Withanolide Sulfoxide from Aswagandha Roots Inhibits Nuclear Transcription Factor-Kappa-B, Cyclooxygenase and Tumor Cell Proliferation

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Investigation of the methanol extract of Aswagandha (Withania somnifera) roots for bioactive constituents yielded a novel withanolide sulfoxide compound (1) along with a known withanolide dimer ashwagandhanolide (2) with an S-linkage. The structure of compound 1 was established by extensive NMR and MS experiments. Compound 1 was highly selective in inhibiting cyclooxygenase-2 (COX-2) enzyme by 60% at 100 μm with no activity against COX-1 enzyme. The IC50 values of compound 1 against human gastric (AGS), breast (MCF-7), central nervous system (SF-268) and colon (HCT-116) cancer cell lines were in the range 0.74–3.63 μm. Both S-containing dimeric withanolides, 1 and 2, completely suppressed TNF-induced NF-κB activation when tested at 100 μm. The isolation of a withanolide sulfoxide from W. somnifera roots and its ability to inhibit COX-2 enzyme and to suppress human tumor cell proliferation are reported here for the first time. In addition, this is the first report on the abrogation of TNF-induced NF-κB activation for compounds 1 and 2.

Keywords: withanolide; cyclooxygenase; tumor necrosis factor; cancer cell proliferation; ashwagandha; Withania somnifera.

INTRODUCTION

Medicinal plants used in Ayurvedic preparations to treat health disorders are gaining much attention in recent years. The plant Withania somnifera, Ashwagandha or popularly called Indian ginseng, has been an important herb in the Indian Ayurvedic system of medicine for over 3000 years. Various parts of the plant have been used for centuries to treat a variety of ailments (Bhattacharya et al., 2001; Kulkarni et al., 1998). Several research studies have shown that the plant preparations possess antiinflammatory (Rasool and Varalakshmi, 2006), anticancer (Dev et al., 1992; Mohan et al., 2004), antistress and immunomodulatory (Rai et al., 2003), adaptogenic (Bhattacharya and Muruganandam, 2003) and cardiovascular (Mohanty et al., 2004; Mishra et al., 2000) activities. The root extract of W. somnifera has also been used as a dietary supplement in the United States and is reported to be a rich source of withanolides.

The plant W. somnifera has been extensively studied for its chemical constituents. A series of withanolides from the roots, leaves and fruits (Lal et al., 2006; Mishra et al., 2005; Jayaprakasam et al., 2003; Jayaprakasam and Nair, 2003; Jayaprakasam et al., 2004; Glotter, 1991) of this plant have been isolated and studied for biological activities. Withanolides, known for their structural diversity and biological activity, are ergostane type steroids with δ-lactone functionality between C-22 and C-26 with an oxidized C-3 moiety in its skeleton. In 2001, Matsuda et al. reported novel withanolide glycosides from W. somnifera roots. Previous studies suggested that alkaloïds and withanolides are responsible for its diversified biological activities (Gupta and Rana, 2007). The dried root of this plant has been considered to be the most active for therapeutic preparations.

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that has been linked with the proliferation, survival, invasion, angiogenesis and metastasis of tumors (Aggarwal, 2003). Most of these TNF effects are mediated through the activation of NF-κB, activated protein 1 (AP-1), c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), p44/p42 MAPK and Akt (Garg and Aggarwal, 2002; Aggarwal, 2003). For example, the activation of NF-κB and AP-1 regulates the expression of genes involved in tumorigenesis. These include antiapoptotic genes (e.g. cIAP1/2, survivin, TRAF, Bel-2 and Bel-xL), COX-2 (MMP-9) genes encoding adhesion molecules, chemokines, inflammatory cytokines and cell cycle regulatory genes (e.g. cyclin D1 and c-Myc).
The present study describes the isolation and characterization of a novel thiowithanolide (1) from the roots of *W. somnifera*. Also, the COX-1 and -2 enzyme and tumor cell proliferation inhibitory activities of compound 1 are reported, along with the inhibition of TNF-induced NF-κB activation of compounds 1 and 2.

