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A Review on the Adaptogenic Activity of Potent Rasayana *Tinospora cordifolia*

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Abstract

Tinospora cordifolia is an herbaceous vine that belongs to the Menispermaceae family, a succulent woody shrub genus, native to the tropical Indian sub-continent, and it is known for its common names: "Guduchi", "giloy", "amrita", "gurjo", and "heart-leaved moonseed". The recent recognition and biological role of active components in disease management in the plant have contributed to an active interest in the plant worldwide. Extracts of *T. cordifolia* are widely used as anti-spasmodic, anti-microbial, antiperiodic, immunomodulatory, anti-inflammatory, anti-arthritic, anti-allergic, endocrine disorders like anti-diabetic, hypolipidaemic, etc. in various herbal formulations to treat different diseases. It helps reduce the resistance to insulin and stress, revitalises all the tissues of the body, and spontaneously promotes metabolism. However, this adaptogenic ability is also under-explored. Stress and ageing disorders need to be treated independently. The current review paper mainly focused on stress, depression, and the anti-stress properties (adaptogen) of *T. cordifolia.* Depression and stress, along with disrupted metabolic and reproductive properties, are high-risk factors in polycystic ovarian syndrome patients. Further studies are needed to focus on adaptogenic activity to relieve certain endocrine disorders that occur due to stress, often ovarian cysts, female menstrual irregularities, and hormonal imbalance.

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1. Introduction

Natural polyherbal formulations are becoming particularly relevant in clinical science as their pre-eminent properties do not have any adverse effects compared to medications. Stress causes very specific physical and physiological changes in the body, including disruptions to the neurology, endocrine, hormonal, and immune systems. Stress is a primary etiological component in a variety of diseases, including endocrine disorders such as diabetes mellitus, peptic ulcerations, male sexual dysfunction, immune suppression, hypertension, ulcerative colitis, and mental disorders such as depression, anxiety, and cognitive and neurological dysfunctions. The herbs that relieve stress are known as adaptogens, or anti-stress agents. In ancient literature, *Tinospora cordifolia,* widely known as the "Guduchi," is known for its immense use in the treatment of different stress-related ailments[1]. Stress could be computed as the total sum of all the responses of the body that disrupt the natural physiological balance and lead to an endangered state of homeostasis[2]. Stress is indeed recognised as an international issue enhanced by advances in industrialization and a prosperous civilization. Adaptogens form a group of herbal products that promote adaptability, pliability, and the endurance of living species under stress conditions. Adaptogens should be healthy and appease minimal disturbance in an organism's physiological activity, as well as increase the tolerance to adverse effects of a large spectrum of physical, chemical, and biological conditions[3].

Tinospora cordifolia (Willd.) Miers. is renowned in Ayurveda for its Rasayana, Deepana, Jwaranashana, and Tridosha Shamaka properties. Rasayana is the name given to a path that leads to the magnificent Rasadi Dhatus. Rasayana restores normality to Rasadhatu and hence maintains the equilibrium of other dhatus (body tissues) for a significant period. Guduchi (*Tinospora cordifolia* (Wild.) Miers.) has been utilised in Ayurveda for its Rasayana effects to improve vigour and immunity for a long time. Its ability to impart youthfulness, vitality, and longevity has earned it the name "Amrita." Deepana (the capacity to promote metabolism), Jwaranashana (the ability to relieve fever), and Tridosha Shamaka are pharmacological qualities of *T. cordifolia* (helps to maintain homeostasis of doshas during stressful situations). It has been confirmed to be safe in haematological and biochemical organ function testing, and it strengthens muscles and lowers cholesterol in healthy people[1].

2. Stress

Stress is a sensation of distress, whether it be mentally, emotionally, or physically. You may make yourself feel upset, furious, or anxious about any event or situation. Stress is an answer to a threat or demand from the body. Stress can be positive in brief bursts, including escaping hazards or meeting a deadline. As per the American Psychological Association, below are three different kinds of stress (duration)—acute stress, acute episodic stress, and chronic stress. Each of the three stress forms has its own features, symptoms, and treatment methods.

