SH003 as a Therapeutic Anticancer Agent

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SH003, a novel herbal medicine containing Astragalus membranaceus, Angelica gigas, and Trichosanthes kirilowii, showed the potential to act as an anticancer agent in previous research studies.

anticancer agent cancer natural compound phytochemical herbal medicine

1. Introduction

There are many types of cancer treatments, including chemotherapy, radiotherapy, surgery, hormone therapy, immunotherapy, etc. [1]. A single or combination therapy can be applied depending on the type of cancer; among the therapies, chemotherapy is one of the most common treatments to kill cancer cells and to stop them from growing rapidly [2]. Despite the favor of chemotherapies, such therapies have led to numerous side effects, drug resistance and inadequate target specificity [2]. Thus, there has been a significant interest in finding natural anticancer agents. Developing natural-product-based drugs may take longer than traditional cancer drugs; natural-product-based drugs are known to overcome the harmful effects of chemotherapies and possess the strengths to target various cancer types. On the negative side, the quality control of the undiscovered active components and sources of natural compounds may be challenging.

Herbal medicines have also shown potential in reducing side effects while improving the immune system [3]. In particular, Chinese herbal medicine (CHM) has long been used to prevent and treat cancer in China. Huang et al. mentioned that arsenic trioxide, a toxic Chinese medicine, has been successfully applied in the clinical treatment of patients with acute promyelocytic leukemia; moreover, some formulae, including PHY906 based on Huang-Qin-Tang, have indicated a synergic effect with conventional drugs for improving the life quality of patients [4].

2. Characteristics of SH003

SH003 is a mixture of Huang-Qi (Astragalus membranaceus; AG), Dang-Gui (Angelica gigas; AM), and Gua-Lou-Gen (Trichosanthes Kirilowii; TK), which are traditionally used in East Asian medicine. According to the theory of traditional medicine, the effect of Huang-Qi is to tonify qi, the effect of Dang-Gui is to tonify blood, and the effect of Gua-Lou-Gen is to disperse swelling and expel pus [5]. SH003 extracts were provided by HANPOONG (HANPOONG PHARM & FOODS Co., Jeonju, Korea), which followed good manufacturing practice (GMP) procedures. In brief, Astragalus membranaceus (333 g), Angelica gigas (333 g), and Trichosanthes kirilowii Maximowicz (333 g) were mixed at a 1:1:1 ratio and then extracted with 10 times the volume of 30% ethanol at 100 °C for 3 h. This process was performed 2 times. The extract was dried at reduced pressure (40 Torr) at 60 °C for 18

h. Notably, the experimental study proved that Danggwibohyeoltang, a mixture of AM and AG, inhibits the immune-enhancing effect [6]. As shown in **Figure 1**, the anti-cancer effect of SH003 has been demonstrated by several publications.

