing the diameter and normal SeT [112][115], testicular weight [112], and Johnsen's mean testicular biopsy score and decreasing the apoptotic index [115]. It was also observed to increase PCNA immunoreactivity [112] and total antioxidant status (TAS) [113] in the enzymes of the antioxidant defense system and genes associated with steroidogenesis and Ki-67 expression [114], and it decreased MDA levels [113][114] and the immunoreactivity of the apoptotic regulator Bax [114]. Grape juice concentrate treatment against cadmium toxicity demonstrated that co-administration restored the testis, epididymis, and ventral prostate weight [116] to normal levels, ameliorating tissue architecture [111][116][117], epididymis

epithelium height (*caput* and *cauda* regions) [111] and improving sperm parameters such as production, counts, transit time [111], and morphology [116]. Additionally, it increased testosterone and GSH levels and decreased cadmium accumulation, MDA levels [111], and SOD and mitochondrial SOD activity [116].

Grape seed extract can also protect the testis against the toxic effects of drugs such as dexamethasone, an immunosuppressive and anti-inflammatory glucocorticoid drug [118]. Using two doses (200 or 400 mg/kg body weight) of grape seed extract administrated with dexamethasone, it was possible to observe histopathological improvement, especially at a dose of 400 mg/kg, which increased body, testis weight, and serum testosterone. It also increased thyroid hormones, (free T3, T4 and thyroid-stimulating hormone); antioxidant defenses (CAT and GSH); total protein content; acid phosphatase (ACP), a specific marker for spermatogenesis; and glucose-6-phosphate dehydrogenase (G-6-PDH). Thyroid hormones are essential in the regulation of the reproductive system, and G-6-PDH is associated with GSH synthesis that when decreased can indicate testicular degeneration [118].

Additionally, grape seed extract seems to attenuate the effects of ethanol by increasing the weight of the testis, epididymis and accessory sex organs, sperm parameters (counts, motility, and morphology), testosterone, and GSH levels and decreasing the MDA levels in the testis [109].

Plant growth regulators, namely gibberellic acid and indoleacetic acid, are chemicals that are used worldwide in agriculture that can induce toxic effects on the male reproductive system [110]. Grape seed pro-anthocyanidin extract co-treatment with different plant growth regulators improved histopathological architecture and the spermatogenesis process and decreased apoptotic cells [110].

Several events/incidents can induce damage in the testis, such as varicocele and testicular torsion. Varicocele is a dilatation of the pampiniform plexus, draining the testes and inducing male infertility [119]. The administration of grape seed pro-anthocyanidin extract in a varicocele model rats improved histological and sperm parameters (concentration and motility). In addition, an increase of the antioxidant enzymes (SOD and GSH-Px), the apoptotic regulator's ratio Bax/Bcl-2, Nrf2 and HO-1 was observed as were decreased levels of MDA, apoptotic cells, and caspase-3 [119]. Grape seed pro-anthocyanidin extract was administrated 7 days prior to the surgical procedure for induced testicular torsion in rats for 2 h followed by administration 2 h after detorsion. Grape seed pro-anthocyanidin extract ameliorated histopathological damage, increasing Johnsen's mean testicular biopsy score and decreasing apoptotic cells, iNOS immunoreactivity, and MDA levels [120].

Trans-Resveratrol (trans-3,4,5-trihydroxystilbene) is a natural antioxidant present in grapes. A study with rats treated with *trans*-resveratrol, which was detected in plasma after 24 h of treatment, showed that it did not have adverse effects. The testicular weight was similar to the control group. However, the *trans*-resveratrol groups showed a reduced SeT diameter but an increased SeT length, increasing the tubular density comparatively to the control group. In addition, it increased the sperm count and the hormonal levels of LH, FSH, and testosterone [121].

In **Table 2**, it is summarized the beneficial effects in male reproductive system.

3.4. Green Tea

Green tea (*Camellia sinensis)* is one of the oldest and most popular drinks worldwide [170]. Green tea leaves contains 30% phenolic compounds, such as flavonols, of which epigallocatechin gallate, epigallocatechin, epicatechin gallate, catechin, epicatechin, and gallocatechin stand out; 15–20% protein; 5–7% carbohydrates; 5% minerals and trace elements; 3–4% methylxanthines; 2% lipids; 1–2% organic acids; and 1–4% amino acids [171][172]. Moreover, it contains around 0.05–0.3% vitamin C [173].

Green tea has several biological characteristics and health benefits, shpwing anti-cancer [174][175], anti-cardiovascular diseases [176], anti-inflammatory [177], anti-arthritic [178], anti-microbial [179][180], neuroprotective [181], cholesterol-lowering [182] and antioxidant [183] effects. Phenolic compounds are potent antioxidants with the ability to scagenge oxygen, hydroxyl, and anion superoxide radicals and have metal chelating functions [122][184].

Green tea consumption is a common practice that is well accepted by modern society, and its beneficial effects are well recognized in our day to day lives. During a 52-day study period, the administration of green tea extract (2 and 5%) in male Wistar rats resulted in the body and reproductive organs weight remaining unchanged compared to control group. Liver weight also remained unchanged, but decreased levels of AST and ALT were observed, suggesting hepatoprotective properties. The testosterone level was similar to the control group as was the weight of the testosterone-dependent organs. Normal histological sections (except an increase in diameter of SeT) were observed between the green tea consumption group and control group. Concerning sperm parameters, green tea increased sperm concentration and viability, but the sperm motility and velocity functions remain similar to the control. However, a significant increase in spontaneous acrosome reactions was observed. Finally, the antioxidant defenses (CAT, GSH, MDA, and SOD levels) remain unchanged, indicating the safety of green tea consumption and a balance of the oxidative stress status of the tissues [123].

Several studies identify green tea as a protective factor against environmental pollutants that are widely used in industry and that can induce oxidative damage. These includes para-nonylphenol, deltamethrin (a synthetic insecticide), cadmium, and nicotine (a volatile alkaloid that is the primary toxic component of cigarette smoking). Green tea extract ameliorated histopathologic damage [122][124][125][126][127] by increasing the SeT diameter [122][126], epithelium height, Johnson's score [122], and the volume of the SeT and testis [124]. Additionally, green tea extract increased testis, body, and reproductive organ weight [124][126][127]. In terms of the sperm parameters (concentration, motility, viability, morphology, production and counts), green tea extract co-administration with these environmental pollutants seemed to induce a beneficial effect [122][124][125][126][127]. Green tea extract increased testosterone levels [122][126][127] and antioxidant defenses (SOD, CAT, and GSH) [126][127], and decreased caspase-3 [122][126] and cholesterol levels [126]. Regarding the lipid peroxidation, green tea extract decreased MDA [122][124][125] and TBARS levels [127] compared to the environmental pollutants groups.

Green tea can also protect against the toxic effects of some drugs, such as doxorubicin, an anthracycline antibiotic [128]. The administrations of two different green tea extract concentrations (200 mg/kg and 500 mg/kg) against doxorubicin-induced toxicity seemed to ameliorate the histological findings and increased sperm parameters

(concentration and mobility), the Sertoli cell index (ratio between germ cells number and Sertoli cells number), and telomerase activity in both concentrations [128]. Several studies have indicated the beneficial effects of green tea, though there are also reports of relevant side effects, such as hepatotoxicity and gastrointestinal disorders as well as drug interactions [185].

In **Table 2**, it is summarized the beneficial effects in male reproductive system.

3.5. Microalgae and Algae

Microalgae are a natural source of various bioactive compounds, such as phycobilins, carotenoids, PUFA, polysaccharides, sterols, and vitamins, which have many applications from animal feed to human nutrition [186]. PUFA are abundant in microalgae, and they are one of the major compounds responsible for its bioactivities [187]. Therefore, their effects on male infertility have been explored because oxidative stress is a major contributor to defective spermatogenesis [188]. Moreover, elevated oxidative stress within semen is also associated with infection/inflammation of the male reproductive system, which compromises sperm quality [189]. After several studies indicating its safety and beneficial effects for human health, namely antitoxic, antigenotoxic, antioxidant effects, and reporting no reproductive and teratogenic toxicity, the microalgae *Chlorella vulgaris* and *Spirulina platensis* were classified as Generally Regarded as Safe (GRAS) substances by the United States Food and Drug Administration (FDA) [190][191]. Additionally, some studies have reported the protective properties of *C. vulgaris* against various noxious stimuli [192][193][194], and it has been suggested that *C. vulgaris* might be helpful in diseases where the maintenance of antioxidant status is crucial [193].

In deltamethrin-intoxicated rats, *C. vulgaris* administered orally for 8 weeks was able to re-establish the serum testosterone concentration, sperm counts, sperm viability, sperm motility, and sperm abnormalities as well as the testicular levels of SOD and CAT antioxidant enzymes and the lipid peroxidation marker MDA to levels similar to the control group [129]. More recently, Eissa et al., demonstrated that pre- and co-treatment with *C. vulgaris* was helpful against sodium nitrite-induced reproductive dysfunction via the partial prevention of negative changes in sperm quality, serum testosterone and FSH levels, testicular oxidant/antioxidant balance, and testicular histological architecture [130].

