

***Withania somnifera* extract induced abdominal pain – case report and literature review**

Ból brzucha wywołany ekstraktem *Withania somnifera* – opis przypadku i przegląd piśmiennictwa

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Summary

Background. *Withania somnifera*, also known as Ashwagandha is a plant that has been valued in Ayurvedic medicine for centuries for a spectrum of properties, i.e., antibacterial, anti-inflammatory, anti-cancer, anti-diabetic and neuroprotective effects. It is known as an adaptogen, helping fight stress, chronic fatigue, musculoskeletal conditions and many other symptoms. The medicinal properties of this herb are due to the presence of bioactive compounds such as alkaloids, flavonoids, steroids, phenolics. Apart from major health benefits, Ashwagandha preparations may also induce unwanted gastrointestinal reactions, such as nausea, vomiting, and diarrhea. **Material and methods.** We describe a case report of a 22-year-old woman who experienced an adverse reaction of abdominal pain during supplementation with a preparation containing *Withania somnifera* (Ashwagandha) root extract. **Results.** Symptoms resolved after discontinuation of the dietary supplement. **Conclusions.** The described case confirms the risk of an adverse reaction in the form of abdominal pain due to taking dietary supplements containing *Withania somnifera* extract. (*Farm Współ* 2021; 14: 223-228), doi: 10.53139/FW.20211428

Keywords: Withania somnifera, Ashwagandha, adverse reaction, abdominal pain

Streszczenie

Wstęp. *Withania somnifera*, znana również jako Ashwagandha jest rośliną od wieków cenioną w medycynie ajurwedyjskiej ze względu na szereg właściwości, m.in. działanie przeciw-bakteryjne, przeciwzapalne, przeciwnowotworowe, przeciwcukrzycowe i neuroprotektoryjne. Jest również określana mianem adaptogenu, pomagającego zwalczać stres, chroniczne zmęczenie, schorzenia układu mięśniowo-szkieletowego i wiele innych dolegliwości. Właściwości lecznicze tego zioła wynikają z obecności związków bioaktywnych, takich jak alkaloidy, flawonoidy, steroidy, fenole. Poza znaczącymi korzyściami zdrowotnymi, preparaty zawierające ekstrakty z Ashwagandhy mogą również wywoływać działania niepożądane w obrębie układu pokarmowego, takie jak, nudności, wymioty i biegunka. **Materiał i metody.** Przedstawiamy przypadek 22-letniej kobiety, u której wystąpiło działanie niepożądane w postaci bólu brzucha w trakcie zażywania preparatu zawierającego ekstrakt z korzenia Witanii ospałej (*Withania somnifera*, Ashwagandha). **Wyniki.** Objawy ustąpiły po odstawieniu suplementu diety. **Wnioski.** Opisany przypadek potwierdza ryzyko wystąpienia działań niepożądanych w postaci bólu brzucha, jako następstw zażywania suplementów diety zawierających ekstrakty z Witanii ospałej. (*Farm Współ* 2021; 14: 223-228), doi: 10.53139/FW.20211428

Słowa kluczowe: Withania somnifera, Witania ospała, Ashwagandha, działania niepożądane, ból brzucha

Introduction

Withania somnifera, also called Ashwagandha, Sattvic Kapha Rasayana, Indian winter cherry or Indian ginseng, is one of the most prominent herbs used in traditional Indian medicine,

Ayurveda [1]. Ashwagandha means “horse’s smell” in Sanskrit, probably because of the odour of its root that is reminiscent of the smell of a horse, but also a belief that it gives the strength of this animal [2-3]. The herb occurs naturally mainly in the semi-arid

