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Role of Antioxidants of Natural Herbs in Management of Male Infertility

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ABSTRACT

If you and your spouse have been trying to conceive for a year and neither of you has been successful, there is a possibility that you are one of the 50–80 million people throughout the world who struggle with infertility. There is a male component present in approximately 20%-30% of these instances. It is common knowledge that low-quality sperm and oxidative stress (OS) both have a role in the aetiology of male infertility. Because of the oxidation of DNA, proteins, and lipids, excessive levels of reactive oxygen species (ROS) have the potential to disrupt the viability, motility, and morphology of sperm cells. ROS are responsible for these changes. Methods: Through the use of the PubMed interface, we searched the MEDLINE database for studies that had been completed and published during the past ten years that analysed the effect that antioxidants had on sperm in infertile guys (2012–2022). A number of different phrases, including infertility, alpha-lipoic acid, zinc, folate, coenzyme Q10, selenium, and vitamin, were utilised during the search. The study's findings indicate that inositol serves a purpose in a number of different mechanisms that foster contacts between sperm and oocytes, and that it also affects OS levels in sperm cells by way of its engagement in mitochondrial events. Alpha-lipoic acid (ALA) lessens the damage caused by reactive oxygen species (ROS) and improves the quality of sperm in a number of ways, including motility, morphology, and count. There might be a connection between not getting enough zinc in your diet and having low-quality sperm. Zinc and folate are two nutrients that can boost the quantity and quality of sperm. When taken orally, coenzyme Q10 increases the number of sperm as well as their overall motility and forward movement. A therapy with selenium (Se) results in an improvement in the sperm's overall quality, and this improvement is connected with an increase in ejaculatory production. Only vitamin B12 has been found to improve the quality of sperm; it does this by boosting sperm count and motility and by decreasing sperm DNA damage. Vitamin B12 is the only vitamin that has been proved to do this. Conclusions: Dietary supplementation with antioxidants may improve sperm quality in men with low-quality semen by reducing OS-induced sperm damage and increasing hormone synthesis and spermatozoa concentration, motility, and morphology. This may be achieved in men who also have low levels of antioxidants in their semen. Antioxidants can exert their effects in a variety of ways; hence, it is important for researchers conducting future clinical trials to study the possibility of combining a number of antioxidants.

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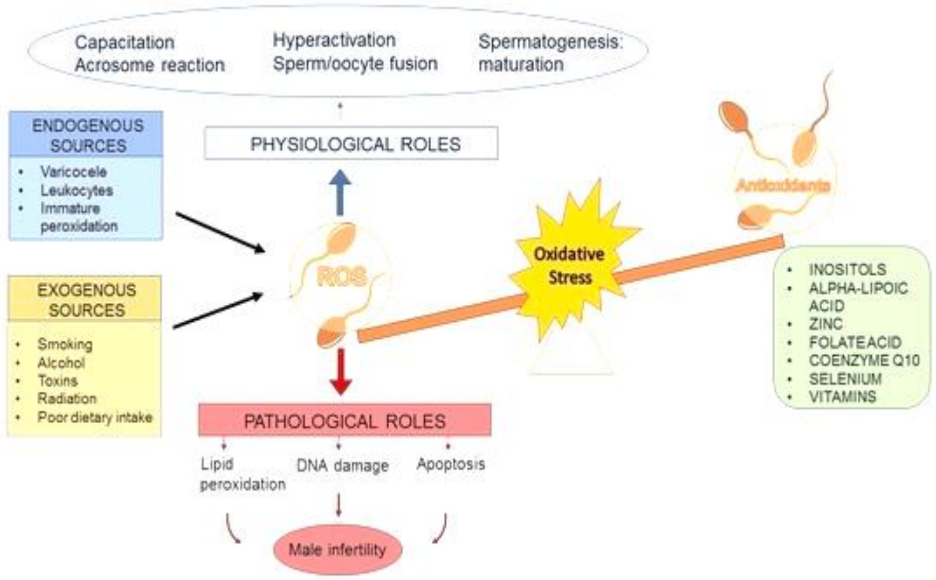
GRAPHICAL ABSTRACT



Keywords- Antioxidant, Herbs, Male infertility, Sperm DNA.

I. INTRODUCTION

Infertility is defined as the inability to conceive within a year of regular, unprotected sexual activity [1-2]. Infertility can be caused by difficulties with either the male or female reproductive system. According to statistics provided by the World Health Organization (WHO), [3] male factors are responsible for something in the range of 20-30% of all occurrences of infertility. This indicates that anything from 50 to 80 million people around the world are affected by infertility. According to the International Classification of Diseases, 11th Revision (ICD-11), the most common reasons for male infertility include changes in the ejection of sperm, a lack of sperm or a low quantity of sperm, as well as abnormalities in sperm morphology and motility (Geneva: WHO 2018) [4,5,6]. The creation of spermatozoa is referred to as the process of spermatogenesis. A reduction division results in the production of haploid spermatids during the process of meiosis, which involves the transfer of genetic material between homologous chromosomes of primary spermatocytes. In the final step of spermiogenesis, spherical spermatids undergo the process of maturation and differentiation into mature spermatozoa, which are then expelled from seminiferous tubules as mature spermatozoa that are capable of fertilisation [7,8]. The process is controlled by the Sertoli cells found in the testes, which regulate it by encouraging the transformation of germ cells into spermatozoa by direct interaction [9,10]. Ejaculation is the point at which mature spermatozoa are expelled into the environment, where they are free to find an egg and begin the process of fertilisation. Capacitation refers to the process by which sperm acquire motility, travel to an egg, attach to it, execute the acrosome reaction, and fuse with the plasma membrane of the oocyte in order to generate a zygote [11] [12,13] This process is necessary for the formation of a zygote. When trying to conceive, one of the most important things to think about is the state of the gametes. The process through which spermatozoa and an oocyte interact to form a healthy embryo [14]. Definition: the process by which spermatozoa and an oocyte interact to produce an embryo. When evaluating the quality of spermatozoa, the standard practise is to do a spermiogram [15,16]. Oxidative stress (OS) has been linked to low-quality sperm, one of the numerous factors that might contribute to male infertility. This is one of the many reasons why. It is believed that the underlying aetiology of OS is an imbalance between ROS defences and antioxidant defences [16,17,18,19]. The first indication that ROS was linked to male infertility was discovered by researchers in the 1940s [20,21,22]. Since then, there have been major advancements in our understanding of ROS and its consequences for infertility and the function of sperm [23]. These advancements include: Hydrogen peroxide, as well as the free radicals hydroxyl (HO), and superoxide (O2), are all examples of highly reactive oxygen species (ROS) (H2O2). ROS are produced in the majority of cases by the iron-catalyzed Fenton reaction, the mitochondrial electron transport chain, enzymatic reactions involving cyclooxygenases, NADPH oxidases (NOXs), xanthine oxidases, and lipoxygenases, and the

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iron-catalyzed oxidation of fatty acids. Last but not least, ROS are generated when cells are exposed to physical agents such as ultraviolet radiation or high temperatures [24,25,26,27]. Antioxidants are beneficial to eukaryotic cells because of their ability to regulate levels of reactive oxygen species (ROS). In spite of the fact that moderate quantities of reactive oxygen species (ROS) are essential for sperm capacitation and fertilisation, it has been discovered that exposure to high levels of ROS can be harmful to spermatozoa [28,29]. Antioxidants provide a line of defence against oxidative stress because they react with reactive oxygen species (ROS) and quench them [30] [31]. Enzymatic and non-enzymatic antioxidants are the two basic groups of antioxidants that can be distinguished from one another based on their mechanism of action. Antioxidant enzymes such as superoxide dismutases (SODs) and glutathione peroxidase and reductase convert harmful oxidative products to hydrogen peroxide (H2O2) and ultimately to water in a multistep process that requires cofactors such as zinc, copper, manganese, and iron. This process is known as the scavenging pathway. Antioxidants, whether they are created naturally or received through diet or supplements, operate to stop additional chain reactions involving free radicals by stopping further chain reactions from occurring.[32,33,34] OS is a key contributor to male infertility because of the deleterious effects it has on spermatogenesis, epididymal maturation, and the capacity of sperm to reproduce [35]. Sperm cells have a lot of unsaturated fatty acids in their membranes because of the significance of sperm capacitation, the acrosome reaction, and the connection between sperm and oocytes. As a result, sperm cells are especially susceptible to damage caused by high levels of reactive oxygen species (ROS). The oxidative peroxidation of unsaturated fatty acids, which is mediated by ROS, is the primary mechanism responsible for ROS-induced sperm destruction, which ultimately leads to infertility [36]. If a couple's regular, unprotected sexual activity over the course of at least a year does not result in a pregnancy, the partners may begin to assume that one or both of them suffers from infertility. The diagnosis of infertility is a worldwide health concern that affects about 187 million couples as a result of the fact that male factors are responsible for more than half of all cases of infertility [37,38,39].

