

# A New Way to Improve Male Reproductive Ability through Gut Microbiome Regulation

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## ABSTRACT

The research of intestinal flora in the field of male infertility is still in its infancy. The author reviewed the relationship between male fertility and intestinal microbiome imbalance in his previous article. There is evidence that the imbalance of intestinal microbiome will change the function and anatomical structure of intestinal barrier, leading to low-grade inflammation, metabolic disorder, endocrine disorder, insulin resistance, which will affect the mechanism of spermatogenesis. It seems that supplementing probiotics, prebiotics and Fecal Microbiota Transplantation (FMT) treatment can have a beneficial impact on patients with male fertility disorder. At present, this field has become a research hotspot. It is necessary to update and supplement new ideas and new treatment concepts.

**Keywords:** Gut microbiome; Reproduction; Vitamin A; Anxiety; Depression; New therapeutic strategies; Botanical drugs

## INTRODUCTION

Gut microbiome is a large ecosystem that interacts with the host. Gut microbiome communicates with the distal organs of the host (including the brain, liver, muscle and testis) through various complex mechanisms. For example, gut microbiome has been found to be the main regulator of androgen production and metabolism, and can even invade the Blood-Testis Barrier (BTB) to regulate spermatogenesis [1]. In the gut microbiome, the increased abundance of *Prevotella\_1* and *Bacteroides* genera was negatively correlated with sperm quality [2]. Obviously, the research of gut microbiome in the field of male infertility is still in its infancy. The author reviewed the relationship between male fertility and gut microbiome disorders in his previous article. There is evidence that the imbalance of gut microbiome will change the function and anatomical structure of intestinal barrier, leading to low-grade inflammation, metabolic disorder, endocrine disorder, insulin resistance, which will affect the mechanism of spermatogenesis. It seems that supplementing probiotics, prebiotics and Fecal Microbiota Transplantation (FMT) treatment can have a beneficial impact on patients with male fertility disorder [3]. At present, this field has become a

research hotspot. It is necessary to update and supplement new ideas and new treatment concepts.

## LITERATURE REVIEW

### New evidence for the relationship between gut microbiome dysbiosis and male reproduction

The effect of interrupted vitamin A absorption mediated gut microbiome on sperm quality: Zhang et al. reported that the modulation of gut microbiome altered bile acids levels and further affected vitamin A absorption in the host gut, and the abnormal vitamin A metabolism was transferable to the testis through the blood circulation, resulting in damaged spermatogenesis in the Metabolic Syndrome (MetS) sheep model [4]. This finding indicated that, through its ability to restore the gut microbial ecosystem, vitamin A metabolism might be a potential candidate for the treatment of male infertility in individuals with MetS. Because reduced vitamin A inhibits the expression of meiotic marker genes *STRA8* and *SYCP3* in testicular tissue resulting in decreased differentiation of early spermatocytes and vitamin A was found to have an anti-

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oxygenation effect, reducing the content of malondialdehyde and Reactive oxygen Species (ROS) in sperm, protecting sperm from ROS damage, and enhancing anti-oxygenation capacity of spermatozoa [5].

Gut microbiota dysbiosis leads to anxiety and depression: As we all know, anxiety and depression are important factors of male infertility. Previous cognition believed that external pressure, family disharmony and other factors caused brain self-regulation dysfunction, leading to anxiety and depression. Current research has increasingly revealed the important role of gut microbiome in regulating brain function and mental health. The study found that anxiety and depressive disorders are linked to human gut dysbiosis with microbiota that secrete Lipopolysaccharide (LPS) endotoxin into plasma, due to the compromised gut barrier integrity (labeled by zonulin and intestinal fatty acid binding protein-2) [6]. Strandwitz, et al. isolated a variety of GABA-producing bacteria, and found that *Bacteroides ssp.* produced large quantities of GABA. By coupling 16s ribosomal RNA sequencing with functional magnetic resonance imaging in patients with major depressive disorder, a disease associated with an altered GABA-mediated response, we found that the relative abundance levels of faecal *Bacteroides* are negatively correlated with brain signatures associated with depression [7]. Research shows that the multi-strain probiotic and glutamine formulation (Cognisol) ameliorated the MS (maternal separation)+UCMS (unpredictable mild stress)-generated anxiety-and depression-like phenotypes by reshaping the gut microbiome-brain activity in both sexes [8]. The above research provides a new treatment idea for male infertility patients with anxiety and depression, that is, to develop microbial targets to treat anxiety and depression and promote the improvement of reproductive health.

### Exploration of botanical drug in the treatment of male infertility by regulating gut microbiome

In China, the use of botanical drugs to treat male infertility has a history of more than 1000 years, and its specific mechanism of action is relatively complex and not completely clear. Studies have confirmed that botanical drugs can effectively improve semen parameters and male fertility by regulating sex hormones, reactive oxygen species, cytokines, and the testis-specific serinekinase-2 (TSSK2) gene [9,10].