S. platensis was also pointed as a promising protective agent to ameliorate diseases and toxicities involving oxidative stress [195], having recognized antioxidant, anti-diabetic, anti-inflammatory and anti-apoptotic properties [196]. At the reproductive level, *S. platensis* has been shown to be beneficial in improving spermatogenesis and steroidogenesis after cadmium intoxication [131] and counteracted furan toxicity in rat testis [132]. Furthermore, *S. platensis* reduced the deterioration induced by mercuric chloride in the sperm quality and testis of rats through the decrease of (i) lipid peroxidation, (ii) mercury accumulation in the testis, (iii) testicular histopathological changes, and iv) sperm abnormalities [133]. *S. platensis* also reverted the mercuric chloride-induced inhibition in the activity of key antioxidant enzymes (SOD, CAT, and GSH-Px) back to normal levels [133]. Moreover, the in vivo protective action of *S. platensis* against bifenthrin-induced reprotoxicity has been documented. In that study, *S. platensis* administrated before bifenthrin partially re-established the oxidant/antioxidant equilibrium, testosterone production,

testicular mRNA, and microRNA levels of the genes involved in spermatogenesis as well as sperm motility and viability [134].

Recently, it was highlighted that *C. vulgaris* or *S. platensis* can have positive effects on testicular dysfunction provoked by lead acetate due to their antioxidant activity, immunomodulatory ability, and anti-apoptotic activity [135].

Spirulina maxima has been shown to improve spermatogenesis and steroidogenesis in diabetic rat testis [136] and also mitigated benzo[alpha]pyrene- and cyclophosphamide-induced injury to male mouse germ cells [137][138].

Although fewer works that compare the effects of microalgae are available, some algae also seem to have garnered interest in terms of reproductive purposes. Such is the case of *Halopteris scoparia*, a brown alga that is generally consumed as a salad in Far East countries, which ha sbeen reported to protect against cadmium chloride-induced testicular damage in mice [139]. In another study, fucoxanthin extract from brown algae *Laminaria japonica* ameliorated male reproductive function in diabetic rats by (i) decreasing the glucose level, (ii) restoring sperm motility, (iii) reducing sperm abnormalities, (iv) enhancing enzymatic antioxidant activity, (v) reducing proinflammatory cytokine levels, and (vi) recovering LH and testosterone levels [140]. Indeed, fucoxanthin is a natural agent with the potential to be considered an anti-diabetic candidate and a functional food to improve male fertility affected by diabetes mellitus [140]. Furthermore, fucoxanthin extract from brown algae *Sargassum glaucescens* increased sperm count, decreased sperm abnormalities, and improved the morphology of SeT as well as improved testosterone levels in hamsters treated with the chemotherapeutic drug cisplatin [141].

In **Table 2**, it is summarized the beneficial effects in male reproductive system.

3.6. Propolis

Propolis or bee glue is a natural resinous mixture produced by honeybees that is used to seal holes in their honeycombs, smooth out the internal walls, and protect the entrance against intruders [197].

Propolis is a complex mixture of several compounds derived from plants and is processed by the salivary enzymes of bees [198], and for this reason, propolis content can vary depending on the plant source used by the bees [142]. Usually, the propolis of Northern temperate climates contains approximately 50% resins and vegetable balsams, 30% waxes, 10% essential oils, 5% pollen, and 5% other organic substances [143][199]. This composition can also change depending on the hive, district, and season [199]. Due to this variability, propolis can have more than 300 compounds with pharmacological activity, such as polyphenolic compounds (e.g., flavonoids), terpenoids, various steroids, amino acids, glucose, fructose, vitamins such as vitamin B1, B2, C, and E, and essential elements such as magnesium, calcium, nickel, iron, and zinc [197][200].

In fact, it has been used in folk medicine [201], and no side effects have been described after propolis administration in humans and mice [202]. Several biological activities with pharmaceutical interest have been described for propolis, such as anti-hyperglycemic, antioxidant, anti-inflammatory, anti-apoptotic [202][203], and anti-microbial [202][204] effects.

Phenolic compounds, such as flavonoids, are the main bioactive components responsible for the biological activity of propolis, specifically antioxidant activity. Flavonoids are capable of scavenging free radicals associated with several diseases, ageing, and toxic substances [145][205]. Additionally, propolis antioxidant activity includes the capacity to activate antioxidant enzymes such as CAT [206] and SOD [207]. Moreover, propolis can inhibit the generation of superoxide anions and can reverse the consumption of glutathione, an enzyme with radical scavenging activity [145][208].

In testis, several studies have described the use of propolis as a protective factor against many different oxidative stress inducers, showing significant improvements in male fertility [209]. In addition, it has been found to have a protective role against oxidative stress-inducers such as copper, cadmium, and aluminum in the reproductive tissues of rats [142][145][146]. Propolis co-treatment improved histopathological changes [142][145][146] by decreasing the number of apoptotic cells [142] and degenerative changes in the tubular epithelium [146] and increasing Johnsen's testicular score [142]. Additionally, propolis coadministration induced an increase in CAT and GSH levels [142][145], SOD [142], testosterone, 17-ketosteroid reductase, and GST levels [145], and it decreased MDA [142][146] and TBARS levels [145] and immunoreactivity of testicular HIF-1α [146]. In terms of sperm parameters, propolis co-treatment increased sperm concentration and motility and decreased abnormal sperm [142][145] and sperm death [145]. Finally, it also increased the weight of the testis [145][146] and epididymis [145].

Diabetes mellitus has been associated with male infertility [143]. Propolis may regulate the testicular and epididymal oxidative stress levels in induced-streptozotocin diabetic rats. Improved histopathologic changes have been found, namely increased SeT diameter and seminiferous epithelial height and decreased germ cells loss and epididymal epithelial height. Propolis co-administration increased the weight of the testes, epididymis, prostate, and seminal vesicles. Additionally, it demonstrated an increase of *Nrf2*, SOD, CAT, GSH-Px, GSH-Rx, GST, and TAC levels, and it decreased NO and TBARS levels, supporting the antioxidant properties of propolis. Concerning the pro-inflammatory mediators and apoptosis-related genes, propolis increased the protein levels of NF-kB, tumour necrosis factor-α, interleukin (IL)-1β, and IL-10 and decreased testicular levels of Bax/Bcl-2 ratio, p53, caspase-8, caspase-9, and caspase-3 [143], demonstrating the anti-inflammatory and anti-apoptotic properties of propolis. Recently, it has also been shown that propolis treatment in diabetic rats ameliorated sperm parameters (counts, motility, viability and morphology) and diminished non-motile spermatozoa and sperm DNA fragmentation. Additionally, it improved steroidogenesis through the increase of testosterone levels, *StAR*, CYP11A1, CYP17A1, 3β-HSD, and 17β-HSD. Relative to the metabolic pathways, propolis increased glucose transporter 3 (GLUT3), MCT2, MCT4, and decreased LDH, intra-testicular glucose, and lactate levels [144].

In the presence of some drugs (paclitaxel, methotrexate and doxorubicin), propolis supplementation seems to a have a beneficial protective effects on the male reproductive system, improving histopathological changes by increasing the Johnsen testicular biopsy score [147] and the diameter of SeT [147][148]; sperm motility, viability [149], and counts [148][149]; and decreasing sperm abnormalities [149]. Moreover, propolis co-administration increases GSH levels [148][149], LDH, sorbitol dehydrogenase, ACP, ALP, G-6-PDH, testosterone, FSH, LH, IL-4, 3β-HSD, 17β-HSD, and *StAR* [148] and decreases MDA [148][149], 8-hydroxy-2-deoxyguanosine (8-OHdG) [149], ALT, AST, MPO, tumor necrosis factor-alpha (TNF-α), Fas-L, and caspase-3 levels [148]. Propolis also increases the ATP level in testis

homogenate and decreases ADP and AMP levels [149]. The existing data show that propolis presents beneficial effects against several diseases. However, it should be considered that there is no standardized propolis extraction method, which causes problems in terms of establishing its safe use. There have also been reports of its toxicity as well. Additionally, propolis has been identified as an allergen with immunological stimulating properties, which may affect human health [197].

In **Table 2**, it is summarized the beneficial effects in male reproductive system.

