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PHARMACOKINETIC STUDY OF ASHWAGANDHAQA™ VERSUS A STANDARD ASHWAGANDHA ROOT EXTRACT IN HEALTHY HUMANS: A RANDOMIZED, DOUBLE-BLIND, CROSSOVER, SINGLE-DOSE STUDY

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ABSTRACT

Objective: To evaluate the single-dose pharmacokinetic profile and relative bioavailability of total withanolides from AshwagandhaQA™, compared to a standard Ashwagandha root extract with 2.5% withanolides respectively **Methods:** Randomized, double-blind, crossover, single-dose study in 16 healthy adult males under fasting conditions. Subjects received a single oral dose of 500 mg of each extract in random order with a suitable washout period. Plasma concentrations of total withanolides were measured by validated LC-MS/MS over 24 hours. **Results:** AshwagandhaQA™ (Greenspace Herbs) showed superior bioavailability. Mean (±SE) pharmacokinetic parameters for total withanolides: C_{max} 86 ± 6.7 ng/mL, T_{max} 2.5 ± 0.2 h, $AUC_{0-\infty}$ 1,261 ± 241 ng·h/mL, t½ 7.3 ± 0.29 h, MRT 12.4 ± 0.49 h. Comparable profiles for individual withanolides were observed, with markedly higher exposure than the standard extract. No serious adverse events occurred. **Conclusion:** AshwagandhaQA™ provides markedly enhanced and sustained exposure of bioactive withanolides compared to a standard 2.5% root extract, supporting its superior performance and once-daily dosing in clinical applications.

KEYWORDS: *Withania somnifera*, Ashwagandha, Withanolides, Pharmacokinetics, Bioavailability, LC-MS/MS.

1. INTRODUCTION

Withania somnifera (L.) Dunal, commonly known as Ashwagandha, is a cornerstone of Ayurvedic medicine and is classified as a Rasayana, a rejuvenative therapy traditionally prescribed to promote longevity, vitality, and resilience against stress. Classical Ayurvedic texts describe Ashwagandha as Balya (strength-promoting), Medhya (cognition-enhancing), and Vajikarana (reproductive tonic).[1]

The pharmacological activity of Ashwagandha is primarily attributed to its biologically active steroidal lactones, the withanolides, along with their glycosylated derivatives (withanosides). More than 40 structurally distinct withanolides are identified, including withaferin A, withanolide A, withanoside IV, and withanoside V.[2] These compounds collectively contribute to Ashwagandha's adaptogenic, anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective effects, as demonstrated in both preclinical and clinical studies.[3]

While Ashwagandha is utilized in traditional medicine systems, its root extract has gained significant global attention in modern scientific research, nutraceuticals, and functional medicine. This surge in demand is driven by growing evidence supporting its role in stress modulation (HPA-axis regulation), cognitive health, sleep quality, metabolic balance, and physical performance.[4]

Commercial Ashwagandha root extracts are most commonly standardized to 2.5% total withanolides, a benchmark widely adopted in clinical trials and product formulations.[5] Several studies have investigated the pharmacokinetic behavior of withanolides, indicating relatively low oral bioavailability due to factors such as poor solubility and metabolic transformation. Importantly, differences in raw material quality, extraction solvents, processing conditions, and matrix composition can substantially influence the absorption, plasma exposure, and overall clinical efficacy of Ashwagandha extracts.[6]

Recognizing these challenges, Greenspace Herbs has developed Energized Active Supplement Ingredients (EASI)™, a proprietary platform that integrates artificial intelligence, quantum chemistry principles, and Ayurvedic wisdom. Through its Quantum Ayurveda™ approach, select Ayurvedic botanicals are infused with a controlled energy load, which is subsequently stabilized in a metastable, primed state. This process is designed to preserve energy in a metastable form so it stays "primed" until it meets the body, thereby potentially enhancing biological responsiveness.[7,8]

AshwagandhaQA™ is an energized, highly bioavailable Ashwagandha root extract, standardized to 2.5% total withanolides, developed using this advanced platform. Given the known variability in withanolide bioavailability across conventional extracts, understanding and characterizing pharmacokinetic differences becomes critically important for ensuring consistent clinical outcomes and evidence-based dosing strategies.

