Chapter 9
An Evidence-based Perspective of *Hedyotis Diffusa* or *Oldenlandia Diffusa* (Spreading Hedyotis) for Cancer Patients

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Abstract *Hedyotis diffusa* or *Oldenlandia diffusa* (spreading hedyotis) is one of the most commonly used anticancer herbs. Its clinical use has a history more than several thousand years. It contains flavones, anthraquinones, polysaccharides, and other compounds possessing anticancer activities. In most cases, it is used together with other herbs. About 15% of the anticancer herbal formulas used in China contain this herb. Both pre-clinical and clinical studies have established the efficacy and safety of spreading hedyotis in treating various cancers including stomach cancer, liver cancer, lung cancer, esophagus cancer, and leukemia. It can directly inhibit the growth of various cancer cells and induce apoptosis both *in vitro* and *in vivo*. It shows selective cytotoxicity against cancerous cells. It can suppress some oncogenes and up-regulate anti-oncogenes. It also has immune modulation functions against cancer. It enhances the activities of natural killer cells and macrophages, promotes the proliferation of spleen cells, and up-regulates interleukin-2 and tumor necrosis factor-alpha. Clinical outcomes have demonstrated that it can enhance the efficacies and reduce the adverse effects (i.e. white blood cell decrease, nausea/vomit) by the conventional chemotherapies. It is also effective in relieving cancerous pain and fever. The commonly used clinical doses of 30–60 g/day usually do not cause any considerable adverse effects.

9.1 Introduction

Hedyotis diffusa Willd. or *Oldenlandia diffusa* (Willd.) Roxb (spreading hedyotis) is a commonly used herb for various diseases, especially for cancer. In Chinese, it is called Bai Hua She She Cao. Spreading hedyotis has been recorded in many Chinese medical literatures. It is usually 15–50 cm in height, and produces small white flowers during the summer. The whole plant is used for medical purposes. It is collected during the

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Fig. 9.1 *Hedyotis diffusa or Oldenlandia diffusa* (spreading hedyotis) modified from Luo et al. 1991

summer or autumn, washed and dried. It can also be used fresh. This herb grows in southern China. Fig. 9.1 is the drawing of the herb.

According to the traditional Chinese medicine (TCM), spreading hedyotis has functions of cleansing heat, detoxifying, promoting blood circulation, dispersing static blood, removing dampness, and facilitating urination. It is commonly used in clinical practice for the treatment of various cancer, hepatitis, gastrointestinal inflammation, urinary infections, pneumonia, etc. It is probably the most widely used herb for cancer treatment. It is generally used in combination with the other herbs. The book *Comprehensive Collection of Single- and Multiple-Ingredient Formulas for Tumor* (Chen et al. 1998) collects about 1,700 TCM formulas for various cancer treatments, and 15% of these formulas contain spreading hedyotis as one of the main ingredients. The anticancer activities of this herb have been demonstrated through many pre-clinical and clinical studies.

9.2 Pre-clinical Studies

9.2.1 Chemical Components

The chemical components of spreading hedyotis are numerous, mainly being anthraquinones such as 2-methyl-3-hydroyanthraquinone, 2-methyl-3-methoxyanthraquinone (Tai et al. 1979), flavones such as quercetin, quercetin-3-O-β-D-glucopyranoside,

Table 9.1 Representative chemical constituents in *Hedyotis diffusa* or *Oldenlandia diffusa* (spreading hedyotis) and their pharmacological activities

Constituents	Biological functions	References
Flavones	Down-regulating *pim-1, rel, fos* and *Bcl-2*; up-regulating TNF-α and IFN-γ; increasing spleen lymphocyte transformation	Zhang et al. 2007b
Methylanthraquinone	Inducing apoptosis *via* Ca^{2+}/calpain/caspase-4 pathway	Liu et al. 2010
Oleanolic acid	Inducing apoptosis; anti-invasion	Zhang et al. 2003
Polysaccharides	Activating p53, inhibiting *Bcl-xl*; inducing apoptosis; inhibiting tumor grow *in vivo*	Meng et al. 2008; Yang et al. 2010b
Quercetin	Anti-proliferation and inducing apoptosis	Ke et al. 2008
Stigmasterol	Up-regulating MAP2K6; inducing apoptosis; increasing G0-G1 proportion; reducing G2/M cells	Zhang et al. 2008
Ursolic acid	Down-regulating VEGF and MVD; inhibiting angiogenesis; up-regulating the expression of CDF15 and p21; inducing apoptosis	Li et al. 2007; Wang et al. 2008; Yang et al. 2010b; Ganbold et al. 2010

