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Applications of Zeolites in the Reproductive System: A Mini-Review

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Abstract: Zeolites are microporous aluminosilicates with ion exchange and adsorption properties. Beyond their antibacterial and biocompatible nature, they show antioxidant and anti-inflammatory activities, which can reduce oxidative stress and apoptosis. Excessive reactive oxygen species (ROS) are implicated in the pathogenesis of infertility, cancer, and other diseases. Preclinical researches in animals demonstrate that zeolites can mitigate ROS-induced tissue damage, improve sperm and oocyte quality, and support reproductive organ function. Moreover, clinical evidence in humans indicates that zeolite supplementation reduces oxidative stress markers as malondialdehyde (MDA) and modulates antioxidant enzyme activity such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) and in addition, regulates the secretion of inflammatory cytokines (such as TNF-α) induced by oxidative stress. Zeolite-based drug delivery systems also show promise in the treatment of reproductive cancers. This mini-review summarizes the therapeutic potential of zeolites in reproductive health, highlighting mechanisms, benefits, limitations, and directions for future research.

Keywords: Ovary, oxidative stress, reproductive system, zeolite, testis

Introduction

Zeolites are porous, hydrated aluminosilicates with a tetrahedral crystal structure composed of dense networks of AlO_4 and SiO_4 units sharing oxygen atoms [1, 2]. These naturally occurring minerals, often called molecular sieves, show exceptional ion-exchange capabilities and are highly effective in removing metals from contaminated environments due to their adsorption properties. The crystalline framework contains micropores and cavities filled with cations and polar molecules such as water, with pore sizes typically ranging from 4 to 12 angstroms. These pores can exchange ions and polar molecules with the surrounding medium, giving zeolites their unique physicochemical characteristics [3-7]. Zeolites function as efficient adsorbents, ion exchangers, and environmentally friendly catalysts [8], are finding extensive use in gas separation, environmental protection, agriculture, and wastewater treatment [9-12]. Generally, zeolites are categorized into natural and synthetic types. Natural zeolites, found in volcanic rocks, include over 40 known varieties such as chabazite and clinoptilolite (isometric forms) and natrolite (fibrous form). To date, more than 230 synthetic zeolites have been developed, each with specific industrial and biomedical applications [5,13-15]. Their classification depends on pore size, structure, and the Si/Al molar ratio, which defines their chemical and physical behavior. Zeolites are nontoxic, antibacterial, biocompatible, and highly absorbent. When combined with drug-loaded polymers, they facilitate controlled and sustained drug release. Additionally, zeolite-based biosensors have been designed for cancer biomarker detection, demonstrating their versatility in biomedical applications [16,17]. Most reproductive system disorders particularly those affecting testicular and ovarian function—are associated with oxidative stress caused by free radicals [18-21]. Increased levels of

reactive oxygen species (ROS) such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-) damage lipids, proteins, and DNA. While ROS play essential roles in processes such as oocyte and sperm maturation, fertilization, and embryonic development, their imbalance leads to cellular and tissue damage, impairing oogenesis and spermatogenesis and ultimately contributing to infertility [22-28]. Endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) are crucial in maintaining ROS homeostasis. Recent advances in materials science have led to the development of antioxidant-based therapies, where the combination of zeolites and antioxidant agents has shown promising outcomes [29]. The present review explores the functional role of zeolites in maintaining reproductive system health and preventing oxidative stress-related disorders.

