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Withaferin A: A potential anticancer candidate drug and its challenges for the clinical trial

Authors:
Sangilimuthu Alagar Yadav[1]
Ranjusha V. Ponattil[1]

Affiliations:
[1]Department of Biotechnology, Karpagam Academy of Higher Education, Coimbatore, India

Corresponding author:
Sangilimuthu Yadav,
smuthu.al@gmail.com

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Introduction

Withaferin A is a naturally occurring compound classified as a withanolide, derived from the plant *Withania somnifera*, also known as Ashwagandha or Indian winter cherry. It is renowned for its diverse pharmacological properties and has been extensively studied for its potential therapeutic benefits including cancer. Withaferin A acts against various types of cancer (Figure 1) such as breast cancer, prostate cancer, colon cancer, lung cancer, pancreatic cancer, leukaemia, melanoma and ovarian cancer (Sivasankarapillai et al. 2020).

Research suggests that it may possess anti-tumour effects by inducing apoptosis (programmed cell death) in cancer cells, inhibiting angiogenesis (the formation of new blood vessels that feed tumours) and modulating various signalling pathways involved in cancer progression. Additionally, withaferin A has demonstrated neuroprotective effects, potentially offering benefits for conditions such as Alzheimer's disease and Parkinson's disease by protecting neurons from oxidative stress and inflammation (Bhatnagar, Sharma & Salvi 2009). Withaferin A exhibits a wide range of biological activities, including antioxidant, immunomodulatory, anti-cancer (Singh et al. 2021) and neuroprotective properties. Overall, withaferin A's multifaceted pharmacological profile makes it a promising candidate for further research and development in the fields of medicine and health.

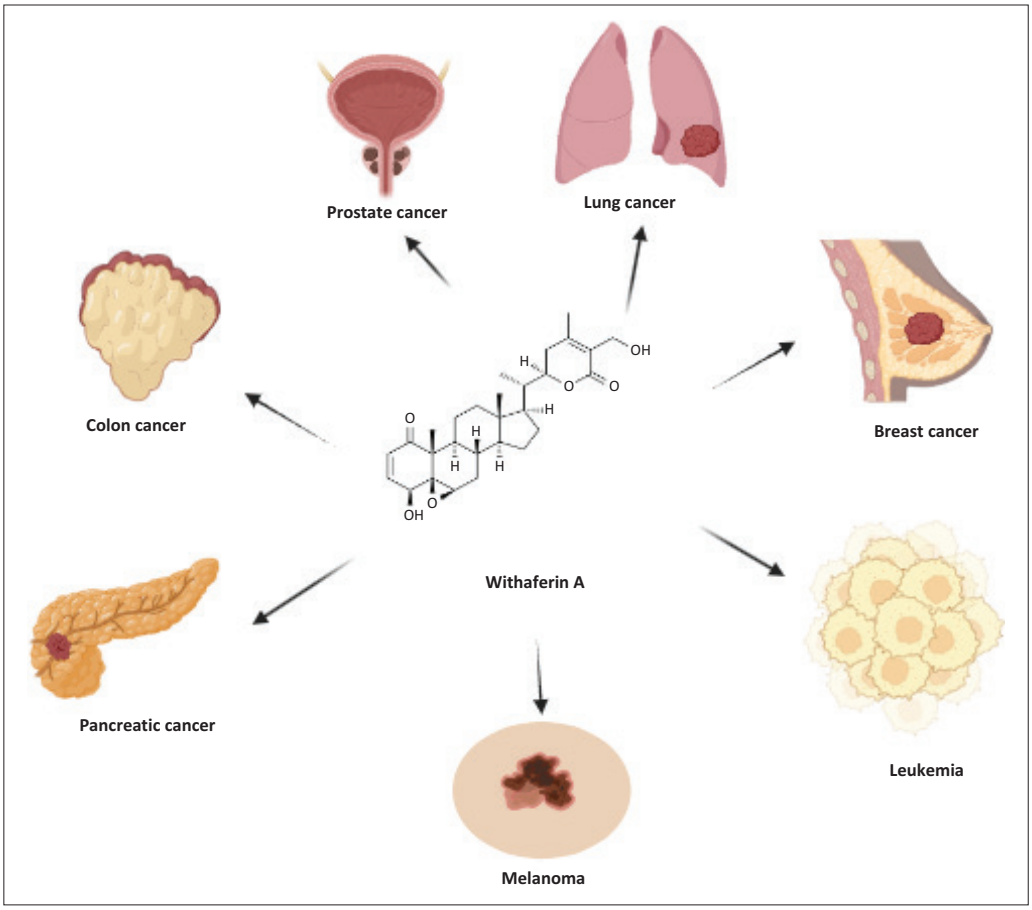

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FIGURE 1: Withaferin A acted against various types of cancer.

