

## **Selected *Andrographis paniculata* Published Scientific Abstracts**

Am J Chin Med. 2007;35(2):317-28.

### **In Vivo and In Vitro Anti-inflammatory Activities of Neoandrographolide.**

*Liu J, Wang ZT, Ji LL.*

Neoandrographolide, one of the principal diterpene lactones, isolated from a medicinal herb *Andrographis paniculata* Nees, was tested in vivo and in vitro for its anti-inflammatory activities and mechanism. Oral administration of neoandrographolide (150 mg/kg) significantly suppressed ear edema induced by dimethyl benzene in mice. Oral administration of neoandrographolide (100-150 mg/kg) also reduced the increase in vascular permeability induced by acetic acid in mice. In vitro studies were performed using the macrophage cell line RAW264.7 to study the effect of neoandrographolide on suppressing phorbol-12-myristate-13-acetate (PMA)-stimulated respiratory bursts and lipopolysaccharide (LPS)-induced production of nitric oxide (NO) and tumor necrosis factor-alpha (TNF-alpha). Respiratory bursts were quantified by chemiluminescence (CL) measurements. Results showed that neoandrographolide suppressed PMA-stimulated respiratory bursts dose-dependently from 30 muM to 150 muM. Neoandrographolide also inhibited NO and TNF-alpha production in LPS-induced macrophages, contributing to the anti-inflammatory activity of *A. paniculata*. These results indicate that neoandrographolide possesses significant anti-inflammatory effects, which implies that it would be one of the major contributing components to participate in the anti-inflammatory effect of *A. paniculata*. and a potential candidate for further clinical trial. PMID: 17436371

Integr Cancer Ther. 2007 Mar;6(1):66-73.

### **Modulation of natural killer cell activity, antibody-dependent cellular cytotoxicity, and antibody-dependent complement-mediated cytotoxicity by andrographolide in normal and ehrlich ascites carcinoma-bearing mice.**

*Sheeja K, Kuttan G.*

Modulation of immune responses is highly relevant in tumor cell destruction. The present study is focused on the effect of *Andrographis paniculata* extract (APE) and its isolated compound andrographolide (ANDLE) on cell-mediated immune responses in normal and tumor-bearing control animals. Treatment with APE and ANDLE significantly enhanced natural killer cell activity in normal (APE, 46.82% cell lysis; ANDLE, 40.79% cell lysis) and tumor-bearing animals (APE, 48.66% cell lysis; ANDLE, 42.19% cell lysis) on the fifth day, and it was observed earlier than in tumor-bearing control animals (12.89% cell lysis on day 9). Antibody-dependent cellular cytotoxicity was also increased in APE (45.17% cell lysis on day 11) as well as ANDLE (39.92% cell lysis on day 11)-treated normal and tumor-bearing animals (APE, 47.39% cell lysis; ANDLE, 41.48% cell lysis on day 11) compared to untreated tumor-bearing control animals (maximum of 11.76% cell lysis on day 17). An early enhancement of antibody-dependent complement-mediated cytotoxicity was also observed by the administration of APE and ANDLE in normal as well as tumor-bearing animals. APE and ANDLE administration could significantly enhance the mitogen-induced proliferation of splenocyte, thymocyte, and bone marrow cells. Moreover, treatment of APE and ANDLE significantly elevated the production of interleukin-2 and interferon-gamma in normal and Ehrlich ascites carcinoma-bearing animals. PMID: 17351028

Int Immunopharmacol. 2007 Apr;7(4):515-23. Epub 2007 Jan 17.

### **Modulation of immune response in mice immunised with an inactivated *Salmonella* vaccine and gavaged with *Andrographis paniculata* extract or andrographolide.**

Xu Y, Chen A, Fry S, Barrow RA, Marshall RL, Mukkur TK.

Gavage of mice, immunised with an inactivated *S. typhimurium* vaccine, with *Andrographis paniculata* extract [APE] or andrographolide [AND] resulted in an enhancement of Salmonella-specific antibody response and induction of cell-mediated response against salmonellosis. Mice were vaccinated with either one or two doses of killed *S. typhimurium* vaccine and fed two different quantities of APE or AND, for 14 days in mice immunised with one dose of the vaccine, and for 28 days in mice immunised with two doses of vaccine, respectively. Both APE and AND were found to enhance IgG antibody levels against *S. typhimurium*, the enhancement being statistically significant in mice receiving two doses of the vaccine. Splenocyte cultures, prepared from mice immunised with the killed Salmonella vaccine and treated with APE or AND, showed a remarkable increase in the production IFN-gamma following stimulation with the bacterial lysate, indicating an induction of Salmonella-specific cell-mediated response/immune response. PMID: 17321475

Asian Pac J Cancer Prev. 2006 Oct-Dec;7(4):609-14.

**Ameliorating effects of *Andrographis paniculata* extract against cyclophosphamide-induced toxicity in mice.**

Sheeja K, Kuttan G.

Major drawbacks of chemotherapeutic agents are their toxic side effects and lack of tumor specificity. Immunological and biochemical studies were here carried out to investigate protective effects of ethanolic extract of *Andrographis paniculata* against cyclophosphamide (CTX) induced toxicity in vivo. Intraperitoneal administration of the extract significantly increased the total WBC account ( $3256.5 \pm 196$  cells/cm<sup>2</sup>), bone marrow cellularity ( $17.1 \pm 10.4 \times 10^6$  cells/femur) and betaesterase positive cells ( $849 \pm 23.2$  cells/4000 cells) in CTX treated animals, when compared to CTX alone treated control mice. Weights of lymphoid organs such as a spleen and thymus, reduced by CTX administration, were also increased by *A. paniculata* treatment. Reduction of GSH in liver ( $4.8 \pm 0.21$  nmol/mg protein) and in intestinal mucosa ( $13 \pm 0.67$  nmol/mg protein) of CTX-treated controls was significantly reversed by *A. paniculata* administration (liver:  $6.4 \pm 0.13$ , intestinal mucosa:  $17.11 \pm 0.06$ ), with amelioration of changes in serum and liver ALP, GPT, LPO (lipid peroxidation). Histopathological analysis of small intestine also suggests that extract could reduce the CTX induced intestinal damage. The level of proinflammatory cytokine TNF-alpha, which was elevated during CTX administration, was significantly reduced by the *A. paniculata* extract administration. The lowered levels of other cytokines like IFN-gamma, IL-2, GM-CSF, after CTX treatment were also found to be increased by extract administration. PMID: 17250437

Phytochemistry. 2007 Mar;68(6):904-12. Epub 2007 Jan 17.

**Semisynthesis and in vitro anticancer activities of andrographolide analogues.**

Jada SR, Subur GS, Matthews C, Hamzah AS, Lajis NH, Saad MS et al.

Faculty of Medicine and Health Sciences, Universiti Putra Malaysia.

The plant *Andrographis paniculata* found throughout Southeast Asia contains Andrographolide 1, a diterpenoid lactone, which has antitumour activities against in vitro and in vivo breast cancer models. In the present study, we report on the synthesis of andrographolide derivatives, 3,19-isopropylideneandrographolide (2), 14-acetyl-3,19-isopropylideneandrographolide (3) and 14-acetylandrographolide (4), and their in vitro antitumour activities against a 2-cell line panel consisting of MCF-7 (breast cancer cell line) and HCT-116 (colon cancer cell line). Compounds 2 and 4 were also screened at the US National Cancer Institute (NCI) for their activities against a panel of 60 human cancer cell lines derived from nine cancer types. Compound 2 was found to be selective towards leukaemia and colon cancer cells, and compound 4 was selective towards leukaemia, ovarian and renal

cancer cells at all the dose-response parameters. Compounds 2 and 4 showed non-specific phase of the cell cycle arrest in MCF-7 cells treated at different intervals with different concentrations. NCI's COMPARE and SOM mechanistic analyses indicated that the anticancer activities of these new class of compounds were not similar to that of standard anticancer agents, suggesting novel mechanism(s) of action.

PMID: 17234223

Int Immunopharmacol. 2007 Feb;7(2):211-21. Epub 2006 Nov 2.

**Antiangiogenic activity of Andrographis paniculata extract and andrographolide.**

*Sheeja K, Guruvayoorappan C, Kuttan G.*

Inhibition of angiogenesis is currently perceived as one of the promising strategies in the treatment of cancer. In this study we analyzed the antiangiogenic activity of Andrographis paniculata extract (APE) and its major component andrographolide (ANDLE) using both in vitro and in vivo models. Intraperitoneal administration of APE and ANDLE significantly inhibited the B16F-10 melanoma cell line induced capillary formation in C57BL/6 mice. Analysis of serum cytokine profile showed a drastic elevation in the proinflammatory cytokines such as IL-1beta, IL-6, TNF-alpha and GM-CSF and the most potent angiogenic factor VEGF in angiogenesis induced animals. Treatment of APE and ANDLE significantly reduced this elevated levels. Moreover, VEGF mRNA level in B16F-10 cell line showed a reduced level of expression in the presence of APE and ANDLE. Serum NO level which was increased in B16F-10 melanoma injected control animals was also found to be significantly lowered by the administration of APE and ANDLE. Antiangiogenic factors such as TIMP-1 and IL-2 level was elevated in APE and ANDLE treated angiogenesis induced animals. In the rat aortic ring assay APE and ANDLE inhibited the microvessel outgrowth at non toxic concentrations. Taken together our results demonstrate that APE and ANDLE inhibit the tumor specific angiogenesis by regulating the production of various pro and antiangiogenic factors such as proinflammatory cytokine, nitric oxide, VEGF, IL-2 and TIMP-1. PMID: 17178389

J Ethnopharmacol. 2007 Apr 20;111(1):13-21. Epub 2006 Oct 28.