Therapeutic Properties of Zeolites

In recent years, the unique properties of natural and synthetic zeolites have attracted significant attention in biomedicine, encompassing a wide range of applications in biotechnology and medicine. These applications largely stem in the adsorption and ion-exchange capabilities of zeolites, including the removal of harmful environmental pollutants, detoxification of living organisms, enhancement of animal nutrition and immunity, separation of proteins and other biomolecules, fabrication of biosensors for biomarker detection, drug delivery, transport of nucleic acids and bioactive molecules, and scavenging of oxygen radicals [30]. Zeolites possess notable antioxidant activity, making them valuable in human medicine, veterinary medicine, and zoological technology. Their antioxidant properties can reduce apoptosis and inflammation in hepatocytes, thus serving as potential therapeutic agents for liver diseases [31]. Furthermore, zeolites' antioxidant activity has been investigated in neurodegenerative disorders like Alzheimer's disease and in dermatological applications for protection against ultraviolet (UV) radiation. Novel zeolite-based sunscreens can protect human skin fibroblasts from reactive oxygen species (ROS) generated by UV exposure [32,33]. In addition, dietary supplementation with natural zeolites has been shown increasing antioxidant enzyme levels, such as catalase (CAT), and decrease ROS and H_2O_2 levels in the plasma of smokers [34]. Zeolites also exhibit high water absorption capacity, which can be exploited as hemostatic agents, particularly when combined with coagulation factors and platelets, to accelerate blood clotting in both humans and animals [35]. Zeolite-based materials are further used in bioactive ceramics for bone tissue engineering scaffolds, providing structural support that mimics natural bone matrices. Consequently, these materials are suitable not only for tissue engineering but also for implant coatings and wound healing applications [36]. Moreover, zeolites demonstrate significant antibacterial, antifungal, and anti-candida activity [37,38]. Ion-containing zeolites have been explored as potential antibacterial agents against oral pathogens [39] and have been used as carriers for antimicrobial drugs, including antibiotics (e.g., gentamicin, cephalexin), chemotherapeutic agents (e.g., 5-fluorouracil, doxorubicin, mitoxantrone), metal ions, and nitric oxide (NO) [40,41]. Another important application involves the selective separation of microbial and mammalian cells, exploiting the differential adsorption of specific cells to zeolite surfaces, which can also be applied for rapid detection of cancer cells [42,43].

Clinoptilolite is the most widely used natural zeolite in the biomedical field, with certain forms approved for clinical use. It seems to be the only zeolite registered as a medicinal substance in the European Union and is used in oral therapies. Clinoptilolite can also function as a drug carrier, facilitating controlled drug delivery. Despite their many beneficial properties, some zeolites can be cytotoxic and carcinogenic. For example, erionite, a fibrous natural zeolite, exhibits asbestos-like behavior and is associated with lung cancer and malignant mesothelioma [2,30,44]. Recently, clear evidence suggests that environmental or occupational exposure to erionite in areas of Turkey and central Mexico is causally related to the high rates of mesothelioma observed in these areas [45]. Therefore, paying attention to the physicochemical properties of the selected zeolite type, its appropriate dosage, and its safety are of particular importance, especially in clinical studies and animal models, and citing the results of past studies and using different doses of various zeolites can be helpful in this regard. For example, various studies with different doses and results have investigated the effect of clinoptilolite in veterinary medicine, and have led to the recording of its potential and limitations, especially in veterinary medicine [46].

Zeolites and the Reproductive System

Testicular Tissue and Sperm

The male reproductive system consists of the testes and associated appendages (Fig.1). The testes are the primary male reproductive organs responsible for spermatogenesis and androgen production. Spermatogenesis the transformation of male germ cells into mature spermatozoa occurs mainly within the seminiferous tubules and requires high testosterone levels produced by

Leydig cells [47,48]. Oxidative stress in males leads to structural abnormalities, reproductive cell damage, and impaired spermatogenesis, ultimately compromising fertility. Testicular tissue is particularly susceptible to oxidative stress due to its high rate of cell division, elevated mitochondrial oxygen consumption, and relatively high content of unsaturated fatty acids [49,50]. Although endogenous antioxidants protect spermatogenesis, various internal and external factors including testicular torsion, elevated temperature, varicocele, diabetes, infections, hyperthyroidism, hormonal imbalances, xenobiotic exposure, toxins, and ionizing radiation can impair antioxidant defenses, inducing oxidative stress [20].

