IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

EFFECT OF GREEN TEA ON REPRODUCTIVE DISORDERS OF MALE AND FEMALE: A REVIEW

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Abstract: Green tea is tea made from *Camellia sinensis* leaves and buds. It contains of different minerals and natural anti-oxidants such as Polyphenols (Catechins etc.). The beneficial effects of green tea and its major bioactive component, (−)-epigallocatechin-3-gallate (EGCG), on health is significant. This review summarizes on the beneficial effects of green tea catechins on selected female reproductive disorders and infertility in males. Green tea or its derivative, EGCG, improves endometriosis mainly through anti-angiogenic, anti-fibrotic, anti-proliferative and pro-apoptotic mechanisms. Moreover, green tea enhances ovulation and reduces cyst formation in PCOS and reduces plasma corticosterone levels and uterine contractility in dysmenorrhea. GrTPs (green tea polyphenols) have antioxidant properties that improve major semen parameters, such as sperm concentration, motility, morphology, DNA damage, fertility rate, and gamete quality improving fertility. Prostate cancer is the most common cancer among men. In this review, current knowledge is presented regarding the antioxidant, antiangiogenic, antifibrotic effects of green tea extracts in the prevention and treatment of reproductive disorders, with particular focus on the molecular mechanisms of action, such as influencing tumour growth, apoptosis, androgen receptor signalling, cell cycle and various malignant behaviours.

Keywords: Catechins, EGCG, Endometriosis, PCOS, Dysmenorrhea, Infertility, Direct and indirect antioxidant effect

INTRODUCTION

Green tea is tea made from *Camellia sinensis* leaves and buds. Green tea originated in China, and since then its production and manufacture has spread to other countries in East Asia. It releases excessive amounts of tannins, leading to its bitter taste. It contains different minerals such as magnesium, alkaloids like caffeine and antioxidants such as Polyphenols. Polyphenols found in green tea include flavonoids and catechins which are under laboratory research and are considered to promote health.

Phenolic compounds of green tea, such as catechins, act as natural antioxidants and constitute 6–16% of its dry leaves. The four major green tea catechins include (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-epicatechin (EC). Catechins neutralize free radicals and facilitate the detoxification of enzymes, such as catalase, glutathione peroxidase and glutathione reductase. Catechins have roles on health, including being a high antioxidant, and having osteoprotective, neuroprotective, anti-cancer, anti-hyperlipidaemia and anti-diabetic effects, and aiding fertility in humans and animals (**Fig. 1**).**[1] [20]**

