

Testosterone is the primary male sex hormone, playing a crucial role in men's overall health. A decrease in testosterone levels can lead to reduced libido, erectile dysfunction, diminished sexual activity, and lower sperm production, ultimately causing infertility - a modern health issue particularly prevalent in developed countries. Low testosterone levels are often linked to metabolic diseases such as osteoporosis, diabetes, metabolic syndrome, and atherosclerosis. Additionally, research indicates an increased incidence of depression in men with low testosterone levels, affecting both older and younger individuals. It is estimated that testosterone deficiency affects about 6% of men aged 30 to 79 years. This deficiency can be congenital or result from pituitary damage or nutritional deficiencies. Endogenously produced testosterone is metabolized in the liver and then excreted into the intestines, where 83% is reabsorbed into the bloodstream. Therefore, the metabolism of steroid hormones by gut microorganisms is crucial and can significantly impact health.

Studies have shown that the gut microbiome of castrated mice can produce androgens from dietary precursors such as cholesterol and phytosterols. Moreover, the bacterium *Mycobacterium neoaurum*, isolated from the fecal samples of patients with depression and low testosterone levels, can degrade this hormone in vitro, reducing its levels in the serum and brain of healthy rats and causing depressive symptoms.

This project aims to identify gut microorganisms capable of metabolizing testosterone and other steroid hormones. We plan to isolate and identify the metabolic products of these compounds, allowing us to obtain a broad spectrum of steroid metabolites potentially formed in the human gut. Next, we will investigate whether flavonoid compounds, known as enzyme inhibitors, can inhibit testosterone degradation by microorganisms. We will utilize *M. neoaurum* strains and other testosterone-metabolizing microorganisms identified during the project. Naturally occurring plant flavonoids, such as quercetin, scutellarin, chrysin, genistein, and daidzein, will be compared with their synthetic derivatives. We will examine the effect of flavonoids on the growth of *M. neoaurum* strains and other gut microorganisms, both beneficial and pathogenic. Additionally, we aim to develop a pool of probiotics capable of reducing androstenedione to testosterone, thereby reversing the initial stage of degradation by harmful microflora.

The planned studies aim to develop strategies to limit the growth of steroid-degrading microorganisms, protect testosterone from degradation, and even reverse this process. We will create a library of inhibitors of testosterone metabolism by gut microorganisms. Ultimately, these results may form the foundation for developing therapies tailored to patients with testosterone deficiency, supporting the restoration and development of beneficial gut flora.