Stress elements are typically categorised into mainly four kinds: physical stress[4], physiological stress[5], psychosocial stress, and psycho-spiritual stress[6]. Stress is characterised as the condition of disrupted homeostasis following exposure to external or internal undesirable events. Acute stress relates to minutes or hours of stress, while chronic stress is subjected to days, weeks, or months of stress[7]. The Hypothalamic-Pituitary-Adrenal (HPA) axis and the autonomic nervous system are the most common primary mechanisms triggered by stressors[8]. Physical stress is linked with parasympathetic innervations, whereas physiological stress is linked to sympathetic innervations. Stress has consistently been linked with depression[9] and metabolic dysregulation, impacting the intensity, duration, and usual course of endocrine disorders. Acute and chronic stressors have been documented to affect the immune system and a rise in different inflammatory markers has been reported in acute stress[10] and chronic stress[11]. Potential relationships between chronic stress and inflammatory cytokine reactions to acute stress have often been reported. Stress can cause a shift in the serum levels of several hormones, including glucocorticoids (cortisol), catecholamines, progesterone, and estrogen, etc.[13]. The HPA-axis stimulation is an influential neuroendocrine reaction to stress that facilitates longevity. This axis activation results in hypothalamic Corticotrophin Release Factor (CRF) secretion. CRF activates adrenocorticotropin, 8-lipotropin, and 3-endorphin through the pituitary gland. During stress, the plasma rate of these hormones will rise two to five times in humans[14]. For the combined

stress response, the paraventricular nucleus of the hypothalamus is essential[15]. Most of the CRF neurogenic activation is mediated by norepinephrine, serotonin, and acetylcholine[16].

3. Stress and Hypothalamic Pituitary Gonadal (HPG)-Axis

Fertility and reproduction are influenced by HPG-axis hormones. Hypothalamic reproductive regulation is guided by the secretion of the hormone that activates Gonadotropin Releasing Hormone (GnRH). Due to the pulsatile release of GnRH, it activates the stimulation of Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), and gonadotropins. The role of these hormones is to promote gamete development and to facilitate the release of gonadal sex steroids [testosterone (T), estradiol (active form 17-estradiol, E2) and progesterone (P4)][17]. Under stress conditions, inhibition of circulating gonadotropins and gonad steroid hormones contributes to the interruption of the regular menstrual cycle, leading to anovulation and amenorrhea. Extended exposure to stress may lead to gross impairment of reproductive activity[18]. Gonadotrophin, which releases the hormone GnRH from the pituitary gland, is reduced, perhaps due to enhanced endogenous CRH secretion. In Figure 1, the correlation between stress and Polycystic Ovarian Syndrome (PCOS), the stress, HPA-axis, HPG-axis, and their metabolic/endocrine effects were mentioned.

How stress interferes with, HPA-axis, HPG-axis and their metabolic/endocrine effects, and hormonal changes on the human physiology correlated with PCOS.

4. Adaptogens

The concept of "adaptogen" was introduced by the Russian scientist Lazarev in 1947 while operating on a synthetic drug, dibazole (2-benzyl-benzimidazole),

