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A review on the effect of knotweed (*Polygonum avicular*) on biological and fertility indices of sperm

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ABSTRACT

Background & Aim: Infertility in humans and animals has always been a common concern, which is important in animals economically and emotionally in humans. The reluctance to use synthetic drugs, as well as the emphasis on the use of traditional medicine to treat impotence, has led to many attempts to use of medicinal plants.
Experimental: In the current literature review key words including *Polygonum avicular*, knotweed, fertility and sperm were searched in scientific websites such as Science Direct, PubMed and Google Scholar to compile the effects of *Polygonum avicular* on fertility of sperm.
Results: The reviews of studies showed that knotweed (*Polygonum avicular*) due to the presence of phenolic compounds active in its chemical structure and therefore having strong antioxidant properties) can be a suitable alternative to synthetic assisted reproductive drugs. This herbal medicine improves the quality of semen and increases the fertility potential of sperm by disrupting the production of free radicals, dissolving the chain reactions of oxidation and reducing oxidative stress. The antioxidant properties of knotweed cause the formation of health sperm with normal morphological structure (head, middle part and tail), and more integrated chromatin. The results of various studies on the effect of knotweed on fertility indicators showed that the rate of DNA failure and mitochondrial genome damage decreased in treated sperms. The treated sperm cells have the highest progressive motility, the highest viability and the best fertility.
Recommended applications/industries: According to the results of previous studies, the use of knotweed in animal and human can increase sperm fertility and hatchability.

1. Introduction

The spermatogenesis occurs during three consecutive stages (spermatocytogenesis, spermiogenesis, and spermation) in the seminiferous ducts of testis. Although males and females both contribute to decreasing fertility, low fertility is thought to be largely a problem in males (Khan, 2011). Nutrition is one of the important factors that affect reproductive health and semen quality (Jorsaraei *et al.*, 2008). It is reported that the administration of natural or artificial antioxidants in the diet can reduce the amount of oxidative stress in sperm and improve semen quality and increase sperm fertility (EL-Shahat *et al.*, 2009). Oxidative stress in semen leads to the lipid peroxidation of the cytoplasmic membrane of the sperm, the damage of the acrosomal membrane, the oxidation and breakdown of

the DNA and eventually chromosomal abnormalities in the sperm (Sikka, 2001). On the other hand, increased oxidative stress by lowering testosterone production, degeneration of Sertoli cells, and rupture of the blood-testicular barrier disrupts the process of spermogenesis and ultimately leads to a decrease in epidermal sperm counts and fertility (Jorsaraei *et al.*, 2008; EL-Shahat *et al*., 2009; Sakr and Badawy, 2011).

Therefore, in order to reduce oxidative stress, improvement in spermatogenesis, and an increase in sperm fertility potential, the use of natural or artificial antioxidant compounds is necessary (Khaki *et al.*, 2014). Herbal medicines with antioxidant properties such as knotweed (*Polygonum avicular*), remove the intermediate free radicals, end the oxidation chain reactions and ultimately lead to the improvement of specific sperm fertility indicators and increase the fertility potential of sperm (Kubra and Jaganmohanrao, 2012; Shokri *et al.*, 2013; Khaki *et al.*, 2014). In this review, the effects of knotweed on the biological parameters of sperm and specific sperm fertility indicators have been collected and analyzed based on available sources.

