SJIF Impact Factor (2025): 8.688| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 10 | Issue: 11 | November 2025 - Peer Reviewed Journal

ENHANCING THE BIOAVAILABILITY OF WITHANIA SOMNIFERA: STRATEGIES, CHALLENGES, AND CLINICAL PERSPECTIVES

Shambhuraje Agam[1], Supriya B. Katgaon[2], Rani M. Mehtre[3], Vijaysinh U. Sable[4]

[1]Student, Lokmangal College of Pharmacy, Wadala, Solapur, Maharashtra, 413222
[2]Assistant Professor, Lokmangal College of Pharmacy, Wadala, Solapur, Maharashtra, 413222
[3]Vice Principal, Lokmangal College of Pharmacy, Wadala, Solapur, Maharashtra, 413222
[4]Principal, Lokmangal College of Pharmacy, Wadala, Solapur, Maharashtra, 413222
Lokmangal College of Pharmacy, Wadala, Solapur, Maharashtra, 413222

Article DOI: https://doi.org/10.36713/epra25127
DOI No: 10.36713/epra25127

ABSTRACT

Withania somnifera, commonly known as "Ashwagandha" or "Indian ginseng" is an essential therapeutic plant of Indian subcontinent regions. It is used in Ayurvedic and indigenous systems of medicine for more than 3,000 years. Withania somnifera indicate various biological actions such as anti-cancer, anti-inflammatory, anti-diabetic, anti-microbial, anti-arthritic, anti-stress/adaptogenic, neuro-protective, cardio-protective, hepato-protective, immunomodulatory properties. These therapeutic effect due to a diverse group of bioactive compounds, particularly withanolides, withaferin-A, withanone, sitoindosides, and alkaloids. But unfortunately, there is the oral bioavailability of these constituents remains a major limitation for clinical efficacy. Many factors responsible for poor bioavailability including low aqueous solubility, poor permeability, extensive first-pass metabolism, and rapid systemic clearance. Accordingly, to overcome these issues, numerous strategies have been proposed and are investigated in this article, such as advanced formulation techniques (nanoemulsions, liposomes, solid lipid nanoparticles, and phytosomes), co-administration with natural bioenhancers like Piperine and curcumin Recent pharmacokinetic studies in both animal models and humans indicate that such approaches significantly improve absorption, half-life, and overall systemic exposure of active constituents However, variability in extract composition, limited clinical trials, and concerns regarding long-term safety of enhanced formulations remain important challenges. Overall, improving the oral bioavailability of W. somnifera constituents holds strong potential to translate its traditional use into consistent therapeutic outcomes, but further well-designed human studies are required to validate these advances.

KEY WORDS: *Withania Somnifera, Oral Bioavailability, Withanolides, Bioenhancers, Nano-Formulations, Pharmacokinetics*

INTRODUCTION

Withania somnifera (Ashwagandha) has gained attention in both traditional and modern medicine for their therapeutic potential. Their are many varieties of medicinal plants which have been utilized for their therapeutic effect. The oldest documented account of healing science can be found in the Vedas [1]. Around 2000 species of medicinal plants and spices are used in India's traditional medical systems (IMS), which include Ayurveda, Siddha, and Unani. The ancient Vedic books discuss the Indian system of medicine between 2500 and 500 BC. *Withania somnifera*, also known as ashwagandha L. Dunal (WS), has been utilized for centuries because of its many health advantages. It is generally located in regions of Africa, Central Asia, and South Asia [2]. It has been widely utilized as a herbal medication for the past 3,000 years in the Ayurvedic and Unani medical systems. [3,4]. In traditional medicine, it has been used as a diuretic, narcotic, anti-stress, aphrodisiac, anti-worm, anti-liver disease, leprosy, anti-inflammatory, cardiovascular, joint pain, antibacterial, nervous system disorders, arthritis, etc. [4,5,6]. Numerous pharmacological properties, such as anti-inflammatory, analgesic, anti-arthritic, hepatoprotective, anti-cancer, anti-epileptic, anti-Alzheimer, anti-Parkinson, cardioprotective, neuroprotective, anti-microbial, anti-fungal, antioxidant, immunomodulatory, anti-depressant, anti-diabetic, anti-platelet, fibrinolytic, etc., have been documented in *W. somnifera*. [7,8,9]. The plant contains many classes of chemical compounds and phytochemicals that have attracted a lot of attention from researchers due to their multifaceted significance and broad range of health benefits [3]. The primary active constituents of the plant that have been identified as bioactive are withanolides A-Y, withaferin A, withasomniferin A, withasomnidienone, withasomnierose A C, withanone, etc [10]. Along with these lactones, the plant extract also contains alkaloids as isopelletierine, anaferine, cuseohygrine, and anahygrine [11]. These bioactive compounds are known to impart the pharmacological effect by targeting different biomolecules in the living systems. The low oral bioavailability of *W. somnifera's* active ingredients is a major barrier to converting the plant's therapeutic advantages into reliable clinical results, even in the face of encouraging preclinical results [12]. The percentage of an oral dose that enters the bloodstream in an active form is known as oral bioavailability. Systemic exposure to phytoconstituents is greatly decreased by characteristics like efflux by intestinal transporters, chemical instability in the gastrointestinal tract, low permeability, poor solubility, and extensive

