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A MINI REVIEW ADDRESSING THE LINK BETWEEN INFLAMMATION AND MALE INFERTILITY AND ITS CORRECTION BY EXOGENOUS ANTIOXIDANT

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Abstract

Inflammation, the protective strategy of our body is compared to the sprinkler system preventing a fire spread in a building. Although the work is executed with positive intentions of limiting the damage but at times can be significantly harmful. The decreased semen quality due to an inflammatory process might be a result of the impairment of an accessory gland's function; sperm transport obstruction and spermatogenetic dysregulation. In male gonads, proinflammatory cytokines are produced physiologically in male gonads and is required in the proper functioning of the reproductive organ. Reactive Oxygen Species (ROS) disarrange probity of sperm DNA and assist to lipid peroxidation. Natural antioxidants which have free radical scavenging activity are potential remedies to treat hormonal imbalance and oxidative stress. Antioxidant can scavenge ROS, disable them and restore damage.

Keywords: Inflammation, interleukin, proinflammatory, antioxidant, spermatogenic, peroxidation.

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1. Introduction

Inflammation is a responsive outcome of the immunological system in our body required to recover and protect oneself against any foreign or non-foreign infection occurring in the organ systems of the body. These responses are an auxiliary mechanism required to maintain tissue homeostasis[1] (Ahmed *et al*, 2011). Inflammation too like any other activities of the body is not entirely the hero but at times acts as an evil. Inflammatory responses are known to hamper the body's well-being at a deeper level when occurs in boundless. Infertility and the mental trauma that follows is an elephant in the room, but it is high time that it requires be discussing and addressing with proper scientific know-how. There have been various reports suggesting its link to infertility in male. Inflammation causes an upliftment of ROS levels that could not be stabilized by the internal antioxidant system[2] (Mitchell and Cotran,2003). Male infertility due to oxidative stress can be ameliorated or rectified till an extent by the use of exogenous antioxidants. Plants are a good source of flavonoids and polyphenols which are potent antioxidants. Many plants till date have been reported to have such beneficial effects. Thus, inflammation leading to infertility can be treated by the mindful use of natural resources.

2. Inflammation

Inflammation is a protective strategy of our body. It is our body's way of fighting back and cleansing the harmful foreign substances. It is a cascade of molecular reactions and cellular activities that is characterized by specific reactions like venule and arteriole dilation, increased permeability of blood vessels and excessive percolation of leukocytes into tissues. It occurs due to the entry of various foreign antigens or pathogens. Sometimes this complex pathological response is occurring due to a cellular or tissue level injury [3](Henson *et al.*, 1984). The complete series of inflammatory activities i.e., the cascade of reactions is preprogrammed in the genes. Various cellular processes like phagocytosis, chemotaxis, mitosis, cell differentiation etc is included in the series of inflammation. Cellular immunity and antibody are a result of these inflammatory processes. The main purpose of this response is to eliminate the foreign particles and antigens from the host body [4](Markiewski and Lambris, 2007). But such a cascade that do not reach the final destination like wound healing or fighting away pathogens in general leads to organ disorder and eventually death.

