Efficacy and Safety of a Full Spectrum Root Extract of Ashwagandha (*Withania somnifera*) in Improving Cardiorespiratory Endurance in Healthy Athletic Adults

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KEYWORDS: Withania somnifera, high-concentration full-spectrum Ashwagandha root extract, adaptogen, cardiorespiratory endurance, quality of life.

ABSTRACT

Background: : Cardiorespiratory endurance is generally recognized as a major component of physical fitness. Maximum oxygen consumption (VO_2max) is an international reference standard for measuring cardiorespiratory fitness. Ashwagandha, an excellent source of antioxidants is an excellent 'adaptogen' that increases the ability of a person to adapt to environmental, physical and mental changes by modulating the metabolism and the body's processes. It leads to cell replenishment that in turn reduces fatigue symptoms and exhaustion, and increases resilience of the body imparting more stamina for physical activities.

Aim: The present study aims to evaluate the safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha roots in enhancing cardiorespiratory endurance and improving the quality of life in healthy athletic adults.

Subjects and Methods: This study was a single center, prospective, double-blind, randomized placebo-controlled trial. A total of 50 subjects were enrolled into the study following a specified screening protocol for determining the baseline values of the parameters to be studied (Day 0). The study subjects were randomized to either: (i) Group I – the Placebo-treatment Group or (ii) Group II – the Study Drug-treatment Group. The study subjects in Group II were administered one capsule (containing 300 mg of high-concentration full-spectrum root extract of the Ashwagandha plant) orally, twice daily for a period of 12 weeks; whereas, in Group I one capsule containing matching placebo 300 mg was administered similarly. During the treatment period (12 weeks), the subjects were required to present themselves at the trial center on specified intervals. Visit 1 was at Day 28 ± 3 days, Visit 2 was at Day 56 ± 3 days and Visit 3 was at Day 84 ± 3 days. Final safety and efficacy assessments were done on Day 84 of the study. Statistical analysis of the data was done using paired and unpaired t tests. Values are expressed as mean ± SD.

Results: Treatment with full-spectrum extract of Ashwagandha roots significantly ($p < 0.0001$) increased the cardiorespiratory endurance and improved the quality of life of the study subjects. A progressive increment in the enhanced cardiopulmonary fitness and the improved quality of life of the study subjects was observed at Day 56 and Day 84 of the study period. The VO_2max increase from the baseline value to at Day 0 of the study period was 4.91 $\pm$ 1.72 Day 0 and to 5.67 $\pm$ 2.15 on Day 56, corresponding to percentage increases of 11.8% and 13.6% respectively. The percentage increase in The quality of life was assessed on the basis of their response to the questions of the World Health Organization, Quality of Life (WHO-QOL) Questionnaire. This suggests sustained beneficial effects of Ashwagandha and evidences the safety of the root extract on moderately long-term use.

Conclusion: The findings of this study suggest that a high-concentration full-spectrum Ashwagandha root extract safely and effectively enhances the cardiorespiratory endurance and improves self-assessed quality of life in healthy athletic adults.

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INTROUCTION

Ashwagandha (*Withania somnifera*), also known as Indian Winter Cherry, is extensively used in Ayurveda, the traditional health care system in India. This herb is used as a general tonic and "adaptogen," helping the body adapt to stress. In addition, it has been shown to possess antioxidant properties as well as an ability to support a healthy immune system (Singh *et al*., 1982; Mishra *et al*., 2000; Provino, 2010).

Ashwagandha is a popular medicinal plant in South East Asia and Southern Europe. Many people use this herb for general vitality. Although it is not botanically related to ginseng, Ashwagandha is often called "Indian ginseng" due to its rejuvenating effects (Weiner *et al*., 1994; Mishra *et al*., 2000). Nonetheless, the specific effects are not similar to ginseng. Rather than providing restless energy as does ginseng, Ashwagandha often causes relaxation. Ashwagandha is known to increase energy and promote weight loss through stress reduction.