**MATERIALS AND METHODS**

**General experimental procedure.** The melting points were determined on Bristoline and V-Scientific melting point apparatus (MP-1) and are uncorrected. NMR spectra were measured at ambient temperature on a Varian UNITYplus 500 spectrometer. The chemical shifts were measured in DMSO-δ6 and are expressed in δ (ppm). Mass spectra were recorded at the Michigan State University Mass Spectrometry Facility using a Jeol HX-110 double focusing mass spectrometer (Peabody, MA). The UV and IR spectra were obtained on a Shimadzu UV-240 and a Perkin-Elmer BX FT-IR spectrophotometer, respectively. The circular dichroism (CD) spectrum was recorded on a Jasco model J-720 spectropolarimeter in MeOH at 25 °C. The LC-MS data were conducted on an Agilent 1100 LC/MSD instrument.

Analytical HPLC experiments were performed with an Altima C18, 5 µm 4.6 × 25.0 mm column equipped with a variable-wavelength UV detector operating at 215 and 227 nm, using 0.1% phosphoric acid in H2O–CH3CN (95:5, v/v) as the mobile phase, at a flow rate of 1 mL/min. Separations were carried out with a Phenomenex Luna 10 C18, 250 × 21.2 mm, 10 µm column (UV detector at 254 nm) with H2O–CH3CN (1:1) as eluant, at a flow rate of 25 mL/min. TLC plates were viewed under UV light at 254 and 366 nm or sprayed with 10% sulfuric acid in methanol. Column chromatography was conducted on silica gel (200–400 mesh size) and thin-layer chromatography (TLC) on silica gel (5 × 10 cm, 0.2 mm thick, E. Merck) plates. HPTLC on RP-18 plates (10 cm, 0.2 mm thick, E. Merck) was developed with methanol–water (70:30) as the solvent system. Spots or bands on TLC were visualized by spraying with 5% sulfuric acid in methanol followed by heating at 70 °C. ACS grade solvents were used for isolation and purification. Fetal bovine serum (FBS), Isocove’s modified Dulbecco’s medium (IMDM) and Iscove’s modified Dulbecco’s medium (IMDM) were obtained from Gibco BRL (Grand Island, NY). Human tumor cell lines breast (MCF-7), central nervous system, CNS (SF-268) and lung (NCI-H460), purchased from the National Cancer Institute (NCI, Bethesda, MD), and colon (HCT-116) and gastric (AGS) cell lines from American Type Culture Collection (ATCC, Rockville, MD) were maintained in our laboratory. The COX-1 enzyme was prepared from rat seminal vesicles purchased from Oxford Biomedical Research, Inc. (Oxford, MI) and COX-2 enzyme from insect cells cloned with human PGHS-2 enzyme. Aspirin, Celebrex and Vioxx® were used as positive controls in COX enzyme inhibitory assays. Bacteria-derived human recombinant human TNF, purified to homogeneity with a specific activity of 5 × 10⁸ units/mg, was kindly provided by Genentech (South San Francisco, CA). Butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), tert-butylhydroquinone (TBHQ) and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) were purchased from Sigma-Aldrich Chemical Co. (St Louis, MO).

**Plant material.** Roots of *W. somnifera* were collected from Kalyanadurg, Andhra Pradesh, India in July 2003, shade dried and stored at room temperature. The plant material was extracted and purified in May 2006 to yield compounds described in this manuscript. The plant material was identified by Dr K. Hemadri and a voucher specimen (No. LIH-6852) has been deposited at the herbarium of the Lalit Research Centre, Vijayawada, India.

**Extraction and isolation.** The dried roots of *W. somnifera* (2 kg) were extracted with MeOH (7 L × 3) at room temperature and the evaporation of the resulting extract under vacuum yielded a dark gummy residue (220 g). It was stirred with hexane (1 L × 2) and the resulting precipitate was further stirred with ethyl acetate (1 L × 3) and filtered. The ethyl acetate extract was concentrated (70 g) and subjected to column chromatography (silica gel 100–200 mesh size) using CHCl3 and MeOH mixtures as eluants. Similar fractions were combined after TLC examination to provide fractions I (5.9 g), II (7 g) and III (10 g). Fraction II (7 g) was chromatographed on silica gel column (200 g, 100–200 mesh size), eluted with CHCl3 and MeOH mixtures. The fractions that were eluted with CHCl3/MeOH 95:5 (v/v) yielded a mixture of two compounds (2 g). It was then subjected to chromatographic purification on a resin column (MCI CHP-20P, 75–150 µm, Mitsubishi Chemical Corporation, Tokyo, Japan) by using 75:25 MeOH/H2O (v/v) as the mobile phase to yield compound 1 (220 mg, R, 30.1 min) along with the dimer 2 (170 mg, R, 18.4 min) reported from our laboratory earlier (Subbaraju et al., 2006).