**Protective activity of andrographolide and arabinogalactan proteins from Andrographis paniculata Nees. against ethanol-induced toxicity in mice.**

*Singha PK, Roy S, Dey S.*

To find out the active principles against ethanol-induced toxicity in mice, Andrographis paniculata Nees. (Ap) was chosen and isolated andrographolide (ANDRO) and arabinogalactan proteins (AGPs). ANDRO was detected by HPTLC, FTIR and quantified by HPLC (10mg/g of Ap powder). AGPs was detected by beta-glucosyl Yariv staining of SDS-PAGE gel, FTIR and quantified by single radial gel diffusion assay with beta-glucosyl Yariv reagent (0.5mg/g Ap powder). The mice are pretreated intra-peritoneally (i.p.) with different doses (62.5, 125, 250, and 500mg/kg) of body weight of mice] of ANDRO and AGPs for 7 days and then ethanol (7.5g/kg of body weight) was injected, i.p. Besides, silymarin was used as standard hepatoprotective agent for comparative study with ANDRO and AGPs. The ameliorative activity of ANDRO and AGP against hepatic renal alcohol toxicity was measured by assessing GOT, GPT, ACP, ALP and LP levels in liver and kidney. It has been observed that pretreatment of mice with ANDRO and AGPs at 500mg/kg of body weight and 125mg/kg of body weight respectively could able to minimize the toxicity in compare to ethanol treated group as revealed by the different enzymatic assay in liver and kidney tissues and the results were comparable with silymarin. Hence, out of several ill-defined compounds present in Ap, ANDRO and AGPs are the potential bioactive compounds responsible for protection against ethanol-induced toxicity. PMID: 17127022

Integr Cancer Ther. 2006 Sep;5(3):244-51.

**Protective effect of *Andrographis paniculata* and andrographolide on cyclophosphamide-induced urothelial toxicity.**

*Sheeja K, Kuttan G.*

The protective effect of *Andrographis paniculata* and andrographolide (ANDLE) against cyclophosphamide (CTX)-induced urothelial toxicity was investigated in this study. Pretreatment of Swiss albino mice with *A. paniculata* extract (10 mg/dose/animal intraperitoneally [ip]) and ANDLE (500 microg/dose/animal ip) could significantly reduce CTX (1.5 nmol/kg body weight)-induced urothelial toxicity. Morphological and histopathological analysis of urinary bladder of CTX-treated mice showed severe inflammation and dark coloration, whereas *A. paniculata* and ANDLE-treated mice showed almost normal bladder morphology. Elevation of urinary protein level (7.33 +/- 0.3 g/L) by CTX administration was reduced by *A. paniculata* (3.78 +/- 0.4 g/L) and ANDLE treatment (4.19 +/- 0.1 g/L). Urinary urea N2 level, which was elevated after 48 hours of CTX administration (24.25 +/- 0.2 g/L) was found to be reduced by the treatment with *A. paniculata* (14.19 +/- 0.5 g/L) and ANDLE (15.79 +/- 0.4 g/L). A decreased level of reduced glutathione (GSH) content in liver (2.81 +/- 0.1 nmol/mg protein) and bladder (1.20 +/- 0.2 nmol/mg protein) after CTX administration was also increased by the treatment with *A. paniculata* (liver: 5.78 +/- 0.3 nmol/mg protein; bladder: 2.96 +/- 0.2 nmol/mg protein) and ANDLE (liver: 5.14 +/- 0.3 nmol/mg protein; bladder: 2.84 +/- 0.2 nmol/mg protein). Production of the proinflammatory cytokine, tumor necrosis factor-alpha, which was elevated during CTX administration, was found to be inhibited by *A. paniculata* and ANDLE treatment. The lowered level of interleukin-2 and interferon-gamma during CTX treatment was elevated by the administration of *A. paniculata* and ANDLE. PMID: 16880430

Biochem Pharmacol. 2006 Jul 14;72(2):132-44. Epub 2006 Apr 29.

**Critical role of pro-apoptotic Bcl-2 family members in andrographolide-induced apoptosis in human cancer cells.**

*Zhou J, Zhang S, Ong CN, Shen HM.*

Department of Community, Occupational and Family Medicine, Yong Loo Lin School of Medicine, National University of Singapore, 16 Medical Drive, Singapore 117597, Republic of Singapore.

Andrographolide (Andro), a diterpenoid lactone isolated from a traditional herbal medicine *Andrographis paniculata*, is known to possess potent anti-inflammatory activity. In this study, Andro induced apoptosis in human cancer cells via activation of caspase 8 in the extrinsic death receptor pathway and subsequently with the participation of mitochondria. Andro triggered a caspase 8-dependent Bid cleavage, followed by a series of sequential events including Bax conformational change and mitochondrial translocation, cytochrome c release from mitochondria, and activation of caspase 9 and 3. Inhibition of caspase 8 blocked Bid cleavage and Bax conformational change. Consistently, knockdown of Bid protein using small interfering RNA (siRNA) technique suppressed Andro-induced Bax conformational change and apoptosis. In conclusion, the pro-apoptotic Bcl-2 family members (Bid and Bax) are the key mediators in relaying the cell death signaling initiated by Andro from caspase 8 to mitochondria and then to downstream effector caspases, and eventually leading to apoptotic cell death.

PMID: 16740251

Immunopharmacol Immunotoxicol. 2006;28(1):129-40.

**Antioxidant and anti-inflammatory activities of the plant *Andrographis paniculata* Nees.**

Sheeja K, Shihab PK, Kuttan G.

Amala Cancer Research Centre, Thrissur, Kerala, India.

In this study, we explored the antioxidant and anti-inflammatory properties of the medicinal herb *Andrographis paniculata* using in vitro as well as in vivo systems. Methanolic extract of *Andrographis paniculata* was found to inhibit formation of oxygen derived free radicals such as superoxide (32%) hydroxyl radicals (80%) lipid peroxidation (80%) and nitric oxide (42.8%) in in vitro system. In vivo studies using BALB/c mice models also showed significant inhibition in PMA induced superoxide (32.4%) and nitric oxide (65.3%) formation. Interestingly we also found that, administration of *Andrographis paniculata* extract produced complete inhibition of carageenan induced inflammation compared with control models. PMID: 16684672

Phytomedicine. 2006 May;13(5):318-23. Epub 2005 Sep 16.

**The effect of Kan Jang extract on the pharmacokinetics and pharmacodynamics of warfarin in rats.**

Hovhannisyan AS, Abrahamyan H, Gabrielyan ES, Panossian AG.

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Significant pharmacokinetic/pharmacodynamic interactions between various herbal products and warfarin have recently been reported. The aim of this study was to determine whether concomitant treatment of rats with Kan Jang (a standardized fixed combination of extracts from *Andrographis paniculata* and *Eleutherococcus senticosus*) and warfarin would lead to an alteration in the pharmacological effects of warfarin. Each day for 5 days a group of animals was treated orally with an aqueous solution of Kan Jang at a dose of 17 mg/kg of the active principle andrographolide (a daily dose some 17-fold higher than that recommended for humans): the control group received similar treatment with appropriate volumes of water only. Sixty minutes after the final daily administration of Kan Jang or water, an aqueous solution of warfarin (0.2 mg/ml) was given to each animal at a dose of 2 mg/kg. From each group, 6 animals were sacrificed at 0, 2, 4, 6, 8, 12, 24, 30 and 48 h after warfarin administration and blood samples taken. The concentration of warfarin in blood plasma was measured by capillary electrophoresis using 50 mM borate buffer (pH 9.3) as mobile phase with simultaneous detection of warfarin at 208.1 and 307.5 nm. Prothrombin time in blood plasma was measured using thromboplastin reagent. The concomitant application of Kan Jang and warfarin did not produce significant effects on the pharmacokinetics of warfarin, and practically no effect on its pharmacodynamics. PMID: 16635739

J Ethnopharmacol. 2006 Sep 19;107(2):205-10. Epub 2006 Mar 17.