There are increased levels of oxidative stress caused by reactive oxygen species (ROS) in the bodies of thirty to eighty percent of people with infertility [40,41]. The key processes by which high levels of ROS induce degradation of sperm quality include reduced motility as well as increased DNA damage, protein oxidation, and lipid peroxidation [42]. The individual's way of life [42,43] their genetics [44,45], and their exposures in the environment, such as chemicals [46,47], can all be contributors to male infertility. [48,49] Infertility can be caused by a number of different conditions, including varicoceles and hormone imbalances, both of which have been linked to oxidative stress and DNA damage [50]. Infectious diseases, particularly those that involve DNA damage, inflammation, or oxidative stress, are known to have a deleterious effect on human fertility. There is a correlation between the presence of viruses and inflammation in tissue, which in turn leads to an increase in ROS formation [51]. One example of a virus that can infect many types of tissues is the severe acute respiratory syndrome coronavirus 2, also known as SARS-CoV2. Angiotensin-converting enzyme 2 (ACE2) is highly expressed in the testis, notably in the Leydig and Sertoli cells. These cells are the ones that are responsible for the process of viruses becoming internalised by the cells [52]. According to the findings of clinical trials, the presence of SARS-CoV2 infection is associated with an increase in levels of both reactive oxygen species (ROS) and malondialdehyde (MDA). Both motility and morphology are affected [53,54], and the virus also seems to reduce the proportion of motile spermatozoa in the population.[55]

It is correct that reactive oxygen species constitute a significant factor in the development of male idiopathic infertility. It has only been in recent years that the phrase "infertile males with aberrant semen characteristics and oxidative stress" (infertile men with MOSI) has emerged. It is estimated that 37.2 million men all over the world are affected by this ailment. Idiopathic infertility can be identified by its telltale symptoms, which include sperm abnormalities and unexplained infertility (MOSI) [56].

It is recommended that antioxidants be used as the initial treatment for idiopathic infertility, and oxidative stress is increasingly becoming acknowledged as a risk factor for male infertility. It is interesting to note that different antioxidants display synergistic effects, which is the reason why multi-antioxidants are a feasible therapeutic option for male infertility [57,58] Treatments for male infertility may involve the use of a variety of substances. They accomplish this by lowering the levels of reactive oxygen species in the body [59][60].

Because of its well-established function as an antioxidant molecule, myo-inositol is an important naturally occurring chemical to consider in this context.[61] Inositols have a structure that looks like a ring and contain six carbon atoms, but each of these carbon atoms is replaced with a hydroxyl group. Myo-inositol is the stereoisomer that is found in the greatest abundance (MI). MI is an essential component of membranes in addition to having a function in the regulation of osmoregulation and the phosphorylation of proteins. Versions of MI that have been phosphorylated are used as second messengers in a variety of pathways. MI is engaged in the transduction mechanisms that regulate the cytoplasmic calcium levels in sperm cells [62]. These mechanisms are similar to those involved in capacitation and mitochondrial activity.[63]

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Recent research has investigated the effects of D-chiro-inositol (DCI) on a number of disorders, such as male infertility, in order to establish the most effective dosages and window of time for dosing. Since the aromatase enzyme is responsible for converting androgens into oestrogens, its expression was also investigated in order to establish the extent to which DCI may have influenced the findings. In particular, DCI treatment is responsible for reduced enzyme expression, which ultimately leads to increased testosterone levels [64,65,66].

The oxidation of sperm cell DNA, proteins, and lipids can be triggered by high amounts of reactive oxygen species (ROS), which can also change sperm vitality, motility, and morphology [67]. This can lead to a higher risk of sperm abnormalities. This is because sperm cells lack cytoplasmic defence mechanisms and have a high concentration of polyunsaturated fatty acids in their plasma membranes [68]. Sperm cells also have a high concentration of polyunsaturated fatty acids. The process of condensing chromatin in sperm and maintaining the integrity of DNA are both necessary steps for conception. Male sterility develops whenever there is any kind of change in the chromatin structure of sperm or whenever there is any form of DNA damage [69] The aetiology of sperm-DNA fragmentation can be broken down into two categories: pre-testicular (defective maturation and abortive apoptosis), and post-testicular (OS). It has been demonstrated beyond a reasonable doubt that alterations in DNA packing can cause chromatin decondensation in sperm, which can increase the risk of infertility. Condensation of chromatin can be influenced by a number of factors, including a deficiency in zinc and shifts in protamines, which are proteins that function in place of histones during the maturation process of spermatozoa [70]. It's fairly common for reactive oxygen species, sometimes known as ROS, to cause damage to DNA. Whether the damage is caused directly or indirectly, ROS can cause single-strand and double-strand breaks, in addition to abnormal apoptosis. These are the results of ROS-mediated damage. [71] Sperm DNA fragmentation can be caused by both intrinsic factors (such as abortive apoptosis, insufficient germ cell maturation, and overstimulation) and external factors (such as smoking, heat exposure, chemotherapeutic drugs, and environmental pollutants).

In human ejaculated sperm, apoptotic signals such as caspase activation, phosphatidyl serine externalisation, a shift in mitochondrial membrane potential, and DNA fragmentation can be found [72]. ROS have an effect on a multitude of signalling pathways, which allows them to activate both the extrinsic and the intrinsic apoptotic pathways. However, substantial evidence suggests that activation of the intrinsic route, which affects the integrity of the mitochondrial permeability transition pores, is required for ROS-induced apoptosis induction in the vast majority of cases. This is the case because activation of the intrinsic route impacts the integrity of the mitochondrial permeability transition pores. Reactive oxygen species (ROS) are responsible for the induction of apoptosis because they either cause the anti-apoptotic protein Bcl-2 to become inactive or cause an increase in the rate at which it is ubiquitinated. In addition, the activation of JNK and p38 kinase causes a change in the mitochondrial membrane potential, which is associated to the ROS-dependent induction of apoptosis [73] and refs. therein). Increased interest in ROS-mediated damage can be attributed to the growing body of information that indicates to the significance of environmental influence on spermatozoa production. Indeed, Gallo et al. [74,75,76] showed that spermatozoa are subjected to a number of environmental variables, every one of which has the potential to amplify the oxidative stress caused by ROS. Recent research has found that a number of naturally occurring antioxidants, such as inositol, alpha-lipoic acid, zinc, folate, coenzyme Q10, selenium, and vitamins, can shield sperm from the damaging effects of oxidative stress, resulting in improved sperm quality (OS). This narrative review's objective is to conduct an analysis of recent results about the functions and mechanisms of action of the antioxidants that are most commonly used in nutritional supplementation in order to improve sperm quality.[77]

II. RESOURCES AND TECHNIQUES

By doing searches in the MEDLINE database (using the PubMed user interface), we looked for research that had been published in the past 10 years (2012-22). During the course of the investigation, the words "infertility," "inositol," "alpha-lipoic acid," "zinc," "folate," "coenzyme Q10," and "selenium," as well as "vitamin," were utilised.