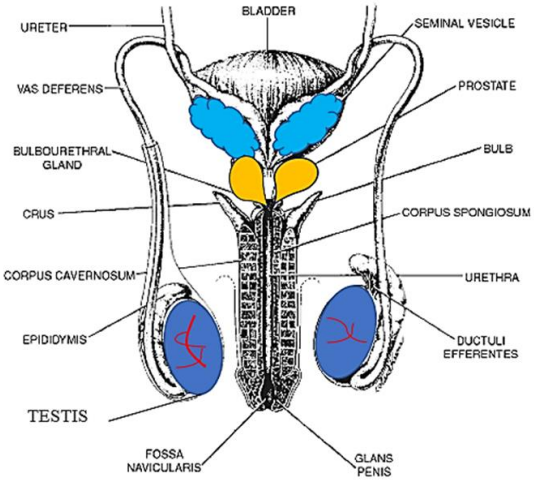

Fig. 1. Schematic image of the male reproductive system

Environmental pollutants, especially heavy metals such as lead (Pb), arsenic (As), cadmium (Cd), and mercury (Hg), contribute to ROS generation, causing oxidative damage through disrupted signaling pathways and epigenetic modifications. Exposure to these metals adversely affects male reproductive function, damaging Sertoli and Leydig cells, altering hormone secretion, and impairing spermatogenesis [51].

Several studies highlight zeolites' protective role against reproductive toxicity. Ibrahim et al. (2024) evaluated clinoptilolite against cadmium-induced testicular damage in adult male Sprague-Dawley rats. Rats orally administered $CdCl_2$ for 28 days were treated with clinoptilolite dissolved in Tween 80. Zeolite treatment significantly improved testicular weight, sperm count, motility, and morphology, increased serum testosterone and LH levels, reduced oxidative stress markers (restoring MDA by 44.6% and increasing GSH by 110%), and decreased inflammatory mediators (NF-κB, TNF-α, IL-1β). Histopathological improvements included restoration of seminiferous tubule organization and reduced sperm cell death, are demonstrating clinoptilolite mitigates cadmium-induced testicular toxicity through antioxidant and anti-inflammatory mechanisms [52]. Conversely, dietary supplementation of healthy rats with high concentrations of zeolite (6%) over eight weeks led to increased sperm abnormalities and decreased testosterone and LH levels, indicating that excessive zeolite intake may negatively affect normal reproductive function [53]. Zeolites also enhance sperm preservation. Mohammed et al. (2021) demonstrated that adding zeolite-loaded semen extenders (Z+, Z-, Z±) improved sperm motility, membrane integrity, and reduced apoptosis and necrosis after cryopreservation, indicating that zeolites can protect sperm during freezing [54].

Ovary and Uterus

The ovary, a vital female reproductive organ, contains follicles the fundamental structural and functional units comprising an oocyte and surrounding granulosa cells (Fig. 2). The ovary fulfills both reproductive and endocrine roles [55]. Garzón Prado et al. (2017) investigated the effect of dietary clinoptilolite supplementation (2% of dry matter intake) in dairy cows during prepartum and postpartum periods. Their findings revealed enhanced return to ovarian activity, improved uterine contraction, and better uterine health. Reproductive parameters, including intervals from calving to first estrus, first service, and pregnancy, were significantly improved in treated cows compared to controls [56]. Uterine fibroids, the most common pelvic tumors in reproductive-aged women, affect over 70% of women worldwide. Studies show that simultaneous administration of magnetized water and zeolite-containing products may serve as a non-hormonal alternative therapy for uterine fibroids [57]. Recent study by Giurgiu et al. (2024) further supports the beneficial effects of clinoptilolite supplementation in postpartum dairy cows, demonstrating improvements in oxidative stress markers, energy status, and reproductive outcomes, such as calving-to-first-service interval and uterine health. These findings reinforce the potential of zeolites to support ovarian and uterine function. Uterine fibroids, prevalent in women of reproductive age, may also benefit from zeolite-based therapies. Combined administration of magnetized water and zeolite-containing products has shown potential as a non-hormonal alternative for fibroid management [58]. These updates integrate human studies (Atitlán et al, (2017) and Bulog et al, (2024)) to strengthen the antioxidant and ROS-protective discussion in section 2 [59,60], and new animal data (Giurgiu et al, (2024)) to enhance section 3.2 on reproductive health outcomes [58].