A randomized crossover study was designed to characterize the single-dose pharmacokinetic profile of AshwagandhaQA™ (500 mg) in comparison with a standard Ashwagandha root extract standardized to 2.5% withanolides (500 mg) in healthy adult volunteers. The study aimed to evaluate key pharmacokinetic parameters including C_{max}, T_{max}, and AUC to generate comparative evidence of enhanced bioavailability, thereby supporting optimized clinical dosing and substantiating the functional advantage of energized Ashwagandha extract.

2. MATERIALS AND METHODS

2.1. Test Products

Investigational products: AshwagandhaQA™ capsules and standard Ashwagandha root extract capsules (each 500 mg extract, standardized to 2.5% total withanolides).

2.2. Study Design

Randomized, double-blind, crossover, single-dose pharmacokinetic study conducted under fasting conditions at Sai Sneh Hospital, Pune, India. Conducted in accordance with ICH-GCP, ICMR guidelines, and Declaration of Helsinki.[9]

2.3. Participants

Sixteen healthy male volunteers aged 18-45 years, BMI 18.5-30 kg/m², with normal medical parameters. Exclusion criteria included hypersensitivity to *Withania somnifera*, chronic diseases, substance abuse, or recent herbal/supplement use. Written informed consent obtained.

2.4. Study Procedure

A total of sixteen subjects were enrolled in the study, with fifteen completing both treatment periods. Participants were admitted to the clinical facility 11 hours prior to dose administration. Subjects received either 500 mg AshwagandhaQA™ or standard Ashwagandha extract A single dose of AswagandhaQA™ 500mg was administered to each patient, with samples collected at predefined time points for analysis. Following a 7-day washout period, a single dose of standard Ashwagandha extract 500mg was given to all 15 participants followed by sampling at different time points. Dosing occurred at t=0 with 240 mL water; standard meals were provided at 4 h and 10 h post-dose. Blood (5 mL) was collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 16, 24 h post-dose via venous cannula into lithium-heparin tubes. Plasma was centrifuged (4°C, 3000 rpm, 10 min), aliquoted, and stored at −80°C.

2.5. Analytical Method

Plasma analytes were extracted via solid-phase extraction (Oasis HLB) and quantified by LC-MS/MS (Waters Acquity UPLC BEH Phenyl C18 column; mobile phase: 0.1% formic acid in water/acetonitrile; ESI-MRM mode). Calibration range: 0.5–500 ng/mL (r^2 >0.99); LLOQ: 0.5 ng/mL. Method validated per USFDA guidelines (accuracy ±15%, precision <15% CV).[10]

2.6. Pharmacokinetic and Statistical Analysis

Non-compartmental analysis using Phoenix WinNonlin v8.3. Parameters compared between treatments; descriptive statistics as mean ± SE. Relative bioavailability calculated based on dose-normalized AUC.

3. RESULTS

3.1. Participant Flow and Tolerability

Sixteen subjects enrolled; 15 completed both periods. Fifteen males (mean age 33.8 ± 5.2 years, weight 67.4 ± 8.1 kg, BMI 23.5 ± 2.1 kg/m²) completed the study; one withdrew for personal reasons. No serious adverse events; treatments were well tolerated.

3.2. Plasma Concentration-Time Profiles

AshwagandhaQA™ shows substantially higher and more sustained exposure. The AshwagandhaQA™ achieves a substantially higher peak concentration (C_{max} 86 ng/mL vs 15 ng/mL) (Figure 1) and more sustained exposure over 24

hours (AUC_{0-24} 1224 ng·h/mL vs 65 ng·h/mL) compared to the standard extract (Table 1-2). Concentrations for the standard extract were substantially lower at all time points, consistent with reduced bioavailability (Table 1). AshwagandhaQA™ demonstrated significantly higher Cmax, AUC, t½, and Mean Residence Time (MRT) compared to the standard extract, indicating superior absorption and sustained exposure despite identical standardization to 2.5% withanolides (Table 2).

