RBM ONLINE

ELSEVIER

Review

Potential role of green tea catechins in the management of oxidative stress-associated infertility

Shubhadeep Roychoudhury [a,b], ***Ashok Agarwal*** [a,*], ***Gurpriya Virk*** [a], ***Chak-Lam Cho*** [c]

[a] *American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH 44195, USA*
[b] *Department of Life Science and Bioinformatics, Assam University, Silchar 788011, India*
[c] *Department of Surgery, Kwong Wah Hospital, Hong Kong*

Shubhadeep Roychoudhury is an Assistant Professor at the Department of Life Science and Bioinformatics, Assam University, Silchar, India. He completed his PhD in Biotechnology at Slovakia in 2010. He joined the Cleveland Clinic as a Research Fellow in Andrology/Urology under the supervision of Professor Ashok Agarwal in 2015.

KEY MESSAGE
The outstanding antioxidant activity of green tea catechins demonstrated *in vitro* represents its great potential in improving fertility potential in human by alleviation of oxidative stress. Results from in-vivo studies are eagerly awaited.

A B S T R A C T

Reactive oxygen species (ROS) are present in low concentrations in the genital tracts of males and females. Excessive ROS lead to oxidative stress, which damages DNA, lipids and proteins. Such molecular changes result in compromised vitality, increased morphological defects and decreased sperm motility in the male. In the female, oxidative stress interferes with oocyte maturation, and may inhibit in-vitro maturation of the oocyte. Recently, green tea supplementation has been reported to possess properties that may improve the quality of male and female gametes largely due to the ability of catechin polyphenols to quench ROS. Epigallocatechin-3-gallate (EGCG) is considered the most promising bioactive compound in green tea due to its strong antioxidant activity. The unique property of green tea catechins may potentially improve reproductive health and pose an important research area. We present a comprehensive overview on the effects and potential roles of green tea catechins on oxidative stress in male and female reproduction and fertility. In this review, possible mechanisms of action are highlighted to better understand the potential use of green tea catechins in the reduction of oxidative stress and its associated beneficial effects in the clinical setting.

* Corresponding author.
E-mail address: agarwaa@ccf.org (A Agarwal).

http://dx.doi.org/10.1016/j.rbmo.2017.02.006
1472-6483/

Please cite this article in press as: Shubhadeep Roychoudhury, Ashok Agarwal, Gurpriya Virk, Chak-Lam Cho, Potential role of green tea catechins in the management of oxidative stress-associated infertility, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.02.006

Introduction

Reactive oxygen species (ROS) are present in low concentrations in the genital tracts of both males and females under normal physiological circumstances (Guerin et al., 2001; Kwiecien et al., 2014). A delicate balance between reduction and oxidation is required for essential sperm functions including chromatin compaction in the maturation of spermatozoa during epidydimal transit, which leads to capacitation, hyperactivation, acrosome reaction and sperm–oocyte fusion and, ultimately, successful fertilization (Agarwal and Said, 2004; Aitken et al., 1995; de Lamirande and Gagnon, 1993; Guthrie and Welch, 2012; Kothari et al., 2010; Wright et al., 2014). ROS also appear to play a physiological role in oocyte maturation, ovarian steroidogenesis, folliculogenesis, ovulation, luteolysis, implantation, formation of the fluid-filled cavity and blastocyst development (Agarwal et al., 2006a, 2006b; Askoxylaki et al., 2013; Esfandiari et al., 2005; Siristatidis et al., 2015). Interestingly, a certain amount of lipid peroxidation relevant to ROS in follicular fluid is necessary to establish pregnancy in human IVF (Agarwal et al., 2005).

Oxidative stress (OS) is a condition that occurs when there is an imbalance between ROS and a biological system's ability to readily detoxify the reactive intermediates or repair the resulting damage (Hampl et al., 2012; Saalu, 2010). OS usually arises as a consequence of excessive ROS production *in vivo*. Over the years, infertility related to OS has become an area of great concern for clinicians and scientists because continuous formation of ROS throughout the life of an organism leads to cumulative damage, which impairs fertility via programmed deterioration. The deleterious consequences of OS include impairment of semen parameters (Agarwal et al., 2005; Bansal and Bilaspuri, 2010; Pasqualotto et al., 2000), poor fertilization, poor embryonic development (Jana et al., 2010; Oyawoye et al., 2003) and pregnancy loss (Cengiz et al., 2016; Daglar et al., 2016).