References

1. Hess, R.A.; de Franca, L.R. Spermatogenesis and Cycle of the Seminiferous Epithelium. In Molecular Mechanisms in Spermatogenesis; Cheng, C.Y., Ed.; Springer: New York, NY, USA, 2008; pp. 1–15.
2. Clermont, Y. Kinetics of spermatogenesis in mammals: Seminiferous epithelium cycle and spermatogonial renewal. Physiol. Rev. 1972, 52, 198–236.
3. Correia, S.; Vaz, C.V.; Silva, A.M.; Cavaco, J.E.; Socorro, S. Regucalcin counteracts tert-butyl hydroperoxide and cadmium-induced oxidative stress in rat testis. J. Appl. Toxicol. 2017, 37, 159–166.
4. Cocuzza, M.; Athayde, K.S.; Agarwal, A.; Pagani, R.; Sikka, S.C.; Lucon, A.M.; Srougi, M.; Hallak, J. Impact of clinical varicocele and testis size on seminal reactive oxygen species levels in a fertile population: A prospective controlled study. Fertil. Steril. 2008, 90, 1103–1108.
5. Fatemi, N.; Sanati, M.H.; Jamali Zavarehei, M.; Ayat, H.; Esmaeili, V.; Golkar-Narenji, A.; Zarabi, M.; Gourabi, H. Effect of tertiary-butyl hydroperoxide (TBHP)-induced oxidative stress on mice sperm quality and testis histopathology. Andrologia 2013, 45, 232–239.
6. Kaur, P.; Kaur, G.; Bansal, M.P. Tertiary-butyl hydroperoxide induced oxidative stress and male reproductive activity in mice: Role of transcription factor NF-kappaB and testicular antioxidant enzymes. Reprod. Toxicol. 2006, 22, 479–484.
7. Aitken, R.J.; Roman, S.D. Antioxidant systems and oxidative stress in the testes. Oxid. Med. Cell. Longev. 2008, 1, 15–24.
8. Agarwal, A.; Rana, M.; Qiu, E.; AlBunni, H.; Bui, A.D.; Henkel, R. Role of oxidative stress, infection and inflammation in male infertility. Andrologia 2018, 50, e13126.
9. Semet, M.; Paci, M.; Saïas-Magnan, J.; Metzler-Guillemain, C.; Boissier, R.; Lejeune, H.; Perrin, J. The impact of drugs on male fertility: A review. Andrology 2017, 5, 640–663.
10. Dias, T.R.; Alves, M.G.; Oliveira, P.F.; Silva, B.M. Natural products as modulators of spermatogenesis: The search for a male contraceptive. Curr. Mol. Pharmacol. 2014, 7, 154–166.

11. Jia, Z.; Anandh Babu, P.V.; Chen, W. Natural Products Targeting on Oxidative Stress and Inflammation: Mechanisms, Therapies, and Safety Assessment. Oxid. Med. Cell. Longev. 2018, 2018, 6576093.
12. Amin, A.; Hamza, A.A.; Kambal, A.; Daoud, S. Herbal extracts counteract cisplatin-mediated cell death in rat testis. Asian J. Androl. 2008, 10, 291–297.
13. Mbongue, G.Y.; Kamtchouing, P.; Dimo, T. Effects of the aqueous extract of dry seeds of Aframomum melegueta on some parameters of the reproductive function of mature male rats. Andrologia 2012, 44, 53–58.
14. Soliman, G.A.; Donia Ael, R.; Awaad, A.S.; Alqasoumi, S.I.; Yusufoglu, H. Effect of Emex spinosa, Leptadenia pyrotechnica, Haloxylon salicornicum and Ochradenus baccatus extracts on the reproductive organs of adult male rats. Pharm. Biol. 2012, 50, 105–112.
15. Muratoğlu, S.; Akarca Dizakar, O.S. The protective role of melatonin and curcumin in the testis of young and aged rats. Andrologia 2019, 51, e13203.
16. Mohamadpour, M.; Noorafshan, A.; Karbalay-Doust, S.; Talaei-Khozani, T.; Aliabadi, E. Protective effects of curcumin co-treatment in rats with establishing chronic variable stress on testis and reproductive hormones. Int. J. Reprod. Biomed. 2017, 15, 447–452.
17. Wei, S.M.; Yan, Z.Z.; Zhou, J. Curcumin attenuates ischemia-reperfusion injury in rat testis. Fertil. Steril. 2009, 91, 271–277.
18. Ammon, H.P.; Wahl, M.A. Pharmacology of Curcuma longa. Planta Med. 1991, 57, 1–7.
19. Inano, H.; Onoda, M.; Inafuku, N.; Kubota, M.; Kamada, Y.; Osawa, T.; Kobayashi, H.; Wakabayashi, K. Chemoprevention by curcumin during the promotion stage of tumorigenesis of mammary gland in rats irradiated with gamma-rays. Carcinogenesis 1999, 20, 1011–1018.
20. Mohebbati, R.; Anaeigoudari, A.; Khazdair, M.R. The effects of Curcuma longa and curcumin on reproductive systems. Endocr. Regul. 2017, 51, 220–228.
21. Moniruzzaman, M.; Min, T. Curcumin, Curcumin Nanoparticles and Curcumin Nanospheres: A Review on Their Pharmacodynamics Based on Monogastric Farm Animal, Poultry and Fish Nutrition. Pharmaceutics 2020, 12, 447.
22. Maheshwari, R.K.; Singh, A.K.; Gaddipati, J.; Srimal, R.C. Multiple biological activities of curcumin: A short review. Life Sci. 2006, 78, 2081–2087.
23. Bala, K.; Tripathy, B.C.; Sharma, D. Neuroprotective and anti-ageing effects of curcumin in aged rat brain regions. Biogerontology 2006, 7, 81–89.
24. Chen, D.-Y.; Shien, J.-H.; Tiley, L.; Chiou, S.-S.; Wang, S.-Y.; Chang, T.-J.; Lee, Y.-J.; Chan, K.-W.; Hsu, W.-L. Curcumin inhibits influenza virus infection and haemagglutination activity. Food Chem. 2010, 119, 1346–1351.

25. Niu, Y.; He, J.; Zhao, Y.; Shen, M.; Zhang, L.; Zhong, X. Effect of Curcumin on Growth Performance, Inflammation, Insulin level, and Lipid Metabolism in Weaned Piglets with IUGR. Animals 2019, 9, 1098.
26. Chainani-Wu, N. Safety and anti-inflammatory activity of curcumin: A component of tumeric (Curcuma longa). J. Altern. Complement. Med. 2003, 9, 161–168.
27. Ozaki, K.; Kawata, Y.; Amano, S.; Hanazawa, S. Stimulatory effect of curcumin on osteoclast apoptosis. Biochem. Pharmacol. 2000, 59, 1577–1581.
28. Larasati, Y.A.; Yoneda-Kato, N.; Nakamae, I.; Yokoyama, T.; Meiyanto, E.; Kato, J.Y. Curcumin targets multiple enzymes involved in the ROS metabolic pathway to suppress tumor cell growth. Sci. Rep. 2018, 8, 2039.
29. Kim, B.H.; Lee, E.S.; Choi, R.; Nawaboot, J.; Lee, M.Y.; Lee, E.Y.; Kim, H.S.; Chung, C.H. Protective Effects of Curcumin on Renal Oxidative Stress and Lipid Metabolism in a Rat Model of Type 2 Diabetic Nephropathy. Yonsei Med. J. 2016, 57, 664–673.
30. Balasubramanyam, M.; Koteswari, A.A.; Kumar, R.S.; Monickaraj, S.F.; Maheswari, J.U.; Mohan, V. Curcumin-induced inhibition of cellular reactive oxygen species generation: Novel therapeutic implications. J. Biosci. 2003, 28, 715–721.
31. Mercantepe, T.; Unal, D.; Tümkaya, L.; Yazici, Z.A. Protective effects of amifostine, curcumin and caffeic acid phenethyl ester against cisplatin-induced testis tissue damage in rats. Exp. Ther. Med. 2018, 15, 3404–3412.
32. Momeni, H.R.; Eskandari, N. Curcumin protects the testis against cadmium-induced histopathological damages and oxidative stress in mice. Hum. Exp. Toxicol. 2020, 39, 653–661.
33. Desai, K.R.; Rajput, D.K.; Patel, P.B.; Highland, H.N. Ameliorative Effects of Curcumin on Artesunate-Induced Subchronic Toxicity in Testis of Swiss Albino Male Mice. Dose-Response 2015, 13, 1559325815592393.
34. Yang, S.-H.; He, J.-B.; Yu, L.-H.; Li, L.; Long, M.; Liu, M.-D.; Li, P. Protective role of curcumin in cadmium-induced testicular injury in mice by attenuating oxidative stress via Nrf2/ARE pathway. Environ. Sci. Pollut. Res. 2019, 26, 34575–34583.
35. Ilbey, Y.O.; Ozbek, E.; Cekmen, M.; Simsek, A.; Otunctemur, A.; Somay, A. Protective effect of curcumin in cisplatin-induced oxidative injury in rat testis: Mitogen-activated protein kinase and nuclear factor-kappa B signaling pathways. Hum. Reprod. 2009, 24, 1717–1725.
36. Mathuria, N.; Verma, R.J. Curcumin ameliorates aflatoxin-induced lipid peroxidation in liver, kidney and testis of mice—An in vitro study. Acta Pol. Pharm. 2007, 64, 413–416.
37. Verma, R.J.; Mathuria, N. Effect of curcumin on aflatoxin-induced biochemical changes in testis of mice. Fertil. Steril. 2009, 91, 597–601.