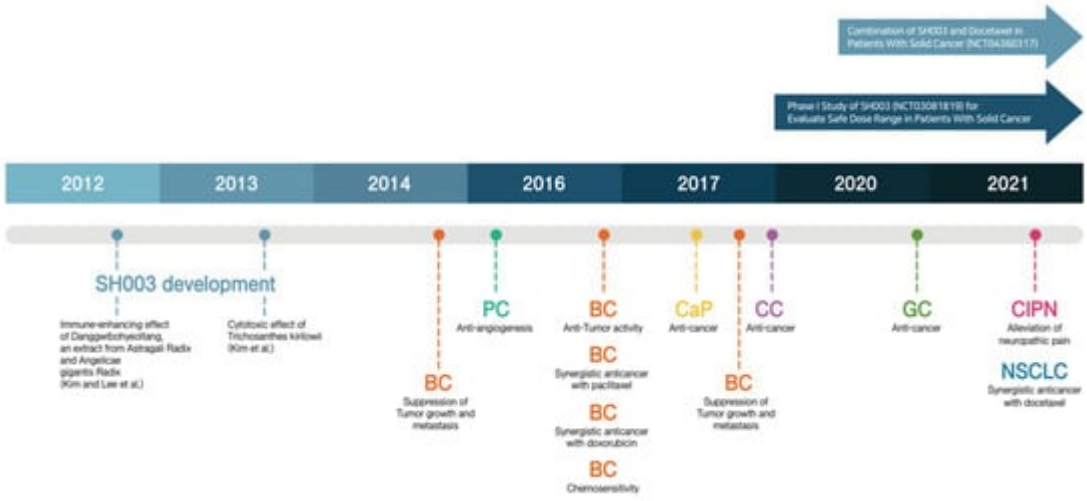

Figure 1. The timeline of SH003 (BC: breast cancer; PC: pancreatic cancer; CaP: prostate cancer; CC: cervical cancer; GC: gastric cancer, CIPN: chemotherapy-induced peripheral neuropathy and NSCLC: non-small cell lung cancer).

3. Current Advances of SH003 in Tumor Suppression

Herbal medicines have been used to prevent or inhibit tumor growth and metastasis. SH003 plays a crucial role in regulating various types of cancer (**Figure 2** and **Table 1**).

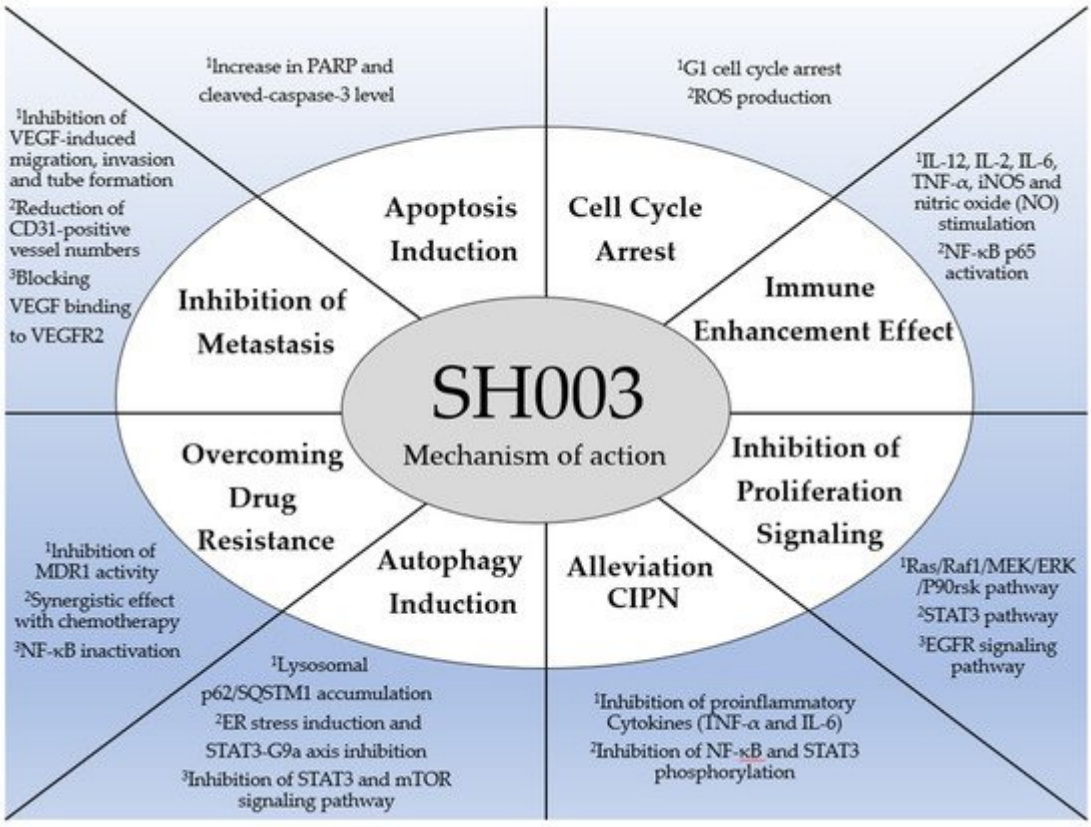

Figure 2. A mechanistic summary of SH003.

Table 1. A summary of the effects of SH003 on cancer, immune system and chemotherapy-related side effects.