**Compound 1.** Colorless solid, mp 201–203 °C; [α]D20 +114 (c 1 mg/mL, MeOH, 25 °C); +180 (c 0.05, CHCl3, 25 °C); CD (nm) Δε +282 (235, c 0.5 mg/mL, MeOH); UV λmax (log ε) 216 nm (4.37); IR νmax 3080, 2943, 1680, 1382, 1188, 1134, 985, 845 cm⁻¹. HRMS m/z 991.5236 (M + H+)(calcd for C28H31O14S, 991.5242); 1H NMR (DMSO-δ6): δ 5.38 (d, J = 10.0 Hz, H-2), 5.87 (d, J = 10.0 Hz, H-3), 6.52 (d, J = 11.0 Hz, H-3), 6.60 (d, J = 10.5 Hz, H-2), 4.81 (d, J = 7.5 Hz, H-4), 4.98 (d, J = 7.5 Hz, H-4), 6.15 (d, J = 6.5 Hz, 4′-OH), 4.75 (s, 5-OH), 6.00 (s, 5′-OH), 3.30 (bss, H-6), 3.38 (bss, H-6), 1.92, 1.36 (m, H-7), 1.65 (m, H-8), 3.38 (m, H-9), 0.77 (m, H-10), 1.03 (m, H-12), 1.11 (m, H-14), 1.48 (m, H-15), 1.72 (m, H-16), 1.37 (m, H-17), 0.67 (s, H-18), 1.14 (s, H-19), 1.85 (m, H-20), 0.88 (d, J = 6.0 Hz, H-21), 4.28 (d, J = 13.0 Hz, H-22), 2.38 (t, J = 15.0 Hz), 2.05 (m, H-23), 4.13 (d, J = 4.5 Hz, H-27), 4.20 (d, J = 4.5 Hz, H-27), 4.56 (brrt, 27-OH), 2.00 (s, H-28); 13C NMR (DMSO-δ6): δ 201.7 (C-1), 201.5 (C-1′), 126.5 (C-2), 126.6 (C-2′), 148.1 (C-3), 149.0 (C-3′), 65.1 (C-4), 65.8 (C-4′), 79.7 (C-5), 83.2 (C-5′), 61.2 (C-6), 57.4 (C-6′), 27.2 (C-7), 27.1 (C-7′), 34.5 (C-8), 34.1 (C-8′), 44.9 (C-9), 45.0 (C-9′), 58.7 (C-10), 58.1 (C-10′), 23.6 (C-11), 23.6 (C-11′), 39.3 (C-12), 39.1 (C-12′), 43.6 (C-13), 43.5 (C-13′), 55.4 (C-14), 55.3 (C-14′), 24.4 (C-15), 24.1 (C-15′), 26.7 (C-16), 51.8 (C-17), 51.8 (C-17′), 12.6 (C-18), 12.6 (C-18′), 10.4 (C-19), 10.1 (C-19′), 39.0 (C-20), 13.8 (C-21), 13.7 (C-21′), 78.3 (C-22), 78.2 (C-22′), 29.5 (C-23), 29.8 (C-23′), 155.3 (C-24 and 24′), 126.2 (C-25 and C-25′), 166.0 (C-26 and C-26′), 55.3 (C-27), 20.6 (C-28).

DOI: 10.1002/ptr
Tumor cell proliferation inhibitory assay. The human tumor cells, MCF-7 (breast), SF-268 (central nervous system, CNS), NCI-H460 (lung), HCT-116 (colon) and AGS (gastric) were initially purchased from NCI and ATCC and maintained in a cryogenic storage at Bioactive Natural Products and Phytoceutical Laboratory at Michigan State University. The cells were thawed and routinely cultured in RPMI-1640 medium containing 0.1% penicillin-streptomycin solution and 10% FBS (fetal bovine serum) at 37 °C in a humidified incubator (5% CO2). After a week, the cells were harvested, counted and plated into 96-well plates. Compound 1 was initially dissolved in DMSO and then with growth media (RPMI-1640) to yield a stock solution. Serial dilutions of this stock solution were prepared using RPMI medium. Test solutions (100 μL) were added to wells and incubated for 48 h. An aliquot (25 μL) of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) solution (5 mg/mL PBS) was added to each well. After 3 h of incubation, the media and MTT were aspirated, the resulting dye crystals were dissolved in DMSO (200 μL) and the optical density was read at 570 nm using a microplate reader (Vareed et al., 2007). Adriamycin was used as a positive control in this assay. Controls and test compound were assayed in triplicate for each concentration and replicated three times for each cell line. The IC50 values were then calculated by importing these data to Microsoft Excel.