2. The effect of oxidants on decreasing fertility

lipids form an integral part of the sperm membrane and are involved in the various stages of maturation, capacitation and acrosome reaction. The high levels of polyunsaturated fatty acids in the plasma membrane and cytoplasm of spermatozoa propose sperm to oxidative stress by reactive oxygen species (ROS). Excessive production of ROS is one of the basic causes of infertility (Khan *et al.*, 2011). Gomez *et al.* (1998) reported that the amount of ROS produced by spermatozoa is inversely proportional to the quality of sperm. Hydrogen peroxide is one of the major ROS produced by the spermatozoa which causes immobilization of spermatozoa. High level of hydrogen peroxide results in the lipid peroxidation and ultimately cell death. Such spermatozoa are thought to be immature, are capable of producing high concentration of ROS (Agarwal *et al.*, 2006). Mitochondria contribute to the production of ROS. Mitochondria are present abundantly in spermatozoa, where they provide energy for motility. Production of ROS is significantly increased in damaged mitochondria, which in turn affect negatively spermatozoa function. Mitochondria play a key role in the process of apoptosis. High levels of ROS disrupt the outer and inner mitochondrial membrane, releasing cytochrome C protein and activating caspase enzymes to induce apoptosis. Elevated level of cytochrome C in seminal plasma indicates significant mitochondrial damage by ROS. DNA damage and cross linking protein can also disturb semen quality. A spermatozoon with dysfunctional DNA is unable to fertilize an ovum and lead to infertility (Khan, 2011).

However, sometimes exposure of the body to certain factors such as drugs, toxins, environmental pollutants, nutritional disorders increases in the production of free radicals and an imbalance between the production of radicals and the body's antioxidant defense which eventually leads to oxidative stress and tissue damage. Oxidative stress leads to lipid peroxidation in sperm membranes, inactivation of glycosylated enzymes, damage to Acrosome membrane, DNA oxidation, and ultimately leads to a reduction of all biological parameters of sperm (number, motility, and normal morphology) (Sikka, 2001). On the other hand, studies have shown that increasing the amount of oxidative stress in the body reduces the production and release of testosterone by Leydig cells, followed by impaired spermogenesis and decreased epidermal sperm count (Cao *et al.*, 2004). In testicular Sertoli cells, an increase in the level of free radicals causes cell degeneration, the disintegration of the cytoplasmic bridges between the cells which results in a decrease in sperm count and an increase in abnormalities (Aziz *et al.*, 2004; EL-Shahat *et al.*, 2009).

In overall, oxidative stress reduces gamete numbers, decreases sperm motility and increases percentage of dead cells (Sikka, 2001; Agarwal *et al.*, 2006). Antioxidants could protect the spermatozoal membrane and increase spermatozoal viability. Variety of defense mechanisms encompassing antioxidant enzymes, biomolecules and vitamins are available which benefits from the risk of ROS and appear to be necessary for survival and functioning of spermatozoa.

3. The protective role of natural herbal antioxidant in increasing fertility

Antioxidants, in general, are compounds that remove, scavenge or suppress the formation of ROS, or oppose their actions (Sikka, 2001). Among the well-known biological antioxidants are superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) have been well documented in literature (Khan, 2011). Within the category of chemical antioxidants, both natural and

synthetic products have garnered attention due to their usefulness in reproduction and fertility management (Agarwal *et al.*, 2006). It has been suggested that natural antioxidants (vitamin E, ascorbic acid) and enzymes (SOD and GSH-Px) create an integral system in avian semen, capable of protecting them against ROS and toxic products of metabolism (Khan, 2011).

According to the WHO's recommendation and given the consumer's negative viewpoint about chemical medications, the demand for herbal medicines, mostly in the developing countries, has increased over the past few years. Among the herbal medicines, those with antioxidant properties that are used for treating diseases like Parkinson's disease, Alzheimer, cancers, cardiovascular diseases, and so on, have drawn a greater deal of attention. These plants are rich of natural antioxidants that interrupt generation and function of free radicals and hold great promises for treating such diseases (Hsu, 2006; Rathore *et al.*, 2015). Natural antioxidants are polyphenolic compounds (Flavonoid, Tannin, and Anthocyanin) that are found in different parts of the plant like leaf, stem, fruit, root, and even seeds (Ahmadvand *et al.*, 2013). Therefore, extractions of secondary metabolites (such as essential oil) from different parts of herbal plants demonstrate antibacterial, antifungal, antiparasitic and antioxidant effects (Semnani *et al.*, 2007). Antioxidant properties of herbal medicines depend on polyphenol compounds found in them. These useful chemicals not only used as medication but also as a unique pattern for the development of medicine analogues and a useful model to have a better perception of biological phenomena (Asgari *et al.*,2013).

