Anticancer effects of Andrographis paniculata

The shrub Andrographis (*Andrographis paniculata*) is highly regarded as a medicinal herb in India where it is known as kalmegh ('king of bitters'), and is also popular in China and other Asian countries. Principal traditional uses include for digestive conditions such as poor appetite, flatulence, dysentery and gastroenteritis, as well as hepatitis, diabetes, skin infections and fevers. Research over the past few years has also reinforced its traditional use for the treatment or prevention of a variety of infections and infestations, including those affecting the bowel, urinary tract and lungs, as well as the common cold[1,2]. Apart from its pronounced hepatoprotective properties[3], anti-inflammatory[4] and antidiabetic[5] activities have also been reported.

With immunosuppression and the consequent impairment of the antitumour function of the immune system being increasingly linked with the onset of cancer, plant medicines that enhance or modulate natural immunity are now regarded as being potentially valuable in the chemoprevention of cancer, or as adjunctive treatments to conventional therapies[6]. Several scientific studies whose results have been published during recent months, support a potential role for Andrographis in this regard.

Evidence of potential protective effects against cancer for Andrographis was first reported in 2001. Investigators reported enhancement of antioxidant enzymes, plus numerous favourable modulatory effects on hepatic and extrahepatic carcinogen metabolising enzymes, in studies on mice[7].

Enhanced tumour necrosis factor alpha (TNF-α) production, and thus cytotoxic activity of lymphocytes, was reported for andrographolide, a key bitter diterpenoid lactone constituent, in 2003[8]. While increased cytotoxic activity of natural killer (NK) cells, and TNF-α was reported in an uncontrolled study in humans in 2002[9], this involved concurrent administration of seven different natural products, and a contribution of Andrographis was therefore undetermined.

Recent studies in mice however, have confirmed both enhancement of NK cell activity, as well as antibody-dependent cellular cytotoxicity in both normal and tumour-bearing mice, for both Andrographis and andrographolide[10].

This same group of Indian researchers have published prolifically on this subject recently[10,11,12], including another paper reporting the effects of Andrographis extract and andrographolide on the production of cytotoxic T lymphocytes in mice[11].

Cytotoxic T lymphocytes are a subset of T cells that play a pivotal role in protection from tumours, causing both tumour lysis directly as well as producing interferon-γ, a cytokine with several direct and indirect antitumour properties.

Lymphomatous cancer cells (EL4) were incubated with alloimmunised spleen cells (effector cells) and administered to mice, resulting in an average survival of 35.8 days. Mice with this type of lymphoma showed decreased immune responses, especially of the cell-mediated type, and this was associated with impaired generation of cytotoxic T lymphocytes.

Following treatment with ten doses of 10mg Andrographis extract or 500μg andrographolide, survival rates increased to 52.1 and 48.1 days, with continued treatment for a further ten days increasing life spans to 62 and 53.8 days respectively. Levels of the cytokines interleukin-2 and interferon-γ were also enhanced during treatment with both extract and andrographolide. The authors correlated this with increased activity of cytotoxic T lymphocytes, these being generated by the above two cytokines *in vivo*, and associated *in vitro* experiments showing that Andrographis and andrographolide enhanced their production[11].

Collectively, these results implicate a large contribution of andrographolide to the immunomodulatory effects of Andrographis, for which inhibitory effects

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on proliferation of a number of cancer cell types have been shown *in vitro*[8]. These effects seem to be mediated by both direct anticancer effects through cell-cycle arrest, as well as increased proliferation of cytotoxic lymphocytes through production of interleukin-2[8] and interferon-γ. Enhancement of TNF-α production resulting in increased cytotoxic activity of lymphocytes against cancer cells may also be contributory.

Andrographolide has also been observed by a group of Malaysian researchers to exhibit selective cytotoxicity to prostate cancer cells and induce apoptosis (cell death) through activation of caspase-3 and caspase-8 enzymes[13].

Results of work by Chinese researchers recently published in the journal *Anticancer Research*, found andrographolide decreased the ability of gastric cancer cells to adhere to human vascular endothelial cells. These effects were mediated by blocking expression of E-selectin by cancer cells and thus inhibiting tumour cell adherence, implicating a further possible mechanism for its anticancer activity[14].

Inhibition of angiogenesis (tumour microvascular growth) is another promising pathway to inhibit cancer cell growth. Another recent study in which treatment with Andrographis as well as andrographolide lead to a marked reduction in elevated levels of the angiogenic factor VEGF and increased the production of antiangiogenic factors in mice, is therefore of interest[12].

Clearly the diverse and positive findings on the anticancer properties of Andrographis and andrographolide are very encouraging. It seems possible that this plant could well be heading down the pathway of joining the several others from which cytotoxic drugs have been developed during recent decades. Several andrographolide derivatives with pronounced anticancer activities against a range of cancer cell types, have in fact been synthesised by Malaysian researchers recently[15].

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