In Ayurveda, certain herbal formulas are considered to be rejuvenating (Singh *et al*., 1982; Shastri, 1999; Andrade *et al*., 2000; Dhuley, 2000; Mishra *et al*., 2000; Mirjalili *et al*., 2009; Singh *et al*., 2011). These formulas are called Rasáyana tonics, taken as a remedy for general weakness and exhaustion, as well as for their stress-relieving qualities. Ashwagandha is valued for its ability to increase vitality, energy, endurance and stamina, promote longevity and strengthen the immune system without stimulating the body's reserves. Chris Kilham, a renowned author, educator and the founder of Medicine Hunter Inc., in accordance to the *Indian Materia Medica*, emphasized the use of Ashwagandha for general debility, impotence, brain fatigue, low sperm count, nervous exhaustion, and in situations in which general vigor must be restored, as Ashwagandha builds strength from within.

Because the *primary* quality and flavor of Ashwagandha is sharp and pungent, this indicates that it raises metabolism, stimulates digestion, clears mucus and improves circulation. However, Ayurveda also identifies a *secondary* post-digestive flavor, which for Ashwagandha is sweet. This effect, though not necessarily directly identified by one's sense of taste, occurs when a substance is converted into a still purer nutritive extract, preserving the critical balance of the various constituents (Sharma, 1976; Subramanian, 1982). The root contains antioxidants, iron, amino acids, flavonoids and many active ingredients of the withanolide class. Numerous studies suggest Ashwagandha can directly and indirectly prevent and treat a number of diseases (Malhotra *et al*., 1981; Mirjalili *et al*., 2009; Sukanya *et al*., 2010).

The present study employs a full-spectrum root extract of Ashwagandha, which retains and potentiates the synergism in the whole root. It is noteworthy that although various Ashwagandha powders and extracts are available commercially, there are serious shortcomings in standardization and optimization of Ashwagandha extracts. The Ashwagandha root extract used in the present study (KSM-66 Ashwagandha from Ixoreal Biomed Private Ltd.) has been extracted with a unique processing technology, producing a broad spectrum phyto-pharmaceutical that potentiates the action of the Ashwagandha manifold, providing pan-therapeutic effects. In addition to the desired quantum of withanolides and alkaloids, KSM-66 Ashwagandha contains short- and long-chain amino acids (theonine, valine, methionine, isoleucine, lysine, aspartic acid and arginine), complex sugars including oligosaccharides/fructo-oligosaccharides, vitamin A, calcium and iron

Earlier studies clearly indicate that the traditional use of Ashwagandha has a logical and scientific basis (Singh *et al*., 1982; Mishra *et al*., 2000). Nonetheless, clinical studies are needed to prove the clinical efficacy of this herb, especially in cardiovascular endurance and physical performance. Hence, the present study was designed with a *two-fold* objective: (i) to evaluate the safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha roots in enhancing cardiorespiratory endurance and (ii) to improve the quality of life in healthy athletic adultsAshwagandha

SUBJECTS AND METHODS

A randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy and safety of a full-spectrum root extract of Ashwagandha

(*Withania somnifera*) in improving cardiorespiratory endurance in healthy athletic adults.

Subject Recruitment and Screening

The subject's eligibility to participate in the study was evaluated on Day 0. Subjects who met the inclusion criteria were randomly assigned to either: (i) Group I – the Placebo-treatment Group or (ii) Group II – the Study Drug-treatment Group. The study subjects in Group II were administered one capsule (containing 300 mg of high-concentration full-spectrum root extract of the Ashwagandha plant) orally, twice daily for a period of 12 weeks; whereas, in Group I, one capsule containing matching placebo 300 mg was administered similarly. During the treatment period (12 weeks), the subjects were required to present themselves at the trial center on specified time points, designated as "Study Visits".

The study comprised of four visits:

Visit 0 – Screening and *Baseline Visit* (Day 0)

Visit 1 – Treatment Visit-I (Day 28 ± 3 days)

Visit 2 – Treatment Visit-II (Day 56 ± 3 days)

Visit 3 – Treatment Visit-III / *Final Visit* (Day 84 ± 3 days) [Table 1].