**The effect of medicinal plants used in Chinese folk medicine on RANTES secretion by virus-infected human epithelial cells.**

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The accumulation of inflammatory cells in the infective sites has been reported to play a crucial role in the progression of chronic inflammation and multiple sclerosis after viral infection. In the present study, nine ethanol extracts of *Forsythia suspensa* Vahl. (Oleaceae), *Lonicera japonica* Thunb. (Caprifoliaceae), *Isatis indigotica* Fort. (Cruciferae), *Strobilanthes cusia* (Ness.) O. Kuntze (Acanthaceae), *Astragalus membranaceus* (Fisch.) Bge. (Leguminosae), *Hedysarum polybotrys* Hand.-Mazz. (Leguminosae), *Andrographis paniculata* (Burm. f.) Ness. (Acanthaceae), *Glycyrrhiza uralensis* Fischer. (Leguminosae) and *Ligusticum wallichii* Franch. (Umbelliferae), medicinal plants traditionally used in China for treating conditions likely to be associated with inflammation and viral infection, were screened for their effect on RANTES secretion by influenza A virus

(H1N1)-infected human bronchial epithelial cells (A549). With exception of *Lonicera japonica*, *Isatis indigotica*, *Astragalus membranaceus* and *Hedysarum polybotrys*, all plants tested at concentration of 200 microg/ml possessed more than 50% suppressing effect on RANTES secretion by H1N1-infected A549 bronchial epithelial cells. Among the plants tested, *Andrographis paniculata* showed the most promising property to inhibit RANTES secretion with an IC(50) of 1.2 +/- 0.4 microg/ml while the next two were *Glycyrrhiza uralensis* and *Forsythia suspensa* (IC(50) ranging from 35 to 48 microg/ml). PMID: 16621378

Planta Med. 2005 Dec;71(12):1106-11.

**Andrographolide isolated from *Andrographis paniculata* induces cell cycle arrest and mitochondrial-mediated apoptosis in human leukemic HL-60 cells.**

*Cheung HY, Cheung SH, Li J, Cheung CS, Lai WP, Fong WF, Leung FM.*

Department of Biology and Chemistry, City University of Hong Kong, Hong Kong  
The in vitro cytotoxicities of the ethanol extract of *Andrographis paniculata* (APE) and its main diterpenoid components were evaluated in various cancer cells. APE was found to be significantly growth inhibitory to human acute myeloid leukemic HL-60 cells with an IC (50) value of 14.01 microg/mL after 24 h of treatment. Among the three main diterpenoids in *A. paniculata*, andrographolide exhibited the highest degree of cytotoxicity followed by deoxyandrographolide while neoandrographolide was the least effective. Laser confocal microscopy and gel electrophoresis studies revealed chromosomal DNA fragmentations suggesting the occurrence of apoptosis. An increase of G (0)/G (1) phase cells from 51.88 % to 78.69 % was noted after andrographolide treatment for 36 h. The G (0)/G (1) phase arrest and apoptosis were associated with disappearance of mitochondrial cytochrome c and increased expression of Bax but decreased expression of Bcl-2 proteins in the inhibited cells. Although the order of all these events has not been determined, it is concluded that APE and andrographolide induce cell cycle arrest and affect an intrinsic mitochondria-dependent pathway of apoptosis by regulating the expression of some pro-apoptotic markers in HL-60 cells. PMID: 16395645

Phytother Res. 2005 Dec;19(12):1069-70.

**Antiviral properties of ent-labdene diterpenes of *Andrographis paniculata* nees, inhibitors of herpes simplex virus type 1.**

*Wiat C, Kumar K, Yusof MY, Hamimah H, Fauzi ZM, Sulaiman M.*

Department of Pharmacy, Faculty of Medicine, University of Malaya, Malaysia.  
Andrographolide, neoandrographolide and 14-deoxy-11,12-didehydroandrographolide, ent-labdene diterpenes isolated from *Andrographis paniculata* showed viricidal activity against herpes simplex virus 1 (HSV-1). None of these compounds exhibited significant cytotoxicity at viricidal concentrations. PMID: 16372376

J Ethnopharmacol. 2006 Apr 21;105(1-2):196-200. Epub 2005 Nov 18.

**Anti-diabetic potentials of *Momordica charantia* and *Andrographis paniculata* and their effects on estrous cyclicity of alloxan-induced diabetic rats.**

*Reyes BA, Bautista ND, Tanquilut NC, Anunciado RV, Leung AB et al.*

Thomas Jefferson University, Department of Neurosurgery, Farber Institute for Neurosciences, Philadelphia, Pennsylvania 19107, USA.

*Momordica charantia* and *Andrographis paniculata* are the commonly used herbs by the diabetic patients in Pampanga, Philippines. While the anti-diabetic potential of *Momordica charantia* is well established in streptozocin- or alloxan-induced diabetic animals, the anti-diabetic potential of *Andrographis paniculata* in alloxan-induced diabetic rat is not known. Neither the effects of these herbs on estrous cyclicity of alloxan-induced diabetic rats are elucidated. Thus, in these

experiments, *Momordica charantia* fruit juice or *Andrographis paniculata* decoction was orally administered to alloxan-induced diabetic rats. Rats that were treated with *Momordica charantia* and *Andrographis paniculata* had higher body weight (BW) compared with diabetic positive control ( $P < 0.01$ ) from day 22 to day 27 (D27) but exhibited lower BW than the non-diabetic control ( $P < 0.05$ ). These rats had lower feed ( $P < 0.05$ ) and liquid intakes ( $P < 0.01$ ) compared with diabetic positive control from day 17 to D27, but similar with the non-diabetic control. The blood glucose levels in these groups were significantly reduced from day 12 to D27 compared with diabetic positive control ( $P < 0.01$ ), however, comparable with non-diabetic control. The diabetic positive control had extended mean estrous cycles (8 days) compared to *Momordica charantia* and *Andrographis paniculata*-treated diabetic rats (5 days;  $P < 0.05$ ). Our results suggest that the anti-diabetic potentials of *Momordica charantia* and *Andrographis paniculata* could restore impaired estrous cycle in alloxan-induced diabetic rats.

PMID: 16298503

J Ethnopharmacol. 2006 Jan 16;103(2):201-7. Epub 2005 Sep 15.

**Screening of plants acting against *Heterometrus laoticus* scorpion venom activity on fibroblast cell lysis.**

Uawonggul N, Chaveerach A, Thammasirirak S, Arkaravichien T et al. Department of Biochemistry, Faculty of Science, Khon Kaen University, Thailand. The aqueous extracts of 64 plant species, listed as animal- or insect-bite antidotes in old Thai drug recipes were screened for their activity against fibroblast cell lysis after *Heterometrus laoticus* scorpion venom treatment. The venom was preincubated with plant extract for 30 min and furthered treated to confluent fibroblast cells for 30 min. More than 40% efficiency (test/control) was obtained from cell treatment with venom preincubated with extracts of *Andrographis paniculata* Nees (Acanthaceae), *Barringtonia acutangula* (L.) Gaertn. (Lecythydaceae), *Calamus* sp. (Palmae), *Clinacanthus nutans* Lindau (Acanthaceae), *Euphorbia neriifolia* L. (Euphorbiaceae), *Ipomoea aquatica* Forssk (Convolvulaceae), *Mesua ferrea* L. (Guttiferae), *Passiflora laurifolia* L. (Passifloraceae), *Plectranthus amboinicus* (Lour.) Spreng. (Labiatae), *Ricinus communis* L. (Euphorbiaceae), *Rumex* sp. (Polygonaceae) and *Sapindus rarak* DC. (Sapindaceae), indicating that they had a tendency to be scorpion venom antidotes. However, only *Andrographis paniculata* and *Barringtonia acutangula* extracts provided around 50% viable cells from extract treatments without venom preincubation. These two plant extracts are expected to be scorpion venom antidotes with low cytotoxicity. PMID: 16169172

Phytomedicine. 2005 Jun;12(6-7):403-9.

**A phase I clinical study of *Andrographis paniculata* fixed combination Kan Jang versus ginseng and valerian on the semen quality of healthy male subjects.**

*Mkrtchyan A, Panosyan V, Panossian A, Wikman G, Wagner H.*

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The safety of different doses of Kan Jang--a fixed combination of *Andrographis paniculata* special extract (SHA-10) and *Acanthopanax senticosus*--compared to two extensively used medicinal plants, *Valeriana officinalis* and *Panax ginseng* in the form of standardized extracts, has been examined. A phase I clinical study was designed to evaluate the effect on semen quality of healthy males in terms of spermatogenesis and quality of semen. The results of the study revealed no significant negative effect of Kan Jang on male semen quality and fertility, but rather a positive trend with respect to the number of spermatozooids in the whole ejaculate, the percentage of active (normokinetic) forms of spermatozooids, and fertility indexes, together with a decrease in the percentage of inactive

(diskinetic) forms of spermatozoids. In the group receiving ginseng, no significant negative effects on the fertility parameters were revealed and there was a clear decrease in the percentage of diskinetic forms of spermatozoids. Subjects receiving valerian showed a temporary increase in the percentage of normokinetic spermatozoids and a decrease in diskinetic forms, but these changes had no effect on fertility indices. The results indicate that Kan Jang, ginseng and valerian are safe with respect to effects on human male sterility when administered at dose levels corresponding to approximately 3 times the human daily dose. PMID: 16008115

J Cell Biochem. 2005 Aug 1;95(5):970-8.