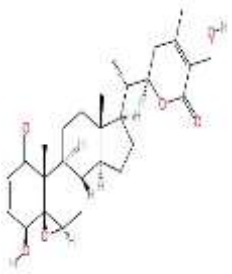
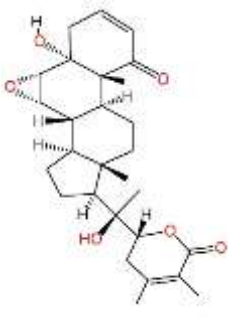
SJIF Impact Factor (2025): 8.688| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 10 | Issue: 11 | November 2025 - Peer Reviewed Journal

first-pass metabolism [13]. For instance, withanone and withaferin A exhibit low oral absorption and rapid metabolism, which limits their therapeutic utility despite their potency in vitro [14]. The chemical nature of these chemical compounds plays a central role in their pharmacokinetic limitations. Many withanolides are lipophilic molecules with poor aqueous solubility, which restricts dissolution in gastrointestinal fluids and subsequent absorption [15]. The effective concentration of some constituents in plasma is further decreased by their susceptibility to hepatic first-pass metabolism or enzymatic degradation [12]. The need for innovative methods to increase bioavailability in order to replicate the therapeutic benefits seen in laboratory studies in clinical practice is highlighted by this pharmacokinetic barrier. Numerous approaches have been studied to get around these restrictions. To increase solubility, stability, and absorption, formulation-based strategies like liposomes, solid lipid nanoparticles, nano-emulsions, and phytosomes have been used [16]. According to reports, using natural bioenhancers like Piperine and curcumin can increase the systemic availability of withanolides by blocking metabolizing enzymes and efflux transporters [17]. Furthermore, compared to conventional extracts, extract standardization toward higher proportions of withanolide glycosides, as in WS-35 or Shoden, has demonstrated superior pharmacokinetic profiles, indicating that constituent composition is a critical factor in determining bioavailability [18].

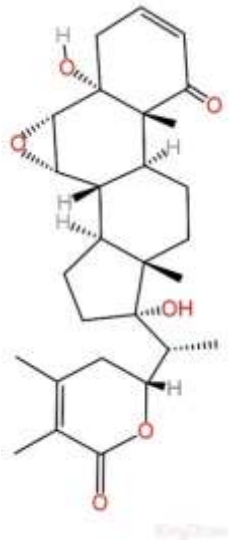
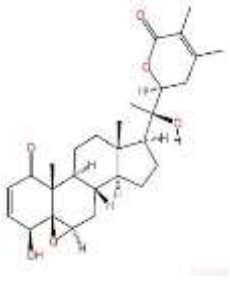
Fig 1 : *Withania somnifera* [50]

Chemical constituent of *Withania somnifera*

Table 1: Summary of major phytoconstituent in plant extract

Phytoconstituent	Plant part used	Biological activity	Compound structure	References
Withaferin-A	Leaf	Neuroprotective, cardioprotective		[19,20,5]
Withanolide-A	Root	Immunomodulatory		[20,5]

SJIF Impact Factor (2025): 8.688| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 10 | Issue: 11 | November 2025 - Peer Reviewed Journal

Withanone	Fruit	Anti-inflammatory		[20,21,5]
Withanolide-D	Leaf	Anti-cancer		[20,5]

Factor Affecting Bioavailability of *withania somnifera*

A complex interplay of physicochemical, biological, and formulation-related factors influences the oral bioavailability of *Withania somnifera's* bioactive chemical compounds. primary barrier is the poor aqueous solubility of withanolides, particularly withaferin A and withanone, which limits their dissolution in gastrointestinal fluids and restricts absorption across the intestinal epithelium [15]. In addition, many withanolides exhibit lipophilic characteristics, which although favorable for membrane permeability, often result in poor dissolution and erratic absorption profiles [12]. An additional significant factor is chemical instability in the gastrointestinal environment, where the integrity of these compounds may be compromised prior to their systemic circulation by enzymatic degradation and acidic pH [14]. Withanolide systemic exposure is significantly reduced by first-pass metabolism, which also improves its solubility and stability. Cytochrome P450 enzymes and conjugation pathways substantially metabolize substances in the liver and intestine upon oral administration, resulting in low plasma concentrations despite good absorption [13]. Furthermore, it is impossible to overlook the role of efflux transporters such as P-glycoprotein (P-gp), which actively lower net absorption by pumping particular phytoconstituents back into the intestinal lumen [17]. Numerous preclinical pharmacokinetic investigations have demonstrated this, pointing to a brief systemic residence time due to the short half-life and rapid elimination of withanolides [18]. Bioavailability results are also determined by the extracts' composition. Standardized extracts with a higher concentration of withanolide glycosides, such as Shoden or WS-35, typically exhibit superior stability and absorption compared to those that primarily contain aglycone withanolides. The reason for this is probably that the glycoside forms are more stable and soluble in the body [11]. Additionally, absorption may be impacted by the presence of co-administered phytochemicals and dietary components. For instance, natural bioenhancers such as Piperine improve the systemic exposure of withanolides by blocking metabolizing enzymes and efflux transporters [17]. Because advanced formulations like nanoemulsions, solid lipid nanoparticles, and phytosomes have been demonstrated to improve solubility, protect unstable molecules, and extend systemic circulation, formulation factors like particle size, excipients, and delivery systems are also very important [16].

