Ashwagandha in restoring healthy circadian rhythm

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There is growing evidence that sleep disorders are an emerging global epidemic. There are over 70 recognized sleep disorders of which insomnia is by far the most commonly experienced. The statistical data available mostly from populations in Western countries point to trends in decreasing duration of sleep and higher prevalence of insomnia and other sleep disturbances. For example, in Canada and the United States more than 20% of the general adult population suffers from insomnia, with a projected increase in cases over the next few decades.

Chronic insomnia is defined as inability to achieve full, undisturbed sleep at least three nights a week for a month or longer. The growing problem when considering resolution of insomnia is finding safe and effective treatments; the safety of sleep aids should be carefully considered to avoid short-term and long-term side effects including dependency and the diminishing efficacy overtime.

This paper will first outline the basics of sleep and insomnia and then discuss a potential emerging class of time-proven, safe and effective nutraceuticals in management of insomnia, as exemplified by an adaptogen and bioprotective botanical, *Withania somnifera* vern. Ashwagandha.

Insomnia is the inability to fall asleep or stay asleep and it is now believed that various physical, psychological factors, and both pathology and physiology, including aging, are related to disruption of our 24-hour wake and sleep time-keeping system – or circadian cycle (Latin meaning "around a day"). The sleep patterns are linked to alterations in the body's normal timekeeping system, with insomnia characterized by several symptoms including: difficulty falling sleep at night, waking often in the middle of the night with trouble returning to sleep, or a repeated pattern of an unusual early morning wakeup. Losing quality of sleep regularly can lead over time to a persistent feeling of being tired, daytime sleepiness, general lack of energy, difficulty concentrating on task at hand, mood and behavioral disturbances such as irritability, aggression and impulsive behavior, failing memory function, troubles in personal and professional relationships and overall decreased quality of life, including mental depression.

THE ROLE OF THE CIRCADIAN CYCLE IN HEALTHY SLEEP

Sleep is controlled by an internal clock regulating the 24-hour day and night cycle known as circadian rhythm or cycle. The cycle controls practically all aspects of the body's physiological and behavioral processes, especially the brain, e.g. brain wave activity, alertness, hormone production and the immune system responsible for body's integrity and regenerative processes. The circadian sleep cycle is controlled by the **suprachiasmatic nucleus**, located at base of the brain at its oldest structure called hypothalamus. This structure regulates circadian rhythm, which depends on the light impulses from the external world entering via the eyes to stimulate or inhibit processes related to sleep, including the release of the sleep hormone, melatonin, from the pineal gland at the base of the brain. Insomnia starts when this mechanism is disrupted as a result of, for example, a psychological stress and being awake at night or jet lag, when the light signals reaching the eyes do not work when we travel in multiple time zones.

Stages of Sleep

Human sleep occurs in two distinct stages which alternate during night sleep. These are known as the Rapid Eye Movement or REM and non-REM sleep. The non-REM initiates the sleep cycle and is based on four stages: non-REM light sleep or stage 1, decreased awareness or non-REM stage 2, and deep sleep or non-REM stages 3 and 4. The deep sleep allows the body to regenerate including patching-up the wear-and-tear conditions, building up bones and muscle, recharging the biochemical energy and strengthening the immune system.

The REM phase of sleep is characterized by dreaming accompanied by so-called rapid eye movement. This stage of sleep is thought of as involved in memory consolidation and formation, i.e. the brain "reviews" the previous day's experiences to store long-term memories. Adult humans spend almost 50 percent of their total sleep in stage 2 non-REM sleep, about 20 percent in REM sleep, and the remaining 30 percent in the other stages. Infants, by contrast, spend about half of their total sleep time deep in REM sleep.