**Andrograpanin, a compound isolated from anti-inflammatory traditional Chinese medicine *Andrographis paniculata*, enhances chemokine SDF-1alpha-induced leukocytes chemotaxis.**

*Ji LL, Wang Z, Dong F, Zhang WB, Wang ZT.*

*Andrographis paniculata* is a traditional Chinese medicine (TCM) that has been effectively used for treatment of infection, inflammation, cold, fever, and diarrhea in China. However, mechanism of its therapeutic function is not well known. In the current study, we showed one of its components, andrograpanin, could enhance chemokine stromal cell-derived factor-1alpha (SDF-1alpha) induced chemotaxis in Jurkat and THP-1 cells. Further study demonstrated that this kind of effect was CXC chemokine receptor-4 (CXCR4) specific, since andrograpanin could not enhance other chemokines, such as RANTES, monocyte chemoattractant protein-1 (MCP-1), etc. induced cell chemotaxis. Mechanisms of andrograpanin exerting its effect were not directly in the receptor and G protein coupling level because it had no effect on the binding of SDF-1 to CXCR4, SDF-1 induced G protein activation and adenylyl cyclase inhibition. However, receptor internalization might be involved, since we found it significantly reduced SDF-1alpha-induced CXCR4 internalization. PMID: 15937916

Nat Prod Res. 2005 Apr;19(3):223-30.

**A new bis-andrographolide ether from *Andrographis paniculata* nees and evaluation of anti-HIV activity.**

*Reddy VL, Reddy SM, Ravikanth V, Krishnaiah P, Goud TV et al.*

Novel bis-andrographolide ether (1) and six known compounds andrographolide, 14-deoxy-11,12-didehydroandrographolide, andrograpanin, 14-deoxyandrographolide, (+/-)-5-hydroxy-7,8-dimethoxyflavanone, and 5-hydroxy-7,8-dimethoxyflavone have been isolated from the aerial parts of *Andrographis paniculata* and their structures were established by spectral data. All the isolates were tested for the anti-HIV and cytotoxic activity. PMID: 15702635

J Ethnopharmacol. 2004 Dec;95(2-3):205-8.

**Screening for antihyperglycaemic activity in several local herbs of Malaysia.**

*Husen R, Pihie AH, Nallappan M.*

School of Bioscience and Biotechnology, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, 43600 Bangi, Selangor, Malaysia. Screening of aqueous extract of *Phyllanthus niruri* (PL), *Zingiber zerumbet* (ZG), *Eurycoma longifolia* (TA-a and TA-b) and *Andrographis paniculata* (AP) to determine their blood glucose lowering effect were conducted in normoglycaemic and Streptozotocin-induced hyperglycaemic rats. Significant reduction in blood glucose level at 52.90% was shown when hyperglycaemic rats were treated with 50 mg/kg body weight (BW) aqueous extract of *Andrographis paniculata* (AP). This effect is enhanced when freeze-dried material was used, where 6.25 mg/kg BW gave 61.81% reduction in blood glucose level. In the administration of TA-a and TA-b, positive results in hyperglycaemic rats were only obtained when 150 mg/kg BW of the aqueous extract was used. No significant reduction in blood

glucose level were shown in hyperglycaemic rats treated with PL and ZG at all concentrations used (50, 100 and 150 mg/kg BW). In normoglycaemic rats, no significant reduction was noted when all the same extracts were used. PMID: 15507337

J Ethnopharmacol. 2004 Jun;92(2-3):291-5.

**Anticancer and immunostimulatory compounds from *Andrographis paniculata*.**

*Kumar RA, Sridevi K, Kumar NV, Nanduri S, Rajagopal S.*

*Andrographis paniculata* extract is traditionally used as a medicine to treat different diseases in India, China and Southeast Asia. In the present study, we evaluated the anticancer and immunomodulatory activity of the methanolic extract of *Andrographis paniculata* in human cancer and immune cells. The methanolic extract of *Andrographis paniculata* was fractionated into dichloromethane, petroleum ether and aqueous extracts and screened for bioactivity. Our results indicate that the dichloromethane fraction of the methanolic extract retains the active compounds contributing for both the anticancer and immunostimulatory activity. Dichloromethane fraction significantly inhibits the proliferation of HT-29 (colon cancer) cells and augments the proliferation human peripheral blood lymphocytes (HPBLs) at low concentrations. On further fractionation of the dichloromethane extract we could isolate three diterpene compounds, i.e. [1] andrographolide, [2] 14-deoxyandrographolide and [3] 14-deoxy-11,12-didehydroandrographolide. Andrographolide showed anticancer activity on diverse cancer cells representing different types of human cancers. Whereas all the three molecules showed enhanced proliferation and interleukin-2 (IL-2) induction in HPBLs. PMID: 15138014

J Ethnopharmacol. 2004 Jun;92(2-3):281-9.

**Inhibitory effect of some herbal extracts on adherence of *Streptococcus mutans*.**

*Limsong J, Benjavongkulchai E, Kuvatanasuchati J.*

Department of Pharmacology, Faculty of Dentistry, Chulalongkorn University, Henri-Dunant Road, Bangkok 10330, Thailand.

The objective of this study was to investigate the inhibitory effect of the crude extracts from some herbs on adherence of *Streptococcus mutans* (*S. mutans*) ATCC 25175 and TPF-1 in vitro. Six herbs, *Andrographis paniculata*; *Cassia alata*; Chinese black tea (*Camellia sinensis*); guava (*Psidium guajava*); *Harrisonia perforata* and *Streblus asper*, were extracted with 50 or 95% ethanol and dried. Herbal extracted solution at 0.5% concentration (w/v) was initially tested for bacterial adherence on glass surfaces. In order to identify type and effective concentration of the extracts, the extracts that showed the inhibition on glass surfaces were then tested on saliva-coated hydroxyapatite by the use of radiolabeled bacteria. To study the mechanism of action, the effect of the extracts at such concentration on glucosyltransferase and glucan-binding lectin activities were examined. It was found that all extracts, but *Streblus asper*, showed significant inhibitory effect on bacterial adherence to glass surfaces. For the saliva-coated hydroxyapatite adherence assay, *Andrographis paniculata*, *Cassia alata*, Chinese black tea and *Harrisonia perforata* could inhibit adherence of *S. mutans* ATCC 25175. Chinese black tea was the strongest inhibitor followed by *Andrographis paniculata*, *Cassia alata* and *Harrisonia perforata*, respectively. For *S. mutans* TPF-1, adherence inhibition was observed from *Andrographis paniculata* and *Cassia alata* at similar levels. The lowest concentrations of the extracts that inhibited the adherence at least 50% were 0.5% of *Andrographis paniculata*, 0.5% of *Cassia alata*, 0.3% of Chinese black tea and 0.5% of *Harrisonia perforata* for *S. mutans* ATCC 25175. For *S. mutans* TPF-1, the effective concentrations were 0.5% of *Andrographis paniculata* and 0.4% of *Cassia alata*. All extracts at such concentrations decreased the activity of

glucosyltransferase from both strains. Only *Andrographis paniculata* and *Cassia alata* eliminated or decreased the activity of glucan-binding lectin from both strains. These findings suggested that *Andrographis paniculata*, *Cassia alata*, Chinese black tea and *Harrisonia perforata* could inhibit adherence of *S. mutans* ATCC 25175, while *Andrographis paniculata* and *Cassia alata* had an effect on *S. mutans* TPF-1 in vitro at the concentrations employed in this study. PMID: 15138013

Planta Med. 2004 Apr;70(4):293-8.

**Andrographis paniculata in the treatment of upper respiratory tract infections: a systematic review of safety and efficacy.**

Coon JT, Ernst E.

Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, UK.

Acute respiratory infections represent a significant cause of over-prescription of antibiotics and are one of the major reasons for absence from work. The leaves of *Andrographis paniculata* (Burm. f.) Wall ex Nees (Acanthaceae) are used as a medicinal herb in the treatment of infectious diseases. Systematic literature searches were conducted in six computerised databases and the reference lists of all papers located were checked for further relevant publications. Information was also requested from manufacturers, the spontaneous reporting schemes of the World Health Organisation and national drug safety bodies. No language restrictions were imposed. Seven double-blind, controlled trials (n = 896) met the inclusion criteria for evaluation of efficacy. All trials scored at least three, out of a maximum of five, for methodological quality on the Jadad scale. Collectively, the data suggest that *A. paniculata* is superior to placebo in alleviating the subjective symptoms of uncomplicated upper respiratory tract infection. There is also preliminary evidence of a preventative effect. Adverse events reported following administration of *A. paniculata* were generally mild and infrequent. There were few spontaneous reports of adverse events. *A. paniculata* may be a safe and efficacious treatment for the relief of symptoms of uncomplicated upper respiratory tract infection; more research is warranted. PMID: 15095142

Phytother Res. 2004 Jan;18(1):47-53.