Strategies to Enhance Oral Bioavailability of Chemical Constituents of *Withania somnifera*

Oral administration of *Withania somnifera* extract is commonly used in both traditional and modern medicine system. However, as was previously mentioned, a number of pharmacokinetic barriers, such as low solubility, poor permeability, first-pass metabolism,

SJIF Impact Factor (2025): 8.688| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 10 | Issue: 11 | November 2025 - Peer Reviewed Journal

and rapid systemic clearance, limit the bioavailability of its main bioactive constituents, especially withanolides like withaferin A, withanone, and withanolide A. Due to these difficulties, methods for improving bioavailability must be developed in order to guarantee reliable therapeutic results. A variety of strategies, from the use of natural bioenhancers and extract standardization to sophisticated formulation technologies, have been investigated during the last ten years. The main methods for improving the oral bioavailability of *W. somnifera* constituents are described in this section.

Enhancing the Bioavailability of *Withania somnifera* Using Bioenhancers

Define Bioenhancers are compounds that, when combined with pharmacological substances, stimulate and enhance drug bioavailability without having a synergistic activity with the drug.

Herbal bioenhancers act through several mechanisms of action. Different herbal bioenhancers may have same or different mechanisms of action. They act by various mechanisms such as inhibiting drug-metabolizing enzymes (CYP450s, UGTs), improving intestinal permeability, suppressing efflux transporters (like P-glycoprotein), and enhancing solubility or gastrointestinal retention. When used with *W. somnifera*, these mechanisms help maximize the absorption and systemic exposure of withanolides and related compounds.

Enhancing the Bioavailability of *Withania somnifera* Using Piperine

Piperine primarily enhances bioavailability through various mechanisms. Piperine inhibits cytochrome P450 (CYP450) enzymes, mainly CYP3A4 and CYP2D6, which are responsible for the metabolism of herbal constituents [22]. Piperine decreases the metabolic breakdown of withanolides by inhibiting these enzymes, which increases the number of active molecules that enter the bloodstream. Furthermore, by inhibiting UDP-glucuronosyltransferase (UGT) activity, Piperine prevents glucuronidation by delaying the quick conjugation and removal of withanolides [23]. Another important mechanism that enhances absorption of substances in the gastrointestinal tract. Through changes in the structure and behavior of membrane lipids, piperine improves the permeability of the intestinal lining, facilitating the better passage of poorly soluble molecules such as withaferin A through intestinal cells [24]. Additionally, it stimulates intestinal blood flow and thermogenesis, both of which improve absorption efficiency [25]. When combined, these effects aid in increasing the bloodstream's concentration and retention of the active ingredients in *Withania somnifera* According to experimental data, Piperine's pharmacological effects can be considerably enhanced when combined with *Withania somnifera* extract. In contrast to the extract alone, [26] discovered that a formulation comprising Piperine (10 mg/kg) and standardized *Withania somnifera* extract (5% withanolides) produced stronger antioxidant and adaptogenic responses. Similarly, Piperine co-administration improved the bioavailability and tissue distribution of withaferin A in rats, according to [27]. This suggests that Piperine improves absorption and lowers hepatic metabolism. Combining Piperine and *Withania somnifera* in a single delivery system, like liposomes, nano-emulsions, or capsules, can enhance stability and absorption from a formulation perspective. Curcumin and resveratrol have already been successfully formulated using Piperine, indicating that ashwagandha could benefit from the same approach