Cyclooxygenase enzyme inhibitory assay. Cyclooxygenase enzyme inhibitory assays of compound 1 were performed according to the previously reported procedure (Vareed et al., 2007). COX-1 enzyme was prepared from ram seminal vesicles purchased from Oxford Biomedical Research, Inc., Oxford, MI. COX-2 enzyme was prepared from HPGHS-2 cloned insect cell lysate and diluted with Tris buffer (pH 7.0), 1 mM phenol and 85 μl hemoglobin. COX-1 or COX-2 enzyme (10 μL) was added to the chamber and incubated for 2 min. The reaction was initiated by the addition of arachidonic acid (10 μL of a 1 mg/mL solution). The percent inhibition was calculated with respect to DMSO control. Each sample was assayed twice, and the standard deviation was calculated for n = 2. The data were recorded using QuickLog for Windows data acquisition and control software (Strawberry Tree, Inc., Sunnyvale, CA). Compound 1 was tested against COX-1 and -2 enzymes at 200 and 100 μg/mL, respectively. Aspirin (60 μM), Celebrex (26 nm) and Vioxx (32 nm) were used as positive controls.

Electrophoretic mobility shift assay (EMSA). To assess NF-κB activation, EMSA was performed as described previously (Chaturvedi et al., 2000). Briefly, KBM-5 cells were pretreated for 12 h separately with compounds 1 and 2, then stimulated with TNF (0.1 nmol/L) for 30 min. Nuclear extracts prepared from TNF-treated cells were incubated with 32P-end-labeled 45-mer double-stranded NF-κB oligonucleotide (15 μg of protein with 16 fmol of DNA) from the human immunodeficiency virus long terminal repeat, 5′-TTGTATTCAAA GGGACTTTC CGCTG GGGACTTTC CAGGGAGCGTG-G3′ (boldface indicates NF-κB-binding sites), for 30 min at 37 °C, and the DNA–protein complex formed was separated from free oligonucleotide on 6.0% native polyacrylamide gels. A double-stranded mutated oligonucleotide, 5′-TTGTATTCAAA CTCACTTTC CGCTG CTCACTTTC CAGGGAGCGTG-G3′, was used to examine the specificity of binding of NF-κB to the DNA. The dried gels were visualized with a Storm820, and the radioactive bands were quantified using ImageQuant software (Amersham Biosciences). Compounds 1 and 2 were tested at 100 μM.

RESULTS

The purification of ethyl acetate soluble fraction by column chromatography, followed by preparative HPLC, resulted in the isolation of compound 1 along with the previously reported thiowithanolide, ashwagandhanolide (2, Fig. 1) (Subbaraju et al., 2006). Compound 1, obtained as a colorless amorphous solid from a mixture of chloroform and methanol, melted at 203–205 °C and gave (α)0 and CD values at +114 and +28.2, respectively. Its MF was determined by HRFABMS as C56H78O13S on the basis of the (M+H)+ ion observed at m/z 991.5242. The UV spectrum of compound 1 showed an absorption peak at 216 nm, characteristic of α,β-unsaturated carbonyl and α,β-unsaturated γ-lactone moieties (Lavie et al., 1965). The IR spectrum (KBr) showed bands at 3436 and 1681 cm−1, indicating the presence of hydroxyl and α,β-unsaturated carbonyl moieties, respectively, in

![Figure 1. Structures of compounds 1 and 2.](image-url)

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DOI: 10.1002/ptr
compound 1 (Pavia et al., 1979). The IR spectrum also displayed a band at 998 cm⁻¹, corresponding to a sulfoxide moiety in the molecule (Melo et al., 1995). Melting point, optical rotation, CD, LCMS and HRMS data of compound 1 were found to be different from those of the reported S-containing withanolide dimer, 2 (Subbaraju et al., 2006).