38. Lin, C.; Shin, D.G.; Park, S.G.; Chu, S.B.; Gwon, L.W.; Lee, J.G.; Yon, J.M.; Baek, I.J.; Nam, S.Y. Curcumin dose-dependently improves spermatogenic disorders induced by scrotal heat stress in mice. Food Funct. 2015, 6, 3770–3777.
39. Baker, M. Deceptive curcumin offers cautionary tale for chemists. Nature 2017, 541, 144–145.
40. Nelson, K.M.; Dahlin, J.L.; Bisson, J.; Graham, J.; Pauli, G.F.; Walters, M.A. The Essential Medicinal Chemistry of Curcumin. J. Med. Chem. 2017, 60, 1620–1637.
41. Abdul-Hamid, M.; Abdella, E.M.; Galaly, S.R.; Ahmed, R.H. Protective effect of ellagic acid against cyclosporine A-induced histopathological, ultrastructural changes, oxidative stress, and cytogenotoxicity in albino rats. Ultrastruct. Pathol. 2016, 40, 205–221.
42. Türk, G.; Ateşşahin, A.; Sönmez, M.; Ceribaşi, A.O.; Yüce, A. Improvement of cisplatin-induced injuries to sperm quality, the oxidant-antioxidant system, and the histologic structure of the rat testis by ellagic acid. Fertil. Steril. 2008, 89, 1474–1481.
43. Goyal, Y.; Koul, A.; Ranawat, P. Ellagic acid ameliorates cisplatin toxicity in chemically induced colon carcinogenesis. Mol. Cell. Biochem. 2019, 453, 205–215.
44. Başak Türkmen, N.; Ayhan, İ.; Taşlıdere, A.; Aydın, M.; Çiftçi, O. Investigation of protective effect of ellagic acid in phthalates-induced reproductive damage. Drug Chem. Toxicol. 2020, 1–14.
45. Guvvala, P.R.; Ravindra, J.P.; Selvaraju, S.; Arangasamy, A.; Venkata, K.M. Ellagic and ferulic acids protect arsenic-induced male reproductive toxicity via regulating Nfe2l2, Ppargc1a and StAR expressions in testis. Toxicology 2019, 413, 1–12.
46. Ateşşahin, A.; Türk, G.; Yilmaz, S.; Sönmez, M.; Sakin, F.; Ceribasi, A.O. Modulatory effects of lycopene and ellagic acid on reproductive dysfunction induced by polychlorinated biphenyl (Aroclor 1254) in male rats. Basic Clin. Pharmacol. Toxicol. 2010, 106, 479–489.
47. Hamza, R.Z.; Al-Baqami, N.M. Testicular protective effects of ellagic acid on monosodium glutamate-induced testicular structural alterations in male rats. Ultrastruct. Pathol. 2019, 43, 170–183.
48. Siervo, G.E.; Vieira, H.R.; Ogo, F.M.; Fernandez, C.D.; Gonçalves, G.D.; Mesquita, S.F.; Anselmo-Franci, J.A.; Cecchini, R.; Guarnier, F.A.; Fernandes, G.S. Spermatic and testicular damages in rats exposed to ethanol: Influence of lipid peroxidation but not testosterone. Toxicology 2015, 330, 1–8.
49. Akinola, B.K.; Olawuyi, T.S.; Ukwenya, V.O.; Daniel, L.D.; Faleye, B.C. Protective effects of aloe vera gel (Aloe baberdensis Miller) on aluminum chloride-induced reproductive toxicity in male Wistar rats. JBRA Assist. Reprod. 2021, 25, 193–201.
50. Jahan, S.; Azad, T.; Ayub, A.; Ullah, A.; Afsar, T.; Almajwal, A.; Razak, S. Ameliorating potency of Chenopodium album Linn. and vitamin C against mercuric chloride-induced oxidative stress in

testes of Sprague Dawley rats. Environ. Health Prev. Med. 2019, 24, 62.

51. Rahmouni, F.; Daoud, S.; Rebai, T. Teucrium polium attenuates carbon tetrachloride-induced toxicity in the male reproductive system of rats. Andrologia 2019, 51, e13182.
52. El Shafai, A.; Zohdy, N.; El Mulla, K.; Hassan, M.; Morad, N. Light and electron microscopic study of the toxic effect of prolonged lead exposure on the seminiferous tubules of albino rats and the possible protective effect of ascorbic acid. Food Chem. Toxicol. 2011, 49, 734–743.
53. Adelakun, S.; Omotoso, O.; Aniah, J.; Oyewo, O. Senecio biafrae defeated Tetracycline-Induced Testicular Toxicity in Adult Male Sprague Dawley Rats. JBRA Assist. Reprod. 2018, 22, 314–322.
54. Farombi, E.O.; Ugwuezunmba, M.C.; Ezenwadu, T.T.; Oyeyemi, M.O.; Ekor, M. Tetracycline-induced reproductive toxicity in male rats: Effects of vitamin C and N-acetylcysteine. Exp. Toxicol. Pathol. 2008, 60, 77–85.
55. Adelakun, S.A.; Akinola, B.K.; Akingbade, G.T. Fertility Enhancing Activities of Bioactive Components of Cochlospermum planchonii Rhizome on Cisplatin Induced Reproductive Dysfunctions in Sprague-Dawley Rats. J. Fam. Reprod. Health 2018, 12, 148–159.
56. Azizollahi, S.; Babaei, H.; Derakhshanfar, A.; Oloumi, M.M. Effects of co-administration of dopamine and vitamin C on ischaemia-reperfusion injury after experimental testicular torsion-detorsion in rats. Andrologia 2011, 43, 100–105.
57. Momeni, H.R.; Oryan, S.; Eskandari, N. Effect of vitamin E on sperm number and testis histopathology of sodium arsenite-treated rats. Reprod. Biol. 2012, 12, 171–181.
58. Mehranjani, M.S.; Noorafshan, A.; Momeni, H.R.; Abnosi, M.H.; Mahmoodi, M.; Anvari, M.; Hoseini, S.M. Stereological study of the effects of vitamin E on testis structure in rats treated with para-nonylphenol. Asian J. Androl. 2009, 11, 508–516.
59. Latchoumycandane, C.; Mathur, P.P. Effects of vitamin E on reactive oxygen species-mediated 2,3,7,8-tetrachlorodi-benzo-p-dioxin toxicity in rat testis. J. Appl. Toxicol. 2002, 22, 345–351.
60. Rahimi Anbarkeh, F.; Nikravesh, M.R.; Jalali, M.; Sadeghnia, H.R.; Sargazi, Z.; Mohammdzadeh, L. Single dose effect of diazinon on biochemical parameters in testis tissue of adult rats and the protective effect of vitamin E. Iran. J. Reprod. Med. 2014, 12, 731–736.
61. Rajeswary, S.; Mathew, N.; Akbarsha, M.A.; Kalyanasundram, M.; Kumaran, B. Protective effect of vitamin E against carbendazim-induced testicular toxicity-histopathological evidences and reduced residue levels in testis and serum. Arch. Toxicol. 2007, 81, 813–821.
62. Yüncü, M.; Bükücü, N.; Bayat, N.; Sencar, L.; Tarakçioğlu, M. The effect of vitamin E and L-carnitine against methotrexate-induced injury in rat testis. Turk. J. Med. Sci. 2015, 45, 517–525.
63. Landete, J.M. Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health. Food Res. Int. 2011, 44, 1150–1160.

64. Seigler, D.S. Tannins. In Plant Secondary Metabolism; Seigler, D.S., Ed.; Springer: Boston, MA, USA, 1998; pp. 193–214.
65. Whitley, A.C.; Stoner, G.D.; Darby, M.V.; Walle, T. Intestinal epithelial cell accumulation of the cancer preventive polyphenol ellagic acid--extensive binding to protein and DNA. Biochem. Pharmacol. 2003, 66, 907–915.
66. Seeram, N.P.; Adams, L.S.; Henning, S.M.; Niu, Y.; Zhang, Y.; Nair, M.G.; Heber, D. In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. J. Nutr. Biochem. 2005, 16, 360–367.
67. Loarca-Piña, G.; Kuzmicky, P.A.; de Mejía, E.G.; Kado, N.Y. Inhibitory effects of ellagic acid on the direct-acting mutagenicity of aflatoxin B1 in the Salmonella microsuspension assay. Mutat. Res. 1998, 398, 183–187.
68. Yu, Y.M.; Chang, W.C.; Wu, C.H.; Chiang, S.Y. Reduction of oxidative stress and apoptosis in hyperlipidemic rabbits by ellagic acid. J. Nutr. Biochem. 2005, 16, 675–681.
69. Papoutsi, Z.; Kassi, E.; Tsiapara, A.; Fokialakis, N.; Chrousos, G.P.; Moutsatsou, P. Evaluation of estrogenic/antiestrogenic activity of ellagic acid via the estrogen receptor subtypes ERalpha and ERbeta. J. Agric. Food Chem. 2005, 53, 7715–7720.
70. Hassoun, E.A.; Walter, A.C.; Alsharif, N.Z.; Stohs, S.J. Modulation of TCDD-induced fetotoxicity and oxidative stress in embryonic and placental tissues of C57BL/6J mice by vitamin E succinate and ellagic acid. Toxicology 1997, 124, 27–37.
71. Hassoun, E.A.; Vodhanel, J.; Abushaban, A. The modulatory effects of ellagic acid and vitamin E succinate on TCDD-induced oxidative stress in different brain regions of rats after subchronic exposure. J. Biochem. Mol. Toxicol. 2004, 18, 196–203.
72. Dalvi, L.T.; Moreira, D.C.; Andrade, R., Jr.; Ginani, J.; Alonso, A.; Hermes-Lima, M. Ellagic acid inhibits iron-mediated free radical formation. Spectrochim. Acta A Mol. Biomol. Spectrosc. 2017, 173, 910–917.
73. Pari, L.; Sivasankari, R. Effect of ellagic acid on cyclosporine A-induced oxidative damage in the liver of rats. Fundam. Clin. Pharmacol. 2008, 22, 395–401.
74. Vattem, D.A.; Shetty, K. Biological functionality of ellagic acid: A review. J. Food Biochem. 2005, 29, 234–266.
75. Abdullah, M.; Jamil, R.T.; Attia, F.N. Vitamin C (Ascorbic Acid) StatPearls 2021. Available online: https://www.ncbi.nlm.nih.gov/books/NBK499877/ (accessed on 18 March 2019).
76. Castro, M.A.; Angulo, C.; Brauchi, S.; Nualart, F.; Concha, I.I. Ascorbic acid participates in a general mechanism for concerted glucose transport inhibition and lactate transport stimulation.