Enhancing Bioavailability of *Withania Somnifera* using Quercetin

There are several complementary mechanisms through which quercetin enhances bioavailability, including the following. It is an inhibitor of cytochrome P450 enzymes, including CYP3A4 and CYP2C9. These enzymes are primarily involved in the metabolism of phytoconstituents and xenobiotics [28]. Inhibition of enzymatic oxidation by quercetin results in decreased metabolic inactivation of withanolides and thereby permits higher concentrations to achieve systemic circulation. Quercetin also inhibits the activity of P-glycoprotein (P-gp), an efflux transporter which exports a number of compounds back into the gut lumen and thus impeded their absorption [29]. This inhibition contributes to enhanced intestinal absorption of withanolides and also prolongs their residence in the systemic circulation. Quercetin's antioxidant characteristics likewise add in no small measure to the safeguard of *Withania somnifera* principles from the oxidative process in which they are liable to be altered during digestive and metabolic phenomena. Oxidative stress injures the active structure of the withanolides, especially withaferin A. Quercetin, in scavenging free radicals from the body, is an effective stabilizer, whereby the molecules of active principle would, as a result, become less vulnerable to oxidization and oxidation products. Moreover, quercetin favours cellular membrane permeability and regulates the tight junction proteins in enteric epithelial cells, thus allowing the passive diffusion of lipophilic compounds such as withanolides [30]. The synergistic relationship is supported by experimental evidence. [12], for example, found that concomitant administration of *Withania somnifera* with quercetin caused a significant increase in plasma concentration of withaferin A in rats relative to administration of the herb alone. The combination of the two also contributed to a greater antioxidant enzyme activity and reduced markers of oxidative stress, suggesting greater bioavailability and pharmacodynamic synergy. Similarly [31], report that quercetin increased the stability and absorption of withanolide-rich extracts, with a corresponding increase in anti-inflammatory action and neuroprotection. To increase the solubility and absorption of the two compounds from a formulation standpoint, joint formulations of *Withania somnifera* and quercetin in lipid-based carriers, nanoparticles, or phytosomes can be utilized. Such systems protect both substances from enzymatic degradation and also improve their gastrointestinal residence time [18]. Such approaches provide a new area of exploration in the development of next generation of Ashwagandha formulations with improved and uniform therapeutic efficacy.

SJIF Impact Factor (2025): 8.688| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 10 | Issue: 11 | November 2025 - Peer Reviewed Journal

Enhancing Bioavailability of *Withania somnifera* using curcumin

Curcumin increases bioavailability mainly by modulating the activity of metabolic enzymes and efflux transporters. It inhibits cytochrome P450 enzymes (particularly CYP3A4 and CYP1A2) and p-glycoprotein (P-gp); both are major determinants of first-pass metabolism and efflux of xenobiotics from the intestine [23]. By inhibiting these pathways, curcumin lowers the metabolic clearance of the withanolides and accomplishes this by producing elevated plasma concentrations and prolonged systemic retention. Subsequently curcumin blocks the conjugative metabolism (glucuronidation and sulfation) associated with the rapid excretion of the withanolides, thus prolonging life and bioefficacy [32]. In addition to inhibiting enzymes, curcumin enhances intestinal absorption through changes in membrane and lipid dynamics. It promotes the permeability of intestinal epithelial cells with concomitant passive diffusion of poorly soluble phytochemicals, including withaferin A and withanolide A [12]. Curcumin's antioxidant and anti-inflammatory effects also play a role in maintaining the integrity of the intestinal mucosa, which can further improve the uptake of *Withania somnifera* constituent [33]. The synergistic properties of these combinations are substantiated by experimental and preclinical studies. It was shown that the coadministration of *Withania somnifera* extract with curcumin significantly increased the plasma concentration of withaferin A, enhancing its neuroprotective activity in rodent models. [12]. Another study by [34] demonstrated that the coadministration of curcumin was capable of improving the antioxidant and antistress activity of *Withania somnifera*. This observation indicates improved bioavailability of *Withania somnifera* and pharmacodynamical synergies in the administration of *Withania somnifera* and curcumin. Apart from increased incidence and action, it was demonstrated that the combination had the potential of improving cognitive performance and decreasing the effects of biochemical markers that are stress related, which is reflected in the increased ability of systemic absorption of the active compounds and retention of such compounds. From a formulation standpoint, nano formulations, liposomes and phospholipid complexes containing both *Withania somnifera* and curcumin have been developed to further improve solubility, stability and permeability [11]. These advanced delivery systems protect both compounds from enzymatic degradation and target delivery, which enhances therapeutic outcomes even at lower doses.