**Comparative controlled study of Andrographis paniculata fixed combination, Kan Jang and an Echinacea preparation as adjuvant, in the treatment of uncomplicated respiratory disease in children.**

Spasov AA, Ostrovskij OV, Chernikov MV, Wikman G.

Research Institute of Pharmacology of Volgograd Medical Academy, Volgograd, Russia.

A three-arm study comparing the efficacy of Kan Jang, a fixed herbal combination containing standardized *Andrographis paniculata* (N.) SHA-10 extract, with Immunal, a preparation containing *Echinacea purpurea* (L.) extract, in uncomplicated common colds was carried out in 130 children aged between 4 and 11 years over a period of 10 days. The study was designed as an adjuvant treatment of Kan Jang and Immunal with a standard treatment. The patients were assigned to one of the three groups. In control group C; 39 patients received only standard treatment. Kan Jang and Immunal were used as an adjuvant to this therapy in the other two groups. Adjuvant group A; 53 patients treated with Kan Jang tablets concomitant to standard treatment, and adjuvant control group B; 41 patients treated with concomitant Immunal. It was found that the adjuvant treatment with Kan Jang, was significantly more effective than Immunal, when started at an early stage of uncomplicated common colds. The symptoms of the disease were less severe in the Kan Jang group. The effect of Kan Jang was particularly pronounced in two objective parameters, amount of nasal secretion g/day and nasal congestion. Kan Jang also accelerated the

recovery time, whereas Immunal did not show the same efficacy. The use of standard medication was significantly less in the Kan Jang adjuvant group than in either the Immunal or standard treatment group. Kan Jang treatment was well tolerated and no side effects or adverse reactions were reported.

PMID: 14750201

Planta Med. 2003 Dec;69(12):1075-9.

**Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats.**

Yu BC, Hung CR, Chen WC, Cheng JT.

Department of Pharmacology, College of Medicine, National Cheng Kung University, Tainan City, Taiwan.

The antihyperglycemic action of andrographolide, an active principle in the leaves of *Andrographis paniculata* (Burm. f.) Nees, was investigated in streptozotocin-induced diabetic rats (STZ-diabetic rats). Oral treatment of andrographolide decreased the plasma glucose concentrations of STZ-diabetic rats in a dose-dependent manner. Similar treatment with andrographolide also decreased the plasma glucose in normal rats and the maximal effect was more marked than that in STZ-diabetic rats. Andrographolide at the effective dose (1.5 mg/kg) significantly attenuated the increase of plasma glucose induced by an intravenous glucose challenge test in normal rats. In the isolated soleus muscle of STZ-diabetic rats, andrographolide enhanced the uptake of radioactive glucose in a concentration-dependent manner. Moreover, the mRNA and protein levels of the subtype 4 form of the glucose transporter (GLUT4) in soleus muscle were increased after repeated intravenous administration of andrographolide in STZ-diabetic rats for 3 days. These results suggest that andrographolide can increase the glucose utilization to lower plasma glucose in diabetic rats lacking insulin.

PMID: 14750020

J Clin Pharm Ther. 2004 Feb;29(1):37-45.

**Andrographis paniculata in the symptomatic treatment of uncomplicated upper respiratory tract infection: systematic review of randomized controlled trials.**

Poolsup N, Suthisisang C, Prathanturug S, Asawamekin A, Chanchareon U.

Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon-Pathom, Thailand.

**OBJECTIVE:** To assess the efficacy of *Andrographis paniculata* in the symptomatic treatment of uncomplicated upper respiratory tract infection. **METHODS:** Systematic review of the literature and meta-analysis of randomized controlled trials. Mean difference in the reduction in symptom severity scores between treatment and control groups was calculated to obtain an overall estimate of effect. **RESULTS:** Four studies met our inclusion criteria and were reviewed. A total of 433 patients reported in three trials were included in the statistical analysis. *Andrographis paniculata* fixed combination with *Acanthopanax senticosus* was more effective than placebo. The mean difference was 2.13 points (95% CI 1.00-3.26 points,  $P=0.0002$ ) on the symptom severity score. The difference in effects between *A. paniculata* and placebo was 10.85 points (95% CI 10.36-11.34 points,  $P<0.0001$ ) in favour of *A. paniculata*. **CONCLUSION:** Current evidence suggests that *A. paniculata* extract alone or in combination with *A. senticosus* extract may be more effective than placebo and may be an appropriate alternative treatment of uncomplicated acute upper respiratory tract infection. PMID: 14748896

J Exp Ther Oncol. 2003 May-Jun;3(3):147-58.

**Andrographolide, a potential cancer therapeutic agent isolated from *Andrographis paniculata*.**

*Rajagopal S, Kumar RA, Deevi DS, Satyanarayana C, Rajagopalan R.*

Andrographis paniculata plant extract is known to possess a variety of pharmacological activities. Andrographolide, the major constituent of the extract is implicated towards its pharmacological activity. We studied the cellular processes and targets modulated by andrographolide treatment in human cancer and immune cells. Andrographolide treatment inhibited the in vitro proliferation of different tumor cell lines, representing various types of cancers. The compound exerts direct anticancer activity on cancer cells by cell-cycle arrest at G0/G1 phase through induction of cell-cycle inhibitory protein p27 and decreased expression of cyclin-dependent kinase 4 (CDK4). Immunostimulatory activity of andrographolide is evidenced by increased proliferation of lymphocytes and production of interleukin-2. Andrographolide also enhanced the tumor necrosis factor-alpha production and CD marker expression, resulting in increased cytotoxic activity of lymphocytes against cancer cells, which may contribute for its indirect anticancer activity. The in vivo anticancer activity of the compound is further substantiated against B16F0 melanoma syngenic and HT-29 xenograft models. These results suggest that andrographolide is an interesting pharmacophore with anticancer and immunomodulatory activities and hence has the potential for being developed as a cancer therapeutic agent. PMID: 14641821

Fitoterapia. 2003 Dec;74(7-8):692-4.

**Antimicrobial activity of *Andrographis paniculata*.**

*Singha PK, Roy S, Dey S.*

The antimicrobial activity of aqueous extract, andrographolides and arabinogalactan proteins from *Andrographis paniculata* were evaluated. The aqueous extract showed significant antimicrobial activity, which may be due to the combined effect of the isolated arabinogalactan proteins and andrographolides. PMID: 14630176

Phytomedicine. 2002 Oct;9(7):598-605.

**Effect of andrographolide and Kan Jang--fixed combination of extract SHA-10 and extract SHE-3--on proliferation of human lymphocytes, production of cytokines and immune activation markers in the whole blood cells culture.**

*Panossian A, Davtyan T, Gukassyan N, Gukasova G, Mamikonyan G et al.*

The immunomodulatory properties of a diterpene lactone andrographolide and Kan Jang--a standardized fixed combination of *Andrographis paniculata* extract SHA-10 and *Eleutherococcus senticosus* extract SHE-3 were investigated. Their role on spontaneous and phytohemagglutinin (PHA)-induced proliferation of human peripheral blood lymphocytes (PBL) and on production of interferon-gamma (INF-gamma) and tumor necrosis factor-alpha (TNF-alpha) were determined in vitro. Proliferation of PBL induced by PHA was enhanced by co stimulation with andrographolide and Kan Jang. At the same time andrographolide and Kan Jang inhibit spontaneous proliferation of PBL in vitro. These preparations also have effect on the formation of INF-gamma, TNF-alpha and some immune activation markers such as neopterin (Neo), beta-2-microglobulin (beta2MG), and soluble receptor for interleukin-2 (sIL-2R or sCD25) in blood cells culture. Andrographolide and Kan Jang stimulate the INF-gamma, Neopterin and beta2MG formation, but do not have any significant effect on the production of INF-gamma and Neopterin in PHA stimulated blood cells. An opposite effect on these immune makers was observed in the PHA-stimulated blood cells: both andrographolide and Kan Jang increase the formation of TNF-alpha and beta2MG in cultivated whole blood cells. Thus, andrographolide and Kan Jang can have an in vitro effect on the activation and proliferation of immunocompetent cells as well on the production of key cytokines and immune

activation markers. The results show an overall higher effect of the fixed combination as compared with the equivalent amount of the pure substance andrographolide. The data are consistent with results from clinical studies of Kan Jang and contributed to a better understanding of these results. PMID: 12487323

Phytomedicine. 2002 Oct;9(7):589-97.