Infertility and the extract of a plant

Phytochemicals are secondary metabolites that are produced by plants during specific metabolic processes. These phytochemicals provide a variety of important benefits to plants, including antioxidant, anti-inflammatory, and antibacterial effects, as well as pigmentation. These phytochemicals have been separated into a number of distinct categories, including alkaloids, phytosterols, polyphenols, and terpenoids [78]. Anthocyanins, flavonols, flavones, flavanones, flavanonols, and flavonols are the six major subclasses of flavonoids that may be identified by the degree of oxidation and unsaturation [79]. Flavonols are also a subclass of flavonoids. Polyphenolic substances known as flavonoids have a scaffolding composed of benzo—pyrone (Figure 1). Flavonoids have been the subject of a significant amount of research because of the promising pharmacological activity they exhibit in the treatment of various male reproductive dysfunctions. The proposed mechanisms by which flavonoids can improve male infertility are as follows: improvement of frozen sperm

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motility; improvement of sperm fertilisation characters; reduction of any alteration that can occur in the endocrine and replacement of testicular damages; and reduction of germ cell apoptosis by improving testicular histology.[80,81,82]

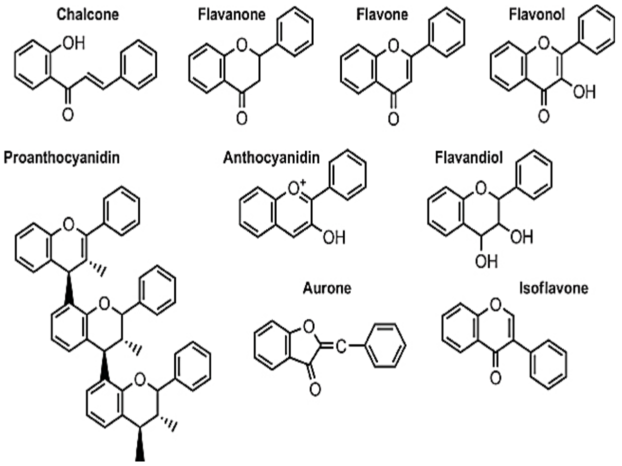

Fig: 1 Flavonoids and the major subclasses' chemical structure

Real alkaloids, proto-alkaloids, and pseudo-alkaloids are the three different varieties of alkaloids that may be separated from one another based on their chemical composition [83]. Previous studies on the effects of nicotine on male fertility revealed that smokers may have decreased sperm motility, viability, and count [84]. However, the effects of alkaloids were the contrary of what those studies had shown.

It has been shown that phytochemicals known as saponins, which contain a sugar moiety, have surfactant properties. Saponins can either be triterpinoidal or steroidal. To provide a concise summary of the effect that saponins have on male infertility, we can say that they protect and regenerate in the face of destructive agents, and that they have an effect on the mobility and viability of sperm, which ultimately leads to increased male fertility [85][86][87]. In other words, we can say that they protect and regenerate in the face of destructive agents.

III. SOME MEDICINAL PLANT MAINLY USED INFERTILITY GROWTH RATE

Allium cepa alliaceae

Onion has been shown to provide a variety of health benefits, including antibacterial, antioxidant, thrombolytic, hypolipidemic, and hypotensive effects, which has led to its widespread use in traditional medicine [88]. The bulbs or juice extracted from the bulbs are recommended by herbalists in Jordan as a treatment for prostate cancer [89]. Because the antioxidant activity of the A. cepa extract improved the oxidative status in their model [90], Serah F. Ige and colleagues (2012) were able to draw the conclusion that A. cepa extracts improved reproductive hormones (FSH and LH), as well as the sperm morphology, viability, and motility in male rats with reproductive dysfunction.[91][92][93][94]

As part of its phytochemical composition, onions have a modest number of saponins, tannins, glycosides, triterpenoids, and sterols, but a high amount of flavonoids [95]. Quercetin, the flavonoid that is found in A. cepa in the highest concentration, is a potent antioxidant that protects the functional properties of spermatozoa from being damaged by oxidation [96]. In another study, the antioxidant activity of Allium cepa extract was confirmed by treating female rats with Allium cepa juice for 21 days after mating. The male pups that resulted from this treatment had greater sperm motility and viability than those of the control group, which had not been treated. This was as a result of a reduction in the levels of testicular epididymal malondialdehyde (MDA) and protection against testicular oxidative stress.[97][98][99][100]

Artemisia judaica asteraceae

Artemisia judaica L., often known as Beithran, is a perennial plant that has a lovely aroma. In Jordan, it is used as a form of traditional medicine to treat gastrointestinal (GI) illnesses, cardiovascular (CV) troubles, diabetes, and erectile dysfunction [101]. [Note: In prior studies examining the effects of an extract of A. judaica on diabetes, it was discovered that the extract was beneficial to diabetic patients who suffered from testicular dysfunctions brought on by low insulin levels. Therefore, this plant has the ability to assist men in maintaining consistent levels of male hormones, which may be essential for the process of spermatogenesis [102]. This plant has a wide range of bioactive components, some of which are referred to as flavonoids, terpenes, alkaloids, tannins, saponins, sterols, and coumarins [103]. Flavonoids may have a role as antioxidants in the treatment of male infertility. This would protect sperm membranes and DNA against reactive oxygen species, which are known to cause sperm membranes and DNA to degrade [104]. It is possible that the antioxidant activity of the active phytochemicals in the extracts, particularly the flavonoids and terpenes [105], may explain why a 12-week treatment with A. judaica extract led to a significant increase in testosterone levels in male Wistar rats. This is important information because testosterone levels have a significant influence on the process of spermatogenesis.[106]

Apium graveolens apiaceae

The Jordanians refer to celery as "Krufs," and it's a good thing that they do because this aromatic plant is loaded with beneficial chemicals such as flavonoids, triterpenes, sulphur glycosides, sterols, and coumarins [107]. Celery is also known as "Krufs" in Jordan. A previous study conducted in Jordan on male rats for sixty days found that there was a dose-dependent decrease in

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spermatogenesis, sperm count, and sperm motility, as well as a decrease in testosterone level [108,109]. Celery can reduce fertility and the number of offspring, according to the findings of another study that was carried out in Iran [108]. This finding suggests that celery could be an effective natural medicinal plant option for the prevention of pregnancy.

Lepidium sativum brassicaceae

Lepidium sativum L., more often known as Habb Al Rashad, is a fast-growing annual plant that is traditionally used to promote the generation of sperm in men. This plant contains an abundance of antioxidant phenolic compounds and terpenoids, as well as the amino acids glutamic and aspartic, the fatty acids stearic and palmitic, as well as the fatty acids lauric and palmitic [109]. It is possible that the effect that Lepidium sativum L. has on the neurotransmitters dopamine and acetylcholine, both of which have been linked to sexual behaviour [110], is the reason that a study by Asi et al., (2021) discovered that it prevents male infertility by boosting testosterone, LH, and FSH levels. Because of its antioxidant action, rashad extract increased male fertility [111]. Specifically, it accelerated sperm production and decreased the rate at which sperm death occurred.

Nigella sativa ranunculaceae

The plant Nigella sativa L., more often known as Habat Al-Baraka, is indigenous to the Middle East, where it is also grown commercially in large quantities. The bitter flavour of the black seeds is caused by a variety of phytochemical components, including phenolic compounds, alkaloids, and essential fatty acids [112]. In Jordan, the use of Nigella sativa L. as a treatment for erectile dysfunction [113] is recommended. The pharmacological impact of this plant on male infertility requires a rise in testosterone and follicle-stimulating hormone (FSH) levels [114]. This is necessary for the plant to improve sperm quality, concentration, and motility, which are all symptoms of male infertility. According to the findings of a clinical trial that was randomised, double-blind, and controlled with a placebo [115], the quality of the sperm was improved as a result of the presence of unsaturated fatty acids in the oil. Another in vivo study demonstrated that giving male rats a high dose (400 mg/kg) of Nigella sativa extract for 60 days significantly increased reproductive indices and sperm count [116]. Mohammad et al. (2019) conducted a study that shown that black seed extract has the ability to stimulate pituitary spermatogenesis hormones, which in turn increases sperm motility and raises the size of male reproductive organs [117]. Both the process of spermatogenesis and the testicular tissue itself can be helped by the extract and oil of this plant [118].

Peganum harmala zygophyllaceae

Throughout its natural state, the flowering plant referred to as "harmal" can be found growing wild in the Eastern Mediterranean. The active metabolite alkaloids are found in the seeds and roots of the plant [119]. These alkaloids cause a reduction in body temperature and cause hallucinations. Rats that were given an ethanolic extract of harmal seeds for 56 days saw significant improvements in both the quantity and quality of their sperm [120]. This treatment resulted in increased gonad and accessory sex organ weight. Peganum harmala is commonly used as an aphrodisiac and fertility booster in Jordan. However, a study carried out in Jordan on male albino rats found that it actually decreased fertility. This was accomplished by lowering the weight of reproductive organs and the primary hormone responsible for spermatogenesis. Additionally, it decreased sperm motility and density [125].