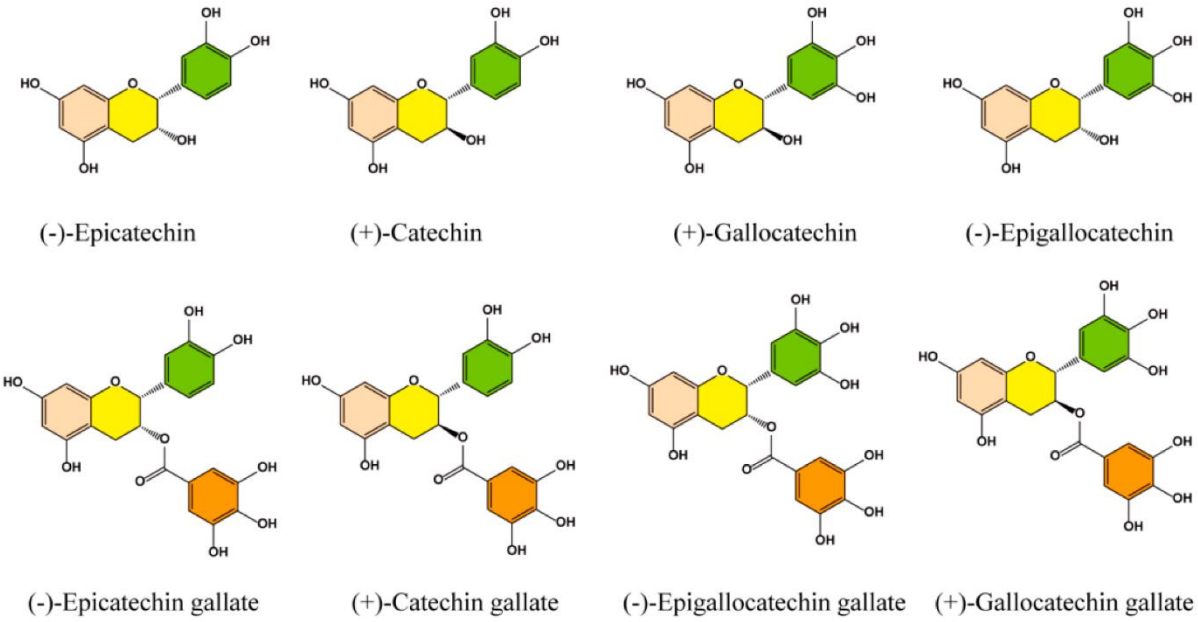

Fig 1: chemical structure of Green Tea Catechins **[1]**

ROLE IN ENDOMETRIOSIS

Endometriosis is a chronic disorder characterized by the implantation of endometrial glands and stroma outside the uterine cavity. It affects adolescent girls and reproductive-aged women and is commonly associated with chronic pelvic pain and infertility. EGCG exerts its effect on endometrium by anti-angiogenic, anti-fibrotic, anti-proliferative and pro-apoptotic mechanisms. The anti-proliferative effect of EGCG reportedly causes regression in the development of endometriosis lesions assessed by size, number, volume and weight, and cell proliferation. The anti-angiogenic properties of EGCG inhibit angiogenesis mainly through the reduction of micro vessel formation, down-regulation of vascular endothelial growth factor C (VEGF-C) and tyrosine kinase receptor VEGF receptor 2 (VEGFR2) expressions, and blood perfusion of endometriotic lesions without affecting blood vessel development in the ovarian follicles. Reported anti-fibrotic effects against endometriosis indicate that EGCG suppresses the expression of αSMA, Col-I, CTGF and FN mRNAs (fibrotic marker) in endometriotic and endometrial stromal cells and attenuates the cell-mediated contraction of collagen gels. EGCG inhibited the TGF-β1-stimulated activation of MAPK, and Smad signaling pathways further elucidated the mechanism of the anti-fibrotic effect of EGCG against endometriosis. The pro-apoptotic feature of EGCG demonstrates an increase in apoptotic activity in endometriosis cells after EGCG treatment. It is also reported that the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase 1 (MAPK1) mRNA levels (apoptosis marker) were elevated after EGCG treatment (**Fig. 2, 3**) **[2] [4] [8] [18] [23] [24] [26] [32] [41]**