**A double blind, placebo-controlled study of Andrographis paniculata fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis.**

Gabrielian ES, Shukarian AK, Goukasova GI, Chandanian GL et al.  
A double blind, placebo-controlled, parallel-group clinical study was carried out to evaluate the effect of an Andrographis paniculata (N.) extract SHA-10 fixed combination, Kan Jang, in the treatment of acute upper respiratory tract infections, including sinusitis. Ninety-five individuals in the treatment group and 90 individuals in the placebo group completed the study according to the protocol. The medication was taken for 5 days. Temperature, headache, muscle aches, throat symptoms, cough, nasal symptoms, general malaise and eye symptoms were taken as outcome measures with given scores. The total score analysis showed a highly significant improvement in the verum group versus the placebo. This result applied to the group as a whole and to the sinusitis subgroups. The individual symptoms of headache and nasal and throat symptoms together with general malaise showed the most significant improvement while cough and eye symptoms did not differ significantly between the groups. Temperature was moderately reduced in the verum group. It can be concluded that Kan Jang has a positive effect in the treatment of acute upper respiratory tract infections and also relieves the inflammatory symptoms of sinusitis. The study drug was well tolerated. PMID: 1248732

Immunol Invest. 2002 May;31(2):137-53.

**Increased tumor necrosis factor alpha (TNF-alpha) and natural killer cell (NK) function using an integrative approach in late stage cancers.**

*See D, Mason S, Roshan R.*

Center for Advanced Medicine, Encinitas, California 92024, USA.  
Natural products may increase cytotoxic activity of Natural Killer Cells (NK) Tumor Necrosis Factor alpha (TNF-alpha) while decreasing DNA damage in patients with late-stage cancer. Pilot studies have suggested that a combination of Nutraceuticals can raise NK cell function and TNF-alpha activity and result in improved clinical outcomes in patients with late stage cancer. The objective of the study is to determine if Nutraceuticals can significantly raise NK function and TNF levels in patients with late stage cancer. After informed consent was obtained, 20 patients with stage IV, end-stage cancer were evaluated (one bladder, five breast, two prostate, one neuroblastoma, two non-small cell lung, three colon, 1 mesothelioma, two lymphoma, one ovarian, one gastric, one osteosarcoma). Transfer Factor Plus (TFP+, 3 tablets 3 times per day), IMUPlus (non denatured milk whey protein, 40 gm/day); Intravenous (50 to 100 gm/day) and oral (1-2 gm/day) ascorbic acid; Agaricus Blazeii Murill teas (10 gm/day); Immune Modulator Mix (a combination of vitamin, minerals, antioxidants and immune-enhancing natural products); nitrogenated soy extract (high levels of genistein and dadzein) and Andrographis Paniculata (500 mg twice, daily) were used. Baseline NK function by standard 4 h 51Cr release assay and TNF alpha and receptor levels were measured by ELISA from resting and phytohemagglutinin (PHA) stimulated adherent and non-adherent Peripheral Blood Mononuclear Cell (PBMC). Total mercaptans and glutathione in plasma were taken and compared to levels measured 6 months later. Complete blood counts and chemistry panels were routinely monitored. As of a mean of 6 months, 16/20 patients were still alive. The 16 survivors had significantly higher NK function than baseline ( $p < .01$  for each) and TNF-alpha levels in all four cell populations studied ( $p < .01$  for

each). Total mercaptans ( $p < .01$ ) and TNF-alpha receptor levels were significantly reduced ( $p < .01$ ). It was also observed that hemoglobin, hematocrit and glutathione levels were significantly elevated. The only toxicity noted was occasional diarrhea and nausea. The quality of life improved for all survivors by SF-36 form evaluation. An aggressive combination of immunoactive Nutraceuticals was effective in significantly increasing NK function, other immune parameters and hemoglobin from PBMC or plasma in patients with late stage cancers. Nutraceutical combinations may be effective in late stage cancers. Clinical outcomes evaluations are ongoing.  
PMID: 12148949

J Agric Food Chem. 2002 Jul 31;50(16):4662-5.

**Mechanism of the superoxide scavenging activity of neoandrographolide - a natural product from *Andrographis paniculata* Nees.**

*Kamdem RE, Sang S, Ho CT.*

Department of Food Science, Rutgers University, 65 Dudley Road, New Brunswick, New Jersey 08901-8520, USA.

It was hypothesized that neoandrographolide might scavenge free radicals by donating the allylic hydrogen of the unsaturated lactone ring. It was found that the stoichiometry of the reaction between neoandrographolide and superoxide radical generated from  $KO_2$  in DMSO was 2 to 1. One major reaction product was isolated and determined to be a diacid formed by the opening of the lactone ring. It was concluded that the antiradical activity of neoandrographolide proceeded by hydrogen abstraction from carbon C-15. A reaction mechanism was proposed. PMID: 12137494

Br J Pharmacol. 2002 Jan;135(2):399-406.

**Andrographolide prevents oxygen radical production by human neutrophils: possible mechanism(s) involved in its anti-inflammatory effect.**

*Shen YC, Chen CF, Chiou WF.*

We have reported that andrographolide (ANDRO), an active component of *Andrographis paniculata*, inhibits inflammatory responses by rat neutrophils. To further elucidate the possible mechanism(s) underlying the ANDRO's effect, N-formyl-methionyl-leucyl-phenylalanine (fMLP)-induced adhesion and transmigration of isolated peripheral human neutrophils were studied. Pretreatment with ANDRO (0.1 - 10  $\mu$ M) concentration-dependently prevented fMLP-induced neutrophil adhesion and transmigration. We further examined the up-expression of surface Mac-1 (CD11b/CD18), an essential integrin mediated in neutrophil adhesion and transmigration. ANDRO pretreatment significantly decreased fMLP-induced up-expression of both CD11b and CD18. Accumulation of reactive oxygen species (ROS) as well as quick intracellular calcium ( $[Ca^{++}]_i$ ) mobilization induced by fMLP displays two important signalling pathways in regulating the up-expression of Mac-1 by neutrophils. That ANDRO pretreatment diminished fMLP-induced production of  $H_2O_2$  and  $O_2^{*-}$ , but failed to block that of  $[Ca^{++}]_i$  mobilization suggested that the ROS but not  $[Ca^{++}]_i$  signalling could be modulated by ANDRO. To clarify whether ROS production impeded by ANDRO could be an antagonism of fMLP binding, phorbol-12-myristate-13-acetate (PMA), a direct protein kinase C (PKC) activator, was introduced to activate ROS production. PMA triggered remarkable ROS production and adhesion, and were partially reversed by ANDRO. This indicated that a PKC-dependent mechanism might be interfered by ANDRO. We conclude that the prevention of ROS production through, at least in part, modulation of PKC-dependent pathway could confer ANDRO the ability to down-regulate Mac-1 up-expression that is essential for neutrophil adhesion and transmigration.

PMID: 11815375

Acta Pharmacol Sin. 2000 Dec;21(12):1157-64.

**Anti-diabetic property of ethanolic extract of *Andrographis paniculata* in streptozotocin-diabetic rats.**

Zhang XF, Tan BK.

Department of Pharmacology, Faculty of Medicine, National University of Singapore,

AIM: To investigate the anti-diabetic effect of a crude ethanolic extract of *Andrographis paniculata* in normal and streptozotocin (STZ)-induced diabetic rats. METHODS & RESULTS: Oral administration of the extract at different doses (0.1, 0.2, and 0.4 g/body weight) significantly reduced the fasting serum glucose level in STZ-diabetic rats compared to the vehicle (distilled water), but not in normal rats. This effect was dose-dependent. A similar result was seen with metformin (0.5 g/body weight). In the glucose tolerance test, an oral administration of the extract at the same doses suppressed the elevated glucose level in normal and diabetic rats, as did metformin. The effects were also dose-responsive. In the long-term experiment, the extract (0.4 g/body weight), metformin (0.5 g/body weight), and vehicle were given twice daily to diabetic rats for 14 d. On d 15, fasting serum glucose levels were found to be significantly lower in the extract- and metformin-treated groups ( $P < 0.001$ ) than in the vehicle-treated group. The mean food and water intakes over 14 days were significantly lower in the extract-treated group ( $P < 0.05$ ,  $P < 0.01$ , respectively) and also in the metformin-treated group (both  $P < 0.001$ ) when compared to the vehicle-treated group. No significant change in insulin level was observed among the 3 groups of diabetic rats. The extract, like metformin, maintained the leptin levels after 14-d treatment, whereas this level was significantly decreased ( $P < 0.05$ ) in the vehicle-treated group. The activity of hepatic glucose-6-phosphatase (G-6-Pase) was significantly reduced by the extract as well as by metformin (both  $P < 0.05$ ). No significant difference in hepatic glycogen stores was noted among the 3 groups. The extract caused 49.8% reduction of fasting serum triglyceride levels, compared to 27.7% with metformin. However, neither the extract nor metformin significantly affected serum cholesterol level. CONCLUSION: The ethanolic extract of *A. paniculata* possesses antidiabetic property. Its antidiabetic effect may be attributed at least in part to increased glucose metabolism. Its hypotriglyceridemic effect is also beneficial in the diabetic state. PMID: 11603293

J Ethnopharmacol. 2001 Nov;78(1):79-84.

**In vitro antifilarial effects of three plant species against adult worms of subperiodic *Brugia malayi*.**

Zaridah MZ, Idid SZ, Omar AW, Khozirah S.

Forest Research Institute Malaysia (FRIM), Kepong, 52109, Kuala Lumpur, Malaysia.