Fig 1

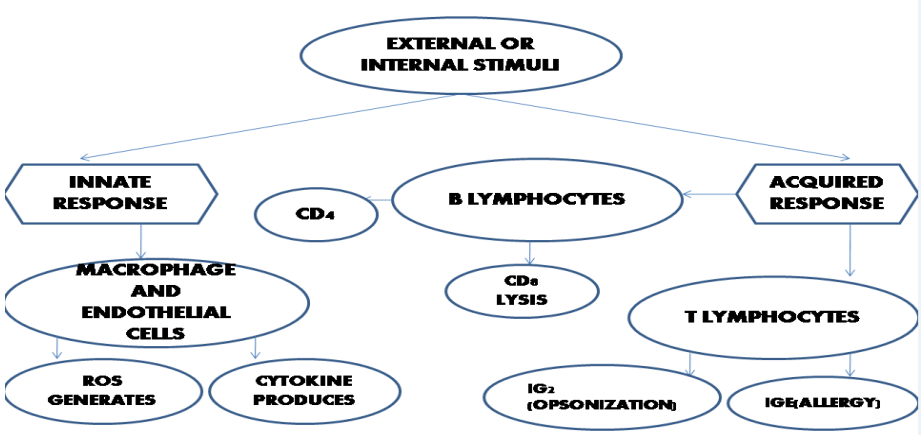

FIG1: ***Mechanism of Inflammation***

2.1. Classification of Inflammation

Inflammation has been divided into two types- acute and chronic based on the time period of its occurrence and the window period of its occurrence. Acute inflammation occurs for a shorter period of time, usually for a few minutes to a few days. The main characteristic of acute inflammation is the plasma protein or fluid leakage from the leukocytes into the extra vascular area. The inflammation and its symptoms i.e., swelling, redness, pain and loss of function are caused by the chemical factors produced from the cells or plasma under stress. The acute immune response is a collection of the three steps- increased blood flow to the specific area, dilation of the vessels and an increased vascular permeability with plasma leaks from the microcirculation and flow of phagocytic leukocytes to the site and its surroundings[5](Arulselvan *et al.,*2016). Chronic inflammation occurs in the absence of real stimuli. It happens when the stimuli creating the acute responses are not resolved or when the innate immunity of the host defense system is a complete failure. Chronic inflammation also occurs due to the long-term exposure towards certain harmful physical or chemical agents, unable to be broken down into less harmful substance by the body. Certain genetic susceptibility too causes chronic inflammatory disorders[6] (Pyles *et al.,* 2008)

2.2. Mechanism of Inflammation

Inflammation is an inbuilt action system of our body that acts through certain steps. This response helps the body to remove any harmful stimuli and heal the body as a whole or a part of it. According to Medzhitov, 2008[7]acute inflammation is a part of the first line of defense and is marked by the basic symptoms like pain, redness and swelling. But recent literatures have suggested that there is a specific molecular pathway which is followed strategically in inflammation[1] (Ahmed *et al.,*2011). As the body is exposed to any internal or external stimuli like the microbial attack, other foreign invading agent or any irritant, an inflammatory response is initiated within a few minutes. Cells of the innate immune system like the macrophages, dendritic cells, mast cells, neutrophils and lymphocytes and certain non-immune cells like the endothelial cells, fibroblasts and the epithelial cells all evoke an inflammatory response [8](Akira *et al.,* 2006). Firstly, the physical and the chemical stimuli are recognized through some Pathogen Specific Receptors (PSRs) or Pattern Recognition Receptors (PRRs) present across the membranes. These germline-encoded receptors are expressed by the cells of both the innate and adaptive immune systems. These receptors can sense the stimuli's mostly the pathogens through the Pathogen-Associated Molecular Patterns (PAMPS) conserved in the membrane of the microorganism. Apart from the PAMPs certain endogenous molecules derived from the internal injuries of the host cell itself i.e., Danger-Associated Molecular Patterns (DAMPs) are also capable of being identified specifically by the transmembrane receptors present in the host cells. Such receptors identified so far are Toll-like receptors, C-type lectin receptors, Retinoic Acid-Inducible Gene-I-like Receptors (RIG-1-like receptors) and Nucleotide-binding Oligomerization Domain-like receptors (NOD-like receptors). The receptor-stimuli interactions evoke a signal that finally gets transmitted to the nucleus where the activation of a selective set of genes takes place via both transcriptional and posttranscriptional mechanisms [8,9](Akira *et al.,* 2006; Medzhitov, 2007). These interactions produce genetically regulated inflammatory responses. These responses are certain chemicals or some cells such as the cytokines (Tumor Necrosis Factor-TNF and Interleukins). Tumor Necrosis Factor (TNF) and Interleukin-6 (IL-6) are synthesized by a

