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Review Article

Efficacy of *Tribulus terrestris* on diabetes and sexual disorders: A narrative review

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Abstract. *Tribulus terrestris* L. (*T. terrestris*) is widely distributed worldwide (Australia, Europe, India, North Africa). It typically contains a substantial amount of active ingredients, especially saponins, alkaloids, flavonoids, tannins, terpenoids, and phenol carboxylic acids. Additionally, T. terrestris has been frequently used in folk medicine and as a food supplement, highlighting the importance of evaluating its phytopharmacological properties. Various hypotheses suggest that this species may have significant potential in preventing and improving various human conditions, including diabetes, inflammatory diseases, low sexual desire, and infertility. Phytochemical studies reveal a significant disparity in the content of active substances, with a notable gap in the concentrations of spirostanol saponins and furostanol, which are the predominant active ingredients associated with therapeutic effects. The objective of this present review is to evaluate *T. terrestris* -based formulations by exploring various potential mechanisms of action, aiming to determine whether the use of *T. terrestris* supplements is justified in the context of diabetes and its complications.

Keywords: Steroidal saponins; Diabetes; Erectile dysfunction; nutraceuticals

1. Introduction

T. terrestris is an annual plant that belongs to the caltrop family (Zygophyllaceae). It grows in warm climate and tropical regions in southern Eurasia and Africa. The name *Tribulus* is derived from the Greek word "tribolos" meaning spike fruit. *T. terrestris* is a crawling herbal plant growing up to one meter high in a sandy soil (Figure 1). The fruits used to treat many medical conditions in traditional Chinese medicine (TCM), traditional medicine in Bulgaria and Ayurvedic medicine in India (Pokrywka et al., 2014).

A variety of compounds with outstanding biological properties and complex chemical structures have been identified in *T. terrestris* extract, including steroidal saponins, tannins, alkaloids, flavonoids, terpenoids and polyphenol carboxylic acids. The factors that affect the results of the extract depend on the methods and whether fruits, leaves or roots were used (Chhatre et al., 2014). Growth conditions such as harvesting period and soil quality are great factors of the chemical composition and biological activity of *T. terrestris* (Neychev et al., 2016). As shown by Dinchev et al., the highest amount of saponins in aerial parts resulted with the preflowering and flowering periods (Dinchev et al., 2008). On the other hand, no correlation was found between the geographical and ecological conditions and the chemical composition. However, remarkable variations in compounds were noticed between samples collected within the same country (Lazarova et al., 2011).

Herbal and pharmaceutically promoted supplements that contain steroidal saponins are so common with many addressing libido disorders for both males and females, erectile dysfunction, and abnormal sperm motility, but crucial certainty for *T. terrestris* being efficient in such disorders is still unguaranteed (Gamal Edin et al., 2018). Consumption of *T. terrestris* supplements by athletes is also increasing for it being a natural performance booster. This review presents the most important phytochemical and pharmacological data with an emphasis on the prominent information related to the chemical composition, antidiabetic studies, and sexual disorder data.

Figure 1. *Tribulus terrestris* from Tunisia flora

2. Methodology

The information on *T. terrestris* was compiled via an electronic search of the following major: Science Direct, Pub-Med, Web of Science, Google Scholar and Scopus, from 2000 to 2020. The query was supplemented by searching the reference lists of papers included in the first selection. The search terms were as follows: "*Tribulus terrestris*" alone or in combination with "phytochemistry", "antidiabetic", "effects", and "sexual disorders". For this review, only full-text articles written in the English language were taken into consideration.

3. Antidiabetic Effect

3. 1. In Vitro Determinations

Studies operated with extracts from *T. terrestris*, were proven to restrain the activity of alpha-amylase and alpha-glucosidase *in vitro*. Alpha-glucosidase and alpha-amylase are enzymes tangled in the hydrolysis of carbohydrates. Alpha-amylase anatomizes the oligosaccharides into disaccharides and alpha-glucosidase anatomizes the disaccharides into absorbable monosaccharides. Inhibition of the activity of both enzymes has been shown to decrease postprandial hyperglycemia in diabetic patients.

The *T. terrestris* extracts revealed a quite high inhibition capacity on alpha-amylase more than that of alpha-glucosidase (Ercanet al., 2016). The activity of the total extract outruns the activity of isolated saponin, which means that there are other constituents in the *T. terrestris* extract that act synergistically.

3.2. In Vivo Determinations

Pharmacological induction of diabetes mellitus type 2 (T2DM) symptoms through the injection of low doses of Streptozotocin (STZ) and a high-fat diet led to morphological changes in the liver with micro vesicular fibrosis and steatosis. Supplementation with *T. terrestris* saponins did not affect the morphology of the liver of control rats, but in T2DM rats, supplementation with saponins decreased fat content in the liver, reducing the level of hepatic steatosis. This reduction can be associated with the fact that *T. terrestris* saponins expose inhibitory activity against α-glucosidase which has been previously reported (Hashim et al., 2014).