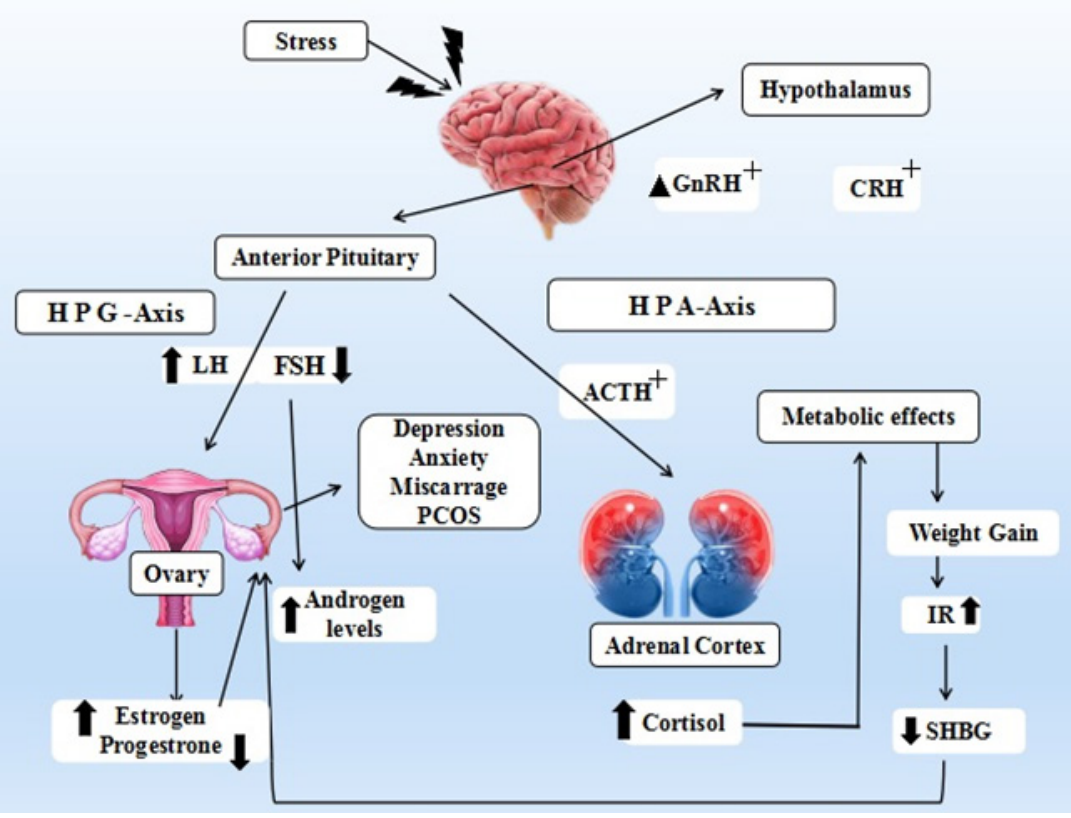


Figure 1. Correlation between stress against PCOS.

which has been found to induce non-specific tolerance of species[19]. Adaptogens are safe, hypoallergenic, non-toxic herbs or plants that are advertised as allowing the body to withstand all sorts of stressors, namely physical, chemical, or biological. These herbs as well as their roots have been used for generations in Chinese and Ayurvedic curative traditions, but today they are revived. *As such, T. cordifolia* has an immense adaptogenic and anti-stress property.

5. *Tinospora cordifolia*'s Role as an Adaptogen in Ayurvedic Formulations

5.1 In Triherbal Rasayana Ayurveda Formulation

Cordifolia is an established stress-reducing activity[19]. In comparison to that, *T. cordifolia* has a variety of properties commonly correlated with adaptogens[20,21] by evaluating Rasayana Ghana Tablet (RGT)'s and antiulcer effectiveness in laboratory animals using a pharmacologically reversed process. Distress is amongst the most serious endemics, with the ability to cause significant somatic and mental disorders. Rasayana (rejuvenation therapy) medications in Ayurveda will be used to reduce stress-induced disorders. Albino rats of the Charles Foster strain are categorised into five groups and treated as stress control, water control, RTG with vehicle control and standard control, ghee and honey treated (vehicle control). All animals received a forced swimming stress pharmacological protocol. For 7 consecutive days before stress, RGT was administered with a vehicle at a dosage of 180 mg/kg orally. Due to forced swimming in laboratory animals, behavioural changes and the animals' ability to respond to stress have been extensively studied[22]. Numerous preceding studies have demonstrated that pretreatment of adpatogenic drugs improves adrenal ascorbic acid values and avoids a reduction of adrenal cortex weight through a sparing effect of corticosteroids[23,24]. From this analysis, *T. cordifolia,* along with ghee and honey as a vehicle, RGT has strong anti-stress, ulcer prevention, and adaptogenic actions in laboratory animals.

5.2 Ayurvedic Medicine's Six Rasayana Herbs

A variety of biological stressors, physical and chemical, were taken by laboratory animals at the extrapolated dose of human dosage, to all aqueous extracts of selected plants (*Tinospora cordifolia, Asparagus racemosus, Emblica officinalis, Withania somnifera, Piper longum, and Terminalia chebula*) administered orally to laboratory animals. (i.e., the weight of dried extract as a percentage of the original plant material). The dry filtrate has been reconstituted in purified water (20 mg/mL). These plants have been shown to provide an anti-stress treatment, as determined by using stress response markers and quantitative criteria for stress events. They used *T. cordifolia* as a template for rasayanas and thus investigated whether there was a correlation between immunostimulation and adaptogenic behavior[19]. The stress symptoms are determined by the mortality rate or colony counts of organisms in the blood. The physical stressor chosen was cold (4°C). Rats are immobilised on a wooden board with their heads in a low position for 1 hour at 45°C. Experiments carried out with the above rasayana plants in the Ayurvedic community have shown the major antifungal effects on a series of stressors from *T. cordifolia, Asparagus racemosus and Emblica officinalis*. Plants that display scientific potential must be formulated into clinically useful formulations, as is being achieved with the aqueous extract of *T. cordifolia.*