How Non-Restorative Sleep Affects Health

Our understanding of the importance of a deep restful sleep grows with accumulating daily discomfort and objective ill-effects from non-restorative sleep or NRS, a condition especially noticeable in aging populations. The non-restorative sleep condition becomes apparent with a persistent complaint of being unrefreshed upon awakening, even with the normal night sleep duration. Typically, the subjective experience comes after a period of a month with a sleep disorder. NRS can be described as a cumulative effect of insomnia. The objective importance of NRS necessitates attention because it may contribute to several health problems, especially cardiovascular disease, fibromyalgia, and chronic fatigue syndrome. The importance of addressing NRS further intensifies because it may be present without obvious insomnia symptoms, such as difficulty in initiating and/or maintaining sleep. Therefore, when NRS exists, one's well-being and health can deteriorate without us knowing or recognizing the underlying problem.

ADJUSTMENT OF CIRCADIAN RHYTHM WITH ADAPTOGENS AND BIOPROTECTANTS

***W**ithania somnifera* (Fam. Solanaceae) known in India as Ashwagandha, is a botanical compound that has been consistently used in Ayurveda traditions to help cope with physical and psychological stress, support memory, executive functions, sleep as well as the immune system functions. As a rule, Ayurveda medical treatments have been designed to be harmless while still offering broad regulating effects for the body. This characteristic applies particularly to the group of botanical and mineral treatments exemplified by traditional Rasayanas or vitalizers. The traditional concept of a vitalizer has likely inspired the contemporary idea of adaptogen – a substance that protects body from the effects of stress – a term that was proposed in the 1950s by Nicholai Lazarev and Izrail Brekhman of the Russian Institute of Marine Biology, Vladivostock. Their work has been influenced by the earlier work of Hans Selye, the endocrinologist from McGill University, Montreal, Canada, who, in the early 1930s, defined stress and its effects on the body. He found that animals subjected to diverse nocuous agents – stress-causing physical, biological and chemical agents – responded with a three-stage reaction:

1. General alarm reaction, characterized by enlarged lymph nodes, spleen and adrenals which were depleted of cortisol and vitamin C;
2. Resistance, characterized by normalization of symptoms seen in previous stage; and
3. Exhaustion, characterized by symptoms similar to the alarm reaction stage – often leading to a chronic disability or death.

Brekhman described the characteristics of compounds considered adaptogens as increasing the non-specific adaptation energy needed to cope with a broad range of physical and psychological stress. In 1995 Badmaev and Sabinsa Corporation proposed the term "bioprotectant" to describe any compound that would protect the integrity of the body's cells, tissues and organs by **preventing** Selye's stress mechanism and **intervening** to stop the stress effects. The term "bioprotectant" is equivalent to the term "adaptogen", but the former may be more practical way in explaining the approach to stress management.

Ashwagandha standardized for its active principles – primarily for alcohol soluble compounds like withanoside IV, withaferin A, withanone, physagulin D, 27-hydroxywithanone, withanoside V & VI, withaferin A, withastramonolide, withanolide A, withanon, withanolide B, sominone, ashwagandhanolide and also water soluble triethylene glycol – exemplifies adaptogens and bioprotectants and has been evaluated in several experimental models of stress induced by physical, chemical or psychological factors.

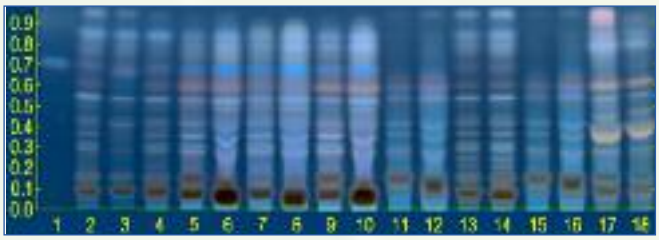
PRECLINICAL AND CLINICAL STUDIES OF ASHWAGANDHA IN SLEEP DISORDERS

Despite the centuries-old applications of Ashwagandha in Ayurveda, the science on its potential in promoting healthy sleep has developed only recently. In a 2017 published preclinical study, researchers evaluated various components derived from Ashwagandha leaf on the sleep patterns in mice (1). The alcoholic extract that had a high content of withanolides was ineffective to induce sleep in mice, however, the water extract standardized for triethylene glycol significantly induced the non-rapid eye movement sleep with only slight change in the rapid eye movement sleep pattern. These findings were further supported by a commercial-grade triethylene glycol inducing in a dose-response manner, 10 to 30 mg/mouse, the non-rapid eye movements in experimental animals. Therefore, the water extract of Ashwagandha leaves could potentially be useful for improving deep restorative sleep in human subjects.

