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File: ■ Ashwagandha (*Withania somnifera*, Solanaceae)
■ Anticancer Activities

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RE: Review of Anticancer Activities of Ashwagandha

Rai M, Jogee PS, Agarkar G, Alves dos Santos C. Anticancer activities of *Withania somnifera*: current research, formulations, and future perspectives. *Pharm Biol*. April 7, 2015; [epub ahead of print]. doi: 10.3109/13880209.2015.1027778.

Of the *Withania* genus' 26 species, ashwagandha (*Withania somnifera*, Solanaceae), indigenous to dry regions of India, Pakistan, Afghanistan, Africa, and the Mediterranean and cultivated in the US, is the best known and most studied. The evergreen shrub flowers nearly all year, with small fleshy fruits conferring another common name, "winter cherry." Metabolic profiling of a crude extract of ashwagandha leaves and roots found 62 primary and secondary metabolites in leaves and 48 in roots; 29 were common to both, including fatty, organic, and amino acids; sugars; flavones; and sterols. Several ashwagandha chemotypes are grown for medicinal use in India. The authors review potential anticancer uses of ashwagandha's parts and extracts, compounds isolated from ashwagandha, and ashwagandha formulations. The abstract states that a search of the literature was conducted in scientific databases and via library search; this is not further discussed.

Ashwagandha extracts show significant anticancer activity through several pathways. Mechanisms of action may include changes in levels of endogenous peroxide dismutase, catalase, and ascorbic acid, and reduced lipids. Antitumor effects may also include increasing the sensitivity of cancer cells to conventional chemotherapeutic drugs and reducing their adverse effects without impeding their efficacy. Ashwagandha may help repair oxidative damage caused by tumor cells and reduce inflammation. Epigenetic changes, critical in cancer etiology, may be reversed by some ashwagandha compounds, including withaferin A (WA). WA occurs at higher levels in chloroform extracts of ashwagandha leaves and bark than in stem and root extracts. An aqueous leaf extract had anticancer effects, with triethylene glycol (TEG), an activator of p53 and pRB (tumor suppressor protein), identified as the active component. A hydroalcoholic leaf extract was more potent against breast than ovary or lung cancer cells. A methanolic leaf extract with WA, withanoside IV, and withanoside VI induced neurite outgrowths in neuroblastomas.

Ethanol, alcohol, and other extracts of ashwagandha roots have been found effective against breast cancer in vitro and in vivo, with reduced cancer cell division and tumor growth. An ethanolic root extract, tested with the conventional anticancer agent doxorubicin, found the former sparing of healthy cells but cytotoxic to breast cancer cells; the latter, cytotoxic to both. In patients with breast cancer undergoing chemotherapy, a root extract aided recovery from cancer fatigue and improved quality of life. A root extract has been reported to be effective against cervical cancer. A cumulative review of methanol, aqueous, chloroform, *n*-

butanol, ethyl acetate, and *n*-hexane root extracts identified anticancer compounds in each, with alkaloids, flavonoids, steroids, and terpenoids most significant.

Withanolides and withaferins, steroidal lactones specific to ashwagandha, are of interest for many potential benefits. Withasomniferin-A and 5-dehydroxy withanolide-R from aerial plant parts have been studied for immunomodulatory effects. For anticancer activity, WA, ashwagandha's main constituent, is considered most important and potent. WA reduced transplanted tumor cell growth in mice and both reduced metastasis and prevented chemically induced as well as oncogenic cancers in rodents. While there are many reports of WA's anticancer effects, its exact mechanism is unknown. WA is target-specific, showing "remarkable" reduction of protein β-tubulin, integral to microtubules. Its specificity extends to mitogen-activated kinases, where it induced breast cancer cell apoptosis. One study found WA's efficacy against breast cancer based on inhibition of epithelial-mesenchymal transition and decreased vimentin protein expression; another study found that Notch signaling, overexpressed in breast cancer cells, was decreased by WA, with reduced Notch1 cleavage.

Hyperthermia, sometimes used with radiology, can induce cancer cell apoptosis but is not an efficient anticancer treatment alone. Hyperthermia can be enhanced with WA; one study found that neither treatment alone was as effective as the combination in promoting apoptosis. WA can regulate dysfunctional and irregular cell cycles at the G2/M phase, inhibiting prostate and some other cancers. Fed to hens, ashwagandha root powder increased their stromal and intratumoral natural killer (NK) cells compared to unsupplemented hens, who had only their stromal NK cells increased.

Among withanolides studied for anticancer effects, withanolide D (witha-D) caused apoptosis in pancreatic cancer cells. A comparative study of 36 WA analogs found that a modified withanolide scaffold could enhance heat-shock-inducing activity (HSA) and might be used to design a novel drug product that would stimulate cellular defenses. A new withanolide, 5,6-de-epoxy-5-en-7-one-17-hydroxy WA, discovered in ashwagandha roots and leaves, has been found more effective against liver and breast cancers than colon and prostate cancers. Withanone (WN), tested alongside WA in many studies mentioned here and found less potent in its anticancer effects, is reported to reduce survivin expression, binding to its active domain and impeding its inhibition of apoptosis. A standardized ashwagandha formula, identified only as "WSF," has been reported to exert anticancer and immunomodulatory effects in vitro and in vivo and is considered a potentially valuable cancer chemotherapy adjunct.

Unfortunately, this complex report on an important subject is rather poorly organized, making it difficult to find all information included about, for example, WA. No studies are described in any detail, nor is their quality assessed. The article might have benefited from copy editing, as it suffers from numerous incomplete sentences and misused or missing words.

—Mariann Garner-Wizard

The American Botanical Council has chosen not to include the original article.