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Review Article

Resveratrol from Red Grapes: An Useful Agent for Oocyte Maturation and Subsequent Embryonic Development

Galeati G* and Spinaci M
Department of Veterinary Medical Sciences (DIMEVET), University of Bologna, Italy

***Corresponding author:** Galeati G, Department of Veterinary Medical Sciences (DIMEVET), University of Bologna, Via Tolara di Sopra, 50, 40064 Ozzano dell'Emilia (BO), Italy

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Abstract

Oxidative stress caused from *in vitro* culture conditions contributes to inadequate oocyte maturation which leads to poor embryo development compared with in *in vivo* produced embryos. Therefore, it is important to protect oocytes and embryos against oxidative stress. One approach is to supplement the culture medium with antioxidant compounds such as resveratrol. Resveratrol (Res) is one of the most important polyphenols found in red wine well known as cardioprotective, anticancer, anti-inflammatory, antioxidant and antiapoptotic.

This review summarizes the effects of Res supplementation on oocyte maturation and embryo development in domestic species. In all species examined (caprine, bovine and porcine) supplementation of culture medium with low levels of Res improves oocyte maturation and blastocyst formation by increasing GSH concentration, decreasing ROS level and reducing apoptosis related gene expression. High concentration of Res decreases nuclear maturation induces apoptosis and is therefore detrimental to the developing embryos.

Keywords: Resveratrol; Oocyte maturation; Embryo development; Domestic species

Abbreviations

GSH: Glutathione; IVM: *In Vitro* Maturation; IVF: *In Vitro* Fertilization; MMP: Mitochondrial Membrane Potential; Res: Resveratrol; ROS: Reactive Oxygen Species; SIRT1: Sirtuin 1

Introduction

The realisation that fruits and vegetables can prevent diseases such as cancer has engendered an intense search for the constituents which may be responsible for these properties. Resveratrol (Res) (3,4,5-trihydroxy-trans-stilbene) is an example of a dietary constituent which has been shown over the last decade to possess a fascinating spectrum of pharmacological properties [1,2]. In recent years, the interest in this molecule has increased exponentially following the major findings that Res exhibits a wide variety of pharmacological properties such as anti-inflammatory, antioxidant, antiproliferative, antiapoptotic, cardioprotective and chemopreventive effect in some cancer models [3].

As a chemical entity, Res is known since the 40s when it was first isolated from the roots of white hellebore and later from Polygonum cupsidatum, a medicinal plant [4]. Res are also present in appreciable amount in a variety of edible fruits including nuts, mulberry, grapes and red wine. From a botanical point of view, Res acts as a phytoalexin, that is a toxic compound produced by a plant in response to a parasitic attack or under stress conditions [5].

Recently, the beneficial effects of Res on mammalian reproduction have drawn increasing attention and it was reported that this antioxidant improves the developmental potential of oocytes and embryo cultured *in vitro*. Under *in vitro* culture condition oocytes and embryos are maintained at higher concentrations of oxygen than in *in vivo* environment, leading to an increased level of Reactive Oxygen Species (ROS). The production of ROS, as superoxide anion, hydroxyl radical, hydrogen peroxide and lipid peroxides, is a normal process that occurs in the cell when there is a deviation of electrons to oxygen during electron transfer reactions in the mitochondrial respiratory chain and in other intracellular electron transfer systems [6].

In vivo, the damaging effects of oxygen radicals are usually prevented or limited by endogenous antioxidants (or scavengers of free radicals). These include enzymes such as superoxide dismutase, catalase and selenium-dependent glutathione peroxidase as well as lipid- and water-soluble antioxidants such as Vitamins C, E and uric acid [7].

Handful number of chemical substances has been supplemented in the media to enhance the developmental potency of *in vitro* matured oocytes. Compounds with antioxidative properties such as β-mercatoethanol, cysteine, cysteamine, that augment intracellular glutathione level, have been added in *In Vitro* Maturation (IVM) [8-10]. Recently, supplementation of Res has been found to have beneficial impact on IVM and embryonic development in many species.

The objective of this review is to summarize the effects of Res supplementation on oocyte maturation and embryos development in domestic species.

Caprine

Mukherjee et al. [11] challenged five different concentrations of Res (0.1, 0.25, 0.5, 2.0 and 5.0 μM) in *in vitro* maturation procedure and demonstrated that this phytoalexin, at the concentrations of

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0.25 and 0.5 μM, positively affects goat oocyte maturation and the subsequent embryonic development. However, maturation rate decreased and morulae and blastocyst development were significantly reduced in 5.0 μM resveratrol-treated group demonstrating that too high concentrations can have a detrimental impact.

The positive effect of Res seems to be due to the decreased ROS level recorded in mature oocytes after IVM in presence of 0.1 - 2 μM Res compared to control and 5.0 μM groups. This effect is probably the consequence of the increased intracellular GSH level observed when Res was added in the IVM media at the low concentrations (0.25, 0.5 and 2 μM).

The increased GSH level induced by the addition of low concentration of Res during IVM seems to promote cytoplasmic maturation of goat oocytes contributing to the higher embryonic development following parthenogenesis and cloning.

Moreover the presence of the Res in the maturation medium has been suggested to be advantageous for cumulus cells to maintain their viability [11]; it is well known that these cells extort cross talking with the oocyte, a fundamental role in the regulation of female gamete development and in promoting meiotic maturation [12].

