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REVIEW

Oxidative Stress and Role of Natural Plant Derived Antioxidants in Animal Reproduction

ZHONG Rong-zhen and ZHOU Dao-wei

Northeast Institute of Geography and Agroecology, Chinese Academy of Sciences, Changchun 130012, P.R.China

Abstract

The experimental knowledge on the role of oxidative stress, and beneficial and detrimental effects of plant derived antioxidants in male and female animal reproduction are reviewed in this article. Free radical-induced oxidative stress in animal reproduction causes great loss to livestock industry. Antioxidant therapy has been implicated to be effective in preventing diseases resulted from oxidative stress. Considering the advantages of lower side effects of natural antioxidants than those of synthetic antioxidants, plants or their extracts have been extensively utilized in animals. Although many advances have been gained on application of plant derived antioxidants in alleviating oxidative stress, debatable issues still exist. Because many opposite effects were observed even using plant extracts containing similar bioactive substances in the same animal species. Therefore, plant derived antioxidants, like free radicals, are "double-edged swords" in animal reproduction, representing that they may exhibit beneficial or detrimental effects in animal reproduction, including spermatogenesis, semen functions, estrous cycles, ovulation, ovary functions, endometrium, embryo development, and pregnancy. Besides dose-dependent manner as an explanation of plant extracts' dual function, future studies are needed to investigate the mechanism of double-edged actions of plant derived antioxidants in different animal reproduction systems.

Key words: oxidative stress, plant extract, antioxidant, double-edged effect, animal reproduction

INTRODUCTION

Free radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), are normal pro-oxidant molecules in aerobic metabolism. The three major types of ROS are superoxide ($O_2^{\bar{\cdot}}$), hydrogen peroxide (H_2O_2), and hydroxyl ($OH^{\cdot}$), while nitric oxide (NO) is a main type of RNS (Dong *et al*. 2001). The production of free radicals is a double-edged sword in reproduction system (Silva *et al*. 2010). Physiological concentrations of free radicals are required to mediate normal processes of capacitation, hyperactivation, acrosome reaction, fertilization, and embryo development (Rhee 2006; Desai *et al*. 2009; Gonçalves *et al*. 2010). However, above-physiological levels of free radicals can result in oxidative stress which lead to sperm or ovum damage, deformity, endometriosis, pre-eclampsia, miscarriage, intrauterine growth retardation, and infertility (Agarwal *et al*. 2005; Bansal and Bilaspuri 2010).

Under normal physiological conditions, living organisms possess a wide range of enzymatic antioxidants, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) (Szczepanska *et al*. 2003; Celino *et al*. 2011), and non-enzymatic antioxidants, including glutathione (Gul *et al*. 2000), uric acid, and coenzyme Q to scavenge excess free radicals

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ZHONG Rong-zhen, E-mail: zhongrongzhen@neigae.ac.cn; Correspondence ZHOU Dao-wei, Tel: +86-431-85542231, Fax: +86-431-85542206, E-mail: zhoudaowei@neigae.ac.cn

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(Agarwal *et al*. 2003). But under pathophysiological conditions, endogenous antioxidants may not counteract excess free radicals. Hence, there is a continuous demand for exogenous antioxidant supplementation (Lykkesfeldt and Svendsed 2007). Nevertheless, study reported that exogenous antioxidants are also a double-edged sword, highlighting that antioxidants at physiological levels are generally safe, while higher levels are detrimental in cellular redox state (Bouayed and Bohn 2010). Moreover, this is the case in animal reproduction.

Many natural plants and their seed, leaf, or root extracts which are rich in polyphenols, flavonoids, carotens, gallic acid, tannins, and essential oil as antioxidants have been recognized to be better than synthetic antioxidants due to lower cytotoxicity and residue (Gupta and Sharma 2006; Nagulendran *et al*. 2007; Sen *et al*. 2010). Most literatures focused on the relationship among free radicals, oxidative stress, and the role of antioxidants in human reproduction (Chatterjee and Chatterjee 2009), but few articles attempted to review these aspects in animal reproduction. Therefore, this review addressed the role of oxidative stress, and double-edged effects and possible mechanism of actions of plant derived antioxidants in male and female animal reproduction.

