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The dark side of herbal medicine - risks of Ashwagandha (*Withania Somnifera*) consumption

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ABSTRACT:

Introduction: Herbal medicine has been growing in popularity over the last few years. One of the most often used herbal remedy is *Withania somnifera*, more widely known as Ashwagandha. Now known for its anti-stress, anti-inflammatory, antioxidant, anti-cancer, anti-anxiety properties it ranks as a cure-all. However, there is a rising amount of alarming reports regarding its safety.

It has been observed that its effects are not always beneficial, and for some patients the risks of taking it may be greater than the promoted benefits.

Aim of study: The aim of this paper is to evaluate possible risks connected to *Withania Somnifera* consumption based on available research articles and case reports.

Materials and methods: This article is based on the literature found in the PubMed Database from the period of 2004-2024 with the use of keywords such as “Ashwagandha”; “*Withania Somnifera*”, “herbal medicine”; “complementary medicine”; “liver injury”; “thyrotoxicosis”; “adrenal insufficiency”; “autoimmune diseases”.

Results: The outcomes of all the reviewed studies in this paper indicate that *Withania Somnifera* might cause a wide range of side effects. They include herb induced liver injury, endocrine complications such as thyrotoxicosis and adrenal insufficiency, acute graft rejection in a kidney transplant recipient and possible contribution to the onset of new autoimmune disease in patient with the history of autoimmune disorders.

Conclusion: Further long-term research is needed on the Ashwagandha's benefits but particularly on its safety and potential side effects. The common education on the risks of taking herbal supplements should be carried out among health professionals and the rest of the society. Ashwagandha should not be used by patients with liver, endocrine and autoimmune disorders as well as transplant recipients.

Key words: “ashwagandha”, “withania somnifera”, “herbal medicine”, “thyrotoxicosis”, “liver injury”

Introduction

It is widely known that complementary and alternative medicine (CAM) has been growing in popularity over the last few years. CAM is a collective term for medical products and practices that are not part of standard medical care. [1] In order to estimate the scale of this phenomenon in Poland, Public Opinion Research Center performed a survey in which almost 1 in 4 people admitted that they or a close family member had used alternative methods of treatment [2] CAM incorporates numerous therapies with herbal medicine being the prevailing one. Previous studies show that the usage of herbal products as an illness treatment is most commonly caused by dissatisfaction with conventional methods, past good experiences and family traditions. [3] There is a harmful misconception regarding herbal medications as safe because they originate from so-called natural sources and it is challenging for the public to understand that natural is not a synonym for effective and harmless. [4] The fact that they are easily accessible in drug stores and supermarkets feeds this illusion even more. In reality, the majority of countries do not monitor source, safety, toxicity, dosage and composition of herbal remedies thus making room for potential abuse.

Thus far, one of the most renowned herb remedies is Ashwagandha (*Withania Somnifera*) with an estimated market size value of 774,47 million USD in 2024. [5] Ashwagandha plays a major role in an alternative Indian medicine system called *Ajurveda* in which this herb has been used since ancient times as an adaptogen, meaning substance that enhances the body's resilience to stress. [6] Furthermore, *Withania somnifera* is known for its claimed pleiotropic effects including anti-inflammatory, neuroprotective, immunomodulatory and antibacterial properties. [7] Even though there are no multi-center randomized, controlled, double-blind trials to prove all these Ashwaganda's properties, it is easy to find numerous studies on stated positive actions of this herb.

On the other hand, research articles and literature reviews regarding unwanted effects linked with Ashwagandha's consumption are scarce, which is one of the reasons to write this paper. However, the main inspiration for this article was the fact that in April 2023 Denmark decided to ban Ashwagandha raising concerns about its safety. The ban was based on a finding in 2020 by the Danish Technical University (DTU) that ashwagandha has a possibly harmful effect on endocrine system and further justified with the statement that it is impossible to find a safe dose given the current data.[8] Information given above, the aim of this paper is to evaluate possible risks connected to Withania Somnifera consumption based on available research articles and case reports.

Medical use of ashwagandha

The Ashwagandha root smells of horse -'ashwa', hence its name - people believed that when consumed it gives the strength of a horse. According to tradition, they were used for asthma, ulcers, arthritis, but also to improve mental condition. Nowadays, it is widely known that the prevalence of stress in the world continues to rise. Chronic stress not only leads to reduced well-being, but also to concentration problems, insomnia, memory disorders, irritability and somatic symptoms. Many studies have shown the efficacy of ashwagandha to alleviate these symptoms. [9,10,11]. It is not only with patients struggling with mental health problems, for which it is currently widely known, that WS is gaining popularity. We now have many studies confirming that this herbal product supports the immune ability by modulating the innate and adaptive immune systems, increasing levels of immunoglobulins as well as IFN gamma, CD3+ and CD4+ T-cells [12]. Its hypoglycaemic and hypolipidemic role has also been noted [13]. There are papers in the literature on the effects of Withania Somnifera on fertility as well [14]. It has been noted that its use has a beneficial effect on sperm quality as a result of increased enzymatic activity and antioxidant properties. Moreover, ashwagandha has a positive effect on folliculogenesis by regulating the balance of luteinising and folliculotropic hormone. Furthermore, beneficial effects on neurological activity and cardiac function have been observed [15,16]. All these claimed Ashwagandha's properties encourage a growing number of patients to implement it on their own without realizing potential risks that come with it.