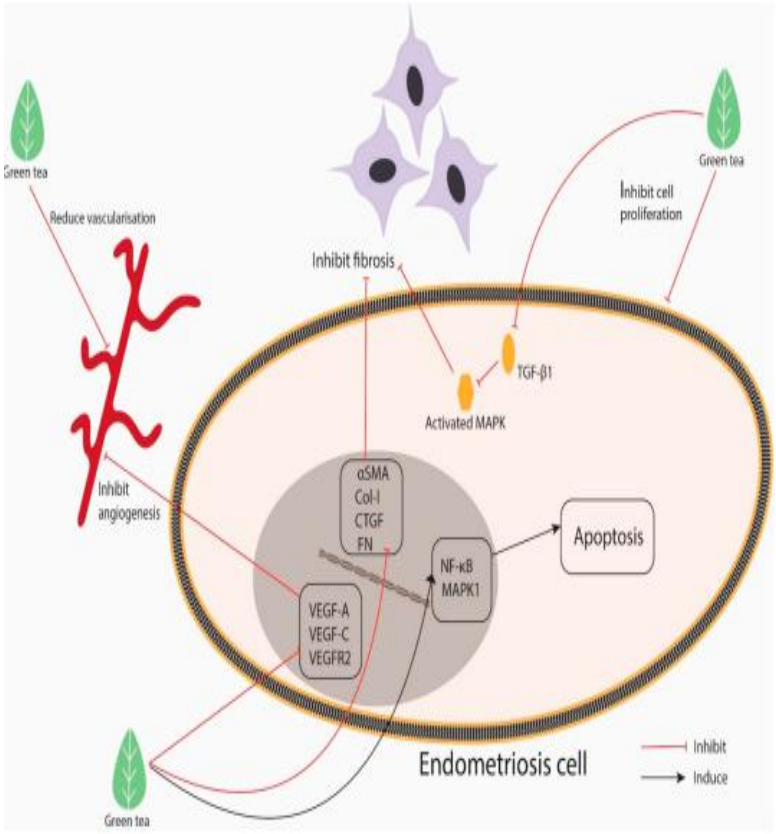

Fig 2: mechanism related to the beneficial effects of green tea catechins on endometriosis **[2]**

ROLE IN POLYCYSTIC OVARIAN SYNDROME (PCOS)

PCOS is a combination of complex reproductive, endocrine and metabolic syndromes. It is a condition in which the ovaries produce an abnormal amount of androgens that are normally present in women in small amounts. The name polycystic ovary syndrome describes the numerous small cysts (fluid-filled sacs) that form in the ovaries. Currently, PCOS has no definite treatment; symptomatic treatment alone is being implemented. Green Tea extract has beneficial health effects against PCOS. One of the factors that may increase the risk of developing PCOS in women is obesity. Obese PCOS women who consumed green tea tablets (unspecified dose) showed a significant reduction in body weight. Clinical trials involving PCOS women who consumed green tea tablet, reported no significant difference among the levels of inflammatory marker TNF-α, IL-6 and hs-CRP. Therefore, more studies should be carried out to prove the anti-inflammatory effects of green tea against PCOS. Green tea or its derivatives inhibits the increase in testosterone level in PCOS women. Half of women diagnosed with PCOS have insulin-resistant hyperinsulinism. Green tea or its derivatives normalize hyperinsulinism in PCOS. Clinical trial recorded a significant reduction in fasting insulin on obese PCOS women after green tea tablet treatment. PCOS is the leading cause of anovulatory infertility in women. Green tea treatment improved ovulation and follicle progression and inhibited cyst formation. Overall, green tea is beneficial in PCOS but studies on the effect of green tea extract in PCOS is limited (**Fig. 3**) **[2] [6] [7] [9] [25][28] [29] [35][45] [49]**

ROLE IN DYSMENORRHEA

Dysmenorrhea refers to the occurrence of painful cramps of uterine origin during menstruation. This pain is caused by natural chemicals called prostaglandins that are made in the lining of the uterus. Prostaglandins cause the muscles and blood vessels of the uterus to contract. It is of two types: primary dysmenorrhea, which refers to pain without any evidence of pathology, and secondary dysmenorrhea, which is caused by specific pelvic pathological conditions, such as adenomyosis, fibroids and endometriosis. Consumption of green tea is associated with a low prevalence of dysmenorrhea. Elevated plasma corticosterone levels induce dysmenorrhea. Treatment with EGCG alleviates generalized hyperalgesia and reduced plasma corticosterone levels.

In addition, EGCG reduced uterine contractility and suppressed myometrial infiltration. However, no mechanistic study has explored the possible molecular pathway of green tea's beneficial effect against dysmenorrhea (**Fig. 3**) **[2] [6] [10][14] [30] [44]**

