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THE ROLE OF WITHANIA SOMNIFERA IN THE TREATMENT OF HYPERTENSION: A BRIEF REVIEW

Sakshi Angural
M.Sc. Student
Food science and technology
Lovely Professional University, Phagwara, Punjab, India

Abstract: One of the important therapeutic plants in Indian systems of medicine is Withania somnifera, popularly known as ashwagandha. It has been utilized as a medication since the dawn of time and is currently employed to treat a wide range of clinical ailments. The plant has a wide variety of various chemical ingredient classes, including flavonoids, steroidal lactones, and alkaloids. Different biological activities of the plant are carried out by these chemical moieties. A plant's anti-inflammatory, anticancer, neuroprotective, antibacterial, antistress, antidiabetic, and cardioprotective properties were proven in laboratory research. These medicinal effects are partly attributable to W. somnifera's capacity to lower reactive oxygen species, modify mitochondrial activity, control apoptosis, lower inflammation, and improve endothelial function. It has also been used alone or in combination to treat several human disorders. Hypertension, commonly known as high blood pressure, is a significant risk factor for cardiovascular diseases and other health complications. Pulmonary hypertension (PH) is a complex and progressive disorder characterized by increased blood pressure in the pulmonary arteries, leading to significant cardiovascular and respiratory complications. Despite advancements in therapeutic options, the management of PH remains challenging. Here, we review the pharmacological, ethnobotanical, and medicinal properties of the plant and its main chemical components. and explore the potential role of Withania somnifera in the treatment of pulmonary hypertension based on its pharmacological properties and relevant preclinical studies.

Index terms- Herb, Hypertension, Inflammation, Withanine, Vasodilation

INTRODUCTION:

An evergreen, sturdy, woody shrub with the scientific name Withania somnifera (Linn.) Dunal can reach a height of 0.5 to 2.0 m above the ground (Dutta et al., 2019). In addition to being called "Indian ginseng" or "Indian winter cherry" in English, the plant is also known as "Ashwagandha" in Sanskrit, "Asgandh" or "Punir" in Hindi, and "Asgand" in Urdu (Ahmad and Dar, 2017). The plant, which is a member of the Solanaceae family of plant species, can be found in hotter and drier regions of India as well as in the Himalayas at elevations of up to 5500 feet (Motti, 2021). The plant is typically found in the drier regions of tropical and subtropical zones of the world, where it is also cultivated or grows unaided. It spreads outward from the Canary Islands in the Mediterranean, crossing tropical Africa, South Africa, Australia, Sri Lanka, the Middle East, China, and India, and eventually reaching warmer regions of Europe (Khabia et al., 2023). It is used as a therapeutic crop in India and even proliferates abundantly in wastelands. The plant has been utilized for more than 5,000 years and has numerous therapeutic and medicinal uses in the Indian Ayurvedic and Unani medical systems. Since the beginning of Ayurveda in 6000 B.C., ashwagandha has been utilized as "Rasayana". This significant herbal Rasayana is referred to as "Sattvic Kapha Rasayana." A herbal or metallic mixture known as Rasayana serves as a tonic, rejuvenator, and agent to enhance health (Joshi and Joshi, 2021).

Therapeutically and/or prophylactically, Ashwagandha is used as/ against aphrodisiac, tonic, adaptogenic, thermogenic, narcotic, diuretic, depurative, antihelminthic, astringent, and stimulant, antistress, antiinflammatory, anticarbuncle, antiulcer, debility from old age, rheumatism, vitiated conditions of Vata, leucoderma, nervous breakdown, goitre, constipation, insomnia, leucorrhoea, boils, pimples, piles, flatulent colic, worms, and oligospermia (Singh et al., 2011). It is also recommended for treating scorpion stings and snake venom (Tiwari et al., 2014).

