

# Zinc and Shell Flour as Innovative Natural Aromatase Blocker to Increase Testosterone Concentration

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**Abstract.** The hormone testosterone is essential in various biological processes, including reproductive function so its presence in the body must remain stable. Low concentrations of testosterone can affect secondary traits and libido in male animals. Testosterone concentrations are usually increased through hormonal induction, but this will harm long-term administration. The alternative offered in this problem is to give aromatase blockers both in the form of commercial drug injection (letrozole) and natural ingredients (shell powder). Aromatase blockers can inhibit the synthesis of estrogen from testosterone at certain doses that are usually different for each animal, administering aromatase blockers has been shown to increase testosterone concentration, in birds and chickens the administration of aromatase blockers did not have any significant side effects.

## 1 Introduction

Testosterone is the main steroid hormone and androgen hormone for males, this hormone is substantial for a variety of biological systems, including sexual function, reproduction process, body composition, cognition, and metabolism [1,2,3]. The testosterone concentration is very substantial in the reproductive process, the lack of testosterone concentration in males is usually induced by subcutaneous administration of GnRH to increase testosterone in the spermatogenesis testes in the seminiferous tubules [4]. Giving GnRH therapy in addition to being expensive can also reduce comfort in animals due to repeated injections [5].

GnRH therapy by intramuscular injection has been shown to maintain testosterone concentrations [6]. Long-term reactions in this therapy result in gradual storage and release thus prolonging testosterone concentrations [7,8] which makes this therapy more cost-efficient, but the use of this therapy in the long term can affect the natural mechanism of testosterone formation itself.

Luteinizing hormone (LH) produces the testosterone that stimulates the negative feedback axis, which regulates LH synthesis in the pituitary, so exogenous testosterone administration holds down LH secretion from the pituitary reducing the production of endogenous hormones and diminishing intratesticular testosterone concentration. Lower intracystic testosterone production induces low stimulation of spermatogenesis, which can lead to low production of spermatozoa and lead to infertility in males [9]. Exogenous testosterone suppresses LH synthesis and can further induce a lower sperm count [10]. [11] reported that exogenous therapy increases testosterone concentration but can decrease sperm quality.

## 2 The important role of the hormone testosterone

The hormone testosterone is also bound in muscle growth stimulation, fat metabolism, bone, and erythropoiesis [12]. The presence of testosterone can be turned into estradiol cause of the aromatase enzyme, so the concentration of testosterone in the body is untenable [13] For that is done through physiological manipulation with the help of anabolic steroids.

Testosterone concentration also impacts sexual behavior, [14] reported that libido characteristics and testosterone concentration have a positive correlation. This is reinforced [15] that a higher concentration of testosterone, is in line with higher libido. However, the concentration of testosterone fluctuates in the body suitable to the mechanism of feedback of LH hormone through the pituitary and GnRH through the hypothalamus [16]. These fluctuations arise as a result of repeated pulses that will form certain patterns, which indicate the normal function of the testes endocrine [17].

Injection of anabolic hormones is often done, GnRH injection therapy aims to increase the production of testicular testosterone and spermatogenesis in the seminiferous tubules [4]. The long-term consequences of this therapy will cause a down-regulation mechanism so that there can be a decrease in testosterone concentration [18], that replacement supplements are needed. Essential minerals for muscle, growth, immune response and reproduction in ruminant animals can be used to initiate an increase in the hormone testosterone in males [19] including Zn.

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### 3 Aromatase blocker

Aromatase blocker is a drug that can block the aromatase enzyme so that it becomes an agent that can prevent the work of aromatase enzymes so that testosterone hormone not be converted into estradiol [20] so that the concentration of testosterone in the body can be defended and spermatogenesis can increase [21, 22]. [23] reported that aromatase blockers are effective in overcoming hypogonadism, as well as minimal side effects. Its use has not been highly recommended because drug preparations are not yet commercially available [24], the drug does not react long-term and the literature is still limited [25].