Ashwagandha-induced liver injury

The most widely described complication of Ashwagandha's consumption appears to be herbal induced liver injury (HILI). It was first mentioned in literature in 2017 when the case report of a 20-year old Japanese man suffering from a liver injury with prolonged severe intrahepatic cholestasis induced by Ashwagandha was published [17]. However it is not clear if the injury in this firstly described patient was directly due to *Withania somnifera* as alongside with this herb he started taking multiple antianxiety drugs which he acquired online without any medical supervision, thus making room for undermining Ashwagandha's hepatotoxic effect. Nevertheless, in subsequent years numerous reports from all over the world were published in which patients who did not consume any other supplements or hepatotoxic drugs experienced liver injury during Ashwagandha administration. In addition, in most papers the chemical composition of consumed *Withania somnifera* products was analyzed to rule out any contamination with toxic compounds. The most common indication for *Withania somnifera* use among reported patients were stress and anxiety but some patients stated used it for post pregnancy detox, as appetite stimulant and even one patient who was in long-term remission from non-Hodgkin lymphoma used it as an anti-cancer prevention. [18]

The leading symptom of Ashwagandha-induced liver injury in described cases was jaundice alongside nausea, lethargy, pruritus, stool discoloration and abdominal discomfort. [19,20] The reported minimal time from the first intake to the onset of symptoms was only 2 weeks but in some Icelandic patients first symptoms appeared after 12 weeks while one Indian patient presented after 540 days of Ashwagandha supplementation. [18,19]

In some cases the biopsy was performed and the results were quite consistent. India i bjorn Histopathological reports revealed signs of cholestasis and portal-based inflammatory infiltrate of lymphocytes and eosinophils. Furthermore, some biopsies demonstrated hepatocellular necrosis. Ashwagandha supplementation is especially dangerous for patients with underlying pre-existing liver disease as there are 3 reported deaths due to development of Acute-On-Chronic Liver Failure (ACLF). [18] In patients with no previous history of hepatic disorder the course of the disease was generally self-limiting with supportive care within a couple months. However, in cited papers one patient developed chronic herb induced liver injury and one patient needed a liver transplantation to recover underlining seriousness of this Ashwagandha use complication. [21]

The substance that is suspected to be responsible for Ashwagandha's hepatotoxic effect is one of its metabolites called withanone. The recent study revealed that the withanone acts as a DNA adduct interfering with DNA's property leading to genotoxicity. It is normally detoxified by glutathione but when the withanone's concentration is exceeding the glutathione's protective capabilities the DNA is damaged leading to hepatotoxicity. [22]

Thyroid and Adrenal dysfunction correlated with Ashwagandha

Although studies indicate that ashwagandha may have a beneficial effect on the normalization of thyroid hormones in patients with hypothyroidism [23], the literature describes cases in which Ashwagandha intake was associated with symptoms of thyrotoxicosis. The first case was reported in 2005, when a healthy 32-year-old woman taking ashwagandha capsules for chronic fatigue developed symptoms of thyrotoxicosis, which was also confirmed by laboratory tests. She was not taking any other medications or supplements, and her symptoms disappeared after she stopped taking ashwagandha. [24] There are also known cases in which the substance was taken to treat excessive stress and anxiety, which was followed by changes in thyroid hormones as well. The average time for symptoms to appear is 2 months after starting to use Ashwagandha products. Observed symptoms include fatigue, fever, weight loss, headaches, and diarrhea. In the case of a 47-year-old, previously healthy Japanese man, after his first visit for thyrotoxicosis, he continued taking ashwagandha despite his symptoms, which exacerbated, and his FT3 and FT4 levels rose more strongly. Only after he stopped taking it did his symptoms disappear and his hormone levels normalized.[25] The risk of ashwagandha-related thyrotoxicosis is not only present in people seeking help for stress or anxiety. Alternative medicine is also becoming increasingly popular among hypothyroid patients. There is a risk of patients trying to use ashwagandha on their own to regulate hypothyroidism, as described in the case of an elderly woman suffering from thyrotoxicosis who replaced levothyroxine with ashwagandha products.[26] It is crucial to determine the etiology of thyrotoxicosis, as this determines the management. Untreated thyrotoxicosis can lead to life-threatening complications, including cardiac arrhythmias or thyroid breakthrough. In this case, treatment consisted of ashwagandha withdrawal, with additional administration of adenosine, diltiazem and metoprolol to restore proper cardiac function.