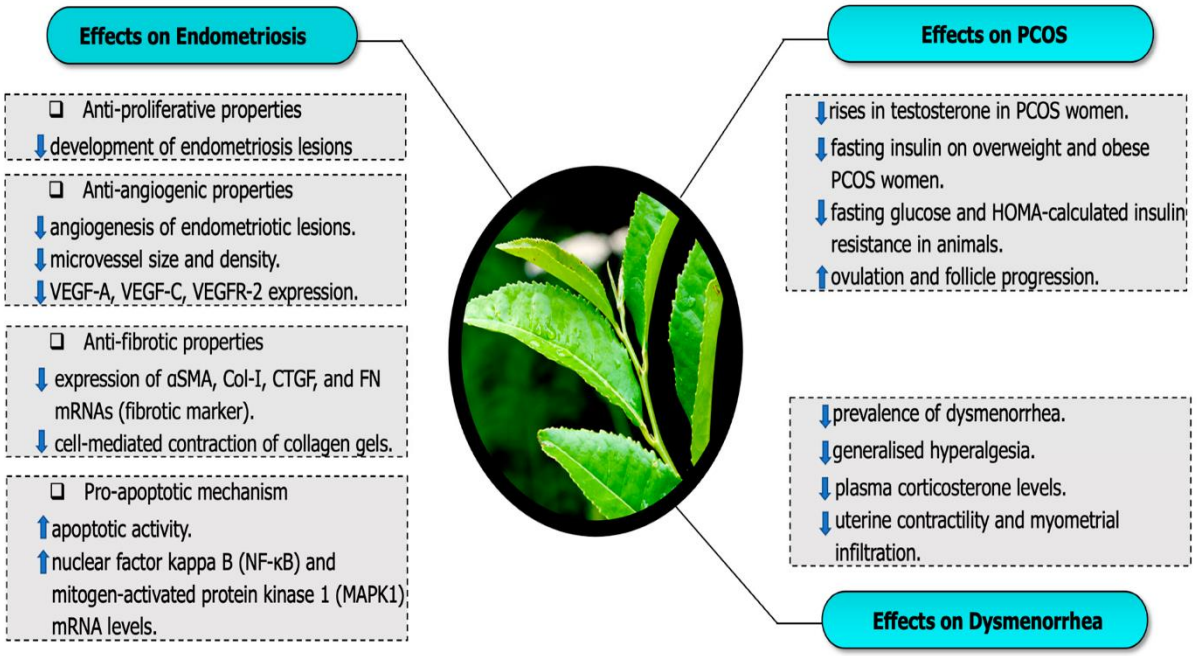

Fig 3: effects of Green Tea and its derivative on selective female reproductive disorders **[2]**

Catechins as Antioxidants

Catechins appear to be able both to generate and to scavenge free radicals and show their beneficial effects due to a combination of both mechanisms. The antioxidant efficacy of catechins is exerted through (1) direct mechanisms—scavenging ROS, chelating metal ions; and (2) indirect mechanisms—inducing antioxidant enzymes, inhibiting pro-oxidant enzymes, and producing phase II detoxification enzymes and antioxidant enzymes. All Catechins have common chemical structures—phenolic hydroxyl groups that are able to stabilize the free radicals. This property is responsible for their direct antioxidant activities. Catechins donate one electron of phenolic OH group, thus reducing free radicals and the aromatic group maintains stability through the resonance of the resultant aroxyl radicals. Following interaction with the initial reactive species, a radical form of the antioxidant is produced, which is stabilized by charge delocalization. The relative hierarchy of effectiveness of catechins as radical scavengers is EGCG > ECG > EGC > EC. The antioxidant capacity of phenolic compounds is also attributed to their ability to chelate metal ions involved in the production of free radicals. Adjacent hydroxyl groups in the molecule can act as iron chelation sites. (**Fig. 5**)

As indirect antioxidants, catechins regulate protein synthesis and signalling pathways. In addition, catechins can up-regulate anti-oxidant enzymes. Catechins can inhibit prooxidant enzymes, e.g., NADPH (nicotinamide adenine dinucleotide phosphate)-oxidase, or modulate interaction of ligands with receptors, e.g., tumour necrosis factor alpha (TNF-α), also, they can suppress many oxidative stress-related pathways responsible for the inflammation processes. Catechins modulate the activities of redox-sensitive transcription factors-nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein-1 (AP-1), which are very important in the response to pathogenesis-related oxidative stress. as catechins are structurally similar to ATP, they could competitively bind to the enzyme ATP-binding sites. Structural/conformational properties and hydrogen bonding are also suggested as mechanisms for catechin interactions with transcriptional factors. (**Fig. 5**) **[6] [12][16] [19] [27] [31]**