Hysteria, anxiety, memory loss, and syncope are all treated by Ashwagandha. When administered to children with milk, ashwagandha functions as a tonic; nonetheless, it is used to treat child emaciation (Zahiruddin et al., 2020). An ancient manuscript, Kitab-al-Hashaish, written by Dioscorides in 78 A.D., mentions the history of Asgand's use in the Unani school of medicine (Azhar, 2020). According to several studies (Tiwari et al., 2014), asgand has been used to treat a variety of conditions, including polyarthritis, rheumatoid arthritis, lumbago, painful swellings, spermatorrhoea, asthma, leucoderma, general and sexual debility, amnesia, marasums, anxiety, scabies, neurosis and leucorrhoea (Lopresti and Smith, 2021).

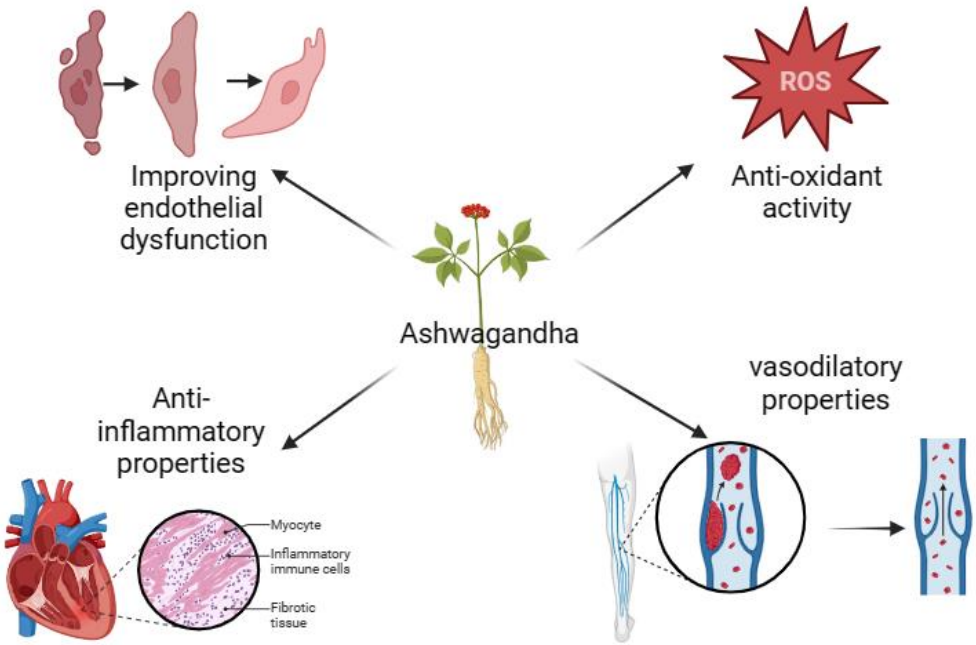

figure 1.1 schematic diagram of properties of ashwagandha plant

Typically, W. somnifera roots are processed for medicinal uses. Due to component breakdown, the plant only retains its pharmacologic efficacy for less than 2 years. Due to this limitation, fresh roots are picked each year between January and March and shade-dried for increased output and improved therapeutic results (Sharifi-Rad et al., 2021). Fever and excruciating swelling can be treated with leaves. Flowers have aphrodisiac, diuretic, astringent, and depurative effects. The seeds are anthelmintic, remove white spots from the cornea, boost sperm count, and promote testicular growth, among other medical effects (Dar et al., 2015). According to Singh et al. (2011), the fruits are traditionally applied topically to treat various skin conditions, carbuncles, and skin ulcers.

Hypertension affects millions of people worldwide and is a leading cause of morbidity and mortality. Conventional antihypertensive medications have been effective in controlling blood pressure; however, they often come with adverse effects and limited long-term compliance (Mills et al.,2020). Pulmonary hypertension is a serious condition that affects the pulmonary vasculature, leading to increased resistance and elevated blood pressure in the lungs. The available treatment options often have limited efficacy and come with adverse effects. Withania somnifera, a medicinal herb with a long history of use, has shown promise as a potential alternative or adjunct therapy for hypertension. Withania somnifera, known for its multiple pharmacological activities, may offer a complementary approach to the management of PH (Foris et al.,2013). It has been traditionally used in Ayurvedic medicine for its various therapeutic properties, making it a promising candidate for novel therapeutic interventions (Joshi and Joshi, 2021).