Subject Selection

Inclusion Criteria

1. Healthy athletic male and/or female adult subjects aged between 20 and 45 years.

2. Subjects within the body mass index (BMI) range of 18.5 to 24.9 kg/m^2

3. Subjects willing to provide written informed consent and

4. Subjects able to communicate effectively and able to comply with protocol requirements

Exclusion Criteria

1 Contraindications or hypersensitivity to Ashwagandha and related herbal products.

2 History or presence of any medical condition or disease according to the discretion of the Investigator.

3 History of significant renal or hepatic impairment.

4 History of significant asthma, urticaria or other allergic reactions

5 History of severe gastrointestinal disorders such as malabsorption syndrome.

6 History of diabetes, coronary artery disease and hypertension with or without complications

7 History of any chronic physical, hormonal or psychiatric disorder

8 Morbid obesity (percent fat 40%)

9 Any medical condition where exercise is contraindicated

10 Recent surgery or trauma that incapacitates the subject for exercise

11 Currently taking any herbal preparations (such as other formulations containing Ashwagandha, ginseng, Brahmi, Ginkgo biloba)

12 Individuals refusing to use appropriate non-hormonal birth control measures

13 Female subjects who were pregnant or breast feeding.

14 Subjects participating in any other trial.

In addition, individuals who were engaged in regular strenuous physical activity were also excluded from the study.

This was a double-blinded study, where the study subjects and the physicians were completely unaware as to whether a subject would receive the test drug or the placebo. Data were recorded in the *Source Document* and *Case Report Forms* (CRF) from available subjects till 12 weeks.

A total of 50 subjects were enrolled in the study. There was no subject attrition in Group II. One sub-

ject discontinued in Group I. The results of the study give the data of 49 subjects.

Parameters to be Assessed

(i) *Efficacy of a full-spectrum root extract of Ashwagandha on cardiorespiratory endurance*

The primary objective of this study was to explore the effect of Ashwagandha on cardiorespiratory endurance. At Visit 0, Visit 2 and Visit 3, the 20 meter shuttle run test was performed and the results translated to VO_2max measures.

The results of Visit 2 and Visit 3 were compared with the results of Visit 0 to evaluate the effect of KSM-66 Ashwagandha on cardiorespiratory endurance.

(ii) *Effect of a full-spectrum root extract of Ashwagandha on Quality of Life (QOL) profile*

For evaluating the effect of Ashwagandha on the quality-of-life (QOL) profile of the study subjects, their response to the World Health Organization's Quality of Life (WHO-QOL) questionnaire was obtained at Visit 0, Visit 2 and Visit 3. The scores of Visit 2 and Visit 3 were compared with the scores of Visit 0.

Drug Dispensing

The coded drug bottles were dispensed at the time of baseline visit. The subjects were asked to take the capsule twice daily, after food with a glass of plain water at the designated time. The subjects were instructed not to break or chew the capsule.

The drug accountability was checked at the final visit by counting the remaining capsules and calculating the missed doses during the study period.

Treatment Compliance

The subjects were instructed not to throw the capsules in case any dose is missed; and to return the unused drug on the final visit – the end of the study (Visit 3); these were counted to check for subject compliance. Subjects should have at least 80% treatment compliance.

Ethical Considerations

This clinical trial has been conducted in compliance with ICH-GCP, Schedule-Y, Institutional research policies and procedures (IRB/IEC) and all other applicable regulations. The protocol of the study was submitted to a properly constituted IEC in agreement with legal prescriptions for formal approval of the study conduct.

Statistical Analysis

The data were analyzed for statistical significance by using the Student's 't'-test and one-way ANOVA for the level of significance. Mann-Whitney U test was used to compare the 20-meter shuttle run test and Borg's Scale Score between groups. Wilcoxon signed rank test was used to test the significance of quality of life change between Visit 0 and after Day 56 (Visit 2) and Day 84 (Visit 3) of the treatment protocol. For all analysis, the *P* value used for statistical significance was 0.05. All results are expressed as mean ± standard deviation.

RESULTS

The collected data characterize the observation of the effect of a full-spectrum root extract of Ashwagandha, on the specified parameters in 49 study subjects aged between 20 and 45 years, with BMI within the range of 18.5–24.9 kg/m^2.