The water extract of Ashwagandha leaves was further studied in sleep-deprived rats for the anxiety-like behavior and the inflammatory and apoptotic markers expression in the hypothalamus, where circadian impulse processing takes place (2). The sleep-deprived animals showed a high level of anxiety in elevated plus maze test, with a significantly improved performance when treated with Ashwagandha water extract. Ashwagandha lowered the sleep-deprivation stress induced inflammatory markers, improved the immunity and alleviated inflammation induced program cell death in the brain. The described pattern of biological response in sleep deprived rats provides molecular grounds for potential anxiolytic properties of the water extract of Ashwagandha leaves.

The correlation between cognitive improvement and the molecular markers was further confirmed in a follow-up preclinical study with water leaf extract of Ashwagandha in sleep deprived rats (3). The Ashwagandha-treated animals improved performance in the elevated maze test vs. untreated rats along with the improvement in the expression of proteins involved in neuronal survival and neural impulses conductivity in the brain.

Based on the literature data, Ashwagandha is an effective and safe compound in reducing chronic inflammation and also exerts anti-anxiety and anti-depressant effects; this profile has recently led to a hypothesized use of this plant in management of NRS. The described hypothesis has resulted in a proposed clinical study to investigate a



*High Performance Thin-Layer Chromatography of Ashwagandha root extract**

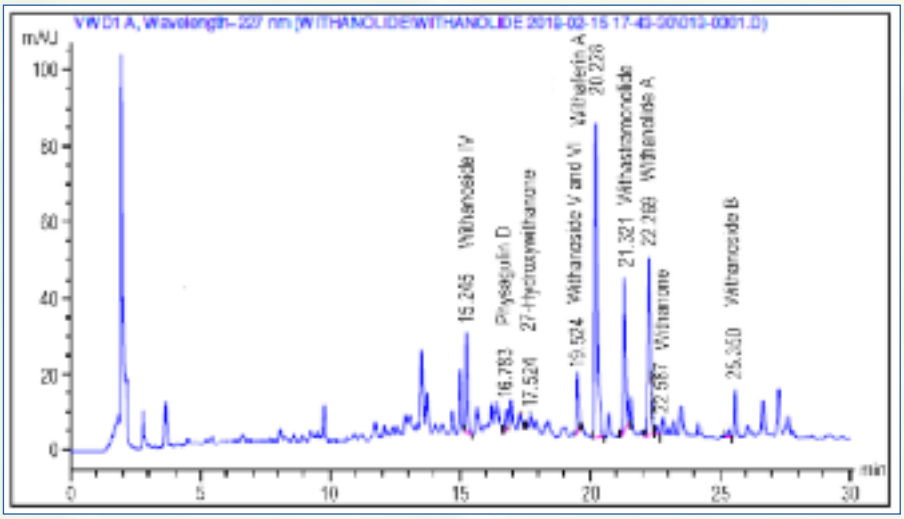


*Figure 2 – USP HPLC of Ashwagandha Root (Extract)**

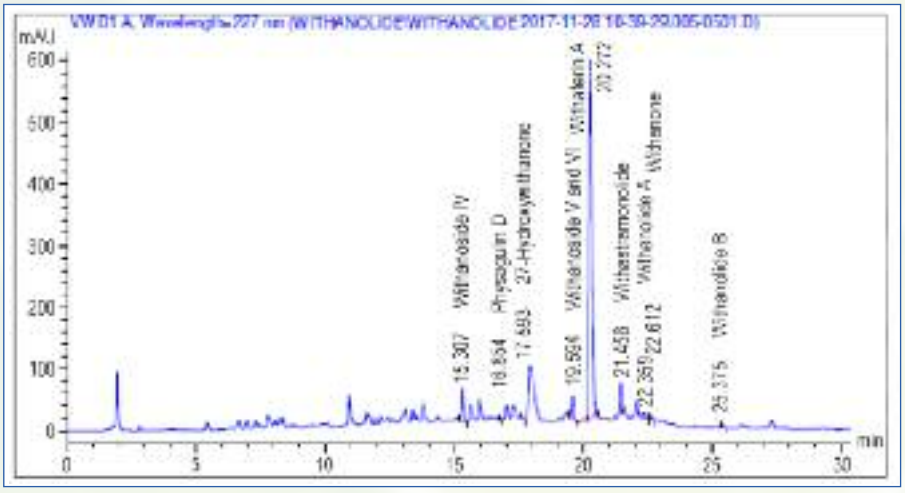


*Figure 3 – USP HPLC of Ashwagandha Whole Plant (Extract)**

hydroalcoholic extract of roots of Ashwagandha standardized for 35% glycowithanolides in subjects with NRS. The standardized extract or matching placebo will be given to the patients to provide 21 mg daily of glycowithanolides, before bedtime, for 6 weeks.

The primary objective of this trial-in-progress is to evaluate effects of daily supplementation of Ashwagandha extract vs. placebo in subjects with NRS for 6 weeks, assessed with a questionnaire for a potential improvement in restorative sleep.

The secondary objectives of the trial are to compare the Ashwagandha extract vs. placebo on a subjective and objective change during the 6 weeks in parameters including an average total sleep time during a week, sleep efficiency – e.g. sleep onset latency, frequency of awakenings during the night – and the questionnaire-based score of quality of life, including depression and anxiety scores.