OXIDATIVE STRESS IN MALE ANIMAL REPRODUCTION

Physiological levels of ROS play important roles in male animal reproduction system (Agarwal *et al*. 2008). Moderately elevated concentrations of ROS induce sperm immobilization *via* depletion of intracellular ATP and subsequent decrease in the phosphorylation of axonemal, but over physiological levels of ROS induce lipid peroxidation and result in sperm cell death (Misro *et al*. 2004). Spermatozoa membranes are vulnerable to free radical-induced damage because they are not only rich in polyunsaturated fatty acids (Maneesh and Jayalekshmi 2006), but also contains low concentration of antioxidant enzymes (Sawyer *et al*. 2001; Saleh and Agarwal 2002; Maneesh and Jayalekshmi 2006). Furthermore, spermatogenesis in testes is an extremely active replicative process to generate sperm at a high rate. This high rate of cell division is accompanied with high production of free radicals due to high amounts of mitochondrial oxygen consumption by germinal epithelium (Aitken and Roman 2008). Hence, an imbalance of free radical generation and detoxification cause oxidative stress and damage to cellular lipids, proteins, amino acids, sugars, nucleic acids, and midpieces in sperm and testicular tissues which lead to subsequent poor semen qualities. Poor semen qualities account for more than 80% failure of fertilization and embryogenesis, miscarriage, and infertility in male animals (Gadea and Matas 2000; Rabbani *et al*. 2010; Enciso *et al*. 2011).

Besides normal generation *via* spermatogenesis *in vivo*, ROS are also generated during *in vitro* storage, such as semen cryopreservation, which is an important procedure in livestock industry, especially for cattle, sheep, and goats (Bucak *et al*. 2008, 2009). During semen collection and freezing/thawing procedures, semen is exposed to cold shock and atmospheric oxygen, which in turn increases the susceptibility to lipid peroxidation (Bucak *et al*. 2011). In addition, many environmental factors, such as extremely high ambient temperature, chemicals, medicines, and other toxins, induce ROS production in reproduction system. Das *et al*. (2002) found that cyclophosphamide increased testicular lipid peroxidation levels and decreased the activity of catalase in rats. The detrimental effects of heat stress on reproduction system of rats (Ikeda *et al*. 1999), bulls (Nichi *et al*. 2006), rams (Marai *et al*. 2009), and chickens (Ayo *et al*. 2011) have been confirmed. Furthermore, it has ascertained that oxidative stress is a possible cause of the heat stress (Hanafi *et al*. 2010).

OXIDATIVE STRESS IN FEMALE ANIMAL REPRODUCTION

Free radicals are generated *via* various ways in female reproductive system *in vivo* and *in vitro* cultures. ROS may be generated directly from oocytes and embryo or from their surroundings, which in turn mediate the processes of embryonic devolvement (Guérin *et al*. 2001). Besides ROS production, RNS are involved in oocyte meiotic maturation of rats (Sela-Abramovich *et al*. 2008), pigs (Chmelíková *et al*. 2009), cattle

(Matta *et al*. 2009), and sheep (Amale *et al*. 2011). Free radicals exert dual roles in female reproduction system, especially for ovulation (Shkolnik *et al*. 2011).

Besides normal generation of free radicals *in vivo*, many *in vitro* factors cause oxidative stress and damage to reproduction system. For examples, higher ambient temperature and various toxins are two main ways inducing oxidative stress. The responses of oocytes or embryos to heat shock include the alternations of membrane characteristic, configuration of the chromatin, and meiotic spindle (Ju 2005). The embryonic and larval stages of animals are generally the most sensitive stages of the life cycle to heavy metals and other toxins (Daka 2002). A tight relationship between high blood and milk lead concentrations and ovarian dysfunction in farm animals has been reported (Ahmed *et al*. 2010), and oxidative stress has been implicated in the pathogenesis of lead- and cadmium-induced reproductive diseases in animals (Patra *et al*. 2011).

Similar to male animals, free radicals exert dual functions in female reproductive system with involvement in the pathophsiology of preeclampsia (Buhimschi *et al*. 1998), endometriosis (Uchiide *et al*. 2002; Gupta *et al*. 2006), hydatidiform mole, birth defects (Williams 2010), infertility (Celi 2011), and abortion. Vandaele *et al*. (2010) reported that short-term exposure to H_2O_2 during oocyte maturation improved bovine embryo development. However, excess free radicals caused adverse effects. Moreover, studies in cattle revealed that early stages of embryonic development, such as two-cell and four-cell stage, are more sensitive to free radical-induced stress than oocytes, morulas, and blastocysts because of more active mitochondria (Tarazona *et al*. 2006; Hansen *et al*. 2007).