CHEMICAL COMPOSITION

Different chemical ingredients are present in different regions of the plant, according to phytochemical characterization. The plant has so far been linked to more than 12 alkaloids, 40 withanolides, and a sizable number of sitoindosides (Abdelwahed et al., 2023)(Mirjalili et al., 2009). The primary components are displayed in Table 2.1 and Figure 2.1.

table 2.1. constituents of different parts of ashwagandha

SR. No.	Part of plant	Bioactive compounds present	References
1.	Root	Sitoindosides VII, VIII (acyl steryl glucoside), sitoindosides IX, X (glycowithanolide), withanine, withananine (alkaloids), withanolide A, viscosa lactone B, stigmasterol, and ashwagandhanolide	Bhattacharya et al., 1987 Ahmad et al., 2017
2.	Leaf	Withaferin: withaferin A; withanone; withanolide D; withanolide E; withanolide B; 27-deoxywithaferin A; 2, 24-dienolide, trienolide (steroidal lactones); withanoside IV; withanolide Z, 7-hydroxywithanolide; 3α -methoxy-2, 3-dihydro; 4β, 17α -dihydroxy-1-1oxo; 5β, 6β-epoxy-22R-witha; 4β-dihydroxy-5β, 6β-epoxy; 1-oxo-22R-witha-2, 14─24, sitoindoside IX; 4-(1-hydroxy-2, 2-dimethylcyclopropanone; 2,3-dihydrowithaferin A; 24,25-dihydro-27 desoxywithaferin A, physagulin D; physagulin D (1–>6)-betaD-glucopyranosyl- (1–>4)-beta-D-glucopyranoside; 27-O-beta-D-glucopyranosylphysagulin D; 27-O-beta-D-lucopyranosylviscosalactone B; 4,16-dihydroxy-5beta, 6beta-epoxyphysagulin D, viscosalactone B; 5,20α (R)-dihydroxy-6α, 7α-epoxy-1-oxo- (5α) -witha-2, 24-dienolide (steroidal lactone) 2,3-dihydrowithaferin-A-3beta-O-sulfate	Vaishnavi et al., 2012 Chen et al., 2011

3.	Fruit	5β, 6α, 14α, 17β,20β-pentahydroxy-1-oxo-20S,22R-witha-2, 2,4-dienolide, 6α,7α -epoxy-5α,14α,17α, 23β- tetrahydroxy-1-oxo-22R-witha-2, 2,4-dienolide, 7 -hydroxy withanolide, withanolide glycosides, 17α - and 17β-withanolides, Withanone, 27-hydroxy withanolide A	Huang et al., 2020 Singh et al., 2010
4.	Seed	Withanolide ─WS-2 (aliphatic ester), withanolide ─WS-1 (aliphatic ketone)	Chen et al., 2011 Misico et al., 2011

figure 2.1. active constituents of *Withania somnifera*

MECHANISMS OF ACTION:

Withania somnifera exhibits a wide range of pharmacological activities, including antioxidant, anti-inflammatory, and adaptogenic properties. These mechanisms of action may contribute to its potential antihypertensive effects (Bhat et al., 2022). The herb's active compounds, such as withanolides and withaferin A, have been shown to modulate several pathways involved in blood pressure regulation, including the renin-angiotensin-aldosterone system (RAAS) and nitric oxide synthesis (White et al., 2016) that is shown in Figure 3.1