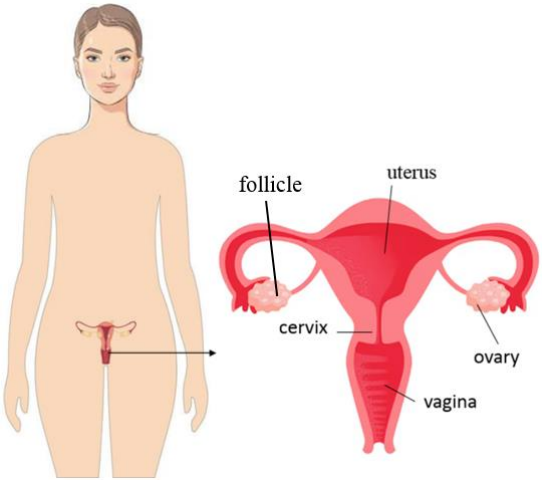

Fig .2. Schematic diagram of the female reproductive system

Treatment of Testicular, Prostate, Ovarian and Uterus Cancer

In vitro studies show that finely ground clinoptilolite inhibits protein kinase B (c-Akt), induces tumor suppressor proteins (p21 and p27), and suppresses proliferation in several cancer cell lines. Topical clinoptilolite reduces tumor formation and growth in canine skin cancer models and induces tumor suppressor gene expression. Pavelic et al. (2001) reported successful treatment of a dog with a testicular tumor using clinoptilolite, with significant tumor size reduction over three months. Similarly, a dog with prostate adenocarcinoma showed remarkable recovery following clinoptilolite administration [61].

For ovarian cancer, Xing et al. (2020) demonstrated that zeolite imidazolate frameworks (ZIF-90) loaded with cisplatin (DDP) efficiently targeted mitochondria, improved drug uptake, and overcame drug resistance in DDP-resistant epithelial ovarian cancer cells [62]. Researchers have recently designed a DNA sensor in clinical settings for the early detection of human papillomavirus (HPV) infections, the leading cause of cervical cancer. This HPV-16 DNA biosensor technology, developed by using zeolite-iron oxide (zeolite-IO) on an integrated electrochemical sensor, could help identify individuals at risk of cervical cancer and guide the development of appropriate care and treatment programs [63].

Mena-Silva et al. (2023) developed a zeolite-based delivery system for prostate cancer treatment, loading zeolite nanoparticles with 2-methoxyestradiol (2ME). This system enhanced apoptosis in prostate cancer cells and demonstrated favorable physicochemical and biological properties for targeted anticancer therapy [64].

Discussion

Various antioxidants are used to reduce ROS in the reproductive system; For example, quercetin can reduce ROS by donating electrons. Melatonin, a natural peptide hormone secreted by the pineal gland and several extra-pineal tissues (such as the placenta, uterus, and ovaries), directly participates in the detoxification of ROS and NOS and indirectly participates in the stimulation of enzymatic antioxidants and the suppression of prooxidants. L-carnitine and acetyl-L-carnitine, as natural derivatives of the amino acids lysine and methionine, ensures the physiological need for ATP in reproductive processes. In addition, can increase the levels of vitamin C, vitamin E and antioxidant enzymes such as CAT and SOD [65,66]. In addition, coenzyme Q10, zinc, and selenium are also beneficial antioxidants for the reproductive system [67]. Various studies have shown that activated and micronized zeolites are considered to be detoxifying agents due to their selective binding properties to heavy metals, O2, and ROS. Zeolite can indirectly increase antioxidant potential in humans and animal models by increasing the levels of antioxidant enzymes and reducing lipid peroxidation [59,68]. Accordingly, since oxidative stress can cause serious damage to the male and female reproductive systems, focusing on the antioxidant potential of zeolite, especially clinoptilolite, can help overcome many of the challenges caused by oxidative stress, especially in the field of infertility. However, in this case, those studies related to human samples are few and require more extensive research with a larger sample size.

Conclusions

Zeolites, particularly clinoptilolite, exhibit significant antioxidant, anti-inflammatory, and detoxifying properties. Animal studies indicate their potential to improve fertility by protecting reproductive tissues from oxidative stress and mitigating the effects of environmental toxins, while human studies suggest similar antioxidant benefits. Zeolite-based drug delivery systems hold promise in treating reproductive cancers and improving sperm and oocyte quality. However, most studies are preclinical, and further clinical investigations in humans are required to confirm efficacy and safety. Attention to proper dosage and formulation is essential to avoid potential toxicity. Future research should focus on translating these findings into human reproductive health applications, exploring long-term safety, and optimizing

zeolite-based therapeutic strategies. It should be noted that this is preliminary clinical evidence and is not yet generalizable to the broader population or specifically to reproductive health, and further studies are needed in this area.

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