Mechanism of action

Withaferin A has been extensively studied for its anticancer activity, showing promise against various types of cancer through multiple mechanisms such as apoptosis induction and inhibition of survival pathways, disruption of microtubule dynamics, inhibition of angiogenesis and modulation of epithelial-mesenchymal transition (EMT). Withaferin A has been shown to induce apoptosis, or programmed cell death, in cancer cells. It activates signalling pathways that lead to the activation of caspases, enzymes responsible for initiating the apoptotic process. Withaferin A selectively targets cancer cells by triggering apoptosis while sparing normal cells (Chang et al. 2017). Withaferin A inhibits several survival pathways that are often dysregulated in cancer cells. One such pathway is the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway, which promotes cell survival, proliferation and inflammation. Angiogenesis, the formation of new blood vessels, is crucial for tumour growth and metastasis. By inhibiting angiogenesis, withaferin A limits the blood supply to tumours, thereby impeding their growth and metastasis (Mohan et al. 2004).

However, it is essential to observe that further preclinical and clinical studies are needed to validate the efficacy of withaferin A against specific cancer types and to determine optimal treatment regimens and potential side effects. Researchers have explored its mechanisms of action and demonstrated its efficacy in preclinical models. Despite its promising properties, further research is needed to assess its safety and efficacy in humans through clinical trials before it can be developed into a pharmaceutical drug. Hence, while withaferin A is not yet available as a conventional drug, its medicinal properties continue to be a subject of scientific interest and exploration.

Even though it has good anti-cancerous effects on various types of cancer it has poor bioavailability and poor water solubility. Recently, liposomal drug delivery system is an appreciable (Abeesh & Guruvayoorappan 2024) method to improve solubility, but still an in-depth molecular mechanistic approach is needed. In improving the bio-availability of withaferin A, numerous approaches have been reported such as encapsulation and conjugation process with other agents such as liposomes and metal nanoparticles. Nevertheless, there is a need for attention to improve the bioavailability of withaferin A to make an active drug for clinical trials. This gap needs to be addressed to make a good anti-cancerous drug with withaferin A to treat various types of cancer as a natural medicine.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

S.A.Y. assisted with the conceptualisation, methodology, investigation, writing the original draft, review, editing and supervision. R.V.P. assisted with the writing, review and editing.

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Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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References

Abeesh, P. & Guruvayoorappan, C., 2024, 'Withaferin A-encapsulated PEGylated nanoliposomes induce apoptosis in B16F10 melanoma cells by regulating Bcl2 and Bcl xl genes and mitigates murine solid tumor development', *Journal of Environmental Pathology, Toxicology and Oncology* 43(2), 29–42. https://doi.org/10.1615/JEnvironPatholToxicolOncol.2023046909

Bhatnagar, M., Sharma, D. & Salvi, M., 2009, 'Neuroprotective effects of *Withania somnifera* dunal: A possible mechanism', *Neurochemical Research* 34, 1975–1983. https://doi.org/10.1007/s11064-009-9987-7

Chang, H.W., Li, R.N., Wang, H.R., Liu, J.R., Tang, J.Y., Huang, H.W. et al., 2017, 'Withaferin A induces oxidative stress-mediated apoptosis and DNA damage in oral cancer cells', *Frontiers in Physiology* 8, 634. https://doi.org/10.3389/fphys.2017.00634

Mohan, R., Hammers, H., Bargagna-Mohan, P., Zhan, X., Herbstritt, C., Ruiz, A. et al., 2004, 'Withaferin A is a potent inhibitor of angiogenesis', *Angiogenesis* 7, 115–122. https://doi.org/10.1007/s10456-004-1026-3

Singh, N., Yadav, S.S., Rao, A.S., Nandal, A., Kumar, S., Ganaie, S.A. et al., 2021, 'Review on anticancerous therapeutic potential of *Withania somnifera* (L.) Dunal', *Journal of Ethnopharmacology* 270, 113704. https://doi.org/10.1016/j.jep.2020.113704

Sivasankarapillai, V.S., Madhu Kumar Nair, R., Rahdar, A., Bungau, S., Zaha, D.C., Aleya, L. et al., 2020, 'Overview of the anticancer activity of withaferin A, an active constituent of the Indian ginseng *Withania somnifera*', *Environmental Science and Pollution Research* 27, 26025–26035. https://doi.org/10.1007/s11356-020-09028-0