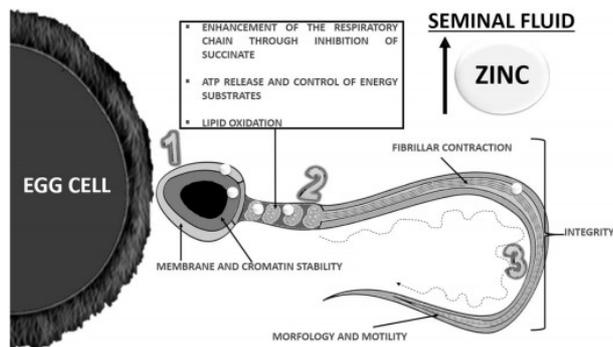


Fig. 1. Zn's steps in improving the function and structure of spermatozoa [30]

The types of aromatase blockers used today are diverse, both commercial and natural alternative products. Commercial materials such as letrozole [26] and Zn are derived from shells [27] Zinc is either the macromineral that serves to increase the concentration of testosterone in humans and mammals, this shows that Zn works by diminishing the enzyme aromatase Cyp19, an enzyme that changes testosterone into estradiol [28] Zinc inhibits the aromatase enzyme that converts estradiol into testosterone as a result, testosterone concentration will advance [29]. [4] reported that Zn improves the morphology and functional aspects of spermatozoa thus affecting spermatogenesis, on the other hand, this signal will be responded to by Leydig cells so that it will increase the concentration of testosterone (Figure 1).

Zinc works on the head (1) on the middle (2) and the tail (3) of spermatozoa. Zn on the head supports the constancy of the membrane and chromatin working on the nucleus. In the middle, Zn promotes the process of mitochondrial energy, increasing substrates by advancing adenosine triphosphate (ATP) and lipid oxidation. Mediated by axioms in the middle and tail, Zn promotes fibrillar contraction to improve the motility of sperm. In addition, Zn is important for the morphology and integrity of sperm. Increased Zn in sperm can improve the function of spermatozoa to interact with the egg [30]

Shell flour (Anadara Granosa) with a high mineral content such as Zn, Mg, Fe, and K, Zn, and Mg is a macromineral that serves to increase testosterone, therefore Anadara Granosa shells have the potential effect to increase testosterone [31]. Zn is an important transition ion and micronutrient in life and is necessary for the

activity of more than 300 enzymes [32]. Homeostasis Zn is tightly controlled in many organs and cells [30] and is largely geared toward the physiological processes of the testes and spermatozoa [33].

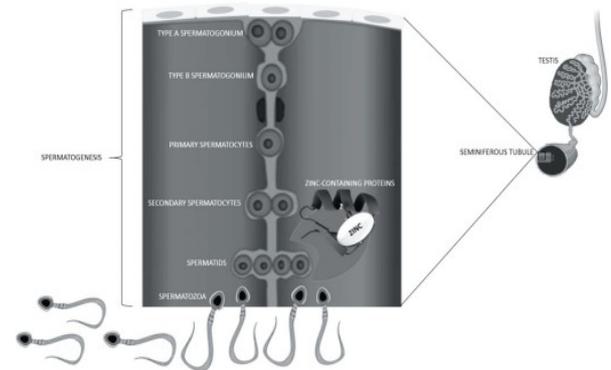


Fig. 2. Zinc is necessary for spermatogenesis, which works in seminiferous tubules. Spermatids develop in spermatozoa utilizing Zn-Containing Proteins and several enzymatic reactions [30]

Dosing in increasing testosterone is different for each type of induction. The dose is usually based on the weight and also the standard dose of the drug itself. The dose of a natural aromatase blocker to increase testosterone is 0.3 mg/30 gr of body weight in canaries [34], 6.6 gr/tail in Bangkok chickens [35], while injection of synthetic aromatase blockers in goats is 2 ml [26]. Administration Zn 0.45 mg/kg of body weight. In addition, the injection dose of testosterone hormone that can be used for chickens is 3 mg/day (0.1 ml) [22] and 500 µg in Balinese cows [36].