single step but the synthesis of IL-1 β requires two steps. Firstly, interleukin is expressed as zymogen also termed as pro-interleukin-1 β (pro-IL-1 β). In the next step the pro-IL-1 β matures. The maturation occurs by the cleavage of the respective zymogen through [1]a caspase mediated process. The caspase-1 is in turn activated by an inflammasomes (assemblies of scaffold proteins). For viral infections there is an involvement of type-1 interferons that is induced by phosphorylation and a nuclear translocation of a gene called factor 3 or Interferon-Stimulated Response Element-3 (ISGF3). ISGF3 is formed by the composition of various signal transducers like Signal Transducer and Activator of Transcription1 (STAT1), Signal Transducer And Activator Of Transcription2 (STAT2) and Interferon Regulatory Factor 3 (IRF3)[10](Honda *et al.*, 2006). ISGF3 again helps in the activation of the expression of some antiviral genes like the protein kinase R or 2 ′,5 ′-oligoadenylate synthase. Thus, viral infected cell proliferation is checked by PKR and the OAS reduces the replication of virus infected cells by the cleavage of the nucleotide. The signal transduced from the Pattern Recognition Receptors finally converges to the final step of activation of certain transcription factors which produces proinflammatory cytokines and certain chemokines. Certain earlier studies on the identification of transcription factors revealed NKκB, the first transcription factor with the presence of the specific DNA binding activity induced by a proper stimulus[11](Sen and Baltimore, 1986). The NKκB family consists of five proteins - p50, p52, RelB, RelA and c-Rel [12](Ghosh *et al.*, 1998). There are various other[2] transcription factors like the AP-1 i.e., Activator Protein-1, cyclic Adenosine Monophosphate (cAMP), response binding element i.e., Cyclic-AMP Response Element Binding (CREB) protein factor, E2 Promoter Binding Factor (E2F), Early Region 1A (E1A) a protein from adenovirus-infected cells along with the NKκB that plays a crucial role in the selective initiation of an inflammatory gene[13,14](Treisman, 1986; Dalton and Treisman, 1992).

2.3. Linking inflammation to male infertility

Male fertility occurs due to the production of sperm cells through step-wise spermatogenetic activities. This process involves an integrated activity of various factors. The presence of certain proinflammatory cytokines, Tumor Necrosis Factor-α (TNF–α), Interleukin-1α (IL–1 α) and Interleukin-1 β (IL–1 β) cytokines required being in the reproductive canal of malef or certain physiological activities. However, increased cytokine levels can hamper the spermatogenesis. Spermatogenesis is a complex process through which a set of interdependent germ cells transforms into spermatozoa by mitotic and meiotic cell division. Spermatogenesis starts from the onset of puberty until senescence. It takes place in the seminiferous tubules[15](Ning *et al.*, 2011). The steps in the spermatogenetic process are extremely organized consisting of multiplication and differentiation of the germ cells. Thus, this extremely organized process can be disturbed at any level. Such disturbances can be caused due to environmental influences and due to various diseases, that may affect the spermatogenesis directly or indirectly. Apart from the environmental

[1] PSR-Pattern Specific Receptor,PRR- Patern Recognition Receptor, PAMP- Pathogen Associated Molecular Pattern, DAMP-Danger Associated Molecular Pattern, RIG-1- Retinoic Acid-Inducible Gene-I, NOD- Nucleotide-binding Oligomerization Domain, TNF- Tumor Necrosis Factor, IL-Interleukin, ISGF3- Interferon-Stimulated Response Element-3, STAT- Signal Transducer and Activator of Transcription, IRF- Interferon Regulatory Factor