The ¹H NMR spectrum of compound 1 displayed signals at δ 6.71, 1.14, 2.00 and 0.88 (d, J = 6.0 Hz), assigned to three tertiary and a secondary methyl groups, respectively. It also displayed signals at δ 6.52 (d, J = 11 Hz) and 5.87 (d, J = 10 Hz) and was assigned to two olefinic protons. The signals at δ 4.28 (d, J = 13 Hz), 4.98 (d, J = 7.5 Hz), 4.56 (brt) and 4.13 (d, J = 4.5 Hz) indicated the presence of two oxygenated methines and a methylene, respectively, similar to aswangandanolide 2 (Subbaraju et al., 2006). The ¹³C NMR spectrum of compound 1 showed signals attributable to a carbonyl carbon (δ 201.7), two olefinic carbons (δ 148.1 and 126.5) and three carbons for an αβ-unsaturated γ-lactone (δ 155.3, 126.2 and 166). Also, the DEPT spectrum revealed the presence of an oxygenated methine carbon at δ 65.8 and a quaternary carbon at δ 79.7, assigned to C-4 and C-5, respectively. In addition, the signals at δ 55.3 and 78.3 were assigned to C-27 and C-22, respectively. The ¹³C NMR spectra showed signals at δ 12.6, 10.4, 13.8 and 20.6 and were attributed to 18, 19, 21 and 28 methyl carbons, respectively. Analysis of ¹H- and ¹³C NMR spectral data revealed that compound 1 was similar in nature to the reported thiowithanolide withanolide, although its MF was different, with the presence of an additional oxygen atom in its structure. Interpretation of ¹H- and ¹³C NMR spectral data of compound 1 revealed that the additional oxygen was part of a sulfoxide moiety in the molecule and was in agreement with the adsorption band at 998 cm⁻¹ observed in its IR spectrum (Melo et al., 1995). Analysis of C-6 proton (δ 3.30, brs) and carbon signals (δ 61.2) further suggested that the withanolide units are linked via the sulfoxide group between the C-6 and C-6' positions. Although both units of the dimer were linked through a sulfoxide group, differences in chemical shifts observed for C-4, C-5 and C-6 of one half of the withanolide dimer revealed that the sulfoxide moiety in compound 1 might be hydrogen-bonded with either the 5- or 5'-OH group. In the HMBC spectrum of compound 1, the C-3 proton exhibited correlation with carbons resonating at δ 201.7 (C-1) and 79.7 (C-5). Also, the C-6 proton showed correlations to carbon signals appearing at δ 65.1 and 79.7 (C-4 and C-5) and C-6' protons with C-4' and C-5' carbons (δ 65.8 and 83.2).

The antinflammatory activity of compound 1 was carried out by using COX-1 and -2 enzymes according to the published procedure (Vareed et al., 2007). Compound 1 showed 60% inhibition against COX-2 enzyme when tested at a 100 µg/mL concentration as shown in Fig. 2. Interestingly it did not show any activity against COX-1 enzyme even at 200 µg/mL. The nonsteroidal anti-inflammatory drugs (NSAIDs) aspirin (60 µm), Celebrex® (26 nm) and Vioxx® (32 nm) inhibited COX-1 and -2 enzymes by 68.6%, 40.7% and 0%, and 26.6%, 72.2% and 92.4%, respectively (Fig. 2). The varying concentrations of positive controls were necessary to obtain the inhibition of enzyme by 50%, since their activities are not the same at the same concentrations.

Compound 1 was also evaluated for its potential to inhibit the proliferation of gastric, breast, colon, CNS and lung human cancer cell lines by MTT cell viability assay, as per procedures reported from our laboratory (Vareed et al., 2007). When tested at 7.5 µg/mL concentration, compound 1 showed 90.7%, 78.9%, 78.8% and 88.0% of inhibition against gastric, breast, CNS and colon cancer cell lines, respectively. In a dose response study of compound 1 using concentrations ranging from 7.5 to 0.45 µg/mL, the 50% growth inhibitory concentrations (IC₅₀) were 0.73, 1.26, 1.78 and 3.59 µg/mL against gastric, breast, CNS and colon cancer cell lines, respectively (Fig. 3). Interestingly, it did not show inhibitory activity against the growth of the lung cancer cell line tested. Among the tested cell lines, the growth of gastric cancer cells was retarded the most by compound 1 with a minimum inhibitory concentration (IC₅₀) value of 0.73 µg/mL (Fig. 3).