5.3 Herbal Adaptogenic Tonic for Fatigue and Stress Management for Assessment

T. cordifolia as one of the principal herbs used for adaptogenic tonics for relieving stress to achieve good quality-of-life, Pharmacologic adaptogens include the most significant aspect of adaptogens' capacity to improve tolerance to both physical and emotional stress, including exposure to cold and heat, oxygen content, atmospheric pressure, radiation, hazardous chemicals, malnutrition, anxiety, and chronic diseases. Basic biochemical measures such as saliva, exhaled air, and Nitric Oxide (NO) levels in the blood, blood ACTH levels, cortisol, and certain other hormones as well as other substances, and cell processes such as phagocytosis and cytokine secretion both *in vivo* and *in vitro*, It's been reported that NO donors enhance and NO-synthesis inhibitors decrease the extent of load-bearing rat swimming, minimise the survival and lifespan of rats under hypoxia, and improve immobilization-induced stomach ulcers in rodents[25].

Considering the theory of "quality of life" with the term "adaptogens," it may be proposed that this category

of botanicals could be effective in enhancing the quality of life[26] in certain types of healthy subjects and patients. Adaptogens are likely to have a significant effect on certain areas of physical and psychological health. However, as far as quality-of-life and associated questionnaire results are concerned, there is no clinical support for this. The reports of these studies would allow the advancement of evidence-based recommendations for adaptogens as therapies to enhance quality-of-life[27].

5.4 Anti-Stress Activity of *T. cordifolia*

The non-specifically increased resistance medicinal agent was termed "adaptogens" or "athenktotropic"[28]. In order for a substance to be an adaptogen, the physiological processes of a body should be reasonably healthy and induce limited disorder; it must be non-specific, i.e., its behaviour. Several mental and physical conditions have recently been studied in order to learn more about their effects on forced swimming endurance, stress-induced gastric ulceration, stress-induced autoanalgesia, tribulin production, and adrenocortical function. Due to the continuous application of tranquillizers, cortical synchrony, skeletal muscle relaxation, and drowsiness will contribute to 28, *T. cordifolia, Centella asiastica*[29], and *Mikania cordata*. A number of stressors, including ulcers and milk-induced leukocytosis, are successful against various stressors[30-32]. The results of shifts in biogenic amines caused by stress were shown. The norepinephrine and dopamine levels of *T. cordifolia* were increased and, after stress, the levels in the whole brain were lowered, which indicated that an anti-stress operation was performed.

Stress in response to demands posed by various types of stressors is the excitation of the body, mind, and actions. Mental stress and blood glucose levels were slightly more strongly related, while serum fluid concentration was weakly connected to mental stress. A significant correlation was found in this research between behavioural phenomena such as fear, depression, and mental stress. Plants with flavonoid and phenolic compounds have good antioxidant characteristics[33]. Several laboratory trials have demonstrated the major antioxidant impact of *T. cordifolia*. Hence, the observed adaptogenic activity of *T. cordifolia* stems is at least partially due to its antioxidant properties.

The results indicate that *T. cordifolia* along with yoga practice[34] have important anti-stress adaptogenic actions, as shown by their mitigation effects on many chronic stress-mediated biochemical and behavioural disruptions, similar to those induced by the well-known adaptogenic agent diazepam.