[2] AP-1- Activator Protein-1, cAMP- Cyclic Adenosine Monophosphate, CREB- Cyclic-AMP Response Element Binding, E1A- Early Region A

factors, hormonal disturbances too cause male infertility [16](Akinloye *et al.,* 2006). Various psychological complications also contribute to male infertility. The diet of an individual plays a great role in this. The intake of various toxic chemicals whether knowingly or unknowingly may impart a negative impact in the spermatogenesis process. These lead to male infertility. Genetic aberrations, certain infections and inflammations all converge to male infertility [17](Choudhury *et al.*, 2001).In the African countries the most common reason of male infertility is inflammation caused by a pathogenic infection. Any infection occurred in the reproductive tract results in the excessive release of phagocytic cells alongwith other effector molecules that rushes to the infection site. Out of the total infertility 30-55% has been caused due to male infertility disorders. According to Poongothai *et al.*,2009[18] male factor is the causative of half of the total cases of infertility. The various causes of inflammation in the reproductive tract of male includes - ejaculatory duct obstruction, epididymitis: inflammation due tocertain sexually transmitted diseases like the gonorrhoea, chlamydia, *Escherichiacoli* and urethritis. Apart from these, testicular torsion, varicocele, blockage in the urogenital tract, chronic inflammatory prostate, orchitis, and some drug usage might also result in male reproductive tract inflammation. The impairment caused by such inflammatory ailments generally accumulates gradually, at times silently bereft of many symptoms for many years which later results in tissue devastation[2](Mitchell and Cotran, 2003). A comparison of the inflammatory system is done with a sprinkler system preventing a fire spread in a building. Although the work is executed with positive intentions of limiting the damage but at times can be significantly harmful. The decreased semen quality due to an inflammatory process might be a result of the impairment of an accessory gland's function, sperm transport obstruction and spermatogenetic dysregulation. In male gonads, proinflammatory cytokines are produced physiologically in male gonads and is required in the proper functioning of the reproductive organ. The main source of cytokines is produced in the male gonads mainly by the testicular macrophages.Apart from these cytokines like interleukin-1 and interleukin-6 are produced by Leydig cells and Sertoli cells [19] (Diemer *et al*., 2003). TNF–α aids in the movement of leukocyte into targets of tissue damage. It also induces some adhesion molecules and certain chemokines on the endothelial layer and thus can activate the microbial system of the phagocytes. In addition to this TNF–α also induces apoptosis. Similarly, IL–1 too operates with the symptoms of redness, pain, heat and swelling in the genital tract of male. The inflammation leads to an increased diameter of the seminal vesicles which ultimately lead to reduced velocity of seminal flow along the complete surface of the local seminal vesicles.

2.4.Oxidative stress, an output of inflammation might result in male infertility

The damage in the male genital tract due to inflammation results in the escalated generation of ROS- Reactive oxygen species. Moreover, increased free radical production can be due to inflammatory reactions caused by bacterial strains that pioneer the male reproductive tract [20](Brostoff *et al.*,2006). For normal cell functioning, the excess oxidative stress must be neutralized by antioxidants in the seminal plasma. Oxidative stress occurs in the male genital tract when the free radicals are in excess and it overruns the capacity of the male genital tract raises when excess free radical defense system. As reported by Duru *et al.*,2000[21] oxidative stress in the seminal plasma negatively impacts sperm function, motility and concentration. These reports also suggest that cytokines and mediators act as the mediators of oxidative damage