It is likely that overall positive impact on maturation and embryonic development exerted by Res is also due to a modulation of apoptosis related genes: the presence of Res in the IVM medium induced a decrease of mRNA expression of proapoptotic gene, Bax in mature oocytes, cumulus cells and partenogenetic blastocysts [11]. Moreover Res, at low concentrations, during IVM, through the creation of a beneficial microenvironment within oocytes, seems to positively modulate gene expression in cloned blastocysts; in fact, an increased transcript levels of a set of genes involved In pre- and postnatal Growth (IGF-1), metabolism (Glut1), pluripotency (Oct4), lineage determination and cavitations (Stat3), gap junction, growth arrest (CHOP-10), oxidative stress (MnSOD), and DNA Methylation (DNMT) were recorded.

Bovine

The beneficial effect of Res at low concentrations on bovine oocyte maturation and subsequent embryonic development after *in vitro* fertilization, has been recently described by different authors [13-15].

Wang et al. [13] demonstrated that the addition of Res (0.1 and 1 μM) to the *in vitro* maturation medium exerts a positive effect on bovine oocyte nuclear maturation, as it significantly promotes polar body emission during oocyte maturation. This positive effect could be due to the increased progesterone secretion that, in turn, enhances the expression of the Mos/ MEK/p42 MAP kinase cascade genes [13].

As demonstrated for goat oocytes, Res has been found to reduce the intracellular ROS level and to increase GSH level in mature oocytes enhancing the quality of oocytes that consequently lead to an improved blastocysts rate, hatching blastocyst rate, and number of blastocyst cells after oocyte maturation and fertilization [13]. The better quality of *in vitro* produced bovine embryos is also demonstrated by the increased resistance to damage induced by cryopreservation even if no positive effect on blastocyst rates and allocation of cells into inner cell mass and trophectoderm lineages was observed [15,16].

Moreover, Res enhances Sirtuin 1 (SIRT1) activity which was identified by Wang et al. [13] in cumulus cells for the first time. SIRT1 belongs to the sirtuin family of class III Nicotinamide Adenine Dinucleotide (NAD+)-dependent protein deacetylases. SIRT1 is critical to cell survival owing to its interactions with a number of factors, including FOXO3A, a regulator of organismal longevity, p53, a cell cycle regulator, and PPARGC1, a regulator of mitochondrial biogenesis and function [17,18]. In addition, Res protects mitochondrial functions from ischemia-induced oxygen radicals through up-regulation of SIRT1 [19].

Takeo et al. [14] showed that supplementation of maturation medium for bovine oocytes with Res (2 μM) enhanced the protein expression of SIRT1 and improved *in vitro* fertilization outcomes by increasing the rate of normal fertilization and decreasing the rate of abnormal fertilization. Specifically, Res increased ATP content, Mitochondrial Membrane Potential (MMP) and induced zona hardening, improving the distribution and exocytosis of cortical granules after *in vitro* fertilization. In addition, similar positive effects were confirmed when the concentration of Res was increased to 20 μM during bovine IVM [20].

Different results have been reported by Pocar et al. [21,22] who showed that, in their culture condition, concentrations of 20 and 40 μM Res during bovine IVM significantly reduced the percentage of oocytes that reached the MII stage by decreasing the level of CYP1A1 (cytochrome P450 1A1) expression in COCS.

Porcine

Lee et al. [23] observed, for the first time, that treatment of pig embryos with 0.5 μM Res enhanced blastocyst formation and improved embryo quality in terms of total cell numbers of parthenogenetic and IVF blastocysts. The treatment also resulted in decreased expression of Bcl-2 and Caspase-3 genes.

After this first work, Kwak et al. [24] demonstrated that treatment of porcine oocytes with 2 μM Res during IVM was advantageous for cytoplasmic maturation by reducing intracellular ROS levels, increasing GSH concentrations, and by significantly decreasing apoptosis-related gene expression (*Bax, Bak*, and *Caspase-3)* in mature oocytes and cumulus cells. Furthermore, 2 μM Res treated oocytes showed a better developmental competence, as an improvement in cleavage rate, blastocysts formation and blastomere viability in parthenogenetic and IVF derived embryos [24].

However, when Res concentration during IVM was increased to 10 μM a negative effect on nuclear maturation rates and down regulated apoptosis-related genes in mature oocytes, cumulus cells, and even in IVF-derived blastocysts was observed [24].

Consistent with previous report on bovine oocytes, Sato et al. [25] demonstrated that Res enhances ATP content and MMP in porcine oocytes. Recently Giaretta et al. [26] demonstrated that 2 μM Res during IVM and vitrification-warming phases improves the resistance of porcine oocytes to cryopreservation-induced damage.

Conclusion

In conclusion, the overall results demonstrate that supplementation of culture medium with low levels of Res improves oocyte maturation and blastocysts formation and reduces apoptosis

related gene expression. It has to be taken in mind that species-specific differences exist in the oocyte maturation and embryonic development with different Res concentrations. This may be due to the species-to-species variation in sensitivity of oocytes to Res and molecular interplay during these procedures. Therefore, the dose dependent effect of Res on oocytes and embryos development should be evaluated specifically in each species without borrowing the results among species.

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