Raphanus sativus brassicaceae

In Jordan, the leaves and seeds of Raphanus sativus L. (Fejil) are utilised for their aphrodisiac action as well as their positive influence on male fertility; these plant parts are rich in alkaloids, flavonoids, saponins, and coumarins [126]. In addition, Jordanian men have reported an increase in their fertility. It has been demonstrated that using the plant extract can significantly raise levels of male fertility hormones. This effect may be caused by the presence of saponin, which has been demonstrated to increase testosterone levels in the body [127]. A 30-day investigation on male Wistar albino rats likewise verified the anti-fertility effect of Raphanus sativus L. [128], however the results of that study were contradictory to the findings of the previous study. Because of the change in androgenic production, the researchers found that after treatment with radish extract, both the motility of rat sperm and the amount of spermatozoa were decreased.

Trigonella foenum-graecum leguminosae

Because of the high concentration of fibres, flavonoids, saponins, proteins, carbohydrates, fixed oils, amino acids, volatile oils, polysaccharides, and alkaloids in the leaves and seeds of the fenugreek plant (Hilba), it possesses a number of pharmacological properties that are associated with health [129]. On the other hand, the extract from the seeds has the opposite effect and reduces fertility. This was supported by the fact that the size of male reproductive tissue shrunk, and as a consequence, alterations occurred in the concentration and motility of sperm [130]. A further study conducted on male albino rats demonstrated that fenugreek seeds directly interfered with spermatogenesis, sperm count, and viability, which led to a reduction in fertility [131]. This study was conducted on rats. On the other hand, Kaur et al. (2020) came to the opposite conclusion, demonstrating that the antioxidants found in fenugreek can be beneficial to males who have testicular damage. [132]

Green tea

It is thought that the green tea leaves contain between 30 and 40 percent of the antioxidants known as polyphenols. Similar to other in vitro studies, our examination of green tea revealed the presence of these

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polyphenols and shown that the amounts of total polyphenols, flavanol, flavonol, and soluble solids rose with the increasing concentration of the tea. Additional in vitro research using ferric reducing antioxidant power (FRAP) showed a concentration-dependent increase in green tea's antioxidant capacity, but it had no effect on the antioxidant capacity of the serum of the treated male rats. [133]They were making the assumption that a higher concentration of the extract would result in a more potent antioxidant effect. In line with the findings of Maxwell and Thorpe, we came to the conclusion that drinking green tea in vivo had no impact on the concentration of FRAP in the serum. Consuming green tea, on the other hand, was found to considerably raise plasma FRAP levels in adults, which runs counter to our findings. [134] This disparity in bioavailability may be to blame for the observed differences in the health benefits provided by green tea. EGCG, the principal catechin found in green tea, is absorbed and metabolised in a different manner in humans, mice, and rats.[135] In addition, the bioavailability of EGCG was shown to be poor in rats when GTP injection was the only source of drinking fluid, although a higher level was seen in mice. [136]

Free-choice access to green tea extract at concentrations of 2 and 5 percent was offered to the animals; their consumption patterns, on average, were comparable to those seen in the control group (equivalent to around 40 cups of tea per day for a man weighing 80 kilogrammes). Throughout the entirety of the study, a consistent weekly weight gain was observed in the animals. [137][138][139] Additionally, the rats did not exhibit any signs of clinical toxicity or atypical behavioural patterns. In addition, there was no discernible change in the rate of weight growth that occurred in the rats who were given treatment. The consumption of green tea at a dose of 70 milligrammes per kilogramme per day by 63 or 90 day old rats in a study revealed that it had no impact on the animals' rate of weight gain. At the end of the fifth week of therapy, the group that received 5% saw a brief dip in body weight, which may have been caused by dislike to flavour and decreased food consumption. According to a study that was conducted by Kao et al., EGCG, which is the primary polyphenol found in green tea, was proven to cause a reduction in body weight in rats. Green tea contains catechins, the most notable of which is EGCG, which are responsible for weight loss. These catechins prevent the differentiation and proliferation of adipocytes during the process of lipogenesis. In addition, drinking a lot of green tea for a period of twelve weeks led to a significant rise in the amount of weight that people lost. One of the possible explanations is that increased adiponectin levels are the result of decreased ghrelin release. [140,141]

Carrot

In comparison to the understanding surrounding other types of antioxidants found in food, there is a knowledge gap concerning carotenoids. [145,146,147] Idiopathic oligoasthenoteratospermia was found in thirty guys, and after they were given lycopene for three months, the results showed a considerable rise in sperm concentration (63%), motility (43%), and morphology (46%). (29). In a case-control study, Mendiola et al. (2010) compared 30 men with moderate to severe oligospermia or teratospermia to 31 normospermic but subfertile men. They discovered that the likelihood of poor semen quality decreased with increased dietary lycopene intake. [148] This was discovered by comparing the two groups of men. A larger cross-sectional study was carried out by Eskenazi et al. (2005) on the effects of beta-carotene on sperm concentration and motility in 97 healthy guys who did not smoke. In the largest and most recent cross-sectional study of healthy university-aged men in Spain, higher intakes of both beta-carotene and lycopene were related with higher total motile sperm counts. The results of this study, which is the only other one that has been done so far to examine lutein consumption, found that there is no connection between lutein consumption and any of the measures of semen quality, including motility.[149,150]

When attempting to make sense of these data, it is important to keep in mind that practically all of the carotenoids you require on a daily basis may be found in fruits and vegetables. The consumption of lycopene was explained by five different foods (tomato soup, tomato juice, salsa, and ketchup), the consumption of beta-carotene was explained by three different foods (carrots, lettuce, and spinach), and the consumption of lutein was explained by two different foods (spinach and lettuce). [151,152,153,154] It is possible that this association between carotenoid consumption and sperm quality is muddied by other healthy practises, or it may be due to some other component in these meals that has been associated to enhanced sperm motility (30). The consumption of carotenoids may improve motility; however, this may be nothing more than a correlation; hence, well-designed randomised trials are required to validate this.

In contrast to the findings of earlier studies, we could not find any evidence of a linear association between the consumption of antioxidant vitamins and the quality of sperm. Consuming more vitamin C was found to be connected with a greater concentration of sperm among males who were healthy and did not smoke, according to the findings of Eskenazi and colleagues (2005). The case-control study conducted by Mendiola et al. (2010) demonstrated a similar link between vitamin C consumption and a higher likelihood of semen quality that exceeded WHO standard levels from the 1999 edition.[155][156]157] Supplementation with 1,000 milligrammes of vitamin C per day improved sperm morphology among smokers with verified fertility (31) and sperm motility among subfertile males with substantial sperm agglutination in two separate randomised controlled studies. A third study found that

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giving males with subfertility or asthenozoospermia a combination of 1,000 milligrammes of vitamin C and 800 milligrammes of vitamin E over a period of ninety days did not result in any changes to the concentration, motility, or morphology of their sperm. It is probable that the inconsistent findings are due to differences in study demographics (healthy versus subfertile men, smokers versus non-smokers), sample sizes, and intake quantities. In contrast, the mean vitamin C intake in the study by Mendiola et al. was only 57.9 mg among controls, while the median vitamin C intake in the study by Eskenazi et al. was 165 mg. The mean vitamin C intake in our research was only around 25% of the dose of vitamin C used in past randomised trials. Men in our study who were in the second quartile of vitamin C intake (corresponding to a median intake of 148 mg/day) had higher mean sperm concentration, count, motility, and motile count than men in the lowest or highest quartiles of vitamin C intake. This finding suggests that vitamin C may have different effects on the quality of sperm depending on the amount that is consumed. More investigation is required on the dose-response correlations that exist between antioxidants and measures of semen quality.[158]159]160]

There were no linear connections found between vitamin A or E intakes and any of the semen metrics that we investigated, which begs the question of why some antioxidants would alter semen quality while others wouldn't affect it at all. There is a lack of information regarding the relationship between food consumption and levels of these antioxidants in the seminal plasma, as well as the molecular mechanisms by which these antioxidants alter the quality of the sperm.[161][162] In addition, there is a lack of information regarding the molecular mechanisms by which these antioxidants alter the quality of the sperm. It is possible that increasing consumption of these micronutrients across the range that was found in our study does not result in a significant rise in the concentrations of these micronutrients in the semen. This is the case for several of these micronutrients. It is also unknown if one form of antioxidant or another is more frequent in one section of the genitourinary system compared to another area of the system.[163][164] If micronutrients were concentrated in the epididymis, that would explain why some of them were associated to motility while others were linked to concentration (seminiferous tubules). These are valid concerns, and while they are outside the scope of our study, they do suggest some exciting new directions to take.