Pflugers Arch. 2008, 457, 519–528.

77. Carr, A.; Frei, B. Does vitamin C act as a pro-oxidant under physiological conditions? FASEB J. 1999, 13, 1007–1024.
78. Fernandes, G.S.; Fernandez, C.D.; Campos, K.E.; Damasceno, D.C.; Anselmo-Franci, J.A.; Kempinas, W.D. Vitamin C partially attenuates male reproductive deficits in hyperglycemic rats. Reprod. Biol. Endocrinol. 2011, 9, 100.
79. Aro, A.; Kyllästinen, M.; Kostiainen, E.; Gref, C.G.; Elfving, S.; Uusitalo, U. No effect on serum lipids by moderate and high doses of vitamin C in elderly subjects with low plasma ascorbic acid levels. Ann. Nutr. Metab. 1988, 32, 133–137.
80. Shibata, M.A.; Tamano, S.; Kurata, Y.; Hagiwara, A.; Fukushima, S. Participation of urinary Na+, K+, pH, and L-ascorbic acid in the proliferative response of the bladder epithelium after the oral administration of various salts and/or ascorbic acid to rats. Food Chem. Toxicol. 1989, 27, 403–413.
81. Gershoff, S.N. Vitamin C (ascorbic acid): New roles, new requirements? Nutr. Rev. 1993, 51, 313–326.
82. Salama, A.F.; Kasem, S.M.; Tousson, E.; Elsisy, M.K. Protective role of L-carnitine and vitamin E on the testis of atherosclerotic rats. Toxicol. Ind. Health 2015, 31, 467–474.
83. Medina, J.; Gupta, V. Vitamin E. StatPearls 2021. Available online: https://www.ncbi.nlm.nih.gov/books/NBK557737/ (accessed on 18 March 2019).
84. Colombo, M.L. An update on vitamin E, tocopherol and tocotrienol-perspectives. Molecules 2010, 15, 2103–2113.
85. Erdemli, Z.; Erdemli, M.E. The effects of acrylamide and Vitamin E administration during pregnancy on adult rats testis. Andrologia 2019, 51, e13292.
86. Lomnitski, L.; Bergman, M.; Schön, I.; Grossman, S. The effect of dietary vitamin E and beta-carotene on oxidation processes in the rat testis. Biochim. Biophys. Acta 1991, 1082, 101–107.
87. Owen, K.N.; Dewald, O. Vitamin E Toxicity StatPearls 2021. Available online: https://www.ncbi.nlm.nih.gov/books/NBK564373/ (accessed on 18 March 2019).
88. Hammami, I.; El May, M.V. Impact of garlic feeding (Allium sativum) on male fertility. Andrologia 2013, 45, 217–224.
89. Rivlin, R.S. Historical perspective on the use of garlic. J. Nutr. 2001, 131, 951s–954s.
90. Block, E. The chemistry of garlic and onions. Sci. Am. 1985, 252, 114–119.
91. Park, J.H.; Park, Y.K.; Park, E. Antioxidative and antigenotoxic effects of garlic (Allium sativum L.) prepared by different processing methods. Plant Foods Hum. Nutr. 2009, 64, 244–249.

92. Srinivasan, K. Antioxidant potential of spices and their active constituents. Crit. Rev. Food Sci. Nutr. 2014, 54, 352–372.
93. Oi, Y.; Imafuku, M.; Shishido, C.; Kominato, Y.; Nishimura, S.; Iwai, K. Garlic supplementation increases testicular testosterone and decreases plasma corticosterone in rats fed a high protein diet. J. Nutr. 2001, 131, 2150–2156.
94. Ola-Mudathir, K.F.; Suru, S.M.; Fafunso, M.A.; Obioha, U.E.; Faremi, T.Y. Protective roles of onion and garlic extracts on cadmium-induced changes in sperm characteristics and testicular oxidative damage in rats. Food Chem. Toxicol. 2008, 46, 3604–3611.
95. El-Akabawy, G.; El-Sherif, N.M. Protective role of garlic oil against oxidative damage induced by furan exposure from weaning through adulthood in adult rat testis. Acta Histochem. 2016, 118, 456–463.
96. Nasr, A.Y. The impact of aged garlic extract on adriamycin-induced testicular changes in adult male Wistar rats. Acta Histochem. 2017, 119, 648–662.
97. Rana, S.V.; Pal, R.; Vaiphei, K.; Sharma, S.K.; Ola, R.P. Garlic in health and disease. Nutr. Res. Rev. 2011, 24, 60–71.
98. Zahedi, A.; Fathiazad, F.; Khaki, A.; Ahmadnejad, B. Protective effect of ginger on gentamicin-induced apoptosis in testis of rats. Adv. Pharm. Bull. 2012, 2, 197–200.
99. Mazani, M.; Ojarudi, M.; Banaei, S. The protective effect of cinnamon and ginger hydro-alcoholic extract on carbon tetrachloride-induced testicular damage in rats. Andrologia 2020, 52, e13651.
100. Akbari, A.; Nasiri, K.; Heydari, M.; Mosavat, S.H.; Iraji, A. The Protective Effect of Hydroalcoholic Extract of Zingiber officinale Roscoe (Ginger) on Ethanol-Induced Reproductive Toxicity in Male Rats. J. Evid. Based Complement. Altern. Med. 2017, 22, 609–617.
101. Afkhami Fathabad, A.; Shekarforoush, S.; Hoseini, M.; Ebrahimi, Z. Attenuation of Sulfite-Induced Testicular Injury in Rats by Zingiber officinale Roscoe. J. Diet. Suppl. 2018, 15, 398–409.
102. Akbari, A.; Nasiri, K.; Heydari, M.; Mosavat, S.H. The Prophylactic Effect of Hydroalcoholic Extract of Zingiber officinale (Ginger) on Ethanol-Induced Reproductive Toxicity in Male Rats. Iran. J. Med. Sci. 2016, 41, S71.
103. Bordbar, H.; Esmaeilpour, T.; Dehghani, F.; Panjehshahin, M.R. Stereological study of the effect of ginger’s alcoholic extract on the testis in busulfan-induced infertility in rats. Iran. J. Reprod. Med. 2013, 11, 467–472.
104. Mohammadi, F.; Nikzad, H.; Taghizadeh, M.; Taherian, A.; Azami-Tameh, A.; Hosseini, S.M.; Moravveji, A. Protective effect of Zingiber officinale extract on rat testis after cyclophosphamide treatment. Andrologia 2014, 46, 680–686.

