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Review article

Oxidative Puzzle of Female Infertility: A Systematic Narrative Review

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Oxidative stress, characterized by an imbalance between the production of the reactive oxygen species (ROS) and the ability of the antioxidant defense systems. It is crucial to the pathophysiology of infertile women, deleterious impacts through the oocyte maturation, ovulatory functions, associated with reproductive disorders as polycystic ovary syndrome (PCOS) and endometriosis. Mitochondria of oocytes and granulosa cells are the leading sources of ROS whose generation is further worsened by ageing, obesity, as well as environmental assaults. Although physiological levels of ROS are necessary to normal follicular growth and ovulation, excessive levels of ROS cause oocyte DNA breakage, meiotic spindle deregulation, and embryonic in survival. The inherent antioxidant enzymes which as superoxide dismutase (SOD) and glutathione, give the cellular systems partial protection against oxidative damage, however significant and the exogenous antioxidant supplementation such as vitamins C and E, coenzyme Q10, N-acetyl cysteine as well as Melatonin have shown an encouraging result in randomized controlled trials (RCTs) and meta-analyses. Clinical evidence shows that there are better ovarian responsiveness and better oocyte yield and better pregnancy rates in assisted reproductive technologies (ART) especially in women with advanced ovarian age or PCOS. A Cochrane systematic review found a moderate relationship between antioxidant use and increased rates of live births, but the evidence quality was overall low because of the study heterogeneity. Notably, antioxidant interventions were generally well-tolerated and portable with minimal side effects. Future studies ought to focus on more rigorously constructed, high quality, RCTs that are targeted at clinically meaningful end point outcomes like live birth rates as well as consider adjunct parameters of sperm DNA fragmentation, which modifies female reproductive outcomes indirectly. Combination of personalized antioxidant treatment and specific lifestyle changes has a significant therapeutic potential for the female reproductive health and optimizing fertility.

INTRODUCTION

Female infertility constitutes a significant health concern, affecting about 10-15% of couples of reproductive ages [1,2] with an estimated global prevalence rate of approximately 40-50% of infertility cases are attributed to female origins [3,4]. Inter alia, ovulatory dysfunctions leading cause (30-40%) [5], subsequent by decreased ovarian reserve (DOR), endometriosis (10-15%), and tubal or uterine pathologies [5,6]. These circumstances are often compounded further by the natural, age-associated deterioration of the reproductive potential, as fertility rates plummet after 35 years of age [3].

Substantial evidence indicates that oxidative stress (OS) is a pathophysiological state and central molecular contributor to these diverse etiologies of female infertility [7]. The leakage of mitochondrial electron transport chain is the outstanding source of reactive oxygen species such as

superoxide anion (O_2^{-*}), hydrogen peroxide (H_2O_2), hydroxyl radical (^{-}OH), and peroxynitrite ($ONOO^-$) [8]. Additional provenance of enzymes, including NADPH oxidase activity in the granulosa and theca cells assist in further genesis of reactive oxygen species (ROS) in the complex process of folliculogenesis [9].

At physiological concentrations, ROS have significant roles in female reproductive activity as indispensable second messengers in intraovarian signal transduction. Transient local elevation of the levels of H_2O_2 during ovulatory surge stimulates Epidermal growth factor receptor (EGFR) and matrix metalloproteinases (MMP-2 and MMP-9) [10]. These redox-regulated signaling pathways are vital in promoting follicle rupture, cumulus oocytes complex (COC) expansion, luteinization and further process of ovulation and fertilization.

ROS intricately modulates the steroidogenesis by increasing the key regulatory proteins such as steroidogenic acute regulatory protein (StAR) and cholesterol side-chain cleavage enzyme, both essentially required to produce progesterone after ovulation. Under physiological conditions, ROS maintain a delicate equilibrium, however; in pathological state, this equilibrium is disrupted by excessive production of ROS. Such dysregulation is further worsened by factors including advanced maternal age (AMA), obesity, polycystic ovary syndrome (PCOS), endometriosis and assisted reproductive technology (ART) procedures [11].