In spite of the fact that ours is only the second study of its sort in young healthy males, it is one of the largest studying the link between dietary antioxidant intake and semen quality indices. Our findings are less likely to be attributed to reverse causation than those from studies of males attending for infertility evaluation because these individuals did not know their reproductive status.[165][166] Studies of males attending for infertility evaluation have a higher chance of attributing their findings to reverse causation. Using a validated food frequency questionnaire, we determined the amount of food and supplements that were consumed. Because our research was of a cross-sectional nature, it was difficult to infer causation from the findings of the study's correlations, which was the principal limitation of the investigation. [168][169]The reported associations may or may not be independent of the intakes of the other antioxidants; however, because individual antioxidant intakes were also related, it is impossible to identify with any degree of certainty whether or not they are independent of the other antioxidant intakes. Additionally, we utilised a wide variety of antioxidants and measures of sperm quality, both of which may have contributed to an increased possibility of identifying coincidental connections. In the end, we were able to collect a single sample of sperm from each participant. In spite of the fact that there is a risk of measurement error, there is evidence that shows the quality of semen measurements do not significantly vary from sample to sample in healthy guys. [170][171]

Ginger

The synthesis of androgens, specifically testosterone, as well as the creation of sperm (also known as spermatogenesis), are two of the testes' most important functions (steroidogenesis).[172][173] Even in typical circumstances, spermatogenesis and sperm production can be negatively impacted by factors such as medication, chemotherapy, pollution, polluted air, and a deficiency in nutrients and vitamins. These factors might be brought about by a lack of nutrients and vitamins. These characteristics render sperm cells more susceptible to damage via a variety of processes, which in turn can have a significant bearing on both the quality and quantity of the sperm produced. Apoptosis is capable of happening during the process of naturally occurring spermatogenesis. In order for regular spermatogenesis to take place, it is necessary to maintain control over both the division of cells and the process of programmed cell death known as apoptosis. [174][175]

It has been demonstrated beyond a reasonable doubt that exposure to environmental risk factors can result in the apoptosis of sperm, an increase in the formation of reactive oxygen species (ROS), and the death of spermatozoa. A condition in which there is an imbalance between the levels of pro-oxidants and anti-oxidants is referred to as "oxidative stress." Free radicals are also known as radical oxidising species (ROS). Radical oxidising species are composed of components such as superoxide ions (O-2), nitrogen oxides (NO), and hydroxyl radicals (HO-).[176][177]

Although reactive oxygen species (ROS) are found in the body, they are often confined to the inside of cells, where they are kept in check by antioxidant molecules such as glutathione, glutathione peroxidase, superoxide dismutase, and vitamins E and C, which scavenge for free radicals. It's possible that oxidative

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stress has a role in more than half of all cases of male infertility. This could be because it causes sperm to be destroyed.[178][179][180]

Studies using chemistry have demonstrated that ginger contains roughly 400 different types of compounds. The majority of ginger rhizomes are made up of carbohydrates (between 50 and 70 percent), lipids (between 3 and 8 percent), terpenes, and phenolic compounds. Ginger contains a number of different terpenes, including zingiberene, -bisabolene, -farnesene, -sesquiphellandrene, and -curcumene; on the other hand, p-gingerol, paradols, and shogaol are all henolic compounds. Gingerols can be discovered in above-average concentrations (23-25%), while shogaol can make up between 18-25% of the total. The unprocessed plant material of Z. officinale contains a variety of essential nutrients, including amino acids, raw fibre, ash, protein, phytosterols, vitamins (particularly nicotinic acid and vitamin A), and minerals. It also has isolated components such as [6], phenolic1,3-diketones, zingerone, and [6]-paradol, which have all been linked to a protective effect against lipid peroxidation in a variety of well-established animal models. -gingerol is another isolated component that has been linked to a protective effect against lipid peroxidation.[180][181][182]

The components of ginger that are responsible for its anti-oxidative properties have been the subject of a number of in-vitro investigations, as well as comparisons to other antioxidants with comparable capabilities. Ginger has a moiety called alpha, beta-unsaturated ketone, which is what gives the pungent component (6)-shogaol its remarkable antioxidant and anti-inflammatory properties. [183] When ginger is dried or cooked, a chemical known as zingerone is produced. Zingerone is an antioxidant similar to shogaol, and both are found in ginger. Zingerone, a chemical found in ginger, has been shown in prior studies to have scavenging activities against intracellular reactive species (RS) (reactive species). The additional gingerols that ginger contains, such as [6]-gingerol, 8-gingerol, 10-gingerol, and 12-gingerol, also have anti-oxidant properties and share those qualities with ginger. In animal studies, it was discovered that ginger significantly decreased the amount of induced lipid peroxidation while simultaneously raising the activity of antioxidant enzymes, sperm count and quality, and serum glutathione levels. These findings are based on the findings of ginger's effects on animals. [184][185]

The sperm count, motility, and viability of diabetic rats with infertility were dramatically enhanced when the rats were fed a mixture of ginger and cinnamon, according to the findings of research conducted in Greece. In another study, Abo-Ghanema and colleagues found that treating infertile rats with ginger and L-carnitine was successful in restoring their fertility. The authors revealed that the mixture improved the quality and quantity of semen as well as the weight of testicles and seminal vesicles. Additionally, the authors found that the weight of testicles and seminal vesicles increased. [186]

Rose oil

Rose oil can be extracted from rose petals by the process of steam distillation. Rose oil is characterised by its clarity, light yellow colour, and high level of effervescence. The Big Five Oil Components consist of phenethyl alcohol, citronellol, geraniol, and linalool, as well as nerol. According to the findings of an aldehyde/carboxylic acid test, which is used to show long-term antioxidant activity, Wei and Shibamo [187] reported that rose oil has an antioxidant activity that is almost equal to that of a-tocopherol, which was used as a reference. This was based on the results of the test. The potential of rose oil to increase sperm count and motility, as well as to enlarge the size of the seminiferous tubules and decrease the percentage of faulty sperm, are just some of the ways that rose oil's favourable effects on the male reproductive system are made apparent. In another study, rats given rose oil plus formaldehyde (FA) had much better testes and total testosterone levels than rats given FA alone [188]. This was compared to animals given FA alone.

Capsaicin

Capsaicin, the principal capsaicinoid found in peppers, has a wide variety of applications in medicine. Some of these applications include acting as an antioxidant, an anti-inflammatory, an anticarcinogenic, an analgesic, and a counterirritant. A number of studies on males with varicoceles have found evidence of increased oxidative stress as a result of spermatic vein dilation and elevated testicular temperature. As a result, the reason for this study was to investigate the effect that capsaicin has on the characteristics of sperm in rats that have been artificially given a varicocele. [89] For the purpose of this investigation, we began by inducing varicocele in thirty Wistar rats. After two months had passed, we employed measurements of sperm parameters, oxidative stress, DNA damage, and persistent histone to validate the varicocele model in ten of the rats. [189] The remaining 20 rats that had been infected with varicoceles were separated into two groups, each of which received either a treatment with 2.5 mg/kg of capsaicin or a control for a period of two months. After that, sperm tests were carried out, and the findings showed that capsaicin has the ability to repair mean sperm oxidative stress (38.78± 3.75 vs 58.37± 4.34; p.05), sperm concentration (60.14 ±7.66 vs 34.87 ±5.78; p.05), and sperm motility (62.43 ±3.10 vs 41.22± 5.11; p.05 As a result, capsaicin may be able to assist enhance the mean of sperm concentration and motility in situations involving varicoceles by lowering levels of oxidative stress. We were able to show that CAP therapy leads to an increase in apoptosis by utilising immuno-cytochemistry to identify activated caspase-3 and flow cytometry to measure DNA fragmentation. Both of these techniques are used in cancer research. Our findings are in line with those

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found in previous research, and they broaden the range of cell types that have been shown to respond to CAP by committing suicide. It has been found that transformed cells benefit from the pro-apoptotic activities of CAP, although to a much lesser level than their non-transformed or quiescent counterparts [190,191]. Because they do not produce metastases after being transplanted in vivo, the spermatogonial cell lines that were examined in this study show no signs of having undergone metamorphosis [192]. On the other hand, the fact that they are constantly replicating makes it likely that their metabolism is particularly active, which may account for their susceptibility to CAP.