Five aqueous extracts from three plant species, i.e., dried husks (HX), dried seeds (SX) and dried leaves (LX) of *Xylocarpus granatum* (Meliaceae), dried stems (ST) of *Tinospora crispa* (Menispermaceae) and dried leaves (LA) of *Andrographis paniculata* (Acanthaceae) were tested in vitro against adult worms of subperiodic *Brugia malayi*. The relative movability (RM) value of the adult worms over the 24-h observation period was used as a measure of the antifilarial activity of the aqueous extracts. SX extract of *X. granatum* demonstrated the strongest activity, followed by the LA extract of *A. paniculata*, ST extract of *T. crispa*, HX extract and LX extract of *X. granatum*. PMID: 11585692

Phytother Res. 2001 Aug;15(5):382-90.

**Modulatory influence of *Andrographis paniculata* on mouse hepatic and extrahepatic carcinogen metabolizing enzymes and antioxidant status.**

Singh RP, Banerjee S, Rao AR.

Cancer Biology Laboratory, School of Life Sciences, Jawaharlal Nehru University, New Delhi-110067, India.

The effects of two doses (50 and 100 mg/kg body wt/day for 14 days) of an 80% hydroalcohol extract of *Andrographis paniculata* and butylated hydroxyanisole (BHA) were examined on drug metabolizing enzymes, antioxidant enzymes, glutathione content, lactate dehydrogenase (LDH) and lipid peroxidation in the liver of Swiss albino mice (6-8 weeks old). The effect of the extract and BHA were also examined on lung, kidney and forestomach for the activities of glutathione S-transferase (GST), DT-diaphorase (DTD), superoxide dismutase (SOD) and catalase. A significant increase in the levels of acid soluble sulphhydryl (-SH) content, cytochrome P450, cytochrome P450 reductase, cytochrome b5 reductase, GST, DTD and SOD were observed at both dose levels of extract treatment while catalase, glutathione peroxidase and glutathione reductase (GR) showed significant increases only at the higher dose in the liver. Both *Andrographis* treated groups showed a significant decrease in activity of LDH and malondialdehyde (MDA) formation. BHA treated mice showed a significant increase in the levels of cytochrome b(5), GST, DTD, -SH content, GR and catalase in liver; while LDH and MDA levels were reduced significantly compared with their control values. In the lung, SOD, catalase and DTD, in the kidney catalase, DTD and GST, and in the forestomach SOD and DTD showed a significant increase at both dose levels of treatment. In BHA treated mice GST, DTD and catalase were significantly induced in the lung and along with these enzymes SOD was also induced in the kidney. In the case of the forestomach of BHA treated mice GST, DTD and SOD were enhanced significantly. These findings indicate the chemopreventive potential of *Andrographis paniculata* against chemotoxicity including carcinogenicity. PMID: 11507728

Indian J Exp Biol. 2001 Jan;39(1):41-6.

**Hepatoprotective and antioxidant property of *Andrographis paniculata* (Nees) in BHC induced liver damage in mice.**

*Trivedi NP, Rawal UM.*

*Andrographis paniculata* (AP) treatment prevents BHC induced increase in the activities of enzymes  $\gamma$ -Glutamyl transpeptidase, glutathione-S-transferase and lipid peroxidation. The activities of antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase and the levels of glutathione were decreased following BHC effect. Administration of AP showed protective effects in the activity of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase as well the level of glutathione. The activity of lipid peroxidase was also decreased. The result indicate antioxidant and hepatoprotective action of *A. paniculata*.

PMID: 11349524

Phytomedicine. 2000 Oct;7(5):351-64.

**Pharmacokinetic and oral bioavailability of andrographolide from *Andrographis paniculata* fixed combination Kan Jang in rats and human.**

Panossian A, Hovhannisyan A, Mamikonyan G, Abrahamian H et al.

Validated analytical methods (HPLC, CE and GC-MS) for determining the amount of andrographolide (AND) in the blood plasma of rats and human volunteers following the oral administration of *Andrographis paniculata* extract (APE) and *Andrographis paniculata* fixed combination Kan Jang tablets were developed and used for the pharmacokinetic study. Andrographolide was quickly and almost completely absorbed into the blood following the oral administration of APE at a dose of 20 mg/kg body wt. in rats. Its bio-availability, however, decreased four-fold when a 10-times-higher dose was used. Since a large part (55 %) of AND is bound to plasma proteins and only a limited amount can enter the cells, the pharmacokinetics of AND are described well by a one-compartment model. Renal excretion is not the main route for eliminating AND. It is most likely intensely and

dose dependently metabolized. Following the oral administration of four Kan Jang tablets (a single therapeutic dose, equal to 20 mg of AND) to humans, maximum plasma levels of approximately 393 ng/ml (approx. 1.12 microM) were reached after 1.5-2 hours, as quantified using a UV diode-array detection method. Half-life and mean residence times were 6.6 and 10.0 hours, respectively. AND pharmacokinetics in humans are explained well by an open two-compartment model. The calculated steady state plasma concentration of AND for multiple doses of Kan Jang (after the normal therapeutic dose regimen, 3 x 4 tablets/day, about 1 mg AND/kg body wt./day) was approximately 660 ng/ml (approx. 1.9 microM), enough to reveal any anti-PAF effect, particularly after drug uptake when the concentration of AND in blood is about 1342 ng/ml (approx. 3.8 microM, while for anti-PAF effect EC50 - 5 microM).  
PMID: 11081986

Phytomedicine. 2000 Oct;7(5):341-50.

**Double-blind, placebo-controlled pilot and phase III study of activity of standardized *Andrographis paniculata* Herba Nees extract fixed combination (Kan jang) in the treatment of uncomplicated upper-respiratory tract infection.**

Melchior J, Spasov AA, Ostrovskij OV, Bulanov AE, Wikman G. et al.  
Two randomized double-blind, placebo-controlled parallel group clinical trials were performed to investigate the effect of a standardized extract (SHA-10) of *Andrographis paniculata* fixed combination (Kan jang) in the treatment of uncomplicated upper-respiratory tract infections. 46 patients in the pilot study and 179 patients in the phase III study completed the study according to the protocol. Medication was taken three times daily for a minimum of 3 days and a maximum of 8 days for the pilot study, and for exactly three days in the phase III study. The primary outcome measures in the patients self-evaluation were: related to pain in the muscle, cough, throat symptoms, headache, nasal symptoms and eye symptoms and temperature. The physician's fixed score diagnosis was based mainly on sign/symptoms: ears, nose, oral cavity, lymph glands-tonsils and eyes. The total symptom score showed a tendency toward improvement in the pilot study ( $p = 0,08$ ), while both the total symptom score and total diagnosis score showed highly significant improvement ( $p < \text{or} = 0.0006$  resp.  $0.003$ ) in the verum group as compared with the placebo. In both studies throat symptoms/signs, were found to show the most significant improvement. PMID: 11081985

Phytother Res. 2000 Aug;14(5):333-8.

**A phase I trial of andrographolide in HIV positive patients and normal volunteers.**

Calabrese C, Berman SH, Babish JG et al.  
Bastyr University Research Institute, Bastyr University, Washington 98028, USA.  
A phase I dose-escalating clinical trial of andrographolide from *Andrographis paniculata* was conducted in 13 HIV positive patients and five HIV uninfected, healthy volunteers. The objectives were primarily to assess safety and tolerability and secondarily to assess effects on plasma virion HIV-1 RNA levels and CD4(+) lymphocyte levels. No subjects used antiretroviral medications during the trial. Those with liver or renal abnormalities were excluded. The planned regimen was 5 mg/kg bodyweight for 3 weeks, escalating to 10 mg/kg bodyweight for 3 weeks, and to 20 mg/kg bodyweight for a final 3 weeks. The trial was interrupted at 6 weeks due to adverse events including an anaphylactic reaction in one patient. All adverse events had resolved by the end of observation. A significant rise in the mean CD4(+) lymphocyte level of HIV subjects occurred after administration of 10 mg/kg andrographolide (from a baseline of 405 cells/mm<sup>3</sup> to 501 cells/mm<sup>3</sup>;  $p = 0.002$ ). There were no statistically significant changes in mean plasma HIV-1 RNA levels throughout the trial. Andrographolide may inhibit

HIV-induced cell cycle dysregulation, leading to a rise in CD4(+) lymphocyte levels in HIV-1 infected individuals. PMID: 10925397

Clin Exp Pharmacol Physiol. 2000 May-Jun;27(5-6):358-63.