EXOGENOUS ANTIOXIDANTS IN ANIMAL REPRODUCTION

Exogenous antioxidants play a key role in the delicate equilibrium between oxidation and antioxidation, but they are double-edged swords in cellular redox state of living organisms. The prooxidant or antioxidant activities intimately depend on their concentrations. In most circumstances, physiological doses of antioxidants exert beneficial effects; while overdoses of them exhibit detrimental effects (Kawanishi *et al*. 2005; Bouayed and Bohn 2010).

Though some synthetic antioxidants, such as vitamin C and vitamin E, have been used to protect ovum and embryo against oxidative stress, disputes still exist indeed because a series of adverse effects in animal reproduction were observed (Nayyar and Jindal 2010). Taking antioxidant vitamins. For example, Olson and Seidel (2000) reported that 100 µmol L^{-1} vitamin E markedly improved bovine blastocyst development. Whereas Sudano *et al*. (2010) found that the addition of 200 µmol L^{-1} vitamin E had a deleterious effect on bovine embryo development *in vitro*. Both above studies found that lower than 50 µmol L^{-1} vitamin C lacked efficiency to improve embryo production. However, Wang *et al*. (2002) reported that 50 µmol L^{-1} vitamin C was effective in improving mouse blastocyst development rate *in vitro*, but 400 to 500 µmol L^{-1} vitamin C significantly retarded the rates of embryo formation and development (Natarajan *et al*. 2010).

Recently, the alternative strategy of using natural plants or their extracts as antioxidants in animals has been confirmed to be effective and utilized extensively. The most effective constituents responsible for antioxidative properties of plants are phenolic compounds, including flavonoids, hydrolysable tannins, phenolic ads, and pholoc terpense (Gupta and Sharma 2006; Ogunlesi *et al*. 2009; Carlsen *et al*. 2010). The antioxidant activities of phenolic compounds are due to their structure and particularly ability to donate a hydrogen ion to the peroxy radical generated as a result of lipid peroxidation (Kashima 1999; Bisby *et al*. 2008).

NATURAL PLANT DERIVED ANTIOXIDANTS IN MALE ANIMAL REPRODUCTION

To evaluate reproduction status of male animals, many factors must be considered, such as spermatogenesis, semen functions, sperm quality, and fertility. Spermatogenesis depends on intratesticular and extratesticular hormonal regulatory processes and functions of the intertubular microvasculature (Holstein *et al*. 2003). Semen parameters such as sperm count and concentration, viability, mobility, and morphology are indicators to evaluate semen functions (Huynh *et al*. 2000; Rodriguez-Martinez 2003, 2006). Infertility is not only a major public health problem in humans, but also the case in animals due to extensive feeding system and application of synthetic feed additives.

Oxidative stress is a main underlying cause which can interfere with spermatogenesis, reduce sperm quality and production, and even cause infertility (Boonsorn *et al*. 2010). Because elevated ROS generation causes damage to the spermatozona DNA, results in increased apoptosis of cells, and therefore, leads to a low fertility rate (Kaur and Bansal 2003). The application of exogenous plant derived antioxidant is likely to improve health status of male animals (Agarwal and Prabakaran 2005; Nantia *et al*. 2009). Numbers of flavonoid-containing plants are known to have antioxidant, androgenic, and anti-infertility activities and have been extensively used against animal reproductive diseases (Middleton *et al*. 2000; Dobrzyñska *et al*. 2004; Purdy *et al*. 2004). In addition to natural herbaceous plants, some fruit and vegetable extracts with antioxidant properties display beneficial effects in animal reproduction system. Nevertheless, some plants, despite containing antioxidant substances, display detrimental effects and therefore cause defects and reproductive failure in male animals (Knight and Walter 2004). The dose-dependent manner may explain such dual functions (Na and Surh 2008; Moskaug *et al*. 2005). Beneficial and detrimental effects of plants, fruits, vegetables or their extracts in male animal reproduction are presented in Tables 1 and 2, respectively.