Enhancing the Bioavailability of *Withania somnifera* Using Lipid-Based Carriers

The main ways that lipid-based carriers increase bioavailability are by making lipophilic phytoconstituents more soluble and by facilitating lymphatic absorption, which helps to avoid hepatic first-pass metabolism [12]. Liposomes can encapsulate hydrophilic and lipophilic compounds, protecting withanolides from degradation and enhancing cellular absorption. [35]. Research has demonstrated that liposomal formulations of *W. somnifera* exhibit greater pharmacological efficacy in comparison to conventional extracts, suggesting improved systemic availability [36]. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are two of the most well studied nano-lipid systems for herbal drugs. NLCs blend solid and liquid lipids to give increased drug loading and controlled release, whereas SLNs are composed of solid lipids stabilized by surfactants. According to a study by [37], SLNs loaded with *W. somnifera* showed improved antioxidant activity and a notable increase in in-vitro dissolution rate, suggesting increased bioavailability. Similar to this, NLC formulations have been shown to sustain withanolide release over time and maintain stability under physiological conditions, leading to long-lasting therapeutic effects [38]. Self-emulsifying drug delivery systems (SEDDS) are one of the most effective lipid-based approaches to improve the absorption of *Withania somnifera*. These systems are made from a blend of oils, surfactants, and co-solvents that spontaneously form tiny oil-in-water emulsions when they come into contact with fluids in the digestive tract. This process helps dissolve and absorb the herb's fat-soluble compounds more efficiently [39]. developed a *W. somnifera* SEDDS that significantly improved the extract's dissolution and intestinal permeability in laboratory studies. The formation of these fine emulsions increased the surface area available for absorption, leading to higher plasma levels of withanolides in animal models. Besides boosting absorption, SEDDS are easy to take, offer consistent dosing, and can be scaled up for clinical use without major formulation issues. Beyond increasing solubility, lipid-based systems like SEDDS offer other advantages. By protecting the active ingredients in *W. somnifera* from oxidation and enzymatic degradation during digestion, they can increase the amount of intact withanolides that enter the bloodstream [40]. Additionally, by helping the compounds move across biological membranes through processes like endocytosis or paracellular transport, lipid nanoparticles can improve the compounds' bioavailability. These formulations are considered safe and suitable for long-term use because the lipids used are typically non-toxic and compatible with the body. In general, they provide a practical and scientifically valid solution to *Withania somnifera* absorption issues, enhancing the consistency and clinical importance of its therapeutic effects.

Clinical Evidence

Clinically focused research on ways to improve oral exposure to *Withania somnifera* (ashwagandha) falls into two main categories: taking it alongside herbal enhancers, mainly piperine, and reformulating it into lipid-based delivery systems, such as phytosomes, self-nanoemulsifying drug delivery systems, and solid lipid or niosomal carriers. Randomized, placebo-controlled human trials that specifically included piperine show the strongest clinical results. A recent double-blind RCT involving a standardized root extract (500 mg, 2.5% withanolides) along with 5 mg of piperine found greater reductions in anxiety and depression scores compared to placebo. The authors suggest this improvement is due to greater availability of active withanolides when combined with a metabolic enhancer [41]. Complementary clinical pharmacology work has focused on developing validated assays and performing human pharmacokinetic (PK) studies to quantify withanolides in plasma; these methods have enabled crossover PK trials and bioequivalence work showing that formulation and extract chemotype materially influence AUC and Cmax in healthy volunteers

SJIF Impact Factor (2025): 8.688| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 10 | Issue: 11 | November 2025 - Peer Reviewed Journal

[42]. A 2025 randomized crossover bioavailability study comparing proprietary high-withanolide formulations to reference extracts reported substantially higher AUC and Cmax for the enhanced product, underscoring that formulation choices including extract standardization and excipient selection drive human exposure even before invoking lipid carriers [43]. Most direct data on lipid-based carriers is still preclinical or only includes early human PK/formulation bridging studies. In vitro and animal research consistently shows that phospholipid complexes (phytosomes), SNEDDS, and solid-lipid or niosomal systems improve dissolution, intestinal permeation, and systemic levels of key withanolides. This strongly supports the biological possibility of clinical translation. However, few large, independent outcome trials compare lipid-based formulations to conventional extracts [44]. Important practical considerations for future clinical work include mandatory reporting of withanolide content and assay methods. There should be a use of standardized PK endpoints, like AUC, Cmax, and Tmax for specific withanolides. It's also necessary to conduct randomized crossover designs that compare the same extract with and without a bioenhancer or lipid carrier. Thorough monitoring for drug interactions and safety is essential, especially when using metabolic inhibitors like piperine. These studies should measure whether increased exposure leads to clinical benefits or changes in safety margins. Piperine affects metabolizing enzymes and transporters, which raises potential interaction risks with other medications. Overall, developing reliable "bioavailability-enhanced" ashwagandha products for therapeutic use requires head-to-head PK studies and well-designed clinical outcome trials. These trials should connect formulation improvements to real clinical benefits [42].