region of India, other countries of Southeast Asia, and some regions of Africa [4]. *Withania somnifera*, which belongs to the Solanaceae family, is an evergreen, erect shrub, characterized by short stems, long tuberous roots, petiolate and ovate leaves and small, green, axillary, bisexual flowers that give rise to orange-red, round fruits [1,5]. This plant has been valued for over 3000 years for its numerous beneficial properties. *W. somnifera* is included in the monographs of medicinal plants identified by the World Health Organization (WHO) [4]. Traditionally, different parts of this herb- leaves, flowers, bark, stem, and roots especially- were used to treat various health problems, i.e., wounds, ulcers, pain, fever, respiratory infections, liver and heart disorders. Ashwagandha has been found to have anti-depressant, anti-epileptic, anti-inflammatory, anti-arthritic, anti-coagulant, antioxidant, antidiabetic, antipyretic, regenerating and growth-promoting effects. Moreover, it improves learning ability and memory capacity and fights impotence and premature ageing by increasing semen and cell production [1,2,4,5]. Ashwagandha is considered an adaptogen and multi-purpose medicinal agent, found to possess potent rejuvenating, strengthening and life-prolonging properties. It is also believed to regulate endocrine functions; in particular, it helps to regenerate and stimulate the thyroid gland, testicles and adrenal glands and thus may help treat hypothyroidism. This herb is especially valued for helping to alleviate many ailments of the nervous system. It effectively fights stress, fatigue, nervous exhaustion, insomnia, anxiety, depressive thoughts, neurasthenia, Alzheimer's and Parkinson's diseases. Ashwagandha is rich in iron. It can be used to treat anemia as a powder mixed with milk and molasses. The plant is also thought to inhibit perimenopausal symptoms (muscle aches and bad mood), and help with neck and back pain syndromes, as well as restless legs syndrome (in combination with magnesium) and arthritis [1,2,5,6].

All of these therapeutic effects is the merit of the bioactive compounds of Ashwagandha. It comprises over 35 chemical constituents including bioactive alkaloids (isopelletierine anaferine), flavonoids, phenolics, steroids, saponins (with an additional acyl group- sitoindoside VII and VIII), which are the source of the medicinal properties of this herb. A group of compounds that exert a wide range of therapeutic applications are withanolides (steroidal alkaloids and steroidal lactones), naturally occurring C-28 steroidal lactones, formed on an ergostane framework (C-22 and C-26

are oxidized and make a six-membered lactone ring) [5,7,8]. Withanolides are present in many structural variants- withaferin A, withanolides A-Y, withasomniferin-A, withasomidienone, withasomniferols A-C, withanone. The principal withanolides are withanolide D and withaferin A present in leaves and roots of the herb (withaferin A is 1.6% of total dry weight according to quantitative analysis of leaves). The chemical composition of *W. somnifera* also includes withanolide glycosides (glycowithanolides) known as withanosides, which mainly have a 6-O- β -D-glucopyranosyl- β -D-glucopyranosyl type of glycosidic linkage [5,8-10]. These constituents exert therapeutic effects, acting through plethora of mechanisms. *W. somnifera* compounds were found to inhibit inflammatory markers such as cytokines including interleukin (IL)-6 and tumor necrosis factor (TNF)- α , nitric oxide (NO), and ROS, and to normalize oxidative free radical scavenging enzymes and lipid peroxidation (LPO)- these actions support anti-inflammatory, antioxidant and anti-stress properties of Ashwagandha. The neuroprotective action of Ashwagandha's compounds briefly relies upon its antioxidant activity, i.e. reducing oxidative stress by restoring antioxidant levels, attenuating synaptic and dendritic loss and reversing levels of SOD (Superoxide dismutase), CAT (Catalase), GPx (Glutathione peroxidase), NO and LPP [11]. Neuroprotective effects of Ashwagandha are especially supportive in Alzheimer's patients- as this herb has anti-stress and anxiolytic effects, which are involved in memory and mental enhancing activity [9,11]. Cardio-protective effects are also due to antioxidant balance, activating Nrf-2 and stimulating phase-II detoxification enzymes. Moreover, Ashwagandha contributes to the increase of hemoglobin (Hb) and hematological markers (MCH – mean corpuscular hemoglobin concentration, MCHC – mean cell hemoglobin concentration, and MCV – mean corpuscular volume), which support cardiorespiratory fitness and endurance performance. However, the molecular mechanisms of Ashwagandha extracts associated with improving physical performance and reducing muscle fatigue in humans are still not thoroughly explained [11-12]. The situation is similar in the case of Ashwagandha's effects on the reproductive system – the exact mechanisms remain not fully expounded; however, it is probably also linked to the antioxidative actions. The herb is thought to improve the hormonal balance of luteinizing hormone (LH), follicle-stimulating hormone (FSH),