In addition to above *in vivo* processes, semen cryopreservation *in vitro* is an important procedure which allows specific advantages to livestock industry. Freezing/thawing procedure of sperm is routinely performed in ruminants breeding industries for artificial insemination (Bucak *et al*. 2008). High ROS production in these procedures induces oxidative stress which in turn causes low quality of seminal material or death of sperm cells, which becomes a major obstacle of successful cryopreservation (Janice *et al*. 2000; Janice *et al*. 2000). Study showed that the conception rates and percentage of fertilized ova with frozen-thawed ram semen were approximately 20% less than that with fresh semen (Maxwell *et al*. 1993). Storey *et al*. (1998) demonstrated that *in vitro* fertilization rates with cryopreservation epididymal mouse sperm were, at best, 62% that of unfrozen controls. To overcome these disadvantages, antioxidant treatment may be a feasible strategy to improve cryopreservation techniques (Anghel *et al*. 2010).

Rhodiola sacra aqueous extract from *Rhodiola rosea* (Crassulaceae) roots, a genus of Chinese herb, has been used as an antioxidant (Ohsugi *et al*. 1999). Zhao *et al*. (2009) indicated that *R. sacra* aqueous extract improved biochemical and sperm characteristics in cryopreserved boar sperm. Rosemary (*Rosmarinus officinalis*) is a perennial herb with antioxidant properties due to bioactive substances, such as diterpenes, triterpenes, flavonoids, and polyphenols, as well as sesquiterpenes (Samotyja and Matecka 2010). Malo *et al*. (2011a) reported that rosemary extract supplementation in freezing medium improved boar sperm mobility and fertility after cryopreservation. *Ferula hermonis* is a wonderful antioxidant, aphrodisiac herb for both sexes (Hanafi *et al*. 2010). Malo *et al*. (2011b) demonstrated that *F. hermonis* extract added in freezing extender increased sperm mobility and viability and decreased lipoxidation during boar sperm cryopreservation. Trehalose is seaweed extract known to protect the sperm membrane structure against oxidative and cold shock damage during the freezing/thawing process. Trehalose supplementation in freezing medium could improve sperm quality of rams (Bucak *et al*. 2007), bovine (Hu *et al*. 2010), and rabbit (Reddy *et al*. 2010).

NATURAL PLANT DERIVED ANTIOXIDANTS IN FEMALE ANIMAL REPRODUCTION

To evaluate reproduction status of female animals, many factors must be considered, such as estrous cycle, ovary functions and ovulation, embryo development, pregnancy and fetal development. The estrous cycle involves many histological, physiological, morphological, and biochemical changes within the ovary. Any imbalance between oxidants and antioxidants in these changes leads to dysfunctions of the ovary and irregular estrous cycle (Gupta *et al*. 2011). Ovulation

Table 1 Beneficial effect of plants or their extracts in male and female animal reproduction[1)]