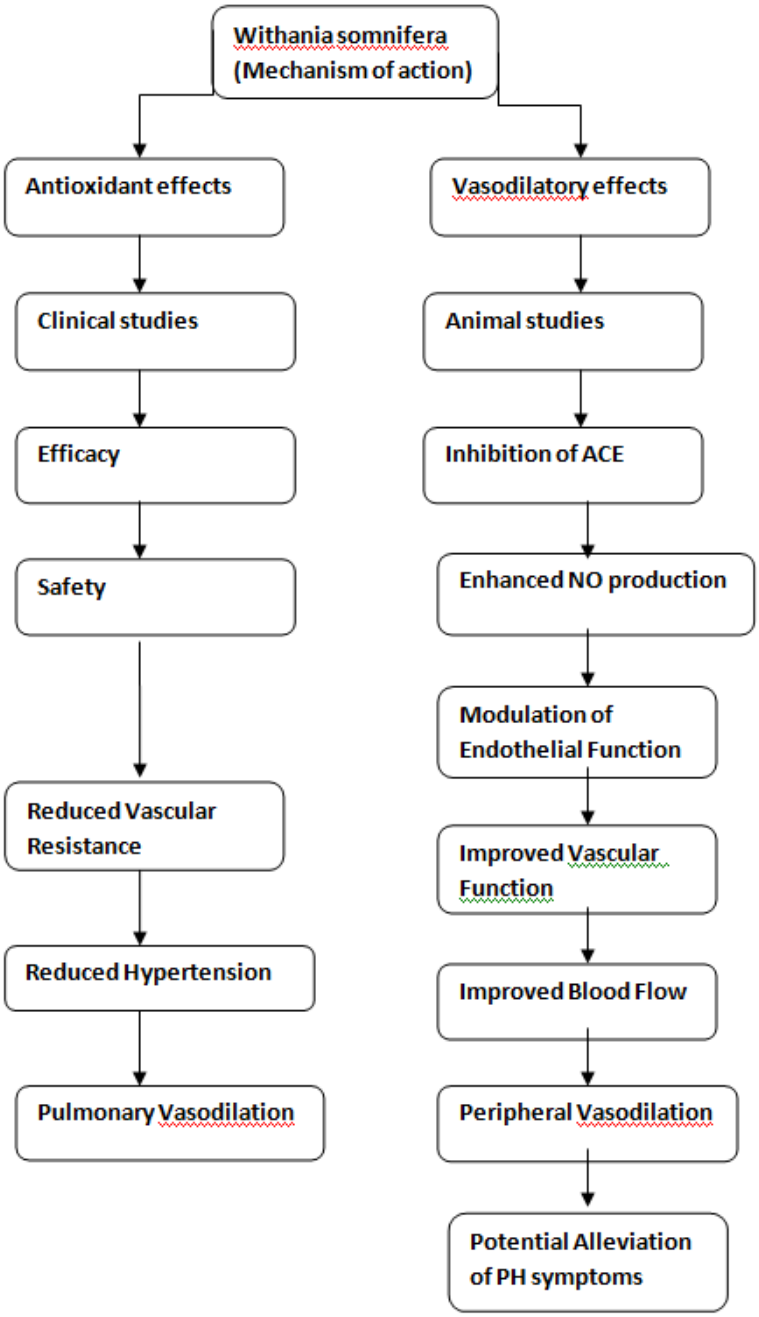

figure 3 mechanism of action of ashwagandha

VASODILATORY AND ANTI-INFLAMMATORY EFFECTS:

Withania somnifera has demonstrated vasodilatory properties, which can potentially alleviate the increased pulmonary vascular resistance seen in PH. Its active components, including withanolides, have been shown to enhance endothelial function and promote the release of nitric oxide, a potent vasodilator (Dar et al.,2015). Additionally, the herb's anti-inflammatory effects may help in reducing pulmonary inflammation and endothelial dysfunction, both of which play critical roles in PH pathogenesis (Ghasemian et al., 2016).

ANTIOXIDANT ACTIVITY:

Oxidative stress is known to contribute significantly to the development and progression of pulmonary hypertension (Ghasemzadeh et al., 2014). Withania somnifera's potent antioxidant properties may counteract oxidative damage, protecting the pulmonary vasculature from injury and supporting overall cardiovascular health (Bhat et al., 2022).

PULMONARY ARTERIAL REMODELING:

In PH, structural changes occur in the pulmonary arterial walls, leading to arterial remodeling and narrowing (Wang and Chesler, 2011). Withania somnifera has been studied for its potential to inhibit smooth muscle cell proliferation and extracellular matrix remodeling, which are crucial processes involved in pulmonary vascular remodeling (Dutta et al., 2019).