which ultimately imply a negative impact on the semen quality and fertility in man. Many scientists have reported that there are 12 interleukins in total which are related to sperm morphology and density. They also reported an increased level of Interleukin6 (IL6) in the infertile men. Tumor Necrosis Factor-α (TNF–α) in the semen is known to be correlated with decreased sperm count, sperm morphology, and sperm motility. An increased level of IL-6 causes apoptosis in the seminal cells which occurs as a result of differentiation and proliferation of the beta cells. Another study reported the increasing Interleukin1-β (IL–1 β) decreases sperm motility. The results showed an association with an increased oxidative stress in the seminal plasma. Malondialdehyde (MDA) was also seen to be increased in the seminal plasma. The cytokines that are known to act as immunomodulators in the male gonads actually appears in massive amounts in the semen during various infections. Inflammation is connected to leukocytospermia [22] (Gruschwitz*et al.*, 1996). Even after decades of study the controversy of the clinical cause of the increased semen leukocytes still remains unsolved. Although some reports have suggested the cause to be disrupted spermatogenesis, others reported that unusual sexual behavior and deleterious effect of certain environmental factors are actually a cause of the increased semen leukocytes. During inflammation White Blood Cell (WBC) from the semen leaks at the site of inflammation. But during normal conditions, White Blood Cell (WBC) don't leak and remain confined to the central area of the seminal vesicles. There is a very important role of the ROS in the process of spermatogenesis in men. But increased Reactive Oxygen Species (ROS) can cause various pathological conditions in the sperm parameters like motility, viability, maturation, hyperactivation, capacitation, and acrosome reaction [23](Baskaran *et al.*, 2021). Supraphysiologically increased levels of Reactive Oxygen Species (ROS) for an extended period induces intense oxidative stress resulting in a toxic consequence for all the associated cells in normal. In this view, spermatozoa are mostly vulnerable due to the distinctive cytoarchitecture and biochemistry of the cell [24](Barati*et al.*, 2020). Sperm's plasma membrane is highly enhanced in Polyunsaturated Fatty Acids, specifically arachidonic acid and docosahexaenoic acid which makes them highly susceptible to any damage induced by the presence of ROS. Increased levels of ROS generation alongwith the poor activity of the antioxidant defense system finally results in the DNA fragmentation of the sperms,i.e.,Sperm DNA Fragmentation (SDF). Towering Sperm DNA Fragmentation (SDF) makes alterations in the ultrastructure of the sperm by vacuolizingthe nucleus alongwith other grave abnormalities of the sperm morphology. This as a result can hinder the fertilization process by adversely impacting the acrosomal reaction and the capacitation and hyperactivation processes of the sperm.This can be taken up as an explanatory reason for uplifted SDF in the couples facing an indefinable recurrent loss of pregnancy. Apart from this the lipid peroxidation induced by oxidative stress can decrease sperm viability and sperm motility as it causes a reduction in the membrane potential of the mitochondria thus leading to a resultant destruction of the adjacent axoneme[25](Fang *et al.*,2020). The propagation of the products and by-products from lipid peroxidation products such as 4-hydroxynonenal (4-HNE), negatively influences the sperm motility. The 4-HNE has the capacity to bind on the heavy chain of dynein protein present in the sperm tail and to the Protein Kinase Anchoring Protein 4 (AKAP4) in the fibrous sheath of sperm. Apoptosis by the reaction of Fas death domain with FasL i.e., the ligand and the autophagy due to the increased levels of expression of the

anti-thymocyte globulin (Atg) & gene i.e., autophagy related gene can cause deterioration of the sperm cells of mice. Apart from apoptosis, another causative villain of spermatogenesis can be reported as autophagy [26](Collier *et al.,* 2021). Acute increased levels of oxidative stress affect the steroidogenesis in the Leydig cells that eventually leads to male infertility. ROS disturbs the mitochondrial membrane of the Leydig cells in declining the expression of Steroidogenic acute regulatory protein (*StAR*), steroidogenic acute regulatory protein which can decrease the mitochondrial transport of cholesterol thusreducing the generation of androgens. This negative impact on the steroidogenesis is a result of the oxidative stress-induced activation of the p38 MAPK protein. Nuclear receptors such as *Nur77* are key transcriptional factors that regulates the steroidogenic enzymes' gene expression[27](Chen *et al.*,2018).Moreover, steroidogenesis is downregulated in paracrine manner. This can be evoked by TNF-α release by the activated macrophage which can address the TNFR1 expressed on the neighboring Leydig cells. This results in the apoptosis of Leydig cell and by activation of p38 MAPK signaling pathway which finally results in the reduced serum testosterone levels.