Plant name	Part used	Form used	Bioactive substances	Dose used	Biological activity reported	Physiological functions	Animals tested	References
Dana racemosa	Whole plant	Whole plant powder	Flavonoids and vitamins	200 and 400 mg kg^{-1} d^{-1} of diet	Antioxidant, aphrodisiac, and antinociceptive activities	Increase sperm mobility and viability	Male rat	Khaki et al. 2009a
Curculigo orchioides	Rhizome	Ethanolic extract	Alkaloids, phenols, tannins, saponins, and steroids	100 and 200 mg kg^{-1} of diet	Antioxidant and aphrodisiac activities	Improve penile erection, mating performance, mount frequency, and mount latency	Male rat	Thakur *et al*. 2012
Daucus carota	Seed	Ethanolic extract	Volatile oils, steroids, tannins, flavonoids, and caroten	200 and 400 mg kg^{-1} of diet	Androgenic and antioxidant activities	Elevate testosterone level	Male rat	Nouri *et al*. 2009
Zingiber officinale	Rhizome	Aqueous extract	Gingerols, shogaols, zingerone, and gingerols	500 and 1 000 mg kg^{-1} body weight	Antioxidant and androgenic activities	Increase sperm counts, viability, and mobility	Male rat	Morakinyo *et al*. 2008
Zingiber officinale	Rhizome	Rhizome powder	Volatile oils, gingerols, shogaols, zingerone, and gingerols	50 and 100 mg kg^{-1} d^{-1} of diet	Antioxidant and androgenic activities	Increase sperm percentage, viability, motility and serum total testosterones	Male rat	Khaki *et al*. 2009b
Lactuca sativa; *Petroselinum hortense*; *Bacopa monniera*	Leaf	Ethanolic extract		40 mg kg^{-1} of diet	Antioxidant activity	Protect testes and epididymis	Male mouse	Patil *et al*. 2009
Lannea acida	Stem bark	Methanolic		50, 100, 200, and 400 mg kg^{-1} of diet	Anti-infertility activity	Protect morphology of testis and decrease spermatozoa abnormality	Male rat	Ahmed *et al*. 2010
Withania somnifera	Whole plant	Whole plant powder	Alkaloids and vitanolids	6.25% of diet	Antioxidant activity	Regulate serum progesterone and FSH levels	Male rat	Kiasalari *et al*. 2009
Lepidium meyenii Walp	Hypocotyls	Aqueous extract		0.01-5 g kg^{-1} of diet	Fertility-enhancing activity	Improve testicular functions and sperm mobility	Male rat	Chung *et al*. 2005
Hylocereus co-staricensis	Flesh	Ethanolic extract	Ascorbic acid, betacyanin, and polyphenols	250, 500, and 1 000 mg kg^{-1} body weight	Antioxidant and anti-proliferative properties	Increase sperm count, sperm viability, and its production rate	Male mouse	Aziz and Noor 2010
Citrus sinesis fruit	Peel	Ethanolic extract	Flavonoids, limonoids, and carotenoids	400 and 600 mg kg^{-1} body weight	Antioxidant activity	Enhance sperm healthy parameters	Male rat	Khaki *et al*. 2011
Kigelia africana fruit	Fruit powder	Methanolic extract	Alkaloids, flavonoids, tannins, cardiac glycosides, cyanogenic glycosides, anthraquinone glycoside, saponins, and antho-cyanosides	100 and 500 mg kg^{-1} of daily	Antioxidant activity	Enhance seminal parameters, increase glutathione and decrease malondiadehyde in sperm	Male rat	Azu *et al*. 2010
Raphanus sativus	Seed	Seed powder		17% of diet	Free radicals scavenging activity	Improve semen characteristic and nutritional performance	Male rabbit	El-Nattat and El-Kady 2007
Momordica charantia	Seed	Methanolic extract	Polyphenols, triterpenes, proteins, and steroids	25 mg 100 g^{-1} body weight	Antioxidant activity	Increase estrous cycle	Female rat	Ifeanyi *et al*. 2011
Asparagus racemosus	Root	Root powder	Phenol and flavonoid	100 and 200 mg kg^{-1} body weight	Antioxidant activity	Reduce first postpartum estrus interval, service period, and rate of uterine involution	Female cow	Kumar *et al*. 2011
Camellia sinensis	Leaf	Commercially provided	Polyphenols and carechin	100 mg kg^{-1} body weight	Antioxidant activity	Increase ovian follicular reserve and prolonge ovarian lifespan	Female rat	Chen *et al*. 2010
Matricaria chamomilla	Flower	Ethanolic extract	Volatile oil, sesquiterpene lactones, and phenols	25, 50, and 70 mg kg^{-1} body weight	Anti-inflammatory, antioxidant, antihepatotoxic, and antiviral activities	Induce recovery from polycystic ovary syndrome and increase dominant follicles	Female rat	Farideh *et al*. 2010
Ferula hermonis	Root	Aqueous extract	Polyphenols	0.025 mL 100 g^{-1} body weight	Antioxidant and aphrodisiac activities	Reduce heat stress in reproduction	Female rat	Hanafi *et al*. 2010
Yucca schidigera	Whole plant	Plant powder	Saponins	60 mg kg^{-1} of diet	Immunomodulating and antioxidant activities	Improve thermoregulatory and survival abilities	Female piglet	Herpin *et al*. 2004

[1)] The blank means no information was mentioned by references. The same as below.

Table 2 Detrimental effect of plants or their extracts in male and female animal reproduction