In summary, supplementation with 100 mg of *T. terrestris* saponins for one month decreased the level of lipid droplets deposited in the hepatocytes of rats with induced type 2 diabetes. In addition, it seemed to have favorable effects on the plasma lipid profile in the rats. While, in the non-diabetes group, additional supplementation with inulin had a negative effect on liver morphology. Supplementation with *T. terrestris* saponins engendered a significant decrease in the liver SCD-18 index in non-diabetes group. In addition, SCD-18 index seems to have diagnostic potential as a marker of steatosis (Chhatre et al., 2014).

3. 3. Preclinical Studies

The saponins from *T. terrestris* given to rats were able to protract the postprandial hyperglycemia by inhibiting alpha-glucosidase (Yanala et al.,2016; Zhang et al., 2005). Studies on diabetic rats and glucose-loaded rabbits lead to a concluding that *T. terrestris* extracts are able to reduce fasting blood glucose levels, which lead to thinking that the active compounds have multiple mechanisms of action (Azam et al., 2019; Sivapalan et al., 2016; Zhu et al., 2017) (El-Tantawy et al., 2007; El-Shaibany et al., 2015; Lamba et al., 2011).

While the majority of the preclinical research for *T. terrestris* extracts was conducted on diabetic rats in order to rate the different diabetes caused complications, many related to sexual disorders, all studies reported the antihyperglycemic effect of *T. terrestris* extracts. (Ghanbari et al., 2016; Tag et al., 2015; Zhang et al., 2019).

Diosgenin (Figure 2) has been shown to promote insulin secretion and induce beta cell regeneration in STZ-induced diabetes in rats through PPARγ activation in adipose tissue and oxidative stress adjustment (Kalailingam et al., 2014; Tharaheswari et al., 2014).

The incentive of PPARγ nuclear receptors assumed a probable mechanism to provoke the antihyperglycemic effect of diosgenin, is able to warrant the insulin-sensitizing action by altercating the free fatty acid/glucose ratio by allowing their intracellular consumption into adipose tissue and muscle. Intracellular consumption of glucose and free fatty acids could result from stimulation of GLUT-4 (glucose transporter 4) expression and CD36 (cluster of differentiation 36 or fatty acid translocase) as a result of PPARγ receptor activation.

Steroidal saponins and alkaloids can interact in synergy, as it was reported that imidazolidine derivatives stimulate insulin secretion by activating the imidazoline receptor type 3 binding sites in the beta cells (Soldatov et al., 2020).

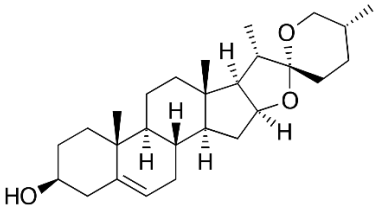

Figure 2. The chemical structure of diosgenin

3. 4. Clinical Studies

The study conducted by Samani et al. (Samani et al., 2016) organized a controlled, double-blind and randomized clinical trial that involving ninety-eight women. It was concluded that *T. terrestris* extract significantly reduced the blood glucose level of diabetic patients as compared with the placebo group. Ramteke et al. included 100 patients with diabetes mellitus and microalbuminuria (Ramteke et al., 2012).

They concluded that the group treated with an ayurvedic preparation that contained *T. terrestris* had fairly low blood glucose after the treatment comparing to the initial blood glucose level, the microalbuminuria was lowered as well.

Recent studies suggest the correlation between testosterone levels and type 2 diabetes and that low testosterone levels in men predict a high risk of type 2 diabetes (Karakas et al 2018). Moreover, the direct and indirect androgenic action of *T. terrestris* extracts can contribute in improving the glycemic profile of diabetic patients, with the fact that androgens increase carbohydrate tolerance and promote glycogenesis (Navarro et al., 2015).

Table sums up the most pertinent pharmacological studies results related to the antihyperglycemic effect of TT.

4. Sexual Problems, Impotence, and Hormonal Disbalance

T. terrestris is widely used for treatment of decreased libido sterility, soothing the menopause symptoms, and for other sexual disorders. The commercial preparations based on *T. terrestris* extracts are recommended for muscle enhancer, erection improvement, libido increase, hot flush in women, and metabolism disorders (Iacono et al., 2012; Neychev et al., 2005; Malavige and Levy 2009; Vale et al., 2018). Analytical experiments related to spermatogenesis increase and sexuality improvement can be divided into 2 main groups.

4.1. In Vivo Activities

The product TB-68 showed important stimulating activity of sexual function, libido and spermatogenesis. Neychev and Mitev,156 classified the studies on animals to determine the stimulating effect of *T. terrestris* extracts into: studies of pituitary-gonadal axis hormones, studies of sexual behavior and studies of biophysical and biochemical aspects of the erectile function effect (Neychev and Mitev, 2005).