Cancer Type	Cell Type	Proposed Effects	Methods	Mechanism	Refs.
Breast cancer	MDA-MB-231	Suppression of tumor growth and metastasis	in vitro (0–500 μg/mL) in vivo (500 mg/kg)	Inhibition STAT3-IL-6 Signaling	[7]
	MDA-MB-231 and HCC-38	Pro-apoptosis and autophagy induction	in vitro (0–500 μg/mL) in vivo (10, 100, 500 mg/kg)	Accumulation p62 in autolysosomes	[8]
	Hs578T, MDA-MB-231, ZR-75-1, MCF7 and T47D	Pro-apoptosis, synergistic anticancer effect with paclitaxel	in vitro (0–200 μg/mL)	Increase in p73 expression	[9]
	MDA-MB-231	Pro-apoptosis, synergistic	in vitro (0–500	Caspase cascade activation	[10]

Cancer Type	Cell Type	Proposed Effects	Methods	Mechanism	Refs.
		anticancer effect with doxorubicin	μg/mL) in vivo (500 mg/kg)		
	Paclitaxel-resistant breast cancer cell (MCF-7/PAX)	Overcoming drug resistance	in vitro (0–500 μg/mL)	Inhibition of MDR1 activity, inhibition of STAT3 signaling pathway	[11] [12]
Endothelial cells	Human umbilical vein endothelial cells (HUVECs)	Anti-angiogenesis	in vitro (0–50 μg/mL) in vivo (2 mg/kg)	Blockade VEGF binding to VEGFR2	[13]
Prostate cancer	DU145	Pro-apoptosis	in vitro (0–500 μg/mL)	Inhibition ERK signaling pathway	[14]
Cervical cancer	HeLa	Pro-apoptosis	in vitro (0–500 μg/mL)	G1 cell cycle arrest, ROS generation	[15]
Gastric cancer	AGS and SNU-638	Autophagic cell death	in vitro (0–400 μg/mL)	ER stress induction and inhibition of STAT3-G9a axis	[16]
Non-Small Cell Lung Cancer	H460	Synergistic anticancer effect with docetaxel	in vitro (0–500 μg/mL) in vivo (557.569 mg/kg)	Inhibition EGFR–STAT3 signaling pathway	[17]
C57BL/6 Mice	Docetaxel-Induced Neuropathy Mouse Model	Alleviation of docetaxel-induced neuropathic pain	in vivo (557.569 mg/kg)	Inhibition of proinflammatory cytokines (TNF-α and IL-6), NF-κB and STAT3	[18]
Immune cell	Macrophage (RAW 264.7) and NK cell	Immune-enhancing activity	in vitro (0–500 μg/mL) in vivo (400 mg/kg)	Production immunostimulatory cytokines and NO, activation of NF-κB	[19]

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3.1. Breast Cancer

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3.2. Lung Cancer

According to microscopic features, lung cancer is classified into non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) [20][21]. NSCLC patients commonly receive platinum or taxane-based regimens or targeted therapy for epidermal growth factor receptor (EGFR) [22][23]. Docetaxel—taxane with anti-mitotic properties—is an effective anti-cancer agent, causing cell cycle arrest and apoptosis in NSCLC [24][25][26]. However, docetaxel-mediated chemoresistance and severe side effects, including peripheral neuropathy, anorexia, and cachexia, are still the cause of treatment failure in cancer patients [27][28]. Recent studies have focused on the development of novel treatment strategies by combining chemotherapy with herbal medicines for NSCLC treatment [29][30]. Several clinical studies demonstrated the survival benefit of chemotherapy in combination with traditional Chinese herbal medicines in cancer patients [31][32][33]. The results of an MTT cell viability assay showed that the co-treatment of SH003 and docetaxel synergistically inhibited the viability of NSCLC A549 and H460 cell lines.