Plant name	Part used	Form used	Bioactive substances	Dose used	Biological activity reported	Physiological functions	Animals tested	References
Rives hypocrateriformis	Whole plant	Ethanolic extract	Steroids	200 and 400 mg kg^{-1} body weight	Antifertility and antiovulatory activities	Induce irregular estrous cycle	Female rat	Shivalingappa *et al.* 2002
Ruellia preaetermissa	Leaf	Mixture extracted by n-hexane, chloroform, ethyl acetate, and methanol	Flavonoids aglycons, glycosides, and triterpens	200 mg kg^{-1} body weight	Antifertility and antiovulatory activities	Decrease ovulation and increase uterine wall	Female rat	Salah and Wagner 2009
Coleus barbatus	Leaf	Hydroalcoholic extract		880 mg kg^{-1} d^{-1}	Contraceptive and abortive activities	Delay fetal development and implantation effect	Female rat	Almeida and Lemonica 2000
Camellia sinensis	Leaf	Commercially provided	Epigallocatechin gallate, epicatechin gallate, epigallocatechin, and epicatechin	25 μmol L^{-1}	Antioxidant activity	Reduce the rate of blastocyst formation	Bovine oocytes *in vitro*	Wang *et al.* 2007
Gossypium hirsutum	Seed		Gossypol	20 and 40 mg kg^{-1} body weight	Antispermatogenic and contraceptive activities	Affect oestrous cycle and ovulation patterns	Female rat	Akinola *et al.* 2006
Bambusa vulgaris	Leaf	Aqueous extract	Alkaloids, tannins, phenolics, glycosides, saponins, flavonoids, and anthraquinones	250 and 500 mg kg^{-1} body weight	Abortifacient activity	Decrease the number of liver fetus and survival rate of fetus	Female rabbit	Yakubu and Bukoye 2009
Areca catechu	Nut	Ethanolic extract	Tannins, gallic acids, oily matter, gum, and alkaloids	100 and 300 mg kg^{-1} diet	Antiovulatory and abortifacient activities	Decrease estrus duration, metestrus phase, and ovarian weight	Female rat	Shrestha *et al.* 2010

is controlled by multiple inputs, including endocrine hormones, immune responses, and metabolic signals (Schoenfelder and Einspanier 2003). Mammalian oocytes develop within follicles in the ovary, so the health status of ovary affect nutrient levels reaching the oocytes, and intrafollicular conditions may affect oocyte maturation, fertility, and embryo development (Gilchrist and Thompson 2007; Clark and Stokes 2011). Endometritis, which can be present in herd from 16 up to 60%, is a common disease in cows. What is worse, endometritis are always ignored in animals. In summary, disorders in ovary and uterus will subsequently result in failure in pregnancy, embryo, and fetal development.

Oxidative stress is an underlying reason of irregular estrous cycle (Martins *et al*. 2011), polycystic ovary syndrome (Wong *et al*. 2010), endometritis (Bedaiwy *et al*. 2002; Lambrinoudaki *et al*. 2009), infertility (Fleischer *et al*. 2001), pregnancy failure (Hansen 2002; Harvey *et al*. 2002), and embryo development. Increased antioxidant status of the reproductive tract may improve competence of oocyte or embryo development (Cerri *et al*. 2009), pregnancy and fetal development (Volpato *et al*. 2008).

In the meantime, considerable livestock losses occur annually as the results of toxic plants containing antioxidant compounds that cause embryonic death, abortion, and fetal abnormalities. The plant toxin readily cross the placenta at a high dose and be present at a specific time in gestation to exert its effect on the developing fetus (Wilson 1977). Several potentially toxin antioxidant compounds-containing plants, such as containing tannins, steroids, terpenoids, saponins, and flavones, are documented earlier and have been used as abortifacient in animals (James *et al*. 1992). An infertility syndrome of sheep, first described in western Australia, is recognized to be caused by ingestion of certain species of clover containing the phytoestrogen isoflavonoid formononetin (Bennetts *et al*. 1946). Beneficial and detrimental effects of plants, fruits, vegetables or their extracts in female animal reproduction are listed in Tables 1 and 2, respectively.

It is worth noting that *in vitro* embryo production represents a feasible way to increase gamete use from animals with high zootechnical value. So the optimal step of embryo production *in vitro* becomes critical to obtain high quality embryos for successful pregnancy and healthy offspring (Blanco *et al*. 2011). Among many factors affected the embryo development *in vitro*, the concentration of oxygen in culture medium is critical because oocyte or embryo culture *in vitro* results in higher oxygen concentrations than *in vivo* environments. On the other hand, the embryonic physiological antioxidants production is not enough to prevent oxidative stress during *in vitro* culture (Ali *et al*. 2003). A study indicated that higher concentrations of ROS over 20% in culture medium exhibited harmful effects to cattle embryonic development due to oxidative stress (Takahashi *et al*. 2000); however, lower or physiological levels of ROS play a positive role during embryo development. Thus, optimal dose of exogenous antioxidant is a key point to successful *in vitro* embryo development.