and eldrin (Lu et al. 2000; Zhou et al. 2007), terpenes such as ursolic acid and oleanolic acid (Cai et al. 1964; Ganbold et al. 2010), sterols such as stigmasterol, β-stigmasterol, and β-sitosterol (Fu et al. 1963; Cai et al. 1964; Zhang et al. 2008), polysaccharides, and essential oils (Ling et al. 2005; Si et al. 2008; Yu et al. 2008; Huang et al. 2008, 2009; Shi et al. 2010).

Aqueous extract of spreading hedyotis was fractioned by HPLC into 11 fractions. It was found that the fraction which was most effective in inducing apoptosis contained ursolic acid and its enantiomer oleanolic acid (Ganbold et al. 2010).

Listed in Table 9.1 are some representative chemical constituents and their pharmacological activities related to cancer treatment.

9.2.2 In Vitro and In Vivo Anticancer Effects and Mechanisms

9.2.2.1 Anticancer Effects

Gupta et al. (2004) studied the *in vitro* and *in vivo* anticancer activities of the aqueous extract of spreading hedyotis. The results demonstrate that the extract could significantly induce apoptosis, with 50% growth inhibition concentrations (IC_{50}) against seven human cancer cell lines in the range of 7–24 mg raw material/ml after 48-hour drug exposure. Human prostate cancer line Ln-Cap was the most sensitive cell line with an IC_{50} of 7 mg/ml. The apoptosis was confirmed by microscopic examination and DNA fragmentation assay. Rounding of the cells, cytoplasmic shrinkage, nucleus segregation and chromatin condensation were observed under the microscope after the cells being exposed to the herbal extract. A significant lad-

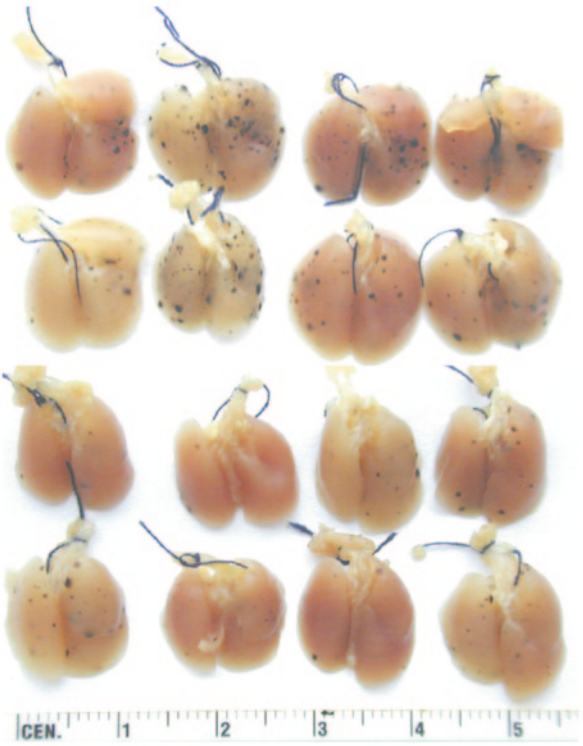

Fig. 9.2 Anticancer activities of *Hedyotis diffusa* or *Oldenlandia diffusa* (spreading hedyotis) in C57BL mice with B16-F10 lung metastases. The animals were iv inoculated through the tail vein with 0.2×10^6 live B16-F10 on day 1. The control group each was given 100 μl phosphate-buffered saline while the treated group each was given 100 μl of the herbal extract (5 g raw material/kg/day) on days 3–12 by oral gavage. The animals were sacrificed on day 14. The upper eight lungs were from the control group and the lower eight lungs from the treated group

der pattern of the DNA fragments was obtained after 24-hour exposure to the herbal extract. Oral administration of the herbal extract effectively reduced B16-F10 murine melanoma cell metastasis in the lungs of C57BL/J mice with a 70% ($P < 0.001$) reduction in lung metastasis colonies at the daily dose of 5 g raw material/kg body weight (Fig. 9.2).

