CHAPTER 14

The Complementary Role of selenium and its botanical combinations in regenerative therapy

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SUMMARY

Selenium (Se) is an essential element for animals. It mainly occurs in two forms; inorganic and organic. It was discovered by Berzelius in 1817 and its role as a micronutrient for the animal's health remained unknown till 1957. It has many health-beneficial effects and acts as an antioxidant, anti-inflammatory, antiviral, antimicrobial, and immune modulator. It is an integral part of many proteins and acts as a cofactor. Its oxidizing property is due to Se-dependent enzymes which maintain homeostasis. Besides these, it also alleviates heat stress, enhances the activity of reproductive organs, and heals histopathological changes induced by toxicants. Additionally, it also has a role in degenerative disorders and regulates wound healing and angiogenesis. In this chapter, the therapeutic potential of Se, its mechanism of action, its combination with botanicals, and regenerative therapy with Se are discussed.

INTRODUCTION

In 1817, the Swedish chemist Jons Jacob Berzelius discovered selenium, and its role as a micronutrient for the health of animals was demonstrated in 1957. It was demonstrated that it has a role in preventing vascular disorders and myopathies in animals due to nutritional deficiencies. Selenium is also part of many proteins and is involved in several physiological processes Fig 1. The physiological processes in which Se plays a role include the metabolism of thyroid hormones, homeostasis of redox reactions, immunity, and antioxidant defense mechanisms (Li et al., 2019). Similarly, in 1973, the role of Se in glutathione peroxidase (GPx) and its ability to prevent necrosis of the liver in rats due to vitamin E deficiency was demonstrated. Selenium is an integral part of GPx which acts as an antioxidant and protects cells from damage caused by oxidative stress via the neutralization of harmful reactive oxygen species (Shi et al., 2023). Moreover, the adequate intake of Se has beneficial effects on animals. For example, the reproductive performance and productivity of poultry could be efficiently improved through the supplementation of Se, carotenoids, and vitamin E that regulate the animal's antioxidant defense system. Additionally, it also prevents oxidative stress in animals and improves growth of animals (Surai et al., 2019). Therefore, it is a useful element for the better health of animals.

Selenium is an essential dietary element for the health of animals. In nature, it exists in two forms namely selenite (Se^{4+}) and selenate (Se^{6+}). All other forms of Se could be derived from

How to Cite: Shakoor A, S Kousar, ZUD Sindhu, MT Aleem, A Ahmed & F Munir, 2023. The complementary role of selenium and its botanical combinations in regenerative therapy. In: Complementary and Alternative Medicine: One Health Perspective (Sindhu ZuD, B Aslam, U Uslu & M Mohsin, eds): FahumSci, Lahore, Pakistan, pp: 103-108. ISBN: 978-627-7745-01-1. https://doi.org/10.61748/CAM.2023/014

these two forms. It is not essential for plants, however, plants absorb it from soil and convert it into various organic forms useful for animals. The inorganic source of Se for animals is cereals and hay. The organic form of Se is formed when it combines with any organic compound for example selenocysteine (combination of Se with cysteine) and selenomethionine (combination of Se with methionine). This element shows synergism with vitamin E and is absorbed efficiently from the duodenum in its presence (Mahima et al., 2012). The other sources of Se for animals include Se-yeast, sodium selenite, Se-enriched alfalfa, and Se-enriched probiotics (Brittany et al., 2022). By supplementing these Se-enriched products into the feed of animals in appropriate concentration, its deficiency could be controlled.

Selenium has been given the title of a double-edged sword because of its dual functions. The deficiency of Se is due to its low concentration in the feed and forage of animals while its excessive concentration led to severe toxicity problems. Marco Polo noticed the symptoms of Se toxicity in animals when the beast ate plants having an excessive quantity of Se and their hoof were dropped off. The other symptoms include fatigue, weight loss, vomiting, diarrhea, lethargy, poor growth, hair loss, irritation, reproductive inefficiency, and even death (Bano et al., 2022). On the other hand, its deficiency may lead to metabolic disorders such as ill-thrift and white muscle disease in calves, exudative diathesis in chickens, and liver damage in pigs (Yang et al., 2022). Therefore, an adequate quantity of Se is essential.

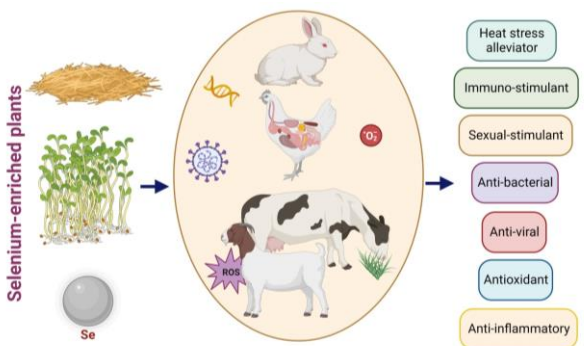

Fig 1. The complementary role of selenium for animals

Besides its alone use, it is also used in combinations with various plant compounds known to have growth-promoting and therapeutic properties in animals. Se is biofortified with plants used as fodder for animals to prevent its deficiency (Smolen et al., 2019). In this chapter, we mainly discuss the role of Se in regenerative medicine, the therapeutic potential of Se and its various combinations with botanicals, and the mechanism of action.