Ashwagandha is known to lower cortisol levels as it reduces stress.[10] The principal bioactive compounds of ashwagandha are withanolides, naturally occurring steroids, so there

is a risk of steroid disruption when taking this herbal product.[27] The literature describes the case of a 41-year-old woman suffering from chronic generalized pain, treated with amitriptyline.[28] Due to the intractability of her symptoms, she decided to seek help on her own, finding an ashwagandha product on the Internet, advertised as an anti-inflammatory substance that relieves pain and lowers cortisol levels. After the patient started taking this product, a Synacthen test showed reduced cortisol levels. When ashwagandha was discontinued, the results normalised, leading to the hypothesis that ashwagandha caused adrenal insufficiency.

Detrimental effect of immunomodulatory properties of Ashwagandha

In spite of the belief that Ashwagandha's immunostimulating features are beneficial, there are groups of people to which it can pose a threat. They include patients with autoimmune disorders as well as transplant recipients. The 2018 case report described the 28-years old female with the history of two autoimmune diseases (celiac disease and systemic sclerosis) who developed an optic neuritis after taking Ashwagandha supplement for 2 weeks. [29] Interestingly, the patient stated that she was unaware of its immunostimulating effect and she took it on a friend's recommendation for "overall health benefits". According to the Naranjo algorithm, it was possible that the onset of the new autoimmune disease was linked to the Withania somnifera supplementation. Optic neuritis is a dangerous autoimmune condition commonly linked to multiple sclerosis with similar suspected pathomechanism. Given that all three mentioned autoimmune disorders involve excessive T-cells activation. Some studies suggested that Ashwagandha may promote T-cell signaling explaining the potential pathomechanism of reported link of Withania somnifera's contribution to the development of next autoimmune disorder in this patient. [30]

The second case report regards a kidney transplant receiver who developed acute rejection requiring a graft nephrectomy after Ashwagandha supplementation. [31] The patient presented with a 3-day history of right lower quadrant abdominal pain as well as vomiting and was diagnosed with acute rejection. It was preceded by 2-week Ashwagandha administration which was recommended to a patient by an alleged healthcare provider on the internet forum. It is important to emphasize that prior to this event the patient had stable graft function for over 2 years and had no history of previous rejection as well as he was compliant with the immunosuppression the whole time. Therefore, this case also strongly suggests that Withania

somnifera can have immunostimulatory activity that in some patients may result in detrimental consequences.

Discussion

Each year, as the group of herbal medicine users is expanding, the bigger impact it has on society and the bigger challenge it creates for healthcare providers. For medical professionals, it is of utmost importance to recognise issues connected with herbal supplementation and implement specific actions to avert any potential complications. Firstly, adequate doctor-patient communication is crucial for the compliance with traditional treatment and preventing patients from reaching alternative medicine specialists for advice. As healthcare providers, we should create a safe environment for patients to enable them to ask questions about any pharmaceuticals they consider to implement on their own and discuss their safety. Moreover, direct questions about using any supplements must be a mandatory part of taking a patient's history as it may be crucial for making a diagnosis or introducing treatment. Healthcare professionals should be mindful of the risks of taking Ashwagandha by patients suffering from hepatic, endocrine and autoimmune diseases as well as transplant recipients as they are especially exposed to serious side effects. Ashwagandha should not be recommended to use by mentioned groups of patients.

Every case of potential complication connected with an herbal supplement should be reported and published. It will contribute to the deeper understanding of Ashwagandha action and will allow better estimation of side effects frequency which still remain intercalculated.

Significant amount of complications connected with herbal medicine arise from lack of appropriate market control regarding supplements. Their formulations are not monitored allowing many forms of abuse such as creating products with much lower or significantly higher dose of given substance or contamination with some toxic compounds. Shockingly, a major part of the community is unaware of herbal supplements market regulation policy thus wider education on such matters is highly needed.

Conclusion

Summing up, further research on mechanisms of Ashwagandha's action, its benefits and especially its safety is highly needed. Multi-center, double-blind, randomized, controlled trials are necessary to form official guidelines on *Withania somnifera* supplementation including

maximum doses and contradictions to the use of it. According to our research, such contradictions should include the history of hepatic, endocrine or autoimmune diseases as well as past organ transplantation.

Moreover, many medical professionals have little knowledge of herbal products, which can affect the disease process itself and the effectiveness of treatment in patients permanently using these preparations. Further education of doctors, nurses, pharmacists is therefore necessary. And most importantly, and something we see a huge problem with in Poland, it is essential that the process of entering the market for herbal products should be done on the same basis as for drugs, evaluating their effectiveness, formulations and safety.

Author's contribution:

Conceptualization: KB and KC; methodology: OS; software: AK; check, EO, AMK, JJ and OS; formal analysis EW; investigation KC; resources OŁ, EO, AK; data curation KB, KS, AMK, KC, OŁ, JJ, EO, EW, OS, AK; writing - rough preparation, KS, EW, KC, KB; writing - review and editing KB, KC, EW, EO, OS, JJ, OŁ, KS, AMK, AK; visualization, JJ and AMK; supervision, KB and KC; project administration, KB, KC, EO, AMK;

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