### 4 Zinc work path analysis

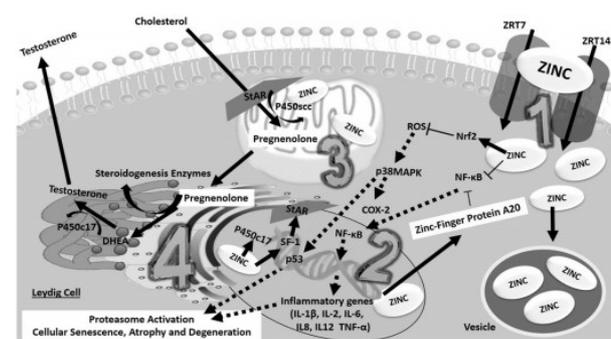


Fig. 3. Proposed Zn pathway hypothesis that might increase testosterone production [4]. Cyclo-oxygenase-2 (COX-2), Dehydroepiandrosterone (DHEA), Interleukin 1 (IL-1b), Interleukin 2 (IL-2), Interleukin 6 (IL-6), Interleukin 8 (IL8), Interleukin 12 (IL12), nuclear factor E2-related factor 2 (Nrf2), factor nuclear kappaB (NF- $\kappa$ B), p38 mitogen-activated protein kinases (p38MAPK), cholesterol side-chain cleavage enzyme (P450scc), steroid 17  $\alpha$ -hydroxylase/17,20 lyase (P450c17), Protein p53 (p53), reactive oxygen species (ROS), Steroidogenic factor-1 (SF-1), steroidogenic acute regulatory protein (StAR), Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), Zn-regulated transporter 1 (ZRT1), Zn-regulated transporter 2 (ZRT2).

Hypothetical pathways to intensify testosterone in Leydig cells are antioxidant action and steroidogenic enzyme

**Table 1.** Comparison of exogenous and endogenous

Therapy	Mechanism	Type	therapies Excess	Deficiency
Exogenous	Restore testosterone levels by supplementing various natural testosterone preparations	Intramuscular, nasal, bucal, oral transdermal, and subdermal.	Some routes of drug administration depend on the sufferer's preferences and are necessary. Increase testosterone and maintain virilization of hypogonadism. Treat hypogonadotropic hypogonadism, in which LH is high but testosterone is low.	It serves negative feedback in the hormonal process, diminishes LH concentration, and endogenous testosterone production. Diminishes the production of intratesticular testosterone, interferes with spermatogenesis, and causes infertility.
Endogenous	Affects various points in the hypothalamus-pituitary-gonadal (HPG) axis to increase endogenous testosterone production	SERM, gonadotropin, aromatase inhibitor, SARM, Leydig stem cell transplant	Increases testosterone and intratesticular levels. Maintaining spermatogenesis and the function of the HPG axis.	Probability decrease in sperm quality and complications associated with conversion in estrogen concentration. Not recognized by the FDA

Description: Luteinizing hormone (LH), hypothalamic-pituitary-gonadal axis (HPG), selective estrogen receptor modulator (SERM), selective androgen receptor modulator (SARM), Food and Drug Administration (FDA) [37].

interactions. Promotion in intracellular Zn is related to promotion in Zn, mitochondria, nucleus, cytoplasm, and vesicles stock (Figure 3). (1) Leydig cells attracted Zn and mediated by ZRT1 and ZRT2 transporters. In the cytoplasm, Zn is combined with Nrf2 stimulating proteins, such as Zn-protein A20, thereby neutralizing the extranuclear and intranuclear pro-oxidative and inflammatory pathways that interfere with Leydig cell metabolism [4].

Zinc can inhibit NF- $\kappa$ B directly. (2) In the nucleus, Zn is increased thru the availability of steroidogenic enzymes, such as P450c17 to increase the regulation of mRNA A20 and act as transcription factors for steroidogenic factor 1 (SF1), which is a precursor to StAR protein synthesis. (3) In mitochondria Zn collaborates with P450scc, and the enzyme reaction through paired with pregnenolone formation. (4) In the endoplasmic reticulum, the final process that Zn acts indirectly in testosterone synthesis since the enzyme P450c17 (that changes DHEA into testosterone) relies on Zn [4].

Zinc can be found in organic form (Zn lysine and Zn methionate), and inorganic Zn (Zn oxide, carbonate, and sulfate) [38] Sulfate is a chemical compound that is more studied in the treatment of hypogonadism, but picolinate, gluconate, and Zn citrate can be alternatives because that more absorbable than Zn oxide [39, 40]. Consensus on the ratio of prescription use of Zn does not yet exist when using anions, so the ratio of recipes should be calculated from compounds whose molecular mass is known [41].

Zinc should be given at night because it can provide high concentrations in the morning although there is no evidence to suggest that Zn is deficient when given in the morning [42]. Predictions of hormone concentration vary widely within 24 hours [43]. One of the causes of high testosterone at night when not active is because energy is not directed to other functions [44]. [45] reported that testosterone samples taken in the morning had lower values than at night, so morning sampling did not reflect endogenous peaks in animals.

## 5 Conclusion

Low concentrations of testosterone can be manipulated in both exogenous and endogenous ways. Exogenous therapy has been shown to increase testosterone concentrations, but it has a fatal impact on the natural production of the hormone. Aromatase inhibitors are an alternative to these problems that have also been shown to increase testosterone, but more research is needed. In addition, commercial preparations of aromatase inhibitors are still minimal and references are still very limited.

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