Challenges of enhancing the Oral Bioavailability of *Withania Somnifera*

Enhancing the oral bioavailability of Withania somnifera faces a cluster of interrelated scientific and practical challenges that slow clinical translation; foremost among these is the intrinsic physicochemical profile of its active constituents, the withanolides, which are often poorly water soluble and chemically diverse, limiting dissolution in the gastrointestinal tract and producing variable absorption [45]. Compounding poor solubility, several withanolides undergo significant first-pass metabolism and rapid clearance, so even when intestinal uptake occurs systemic exposure can remain low and short lived a pattern borne out in targeted pharmacokinetic studies [46]. The complexity of *W. somnifera* extracts themselves creates another barrier: multiple withanolides and glycosides have differing absorption and metabolic fates, and commercial products show wide batch-to-batch variability in composition, which makes it hard to predict or reproduce pharmacokinetics across formulations and studies [47]. Analytical challenges add a further layer of difficulty because reliable quantification of many structurally similar withanolides in plasma requires sensitive, validated LC-MS methods and careful isomer separation methods that have only recently been standardized and are still not universally applied in human trials [48]. On the formulation side, although nanotechnology approaches, lipid carriers, phytosomes, and solid lipid nanoparticles can improve solubility and protect compounds from degradation or early metabolism, these systems introduce new hurdles: formulation stability, scale-up reproducibility, regulatory uncertainty, and unclear long-term safety profiles when used for prolonged human consumption [45]. Safety and interaction concerns are particularly important when bioenhancers such as piperine are used; while these agents can boost absorption by inhibiting metabolic enzymes and efflux transporters, they also risk altering the metabolism of co-administered drugs or producing unanticipated pharmacodynamic effects, necessitating careful drug–drug interaction studies [49]. Translational issues loom large because many promising gains in cell or animal models fail to scale to humans due to species differences in metabolism, transporter expression, and gut physiology, so there is an urgent need for well-designed human pharmacokinetic studies that link plasma exposure to clinical endpoints. Finally, regulatory and commercial obstacles inconsistent extract standardization, limited intellectual property incentives for traditional botanicals, and the high cost of clinical development for novel delivery systems slow investment and large-scale trials, leaving a gap between promising laboratory methods and approved, reliable products for patients. Taken together, these scientific, methodological, safety, and regulatory challenges explain why improving *W. somnifera* bioavailability remains an active, multidisciplinary problem that requires harmonized analytical standards, cautious safety testing, and rigorous human pharmacology to move forward [48].

Future Direction

Future research to improve the bioavailability of *Withania somnifera* should bring together modern formulation science and detailed pharmacokinetic studies to better understand how its active compounds are absorbed and used in the body. Nanotechnology-based carriers such as lipid nanoparticles, nanoemulsions, and liposomes look promising for increasing solubility and intestinal absorption, though more clinical data and safety studies are needed before they can be widely adopted [26]. Formulation strategies like phytosomes and solid lipid carriers could also help protect withanolides from early metabolism and allow for more controlled, sustained release [12]. Another important direction is combining W. somnifera with natural bioenhancers like piperine, curcumin, or quercetin, which can slow down metabolic breakdown and improve systemic absorption, though standardizing doses and evaluating long-term safety remain key [27]. Future studies should include well-designed human pharmacokinetic trials using validated analytical tools to connect blood levels of active compounds with clinical outcomes. Using metabolomics and multi-omics approaches can also reveal new insights into absorption and metabolism. Consistent standardization of extracts and the use of predictive in vitro and computational models will help create more reliable formulations. Ultimately, collaboration among researchers, formulation experts, and clinicians will be essential to move laboratory findings into real therapeutic products. Stronger regulatory frameworks and ongoing safety monitoring will ensure that future *Withania somnifera* formulations not only achieve better bioavailability but also maintain quality and safety for long-term human use.

SJIF Impact Factor (2025): 8.688| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 10 | Issue: 11 | November 2025 - Peer Reviewed Journal

CONCLUSION

In conclusion, improving the bioavailability of *Withania somnifera* using natural bioenhancers is a simple yet powerful way to boost its overall benefits. The herb is rich in active compounds like withanolides, withaferin A, and withanone, but their effects are often limited because they don't dissolve well and get metabolized too quickly in the body. Bioenhancers such as piperine, curcumin, Quercetin, help fix this by increasing absorption, slowing down metabolism, and making the active parts more available to cells. For instance, piperine improves intestinal permeability and prevents the fast breakdown of withanolides, while curcumin and quercetin act as antioxidants and help maintain better absorption over time. These combinations not only improve how the body uses *Withania somnifera* but also make its actions like anti-inflammatory and stress-relieving effects stronger. Using such natural enhancers also means smaller doses can work better, which lowers the risk of side effects and helps people stay consistent with use. Still, to get the best and safest results, researchers need to fine-tune formulations, dosage, and clinical testing. Overall, adding bioenhancers to *Withania somnifera* products is a smart and natural step forward that connects traditional Ayurvedic wisdom with modern science, even though there's still some work left to make it perfect**.**