Intraperitoneal (ip) injection of the extract of spreading hedyotis at the daily dose of 15–60 mg/kg for 10 consecutive days inhibited the transplanted H22 liver cancer in Kunming mice. The reduction in tumor weight was 35–60% ($P < 0.05$), respectively, corresponding to the given doses. The study also found that treatment with the herbal extract could increase the G0-G1 cell portion and reduce the G2/M portion (Zhang et al. 2008). Another study showed that the aqueous extract of spreading hedyotis could induce apoptosis of H22 cells *in vitro*. This was shown to be related with the up-regulation of HSP 70 (heat shock protein 70) and anti-oncogene protein P16 (Hu et al. 2009).

Spreading hedyotis is effective in treating cervical cancer. The growth of U14 cervical cancer in BALB/c mice was significantly inhibited by 28–49% by the oral administration of the aqueous extract at the dose of 30–120 mg/kg/day for 10 days. The treatment also significantly reduced the telomerase activities of the cancer cells, considered to be an important mechanism for its anticancer effect (Gao et al. 2007).

Total flavonoids extracted from spreading hedyotis inhibited the proliferation of human hepatic cancer cell line SMMC-7721 *in vitro*. The oncogenes such as *pim-1, rel, ras, fos, myc*, and *met* were down-regulated (Zhang et al. 2007a). The treatment of the flavonoids on Kunming mice transplanted with H22 mouse hepatic cancer cells showed inhibition of tumor growth, increase in G0/G1, increase in the plasma levels of tumor necrosis factor-alpha (TNF-α) and IFN-γ ($P<0.01$) as compared to the controls. The treatment also significantly ($P<0.05$) enhanced the spleen lymphocyte transformation rate as compared to the control (Zhang et al. 2007b).

Studies showed that the polysaccharides of spreading hedyotis were effective in inhibiting tumor growth *in vivo*. One hundred grams of the dried herb was extracted with 12 times of water. The extraction was repeated three times. After further purification, total 2.1 g of polysaccharides with molecular weight less than 10 K were obtained. Oral administration of the polysaccharides at the dose of 10–30 mg/kg/day for 10 consecutive days inhibited the growth of the transplanted S180 sarcoma in Kunming mice by 18–36%. Although the positive control with the treatment of cyclophosphamide with 30 mg/kg/day for 3 consecutive days through ip injection achieved 61% tumor growth inhibition, it showed 28% decrease in body weight. In contrast, the treatment with the polysaccharides of spreading hedyotis only resulted in negligible decrease in body weight (Yang et al. 2010b). The same group also studied the efficacy of the polysaccharides on the transplanted H22 hepatoma in Kunming mice. Oral administration of the polysaccharides at the dose of 10–30 mg/kg/day for 10 consecutive days achieved 27–50% tumor growth inhibition.

Treatment with stigmasterol from spreading hedyotis (15–60 mg/kg/day, ip injection for 10 consecutive days) on Kunming mice transplanted with H22 mouse hepatic tumor suppressed the tumor growth by 35–60% ($P<0.05$), increased the G0-G1 portion, and decreased the G2/M portion. (Zhang et al. 2008) In this study, 5-FU was used as the positive control at the dose of 30 mg/kg/day through ip injection for 10 consecutive days. This treatment resulted in 67% inhibition in tumor growth ($P<0.05$), slightly higher than the best efficacy achieved by spreading hedyotis stigmasterol (60% inhibition by the highest dose). However, treatment of 5-FU caused a significant decrease in body weight ($P<0.01$). The body weight of the positive control group was only 64% of the model control group receiving the treatment of normal saline, while the body weight of the groups treated with spreading hedyotis stigmasterol showed negligible differences from the model control group. These results demonstrated spreading hedyotis stigmasterol was as effective as 5-FU in treating H22 tumor but had much less adverse effects than 5-FU.