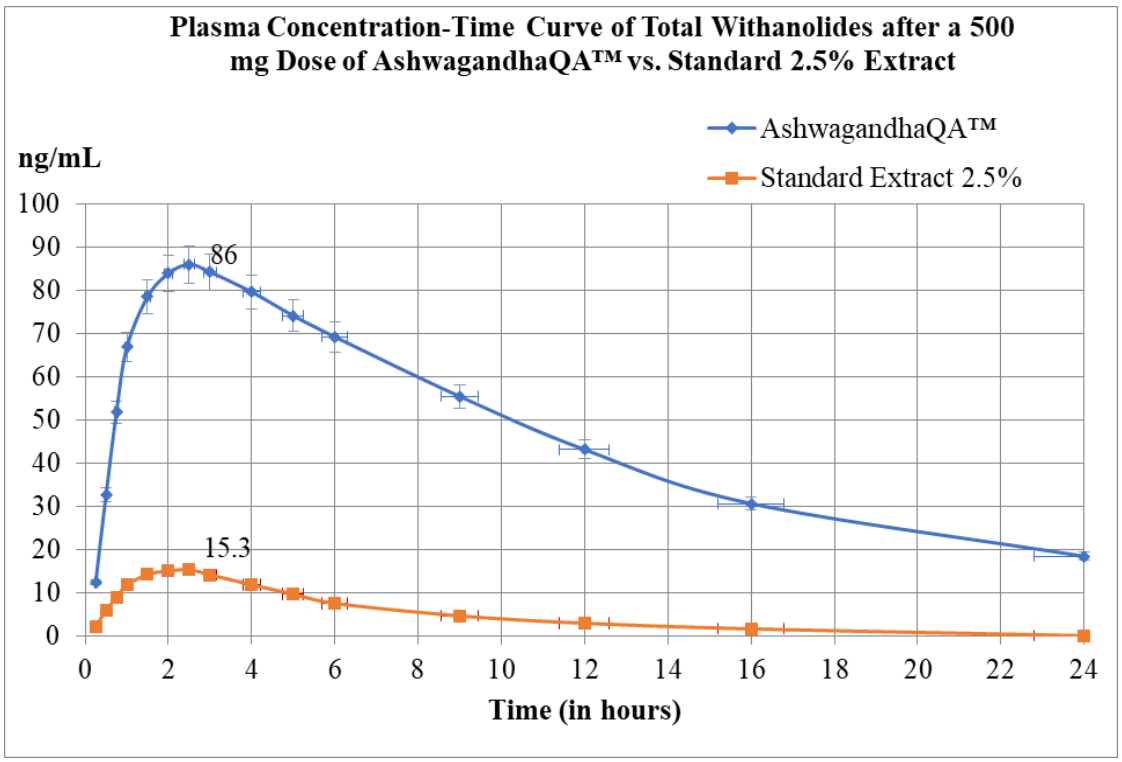

Figure 1: Mean ± SE plasma concentration-time curves of total withanolides after 500 mg AshwagandhaQA™ 2.5% versus 500 mg standard Ashwagandha 2.5% extract.

Table 1: Mean (±SE) plasma concentrations (ng/mL) of total withanolides (n=15); BLQ = Below limit of quantification (<0.5 ng/mL).

Time (h)	AshwagandhaQA™	Ashwagandha Standard Extract 2.5%	Notes
0	BLQ	BLQ	BLQ (<0.5 ng/mL)
0.25	12.4 ± 1.0	2.1 ± 0.5	
0.5	32.6 ± 2.5	5.8 ± 1.3	
0.75	51.8 ± 4.0	8.9 ± 2.0	
1	66.9 ± 5.2	11.7 ± 2.6	
1.5	78.5 ± 6.1	14.2 ± 3.1	
2	83.9 ± 6.5	15.0 ± 3.3	
2.5	86.0 ± 6.7	15.3 ± 3.4	Peak concentration
3	84.2 ± 6.6	14.1 ± 3.1	
4	79.6 ± 6.2	11.8 ± 2.6	
5	74.1 ± 5.8	9.6 ± 2.1	
6	69.2 ± 5.4	7.5 ± 1.7	
9	55.4 ± 4.3	4.6 ± 1.0	
12	43.1 ± 3.4	2.9 ± 0.6	
16	30.6 ± 2.4	1.6 ± 0.4	
24	18.4 ± 1.4	BLQ	Sustained exposure at 24 h

Table 2: Pharmacokinetic parameters for total withanolides (Mean ±SE; n=15).