ANIMAL STUDIES:

Numerous animal studies have investigated the antihypertensive effects of Withania somnifera. For instance, a study by Ahmad et al. (2017) conducted on hypertensive rats demonstrated that Withania somnifera root extract significantly reduced blood pressure levels by inhibiting angiotensin-converting enzyme (ACE) activity and enhancing nitric oxide production (Mikulska et al., 2023).

Several animal studies have explored the effects of Withania somnifera in various models of pulmonary hypertension. For example, a study by Sharma et al. (2018) demonstrated that Withania somnifera extract attenuated pulmonary arterial hypertension in rats by improving endothelial function and reducing pulmonary artery pressure (Rayees and Malik, 2017).

HUMAN CLINICAL TRIALS:

Several clinical trials have been conducted to evaluate the efficacy of Withania somnifera in hypertensive patients. In a randomized, double-blind, placebo-controlled trial by Raut et al. (2019), Withania somnifera supplementation was shown to significantly lower both systolic and diastolic blood pressure levels in hypertensive participants after 12 weeks of treatment. Another study by Kushwaha (2012) revealed a significant decrease in blood pressure by using the root powder of ashwagandha. 51 subjects in all were chosen, of which 26 were placed in group I and given ashwagandha root powder with milk for 91 days. The remaining 25 subjects received ashwagandha root powder with water. The doctor used a sphygmomanometer to measure the patient's blood pressure before, during, and after supplementation (Tiwari et al., 2021). An interview schedule and anthropometric measures served as the main data-gathering instruments. BMI was computed after height and weight were reported (Kushwaha et al., 2012). According to Mehra et al. (2009), Ashwagandha is recommended as a preventative medication for coronary heart disease, hypertension, and atherosclerosis. It lessens the heart's vulnerability to adrenergic stimulation, shielding it from sympathetic outbursts. Systolic and diastolic blood pressure was evaluated between group I and group II before and after supplementation. There was a significant decrease in diastolic blood pressure but not so significant in systemic blood pressure (Joyner et al., 2010). According to Moharana (2008), Ashwagandha roots and leaves are traditionally utilized in the form of powder, decoction, oil, etc. These have been used in traditional medicine to treat wounds, inflammation, hypertension, and overall infirmity (Singh et al., 2011). A decrease in systolic and diastolic blood pressure is seen in those getting a dose of milk more than those who are getting a dose of water. This indicates that Ashwagandha with milk is more effective than with water (Joshi and Joshi, 2021).

COMBINATION THERAPY:

Withania somnifera has also been studied in combination with conventional antihypertensive medications for both systemic hypertension and pulmonary hypertension. Sharma et al. (2021) found that the addition of Withania somnifera extract to the existing antihypertensive regimen resulted in better blood pressure control and reduced dosage requirements of conventional medications (Afewerky et al., 2021)

SAFETY AND TOLERABILITY:

The use of Withania somnifera in various studies has generally shown it to be safe and well-tolerated. However, some individuals may experience mild gastrointestinal disturbances or allergic reactions. As with any herbal supplement, healthcare professionals need to monitor patients closely for adverse effects and potential drug interactions (Tandon and Yadav, 2020).

FUTURE PERSPECTIVES:

While the preclinical evidence for Withania somnifera's role in hypertension and pulmonary hypertension is promising, further well-designed clinical trials are warranted to establish its long-term efficacy and safety in human subjects (Ravindran et al., 2015). Additionally, understanding the specific mechanisms of action and potential synergies with existing treatments will be essential for optimizing its therapeutic use both as a monotherapy and in combination with standard PH treatments (Dhawan et al., 2021).

CONCLUSION:

Withania somnifera, with its diverse pharmacological properties such as its potential vasodilatory, anti-inflammatory, and antioxidant properties and positive results from preclinical and clinical studies, appears to hold promise as an adjunct therapy for the management of hypertension. However, further large-scale, well-designed clinical trials are warranted to establish its long-term efficacy and safety in hypertensive patients.

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