Ursolic acid was able to inhibit the proliferation of doxorubicin-resistant hepatoma cell line *in vitro*. It activated *Bak* but not *Bax*. Apoptosis was mainly through the caspase-independent apoptosis-inducing factor signaling pathway. Ursolic acid was also effective in inhibiting doxorubicin-resistant hepatoma cell line growth in athymic mice without any serious adverse effect on body weight, liver, heart and spleen (Yang et al. 2010a).

Oleanolic acid was found to be able to inhibit the growth of *ras* oncogene transformed Rat 6 fibroblast while not exhibiting any cytotoxic effect to the normal

fibroblast cells. The results also suggest that oleanolic acid might induce the normal cells to secrete some inhibitory factor(s) against the transformed cells (Wu et al. 2009).

Spreading hedyotis also shows synergistic effect with chemo-therapeutic agents. Co-administration of the aqueous extract of spreading hedyotis (oral, 20 g raw material/kg/day for 10 consecutive days) with cisplatin (ip, 2.0 mg/kg/day for 2 days) achieved 60% inhibition of H22 tumor weight in Kunming mice in contrast to 49% and 40% inhibition by cisplatin and the herbal extract alone. This increase in efficacy was statistically significant ($P<0.01$). Interestingly, the treatment by the herb alone increased survival time by 43% in contrast to 34% and 21% by the co-administration and cisplatin alone. The differences in the survival time among the three groups were significant ($P<0.05$). Treatment by the herb alone could increase the body weight by 19% while the treatment by cisplatin alone decreased the body weight by 10%. Co-administration did not cause more body weight decrease than the treatment by cisplatin alone (Li et al. 2009).

9.2.2.2 Immune Modulation

Spreading hedyotis can increase immune functions. Studies showed that it could significantly increase the proliferation of spleen cells induced by Con A and lipopolysaccharides, and increase the killing effect of T cells (Qin 1990). It stimulated macrophages to produce interleukin (IL)-6 and tumor necrosis factor (Yoshida et al. 1997). Studies on the mice transplanted with S180 tumor cells indicated that intravenous injection of spreading hedyotis extract at the dose of 3.75 mg raw material/kg could significantly increase the natural killer (NK) cell and macrophage activities, promote the proliferation of spleen cells and enhance the biological activity of IL-2 (Liu et al. 2008). Oral administration of the aqueous extract of spreading hedyotis at the dose of 25 g raw material/kg/day for 12 days increased CD_4^+ and CD_8^+ T cells in H22-bearing Kunming mice (Hu et al. 2007).

In vitro studies found that spreading hedyotis could augment oxidative burst of murine macrophage cell line J774, indicating the enhancement of the macrophage functions. The results showed a dose-dependent increase in oxidative burst (Wong et al. 1996).

Studies also showed that spreading hedyotis reduced the adverse effects of cyclophosphamide in terms of white blood cell decrease. Oral administration of aqueous extract of spreading hedyotis at the doses of 2.74 and 5.48 g raw material/kg/day for 5 days counteracted the adverse effect of cyclophosphamide (ip 100 mg/kg/day for consecutive 3 days) on white blood cells in Kunming mice. Compared to the control group without any treatment, cyclophosphamide caused 63% decrease in white blood cells, while the treatment of low and high doses of spreading hedyotis reduced the decrease of white blood cell to 25% and 16% ($P<0.05$), respectively. The high dose treatment also significantly increased the mouse bone marrow karyocytes by 85% compared to the control group ($P<0.05$) (Su and Zhao 2007).

9.2.3 *Toxicity and Side Effects*

According to TCM practice, spreading hedyotis is generally considered as a relatively safe herb. Most TCM medical textbooks suggest not using the herb during pregnancy, which is the only caution listed. Acute toxicity study on the concentrated aqueous extract indicates that the LD_{50} for mice was 104 g/kg (raw material/body weight) through ip injection (Bureau of Traditional Chinese Medicine 1999).