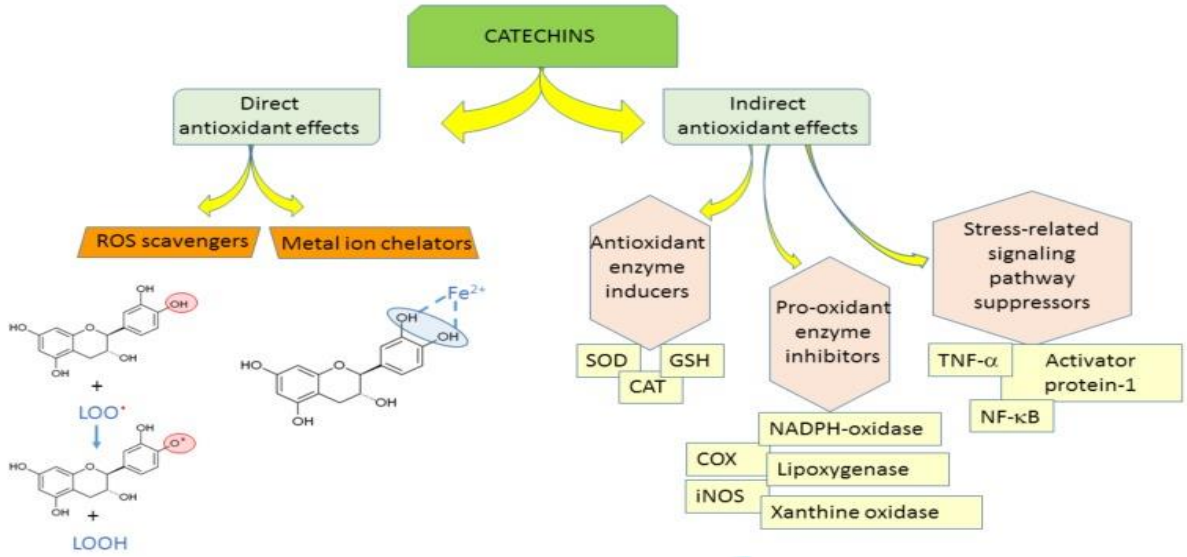

Fig.5: antioxidant properties of catechins. ROS-reactive oxygen species, SOD-superoxide dismutase, CAT-catalase, GSH-glutathione peroxidase, NADPH-oxidase-nicotinamide adenine dinucleotide phosphate oxidase, COX-cyclooxygenase, iNOS-inducible nitric oxide synthase, TNF-α–tumor necrosis factor alpha, NF-κB-nuclear factor kappa-light-chain-enhancer of activated B cells. **[12]**

SOURCES OF OXIDATIVE STRESS AND THEIR IMPACT ON REPRODUCTION AND FERTILITY

ROS are reactive species that cause oxidative damage to cellular biomolecules, including proteins, lipids, and nucleic acids. ROS, generated from various endogenous and exogenous sources, have a tremendous impact on reproduction and fertility. Activated leukocytes, Immature, defective, senescent and apoptotic sperm, produce high levels of ROS, adversely affect sperm motility, morphology and concentration. They also cause acrosomal damage, hyperactivation, DNA damage, and impair oocyte penetration.**[17][40][43]** ROS are involved in the initiation of apoptosis in antral follicles caused by several chemical and physical agents. It has a role in primordial and primary follicle death. Elevated levels of OS caused a decrease in oocyte numbers leading to a reduction in follicles, and these changes ultimately resulted in sub-fertility. OS influences early embryo development too. (**Fig. 6**) **[15] [50]**