IV. ROLE OF ANTIOXIDANT IN FERTILITY

Protective antioxidants in the sperm consist of both enzymatic and non-enzymatic components, in addition to molecules with a low molecular weight that have the ability to act as antioxidants. These components have a close working relationship with one another in order to offer the semen with the highest possible level of protection against reactive oxygen species. It would appear that the total antioxidant capacity of plasma can be lowered by the absence of any one of these factors. The principal antioxidant enzyme system found in the semen is a triad of enzymes called superoxide dismutase, catalase, and glutathione peroxidase. [193][194][195]

Metaloenzymes known as superoxide dismutases (SOD; also known as superoxide oxidoreductases) are responsible for catalysing reactions that include the superoxide anion in the dismutation process. Both within and outside of cells, they are able to be discovered. Two of the intracellular types of superoxide dismutase are copper-zinc SOD, which is primarily located in the cytoplasm and includes copper and zinc (Cu, ZnSOD, SOD-1), and manganese SOD, which is primarily located in the mitochondrial matrix and contains manganese at its active core. Both of these intracellular types of superoxide dismutase are copper-zinc SOD (MnSOD, SOD–2). EC-SOD, also known as SOD-3, is the name given to the form of SOD that is active in the extracellular environment. It is possible that it is present in a free form; nonetheless, it is connected to the surface polysaccharides in some way. Zinc and copper, instead of manganese, are the active metals in its centre, which gives it a structure that is analogous to that of the superoxide dismutase type 2 [196,197]. The SOD activity in seminal plasma is quite high, with SOD-1 activity making up 75% of the total and SOD-3 activity making up the remaining 25%. It has been determined [198] that the prostate is most likely the source of these two isoenzymes.

Non–enzymatic antioxidants

Carotenoids are a type of chemical compounds that are fat-soluble and can be found in high concentrations in the vividly coloured vegetable pigments yellow, red, orange, and pink. These are the retinoids from which vitamin A is derived. They are the building blocks from which retinol, the active form of vitamin A, is derived in the digestive tract, making them the precursor to retinol. Carotenoids are natural antioxidants that control epithelial cell proliferation, preserve the integrity of cell membranes, and have a function in managing spermatogenesis [199]. Carotenoids can be found in a variety of fruits and vegetables. A lower rate of sperm motility has been seen in several regions, which has been connected to dietary deficits.

Because it is fat-soluble, the organic chemical component known as vitamin E (-tocopherol) can be found almost exclusively in the membranes of cells. This molecule's capacity to scavenge free hydroxyl and superoxide radicals, as well as its ability to inhibit ROS-induced lipid peroxidation, are the primary contributors to the antioxidant activity of the compound. As a result, vitamin E is largely responsible for preventing damage to the components of the sperm cell membrane, and it also plays a supporting role in the reduction of ROS generation. In experiments conducted in vitro, it was found that vitamin E increased both the motility of sperm and the penetration of hamster eggs, two factors that are essential for fertilisation [200]. In in vivo studies of male infertility, supplementation with vitamin E was shown to be beneficial in cases of oxidative stress-induced low sperm count and motility (oligoasthenozoospermia) [201]. This was the case in patients who had a low sperm count and low motility. Its oral administration significantly improved sperm motility [202], and this was achieved by decreasing the production of malonic dialdehyde (MDA), which is an end product of lipid peroxidation and, as such, is an indirect indication of the intensity of the process in the cell. The level of malondialdehyde (MDA) in the sperm of men with asthenozoospermia is twice as high as the level in the sperm of normozoospermic men, and a reduction in this level has been shown to correspond positively with an increase in the success rate of in vitro fertilisation (IVF). Researchers observed a higher improvement in sperm motility [203] when vitamin E and selenium were given jointly rather than individually. In addition, it was found that selenium, on its own, protects sperm DNA from the damaging effects of oxidative stress. It has been shown that a sufficient amount of selenium in the diet is necessary for normal spermatogenesis, sperm motility, and sperm function [204]. A lack of selenium can lead to a decreased testicular volume, problems in spermatogenesis and the maturation of spermatozoa in the epididymis, and atrophy of the seminiferous epithelium [205]. The number of sperm cells in the semen that have faulty morphology (particularly in the head and midpiece) and low motility is increased [206]. In addition to selenium, zinc and copper are other critical trace elements for healthy testicles and the production of sperm. Selenium

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is the most important of these three. Zinc is a component of more than 200 enzymes that are necessary for the production of proteins and nucleic acids as well as the division of cells. It has been discovered that the quantities of zinc, copper, and selenium in seminal plasma have a strong correlation with the quality of sperm in men [207,208].

Vitamin C, also known as ascorbic acid, is a nutrient that is water-soluble and has a concentration that is approximately ten times higher in seminal plasma than in blood serum. Because of its potent antioxidant effects, this vitamin is particularly useful for protecting sperm DNA from damage caused by ROS [209]. Vitamin C levels are low, and reactive oxygen species (ROS) levels are high in the seminal plasma of males who have asthenozoospermia [210,211]. On the other hand, the level of vitamin C and sperm motility are related to one another in a manner that is depending on the dose. It would appear that taking a supplement that contains both vitamin C (a vitamin that is hydrophilic) and vitamin E (a vitamin that is lipophilic) can have a synergistic effect in terms of reducing the effects of oxidative stress on sperm [212].

Glutathione is the thiol (a component containing sulphur) found within cells that is present in the highest concentration. Oxidative stress results in the removal of thiol groups (-SH) from proteins, however this chemical has the ability to repair them. In addition to this, glutathione prevents oxidative damage to cellular membranes and reduces the amount of free oxygen that is produced in the body. Low amounts of glutathione make the sperm's midsection less stable, which in turn disrupts the motility of the sperm [213]. Supplemental glutathione has been shown to result in a considerable improvement in sperm parameters in infertile men who have unilateral varicoceles or inflammation of the urogenital system [214]. N-acetyl-cysteine is a precursor to glutathione. It has been shown to improve the motility of sperm and protect sperm DNA from being damaged by oxidative stress [215]. Pantothenic acid not only raises glutathione levels but also shields cells from the damaging effects of oxidative stress [216].

Antioxidant therapy for infertile men

The potential therapeutic benefits of treatment with antioxidants on improving sperm parameters in men and their partners' chances of conception or pregnancy have been established by a multitude of clinical investigations over the past two decades. These investigations took place over a span of twenty years. On the other hand, the majority of them do not agree with one another, which makes it difficult to compare and contrast their findings and come at a conclusive finding on the most effective nutritional supplements. The majority of studies have relatively small sample sizes (with fewer than one hundred male participants), and they do not concentrate on any one particular group. Not all studies that looked at the same population utilised the same inclusion criteria, and not all studies analysed the same outcomes or used the same exclusion criteria. [217] The use of randomization or placebo control groups is uncommon in scientific research. Antioxidant therapy can look very different depending on the type of antioxidant, the dosage, and the time of treatment. The length of the therapy ranged from four weeks to forty-eight weeks across a variety of studies examining everything from a single antioxidant to numerous combinations of a dozen or more different antioxidants. [218] The antioxidants vitamin C, vitamin E, selenium, zinc, glutathione, L-carnitine, and N-acetylcysteine have received the greatest attention from researchers. [219] However, only recently have studies been published that attempt to summarise the findings of carefully selected clinical trials in order to establish the most recent medical data regarding the effect that oral antioxidants have on sperm quality and pregnancy rate in infertile men. [220] These studies were published in an effort to establish the most current medical data. Ross et al. [221] examined the data from 17 different trials that had a total of 1,665 male participants. The participants in all of these research were males who were unable to conceive, the studies used a randomised design, and all of the studies compared oral antioxidants to a placebo or to no treatment at all. Indicators of success included the rate of successful pregnancies and/or features of sperm quality (such as concentration, motility, and morphology). Despite the methodological and clinical heterogeneity concerning the studied population as well as the type, dosage, and duration of antioxidant therapy, 14 of the 17 trials (82%) showed an improvement in sperm quality, most notably motility (63%) but also sperm concentration (33%) and/or morphology (17%). This was the case despite the fact that there was a wide range of antioxidant therapies used in the trials. In six out of ten trials, there was an increase in the number of pregnancies that occurred. Gharagoozloo and Aitken [222] selected twenty trials to examine the effect of oral antioxidants on a measure of oxidative stress or DNA damage in sperm. This was done so that they could draw conclusions from the data. Again, the trials were small and diverse, but the analysis showed that 95% of them reported a substantial decrease in oxidative stress or DNA damage following treatments with antioxidants. This is despite the fact that the trials were both small and different. In addition, ten out of sixteen investigations discovered an enhancement in the motility of the sperm, but it is essential to keep in mind that this enhancement was only observed in the clinical tests in which asthenozoospermic men served as the primary focus (seven groups). In 15% of the cases, an increase in sperm count was seen, but this was by far the exception rather than the rule. Antioxidants that have been investigated for their effects on sperm include vitamin C, vitamin E, selenium, zinc, folic acid, N-acetyl-cysteine, L-carnitine, L-acetyl carnitine, and N-acetyl-cysteine. Folic acid is also an antioxidant. Zinni and Al-Hathal [223] analysed the findings of 24 randomised controlled