Based on the COX enzymes and tumor cell proliferation inhibitory activities, compounds 1 and 2 were tested...
withanolide sulfoxide from Aswagandha roots

DISCUSSION

Exploring plant-derived antinflammatory agents is a high priority in natural products research. Therefore, evaluation of plant extracts and purified compounds for their inhibition of COX enzymes in vitro is the first step in developing new antinflammatory agents. Prostaglandins cause inflammation in the body and it is generated by COX-1 and -2 enzymes by the conversion of arachidonic acid, a cellular lipid. The COX-2 enzyme is a major target of nonsteroidal antinflammatory drugs (NSAIDs) due to its involvement in a range of pathologies (Patrono, 1994; Hwang et al., 1998; McGeer and McGeer, 1999).

Several withanolides, isolated from W. somnifera leaves, are reported to be excellent COX-2 inhibitors (Jayaprakasam and Nair, 2003). Therefore, the withanolide sulfoxide (1) was tested for its COX-1 and -2 enzyme inhibitory activities. Expression of COX-2 enzyme was observed, not only in inflamed cells, but also in various types of tumor cells. In addition, it has been demonstrated that COX-2 plays an important role in carcinogenesis. The results clearly indicate that the preferential COX-2 inhibitory activity of compound 1 is similar to the selective COX-2 enzyme inhibition of withanolides from the leaves of W. somnifera (Jayaprakasam and Nair, 2003).

Medicinal plants are considered as useful leads for novel chemotherapeutic agents. An in vitro assay such as inhibition of tumor cell proliferation is one of the rapid methods for screening a large number of medicinal plants for anticancer principles. The root of W. somnifera has been used in formulations to treat cancer (Sharma and Dandiya, 1992). Several reports have confirmed the anticancer activity of root extract of W. somnifera in experimental models (Prakash et al., 2001). In vitro cytotoxicity study as determined by MTT assay is one of the widely used screening methods for cell viability and proliferation. In this study, compound 1 exhibited 90.7%, 78.9%, 78.8% and 88.0% of inhibition against gastric, breast, CNS and colon cancer cell lines, respectively, when tested at 7.5 μg/mL.

Further dose response study indicated an IC50 (50% growth inhibition concentration) value of 0.73 μg/mL for compound 1. The IC50 of compound 1 against breast, CNS and colon cancer cell lines were 1.26, 1.78 and 3.59 μg/mL, respectively. However, compound 1 did not show any activity against lung cancer cell lines. These results are similar to the tumor cell proliferation inhibitory activities of withanolides isolated from W. somnifera leaves reported from our laboratory (Jayaprakasam et al., 2003).

Tumor necrosis factor α, or TNF-α, is a key cytokine that exerts its biological effects through interaction with one of two ubiquitously expressed cell surface receptors. It also causes activation of the transcription factor NF-κB, which plays a critical role in cellular stress-, immune- and inflammatory responses (Karin et al., 2002). Recent studies have identified NF-κB as a direct link between inflammation and cancer (Feldmann et al., 2002; Luo et al., 2004). Efforts are under way in the screening of plants used as traditional medicines and compounds derived from them to modulate the activity of NF-κB.

Recently, Singh et al. (2007) demonstrated that W. somnifera inhibited NF-κB and AP-1 transcription factors in human peripheral blood and synovial fluid mononuclear cells. Also, the ability of withanolides to enhance apoptosis and to inhibit invasion and osteoclastogenesis by inhibiting NF-κB and NF-κB-regulated gene expression has been reported (Ichikawa et al., 2006). One of the withanolides from W. somnifera, withaferin A, inhibited TNF-α induced NF-κB activation via inhibition of IKKβ kinase activity in the nanomolar range (Kaileh et al., 2007). In this study, compounds 1 and 2, isolated from the root extract of W. somnifera, completely suppressed the TNF-α induced NF-κB activation at 100 μM. Compounds which suppress NF-κB may help in halting tumor progression and hence they are ideal to treat the later stages of cancer (Paul, 2005).

Therefore, these thiowithanolide dimers shall be considered as potential NF-κB inhibitors and as antinflammatory agents for the treatment of cancer and inflammatory disorders. The study also validates further the use of W. somnifera as a traditional medicine to treat cancer and inflammation.
REFERENCES