Studies have shown that treatment with natural or artificial antioxidants not only stabilizes the blood-testicular barrier but also protects sperm DNA and increases fertility (Lombardo *et al.*, 2011). By removing intermediate free radicals, these compounds terminate the oxidation chain reactions, and on the other hand, by oxidizing themselves, inhibit other oxidative reactions (Bjelakovic *et al.*,2007). Today, antioxidants such as vitamin C, vitamin E, vitamin A, zinc sulfate and selenium has been widely used in the treatment of infertility in males (Gil-Guzman *et al.*, 2001; Agarwal *et al.*, 2006). It seems that the use of antioxidants of plant origin also increases sperm quality and improves the specialized parameters of sperm fertility.

In overall, the delicate balance between the production of ROS and antioxidants defense is considered to be an important determinant of semen quality particularly its fertilizing ability. The relationship between ROS and antioxidant status in semen, as well as the possibility of modulation by medicinal plant are important considerations (Khan,2011).

4. Biological effects of knotweed

Polygonum is a genus of about 130 species of flowering plant in the buckwheat and knotweed family, Polygonaceae. Common names include knotweed and knotgrass. Knotweed or *polygonum avicular* from polygonaceae family has stem that reaches 50cm in length. The leaves are alternate and narrow with pointy tip and separate with odorless, and small flowers in green with pink edges. Knotweed is highly resistant to external factors like cold, heat, or being trodden and it is found in grasslands, road side, abandoned farms, and rock cracks. This annual plant is found in Australia, Europe, north/south of Africa, Mediterranean, the Middle East, and India (Rathore *et al*., 2015). In Iran, it can be seen in forests and humid climates like Guilan, Mazandaran, Azerbaijan, and Chahrmahl-va-Bakhtirai provinces (Ansari *et al.*,2014).

The chemical composition of knotweed includes oxalic acid, acetic acid, formic, tannin, nitrate, potassium, glucose, essential oil, silica, oxymethyl-anthraquinone, resins, saccharides, and mucilage (Asgari *et al.*,2013; Rathore *et al.*, 2015). The fruits contain 18% protein, 71% carbohydrate, 64% fat, and 9.1% fiber; along with 0.7mg vitamin B2, 670mg calcium, 420mg phosphor, 12.7mg iron in each 100g (Srivastava, 2006; Rahore *et al.*, 2015). The herbal plant is astringent and prescribed for diarrhea and bloody diarrhea in particular and to control bleeding. In addition, it is used to treat asthma, bronchitis, pulmonary tuberculosis, eczema, intestine inflammation, edema, stomachache, migraine, infected wounds, sciatica pain, backache, Gout pain, rheumatism, burn and blister. The plant is also used to control fever, stomach secretions, female secretion, blood glucose, constipation, pain, and bile and urinary stones. It is notable that excessive use of the plain results in eczema, hives, skin allergy, and seizure (Liu *et al.*, 2001; Ahmadvand *et al.*, 2013; Hsu, 2006).

Studies have shown that knotweed is rich of phenolic and flavonoid compounds (catechin, epicatechin,

isoprotein, genistein, Kaempferol, and quercetin) in the stem, seed, shoot, and flowers (Badria *et al.*, 2007; Hsu, 2006; Rathore *et al.*, 2015). Quercetin is one of the main flavonoid compounds with high antioxidant effect. It is extensively found in knotweed essential oil as an antioxidant without carbohydrate, which makes it more efficient than glycosides (Justesen and Knuthsen, 2001). Studies have also shown that antioxidant effect of quercetin is about six times higher than vitamin C. The antioxidant (quercetin) is found in onion, red grape, citrus, apple, tea, and some herbs like knotweed. Antiviral, antibacterial, and anti-inflammation effects of the compound are proven (Bleys *et al.*, 2006; Knekt *et al.*, 2002). Quercetin therapeutic effects have been reported in cardiovascular diseases (CVDs), cancers, asthma, eczema, and infertility (Knekt *et al.*, 2002). A few studies on the effect of quercetin on spermatogenesis have supported in diabetic rats that have positive effect on testicle reproductive cells (Askari-Jahrom *et al.*, 2014; Khaki *et al.*, 2010; Coskun *et al.* 2005; Hafez, 2010). The compound increases secretion of testosterone and its effect on the receptors increases testicle reproductive cell division; it also improves qualitative and quantitative performance of epididymis. In addition, quercetin neutralizes oxidative stress and free radicals, which in retune improves biological parameters of sperm and increases number and mobility of sperms (Zohreh *et al.*, 2015). Given the high concentration of quercetin in some herbs like knotweed, it appears that the plant has similar effects on spermatogenesis process.