In the present study, treatment with the root extract of *Ashwagandha* resulted in significantly ($p < 0.0001$) increased maximum oxygen consumption (VO_2max) at Day 56 and Day 84 of the study period as compared to the baseline value. In the Ashwagandha treatment group, the VO_2max measure on Day 0 was 41.74 ± 5.21. On Day 56 and on Day 84, the VO_2max measures were 46.65 ± 6.29 and 47.41 ± 6.63 respectively. These correspond to increase in VO_2max from the baseline value to at Day 0 of the study period was 4.91 ± 1.72 Day 0 and to 5.67 ± 2.15 on Day 56. See Table 2. The corresponding percentage increases are 11.8% and 13.6% respectively. These increases are highly statistically significantly different from the corresponding changes in the placebo control group at the $p < 0.0001$ level.

Furthermore, in the present study, Ashwagandha was shown to exert a highly significant beneficial effect on the QOL of the study subjects, assessed on the basis of their response to the questions of the WHO-QOL Questionnaire. The results are summarized in Table 3. The data of the present study show highly significant ($p < 0.0001$) improvements in the physical and psychological health and the social relationship status of the study subjects at Day 56 and Day 84 of the study. The status of the environmental impact on the QOL of the study subjects was found to be increased substantially; *albeit,* not significantly at Day 56 and significantly ($p < 0.01$) at Day 84 of the study period.

DISCUSSION

The present study aimed to assess the effects of a full-spectrum extract of Ashwagandha root on cardiorespiratory endurance in healthy athletic adults and to evaluate the QOL of these subjects.

A number of normal daily and athletic activities require isometric activity that significantly increases blood pressure, heart rate, myocardial contractility, and cardiac output. A study in children and adolescents suggests that low cardiorespiratory fitness is strongly associated with the clustering of CVD risk factors in children independent of country, age and sex (Longhurst *et al.*, 1997; Anderssen *et al.*, 2007).

Cardiorespiratory endurance is generally recognized as a major component of physical fitness. Maximum oxygen consumption (VO_2max) is considered by many as the most valid measure of cardiorespiratory fitness (Jones *et al.*, 1985; Zamuner *et al.*, 2011). The test for VO_2max is perhaps the most commonly employed procedure in exercise physiology. This measurement determines an athlete's ability to take in, transport and utilize oxygen, and is probably the best assessments of the athlete's endurance capabilities.

Ashwagandha is known as an '*adaptogen*', as it increases resistance to physical, chemical and biological stressors, builds energy and general vitality (Dhuley, 2000; Mishra *et al.*, 2000; Sandhu *et al.*, 2010; Raut *et al.*, 2012). In the present study, the root extract of Ashwagandha significantly improved the physical performance and cardiovascular endurance parameter after 8 weeks and 12 weeks, respectively, following regular consumption (300 mg twice a day).

Endurance activities characteristically require high repetitions and low resistance (Jones *et al.*, 1985). Subjective scales such as Borg's perceived exertion and breathlessness scales have a sound physiological basis and can be used to monitor an individual's subjective responses during activity and testing.

Borg (1982) demonstrated that the general perception of physical exertion comes from the integration of different symptoms arising from active muscles, cardiovascular and respiratory systems, joints, perspiration, possible pain, dizziness and such. The rating of perceived exertion (RPE) has been used in several studies to quantify training session or exercise intensity, as well as predominantly for aerobic activities guided by the Borg CR-10 scale (Zamuner *et al.*, 2011).

Maximum oxygen consumption (VO_2max) is a measure of long-term aerobic and cardiovascular endurance parameters. We see a significant increase in VO_2max in this study. VO_2max represents a long-term aerobic and cardiovascular endurance. VO_2max is considered to be a gold standard for measuring the cardiorespiratory fitness level (Jones *et al.*, 1985; Sandhu *et al.*, 2010).