105. Amin, A.; Hamza, A.A. Effects of Roselle and Ginger on cisplatin-induced reproductive toxicity in rats. Asian J. Androl. 2006, 8, 607–612.
106. El-Mehi, A.E.; Faried, M.A. Effect of high-fructose diet-induced metabolic syndrome on the pituitary-gonadal axis from adolescence through adulthood in male albino rats and the possible protective role of ginger extract. A biochemical, histological and immunohistochemical study. Folia Morphol. 2020, 79, 690–708.
107. Al-Shathly, M.R.; Ali, S.S.; Ayuob, N.N. Zingiber officinale preserves testicular structure and the expression of androgen receptors and proliferating cell nuclear antigen in diabetic rats. Andrologia 2020, 52, e13528.
108. Ghlissi, Z.; Atheymen, R.; Boujbiha, M.A.; Sahnoun, Z.; Makni Ayedi, F.; Zeghal, K.; El Feki, A.; Hakim, A. Antioxidant and androgenic effects of dietary ginger on reproductive function of male diabetic rats. Int. J. Food Sci. Nutr. 2013, 64, 974–978.
109. El-Ashmawy, I.M.; Saleh, A.; Salama, O.M. Effects of marjoram volatile oil and grape seed extract on ethanol toxicity in male rats. Basic Clin. Pharmacol. Toxicol. 2007, 101, 320–327.
110. Hassan, H.A.; El-Kholy, W.M.; Nour, S.E. Proanthocyanidin as a cytogenetic protective agent against adverse effects of plant growth regulators supplementation in rats. Cytotechnology 2014, 66, 585–596.
111. Lamas, C.A.; Cuquetto-Leite, L.; do Nascimento da Silva, E.; Thomazini, B.F.; Cordeiro, G.D.S.; Predes, F.S.; Gollücke, A.P.B.; Dolder, H. Grape juice concentrate alleviates epididymis and sperm damage in cadmium-intoxicated rats. Int. J. Exp. Pathol. 2017, 98, 86–99.
112. Morsi, A.A.; Shawky, L.M.; El Bana, E.A. The potential gonadoprotective effects of grape seed extract against the histopathological alterations elicited in an animal model of cadmium-induced testicular toxicity. Folia Morphol. 2020, 79, 767–776.
113. Evcimen, M.; Aslan, R.; Gulay, M.S. Protective effects of polydatin and grape seed extract in rats exposed to cadmium. Drug Chem. Toxicol. 2020, 43, 225–233.
114. Alkhedaide, A.; Alshehri, Z.S.; Sabry, A.; Abdel-Ghaffar, T.; Soliman, M.M.; Attia, H. Protective effect of grape seed extract against cadmium-induced testicular dysfunction. Mol. Med. Rep. 2016, 13, 3101–3109.
115. Sönmez, M.F.; Tascioglu, S. Protective effects of grape seed extract on cadmium-induced testicular damage, apoptosis, and endothelial nitric oxide synthases expression in rats. Toxicol. Ind. Health 2016, 32, 1486–1494.
116. Pires, V.C.; Gollücke, A.P.; Ribeiro, D.A.; Lungato, L.; D'Almeida, V.; Aguiar, O., Jr. Grape juice concentrate protects reproductive parameters of male rats against cadmium-induced damage: A chronic assay. Br. J. Nutr. 2013, 110, 2020–2029.

117. Lamas, C.A.; Gollücke, A.P.; Dolder, H. Grape juice concentrate (G8000®) intake mitigates testicular morphological and ultrastructural damage following cadmium intoxication. Int. J. Exp. Pathol. 2015, 96, 301–310.

118. Hasona, N.A. Grape seed extract attenuates dexamethasone-induced testicular and thyroid dysfunction in male albino rats. Andrologia 2018, 50, e13002.

119. Wang, Y.; Chen, F.; Liang, M.; Chen, S.; Zhu, Y.; Zou, Z.; Shi, B. Grape seed proanthocyanidin extract attenuates varicocele-induced testicular oxidative injury in rats by activating the Nrf2-antioxidant system. Mol. Med. Rep. 2018, 17, 1799–1806.

120. Bayatli, F.; Akkuş, D.; Kilic, E.; Saraymen, R.; Sönmez, M.F. The protective effects of grape seed extract on MDA, AOPP, apoptosis and eNOS expression in testicular torsion: An experimental study. World J. Urol. 2013, 31, 615–622.

121. Juan, M.E.; González-Pons, E.; Munuera, T.; Ballester, J.; Rodríguez-Gil, J.E.; Planas, J.M. trans-Resveratrol, a natural antioxidant from grapes, increases sperm output in healthy rats. J. Nutr. 2005, 135, 757–760.

122. Bagherpour, H.; Karimpour Malekshah, A.; Talebpour Amiri, F.; Azadbakht, M. Protective effect of green tea extract on the deltamethrin-induced toxicity in mice testis: An experimental study. Int. J. Reprod. Biomed. 2019, 17, 337–348.

123. Opuwari, C.; Monsees, T. Green tea consumption increases sperm concentration and viability in male rats and is safe for reproductive, liver and kidney health. Sci. Rep. 2020, 10, 15269.

124. Azizi, P.; Soleimani Mehranjani, M. The effect of green tea extract on the sperm parameters and histological changes of testis in rats exposed to para-nonylphenol. Int. J. Reprod. Biomed. 2019, 17, 717–726.

125. Mahmoudi, R.; Azizi, A.; Abedini, S.; Hemayatkhah Jahromi, V.; Abidi, H.; Jafari Barmak, M. Green tea improves rat sperm quality and reduced cadmium chloride damage effect in spermatogenesis cycle. J. Med. Life 2018, 11, 371–380.

126. Abdelrazek, H.M.; Helmy, S.A.; Elsayed, D.H.; Ebaid, H.M.; Mohamed, R.M. Ameliorating effects of green tea extract on cadmium induced reproductive injury in male Wistar rats with respect to androgen receptors and caspase-3. Reprod. Biol. 2016, 16, 300–308.

127. Mosbah, R.; Yousef, M.I.; Mantovani, A. Nicotine-induced reproductive toxicity, oxidative damage, histological changes and haematotoxicity in male rats: The protective effects of green tea extract. Exp. Toxicol. Pathol. 2015, 67, 253–259.

128. Sato, K.; Sueoka, K.; Tanigaki, R.; Tajima, H.; Nakabayashi, A.; Yoshimura, Y.; Hosoi, Y. Green tea extracts attenuate doxorubicin-induced spermatogenic disorders in conjunction with higher telomerase activity in mice. J. Assist. Reprod Genet. 2010, 27, 501–508.

129. Osama, E.; Galal, A.A.A.; Abdalla, H.; El-Sheikh, S.M.A. Chlorella vulgaris ameliorates testicular toxicity induced by deltamethrin in male rats via modulating oxidative stress. Andrologia 2019, 51, e13214.

130. Eissa, M.M.; Ahmed, M.M. Methanolic extract of Chlorella vulgaris protects against sodium nitrite-induced reproductive toxicity in male rats. Andrologia 2020, 52, e13811.

131. Farag, M.R.; Abd El-Aziz, R.M.; Ali, H.A.; Ahmed, S.A. Evaluating the ameliorative efficacy of Spirulina platensis on spermatogenesis and steroidogenesis in cadmium-intoxicated rats. Environ. Sci. Pollut. Res. Int. 2016, 23, 2454–2466.

132. Abd El-Hakim, Y.M.; Mohamed, W.A.; El-Metwally, A.E. Spirulina platensis attenuates furan reprotoxicity by regulating oxidative stress, inflammation, and apoptosis in testis of rats. Ecotoxicol. Environ. Saf. 2018, 161, 25–33.

133. El-Desoky, G.E.; Bashandy, S.A.; Alhazza, I.M.; Al-Othman, Z.A.; Aboul-Soud, M.A.; Yusuf, K. Improvement of mercuric chloride-induced testis injuries and sperm quality deteriorations by Spirulina platensis in rats. PLoS ONE 2013, 8, e59177.

134. Barkallah, M.; Slima, A.B.; Elleuch, F.; Fendri, I.; Pichon, C.; Abdelkafi, S.; Baril, P. Protective Role of Spirulina platensis Against Bifenthrin-Induced Reprotoxicity in Adult Male Mice by Reversing Expression of Altered Histological, Biochemical, and Molecular Markers Including MicroRNAs. Biomolecules 2020, 10, 753.

135. Ibrahim, I.A.; Shalaby, A.A.; Abd Elaziz, R.T.; Bahr, H.I. Chlorella vulgaris or Spirulina platensis mitigate lead acetate-induced testicular oxidative stress and apoptosis with regard to androgen receptor expression in rats. Environ. Sci. Pollut. Res. Int. 2021, 28, 39126–39138.

136. Nah, W.H.; Koh, I.K.; Ahn, H.S.; Kim, M.J.; Kang, H.-G.; Jun, J.H.; Gye, M.C. Effect of Spirulina maxima on spermatogenesis and steroidogenesis in streptozotocin-induced type I diabetic male rats. Food Chem. 2012, 134, 173–179.

137. Chamorro-Cevallos, G.; Garduño-Siciliano, L.; Martínez-Galero, E.; Mojica-Villegas, A.; Pages, N.; Gutiérrez-Salmeán, G. The protective effect of dietary Arthrospira (Spirulina) maxima against mutagenicity induced by benzopyrene in mice. J. Med. Food 2014, 17, 527–534.

138. Chamorro-Cevallos, G.; Garduño-Siciliano, L.; Barrón, B.L.; Madrigal-Bujaidar, E.; Cruz-Vega, D.E.; Pages, N. Chemoprotective effect of Spirulina (Arthrospira) against cyclophosphamide-induced mutagenicity in mice. Food Chem. Toxicol. 2008, 46, 567–574.

139. Güner, Ö.; Güner, A.; Yavaşoğlu, A.; Karabay Yavaşoğlu, N.Ü.; Kavlak, O. Ameliorative effect of edible Halopteris scoparia against cadmium-induced reproductive toxicity in male mice: A biochemical and histopathologic study. Andrologia 2020, 52, e13591.

