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Review

Keeping abreast about ashwagandha in breast cancer

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Abstract

Ethnopharmacological relevance

Ashwagandha has been used as an ayurvedic medicine in the form of 'Rasayana' (as a tonic) even before 3000 BCE in India. As per Ayurveda, it has long been used traditionally for the treatment of inflammation, weakness, impotence, pulmonary tuberculosis. This plant is also beneficial in lumbago and leucorrhea in the female. In the recent past, Withania has shown its anti-cancerous activity in various experimental models. In addition, Withania also possesses many other properties such as anti-oxidant, anti-stress, adaptogenic, and regenerative which will eventually be beneficial and safe in treating cancer patients.

Aim of the study

This review aims to provide experimental evidence along with a deeper insight into molecular mechanisms of Ashwagandha (Withania *somnifera* (L.) Dunal) through which it acts as a chemotherapeutic agent against different types of breast cancer.

Materials and methods

Literature searches with the help of electronic online databases (Elsevier, Google Scholar, Scopus, Springer Link, ScienceDirect, ResearchGate, PubMed) were carried out. The timeline for collection of data for the review article was from 2000 to 2019. The plant name was validated from *The Plant List* (2013). Version 1.1. Published on http://www.theplantlist.org/ ↗(accessed 21st March 2020).

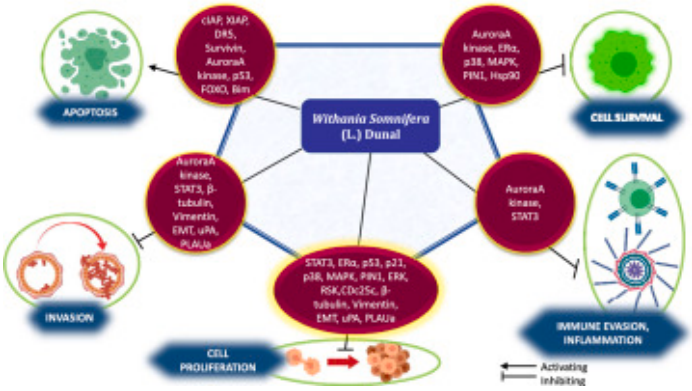
Results

Various forms of *Withania somnifera* were used and several *in vitro*, *in vivo*, and clinical studies were reported by researchers. They found ashwagandha to exhibit anti-apoptotic, anti-metastatic, anti-invasive and anti-inflammatory properties and gave the evidence that ashwagandha has a capability for averting and treating breast cancer.

Conclusion

Various *in vitro* and *in vivo* studies suggested Ashwagandha may possess a potential for treating breast cancer, especially ER/PR positive breast cancer and triple-negative breast cancer. A clinical trial has also been conducted in the past that suggested its potential in refining quality of life in breast cancer patients. Studies directed towards molecular pathways have helped in unravelling the key mechanisms of ashwagandha. Future research should be directed towards translational studies involving breast cancer patients. These will reinforce the ancient power of our Ayurvedic medicine.

Graphical abstract



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Introduction

The commonest malignancy in women across the globe is breast cancer (Ghoncheh et al., 2016). As per WHO reports, there have been over 2.09 million new cases of breast carcinoma in 2018 and it was reportable to be the second commonest cancer worldwide (Bray et al., 2018). Indian Council of Medical Research reports 1.5 lakh new breast carcinoma cases in India, of that 70,000 succumb each year (Indian Council of Medical Research). As per the American Cancer Society, two-thirds of breast carcinoma cases are hormone receptor-positive (HR+) (Hormone Therapy for Breast Cancer), . Based on 2012–2016 cases, the carcinoma subtype HR+/HER2- (hormone receptor-positive and human epidermal growth factor 2-negative) and HR-/HER2+ have an age-adjusted rate of 85.8 and 5.4 new cases per 100,000 women (Howlader et al., 2016). Around 10–20% of freshly diagnosed early breast cancers are Triple-negative carcinoma (TNBC) (Foulkes et al., 2010; Garrido-Castro et al., 2019; Marra et al., 2019).