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trials that investigated the impact of various antioxidants on the quality of sperm and compared the findings. [224] 18 pieces of research demonstrated some sort of benefit, whereas 6 found none. When the effects of antioxidants were evaluated across eight trials that assessed the treatments' influence on sperm DNA damage, it was found that antioxidants increased the integrity of sperm DNA and helped increase the success rate of conception. However, the exact mechanism of action of these antioxidants on sperm DNA quality is still unknown. The authors reported that none of them estimated seminal oxidative stress, seminal vitamin levels, or used oxidative DNA damage (for example, by estimation of 8-hydroxy-2'-deoxyguanosine) as a selection criterion for monitoring the response to the therapy. This is one reason why the exact mechanism of action of these antioxidants on sperm DNA quality is still unknown. The authors drew the conclusion that in vitro antioxidant supplements have a beneficial effect in protecting spermatozoa from exogenous oxidants and cryopreservation and thawing. In addition, the articles that evaluated the role of in vitro antioxidants in protecting spermatozoa from loss of motility and DNA damage due to 1) exogenous ROS, 2) semen processing, or 3) cryopreservation and thawing were also summarised. A Cochrane review titled "Evaluating the Efficacy of Oral Supplementation with Antioxidants for Male Partners of Couples Undergoing Assisted Reproduction Procedures" [225] was published by Showell et al. and looked at the effectiveness of antioxidant oral supplementation for male partners of couples who were undergoing assisted reproduction A total of 2,876 people participated in the trials, which were spread throughout 34 different research. In this study, the outcomes that were evaluated included live birth, pregnancy, miscarriage, stillbirth, sperm DNA damage, sperm motility, sperm concentration, and side effects. The scientists came to the conclusion that the usage of oral antioxidants was strongly associated with an increase in both the live birth rate and the pregnancy rate among subfertile couples who were undergoing assisted reproduction methods cycles.

V. ANTIOXIDANTS AND ASSISTED REPRODUCTIVE TECHNOLOGIES

The methods that are used to prepare the sperm for use in assisted reproductive technology (ART) procedures have the potential to influence the results of those procedures. After being washed, centrifuged, and then cultured under a variety of different conditions for development, sperm may produce more reactive oxygen species (ROS). This is due to the fact that antioxidant-rich seminal plasma is lost during the process of separating the sperm from the seminal fluid. A common side effect of utilising these methods is a decrease in the motility of the sperm. Antioxidants such as vitamin E, glutathione, N-acetyl-cysteine, and catalase have been shown to be effective in reducing reactive oxygen species (ROS) and preventing a loss in sperm motility [226,227,228]. Other antioxidants include catalase and N-acetyl-cysteine. Because of the high levels of oxidative stress that are present during the process of making sperm, the testicular sperm of infertile men could require additional antioxidant protection.

A further essential concern is ensuring that neither the motility of the sperm nor the DNA is damaged in the process of cryopreservation and subsequent thawing. It has been demonstrated that the essential antioxidant pentoxifylline can improve both the motility and function of sperm throughout the thawing process [229,230]. Green tea is the only antioxidant that has been shown to significantly increase sperm motility, whereas the other two antioxidants investigated, vitamins E and C, did not [231,232]. However, research [233-235] shows that vitamin C, catalase, and genistein can reduce DNA damage in sperm that is caused by oxidative stress.

The protection of sperm chromatin from damage is achieved through the incorporation of N-tert-butyl hydroxylamine (NTBH) and SOD/catalase mimetics into the culture conditions. Because research has shown that the production of reactive oxygen species (ROS) increases with increasing incubation time, it is recommended that the incubation period between sperm and oocytes be as short as is practically possible [236]. The makeup of the medium that is used for in vitro fertilisation can have a significant impact on the state of the oocytes and embryos that are to be implanted before they are successfully fertilised (IVF). It was only fairly recently discovered that the level of reactive oxygen species (ROS) present in sperm has a strong bearing on whether or not in vitro fertilisation is successful. This suggests that the amount of reactive oxygen species present in the sperm is an essential component in deciding whether or not this approach will be successful. This indicates that the addition of antioxidants to the medium could aid in the growth of the embryos, which would ultimately result in more births [237].

Inositols

The most common form of inositol that can be found in nature is called myoinositol (myo-Ins). Since serum myo-Ins cannot pass through testicular tight junctions, it is necessary for it to be transported into cells via a sodium/myo-Ins cotransport protein, the synthesis of which is regulated by osmotic changes [238]. This indicates that myo-Ins are present in the fluid of the seminiferous tubules at a concentration that is greater than that which is found in the plasma of the seminal fluid. Through the regulation of the amounts of calcium within the cell, myo-ins control the oxidative metabolism of the mitochondria and the production of ATP in spermatozoa. Mitochondrial activity in sperm is improved by Myo-Ins, which has a positive impact on a wide variety of sperm processes [239], including capacitation, acrosome response, and motility regulation.

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This results in an increase in the motility of sperm in patients who already have aberrant sperm parameters [240]. In this regard, Governini et al. [241] demonstrated that sperm motility is noticeably enhanced following treatment with myo-Ins. After being ejaculated, spermatozoa go through a sequence of processes, including capacitation, the acrosome response [242], and sperm-oocyte interactions [243], in which myo-Ins plays a part. In addition, research conducted by Calogero and colleagues has shown that taking myo-Ins is a risk-free supplement that has the ability to significantly restore normal levels of serum gonadotropins and inhibin B (a serum marker that evaluates the presence and function of testicular tissue [244], as well as increase the percentage of acrosome-reacted spermatozoa, the concentration of sperm, the total number of sperm, and progressive motility [245].

Myo-Ins prevents abnormal sperm shape and boosts ATP synthesis in the mitochondria, both of which lead to improved progressive and total motility in test tubes [246,247].

Myo-Ins plays a role in mitochondrial reactions that regulate OS levels in sperm cells, helps restore the balance of certain hormones in infertile men, and promotes sperm production and sperm-oocyte interactions that lead to fertilisation. All in all, myo-Ins is important for fertility because it helps regulate OS levels in sperm cells, helps restore hormone balance in infertile men, and promotes sperm production. [248]

Alpha-Lipoic Acid

Alpha-lipoic acid, also known as ALA, is a cofactor for the mitochondrial enzymes pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase [249]. These enzymes are required for the production of ATP, which is necessary for sperm viability. Dihydrolipoic acid (DHLA), which is an intracellularly reduced version of alpha-lipoic acid, possesses a higher capacity for antioxidation [250]. Because ALA and DHLA are able to bind reactive oxygen species (ROS) and transition metals, they are able to prevent oxidative damage to membrane lipids and proteins [251].

In a clinical trial that was randomised, triple-blind, and controlled by a placebo, Haghighian et al. compared the effects of taking ALA supplements to those of taking a sugar pill. Following a course of treatment lasting around three months, the sperm concentration, sperm count, and overall motility of the treated group were dramatically enhanced [252].

Taherian and colleagues conducted a study on infertile males in which they assessed the intracellular OS as well as the degree to which sperm DNA was fragmented. The in vitro production of ALA resulted in a significant reduction in both values. It is quite likely that this was achieved by reducing the levels of ROS [253].

In order to achieve this goal, Di Tucci et al. undertook a methodical investigation of the effects that ALA has on the quality of sperm and eggs in couples. According to the findings of their research, ALA possesses the capacity to perform the role of an antioxidant, thereby reducing the damage caused by ROS and contributing to improved sperm parameters such as motility, morphology, and count [254].