REFERENCE

1. *Šantić Ž, Pravdić N, Bevanda M, Galić K. The historical use of medicinal plants in traditional and scientific medicine. Psychiatria Danubina. 2017 Sep 13;29(suppl. 4):69-74*
2. *Basudkar V, Gujrati G, Ajgaonkar S, Gandhi M, Mehta D, Nair S. Emerging vistas for the nutraceutical Withania somnifera in inflammaging. Pharmaceuticals. 2024 May 7;17(5):597.*
3. *Ahmad, M., and Dar, N. J. (2017). "Withania somnifera: Ethnobotany, pharmacology, and therapeutic functions," in Sustained energy for enhanced human functions and activity (Academic Press), 137–154. doi:10.1016/B978-0-12-805413-0.00008-9*
4. *Behl T, Sharma A, Sharma L, Sehgal A, Zengin G, Brata R, Fratila O, Bungau S. Exploring the multifaceted therapeutic potential of withaferin A and its derivatives. Biomedicines. 2020 Dec 6;8(12):571.*
5. *Saleem S, Muhammad G, Hussain MA, Altaf M, Bukhari SN. Withania somnifera L.: Insights into the phytochemical profile, therapeutic potential, clinical trials, and future prospective. Iranian journal of basic medical sciences. 2020 Dec;23(12):1501.*
6. *Paul S, Chakraborty S, Anand U, Dey S, Nandy S, Ghorai M, Saha SC, Patil MT, Kandimalla R, Proćków J, Dey A. Withania somnifera (L.) Dunal (Ashwagandha): A comprehensive review on ethnopharmacology, pharmacotherapeutics, biomedicinal and toxicological aspects. Biomedicine & Pharmacotherapy. 2021 Nov 1; 143:112175.*
7. *Ku SK, Han MS, Bae JS. Withaferin A is an inhibitor of endothelial protein C receptor shedding in vitro and in vivo. Food and chemical toxicology. 2014 Jun 1;68:23-9.*
8. *Kumar V, Dey A, Hadimani MB, Emeraldjavascript M. Chemistry and pharmacology of Withania somnifera: An update. CellMed. 2015 Feb 28;5(1):1-13.*
9. *Parihar S. A literature review on pharmacological activities of Withania somnifera. Biological Sciences. 2022 Mar 7;2(1):147-54.*
10. *Srivastava A, Srivastava P, Pandey A, Khanna VK, Pant AB. Phytomedicine: A potential alternative medicine in controlling neurological disorders. InNew look to phytomedicine 2019 Jan 1 (pp. 625-655). Academic Press.*
11. *Singh N, Bhalla M, de Jager P, Gilca M. An overview on ashwagandha: A Rasayana (rejuvenator) of Ayurveda. Afar J Tradit Complement Altern Med. 2021.*
12. *Kumar S, Dey S, Singh A. Bioavailability challenges of phytoconstituents and strategies for enhancement with reference to Withania somnifera. J Ethnopharmacol. 2022; 284:114743.*
13. *Goyal S, Sharma C, Mahajan R. Factors affecting oral bioavailability of herbal constituents: Special reference to ashwagandha. Phytother Res. 2021;35(6):2938–2950.*
14. *Patil S, Deshmukh V, Joshi P. Pharmacokinetics of withanolides: Implications for drug development from Withania somnifera. Phytomedicine Plus. 2023;3(1):100315*
15. *Dar NJ, Hamid A, Ahmad M. Pharmacologic overview of Withania somnifera, the Indian ginseng: Emerging molecular targets for potential therapeutic benefits. Front Pharmacol. 2020; 11:569*
16. *Sumantran VN, Tillu G, Thatte UM. Complementary formulations to improve bioavailability of herbal drugs. Curr Drug Metab. 2017;18(12):1093–1103.*
17. *Patel P, Rane P, Nayak S. Role of bioenhancers in improving pharmacokinetic profile of herbal actives. J Ayurveda Integer Med. 2021;12(3):536–542*
18. *Tripathi R, Sharma N, Gupta P. Comparative pharmacokinetics of standardized ashwagandha extracts with varying withanolide glycoside content. Heliyon. 2023;9(1): e12843*
19. *Konar A, Shah N, Singh R, Saxena N, Kaul SC, Wadhwa R, Thakur MK. Protective role of Ashwagandha leaf extract and its component withanone on scopolamine-induced changes in the brain and brain-derived cells. PloS one. 2011 Nov 11;6(11):e27265.*
20. *Dar NJ, Hamid A, Ahmad M. Pharmacologic overview of Withania somnifera, the Indian Ginseng. Cellular and molecular life sciences. 2015 Dec;72(23):4445-60.*
21. *Purushotham PM, Kim JM, Jo EK, Senthil K. Withanolides against TLR4-activated innate inflammatory signalling pathways: A comparative computational and experimental study. Phytotherapy Research. 2017 Jan;31(1):152-63.*
22. *Bhardwaj RK, Glaeser H, Becquemont L, Klotz U, Gupta SK, Fromm MF. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. J Pharmacol Exp Ther. 2020;302(2):645–650.*
23. *Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of Piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998;64(4):353–356.*

SJIF Impact Factor (2025): 8.688| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 10 | Issue: 11 | November 2025 - Peer Reviewed Journal