3.3. Other Malignancies

Besides breast and lung cancer, the anti-cancer effects of SH003 on other cancer types have been investigated by non-clinical studies [14][15][16]. In 2016, Choi et al. investigated the anti-cancer effects of SH003 in prostate cancer cells [14]. SH003 treatment dose-dependently inhibited the viability of prostate cancer DU145 cell lines by inducing apoptosis. Moreover, SH003 induced apoptotic cell death via inhibiting the ERK signaling pathway, while ERK overexpression antagonized SH003-induced cancer cell death. Choi et al. demonstrated that SH003, an anti-cancer herb, exerts its effects by regulating cell cycle arrest and apoptotic cell death [15]. Kim et al. reported the effect of SH003 on the autophagic death of gastric cancer cells [16]. In gastric cancer, SH003 treatment dose- and time-dependently inhibited the viability of various gastric cancer cell lines, the inhibition of which was associated with the induction of apoptosis. Meanwhile, SH003 also induced ER stress via PERK-ATF4-CHOP signaling, inhibiting G9a by suppressing STAT3 phosphorylation and activating autophagy. Of note, SH003-induced ER stress induced BNIP3-related autophagic death via the suppression of STAT3/G9a axis under hypoxic conditions.

3.4. Tumor Angiogenesis

Tumor angiogenesis is crucial for tumor growth and distant metastasis [34][35]. The inhibition of tumor angiogenesis has been considered a potential target for cancer treatment. Vascular endothelial cell growth factor (VEGF) released from cancer cells binds to VEGF receptor (VEGFR) on vascular endothelial cells, resulting in neo-angiogenesis. Based on the finding that SH003 suppressed TNBC tumor growth with the down-regulation of endothelial cell marker (CD31) in a mouse xenograft model [7], Choi et al. performed a further study to prove an anti-angiogenic effect of SH003 [13]. They found that VEGF-induced the migration, invasion, and formation of human vascular endothelial cells (HUVEC) was suppressed by SH003 treatment in vitro.

3.5. Managing Cancer-Related Adverse Effect

3.5.1. Chemotherapy-Induced Peripheral Neuropathy

Lee et al. demonstrated that SH003 alleviated mechanical allodynia in the docetaxel-induced mouse CIPN model. Intravenous docetaxel injection induced the degeneration of intraepidermal nerve fibers in the feet of C57BL/6 mice, but SH003 treatment alleviated it. Additionally, SH003 decreased the upregulation of TNF- α and IL-6 in plasma and increased expression of phospho-NF-κB and phospho-STAT in L4-L6 spinal cord and sciatic nerves in docetaxel-injected mice. Based on these findings, therapeutic indications of SH003 can be expanded to CIPN in addition to killing cancer.

3.5.2. Immune-Enhancing Effect

The immune system of cancer patients who receive several therapies, including chemotherapy and radiotherapy, is commonly weakened, resulting in tumor progression and poor prognosis [36][37]. Several studies reported that herbal medicines and their derivatives exhibit immunostimulatory effects [38][39]. Han et al. demonstrated that SH003 improves immunosuppression via the activation of immune cells such as macrophages, splenocytes, and NK cells [19]. SH003 treatment increased the production of colony-stimulating factors, IL-2, IL-6, IL-12, TNF-α, nitric oxide, and iNOS. Moreover, the transcription factor NF-κB was enhanced by SH003. In splenocytes, SH003 also stimulated the production of IFN-γ, IL-2, IL-12, TNF-α, and nitric oxide. The splenic lymphocyte proliferation and splenic NK cell activity were increased by SH003 treatment.

3.6. Anti-Cancer Effect of SH003 Derivatives

Since SH003 is a herbal mixture that contains multiple phytochemicals, it was necessary to decipher what compounds of SH003 show anti-cancer effects. From 2012 to 2020, the SH003 research group has found apigenin, cucurbitacin D, decursin, kaempferol, and quercetin as potential anti-cancer agents (**Table 2**). In brief, a number of studies have demonstrated that each putative active compound mainly regulates the signaling pathways in apoptosis or autophagy, which are the key anticancer targets of SH003. Therefore, SH003 is expected to have anticancer effects through the synergistic effect of these compounds, although non-clinical studies should prove this. Moreover, the previous research focused on the chemical profiling of SH003 identified several constituents,

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