Cell culture studies demonstrate about 10% growth inhibition on normal human pancreatic cells at the concentration of 50 mg raw material/ml while the IC_{50} against several human cancer cell lines fell in the range of 7–25 mg raw material/ml after 48 drug exposure (Gupta et al. 2004).

In vitro cell culture studies found that spreading hedyotis significantly inhibited the growth and induced apoptosis of leukemic cells HL60 while it did not induce apoptosis in human blood lymphocytes. However, the presence of spreading hedyotis prevented the progression of the stimulated human blood lymphocytes through the cell cycle, suggesting certain cytotoxicity against normal cells. In general, spreading hedyotis demonstrated selective cytotoxicity toward cancerous cells (Willimott et al. 2007).

Intraperitoneal injection to the Kunming mice at a daily dose of 60 mg extract/kg for 10 consecutive days did not cause significant change in body weight, while the same treatment with 5-FU at the dose of 30 mg/kg significantly reduced the body weight by 30% ($P<0.01$) (Zhang et al. 2008).

Oral administration of the aqueous extract of spreading hedyotis at the dose of 20 g raw material/kg/day for 10 consecutive days did not cause significant side effect in H22 hepatoma-bearing Kunming mice. However, 40 g raw material/kg/day for consecutive 10 days could cause 5% decrease in body weight, which was less than the 10% decrease caused by cisplatin (ip 2.0 mg/kg/day for 2 days) (Li et al. 2009).

Oral administration of the polysaccharides of spreading hedyotis at the dose of 30 mg/kg/day for 10 days did not cause any significant adverse effect on the weight of spleen and thymus in Kunming mice (Yang et al. 2010b).

9.3 Clinical Studies and Applications

Spreading hedyotis has been used clinically for a long time in China. It is mainly used for various cancer treatments in addition to other disease treatments. Clinical studies have demonstrated the effectiveness of this herb in treating many types of cancer including gastro-intestinal cancer, liver cancer, lung cancer, and leukemia. It can also improve the efficacy and reduce the adverse effects of the conventional chemotherapies.

9.3.1 Esophagus Cancer

Tang et al. (2003) studied the efficacy of spreading hedyotis in treating 106 cases of esophagus cancer of middle-late stage. The patients were given spreading hedyotis extract through iv infusion (40–60 drops/minute) at the dose of 24–60 g raw material/day. Each treatment cycle was consisted of 26 days: the treatment was given on days 1–5, 8–12, 15–19, and 22–26. The treatment lasted for total 4 cycles. There was a rest of 2 weeks between the treatment cycles. The treatment achieved 18% complete relief, 41% partial relief, 26% stabilization, and 16% progression. The treatment also resulted in complete disappearance of pain in 36/52 patients, partial relief of pain in 16/52 patients. The treatment was also effective in reducing cancerous fever—12/12 patients experienced complete relief of fever. There were 4 patients with lung metastases having chest edema and 2 with liver metastases having abdominal edema. After the treatment, all the edemas disappeared. No bone marrow suppression or renal toxicity was observed. The only adverse reaction observed was gastrointestinal reactions which occurred when the iv infusion rate was high.

9.3.2 Leukemia

Huang et al. (2001) studied the co-administration of spreading hedyotis with chemotherapeutic agents in treating acute non-lymphocytic leukemia. The control group of 21 patients received only chemotherapy of daunorubicin (45–60 mg/m^2/day for 3 days) and cytosine-1-β-D-arabinofuranoside (100–200 mg/m^2/day for 7 days); and the treated group of 19 patients received the same chemotherapy together with intravenous infusion of spreading hedyotis extract injection at the dose of 30 ml/day for 21 days (the injection concentration was not reported in the original paper; it was probably 1 g raw material/ml since this is the concentration of the commercially available products). After 2–3 terms of treatment, the treated group achieved 74% complete reliefs compared to 57% in the control group. The overall effective rate in the treated group was 95% compared to 71% in the control group ($P < 0.01$).