24. *Khajuria A, Thusu N, Zutshi U. Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: Influence on brush border membrane fluidity and enzyme kinetics. Phytomedicine. 2002;9(3):224–231.*
25. *Srinivasan K. Black pepper and its pungent principle-piperine: A review of diverse physiological effects. Crit Rev Food Sci Nutr. 2007;47(8):735–748.*
26. *Patil R, Padhye S, Dandawate P. Enhancement of adaptogenic and antioxidant potential of Withania somnifera by piperine co-administration in animal model. Phytother Res. 2018;32(12):2363–2370*
27. *Bano S, Kumar N, Sharma M. Effect of piperine on pharmacokinetics and tissue distribution of withaferin A in rats. J Ethnopharmacol. 2020; 258:112867.*
28. *Choi JS, Choi BC, Kang KW. Effect of quercetin on the pharmacokinetics of oral cyclosporine in rats: Inhibition of CYP3A and P-glycoprotein. Pharmacol Res. 2018; 129:205–211*
29. *Kim KA, Park PW, Park JY. Inhibition of cytochrome P450 enzymes and P-glycoprotein by quercetin. Arch Pharm Res. 2005;28(8):993–998.*
30. *Li Y, Yao J, Han C, Yang J, Chaudhry MT, Wang S, et al. Quercetin, inflammation and immunity. Nutrients. 2016;8(3):167*
31. *Sharma M, Pandey AK, Bhattacharya SK. Quercetin improves pharmacokinetics and anti-inflammatory potential of withanolides in Withania somnifera. Phytother Res. 2021;35(8):4514–4524*
32. *Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. Mol Pharm. 2007;4(6):807–818*
33. *Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: Lessons learned from clinical trials. AAPS J. 2013;15(1):195–218.*
34. *Bhattacharya S, et al. Curcumin co-administration increases Withania somnifera antioxidant and anti-stress activity: pharmacodynamic synergy and improved bioavailability. 2020.*
35. *Pawar RS, et al. Liposomal encapsulation of Withania somnifera extract enhances adaptogenic and antioxidant potential. Phytomedicine. 2021;85:153528.*
36. *Singh A, et al. Comparative evaluation of conventional and nano-lipid formulations of Withania somnifera in stress models. J Ethnopharmacol. 2023;310:116375.*
37. *Yadav V, et al. Formulation and evaluation of solid lipid nanoparticles of Withania Somnifera for enhanced bioavailability. Int J Pharm Sci Res. 2021;12(5):2750-2758.*
38. *Gupta A, Sharma R, Yadav P. Nanostructured lipid carriers of Withania somnifera improve stability and sustain release of withanolides. Drug Dev Ind Pharm.2020;46(10):1678-1687*
39. *Patel R, et al. Self-emulsifying drug delivery system of Withania somnifera: formulation and in-vitro assessment. J Drug Deliv Sci Technol. 2022;73:103456*
40. *Dey S, Singh R, Kumar S. Lipid-based delivery systems for herbal bioactives: an emerging approach to enhance therapeutic efficacy. Front Pharmacol. 2021;12:731780.40*
41. *Majeed M, Nagabhushanam K, Murali A, Vishwanathan DT, Mamidala RV, Mundkur L. A standardized Withania somnifera (Linn.) root extract with piperine alleviates the symptoms of anxiety and depression by increasing serotonin levels: a double-blind, randomized, placebo-controlled study. Journal of integrative and complementary medicine. 2024 May 1;30(5):459-68.*
42. *Vaidya VG, Naik NN, Ganu G, et al. Clinical pharmacokinetic evaluation of Withania somnifera (L.) Dunal root extract in healthy human volunteers: development of validated bioanalytical methods and application to human PK. J Ethnopharmacol. 2024;381:117603. doi:10.1016/j.jep.2023.117603. PMID: 38122911.*
43. *Rathi P, Kim SK. Randomized, double-blind, crossover study comparing the bioavailability of four Ashwagandha (Withania somnifera (L.) Dunal) extracts in healthy, adults under fasting condition. Short Title: Bioavailability of four Ashwagandha extracts. Current Therapeutic Research. 2025 Jul 10:100805.*
44. *Basudkar V, Gujrati G, Ajgaonkar S, Gandhi M, Mehta D, Nair S. Emerging vistas for the nutraceutical Withania somnifera in inflammaging. Pharmaceuticals. 2024 May 7;17(5):597.*
45. *Saoji SD, et al. Phospholipid Based Colloidal Nanocarriers for Enhanced Delivery of Phytochemicals. 2022.*
46. *Dai T, et al. Studies on oral bioavailability and first-pass metabolism of Withaferin A in rats. 2019.*
47. *Zellner L, et al. Determination of Withanolides and Withanosides in commercial products. 2025.*
48. *Marney LC, et al. Liquid chromatography-mass spectrometry quantification of withanolides and standardization issues. 2024.*
49. *Tripathi AK, Ray AK, Mishra SK. Molecular and pharmacological aspects of piperine as a potential molecule for disease prevention and management: evidence from clinical trials. Beni-Suef university journal of basic and applied sciences. 2022 Jan 28;11(1):16.*
50. *https://share.google/aLTmaE7cbMecfBgKi*