and testosterone, leading to enhancement in semen quality and folliculogenesis [12]. Ashwagandha also may help to fight diabetes as it stabilizes blood glucose, urine sugar, and glucose-6-phosphate levels [11]. The bioactive substances of Ashwagandha have also been noted to perform an antibacterial and antiviral activity, and yet, some researchers pointed out the potential protective and therapeutic effects in the management of COVID-19 [11,14,15]. However, despite the medicinal use of Ashwagandha for thousands of years, its supplementation still raises some concerns.

Case report

A 22-year-old healthy woman, due to sleep problems and to improve her physical and mental well-being, purchased an Ashwagandha root preparation. A single capsule of this preparation contains 300 mg of Ashwagandha root extract, including 4.5 mg of withanolides and 100 mg of raw root. Following the manufacturer's recommendations, the patient used this preparation in a dose of 1 capsule a day after a meal. On the 4th day of use, she developed abdominal pain, which was unsuccessfully treated with drotaverine in a dose of 120-160 mg and a tincture containing plant extracts of valerian root, peppermint leaves and St. John's wort extract for three days. Since the patient did not associate the pain with the phase of the menstrual cycle and diet, she decided to stop taking the preparation with Ashwagandha, which resulted in resolution of the symptoms. The interview excluded previous adverse effects of the drugs used by the patient so far.

Discussion

Ashwagandha, available in powder, capsules, tinctures, and teas, seems to be a panacea for most health problems. There are many reports concerning the positive effects of *W. somnifera* on nervous system health and psyche. Chandrasekhar et al. aimed to evaluate the safety and efficacy of Ashwagandha root extracts in reducing stress and anxiety and improving adults' general well-being. This prospective study involved 64 subjects with a history of chronic stress, who underwent serum cortisol measurements, and stress-assessment questionnaires. Participants were allocated to either the placebo control group or the study drug treatment group (300 mg of high-concentration full-spectrum extract from the root of the Ashwagandha twice a day for 60 days). There was a significant reduction in all parameters of examined stress-assessment

scales after 60 days of supplementation, with no serious adverse events reported in the treatment group compared to the placebo [16]. Also, Salve et al. performed an eight-week, prospective study, to scrutinize the properties of Ashwagandha in reducing stress. Sixty male and female healthy adults between 18-55 years of age were divided into three groups- two study treatment groups, in which patients received capsules containing Ashwagandha root extract: Ashwagandha 250 (125 mg twice daily), Ashwagandha 600 (300 mg twice daily) and one placebo group- patients received capsules with starch (125 mg twice daily). The participants were assessed using the Perceived Stress Scale (PSS), Hamilton Anxiety Rating Scale (HAM-A), serum cortisol measurement, and sleep quality questionnaire at baseline and after eight weeks. There was a statistically significant reduction in the stress levels and serum cortisol as well as the sleep quality improvement in the group receiving 250 mg of Ashwagandha extract. In comparison to the placebo group, the anxiety reduction was not statistically significant here. Participants from the second study group (Ashwagandha 600 mg) also significantly reduced all the components used for stress and anxiety and improved sleep quality [17]. Effects of Ashwagandha on sleep quality were also examined by Langade et al. in an 8-week study to evaluate its impact on sleep in 80 participants- 40 healthy subjects and 40 subjects with insomnia, divided into two groups: Ashwagandha (one 300 mg capsule twice daily for eight weeks) or placebo. In both healthy and insomnia participants, there was a significant improvement in the sleep parameters after supplementation with Ashwagandha root extract, but the improvement was found more significant in insomnia subjects than in healthy ones. These studies prove that Ashwagandha root extract can help managing stress and sleep disorders [18]. Ashwagandha is also known to improve memory and cognition. A prospective study by Choudhary et al. was aimed to evaluate the efficacy and safety of Ashwagandha in 50 adults with mild cognitive impairment (MCI). The participants were given ashwagandha-root extract (300 mg twice daily) or placebo for eight weeks. After this period of time, the subjects treated with Ashwagandha preparation demonstrated significant improvements in both immediate and general memory [Wechsler Memory Scale III scores- logical memory I ($p = 0.007$), verbal paired associates I ($p = 0.042$), faces I ($p = 0.020$), family pictures I ($p = 0.006$), logi-