HOW DOES SELENIUM PRODUCE BENEFICIAL EFFECTS FOR ANIMALS?

Selenium is known for its health-beneficial effects. It mitigates several infections by stimulating the immune responses against them through multiple mechanisms. The antioxidant property of Se to regulate GPx causes an elevated immune response and reduces inflammation. The hydrogen peroxide level is reduced by GPx which in turn has detrimental effects on the generation of ROS (reactive oxygen species) and free radicals. In the arachidonic acid metabolic pathway, it reduces the hydrogen peroxide intermediates ultimately leading to decreased leukotrienes and prostaglandins production. Thus ameliorate the effect of inflammation (Shojadoost et al., 2019). Additionally, it increases T cell production, the proliferation of lymphocytes, stimulates cytokine (IL-2) secretion, and enhances the activity of natural killer cells. However, its main immunogenic action is due to its selenoproteins (Fairweather et al., 2011). Se also has antiviral properties. The supplementation of Se in the feed of poultry could lead to the expression of interferon and interferon-stimulated genes in lymphoid tissues. Their elevated expression combats infections caused by viruses. Besides these, it also has a role in activating the immune cells such as macrophages, and neutrophils, promoting antibody production, and reducing interleukin-8 as well as tumor necrosis factor. Moreover, Se has cytotoxic effects, could induce apoptosis in tumor cells, protect against ultraviolet radiations, and prevent cardiovascular diseases and atherosclerosis in animals (Steinbrenner et al., 2015).

Selenium shows promising antimicrobial properties. It has the potential to interfere with the metabolism and growth of various antimicrobial species and serve as the best candidate for the control and treatment of infections caused by bacteria as well as viruses. It has direct growth-inhibiting effects on various pathogenic species of bacteria and could enhance the antibacterial effects of many antibiotics leading to reduced resistance to antibiotics. Selenium shows wide therapeutic potential against many infections caused by *Staphylococcus aureus*, *Escherichia coli*, *Helicobacter pylori*, Human immunodeficiency virus, and Influenza virus, etc. (El-Deeb et al., 2018). These properties of Se make it a useful candidate for the treatment of pathogenic infections in animals.

COMBINATION OF SE WITH BOTANICALS

The traditional practices of farmers for maintaining health, diagnosis, controlling diseases, and animal husbandry are termed ethnoveterinary medicine. It is gaining the interest of people because of its usefulness, delaying the emergence of drug resistance, preventing drug residues in food of animal origin, and local availability of herbs. It is based on the skill, knowledge, and healthcare experiences of farmers passed from

one generation to another for maintaining the well-being of animals. Ethnoveterinary medicine plays a vital role in the treatment of some common ailments of animals such as diarrhea, parasitic infections, wounds, skin diseases, and stunted growth (Saira et al., 2023). Besides the therapeutic potential of traditional herbal plants used for the treatment, they also have certain limitations such as they are unstandardized, lack a dosing regimen, varying efficacy, and may exert toxic effects because the constituent of plants varies according to different regions and soil (McGaw et al., 2020).

The medicinal plants could also be used in combination with minerals and may have additive, synergistic, or antagonistic effects. *Nardostachys jatamansi* has antioxidant and antistress effects as Se on the central nervous system because its roots and rhizomes contain sesquiterpenes. Moreover, it also enhances the memory and learning efficiency of animals. Therefore, in a study, the combined effect of *N. jatamansi*, crocetin, and Se were investigated for their antioxidant effects. The supplementation of this combination effectively treated cognitive impairment in rats reflecting synergism (Khan et al., 2012). Similarly, the reproductive performance of animals could be affected by heat stress. It has an important role in the quality, quantity, and fertility of sperm cells. Additionally, heat stress affects the functions of the testes. Spirulina is an alga which has an ameliorating effect on heat stress causing reproductive inefficiency. Moreover, it is also known for its immune-enhancing, growth-promoting, antimicrobial, and antioxidant properties. The dietary inclusion of Se with spirulina enhances the antioxidant activity which indicates a synergistic effect and improves libido, sperm quality (livability, integrity, and intactness), and sperm quantity in rabbits (El-Ratel et al., 2023a, 2023b). In another study, the reproductive performance of the female rabbit was evaluated when asphaltum was combined with vitamin E and Se supplemented in their feed. Results indicated that this combination significantly increased the serum concentration of progesterone (Idrees et al., 2015). These combinations have promising results on the reproductive performance of animals when included in their feed.