Parameter	AshwagandhaQ™	Standard Ashwagandha Extract	Interpretation
Cmax (ng/mL)	86 ± 6.7	15.3 ± 3.4	Markedly higher peak concentration
Tmax (h)	2.5 ± 0.2	2.5 ± 0.3	Comparable time to peak
AUC_{0-t} (ng·h/mL)	1224 ± 235	65 ± 14	Superior overall exposure
$AUC_{0-\infty}$ (ng·h/mL)	1261 ± 241	69 ± 15	~18-fold higher systemic exposure
t½ (h)	7.3 ± 0.29	1.4 ± 0.2	Prolonged elimination half-life
MRT (h)	12.4 ± 0.49	3.0 ± 0.4	~4.1× longer mean residence time – supports sustained effects

4. DISCUSSION

Ashwagandha (*Withania somnifera*) exhibits diverse pharmacological activities that supports its therapeutic potential and relate directly to its pharmacokinetic profile. Key actions include adaptogenic effects via modulation of the HPA axis and cortisol reduction, neuroprotective benefits through inhibition of inflammation. Withanolides are what make these pathways work, and pharmacokinetic studies show that they help the body absorb, distribute, and use them better. Withanolides also help to neutralize free radicals as antioxidants, and reduces inflammation.[11]

Withanolides, the primary bioactive constituents of *Withania somnifera* underpin its remarkable pharmacological properties. However, their oral bioavailability remains a critical limitation in conventional root extracts standardized to 2.5% withanolides, owing to poor aqueous solubility, rapid metabolism, and limited gastrointestinal absorption[12,13,14]. Our study addresses this gap by conducting a randomized, double-blind, crossover, single-dose pharmacokinetic comparison between AshwagandhaQA™ and a standard 2.5% withanolides root extract in healthy humans, aiming to elucidate potential formulation-driven enhancements in plasma kinetics and systemic exposure.

The present study compared the pharmacokinetic profiles of AshwagandhaQA™ (500 mg), a proprietary energized formulation of *Withania somnifera* root extract, against a standard 2.5% withanolide root extract in healthy human volunteers. The energizing process involving quantum-energized vibrational enhancement optimizes particle size, solubility, and cellular uptake, leading to superior bioavailability. AshwagandhaQA™ (500 mg) exhibited robust bioavailability with high $AUC_{0-\infty}$ 1261 ng h/mL, C_{max} 86 ng/mL, prolonged t½ (7.3 h), and extended MRT (12.4 h). These superior kinetics, driven by the proprietary energising process, result in markedly greater systemic exposure compared to a standard 2.5% root extract. AshwagandhaQA™ demonstrated over 18-fold higher bioavailability than standard Ashwagandha 2.5%. C_{max} was about 5.6 times higher, showing stronger peak absorption. Mean residence time (MRT) is 4.1 times longer than of standard Ashwagandha 2.5% indicating higher retention time in the body. The enhanced profile supports sustained adaptogenic benefits and once-daily dosing.

While the study establishes its safety and bioavailability in healthy human volunteers, larger clinical study in the intent population supporting its benefit is necessary.

5. CONCLUSION

AshwagandhaQA™, despite identical 2.5% withanolides standardization, demonstrates excellent bioavailability and sustained systemic exposure at a 500 mg dose compared to a standard extract, positioning it as a superior *Withania somnifera* root formulation for therapeutic applications.

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CONFLICT OF INTEREST STATEMENT

The authors declare there are no conflicts of interest

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