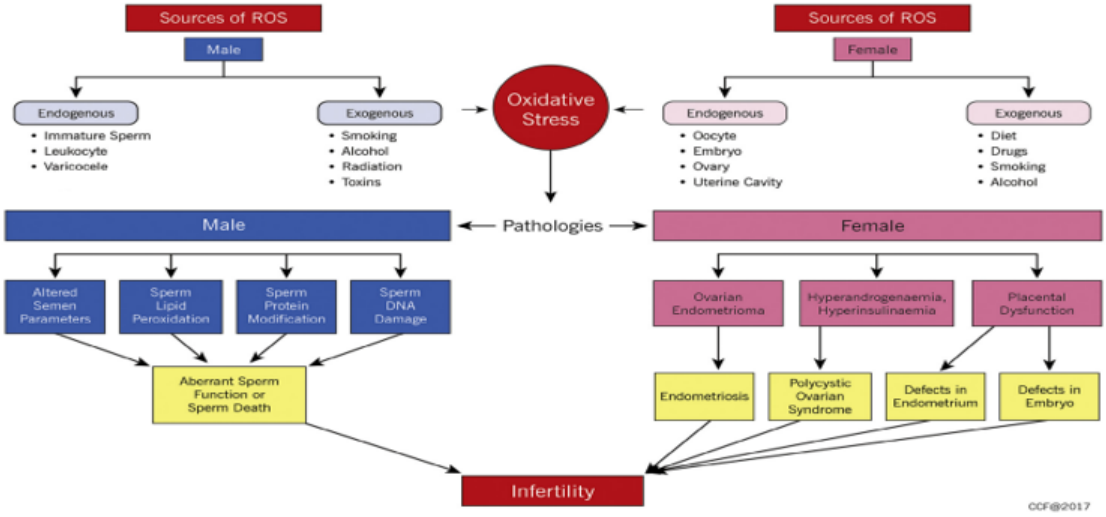

Fig.6: various endogenous as well as exogenous sources of ROS and the association between OS and pathological conditions in male and female reproduction **[15]**

FEMALE INFERTILITY

Every month, a cohort of oocytes begins to grow and enlarge in the ovary, but meiosis I resumes in only one of them – the dominant oocyte. Meiosis is initiated by an increase in ROS and inhibited by antioxidants. In contrast, the progression of meiosis II is promoted by antioxidants, signifying that there is an intricate relationship between ROS and antioxidants in the ovary. GT catechins have two different actions: an antioxidant effect at a lower concentration (10 mg/ml) and a prooxidant effect at a higher concentration (25 mg/ml). EGCG supplementation to the culture media at a lower concentration (10 mg/ml) during IVF increase the fertilization rate whereas a higher EGCG concentration (25 mg/ml) decreases the percentage of fertilized oocytes. Low concentration of it, improves embryo quality. Adding a low concentration of GTE as a source of antioxidant in maturation medium increased the maturation rate of oocytes and improved morula and blastocyst formation rates. **[15] [20] [36] [46]**

MALE INFERTILITY

Green tea polyphenols (GrTPs) are potentially effective in ameliorating inflammatory bowel disease (IBD) and related disorders via their known anti-inflammatory, antioxidative, and anti-bacterial properties. GrTPs have been shown to reduce inflammatory reactions by targeting several signalling pathways. GrTPs down-regulate IκB kinase (IKK), c-Jun N-terminal kinase-mitogen-activated protein kinase (JNK-MAPK), nuclear factor-Kappa B (NF-kB), cytokine-like tumour necrosis factor-α (TNF-α), cyclooxygenase-2 (Cox-2), and B-cell lymphoma (Bcl-2). The antioxidant properties of polyphenols comprise scavenging and destroying free radicals. Testicular tissue is predisposed to suffer from the action of free radicals and oxidative stress because of its high cell division rate, oxygen consumption rate, and low oxygen pressure, debilitated vessels, and high levels of unsaturated fatty acids. In addition to its antioxidant properties, green tea may also decrease inflammation, reduce DNA fragmentation, and increase the motility and viability of semen. Normally, sperm cells produce significant amounts of reactive oxygen species (ROS) during their physiological metabolism. There are many factors that affect fertility traits directly or indirectly. ROS have devastating effects via lipid peroxidation which damages the structure of the lipid matrix in semen membranes and reduces intracellular levels of adenosine triphosphate (ATP) which may lead to reduced sperm viability, axonemal injury, and an increase in mid-piece morphological defects. EGCG prevents spontaneous mutation, low-density lipoprotein (LDL) oxidation, and chromosomal impairment induced by ROS. GrTPs may exert their antioxidative effects on spermatozoa, and improve the motility and capability of semen. Semen motility in infertile humans is affected by seminal ROS. An increased level of seminal ROS may be associated with an increase in sperm DNA fragmentation. Proliferation of semen lipid peroxidation significantly reduces sperm motility. Catechins were observed to reduce ROS levels, regulate gene expression, and increase in sperm capability. GrTP supplementation significantly increased the sperm count and motility. GrTPs have also been shown to decrease lipid peroxidation, protein carbonylation, and DNA damage, improve fertility (**Fig. 7**) **[1] [3] [5] [11] [13] [17] [21] [22] [33] [34] [37] [38] [39] [42][47][48]**