cal memory II ($p = 0.006$), verbal paired associates II ($p = 0.031$), faces II ($p = 0.014$), and family pictures II ($p = 0.006$); moreover, there was also an improvement in executive function, sustained attention, and information-processing speed ((Eriksen Flanker task ($p = 0.002$), Wisconsin Card Sort test ($p = 0.014$), Trail-Making test part A ($p = 0.006$), and the Mackworth Clock test ($p = 0.009$)) [19].

Ashwagandha has also been noted to have a therapeutic effect on thyroid functions in subclinical hypothyroidism. The efficacy and safety of Ashwagandha root extract in patients with this ailment were evaluated in a study by Sharma et al. Fifty patients aged between 18 and 50, with elevated serum thyroid-stimulating hormone (TSH) levels (4.5-10 μ IU/L) were randomized in either treatment ($n = 25$) or placebo ($n = 25$) group. Subjects from the treatment group were asked to take Ashwagandha root extract (600 mg daily), while the placebo group received starch for an 8-week treatment period. Serum TSH, serum triiodothyronine (T3), and thyroxine (T4) levels were measured and after an 8-week period they were improved (TSH ($p < 0.001$), T3 ($p = 0.0031$), and T4 ($p = 0.0096$)) in patients taking the supplement in comparison to scores of the placebo patients. There were only minor temporary adverse effects during this study in four out of 50 participants [20].

One of the most potent properties of *W. somnifera* (especially one of its constituents- withaferin A) is anti-cancer action, extensively described in a review by Dutta et al. Withaferin A was reported to have curative effects in many types of cancer. These include, among others, breast, ovarian, prostate, gastric, colorectal, lung cancers, melanomas, renal carcinoma and promyelocytic leukemia. The mechanisms through which the Ashwagandha's molecules act on cancer cells vary, e.g. generating reactive oxygen species (ROS) and sensitization of cancer cells to apoptosis. Considering the anti-cancer and anti-inflammatory properties of *W. somnifera*, it might be used as an adjunct therapy that would help reduce the adverse effects associated with radio- and chemotherapy. The conventional therapies could also be combined with therapy with *W. somnifera* extracts, as their synergistic effects could be even more effective in treating cancers. Nevertheless, this procedure requires appropriate clinical testing and validation [1].

Preparations with Ashwagandha are usually considered well-tolerated, with no significant adverse