Studies conducted on albino rats overall have shown an improvement of spermatogenesis, an increase in the number of spermatogonia, spermatozoa and spermatocytes (Tag et al., 2015; Zhang et al., 2019). There are many publications on *T. terrestris* from India, Iran and Singapore. Anderson et al. tested *T. terrestris* on castrated rabbits to develop the effects in female rabbits and the change of testosterone serum levels (Anderson et al., 2010). They concluded that there was no androgenic and estrogenic activity in castrated rabbits. *T. terrestris* did not stimulate the prostate and endocrine system; there was no activity on albino rats on the seminal vesicle, uterus, or vagina (Gauthaman et al., 2002). Gauthaman and Ganesan tested the hormonal effects of *T. terrestris* extracts in primates, rats and rabbits (Kalamegam and Adaikan, 2010). They reported an erectile dysfunction improvement and an increase in androgenic hormone levels. They concluded that *T. terrestris* had aphrodisiac activity, probably due to its androgen increasing property.

Abadjieva and Kistanova conducted an experiment on rabbits, adding dry *T. terrestris* extract to their diet for 45 days before insemination (Abadjieva and Kistanova, 2016). The authors described the changes in growth factors BMP15 and GDF9 at the mRNA and protein levels in the follicular structures of female rabbits in 2 generations: mothers and F1 female off spring. Results showed that BMP15 and GDF9 were sensitive to *T. terrestris* bioactive compounds.

4.2. Clinical Studies

Research revealed that the basic *T. terrestris* activity was due to protodioscin (PD) (Figure 3). This helps with muscle strength and the treatment of male sterility (Rogerson et al., 2007; Zhang et al., 2016).

Some authors consider that PD increases the level of dehydroepiandrosterone (DHEA) in infertile men. It can be concluded that this hormone is a precursor of Dehydroepiandrosterone (DHEA) in patients with low hormone levels (Haghmorad et a., 2019). This hormone is believed to play a role in improving cell membrane functions, and consequently in improving health in general.

Milanov et al. and Arsyad et al. suggested that PD increases the testosterone level and turns it into a strong dehydrosterone (Arsyad et al., 1996). As a result, there is an increase in red blood cells, which therefore leads to better blood circulation and better oxygen supply to the body (Karakas et al., 2018)

Tribestan (Figure 3) Tablet contains *T. terrestris* as an active ingredient. It is recommended for treatment some cases of infertility in men and women, for male impotence, for improving lipid metabolism and for the relief of neurovegetative and neuropsychic symptoms (post-castration syndrome in women).

Experiments conducted with volunteers show that PD, the major constituent of Tribestan, influences the hormone serum level of the hypothalamic-pituitary-gonadal axis without variation in concentration of adrenal hormones and adrenocorticotropic hormone. The author insisted that Tribestan is a safe preparation, with no side effects.

Kamenov et al. tested men with erectile dysfunction and hypoactive sexuality for a period of 12 weeks, and reported similar results (Kamenov et al., 2017). Tribestan improved sexual function, and the treatment was safe and easy for patients. Tabakova et al. established that *T. terrestris*'s PD improved the menopause libido disorders in women as well as spermatogenesis in onerous men (Tabakova et al., 2012).

T. terrestris extracts can be used as an alternative treatment for hypoactive libido in women during postmenopause (De Souza *et al* 149). The authors underline that *T. terrestris* is an effective source for reducing menopause symptoms and side effects. Its activity is based on the increasing of serum levels of free and bioavailable testosterone (Vale et al., 2018).

Human semen incubated with 40 and 50 μg/mL of *T. terrestris* extract showed improvement of sperm concentration, spermatozoa morphology and spermatozoa mobility in men (Khaleghi *et al*., 2017) and Shaiful et al. The authors concluded that *T. terrestris* extracts improve male fertility.

Based on this research, (Asadmobini et al., 2017) conducted that sperm vitality and mobility were improved due to antioxidant properties of *T. terrestris* extracts, and they concluded that *T. terrestris* could be used as a safe alternative for treatment of sexual disorders.

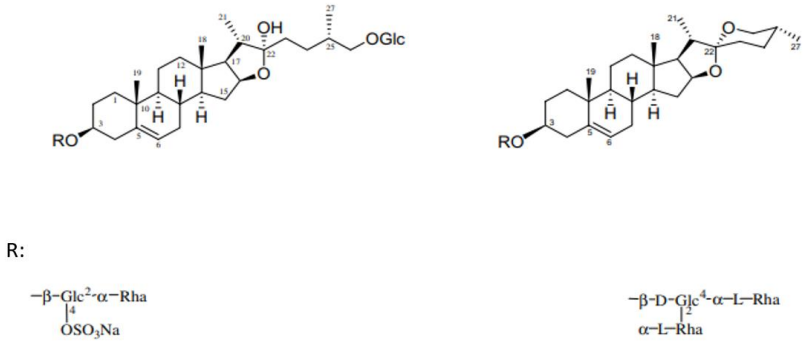

Figure 3. The chemical structure of saponin: left, protodioscin; right, tribestin

5. Conclusion

Diabetes has been associated with sexual dysfunction both in men (Feldman et al., 1994; Lu et al., 2009; Penson et a., 2003) and in women (Abu Ali et al., 2008; Enzlin et al., 2009; Olarinoye et al., 2008). *T. terrestris* is considered as a miracle

plant as it has the potential to reduce hyperglycemia due to the presence of diosgenin as well as it can alleviate the testosterone level due to the presence of protodioscin in high amount.

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