Based on the above discussed published preclinical studies and the above outlined clinical study in-progress, it is plausible to assume that various parts of the Ashwagandha plant may provide more than one active ingredient improving quality of sleep. There are multiple biological mechanisms offered by Ashwagandha that may directly or indirectly affect the quality of sleep, e.g. lowering markers of inflammation like c-reactive protein and TNF-alpha, preventing inactivation of neurotransmitters like acetylcholine, suppressing overproduction of the stress hormone like cortisol, preventing wear-tear of the neurons and regenerating their function, and lessening risk of development of chronic degenerative and neurodegenerative conditions.

STANDARDIZATION OF ASHWAGANDHA EXTRACTS

Consideration of Ashwagandha in management of sleep disorders should take in account, that various parts of the plant may have different ingredients affecting sleep in a unique way, and that the specific sleep-improving ingredients maybe obtained in different extraction methods and with different solvents, e.g. triethylene glycol obtained with water extract of leaves and whitanolides with alcohol extract of roots. The process of traceability of the Ashwagandha plant and identification of parts of the plant, e.g. leaves and/or roots is practically important and can be accomplished by the thin-layer-chromatography, TLC method, or the so-called "fingerprinting" of tracer chemicals method (Figure 1)*. The composition of the extract studied for sleep disorders should be evaluated with the USP monographed method by the HPLC (Figures 2, 3)*. As previously mentioned, the active components of Ashwagandha extract may vary depending on the part of plant subject to extraction process, e.g. leaf, bark, stem and roots of the plant, showing that the rigorous analytical process is necessary to obtain a quality product standardized for a specific content (4) (Figures 2, 3)*.

The potential role of Ashwagandha in restoring healthy, normalized circadian rhythm function goes beyond giving us a quality and restful sleep; it may potentially address the cardiovascular function, functioning of the central nervous system and the regenerative and immune responses of the body. Ultimately, our optimal life-span may depend on securing an undisturbed circadian cycle.

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* Analytical data provided by Unicorn Natural Products Ltd., Hyderabad, India.