Botanical drugs promote the growth of beneficial bacteria, increase the abundance of beneficial bacteria, and improve reproductive function: Wolfberry is the main drug of Wuzi Yanzong Pill, a traditional Chinese medicine for the treatment of male infertility. According to the theory of traditional Chinese medicine, it has the effect of tonifying the kidney and generating sperm. Its mechanism may be partly through the regulation of gut microbiome to promote immune function. Ding, et al. suggest that Lycium Barbarum Polysaccharides (LBPs) can promote the production of short-chain fatty acids and modulate the composition of the gut microbiota, increase the relative abundances of Bacteroidaceae, Lactobacillaceae, Prevotellaceae and Verrucomicrobiaceae, and enhance immune related cytokines (IL-2, IL-6, IL-1 $\beta$ , TNF- $\alpha$  and IFN) [11]. *Cistanche deserticola* has the functions of tonifying the kidney, strengthening

yang (Improving erectile function) and spermatogenesis, and also has a regulatory effect on gut microbiome. Research indicated that all the cistanche polysaccharides, particularly low molecular weight polysaccharides, could regulate the gut microbiota diversity, increase beneficial bacteria and particularly enhance the growth of *Prevotella spp* [12]. Chinese yam has the effect of invigorating the spleen and kidney, which is more suitable for patients with diarrhea caused by gut microbiome imbalance. Bacterial community analysis revealed that Chinese yam contributed to repair the ampicillin-induced gut microbiome disorder, enrich the abundance of *Bacteroides spp.* and *Clostridium spp.* Additionally; Chinese yam supplementation increased the production of Short-Chain Fatty Acids (SCFA) [13].

Chestnut is a common food, but it also has medicinal value. It has the effects of Supplementing Qi, strengthening spleen, tonifying kidney and strengthening tendons. Studies have confirmed that Chestnut Polysaccharides (CPs) can promote spermatogenesis, and its mechanism is that CPs can restore the damaged spermatogenesis process by regulating gut microbiome and intestinal structure. The study found that compared with the control group, the number of germ cells of mice treated with busulfan decreased, the structure of small intestine changed, and the composition of gut microbiome changed at many levels, including the phylum and genus. In contrast, the number of germ cells in seminiferous tubules was significantly increased, and the structure of the small intestine and the composition of the gut microbiota were altered in the busulfan-treated mice after the CPs treatment. The results of 16s rRNA analysis showed that the Firmicutes was the predominant phylum in all groups followed by Proteobacteria, Bacteroidetes, Actinobacteria, Tenericutes, Cyanobacteria and unidentified bacteria [14].

Botanical drugs can improve anxiety and depression and reproductive health by regulating gut microbiome: Inulin-type Fructo-Oligosaccharides (FOSs) purified from *Morinda officinalis* How, an effective oral antidepressant for mild to moderate depression. Chi et al. reported that FOSs promoted the abundance of the bacterial phylum Cyanobacteria, a group of bacteria known for the secretion of pharmacologically important metabolites, such as H<sub>2</sub>S, that exhibit antidepressant like properties. This study implied that antidepressant efficacy of FOSs was inseparable from and strongly associated with the modulation of the host's Gut Microbiota (GM) [15]. *Morinda officinalis* has the same effect as *Cistanche deserticola*. It also has the functions of tonifying the kidney, strengthening yang and generating sperm. It is a commonly used drug in traditional Chinese medicine for the treatment of oligo astheno spermia and erectile dysfunction. The above research shows that *Morinda officinalis* has antidepressant effect by regulating gut microbiome, which provides a new means for the treatment of male reproductive dysfunction patients with depression. In addition, LBP can also regulate gut microbiome, thereby reducing emotional damage caused by stress factors [16].

Botanical drugs can improve anxiety and depression and reproductive health by regulating gut microbiome: Traditional Chinese medicine commonly uses blood activating and stasis removing drugs, such as *Angelica sinensis* and *Guizhi Fuling* pills,

to treat male infertility related to metabolic disorders and insulin resistance, but the specific mechanism is not clear. In recent years, some scholars have opened up a new way for the treatment of male infertility related to metabolic disorders and insulin resistance with blood activating and stasis removing drugs from the perspective of regulating gut microbiome. Zhang, et al. reports *Angelica Keiskei* Juice (AKJ), which is rich in polyphenols, coumarins, and other healthful agents, may prevent High-Fat Diet (HFD)-induced obesity and metabolic disorders *via* changes in metabolic genes and gut microbiota composition [17]. Zhu, et al. found that Guizhi Fuling Wan can alleviate inflammation, improve insulin resistance. This effect is related to the regulating effect of Guizhi Fuling Wan on gut microbiome [18].

## DISCUSSION AND CONCLUSION

This paper quotes new ideas, such as the effect of gut microbiome on sperm quality mediated by the interruption of vitamin A absorption, and the relationship between gut microbiome disorders and anxiety and depression, which enriches the specific mechanism of gut microbiome on male reproduction and opens up new ideas for the treatment of male infertility. This paper focuses on the mechanism research of botanical drugs in treating male infertility by regulating gut microbiome and restoring intestinal micro ecology in recent years, including increasing the abundance of beneficial bacteria, improving anxiety and depression, improving metabolic disorders and insulin resistance, which provides important evidence for the treatment of male infertility with botanical drugs. Of course, at present, most of the research on gut microbiome in male infertility is focused on animal experiments, and there is a lack of large sample clinical randomized controlled trials. In the future, it is necessary to further explore the specific mechanism of gut microbiome interfering with male fertility in combination with the evidence-based medicine system. The interaction mechanism between botanical drugs and gut microbiome also needs to be further studied, such as the screening of effective components of botanical drugs, the development of accurate research models of gut microbiome, and the specific action targets of botanical drugs regulating gut microbiome.

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