3. Antioxidant as a solution to the inflammation causing male infertility

Men with issues of idiopathic infertility usually exhibit an increased level of Reactive oxygen species. Reactive oxidative stress induces infertility by the Deoxyribonucleic Acid (DNA) damage. This occurs due to the presence of exceedingly large amounts of Poly Unsaturated Fatty Acid (PUFA) in the sperm membrane. Moreover, a feeble endogenous antioxidant system aids in the ROS built up. Antioxidant system encompasses many enzymatic factors like Superoxide [3]Dismutase (SOD), catalase(CAT) glutathione peroxidase (GPX) and nonenzymatic factors, most of which are compounds with a low molecular weight like glutathione, N-acetyl-cysteine, vitamins A, E, and C, coenzyme Q10, carnitines, myoinositol, lycopene, astaxanthin, and micronutrients like the zinc, copper and selenium which if actively performing can assure an optimal resistance against the stress caused by ROS. Chabory *et al*,2009[28] reported a study where the activity of antioxidant enzymes was incapacitated in male mice was done by the deletion of a gene named GPx5. This led to the generation of oxidative stress in the male mice which finally led to infertility and also when these mutant male mice were mated with wild-type females the resultant pregnancies were highly unsuccessful with numerous miscarriages and if any births resulted, it turned out to produce litters with birth defects. Sub fertile men are reported to have a low count of antioxidants like the vitamin C, vitamin E, selenium and other such free radical scavengers[29](Balercia *et al.,* 2000). All these scientific literature throws a light on the fact that antioxidant can be used as dietary supplement to improve sperm health thus correcting infertility. However, most trials are small in size and differ in the target population selected as well as the type, dose and duration of antioxidant therapy. Several reviews of clinical studies addressing the effect of oral antioxidants on male infertility have been published recentlythat links inflammation. Showell *et al*,2022[30] presented a detailed report on the influence of the dietary antioxidants in male fertility. They finally concluded that germ cell DNA damage is a major cause of infertility or subfertility and further prolific research is required to rectify this by the action of potential antioxidants and

[3] SDF- Sperm DNA Fragmentation, 4-HNE- 4-hydroxynonenal, AKAP4- Protein Kinase Anchoring Protein 4, StAR- steroidogenic acute regulatory protein.

already established antioxidants. The most common vitamin i.e., vitamin C was first established as an antioxidant by Fraga *et al.*, 1996[31]. They carried the experiment on a small population of smokers. Later, studies by various scientists reported this vitamin as a profertile agent in cases of male reproduction. Vitamin E, another antioxidant also was reported to have positive effect on the semen parameters. Zinc, carnitine and many such others antioxidants are known to have positive effects on male fertility. Zinc has a multifaceted action on the human physiology, mostly on the immune system. Zinc is an essential element required for the proper functioning and development of cell-mediated innate immunity,i.e., the neutrophils, macrophages and natural killer cells. Zinc deficiency has a negative impact on the phagocytosis and production of cytokines. T cell and B cell growth is also affected due to decreased zinc in one's body. Zinc, thus can be concluded as an anti-inflammatory agent.