5. The effects of knotweed on fertility

In recent decades, infertility has increased in all living creatures (including human, mammals, and birds). In addition, there is a growing reluctance to use of synthetic drugs and antioxidants. On the other hand, a surge of attention to traditional medicine and herbal medicines to treat infertility have led to an increase in the studies in the field of using herbal medicines with antioxidant effects. It appears that strong antioxidant effects (due to active phenolic compounds) can be a promising replacement for synthetic fertility medications (Bjelakovic *et al.*, 2007). The herbal medicine interrupts production of free radicals, and oxidation chain reactions. In addition, a decrease in oxidative stress improves the quality of semen and fertility potential of sperm. Antioxidant effects of knotweed generates sperms with healthier morphology (tip, middle part, and tail) and more integrated chromatin (Aziz *et al.*, 2004). In addition, following utilization of knotweed, DNA breakage and damage to mitochondria genome in the cells are minimized and the fertilization is improved with maximum mobility and survival rate of sperm (Agarwal *et al.*, 2006). Therefore, using knotweed as edible or drinkable medication is recommended to individuals with low fertility capability. Ekrami *et al.* (2014) studied the effects of knotweed extract on biological parameters of frozen sperm of man. After melting the sample, it was placed for 1h next to 10µm of knotweed extract and a significant increase in total mobility and forward movement in the sperm was observed. They reported no significant difference in the number of normal sperms (Ekrami *et al.*, 2014). Asgari-Jahromi *et al.* (2013) examined the effect of knotweed extract (10, 30 and 50 mg/kg) on sperm parameters and cell apoptosis in old rats. They injected extracts weekly for 5 weeks, via intraperitoneal. They showed that the knotweed extract caused a significant improvement in mobility and natural morphology of sperms and also in the survival rate. They found that minimum cell apoptosis and higher sperm fertility indicators was obtained with 30mg/kg (Asgari *et al.*,2013). Milan *et al.* (2011) examined the knotweed extract at a concentration of 50mg/kg for 2 months on rats that had been exposed to electromagnetic field. They confirmed the destructive effects of electromagnetic fields on biological parameters of sperm (mobility and normal morphology) and showed that treatment with knotweed extract can create a significant increase in mobility and normal morphology of sperms (Milan *et al.*, 2011). Ansari *et al.* (2014) reported that an efficient way to decrease the damages caused by electromagnetic fields on testis of rats is utilization of herbal medicine rich of antioxidant. The study consisted of Balb/c rates under electromagnetic fields of 3mT for eight weeks and giving 50mg of knotweed as a treatment. The results of histology tests showed that the electromagnetic fields had a severe damage to reproductive epithelium of testicle tissue by producing free radicals, which led to infertility. On the other hand, knotweed essential oil significantly decreased the damages (Asgari *et al.*, 2013).