Treatment for breast cancer incorporates a major challenge in treating patients because of its heterogeneous nature that discerns the therapeutic options (Polyak, 2011). Endocrine therapy (ET) presently involves ovarian function suppression, selective estrogen receptor modulators (SERMs), selective estrogen receptor down-regulators (SERDs) and aromatase inhibitors (AIs), or a mixture of two or more drugs. Many molecules that target the receptor have been approved for HER2+ (ERBB2+), a proto-oncogene Neu breast carcinoma, to be used as and with a standard therapy. They include trastuzumab, pertuzumab (both monoclonal antibodies), ado-trastuzumab emtansine (antibody-cytotoxic agent conjugate) and lapatinib, a dual tyrosine kinase inhibitor (TKI) that interrupts both HER2 and epidermal growth factor receptor (EGFR) pathways (Tong et al., 2018). As per a study conducted in early stage breast cancer patients who had HER2 overexpressed/amplified HER2+, the three-year overall survival for all patients was 92.0% and relapse-free survival was 79.6%. Triple-negative breast cancers (TNBCs) is the term used to describe types of breast cancers that do not express the ER and PR as well as lack overexpression of HER2. The therapeutic approaches for managing TNBC include targeting DNA repair complex with the help of platinum compounds and taxanes, P53 with taxanes, cell proliferation with anthracyclines and other targeted therapies (Berrada et al., 2010).

Side effect profiles of AIs and SERMs vary, with AIs increasing rates of bone loss and skeletal muscle disorders, and tamoxifen have an increased risk of thromboembolic disease and uterine cancer (Bonneterre et al., 2000; Gaillard and Stearns, 2011). A 2018 cohort study noted a high risk of diabetes that was estimated to be 240% greater in women on aromatase inhibitors than in the general population (Hamood et al., 2018). Observed side effects of chemotherapy in breast cancer patients included alopecia (because of anthracyclines), nausea and vomiting, fatigue, loss of

appetite, anaemia, sleep issues, muscle or joint pain, etc (Kayl and Meyers, 2006). Some of the side effects of radiotherapy are fatigue, hair loss, skin changes, edema, tenderness (Sharma and Purkayastha, 2017). These point out towards the necessity of novel drugs that are safe and efficacious.

Ashwagandha (*Withania somnifera* (L.) Dunal) is commonly referred to as "Indian Winter cherry" or "Indian Ginseng" (Singh et al., 2011). It belongs to the family Solanaceae family of flowering plants (Palliyaguru et al., 2016). *Withania somnifera* has been described thoroughly in classical texts of Ayurveda such as *Charaka Samhita, Bhavprakash Nighantu* and *Sushruta Samhita* for boosting immunity, promoting vitality, and maintaining homeostasis. Ashwagandha has been used as an ayurvedic medicine in the form of 'Rasayana' (as a tonic) even before 3000 BCE in India. Ashwagandha has been used in Ayurvedic system of medicine as 'Rasayana' botanicals even before 3000 BCE in India. As per Ayurveda, it has long been used traditionally for the treatment of inflammation, weakness, impotence, pulmonary tuberculosis, lumbago, female reproductive disorders, etc. Ashwagandha is considered as the best tonic for geriatrics and pediatrics.

Withania somnifera (WS) is a plant that has been utilized in Ayurveda (an ancient form of medication in Asia) and within the recent past, has been incontestable to own anti-tumorigenic properties in experimental models. In 1967, it was first demonstrated through an experiment that the root extract resulted in lowered cancer incidence *in vivo* (Shohat et al., 1967). Numerous studies have been carried out on WS in recent years which helped the researchers gain newer insights in pharmacology and molecular mechanisms of this medicinal herb (Saggam et al., 2020). It is also used to treat cancers including prostate and lung cancer improving the patients' quality of life (Singh et al., 2011). Many clinical trials are being conducted for ashwagandha for various disorders in which the majority of them are CNS disorders (Table 1). In this review, we tend to discuss the experimental evidence supporting the chemopreventive potential of ashwagandha (*Withania somnifera*) to be evaluated as a chemopreventive agent in different types of breast cancer.