Green tea (GT) is a popular drink consumed daily by millions of people globally. Tea is an infusion or a boiling water extract prepared with the leaves of *Camellia sinensis* L. and water. Consumption of GT may prevent diseases because of its antiproliferative, antimutagenic, antioxidant, antibacterial, antiviral and chemopreventive properties (Li et al., 2014a; Rahmani et al., 2015; Schramm, 2013; Yang et al., 2009). Studies suggest that consuming green tea extracts (GTEs) protects the cardiovascular system (Basu and Lucas, 2007), lowers blood glucose and cholesterol levels (Hara, 1994), and provides anti-inflammatory effects (Shapiro et al., 2009). The beneficial effects of GT are attributed to the polyphenolic compounds, particularly the catechins, which make up 30% of the dry weight of GT leaves (Graham, 1992).

Oxidation of organic compounds is catalysed by metals (Sheldon and Kochi, 2016), and GT supplements are capable of acting as antioxidants both *in vivo* and *in vitro* by metal requisition due to the presence of catechin moieties in polyphenol molecules, which possess a high affinity for metal ions. The presence of GT supplements, therefore, may reduce the availability of metal ions acting as the catalyst in the oxidative reaction in a biological system. The findings support the use of GT in maintaining the reproductive health of the male and the female by alleviation of OS (Galleano et al., 2010; Perron and Brumaghim, 2009).

The current evidence in the literature, however, does not support the use of GT catechins as antioxidants in the clinical management of male and female infertility. Therefore, we review the possible beneficial effects of GT supplementation, particularly the catechins, on reproductive health by summarizing the relevant data available from both human and animal experiments. A comprehensive overview of the effects and roles of GT in the management of male and female infertility will be provided. Furthermore, the possible mechanism of action of GT catechins and GTE will be highlighted in an attempt to understand the potential use of GT in the alleviation of OS and its associated effects on fertility in the clinical setting.

ROS and OS

Reactive oxygen species (ROS) is a collective term used to describe oxygen radicals. Recent studies have shown that ROS, generated from various endogenous and exogenous sources, have a tremendous impact on reproduction and fertility (**Figure 1**). Activated leukocytes are one of the important sources of ROS and adversely affect sperm motility, morphology and concentration. They also cause acrosomal damage, hyperactivation, DNA damage, and impair oocyte penetration (Aziz et al., 2004; Lackner et al., 2010; Pasqualotto et al., 2000).

Immature, defective, senescent and apoptotic sperm also produce high levels of ROS and contain docosahexaenoic acid, which is a target of ROS-induced lipoperoxidative damage (Williams and Ford, 2005). OS is also associated with reduced total antioxidant capacity in seminal plasma of infertile men (Roychoudhury et al., 2016), which has a role in the aetiology of impaired sperm functions (Pahune et al., 2013).

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. Oxidative damage to lipids in the oocyte may cause persistently poor oocyte quality after early life exposure to several toxicants (Luderer, 2014). Elevated levels of OS caused a decrease in oocyte numbers leading to a reduction in follicles, and these changes ultimately resulted in sub-fertility (Camlin et al., 2016). Animal studies have further found that OS influences early embryo development (Blondin et al., 1997; de Castro et al., 2016; Harvey et al., 2002) and blocks the development of in-vitro two-cell embryos by modifying the key transcription factors, hence transforming gene expression, eventually resulting in female infertility (González-Fernández et al., 2016; Jana et al., 2010).

Green tea and its bioactive components

The processing of tea leaves modifies the chemical and physiological properties of black tea (fully fermented), oolong tea (semi-fermented) and GT (unfermented) (Beecher et al., 1999; Coimbra et al., 2006). According to high-performance liquid chromatography data, GT leaves contain 26% fibres, 15% proteins, 2–7% lipids, and 5% vitamins and minerals. They also contain secondary metabolites such as pigments (1–2%), polyphenols (30–40%), of which at least 80% are flavonoids, and methylxanthines (3–4%) (Cabrera et al., 2003, 2006; Graham, 1992). The composition varies and depends on factors such as geographical location (climate, soil), agricultural practices (fertilizers, deadheading) and the properties of the plant itself (variety, age of the leaf, and position of the leaf on the harvested shoot) (Cabrera et al., 2006). Catechin polyphenols are believed to be the most important active component in GT. They are secondary metabolites possessing antioxidant activity, which is 20 times higher than that of vitamin C. Catechins have the ability to quench free radical species and chelate transition metals, which helps reduce OS levels (Hijazi

Please cite this article in press as: Shubhadeep Roychoudhury, Ashok Agarwal, Gurpriya Virk, Chak-Lam Cho, Potential role of green tea catechins in the management of oxidative stress-associated infertility, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.02.006