140. Kong, Z.L.; Sudirman, S. Fucoxanthin-Rich Brown Algae Extract Improves Male Reproductive Function on Streptozotocin-Nicotinamide-Induced Diabetic Rat Model. Int. J. Mol. Sci. 2019, 20,

4485.

141. Wang, P.T.; Sudirman, S.; Hsieh, M.C.; Hu, J.Y.; Kong, Z.L. Oral supplementation of fucoxanthin-rich brown algae extract ameliorates cisplatin-induced testicular damage in hamsters. Biomed. Pharmacother. 2020, 125, 109992.
142. Seven, I.; Tatli Seven, P. Bee glue (propolis) improves reproductive organs, sperm quality and histological changes and antioxidant parameters of testis tissues in rats exposed to excess copper. Andrologia 2020, 52, e13540.
143. Nna, V.U.; Abu Bakar, A.B.; Ahmad, A.; Eleazu, C.O.; Mohamed, M. Oxidative Stress, NF-κB-Mediated Inflammation and Apoptosis in the Testes of Streptozotocin-Induced Diabetic Rats: Combined Protective Effects of Malaysian Propolis and Metformin. Antioxidants 2019, 8, 465.
144. Nna, V.U.; Bakar, A.B.A.; Ahmad, A.; Umar, U.Z.; Suleiman, J.B.; Zakaria, Z.; Othman, Z.A.; Mohamed, M. Malaysian propolis and metformin mitigate subfertility in streptozotocin-induced diabetic male rats by targeting steroidogenesis, testicular lactate transport, spermatogenesis and mating behavior. Andrologia 2020, 8, 731–746.
145. Yousef, M.I.; Salama, A.F. Propolis protection from reproductive toxicity caused by aluminium chloride in male rats. Food Chem. Toxicol. 2009, 47, 1168–1175.
146. Çilenk, K.T.; Öztürk, İ.; Sönmez, M.F. Ameliorative effect of propolis on the cadmium-induced reproductive toxicity in male albino rats. Exp. Mol. Pathol. 2016, 101, 207–213.
147. Sönmez, M.F.; Çilenk, K.T.; Karabulut, D.; Ünalmış, S.; Deligönül, E.; Öztürk, İ.; Kaymak, E. Protective effects of propolis on methotrexate-induced testis injury in rat. Biomed. Pharmacother. 2016, 79, 44–51.
148. Rizk, S.M.; Zaki, H.F.; Mina, M.A. Propolis attenuates doxorubicin-induced testicular toxicity in rats. Food. Chem. Toxicol. 2014, 67, 176–186.
149. Abd-Elrazek, A.M.; El-Dash, H.A.; Said, N.I. The role of propolis against paclitaxel-induced oligospermia, sperm abnormality, oxidative stress and DNA damage in testes of male rats. Andrologia 2020, 52, e13394.
150. Khodaie, L.; Sadeghpoor, O. Ginger from ancient times to the new outlook. Jundishapur J. Nat. Pharm. Prod. 2015, 10, e18402.
151. Khaleghi Ghadiri, M.; Gorji, A. Natural remedies for impotence in medieval Persia. Int. J. Impot. Res. 2004, 16, 80–83.
152. Kamatenesi-Mugisha, M.; Oryem-Origa, H. Traditional herbal remedies used in the management of sexual impotence and erectile dysfunction in western Uganda. Afr. Health Sci. 2005, 5, 40–49.
153. Ghasemzadeh, A.; Jaafar, H.Z.; Rahmat, A. Antioxidant activities, total phenolics and flavonoids content in two varieties of Malaysia young ginger (Zingiber officinale Roscoe). Molecules 2010,

15, 4324–4333.

154. Lantz, R.C.; Chen, G.J.; Sarihan, M.; Sólyom, A.M.; Jolad, S.D.; Timmermann, B.N. The effect of extracts from ginger rhizome on inflammatory mediator production. Phytomedicine 2007, 14, 123–128.
155. Ramachandran, C.; Lollett, I.V.; Escalon, E.; Quirin, K.W.; Melnick, S.J. Anticancer potential and mechanism of action of mango ginger (Curcuma amada Roxb.) supercritical CO2 extract in human glioblastoma cells. J. Evid. Based Complement. Altern. Med. 2015, 20, 109–119.
156. Shukla, Y.; Singh, M. Cancer preventive properties of ginger: A brief review. Food Chem. Toxicol. 2007, 45, 683–690.
157. Chrubasik, S.; Pittler, M.H.; Roufogalis, B.D. Zingiberis rhizoma: A comprehensive review on the ginger effect and efficacy profiles. Phytomedicine 2005, 12, 684–701.
158. Al-Amin, Z.M.; Thomson, M.; Al-Qattan, K.K.; Peltonen-Shalaby, R.; Ali, M. Anti-diabetic and hypolipidaemic properties of ginger (Zingiber officinale) in streptozotocin-induced diabetic rats. Br. J. Nutr. 2006, 96, 660–666.
159. Kamtchouing, P.; Mbongue Fandio, G.Y.; Dimo, T.; Jatsa, H.B. Evaluation of androgenic activity of Zingiber officinale and Pentadiplandra brazzeana in male rats. Asian J. Androl. 2002, 4, 299–301.
160. Morakinyo, F.; Achema, P.; Adegoke, O. Effect of Zingiber officinale (Ginger) on Sodium Arsenite–Induced Reproductive Toxicity in Male Rats. Afr. J. Biomed. Res. 2010, 13, 39–45.
161. Sakr, S.; Badawy, G. Effect of ginger (Zingiber officinale R.) on metiram-inhibited spermatogenesis and induced apoptosis in albino mice. J. Appl. Pharm. Sci. 2011, 1, 131–136.
162. Gupta, M.; Dey, S.; Marbaniang, D.; Pal, P.; Ray, S.; Mazumder, B. Grape seed extract: Having a potential health benefits. J. Food Sci. Technol. 2020, 57, 1205–1215.
163. Matthäus, B. Virgin grape seed oil: Is it really a nutritional highlight? Eur. J. Lipid Sci. Technol. 2008, 110, 645–650.
164. Farzaei, M.H.; Abdollahi, M.; Rahimi, R. Role of dietary polyphenols in the management of peptic ulcer. World J. Gastroenterol. 2015, 21, 6499–6517.
165. Kaur, M.; Agarwal, C.; Agarwal, R. Anticancer and cancer chemopreventive potential of grape seed extract and other grape-based products. J. Nutr. 2009, 139, 1806s–1812s.
166. Terra, X.; Pallarés, V.; Ardèvol, A.; Bladé, C.; Fernández-Larrea, J.; Pujadas, G.; Salvadó, J.; Arola, L.; Blay, M. Modulatory effect of grape-seed procyanidins on local and systemic inflammation in diet-induced obesity rats. J. Nutr. Biochem. 2011, 22, 380–387.
167. Bagchi, D.; Garg, A.; Krohn, R.L.; Bagchi, M.; Tran, M.X.; Stohs, S.J. Oxygen free radical scavenging abilities of vitamins C and E, and a grape seed proanthocyanidin extract in vitro. Res.

Commun. Mol. Pathol. Pharmacol. 1997, 95, 179–189.

168. Maffei Facino, R.; Carini, M.; Aldini, G.; Bombardelli, E.; Morazzoni, P.; Morelli, R. Free radicals scavenging action and anti-enzyme activities of procyanidines from Vitis vinifera. A mechanism for their capillary protective action. Arzneimittel-Forschung 1994, 44, 592–601.
169. Shi, J.; Yu, J.; Pohorly, J.E.; Kakuda, Y. Polyphenolics in grape seeds-biochemistry and functionality. J. Med. Food 2003, 6, 291–299.
170. Musial, C.; Kuban-Jankowska, A.; Gorska-Ponikowska, M. Beneficial Properties of Green Tea Catechins. Int. J. Mol. Sci. 2020, 21, 1744.
171. Chacko, S.M.; Thambi, P.T.; Kuttan, R.; Nishigaki, I. Beneficial effects of green tea: A literature review. Chin. Med. 2010, 5, 13.
172. Graham, H.N. Green tea composition, consumption, and polyphenol chemistry. Prev. Med. 1992, 21, 334–350.
173. Hasegawa, N.; Niimi, N.; Odani, F. Vitamin C is one of the lipolytic substances in green tea. Phytother. Res. 2002, 16 (Suppl. S1), S91–S92.
174. Kavanagh, K.T.; Hafer, L.J.; Kim, D.W.; Mann, K.K.; Sherr, D.H.; Rogers, A.E.; Sonenshein, G.E. Green tea extracts decrease carcinogen-induced mammary tumor burden in rats and rate of breast cancer cell proliferation in culture. J. Cell. Biochem. 2001, 82, 387–398.
175. Sartippour, M.R.; Shao, Z.M.; Heber, D.; Beatty, P.; Zhang, L.; Liu, C.; Ellis, L.; Liu, W.; Go, V.L.; Brooks, M.N. Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells. J. Nutr. 2002, 132, 2307–2311.
176. Sueoka, N.; Suganuma, M.; Sueoka, E.; Okabe, S.; Matsuyama, S.; Imai, K.; Nakachi, K.; Fujiki, H. A new function of green tea: Prevention of lifestyle-related diseases. Ann. N. Y. Acad. Sci. 2001, 928, 274–280.
177. Donà, M.; Dell'Aica, I.; Calabrese, F.; Benelli, R.; Morini, M.; Albini, A.; Garbisa, S. Neutrophil restraint by green tea: Inhibition of inflammation, associated angiogenesis, and pulmonary fibrosis. J. Immunol. 2003, 170, 4335–4341.
178. Haqqi, T.M.; Anthony, D.D.; Gupta, S.; Ahmad, N.; Lee, M.S.; Kumar, G.K.; Mukhtar, H. Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea. Proc. Natl. Acad. Sci. USA 1999, 96, 4524–4529.
179. Sudano Roccaro, A.; Blanco, A.R.; Giuliano, F.; Rusciano, D.; Enea, V. Epigallocatechin-gallate enhances the activity of tetracycline in staphylococci by inhibiting its efflux from bacterial cells. Antimicrob. Agents Chemother. 2004, 48, 1968–1973.
180. Weber, J.M.; Ruzindana-Umunyana, A.; Imbeault, L.; Sircar, S. Inhibition of adenovirus infection and adenain by green tea catechins. Antivir. Res. 2003, 58, 167–173.

