Antitumor withanolides from *Withania somnifera*

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Withania somnifera L. Dunal (Solanaceae) is an Indian plant commonly known as “ashwagandha”. This traditional plant has been used in Ayurvedic medicine for over 3,000 years for the treatment of arthritis, tumors, tuberculosis, chronic liver diseases and for immunomodulatory effects. Biological activity in this species is attributed to withanolides, a group of naturally occurring C_{28}-steroidal lactones including withaferin A. During our investigation in the search for anticancer natural products from plant biodiversity, we previously reported that withaferin A induces apoptosis in human head and neck squamous cell carcinoma (HNSCC cells MDA1986 and JMAR). In order to establish antitumor structure activity relationships, we isolated from this species additional amounts of withaferin A as well as its related withanolides. In the course of this investigation we isolated and identified eight withanolides including withaferin A; 2,3-dihydrowithaferin A; 2,3-didehydrosomnifericin; withanone; 3-methoxy-2,3-dihydrowithaferin A; 6□-chloro-5□-hydroxywithaferin A; 6□-chloro-5□ı□□-dihydroxywithaferin A as well as (22R)-5b-formyl-6b,27dihydroxyl-1-oxo-4-norwith-24-enolide. All compounds were tested by MTS (3-[4,5-dimethylthiazol-2yl]-5-[3-carboxymethoxyphenyl]-2-[4-sulfophenyl]-2H tetrazolium) assay using thyroid, squamous cell carcinoma of head and neck and breast cancer cell lines. The bioassay results showed that with the exception of withaferin A, the other seven withanolides are devoid of activity. Pre-clinical research is underway in order to establish additional mechanisms of action for withaferin A.