**Antihyperglycaemic and anti-oxidant properties of *Andrographis paniculata* in normal and diabetic rats.**

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Oxidative stress is believed to be a pathogenetic factor in the development of diabetic complications. In the present study, we investigated the ethanolic extract of the aerial parts of *Andrographis paniculata* for antihyperglycaemic and anti-oxidant effects in normal and streptozotocin-induced type I diabetic rats. 2. Normal and diabetic rats were randomly divided into groups and treated orally by gavage with vehicle (distilled water), metformin (500 mg/kg bodyweight) or the extract (400 mg/kg bodyweight), twice a day for 14 days. 3. At the end of the 14 day period, the extract, like metformin, significantly increased bodyweight ( $P < 0.01$ ) and reduced fasting serum glucose in diabetic rats ( $P < 0.001$ ) when compared with vehicle, but had no effect on bodyweight and serum glucose in normal rats. Levels of liver and kidney thiobarbituric acid-reactive substances (TBARS) were significantly increased ( $P < 0.0001$ ,  $P < 0.01$ , respectively), while liver glutathione (GSH) concentrations were significantly decreased ( $P < 0.005$ ) in vehicle-treated diabetic rats. Liver and kidney TBARS levels were significantly lower ( $P < 0.0001$ ,  $P < 0.005$ , respectively), whereas liver GSH concentrations were significantly higher ( $P < 0.05$ ) in extract- and metformin-treated diabetic rats compared with vehicle-treated diabetic rats. *Andrographis paniculata* significantly decreased kidney TBARS level ( $P < 0.005$ ) in normal rats. Hepatic superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) activities were significantly lower in vehicle-treated diabetic rats compared with vehicle-treated normal rats. The extract, as well as metformin, significantly increased the activity of SOD and CAT, but had no significant effect on GSH-Px activity in diabetic rats. The extract and metformin did not produce significant changes in the activity of these anti-oxidant enzymes in normal rats. 4. Our results show that oxidative stress is evident in streptozotocin-diabetic rats and indicate that the ethanolic extract of *A. paniculata* not only possesses an antihyperglycaemic property, but may also reduce oxidative stress in diabetic rats.

PMID: 10831236

J Ethnopharmacol. 1999 Mar;64(3):249-54.

**Antimalarial activity of extracts of Malaysian medicinal plants.**

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In vitro and in vivo studies revealed that Malaysian medicinal plants, *Piper sarmentosum*, *Andrographis paniculata* and *Tinospora crispa* produced considerable antimalarial effects. Chloroform extract in vitro did show better effect than the methanol extract. The chloroform extract showed complete parasite growth inhibition as low as 0.05 mg/ml drug dose within 24 h incubation period (*Andrographis paniculata*) as compared to methanol extract of drug dose of 2.5 mg/ml but under incubation time of 48 h of the same plant species. In vivo activity of *Andrographis paniculata* also demonstrated higher antimalarial effect than other two plant species.

PMID: 10363840

Clin Exp Pharmacol Physiol. 1996 Aug;23(8):675-8.

**Hypotensive activity of aqueous extract of *Andrographis paniculata* in rats.**

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The hypotensive activity of an aqueous extract of *Andrographis paniculata* was studied using chronic intraperitoneal (i.p.) infusions by osmotic pumps. The extract exhibited a dose-dependent hypotensive effect on the systolic blood pressure (SBP) of spontaneously hypertensive rats (SHR). 2. The optimum hypotensive dose determined was repeated in a study in SHR and their normotensive controls, Wistar-Kyoto (WKY) rats, to demonstrate its comparative effects on the SBP, plasma and lung angiotensin-converting enzyme (ACE) activities, as well as on lipid peroxidation in the kidneys, as measured by the thiobarbituric acid (TBA) assay. 3. The extract significantly lowered the SBP of both SHR and WKY rats. 4. Plasma, but not lung, ACE activity and kidney TBA level were significantly lower in extract-treated SHR when compared with vehicle-treated SHR controls. 5. Plasma and lung ACE activities as well as kidney TBA levels were not significantly different between extract- and vehicle-treated WKY rats. 6. This study indicates that the aqueous extract of *A. paniculata* lowers SBP in the SHR possibly by reducing circulating ACE in the plasma as well as by reducing free radical levels in the kidneys. The mechanism(s) of hypotensive action seems to be different in WKY rats.

PMID: 8886488

Chin Med J (Engl). 1994 Jun;107(6):464-70.

**Prevention of atherosclerotic arterial stenosis and restenosis after angioplasty with *Andrographis paniculata* nees and fish oil. Experimental studies of effects and mechanisms.**

*Wang DW, Zhao HY.*

Restenosis rate after coronary angioplasty has been up to 30%-40%. To solve this problem, we studied the effects of *Andrographis Paniculata* Nees (APN) and fish oil (FO, omega 3 polyunsaturated fatty acids over 70%) on atherosclerotic stenosis and restenosis after experimental angioplasty and the relevant mechanisms of APN and FO. Preliminary results showed that APN can significantly alleviate atherosclerotic iliac artery stenosis induced by both deendothelialization and high cholesterol diet (HCD) and restenosis following angioplasty in rabbits. FO showed the same but milder effects than APN did. Both APN and FO significantly inhibited blood monocytes to secrete growth factors in vivo. Ca(++)-ATPase activity of cell membrane of atherosclerotic rabbits was significantly decreased, while APN or FO, especially the former alleviated this reduction. Refined extract of APN significantly decreased in vitro resting platelet [Ca<sup>++</sup>]<sub>i</sub> and in vivo the resting and thrombin-stimulated platelet [Ca<sup>++</sup>]<sub>i</sub> after oral administration of APN for 2 weeks. APN significantly inhibited cell growth or DNA synthesis in dose-dependent manner. In conclusion because of the mechanisms described above, APN can alleviate atherosclerotic artery stenosis induced by both deendothelialization and HCD as well as lower restenosis rate after experimental angioplasty. The effects of APN are evidently superior to those of FO. PMID: 7956489

Bangladesh Med Res Counc Bull. 1994 Apr;20(1):24-6.

**Hypoglycaemic effects of *Andrographis paniculata* Nees on non-diabetic rabbits.**

*Borhanuddin M, Shamsuzzoha M, Hussain AH.*

So far known *Andrographis paniculata* Nees (AP) is a hepatoprotective, antiplatelet and antithrombotic drug. In this experiment its hypoglycaemic effect has been tried in various way. Water extract of AP 10 mg/kg body weight can prevent induction of hyperglycaemia significantly ( $P < 0.001$ ) induced by oral

administration of glucose 2 mg/kg body weight. But any how failed to do so in adrenaline induced hyperglycaemia. It also failed to demonstrate any "fasting blood sugar lowering effect" upon chronic administration (6 weeks) of AP. So probably AP prevents glucose absorption from gut. Whole experiment was done on rabbits.

PMID: 7880153

J Ethnopharmacol. 1993 Oct;40(2):131-6.

**Andrographolide protects rat hepatocytes against paracetamol-induced damage.**

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Andrographolide, the active constituent isolated from the plant *Andrographis paniculata*, showed a significant dose dependent (0.75-12 mg/kg p.o. x 7) protective activity against paracetamol-induced toxicity on ex vivo preparation of isolated rat hepatocytes. It significantly increased the percent viability of the hepatocytes as tested by trypan blue exclusion and oxygen uptake tests. It completely antagonized the toxic effects of paracetamol on certain enzymes (GOT, GPT and alkaline phosphatase) in serum as well as in isolated hepatic cells. Andrographolide was found to be more potent than silymarin, a standard hepatoprotective agent.

PMID: 8133653

Biochem Pharmacol. 1993 Jul 6;46(1):182-5.

**Antihepatotoxic effects of major diterpenoid constituents of *Andrographis paniculata*.**

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The diterpenes andrographolide (I), andrographiside (II) and neoandrographolide (III) isolated from *Andrographis paniculata* were investigated for their protective effects on hepatotoxicity induced in mice by carbon tetrachloride or tert-butylhydroperoxide (tBHP) intoxication. Pretreatment of mice with the diterpenes (I, II & III; 100 mg/kg, i.p.) for 3 consecutive days produced significant reduction in malondialdehyde formation, reduced glutathione (GSH) depletion and enzymatic leakage of glutamic-pyruvate transaminase (GPT) and alkaline phosphatase (AP) in either group of the toxin-treated animals. A comparison with the known hepatoprotective agent silymarin revealed that I exhibited a lower protective potential than II and III, which were as effective as silymarin with respect to their effects on the formation of the degradation products of lipid peroxidation and release of GPT and AP in the serum. GSH status was returned to normal only by III. The greater protective activity of II and III could be due to their glucoside groups which may act as strong antioxidants.

PMID: 8347130

J Nat Prod. 1993 Jul;56(7):995-9.

**Immunostimulant agents from *Andrographis paniculata*.**

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EtOH extract and purified diterpene andrographolides of *Andrographis paniculata* (Acanthaceae) induced significant stimulation of antibody and delayed type hypersensitivity (DTH) response to sheep red blood cells (SRBC) in mice. The plant preparations also stimulated nonspecific immune response of the animals measured in terms of macrophage migration index (MMI) phagocytosis of <sup>14</sup>C-leucine labelled *Escherichia coli* and proliferation of splenic lymphocytes. The stimulation of both antigen specific and nonspecific immune response was, however, of lower order with andrographolide than with the EtOH extract,

suggesting thereby that substance(s) other than andrographolide present in the extract may also be contributing towards immunostimulation.  
PMID: 8377022