In the present study, a statistically highly significant ($p < 0.0001$) increase from baseline value was observed in Group II (the Ashwagandha root extract-treated group) as compared to Group I (the placebo-treated group) at both the pre-selected time periods of 8 weeks (56 days) and 12 weeks (84 days). The data of the present study define an excellent range of VO_2max following administration of Ashwagandha root extract. Previous studies assessing physical and cardiorespiratory endurance of healthy adult subjects have also reported similar beneficial results with the use of Ashwagandha, underscoring the significant increase in VO_2 max and muscle strengthening (Sandhu *et al.*, 2010; Raut *et al.*, 2012).

Sandhu *et al*. (2010) documented the safety and efficacy of Ashwagandha root extract in the form of 500 mg gelatin capsules in the dose of 1 capsule/day orally for 8 weeks. These workers reported marked muscle strengthening and a significant increase in the maximum oxygen consumption after an 8-week treatment with *Withania somnifera* (Ashwagandha). Similar results have been reported by Raut *et al*. (2012) who demonstrated that *Withania somnifera* administered in the form of aqueous extract in capsules with gradual escalating doses from 750 to 1250 mg/day was found to be safe and well tolerated. This study also demonstrated marked muscle strengthening, exercise tolerance and lipid-lowering potential of Ashwagandha, along with improved quality of sleep and QOL.

Singh *et al*. (2002) have demonstrated the beneficial effect of *Withania somnifera* in chronic fatigue syndrome, stating that it helps in delaying onset of fatigue and thus increasing the time to exhaustion and maintaining power for a relatively longer period.

It is known that the capacity for aerobic energy production is generally adapted to the energy requirement and that physical exercise increases skeletal muscle energy demand many-fold. Adenosine triphosphate is responsible for the maintenance of the energy processes at the cellular level. Ashwagandha has been shown to exert significant effects on the energy levels and mitochondrial health, beneficially influencing Mg2+-dependent ATPase activity and reducing the succinate dehydrogenase enzyme activity in the mitochondria of granulation tissue of carrageenin-induced air pouch granuloma in an experimental study (Begum *et al*., 1987). In agreement with the fact that exercise endurance capacity is largely determined by the functional mitochondrial content of muscle, this study confirms the energizing effect of Ashwagandha.

An animal study reported a two- to three-fold increase in free radical ($R^{\bullet}$) concentrations of muscle and liver following exercise to exhaustion. Exhaustive exercise also resulted in decreased mitochondrial respiratory control and increased levels of oxidative stress (Davies *et al*., 1982). Ashwagandha on chronic administration markedly augmented antioxidants and significantly reduced ischemia-reperfusion-induced myocardial injury as reported in an earlier experimental study (Gupta *et al*., 2004; Mohanty *et al*., 2004). These observations are indicative of its cardioprotective potential.

The WHO-QOL Questionnaire is used to evaluate a given subject's QOL. It comprises 26 items, which measures the following broad domains: physical health, psychological health, social relationships and the environment (WHO-QOL Questionnaire, 1996). The procedure entails each question being read out to the subjects, along with the response options.

In the present study, as assessed by the WHO-QOL Assessment Field Trial Questionnaire, a highly significant increase was observed in the physical and psychological health, social relationship and status of the environmental impact on the QOL of the healthy athletic adult subjects. This increase in the above-mentioned parameters after 50 days (8 weeks) and 84 days (12 weeks) of continuous use of a full-spectrum root extract of Ashwagandha, evidences the benefits of Ashwagandha as a superior adaptogen, strengthening resistance to stress while enhancing energy.

Conclusion

Earlier studies clearly indicate that the traditional use of Ashwagandha has a logical and scientific basis. Hence, Ashwagandha can be safely considered useful for ameliorating general weakness and improving endurance performance, that is, time to exhaustion, speed and lower limb muscular strength in conjunction with the necessary neuromuscular coordination therein, significantly improving cardiorespiratory endurance in healthy athletic adults. However, the exact role of the root extract in modifying the metabolic pathways is yet to be established.