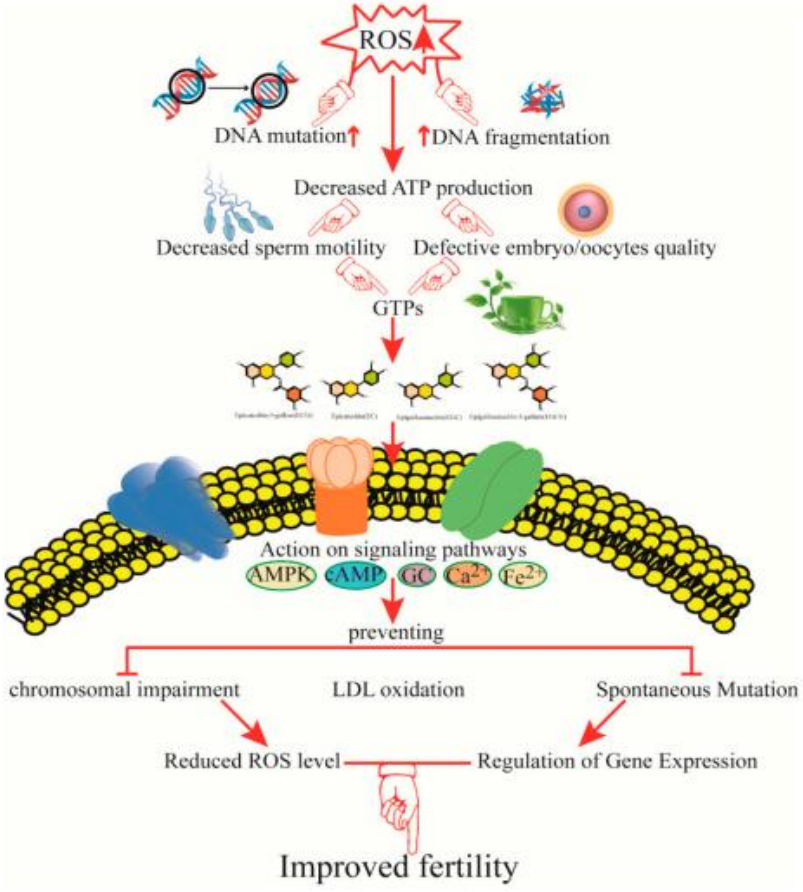

Fig 7: mechanisms by which green tea catechins improve fertility and reproductive function

the figure shows potential mechanisms of action of green tea catechins in different pathways and proposes that green tea polyphenols (GrTPs) are capable of improving fertility by improving sperm and embryo quality **[1]**

ROS, reactive oxygen species; ATP, adenosine triphosphate; AMPK, adenosine monophosphate-activated protein kinase; cAMP, cyclic adenosine monophosphate; Ca^{2+}, calcium ion; Fe^{2+}, ferric iron; LDL, low-density lipoprotein

CONCLUSION

The health benefits of green tea (*Camellia sinensis*) catechins are becoming increasingly recognized. A positive effect of green tea catechins on reproductive function is becoming apparent. The main polyphenol in green tea is epigallocatechin gallate (EGCG). Scientific studies suggest that EGCG and green tea polyphenols have anti-inflammatory and anticancer properties. Further studies in animal and human cell models using physiological concentrations of catechins and their metabolites are warranted in order to gain some insight into the physiology and molecular basis of the observed beneficial effects.

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