The potential anti-cancer effects of the herbal medicine SH003

Cancer presents a significant health burden worldwide. Research into the use of herbal medicines as an alternative treatment or in combination with conventional pharmaceuticals is ongoing. The herbal medicine SH003 demonstrates anti-cancer effects in a variety of cancers, and studies have moved into randomised clinical trials to assess the safety and efficacy of this herbal medicine. Professor Seong-Gyu Ko of Kyung Hee University, South Korea, and Seong-Gyu Ko of Kyung Hee University, South Korea, and colleagues published in the journal Cancers summarises the molecular biology and studies investigating SH003 as an anti-cancer treatment. Their review, consisting of fifteen articles over the past nine years, shows SH003 to have cytotoxic effects (meaning they are toxic to cancer cells) and the ability to limit the growth of lung, breast, prostate, cervical, and gastric cancer cells.

MECHANISMS OF SH003

Herbal medicines can contain natural products such as flavonoids and carotenoids, among others. The herbal treatment, SH003, is a mixture of herbal extracts including Astragalus membranaceus, Angelica gigas and Trichosanthes kirilowii. Each of these herbal extracts has different therapeutic effects according to traditional East Asian and Korean medicine. Studies reveal the mechanisms of action of SH003 and the metabolic pathways that this treatment targets.

Such mechanisms include induction of apoptosis (causing programmed cell death), cell cycle arrest (stopping of the cell division cycle), inhibition of EGFR signalling pathway (targeting signal pathways involved in cell proliferation) and autophagy induction (causing self-degradation of cell organelles and components). Furthermore, inhibition of metastasis (targeting mechanisms that facilitate further secondary cancers), alleviation of chemotherapy-induced peripherial neuropathy (relief of chemotherapy induced damage to peripheral neurons), immune enhancement effects, and overcoming drug resistance are also proposed mechanisms which encompass the anti-cancer properties of SH003.

Tumour angiogenesis (meaning the supply of new blood vessels to a tumour) is needed for the tumour to continue to grow and spread (metastases). Therefore, targeting and stopping this process may help in treating cancer. The ability of SH003 to inhibit the migration and formation of human vascular endothelial cells (needed for angiogenesis) as well as increasing apoptosis markers has been demonstrated.

Such findings highlight the need for further research into these anti-angiogenic properties of SH003. This herbal medicine has also been shown to relieve chemotherapy-induced peripheral neuropathy in mouse models and specifically alleviated the degeneration of intra-epidermal nerve fibres in mice. Another issue facing cancer patients following conventional therapy treatments is a weakened immune system. Studies reveal SH0003 can activate immune cells such as natural killer cells, macrophages and splenocytes as well as colony stimulating factors (needed for the production and regulation of white blood cells which are essential to the functions of the immune system). Additionally, SH003 was shown to increase splenic lymphocyte proliferation and natural killer cell activity. The team suggest SH003 should also be explored in immunosuppressive diseases due to these promising immune enhancing effects.
This research importantly paves the way for herbal medicines to play a more active role in future cancer treatments.

**SH003 IN VARIOUS CANCER TYPES**
The review details several cancer types where SH003 has been investigated for anti-cancer effects. In triple negative breast cancer, the team have demonstrated that SH003 can suppress the tumour in various breast cancer cell lines via several mechanisms including induction of autophagy and apoptosis.

To address the issue of conventional therapy drug resistance, combination therapies are proposed to help sensitise cancer cells to the chemotherapy drug. A number of studies investigated SH003 in cancer cell lines resistant to the chemotherapy drug, paclitaxel. Results indicated that SH003 sensitised the cancer cell line to paclitaxel in addition to synergistically acting to reduce the cancer cell viability via apoptosis and cell cycle arrest induction. Such studies indicate the potential of SH003 to be used as part of a combination therapy to tackle the issue of drug resistance.

Drug resistance to chemotherapy drugs is also a problem in lung cancer treatments such as docetaxel. Studies investigating SH003 in combination with docetaxel revealed synergistic benefits of the combination therapy in inhibiting viability and inducing apoptosis of lung cancer cell lines by targeting the epidermal growth factor receptor (EGFR) signal transducer and activator of transcription 3 (EGFR-STAT3) signalling pathway. In vitro studies of other malignancies demonstrated the induction of apoptosis by SH003 in prostate cancer, cervical cancer, and gastric cancer cell lines.

**SH003 NATURAL COMPOUNDS WITH ANTI-CANCER EFFECTS**
There are several derivatives or natural compounds in SH003 which have anti-cancer effects. These are apigenin, cucurbitacin D, decursin, kaempferol and quercetin. These compounds mostly target the signal pathways involved in apoptosis and autophagy. In addition, apigenin also inhibits vascular endothelial growth factor (VEGF) production in hypoxic conditions, suggesting an anti-angiogenic property.

Another therapeutic effect of cucurbitacin D demonstrated in a study was its potential in overcoming drug resistance to gefitinib in a non-small cell lung cancer cell line. Decursin, a natural compound abundant in Astragalus membranaceus, reportedly sensitises drug resistant cervical cancer cells to doxorubicin and, when in combination with doxorubicin, induces cancer cell death. Kaempferol has been shown to induce autophagy of gastric cancer cells while there are reports of quercetin having anti-proliferative effects in HER2 breast cancer cells as well as possessing anti-inflammatory, antioxidant, and anti-angiogenic abilities. The research team suggest there are still undiscovered natural compounds in SH003 which require elucidation. Such compounds, if discovered, should be investigated for possible effects in both their individual form and in combination with other natural compounds to assess any possible synergistic interactions.

**CLINICAL TRIALS AND THE FUTURE**
A phase 1 clinical trial has ascertained the daily safe dose of SH003 in patients with solid cancers. Another trial is underway to determine the maximum tolerated dose of SH003 in combination with the chemotherapy drug docetaxel. More randomised clinical trials are needed to determine the side effects, drug related toxicity, tumour response to treatment and survival rates in patients. Such studies are required to build the required evidence for the safety and efficacy of SH003. So far, a total of four Investigation New Drugs (IND) applications have been approved by the Korean FDA: two cases of phase I, one case of phase II, and one case of phase II~III with the docetaxel combination. The two cases of phase I clinical trials are in the final stage, and 22 solid cancer patients have participated. In addition, the dose-escalation phase I of a clinical trial with SH003 and docetaxel was carried out by four medical institutions in Korea, and the dose-escalation phase II clinical trial will be conducted with ten medical institutions. Furthermore, additional research is needed to explore integrative cancer therapies and the efficacy of SH003 in combination with conventional therapies. Overall, future studies are focused on assessing the effectiveness of SH003 for cancer patients.

This important review by Professor Seong-Gyu Ko and team review the anti-cancer effects of the herbal medicine SH003.

**References**