With relatively small cytoplasmic volume with limited antioxidant enzyme activity, and enriched with polyunsaturated fatty acids (PUFAs) in their plasma membranes, oocytes are extremely susceptible to OS. The cascade of lipid peroxidation impairs membrane fluidity and receptor signaling pathways, resulting in decline oocyte functionality. Concurrently, protein carbonylation disrupts meiotic spindle integrity and instability, cause aneuploidy rates up to 50% in oocytes of advance maternal age women (>40 years) [12].

Amplification of ROS within oocytes mitochondria primarily due to impaired electron transport chain complex I/III activity, leading to decreased ATP (reduced by 40-60% in DOR) and mutations in mtDNA such as characteristic 4977-bp deletion. These alterations analogous to oxidized purine (8-oxo-deoxy Guanosine) and DNS strand breaks that inhibit fertilization in male infertility. Similarly, oocyte DNA damage, quantified using assay such as TUNEL or 8oxoH2A foci interrelated with implantation failure in females [13-15].

Environmental and metabolic factors amplify further ROS generation such as smoking (reduces glutathione (GSH) by 30%), bisphenol A (BPA) upregulates NOX_4, hyperglycemia in PCOS promotes the formation of advanced glycation end-products which in turns increased xanthine oxidase activity, thereby tigers ROS generation further [16]. Endometriosis elevates peritoneal ROS through iron-mediated Fenton reactions ($Fe^{2+} + H_2O_2$ OH·), leading to fragmentation of oocyte DNA and 50% decline in blastocysts formation rate. Chronic low-grade inflammation, maintained by adipokines such as leptin, resistin in obesity, which further augments follicular fluid ROS concentration, reaching levels predictive of poor ovarian response (oocytes retrieved <5) [14, 17].

Antioxidants provides crucial protection against these effects. Endogenous enzymatic antioxidants such as superoxide dismutase (SOD 1-3), catalase, glutathione peroxidase (GPx) and non-enzymatic antioxidants like GSH, vitamins C/E, and coenzyme Q10 (CoQ10) counters oxidate stress and provide partial defense. However, their efficacy declines with aging, necessitating exogenous antioxidant aid [18,19]. Antioxidant supplementation replenishes the redox homeostasis, enriches follicular fluid antioxidant capacity (achieve up to100-fold) and improves oocyte yield, embryo quality and live birth rates in ART [8, 20, 21]. Despite existing research gaps, the antioxidant therapeutic aid promises pivotal improvement, and recommends precision tailored strategies for the management of PCOS, endometriosis, DOR, and ART related to oxidative stress to optimize reproductive outcomes.

Pathophysiology of Oxidative Stress in Female Reproduction

Sources of Reactive Oxygen Species: During follicular development, the mitochondrial oocytes and granulosa cell are generating approx. 90% of intercellular ROS via electron transport chain leakage. In vivo, oscillations between oxygenation-hypoxia during ovulation result in outbursts of H O , which play a significant physiological role in cumulus expansion deliberation by luteinizing hormone (LH) [22,23]. Conversely, in vitro conditions used in ART culture media especially high O_2 tension, enhances ROS production (5-20%) and lowering blastocysts formation rate by 15-20% [24]. Pathological amplifiers of OS such as PCOS (in which insulin resistance enhances xanthine oxidase activity), endometriosis (iron-catalyzed Fenton reactions), and smoking (acrolein depletes GSH stores) (fig 1,2) [25].

Impact on Oocyte Quality and Ovulation

Oocytes are vulnerable to ROS due to their abundance of polyunsaturated fatty acids (PUFAs) and slender cytoplasm antioxidant proportions. Sustained upsurge of ROS interferes with meiotic spindle assembly through tubulin oxidation, chromosomal deregulation and promote aneuploidy - effects parallel to those of sperm DNA fragmentation impairs fertilization capacity (fig 3) [26, 27]. This persistent OS leads to mitochondrial DNA mutations during ovarian aging, resulting reducing in ATP production and approx. 50% reduction in Oocytes yield [28]. Ovulation falters, as elevated ROS inhibits production of prostaglandins and collagenolysis; sub physiological ROS produces delay rupture, while elevated levels induce in follicular atresia. An uplifted follicular fluid ROS levels (~100µM) is associated with a poor ovarian response.[29].