6. Stress and PCOS

PCOS has a diversified etiology, comprising a number of heterogeneous variations, i.e., metabolic, reproductive, genetic, and environmental (stress) factors. To date, no single aetiology has been shown to have particular predictive ability to explain the phenomenon of PCOS. Investigators conclude that environmental factors (such as diet, pollution, and exercise) and stress have an impact on the occurrence of PCOS. Certain potential factors entail inadequate prenatal sensitivity to androgens and excessive[35] production of insulin. The exact aetiology of PCOS is unclear, but many of them believe that it may be caused by:

- Excess LH secretion in comparison to FSH Hyperinsulinemia: a defect in insulin action or production (i.e., insulin resistance, Type II diabetes).
- Androgen excess: ovarian or adrenal stress is an unseen feature influencing daily life and is closely correlated with multiple disorders, particularly PCOS[36]. Eventually, the hyperactivity of the HPA-axis might be related to the high frequency of psychopathological and eating disarray in women with PCOS, reflecting a deviant metabolic rate in acclimatisation strategies to chronic stress exposure[37].

7. Stress and Insulin Resistance (IR)

Besides this, there is a somewhat limited knowledge of the mechanisms relating insulin resistance to acute psychological stress. We also presumed that acute psychological stress can affect the development of insulin resistance, which may be a contributor to the cause of type 2 diabetes[38]. IR can arise from several pathways, involving a change in the number or role of the insulin receptor or

a defect in the insulin signalling pathway[39]. IR is found in secondary tissues such as the liver, muscles, and adipose, but also in the brain, which is the core function of insulin that involves controlling food consumption, body weight, learning, and memory[40,41]. Within reach are several pathophysiological pathways hypothesised to link persistent psychologic stress or depression with IR or diabetes[42-46]. *T. cordifolia* is a plant having good anti-depressant like action; three is a clear manifestation of the participation of monoaminergic and GABAergic transmission in the mice, proving the antidepressant function of *T. cordifolia. In the Indian Ayurvedic system, Cordifolia* is used as an immunostimulant and for the treatment of diabetes, rheumatoid arthritis, and jaundice. Experimental studies have looked into its anticancer, antioxidant[48], hepatoprotective[49], hypolipidemic, hormonal disorders (PCOS), and immunologic properties, but there have been few clinical trials.

Herbs that undertook PCOS clinical trials in 25-40-year-old subfertility women referred to *T. cordifolia* were taken twice a day at a dose of 5 gms. They reported improvements in ovarian weight and size accompanied by an LH/FSH ratio by ultrasonography[50]. Based on Ayurveda (Ayurvedic regimen 5g of *T. cordifolia* has been taken in stage 2 twice a day in the morning and evening), shodhana's, shamana's, and Tarpana's beliefs and the clinical efficacy, a total of 40 patients were chosen by a purposeful process of sampling. For a total of 6 months, therapy was performed in 3 stages. The clinical effect was noted and months of therapeutic effects were evaluated. Transvaginal screening, LH, FSH, and hormonal levels were improved, hence subfertility because of PCOS has been successfully treated using the Ayurvedic care protocol[51]. From the above regimens, we conclude that *T. cordifolia is* not only a good adaptogenic but also has good therapeutic value in treating endocrine disorders like cognitive deficits[52], anxiety, depression[53], diabetes (IR)[54], PCOS, anti-inflammatory[55], anti-oxidant and antibacterial[56], etc. Beyond this, in Ayurveda, *T. cordifolia* has many such medicinal qualities, including immunity ("Ojas") booster, cures fever, jaundice, chronic diarrhea, cancer, skin diseases, bone fractures, eye disorders[57], poison insect bites, anemia, asthma, snake bites etc.

In a recent study, Insilico findings indicate that the antagonistic ligands Rumphioside I, Syringin, and Berberine inhibit IRS1 and IRS2 receptors[58]. Following thorough preclinical and clinical testing, it can be concluded that these compounds can be used to treat PCOS.

8. Conclusion

Very few rasayan medicinal herbs have been found to be neuropsychology, immunomodulation, and adaptogenic. *T. cordifolia* Miers (Menispermaceae) is the one such plant having essential rasayan medicinal properties that has historically been used since ancient times. Adaptogens usually mean that they adapt or induce an adaptation response and tend to improve the organism's or individual's general defensive strength and increase physical tolerance for functioning even in challenging situations. *T. cordifolia* enhances tolerance for environmental changes and susceptibility to adverse stimuli, such as temperature, cold, pain, and infectious organism exposure. Further detailed investigation has to be done to enhance awareness and usefulness for the wellbeing of individuals.

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