Fig 2

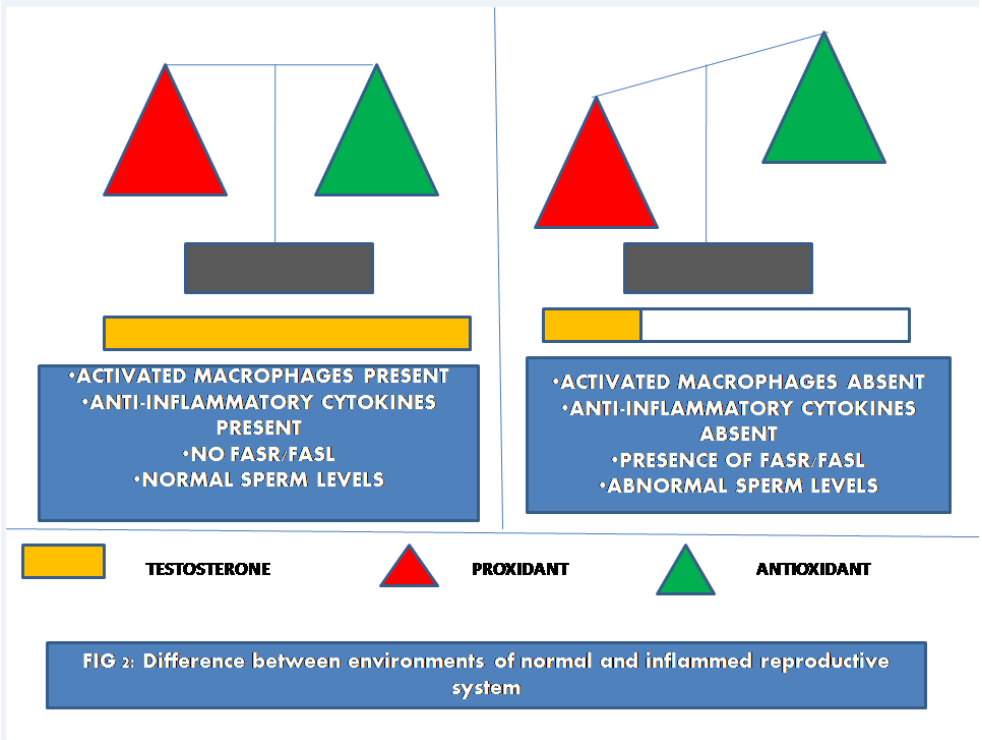

FIG 2: Difference between environments of normal and inflammed reproductive system

3.1. Plants with anti-inflammatory properties and antioxidant properties curing male infertility

Oxidative stress affects the reproductive life of male and female. Oxidative stress emerges due to disproportion between reactive oxygen species and defensive antioxidants. ROS disarrange probity of sperm DNA and assist to lipid peroxidation. Natural antioxidants which have free radical scavenging activity are potential remedies to treat hormonal imbalance and oxidative stress. Antioxidant can scavenge ROS, disable them and restore damage[32](Smits *et al.*, 2018).Acacia species shows antioxidant activity which helps in curing problems related to oxidative stress[33](Afsar, 2017).*Acacia hydaspica* belonging to Leguminosae family possesses anti-cancer, anti-inflammatory, anti-oxidant and anti-pyretic activities because of presence of secondary metabolites like rutin, catechin, gallic acid, methyl gallate, caffeic acid [34](Chakrabarty, 1996). Due to presence of these secondary metabolites *Acacia hydaspica* when tested over cisplatin induced testicular injuries showed antioxidant defense, restored the hormones, altered the histological changes

in testis and also restored DNA damage. *Achillea millefolium* is known for its anti-oxidant and anti-inflammatory properties. In a study achillea inflorescence was extracted with alcohol to test over nicotine induced reproductive disorders. Nicotine induced animals exhibited significant decrease in sperm count, sperm motility, tubular differentiation index, and increase in number of dead sperm. Nicotine treated group also showed decrease in total antioxidant capacity, superoxide dismutase activity, Follicle Stimulating Hormone (FSH), Luteinising Hormone (LH) and testosterone level in serum. Co-administration of Achillea extract with nicotine restored and altered almost all the toxic effects made by nicotine signifying protective nature of the achillea millefolium against nicotine induced toxicity[35](Salahipour, *et al.,* 2017). *Cymbopogon citratus* aqueous extract was studied on hydrogen peroxide induced male reproductive injury. *Cymbopogon citratus* having anti-inflammatory and antioxidant properties showed protection over hydrogen peroxide induced reproductive injury in [4]male rats[36](Rahim*et al.,* 2013). Prophylactic action of *Echinacea* extract was studied on anti-androgen induced reproductive disorders. Significant protective effects were recorded in antioxidant status of testicular tissue. SOD and GST activity increased, NO and MDA decreased with Echinacea extract treatment to male rats. In a study grape seed Proanthocyanidin extract was tested in mitigating arsenic-induced toxicity in reproductive system. Arsenic trioxide was given to the animals which diminished testis somatic index, sperm count, SOD and GSH. Whereas in grape seed proanthocyanidin extract treated group significant increase in the parameters were observed. Highest mRNA expression of *Nrf2, HO, NQO1, GST* was seen in arsenic trioxide treated animals when treated with the extract. Plants from Brassicaceae family like *Lepidium meyenii* donot act on the serum hormone levels and have shown beneficial effects on spermatogenesis. The extracts of this plant probably work on the sperm levels without acting on the steroidogenesis of the males. Many other plants with reported antioxidant effects like those from the Garcinia genus can be active as profertile agents with the capacity of acting on testosterone levels.