Studies on the benefits of adding ALA to the diet of men undergoing varicocelectomy for subfertility caused by varicocele have shown positive results (varicocele has been one of the conditions potentially involved in the genesis of sperm OS [255]. Over the period of eighty days after surgery, Abbasi et al. carried out a randomised, double-blind, placebo-controlled research to evaluate the efficacy of ALA in comparison to that of a placebo medicine. Following surgical correction of varicocele, treatment with ALA was found to have additional benefits, one of which was an improvement in sperm quality [256].

ALA was also studied for its potential use as a cryoprotection agent during the freezing and thawing process that is a part of the ART (ART). Sperm are subjected to a multitude of challenges throughout the cryopreservation process, which has the potential to induce extra oxidative stress (OS) as well as negative repercussions due to cryodamage. When used at the optimal dose, Asa et al. demonstrated that ALA offers protection against the production of reactive oxygen species (ROS) as well as cryodamage. This is evidenced by a decrease in DNA damage and the consequent occurrence of apoptosis [257], as well as an improvement in the motility and viability of sperm.

Zinc

Zinc is by far the most prevalent element in human sperm, in contrast to its significantly lower abundance in blood. The presence of zinc in the seminal plasma is an indication of the secretory activity of the prostate [258]. Zinc is produced in the prostate. Zinc is involved in a variety of essential physiologic processes, including OS-cell contacts, the repair of DNA, the advancement of the cell cycle, and the process of programmed cell death (apoptosis) [259].

The creation of healthy sperm and the maturation of the testicles in the correct manner are both dependent on having enough quantities of zinc. In addition to the antioxidant defence it offers, it is also responsible for the production, storage, secretion, and activity of a large number of enzymes, all of which play critical roles in meiosis at various phases of spermatogenesis and gametogenesis [260]. It does this by modulating the fluidity of lipids, which in turn affects the integrity of sperm chromatin and the integrity of cellular membranes in general [261]. Normozoospermic men have the highest quantities of zinc in their seminal plasma, followed by asthenoteratozoospermic men, and azoospermic men have the lowest levels [262].According to the findings of the study that was conducted by Colagar and colleagues, an inadequate consumption of zinc may be a factor in the production of low-quality sperm as well as idiopathic male infertility. Because of this, it is strongly recommended [263] that

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zinc levels be tested on a consistent basis for the entirety of the investigation into infertility.

In a randomised clinical trial that was carried out by Alsalman et al., the researchers compared the impact that zinc supplementation had on the concentration of seminal plasma in fertile and infertile males. Supplementation with zinc increased the quality of sperm in males who were infertile. This effect was characterised by an increase in the activity of zinc-containing enzymes, which led to an improvement in the motility of sperm [264]. It was also demonstrated that this impact could trigger spermatogenesis and stimulate the development of sex organs.

However, a different study that looked at the role of zinc in male fertility came to the conclusion that dietary supplementation with zinc does not increase the rate of pregnancy in humans [265]. This study found that zinc increases sperm motility and capacity in vitro, but it does not do so in humans.

When everything is taken into account, it is abundantly evident that additional research is required in both fertile and infertile men in order to pinpoint the particular advantageous effects of zinc and the optimum dosages for treating male infertility.

Zinc and Folic Acid

The production of nucleic acids and the breakdown of amino acids are both considerably helped by folic acid. Folic acid can be found in leafy green vegetables. It also has the ability to scavenge reactive oxygen species (ROS), which lends credence to the notion that it could be utilised as an antioxidant in the treatment of male infertility.

Folic acid has a specific effect when paired with zinc; nevertheless, there is currently insufficient data to advocate treatment with folic acid alone for subfertile men. [266] Folic acid has been shown to prevent birth defects in animals when taken with zinc. The ramifications of this link have been the subject of investigation by a number of researchers. The administration of zinc and folic acid as a dietary supplement resulted in an increase in the amount of inhibin B found in the bloodstream [267]. Because it indicates that the Sertoli cells are in good condition, the presence of inhibitin B is a good indicator of healthy human spermatogenesis [268].

Coenzyme Q10

Coenzyme Q10, often known as CoQ10, is a potent antioxidant that is also an essential component in the process of producing energy [269]. It is a component of the mitochondrial respiratory chain that controls the formation of reactive oxygen species (ROS), thereby protecting membranes from damage caused by lipid peroxidation [270]. Mitochondrial oxidative phosphorylation is essential for the production of large levels of viable energy within sperm cells, which is required for normal motility. Coenzyme Q10, also known as CoQ10, is an antioxidant that assists in the elimination of potentially dangerous free radicals that are produced in the mitochondria as a result of the electron transport chain [271]. In spite of this, low levels of CoQ10 have been seen in males who are unable to father children [272].

A decrease in sperm characteristics such as motility has been linked to lower levels of coenzyme Q10 (CoQ10) in the plasma that is found in the seminal fluid. CoQ10 has been proven to improve sperm count as well as sperm motility in men who are unable to father children [273,274].

A double-blind, randomised clinical experiment was carried out by Nadjarzadeh et al. in order to ascertain the role that CoQ10 supplementation has in boosting seminal parameters in oligoasthenoteratozoospermic (OAT) men as well as the potential benefits of doing so. They found that the majority of men with OAT had elevated amounts of OS in their sperm, which has a deleterious effect on the characteristics of sperm and eventually leads to dysfunctional sperm. It has been demonstrated that levels of coenzyme Q10 (CoQ10) have a direct correlation to sperm motility and morphology, and seminal plasma testing has recently corroborated this hypothesis. According to the findings of their research [275], the administration of CoQ10 for a period of at least three months lowered OS in seminal plasma and boosted the antioxidant enzyme activity.

Males who took CoQ10 supplements for a period of three months experienced significant increases in the concentration of their sperm as well as their total and progressive motility. [276] found that raising the total antioxidant capacity led to an increase in the seminal concentration of CoQ10, which in turn led to a connection being made between the seminal concentration of CoQ10 and important semen parameters such as sperm concentration, motility, and morphology.

The optimal amount of coenzyme Q10 to consume each day has not been established by anyone as of yet. CoQ10 is one of the most promising molecules, despite the difficulty of treating idiopathic male infertility, which is a challenging condition to treat [278].

Selenium

Selenoproteins are integrated proteins that contain selenium (Se), and they are essential for a wide variety of metabolic functions, including antioxidant defence, redox state modulation, and the prevention of cancer [279].

During normal spermatogenesis, mitochondrial activity, and capacitation, Se serves as a cofactor for antioxidative enzymes. These enzymes are responsible for neutralising and preventing the production of reactive oxygen species (ROS). [280] Se also plays a role in capacitation. Glutathione peroxidase is one of the multiple selenoproteins that take part in redox reactions. Selenoproteins are proteins that are required for male reproduction. It is incorporated into the mitochondrial

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membrane of spermatozoa to operate as a defence mechanism against the formation of ROS that takes place during motility.

VI. CONCLUSION

In conclusion, the purpose of this review was to attempt to provide a synopsis of the existing body of knowledge addressing the effects of natural biomolecules on the spermatogenesis, structural integrity, and functional activity of male gametes. In a general sense, natural chemicals have positive impacts on the fertility of men. This is because they have antioxidant, antiapoptotic, and DNA-protecting characteristics. Furthermore, they have the ability to promote mitochondrial metabolism and, consequently, sperm motility and the effectiveness of fertilisation. Because the actual processes that underlie this behaviour have only just recently started to be examined more thoroughly, a critical approach is strongly encouraged before arriving at definitive conclusions regarding the potential benefits or drawbacks of the effects of phytochemicals on the male reproductive system. Because a compound that demonstrates a particular biological function might not be the same native molecule that is found in natural resources, there is a need for additional research to evaluate the activity of neighbouring metabolites. Currently, the native biomolecules that are receiving the most attention in the scientific community are the focus of the majority of this attention. However, when evaluating their behaviour in vitro, it is essential to keep in mind that, depending on the conditions, the vast majority of compounds may work either in synergy or in antagonism in vivo. This is something that must be kept in mind. Because some scientific research may use doses that are higher than normal physiologic levels, it is essential to determine the normal physiologic range for biomolecules such as polyphenols, flavonoids, and carotenoids in reproductive fluids and tissues. This is because some scientific research may use doses that are higher than normal. This could be useful in determining whether or not the effects obtained from a certain dose in an experimental investigation are physiologically relevant. As a result, future research aimed at elucidating whether natural biomolecules have a favourable or detrimental impact on the production and function of sperm should take all of these considerations into account.

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