Polysaccharides are polymeric carbohydrates held together via glycosidic linkages. These are widely present in animals, plants, and microorganisms and serve as a structural and functional constituent of the cells. Additionally, polysaccharides have nutritional and medical properties and may act as regulators of glucose, immunomodulators, anti-tumor, anti-viral, and antioxidant agents in animals (Bai et al., 2012). Since both polysaccharides and selenium have beneficial effects in animals, therefore, their combinations may bring promising results as well. Moreover, their combination increases their applications in the field of medicine as they have low solubility. Naturally, Se-enriched carbohydrates could be isolated from microorganisms, mushrooms, and plants (Sun et al., 2017). The Se content of natural polysaccharides is low, very rare in nature, and the extraction method is laborious. Therefore, these could also be produced synthetically. Similarly, the synergistic effect of Se and mannan oligosaccharide on growth performance under the high stocking density of broilers was studied. The results demonstrated that the stress imposed by the high stocking density on the growth performance of broilers was reduced when supplemented with Se and mannan oligosaccharides. This combination partially improved the gut microarchitecture leading to proper digestion of feed and nutrient absorption in chicken (Rehman et al., 2022). Based on the therapeutic properties of both polysaccharides and Se, they could lead to improved growth performance in animals.

THE THERAPEUTIC POTENTIAL OF SE IN REGENERATIVE MEDICINE

Regenerative medicine deals with the repair or replacement of damaged cells, tissue, or organs by using the transplantation

Tab 1. Role of selenium in regenerating body tissues.

Combination of selenium (Se)	Studied traits Biological effect	Benefits	References
Se-hydroxyapatite	Bone regeneration	It exhibits good osteogenic ability	Muthusamy et al., 2023
In organic and organic Se	Cancer treatment	It has anti-cancer activity against the breast, lungs, liver, prostate, and bone	Hou et al., 2021
Selenite	Stem cell	It can be used in the procedures of tissue engineering and gene therapy	Ebert et al., 2006
Reactive selenium	Homeostasis	it could regenerate bone cells, provide protection, and maintain a healthy bone environment and homeostasis	Gilbert et al., 2022
Combination of Se with mesenchymal stem cells	Wound healing	It could enhance the effect of adipocyte-derived MSCs exosomes for the healing of wounds	Heo, 2022
Se nanoparticles	Neuroprotective role	It could provide better results in Alzheimer's disease in the protection of neurons as well as in spinal cord injury	Gholamigerava nd et al., 2021; Javadani and Barzegar, 2023
The combination of Se with MSCs-derived exosomes	Regeneration	It can ameliorate acute myocardial infarction by healing cardiac vascular diseases	Lin et al., 2023

of cells and organs and tissue engineering. The main purpose of regenerative medicine is to restore the normal functioning of the body's cells, tissues, or organs by replacement, repair, and regeneration (Beetler et al., 2023).

Bone is composed of both organic and inorganic material and has the tendency of spontaneous self-repair. However, still, many defects of the bones require grafting for regeneration. Bioceramics and hydroxyapatite are important in the remodeling of bones due to their osteoconductivity and biocompatibility. Likewise, Se has a role in maintaining the health of bone. It protects bones from ROS and helps the resorption of bone by inactivating the osteoclasts (bone cells which break bone tissue). It also exhibits good osteogenic ability, therefore, could be helpful in the proper function of bones (Muthusamy et al., 2023). Among different types of bone disorders, cancer is one of them. However, it is less common, and limited therapeutic strategies are employed for its treatment. Selenium has the ability to inhibit specifically targeted cancer cells of the bone without harming the healthy neighbor cells (Hou et al., 2021). In regenerative medicine, bone marrow stromal cells derived from mesenchymal stem cells are used. These are the precursors of chondrocytes, adipocytes, osteoblasts, and myotubes. The precursor cells could be used in the tissue engineering of cartilage and bones, as well as for targeted gene therapy. During the *ex vivo* procedures for gene therapy and tissue engineering, these cells undergo cellular stress. The environmental and cellular ROS cause damage to the cells (proteome and genome) resulting in the development of tumors. The cellular enzymes (glutathione peroxidases, catalases, and thioredoxin reductases) minimize oxidative stress by neutralizing hydrogen peroxide to water. There are three thioredoxin reductases and four GPx enzymes which are selenium-dependent because their active sites have selenocysteine. The deficiency of selenium could impair the proper functioning of these enzymes. Therefore, adequate supplementation of Se could restore the antioxidative potential of these enzymes leading to reduced oxidative stress during the procedures of tissue engineering and gene therapy (Ebert et al., 2006). Therefore, it could regenerate bone cells, provide protection, and maintain a healthy bone environment and homeostasis (Gilbert et al., 2022).