POTENTIAL MECHANISM OF DOUBLE-EDGED ACTIONS OF PLANT DERIVED ANTIOXIDANTS

Though the exact mechanisms of double-edged actions of plant derived antioxidants in animal reproduction system are unclear, four possible reasons may explain them. The first main reason is dose-dependent manner. The second underlying reason may be attributed to that the individual isolated compounds lose the chances of synergistic interactions with other substances (Zielinska *et al*. 2007; Bouayed and Bohn 2010). The third reason of the same antioxidative substances displaying slightly different pharmacological efficiency may be attributed to plant characteristic and animal species tested. For instance, the toxicity appears to be quite variable, with animal susceptibility being dependent on the quantity and type of plant extracts. Snakeweed contains steroids, terpenoids, saponins and is referred as teratogens. Cattle on a good plane of nutrition can consume up to 30% dried snakeweed without apparent detrimental effect; however, the fresh and to a lesser extent the dried snakeweed may cause abortions in cattle, sheep, and goats at any stage of gestation (Martinez *et al*. 1993). The last possible reason may be due to that they may have different chemical structures, for instance, the pharmacological function of phenolic compounds with different positions of hydroxyl groups attached to the benzene rings may vary. In this regards, further studies are needed to study the characteristic of individual antioxidants and the synergistic reactions with other nutrients in plants or animals' diets.

FUTURE TREND

The balance between oxidation and antioxidant is critical in maintaining healthy reproduction system of animals. Although many advances are being made in the field of plant derived antioxidant therapies, the data are still debatable and the molecular mechanisms are not fully understood yet. Therefore, two important issues need to be solved in the future.

The first one is the dose-dependent manner of plant extracts as antioxidants. Future studies are needed to identify the species of bioactive substances and the optimal and range of effective administered dose of each plant extract and individual constituent of extracts. In addition, based on previous studies, different extraction solvents may extract different bioactive substances from the same plants, and even functions of the same compounds extracted from different plants may be total opposite in animal reproduction system. So, extraction methods should be determined and standardized and then the chemical structures should be identified.

The second problem is that although many studies reported the adverse effects of oxidative stress and efficiency of plant extracts in animal reproduction system, most of them were focused in humans, rats, or mice models and little evidence are available in cattle, sheep, goats, and pigs. Moreover, most of studies only obtained observed results and did not explain detail mechanisms. Though one known reason is that most plant extracts is expensive and it will cost much for *in vivo* trials in big animals, the immediate need is to confirm the pharmacological functions of plants extracts as antioxidant in different animals using *in vivo* and *in vitro* trials to obtain wide range of results. Only by these ways, we can clarify further mechanisms of plants extracts and thereafter utilized them in scientific ways.

CONCLUSION

This review addressed the growing literature on the adverse effects of free radical-induced oxidative stress and the roles of antioxidants in female and male animal reproduction systems. The ROS are double-edged swords and display dual functions in animal reproduction system. The adverse affects of oxidative stress to reproduction system involves damage to sperm and oocyte DNA, disrupt testicular functions, cause dysfunction of ovary and endometrium, and therefore decrease fertility rate of animals. Antioxidant therapy and efficiency, such as vitamin E, C, and glutathione, has been well documented in many research fields of animals; however, concerning the side effects of synthetical antioxidants on animal production, plants and their extracts as antioxidants are booming in past decade. Hence, this review attempts to summarize evidence of oxidative stress and the role of plants or their extracts in the entire reproductive span of female and male animals, including spermatogenesis, semen functions, semen cryopreservation, estrous cycle, ovary functions, ovulation, endometrium, embryo development, and pregnancy. However, most of evidence in animals are obtained either from observation or case control trials conducted in rats and mice models and few are available in livestock and poultry, such as cattle, goats, pigs, and chicken. Based on limited known findings, we still cannot speculate parallel results arbitrarily to other animals without further investigated. Moreover, the reported extracts are mainly from roots, leaves, stem, or seeds of plants throughout the world. Some studies even did not list the detailed chemical compositions of extracts. In addition, exogenous antioxidants are also a double-edged sword like ROS in reproduction system, because though some plant extracts have antioxidant activities, they also exhibit detrimental effects in animal reproduction, and the exact mechanism of actions are unclear. Therefore, further studies are required to identify the bioactive substances and their chemical structures in plants extracts and investigate the effects and effective dosage in different animals using *in vivo* and *in vitro* trials. In this way, we can obtain detailed results and exact mechanism of actions of plants derived antioxidants in animal reproduction system.

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