Endogenous and Exogenous Antioxidant Systems

Enzymatic antioxidants constitute primarily within ovarian microenvironment such as granulosa cytoplasm and oocyte mitochondria. Within these cells SOD 1-3 isomers catalyze the dismutation of superoxide anions O_2^- in to H_2O_2. Subsequently, Catalase present in follicular fluid decompose the H_2O_2in to water and oxygen; glutathione peroxidase (GPx) breaks lipid hydroperoxides and H_2O_2into alcohol and water, which protect cellular membranes from peroxidative damage [30].

Non enzymatic antioxidants provide addon protection by scavenging ROS and maintains antioxidant balance. GSH present at 5-10mM concentration within oocytes, conjugates the ROS and maintains intracellular redox balance. Vit E breakup lipid peroxidation chain reactions in cellular membranes, while ascorbic acid 50-100 µM concentration found in follicles, convert oxidized vit E to its active form, and maintains antioxidant capacity. Uric acid, and albumin act as extracellular antioxidants, buffering ROS in follicular fluid and plasma. Coenzyme Q10 (Ubiquinol) serves as a vital electron carrier in the mitochondria, preserves membrane potential and preventing electron leakage [31,32].

Association with Specific Infertility Conditions , Supplementation Strategies

Exogenous antioxidants supplementation replenishes endogenous deficiencies and support oocyte function. N-acetylcysteine (NAC), GSH precursor (1.2-1.8g/day) boosts IVF oocyte yield; melatonin (3-6mg) crosses blood-follicle barrier, reducing 8-OHdG levels by 40%; while Vit C/E (500mg/400IU) synergize antioxidant capacity especially in PCOS ovulation induction (fig 1-3).

Table1: Antioxidants, their mechanism, dosage and clinical condition use.

Antioxidant	Mechanism	Dosage	Treatment Condition
Vit C	$^{\cdot}OH$ scavenger	500-100mg	PCOS, ART [33]
Vit E	Peroxidation inhibitor	400-800IU	Endometriosis [34]
NAC	GSH synthesis	1.2g	Ovarian aging [35]
Melatonin	mtROS quencher	3mg	IVF [4]
CoQ10	Electron transport chain support	200-600mg	DOR [35]