4. Discussion

This review has been written with the view of discussing about the treatment and prevention of male infertility due to the occurrence of Oxidative stress created by an immune response. Infertility in males due to various idiopathic reasons is the causative of 50% of total infertility worldwide. Inflammation, a responsive outcome of the immunological system is an auxiliary mechanism required to maintain the homeostasis tissue[1] (Ahmed *et al*, 2011). Inflammation a hero-evil. Inflammatory responses are known to hamper the body's well-being at a deeper level when occurs in boundless. Infertility and the mental trauma that follows is an elephant in the room, but it is high time that it requires be discussing and addressing with proper scientific know-how. There have been various reports suggesting its link to infertility in male. Inflammation causes an upliftment of ROS levels that could not be stabilized by the internal antioxidant system[2](Mitchell and Cotran,2003). An increased level of Reactive Oxygen Species (ROS) for an extended period results in excessive oxidative stress. This might cause toxicity in the cellular environment. In this view, spermatozoa are mostly vulnerable due to the distinctive cytoarchitecture and biochemistry of the cell [24](Barati*et al.,* 2020). The DNA damage of sperm caused by the high levels of oxidative stress can be detected by various techniques like Sperm Chromatin Dispersion (SCD).

[4] MDA- Malonaldehyde, SOD- Superoxide Dismutase, SCD- Sperm Chromatin Dispersion.

Inflammation also makes the testicular environment hostile for the spermatogenesis. Various scientists reported that vitamin is a profertile agent in male reproduction. Vitamin E is a potent antioxidant and is reported to have positive effects on the semen parameters. Zinc, carnitine and many such others antioxidants are known to have positive effects on male fertility. Zinc has a multifaceted action on the human physiology, mostly on the immune system (Adeoye et al.,2018). Zinc is an essential element required for the proper functioning and development of cell-mediated innate immunity,i.e., the neutrophils, macrophages and natural killer cells. Zinc deficiency has a negative impact on the phagocytosis and production of cytokines. T cell and B cell growth is also affected due to decreased zinc in one's body. Zinc, thus can be concluded as an anti-inflammatory agent. Natural antioxidants which have free radical scavenging activity are potential remedies to treat hormonal imbalance and oxidative stress. The plants and its extracts can be beneficial in ameliorating the male fertility i.e., linked to the oxidative stress caused by the inflammatory responses of our body (Li et al.,2015). Thus, study and extensive research can allow the scientists to discover the drugs from natural sources. The proper drug designing can lead to innovative ways to manipulate the inflammatory responses in a way that it only remains useful and never harmful. Controlling this phenomenon can lead to the prevention and cure of various disorders like the male infertility (Azenabor et al.,2015) .

5. Conclusion

Dietary Antioxidants present in the natural sources like the plants rich in polyphenols and flavonoids can be used to balance the ROS. The evoked inflammatory responses needs to be resolved or it creates an environment with an unbalanced ROS that leads to DNA damage in the spermatogonium which leads to male infertility. The rectification of ROS by the plants can be a proper way as it has least side-effects. Inflammation caused by various exogenous pathogen and toxins leads to the stress that can be balanced by the bioactive compounds of the plants i.e mostly the flavonoids and thus a proper study relating these and trying to learn the underlying mechanism is the need of this hour.

6. Author Contribution

The first three author had equally contributed towards the paper, the last author i.e., our guide have guided through the writing and edited things when required.

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9. Conflict of interest

There has been no any conflict of interest amongst the authors regarding the writing of this Review Paper.

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