In poultry, Hemmati *et al.* (2019) prepared hydroalcoholic extracts of knotweed in four concentrations of 0, 500, 1000 and 2000 mg/L and added to drinking water in cooks for 4 weeks. They

reported that knotweed extract can improve the number of sperms with rapid progressive motility (PMSCa), percentage of sperm motility index (SMI), percentage of motile sperm (MSC) and functionally active sperm (FSC) in concentrations of 1000 and 2000 mg/L. No significant difference was observed between the medium and high concentrations of the extract in specialized indices. Furthermore, they represented that the highest number of live sperm with the highest motility and normal morphology was observed in the roosters receiving 2000 mg/L of knotweed extract. Also, high dose of extract significantly reduced head, medulla and sperm motility abnormalities ($P \leq 0.05$). In overall, the use of hydroalcoholic extracts of knotgrass improved some of the biological parameters (such as number, mobility, survival and normal sperm morphology) of sperm (Hemmati *et al.*, 2020).

It seems that other genus of ploygonaceae can also effect on fertility of sperm. Soliman *et al.* (2011) showed the effect of *Emex spinosa* extract (100, 200 and 400 mg/kg) on reproductive organs of adult male rats. They found that the treatment with the ethanol extracts of *E. spinosa* improve the relative weight of reproductive organs, sperm count, sperm motility and total sperm abnormality. The mean sperm count for the group that received 400 mg/kg of *E. spinosa* extract was $233.7 \pm 4.50 \times 10^6$/ml. Also, the sperm motility in this group was $87.3 \pm 3.50\%$. Ethanol extract of *E. spinosa* (400 mg/kg) significantly elevate the serum levels of testosterone (5.30 ± 0.15 vs 4.64 ± 0.16 ng/ml) and luteinizing hormone (0.69 ± 0.03 vs 0.59 ± 0.02 mIU/ml). Therefore, *E. spinosa* extracts appear to possess fertility improvement activity in male rats due to their testosterone increasing property. Escanbil (Calligonum) is another plant from *Polygonaceae* family with antioxidant property due to the presence of quercetin and catechin. Therefore, this plant can play a role in sperm motility and viability. Administration with calligonum caused increase in the expression of the gene Catsper and subsequently improvement of sperm parameters in male mice (Askari Jahromi *et al.*, 2014).

Interestingly, Qilin pill, a complex traditional Chinese formula, has been used in the management of oligoasthenospermia. The principal action of Qilin pill is kidney tonication and essence replenishment, thereby supplementing Qi and nourishing blood. This product contains 15 plants, one of the main of which is Fallopia multiflora (as polygonacea). Several studies have shown promising beneficial effects of Qilin pill on the improvement of sperm quality. Systematic review showed that Qilin pill treatment significantly increased semen volume and improvement of pregnancy rate. However, meta-analysis showed that the effects of Qilin pill on serum levels of FSH and LH were not significant (Jin *et al.*, 2017).

Apparently, the effect on *polygonaceae* on male fertility was different from effects on reproductive indices of females. For example, adult cycling female rats were oral administered by *Polygonum hydropiper* crude root extract at a dose of 1g/kg body weight/day for 12 days. After that, the rats were allowed to mate with males and to complete the full term of gestation. The oestrous cycle of the extract treated rats became irregular, resulting in failure of gestation. The oestrous cycle was restored following the recovery period. However, the number of newborn pups was significantly lesser than in the controls. The results reveal that the root of *polygonum hydropiper* contains steroidal/estrogenic compounds which can affect the female reproduction in rat (Sathiyaraj *et al.*, 2010).

Also, the methanolic extract of the roots of Tult (*Rumex steudelii*), another plant belonged to polygonacea, were investigated for their antifertility activity in female rats. The extract reduced significantly the number of litters. It also produced antifertility effect in a dose dependent manner and the contraceptive effect was manifested for a define period of time. Furthermore, the extract prolonged significantly the estrus cycle and the dioestrous phase of the rats. The oral LD_{50} of the extract was found to be 5g/kg (Gebrie *et al.*, 2005).

6. Conclusion

In conclusion, knotweed, with high concentration of catechin, epicatechin, isoprotein, genistein, kaempferol, and quercetin, has a high antioxidant effect. Its essential oil significantly increases biological indices of sperm comprising mobility, survival, and normal morphology of sperm. It also improves all specific indices of sperm fertility.

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