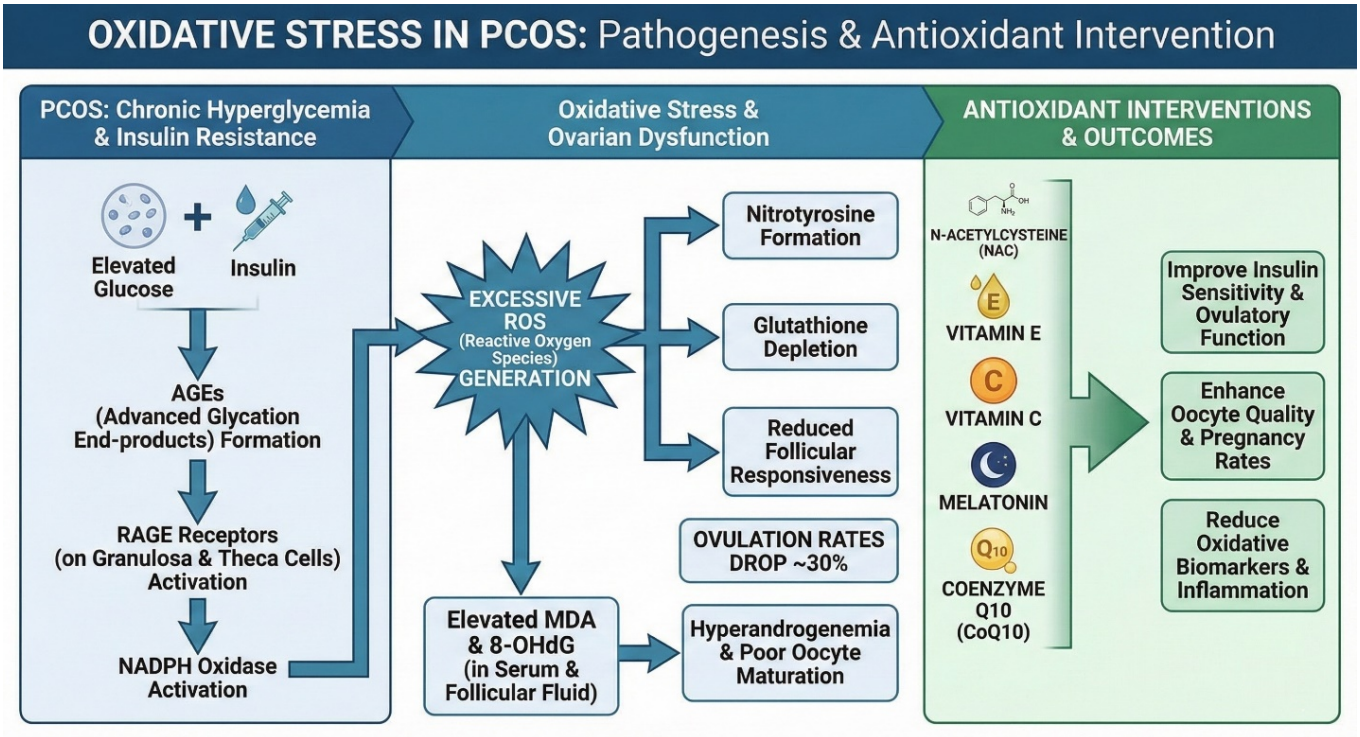

Fig 1: Oxidative stress in PCOS, Pathogenesis & Antioxidant intervention

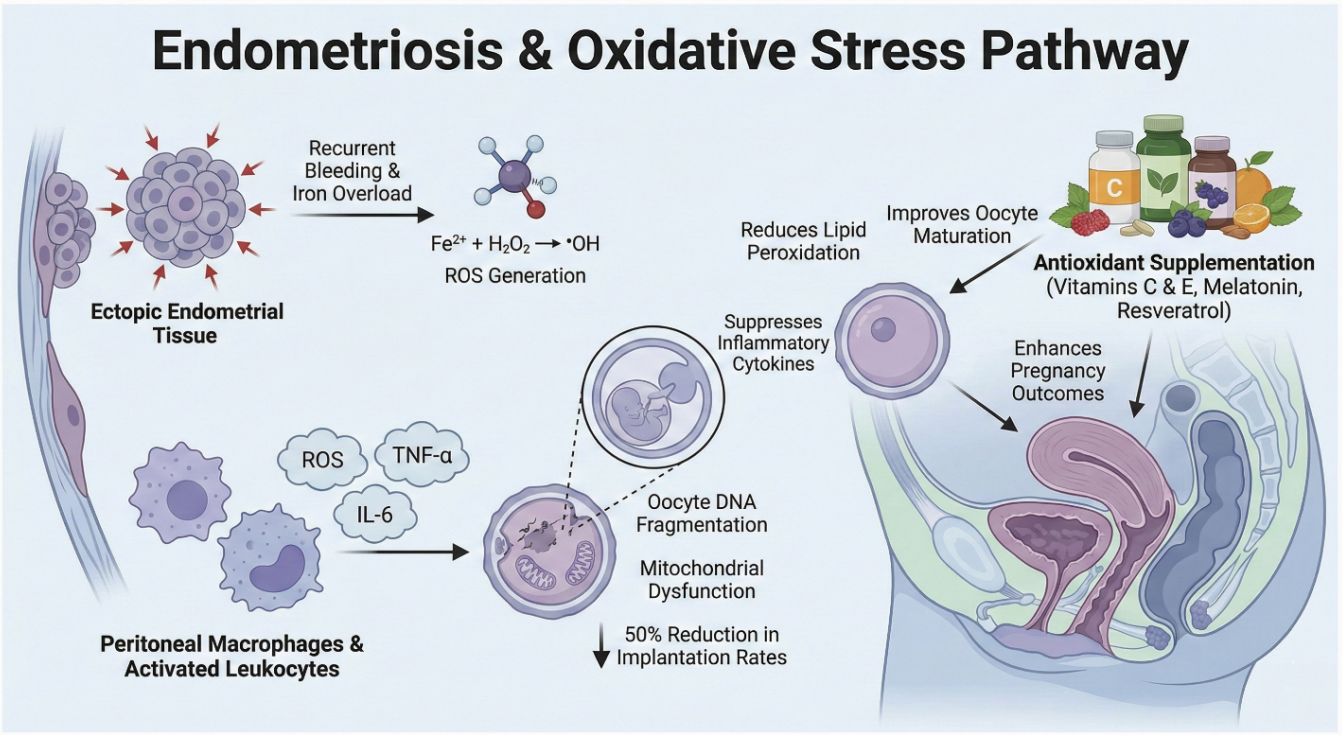

Fig 2: Endometriosis & oxidative pathway

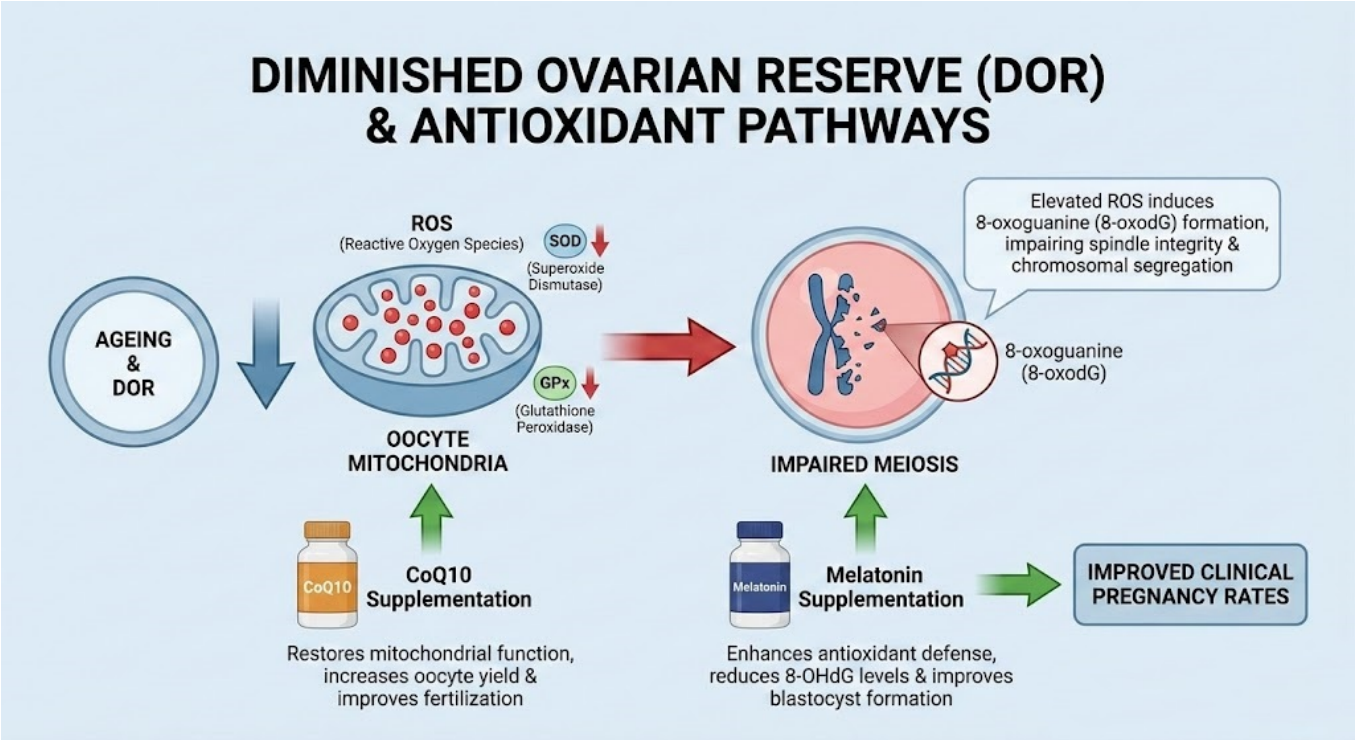

Fig 3: Diminished ovarian reserve & antioxidant pathways

Clinical Evidence from Trials and Meta-Analyses

There is robust clinical evidence supporting the use of antioxidant supplementation in female infertility, with meta-analyses showing significant improvement in ovulation induction, oocyte quality, and reproductive outcomes- especially in PCOS, DOR and ART settings.