This study opens the possibility of identifying the role of Ashwagandha in improving cardiovascular dynamics, enhancing cardiorespiratory endurance, increasing energy and physical activity. Hence, fur-

ther advanced studies with KSM-66 Ashwagandha are planned

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Table 1: Flow chart of the a randomized, placebo controlled study evaluating the efficacy of a full spectrum root extract of Ashwagandha (*Withania somnifera*) in improving cardio-respiratory endurance in healthy athletic adults

Procedure	Screening/ Baseline Visit	During the trial		End of Study
Visit and Study Day	Visit 0 Day 0	Visit 1 (Treatment Visit-I) Day (28±3 days)	Visit 2 (Treatment Visit-II) Day (56±3 days)	Visit 3 (Treatment Visit-III) Day (84±3 days)
Informed Consent	+			
Medical history	+			
Inclusion/exclusion criteria	+			
Demography	+			
Physical examination	+	+	+	+
Vital signs[1]	+	+	+	+
Urine pregnancy test[2]	+			
Randomization	+			
Study Drug/Placebo treatment group	+[3]	+	+	+
20M Shuttle Run Test	+		+	+
Borg's Scale Test	+		+	+
WHO-QOL Questionnaire	+		+	+
Adverse events assessment		+	+	+

Note: 'Day 0' was the day of screening and administration of the first dose.

1. Vital signs include temperature, BP, pulse rate and respiratory rate.

2. Urine pregnancy test was performed in female subjects of child bearing age at screening and before the study drug was administered to confirm negative result of the test.

3. The study Drug/Placebo administration was done at the end of the baseline visit.

Table 2: Assessment of VO_2 max by Shuttle Run Test

	Placebo Mean ± SD 24 subjects	Ashwagandha Mean ± SD 25 subjects	P value
Day 0	42.18 ± 5.3	41.74 ± 5.21	= 0.7714
Day 56	43.59 ± 4.97	46.65 ± 6.29	= 0.0651
Day 84	44.03 ± 5.95	47.41 ± 6.63	= 0.0668
Change at day 56 from baseline	1.42 ± 1.92	4.91 ± 1.72	< 0.0001**
Change at day 84 from baseline	1.86 ± 2.28	5.67 ± 2.15	< 0.0001**

VO_2 max measurements are generally displayed in $L \cdot min^{-1}$ (i.e. litres per minute, representing the volume of oxygen consumed by the entire body each minute)

Table 3: Outcome of WHO Quality of Life Assessments

	WHO Quality of Life Assessments											
	Physical Health			Psychological			Social Relationships			Environmental		
	Placebo	Ashwagandha	P value	Placebo	Ashwagandha	P value	Placebo	Ashwagandha	P value	Placebo	Ashwagandha	P value
	Mean ± SD (n=24)	Mean ± SD (n=25)		Mean ± SD (n=24)	Mean ± SD (n=25)		Mean ± SD (n=24)	Mean ± SD (n=25)		Mean ± SD (n=24)	Mean ± SD (n=25)	
Day 0	58.88 ± 15.12	62.88 ± 12.31	0.3159	60.71 ± 21.85	63.28 ± 11.64	0.6125	57.79 ± 23.21	60 ± 21.94	0.7339	58.79 ± 16.97	65.52 ± 12.37	0.1214
Day 56	60.71 ± 13.86	70.96 ± 10.36	0.0055	61.08 ± 13.86	71.5 ± 12.15	0.0076	60.54 ± 18.89	70.2 ± 20.56	0.0932	63.42 ± 12.07	71.64 ± 14.79	0.0381
Day 84	56.58 ± 10.82	72.16 ± 13.64	< 0.0001	63.17 ± 14.12	75.72 ± 12.78	0.0021	63.12 ± 18.13	72.96 ± 17.11	0.0571	60.17 ± 13.21	71.88 ± 12.44	0.0025
Change at day 56 from baseline	1.83 ± 7.7	8.08 ± 6.29	= 0.0033**	0.37 ± 11.41	8.22 ± 7.65	= 0.0075**	2.75 ± 08.4	10.20 ± 6.16	= 0.001**	04.63 ± 7.86	6.12 ± 5.91	= 0.4575 NS
Change at day 84 from baseline	5.97	9.28 ± 7.6	< 0.0001**	2.46 ± 15.07	12.44 ± 9.16	= 0.0083**	5.33 ± 08.5	12.96 ± 9.46	= 0.0047**	01.38 ± 7.39	6.36 ± 4.62	= 0.0076*