Animals may suffer from degenerative disorders such as refractory wound healing because of excessive inflammation and abnormal angiogenesis. Stem cell therapy is used for the treatment of regenerative deficiencies. However, due to the expensive and laborious work associated with stem cell therapies, alternate treatment options must be discovered. The regeneration of tissues has complex physiological procedures such as cell growth, angiogenesis, inflammatory responses, remodeling of tissues, homeostasis, vascularization, and redox reactions. (Cao et al., 2023). Mesenchymal stem cells (MSCs) could be obtained from the placenta, adipose tissue, blood, and bone marrow. These are known for their tissue regeneration capacities. Sometime MSCs may undergo chromosomal abnormalities. On the other hand, exosomes are membrane-bound extracellular small vesicles that could be derived from MSCs carrying bioactive molecules such as proteins, lipids, and nucleic acids. They are involved in the healing of wounds, damaged tissue, or organs, regulating angiogenesis and inflammation in a paracrine manner by transferring peptides, proteins, lipids, cytokines, mRNAs, and miRNAs originated from MSCs. However, *in vitro*, large-scale production without senescence still needs to be overcome. The stem cell proliferative properties of Se could enhance the effect of adipocyte-derived MSCs exosomes for the healing of wounds (Heo, 2022). Similarly, the combination of Se with MSCs-derived exosomes could also ameliorate acute myocardial infarction by healing cardiac vascular diseases (Lin et al., 2023). Additionally, Se nanoparticles combined with MSCs derived from adipose tissue could provide better results in Alzheimer's disease in the protection of neurons (Gholamigeravand et al., 2021). Likewise, Liu et al., (2022) and Javadani and Barzegar (2023) independently demonstrated the nerve regenerative properties of Se. They markedly observed that the nanoparticles of Se are effective in spinal cord injury repair. It improved the regeneration of nerves to a higher extent than astrocytes. Therefore, Se could be efficiently used in regenerative medicine Tab 1.

THERAPEUTIC POTENTIAL OF SE IN HISTOPATHOLOGICAL CHANGES IN ANIMALS

Selenium alone or in combinations with other compounds such as botanicals or other elements may have a therapeutic role in reversing the histopathological changes induced by toxicants or pathogens. This is due to the antioxidant properties of Se that diminish the effects caused by ROS. In a study, it was demonstrated that the oxidative damage of lipoproteins, lipids, or other cellular components such as proteins, enzymes, and nucleic acids results in degenerative liver diseases. In the liver, cellular degeneration due to free radicals may affect the enzymatic level of enzymes produced by the liver. Therefore, the injection of Se prevents the variation in liver enzymatic level indicating its potential in healing hepatic cellular injury (Ozardali et al., 2004; Adali et al., 2019). Sallam et al. (2018) demonstrated the toxic effect of cypermethrin in female rabbits and its treatment with Se and vitamin E. The histopathological changes induced by cypermethrin include bile duct hyperplasia and degeneration of hepatocytes in the liver, degeneration of alveoli and edema in the lungs, atrophy of uterine glands, and sloughing off the epithelium of the uterus. The administration of Se with vitamin E partially ameliorated the toxic effect produced by cypermethrin.

The use of pesticides for the control of agricultural pests is a common practice all over the world. However, animals may accidentally consume fodder before the withdrawal period of drugs that leads to toxicity. Organophosphorus (OP) compounds are widely used and their toxicity in male animals may have adverse effects on the reproductive organs. Histopathologically, the toxicity of methyl parathion (OP compound) in males causes cellular damage and necrosis in the testes, increased cellular spaces, tubular elements disorganization, and fragmentation of sperm DNA (El-Gerbed, 2013). Similarly, certain drugs may also cause histological and histochemical changes in the prostate gland of animals (Sakr et al., 2012). In such cases, treatment of animals with Se ameliorates the histopathological changes which are due to its oxidative properties. Moreover, if animals are not getting an adequate quantity of Se, they may also suffer from histopathological, hematological, and histochemical alterations of the body organs (Sobiech and Zarczynska, 2020). Additionally, Se also enhances the immune response of animals against various pathogenic diseases and provides protection (Battanyi et al., 2023).

CONCLUSION

Selenium has many health-beneficial activities for animals. It maintains the homeostasis of the body via GPx, has a role in regulating inflammatory responses, modulates angiogenesis, alleviates heat stress, and has the capacity of healing refractory wounds. Animals can get Se from plants enriched with the element. To get appropriate health benefits from the Se, the administration of adequate concentration of Se is necessary. It acts as a double-edged sword meaning that has the characteristics of both remedies as well as toxicity. Animals will be in trouble if they consume its high concentration. Additionally, its low concentration will also lead to detrimental effects. It could be used to complement healing and treatment of wounds and other diseases respectively.

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