Section snippets

Phytoconstituents of ashwagandha

Ashwagandha consists of phytochemicals which have a great nutraceutical value. It includes withanamides, withanolides, withanosides, withanolide glycosides, steroidal saponins and lignanamides (Wadhwa et al., 2013). *Withania somnifera* consists of 5-dehydroxy withanolide-R and

withasomniferin-A in the aerial region of the plant (Atta-ur-Rahman et al., 1993). *Withania* consists of various biologically active chemical constituents which includes anaferine, anahygrine (alkaloids), cuseohygrine, …

Pathophysiology of breast cancer

DNA damage and genetic mutations are the major causes of development of breast cancer that can be influenced by exposure to estrogen. BRCA1, BRCA2, HER2, EGFR, c-Myc, Ras, etc are some of the genes which play a major role in breast cancer (Sun et al., 2017). The inheritance of DNA defects or genes like BRCA1 and BRCA2 would increase the chances of breast cancer up to 70% (Feng et al., 2018; Polyak, 2007). Various other risk factors cause breast cancer such as family history, race, exposure to …

ER/PR positive breast cancer

MCF-7 is a breast cancer cell line which is being generally used for many years in *vitro* analysis (Baguley and Leung, 2011; Comşa et al., 2015). The cell line is estrogen receptor-positive (ER-positive) as well as progesterone receptor-positive (PR-positive) (Shirazi et al., 2011). MCF-7 breast cancer cells are sensitive to estrogen (E2) and depend on estrogen to proliferate (Perrot-Applanat and Benedetto, 2012). Aqueous extract of Ashwagandha leaves showed to possess anticancer activity which …

Ashwagandha as adjunct therapy

A prospective non-randomized clinical trial was conducted in female breast cancer patients in which the outcomes were compared to *W. somnifera* plus chemotherapy and chemotherapy alone (control). A vegetarian capsule was prepared using *withania* root extract and was given at an oral dose of 2 g during chemotherapy to the patients. This study concluded that the addition of *W. somnifera* to chemotherapy could have a positive effect on fatigue and improve the quality of life in patients with breast …

Conclusions and future aspects

Ashwagandha, as per Ayurveda, is one of the most potent immune enhancers. In recent decades, extensive research is carried out exploring its potential in various cancer including breast cancer. The above review provides an overview of the phytoconstituents of ashwagandha and also various

in vitro and *in vivo* studies using such chemical constituents have been discussed. Future research should be directed towards translational studies involving breast cancer patients. This can be carried out by …

Author's contribution

Dr. Goyal was involved in conceptualizing the idea and along with Dr. Patel discussed the flow and decided the layout. Ms. Vashi compiled the information which was approved by Dr. Patel and Dr. Goyal. …

Conflicts of interest

Authors declare no conflict of interest. …

Acknowledgements

We are thankful to Ms. Karmani Shah, M. Pharm. Student of Department of Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University, for providing kind assistance for drawing of chemical structures of phytoconstituents. …

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Effects of Ashwagandha (Withania Somnifera) on stress and anxiety: A systematic review and meta-analysis

2024, Explore

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Sub-acute toxicity of Ashwagandha (Withania somnifera) root extract in wistar rats

2023, Toxicology Reports

> *Citation Excerpt :*
>
> ...It can maintain health, rejuvenate the body, may enhance longevity and is used as herbal tonic and health food. This herb has been tested for various pharmacological activities like anti-inflammatory [1], analgesic [2], anxiolytic & hypnotic [3], antidepressant[4], nootropic [5], antimicrobial [6], antioxidant [7], anticonvulsant [8], cardioprotective [9], anticancer [10], etc and these activities have been attributed to the phytochemical constituents such as alkaloids, steroidal lactones, saponins, glycol-withanolides present in it [11]. As the pharmacological activities are being tested using modern evaluation methods, it is also necessary to prove its safety and tolerability in animals and humans....

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Deciphering the multi-scale mechanism of herbal phytoconstituents in targeting breast cancer: a computational pharmacological perspective ↗

2024, Scientific Reports

Ashwagandha (Withania somnifera)—Current Research on the Health-Promoting Activities: A Narrative Review ↗

2023, Pharmaceutics

Recent findings by high-performance thin-layer chromatographic separation for a comprehensive analysis of Withania somnifera by densitometry and mass spectrometry: an assessment to quality and adulteration ↗

2022, Journal of Planar Chromatography Modern TLC

Preparation, characterization, and pharmacological investigation of withaferin-A loaded

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2021, Molecules

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