effects. Many animal studies confirmed the benefits of therapy with *W. somnifera* extracts with minor adverse events [7]. However, the data on the posology are pretty divergent. According to the WHO monograph, a safe therapeutic dose ranges between 3-6 g of the dried powdered root [21]. Following the guidelines issued in 2020 by the Team for Diet Supplements – a consultative and advisory body of the Chief Sanitary Inspector (GIS), the dose of the powdered root of the plant has been set at a level below 3 g/day, while the maximum level of withanolides in the recommended daily dose should not exceed 10 g [22]. In the research by Verma et al., the amount of 300 mg of Ashwagandha root extract taken for eight weeks was found safe, tolerable, and did not exert an unwanted toxic effect in healthy subjects [4]. Salve et al. reported that Ashwagandha supplementation with a dose of 600 mg per day per eight weeks was well tolerated by the subjects (no adverse events) [17], while Raut et al. concluded, that increasing doses of 750 to 1250 mg per day for 30 days (750 mg/day for 10 days, 1000 mg/day for 10 days, 1250 mg/day for 10 days) were well tolerated- out of 18 volunteers, only one experienced adverse effects (increase in appetite, libido, and hallucinogenic effects with vertigo – symptoms appeared on third day of drug administration and after withdrawal on sixth day, they subsided within a couple of days) [12,23]. In the current literature, sufficiently rigorous prospective studies confirming the efficacy and safety of this plant are still lacking. Because of limited safety data, preparations with this herb are not recommended for pregnant and breastfeeding women (reports of potential abortifacient activity in large doses) and children. Patients taking sleeping pills, sedatives and anxiolytics should be cautious, as *W. somnifera* may intensify the effects of these medicines [24,25]. When taken in large amounts, Ashwagandha's extracts may induce some gastrointestinal adverse reactions, such as upset, nausea, vomiting, and diarrhea [26-28]. Commercially available Ashwagandha products have been recently reported to induce few cases of liver toxicity. The first report of liver injury caused by Ashwagandha described a 20-year-old male patient (from Japan) suffering from an anxiety disorder, who used twice the recommended dose of Ashwagandha in combination with various anti-anxiety drugs. The liver biopsy revealed severe intrahepatic cholestasis with extensive canalicular bile plugs, developed due to drug interactions between Ashwagandha, propranolol, and alprazolam. The patient recovered within

two months after withdrawal of the offending drug and undergoing treatment with ursodeoxycholic acid and phenobarbitone. Similar cases were reported in five patients from Iceland and the United States- mostly men aged between 21-62 years, who developed cholestatic jaundice, with symptoms such as nausea, lethargy, pruritus and abdominal discomfort (after a latency of two to twelve weeks) after supplementation with herbal preparations containing Ashwagandha (chemical analysis proved the absence of other toxic compounds or the presence of potentially hepatotoxic conventional drugs). These were the cases of cholestatic or mixed type liver injury, with severe cholestatic hepatitis (biopsy results)- none of the patients developed liver failure. Liver tests normalized within 1-5 months in most of these patients [29]. The potential mechanism for this event was revealed by Siddiqui et al., who concluded that Ashwagandha compound, withanolone, is detoxified by GSH, but under limiting GSH levels, it can cause DNA damage and lead to liver injury [30].

Other precautions for *W. somnifera* are:

- hypertension/hypotension (the herb may interfere with medications used to treat high blood pressure, but it may lower blood pressure too much in people with low blood pressure);
- diabetes (due to lowering blood sugar levels- interference with medications used for diabetes, risk of hypoglycemia);
- thyroid conditions (Ashwagandha may increase thyroid hormone levels- it should be avoided in people with a thyroid condition and with those on thyroid medication);
- stomach ulcers (possible irritation of the gastrointestinal tract by herbal extracts);
- autoimmune conditions (many immunosuppressant medications may interact with *W. somnifera* extracts, leading to worsening of symptoms of some autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis);
- surgery (because of Ashwagandha's sedative effect on the central nervous system, it is worth

consulting its supplementation with a doctor when planning a surgery) [24,25].

As previously mentioned, Ashwagandha may improve the reproduction system. However, there is some evidence that *W. somnifera* may cause reversible spermicidal and infertilizing effects in males and delayed puberty in both sexes (animal study). Thus, emphasis should be put on dosing, preparation method, adjuvant components, and duration of therapy with this herb [13].

Conclusion

Ashwagandha is considered to be a generally safe and potent supplement with plethora of applications. It is worth emphasizing its role in the treatment of stress, insomnia and even neurodegenerative diseases. However, the clinical research on herbal medications and supplements is limited and there is a lot of discrepancy in the data, depending on the composition and source of the preparations. Although recommended doses of this herb generally do not induce severe adverse reactions (in case of large doses some people may experience gastrointestinal upset, diarrhea, nausea, vomiting, and drowsiness; there were also few reports of temporary liver injury), one should be aware of all precautions and the best would be to consult a healthcare provider before starting supplementation with this and any other herb.

Conflict of interest

None

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