181. Weinreb, O.; Mandel, S.; Amit, T.; Youdim, M.B. Neurological mechanisms of green tea polyphenols in Alzheimer’s and Parkinson’s diseases. J. Nutr. Biochem. 2004, 15, 506–516.

182. Raederstorff, D.G.; Schlachter, M.F.; Elste, V.; Weber, P. Effect of EGCG on lipid absorption and plasma lipid levels in rats. J. Nutr. Biochem. 2003, 14, 326–332.

183. Osada, K.; Takahashi, M.; Hoshina, S.; Nakamura, M.; Nakamura, S.; Sugano, M. Tea catechins inhibit cholesterol oxidation accompanying oxidation of low density lipoprotein in vitro. Comp. Biochem. Physiol. C Toxicol. Pharmacol. 2001, 128, 153–164.

184. Soussi, A.; Gaubin, Y.; Beau, B.; Murat, J.C.; Soleilhavoup, J.P.; Croute, F.; El Feki, A. Stress proteins (Hsp72/73, Grp94) expression pattern in rat organs following metavanadate administration. Effect of green tea drinking. Food Chem. Toxicol. 2006, 44, 1031–1037.

185. Bedrood, Z.; Rameshrad, M.; Hosseinzadeh, H. Toxicological effects of Camellia sinensis (green tea): A review. Phytother. Res. 2018, 32, 1163–1180.

186. Saha, S.K.; McHugh, E.; Murray, P.; Walsh, D.J. Microalgae as a source of nutraceuticals. In Phycotoxins; Wiley-Blackwell: Hackensack, NJ, USA, 2015; pp. 255–291.

187. Plaza, M.; Herrero, M.; Cifuentes, A.; Ibáñez, E. Innovative natural functional ingredients from microalgae. J. Agric. Food Chem. 2009, 57, 7159–7170.

188. Aitken, R.J.; Curry, B.J. Redox regulation of human sperm function: From the physiological control of sperm capacitation to the etiology of infertility and DNA damage in the germ line. Antioxid. Redox Signal. 2011, 14, 367–381.

189. Tremellen, K. Oxidative stress and male infertility—A clinical perspective. Hum. Reprod. Update 2008, 14, 243–258.

190. U.S. Food and Drug Administration. Re: GRAS Exemption Claim for Chlorella Vulgaris as an Ingredient in Foods. Available online: https://www.isditwelgezond.nl/wp-content/uploads/2017/04/ucm277773.pdf (accessed on 18 March 2019).

191. U.S. Food and Drug Administration. Re: GRAS Exemption Claim for Spirulina Platensis as an Ingredient in Foods. Available online: http://sdlbl.in/wp-content/uploads/2014/09/FDA-United-States.pdf (accessed on 18 March 2019).

192. Vecina, J.F.; Oliveira, A.G.; Araujo, T.G.; Baggio, S.R.; Torello, C.O.; Saad, M.J.; Queiroz, M.L. Chlorella modulates insulin signaling pathway and prevents high-fat diet-induced insulin resistance in mice. Life Sci. 2014, 95, 45–52.

193. Li, L.; Li, W.; Kim, Y.H.; Lee, Y.W. Chlorella vulgaris extract ameliorates carbon tetrachloride-induced acute hepatic injury in mice. Exp. Toxicol. Pathol. 2013, 65, 73–80.

194. Saberbaghi, T.; Abbasian, F.; Mohd Yusof, Y.A.; Makpol, S. Modulation of Cell Cycle Profile by Chlorella vulgaris Prevents Replicative Senescence of Human Diploid Fibroblasts. Evid. Based

Complement. Altern. Med. 2013, 2013, 780504.

195. Sayed, A.E.-D.H.; El-Sayed, Y.S.; El-Far, A.H. Hepatoprotective efficacy of Spirulina platensis against lead-induced oxidative stress and genotoxicity in catfish; Clarias gariepinus. Ecotoxicol. Environ. Saf. 2017, 143, 344–350.
196. Sadek, K.M.; Lebda, M.A.; Nasr, S.M.; Shoukry, M. Spirulina platensis prevents hyperglycemia in rats by modulating gluconeogenesis and apoptosis via modification of oxidative stress and MAPK-pathways. Biomed. Pharmacother. 2017, 92, 1085–1094.
197. Burdock, G.A. Review of the biological properties and toxicity of bee propolis (propolis). Food Chem. Toxicol. 1998, 36, 347–363.
198. Zabaiou, N.; Fouache, A.; Trousson, A.; Baron, S.; Zellagui, A.; Lahouel, M.; Lobaccaro, J.A. Biological properties of propolis extracts: Something new from an ancient product. Chem. Phys. Lipids 2017, 207, 214–222.
199. Tohamy, A.A.; Abdella, E.M.; Ahmed, R.R.; Ahmed, Y.K. Assessment of anti-mutagenic, anti-histopathologic and antioxidant capacities of Egyptian bee pollen and propolis extracts. Cytotechnology 2014, 66, 283–297.
200. Collodel, G.; Moretti, E.; Del Vecchio, M.T.; Biagi, M.; Cardinali, R.; Mazzi, L.; Brecchia, G.; Maranesi, M.; Manca, D.; Castellini, C. Effect of chocolate and Propolfenol on rabbit spermatogenesis and sperm quality following bacterial lipopolysaccharide treatment. Syst. Biol. Reprod. Med. 2014, 60, 217–226.
201. Khalil, M.L. Biological activity of bee propolis in health and disease. Asian Pac. J. Cancer Prev. 2006, 7, 22–31.
202. Sforcin, J.M. Biological Properties and Therapeutic Applications of Propolis. Phytother. Res. 2016, 30, 894–905.
203. Nna, V.U.; Abu Bakar, A.B.; Md Lazin, M.; Mohamed, M. Antioxidant, anti-inflammatory and synergistic anti-hyperglycemic effects of Malaysian propolis and metformin in streptozotocin-induced diabetic rats. Food Chem. Toxicol. 2018, 120, 305–320.
204. Orsi, R.O.; Fernandes, A.; Bankova, V.; Sforcin, J.M. The effects of Brazilian and Bulgarian propolis in vitro against Salmonella Typhi and their synergism with antibiotics acting on the ribosome. Nat. Prod. Res. 2012, 26, 430–437.
205. Selamoglu Talas, Z. Propolis reduces oxidative stress in l-NAME-induced hypertension rats. Cell Biochem. Funct. 2014, 32, 150–154.
206. Sobocanec, S.; Sverko, V.; Balog, T.; Sarić, A.; Rusak, G.; Likić, S.; Kusić, B.; Katalinić, V.; Radić, S.; Marotti, T. Oxidant/antioxidant properties of Croatian native propolis. J. Agric. Food Chem. 2006, 54, 8018–8026.

207. Jasprica, I.; Mornar, A.; Debeljak, Z.; Smolcić-Bubalo, A.; Medić-Sarić, M.; Mayer, L.; Romić, Z.; Bućan, K.; Balog, T.; Sobocanec, S.; et al. In vivo study of propolis supplementation effects on antioxidative status and red blood cells. J. Ethnopharmacol. 2007, 110, 548–554.

208. Castaldo, S.; Capasso, F. Propolis, an old remedy used in modern medicine. Fitoterapia 2002, 73 (Suppl. 1), S1–S6.

209. Capucho, C.; Sette, R.; de Souza Predes, F.; de Castro Monteiro, J.; Pigoso, A.A.; Barbieri, R.; Dolder, M.A.; Severi-Aguiar, G.D. Green Brazilian propolis effects on sperm count and epididymis morphology and oxidative stress. Food Chem. Toxicol. 2012, 50, 3956–3962.