The landmark Cochrane systematic review (28 RCTs, n= 3239 women) reported notable gains in live births (OR 1.33, 95% CI) and clinical pregnancy rates (Odds Ratio {OR} 1.52, 95% CI 1.29-1.78), and observed decreases miscarriage (OR 1.13, 95% CI 0.84-1.53) in women receiving antioxidant supplements compared to placebo or no treatment. Subgroup comparison revealed better outcomes with combinations (e.g., vitamin C/E + N-acetylcysteine [NAC]) compare to monotherapy, particularly significant differences (OR ratio increased two folds) in case of unexplained infertility [4]. Further antioxidants regimens primarily NAC (1.2g/day), CoQ10 (200-600mg) increased oocytes recovered (MD +0.98, 95% CI 0.52-1.44), and high-quality embryo formation (MD +0.75, 95% CI 0.32-1.18), and decreased cycle cancellation rates [35]. Fertilization rates also improved, but the live births showed a positive trend without statistical significance. These effects are attributed to ROS quenching and maintenance of meiotic spindle, and enhancement of mtDNA replication (approx. 15-20%) [35]. (Table 2)

Table 2: Comparison of antioxidants and outcome, grade

Author (Study year)	Antioxidants /dose	Primary outcome	Grade
Showell (2020) [4]	Multi (Vit C/E/NAC)	Live birth	Low

Shang (2024) [35]	CoQ10 (600-1200mg)	Oocyte retrieved	Moderate
Panti AA (2018) [33]	Multi	Ovulation rate	High
Boudhadana (2025) [39]	CoQ10 (300mg)	Fertilization rate	High
Kun Peng (2022) [38]	Vit C/E (0.5 to 1g/ 40mmg/600IU)	Mature oocytes	Moderate
De Lingey (2022) [37]	NAC 1.8g	Pregnancy rate	Moderate

Vit C supplementation showed a grater benefit in smokers, reducing approx. 50% DNA adduct formation and improved pregnancy rate. In women of advance maternal age (>38 years) with combination supplementation of CoQ10, melatonin resulted 25% increase in blastocysts formation. However, variation in study design heterogeneity and treatment durations (2-6 months), changes baselines (PCOS vs idiopathic), and antioxidants assessment assay method contributed heterogenicity in outcome [4, 14, 31].

PCOS-Specific Evidence: OS caused by hyperinsulinemia increases follicular malondialdehyde (MDA) levels were doubled compared to healthy controls. A double blind RCT found that multi-antioxidants combination therapy (Vit C 500mg + Vit E 400IU + selenium 200µg) + clomiphene citrate (CC) significantly improved with ovulation rates (78%), to clinical pregnancies (22%), increased total antioxidant capacity by 28%, and decreased menstrual irregularities and MDA levels by 35%. Combined therapy was found to lead to better ovulation and live births. NAC monotherapy (1.8g/day) in 3 RCTs meta-analysis, increased insulin sensitivity, ovulation (RR 1.9), and hirsutism scores [38, 36, 37].

Endometriosis: Peritoneal OS impairs the retrieval of oocytes efficiency. Vit C/E (1g/600IU; 3 months pre-IVF) supplementation for 3 months prior to IVF in a RCT found that decreased follicular 8-OHdG by 42%, increased the number of mature MII oocytes (+1.8/cycle) and improved implantation (28 %). Peritoneal TNF- α IL-6 downregulation with antioxidants, such as resveratrol (1.5g/day), reduced the post operative recurrence of endometriomas [34,38].

ART and IVF Results: In ART settings, exposure to High O_2 concentration during embryo culture increases ROS. Meta-analysis of pretreatment with oxidants showed better ovarian response in poor responders [35]. Melatonin (3mg/night) was shown to penetrate to blood follicle barrier, and significant hacked the oocyte DNA fragments (25% to 12%) and boosted the blastocyst rates. CoQ10 (600mg) supplementation improved mitochondrial membrane, potential fertilization (67%), and clinical pregnancy outcome (34%) [14, 35].

The above clinical studies reinforce the therapeutic potential of antioxidants supplementation as an adjunct in female infertility specially mediated by oxidative stress such as PCOS, endometriosis, DOR and ART. Further clinical findings suggest that the efficacy of antioxidant therapy is influenced by dosage, treatment duration, and combination of regimens.

CONCLUSION

Antioxidant supplementation counters oxidative stress, enhancing ovulation and oocyte quality in female infertility. Evidence supports modest benefits in PCOS, aging, and ART, warranting integration into protocols. Rigorous trials are essential for precision medicine.

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