9.3.3 Non-small Cell Lung Cancer

A clinical study on the treatment of late-stage non-small lung cancer shows that the addition of spreading hedyotis extract injection could significantly improve the efficacy and reduce the adverse effect of the chemotherapy. Thirty-three patients (38–69 years old with an average age of 55.5 years) in the control group were given only chemotherapy of cyclophosphamide (600–800 mg/day on day 1 and day 8), doxorubicin (40–60 mg on day 1), and cisplatin (50–60 mg/day on day 1 and day 2). Fifty-three patients (41–82 years old with an average age of 54.8 years old) in the

treated group were given the same chemotherapy together with spreading hedyotis extract injection at the dose of 30 ml, twice daily, for 21 days (the injection concentration was not reported in the original paper; it was probably 1 g raw material/ml since this is the concentration of the commercially available products). The treatment efficacy on tumor was evaluated according to international objective efficacy evaluation standards. After 2–3 terms of treatment, in the treated group, 0/53 experienced complete relief, 23/53 partial relief, 18/53 no change, and 12/53 progression; in the control group, 0/33 experienced complete relief, 11/33 partial relief, 6/33 no change, and 16/33 progression. There was no significant difference in partial relief rate between the 2 groups. However, the rate of partial relief and stabilization was 77% in the treated group compared to 51% in the control group, showing significant difference ($P<0.05$). The clinical symptoms including cough, chest tightness, chest pain, short breath, fever, cold sweat, and fatigue were monitored before and after the treatment. In the treated group, 13/53 experienced complete relief of the symptoms, 24/53 partial relief, and 16/53 no change or progression. In the control group, 6/33 experienced complete relief, 7/33 partial relief, and 20/33 no change or progression. There was a statistical significant difference in the improvement of clinical symptoms between the 2 groups ($P<0.05$). The treated group had less adverse effects in terms of white blood cell decrease and nausea/vomiting than the control group ($P<0.05$). In the treated group, 12/53 had degree I white blood cell decrease, 10/53 degree II white blood cell decrease, and 4/53 degree III white blood cell decrease; in the control group, 13/33 had degree I white blood cell decrease, 11/33 degree II white blood cell decrease, and 6/33 degree III white blood cell decrease. For nausea/vomiting, in the treated groups, there were 14/53 experiencing degree I, 11/53 degree II, and 4/53 degree III; in the control group, there were 17/33 experiencing degree I, 10/33 degree II, and 5/33 degree III (Li and Huang 2000).

9.3.4 Liver Cancer

Liu et al. (2004) studied the treatment of late-stage primary liver cancer with spreading hedyotis. Forty patients were given spreading hedyotis extract injection at the dose of 4 ml, 3 times daily, for 56 days (the injection concentration was not reported in the original paper). The treatment achieved 18% effective rate (complete and partial relief), and 63% stabilization rate (complete and partial relief and no change). The half-year and one-year survival rate was 60% and 28%, respectively. No adverse effect was observed during the treatment. The treatment also improved the conditions of liver pain, poor appetite, abdominal edema, fever, and fatigue. The improving rates were in the range of 58–76%. Total 75% of the patients experienced improved or stabilized life quality, which was an important aspect of the efficacies of cancer treatment. The authors also examined the effect of the treatment on the transformation rate of T cells and the subpopulations of T cells. The results showed that the treatment significantly ($P<0.05$) increased the CD3 T cells by 11% and CD4/CD8 by 15%, respectively. T cell was also increased by 5%.

9.3.5 *Various Cancers*

Zhao and Zhang (2007) reported the efficacy of spreading hedyotis together with chemotherapies in treating various cancers of stages III and IV (Table 9.2). In general, the addition of spreading hedyotis extract injection at the dose of 4 ml, twice daily, for 19 days/term, total 2–4 terms (the injection concentration was not reported in the original paper) to the standard chemotherapies could significantly increase

Table 9.2 Efficacy and adverse effects of *Hedyotis diffusa* or *Oldenlandia diffusa* (spreading hedyotis) injection (intramuscular, 4 ml, twice daily) in combination with chemotherapy

			Spreading Hedyotis + Chemotherapy	Chemotherapy
N			78	76
Baseline KPS score	>60		61	58
	<60		17	18
Cancer stage	III		33	31
	IV		45	45
Cancer type	Lung		18	17
	Breast		19	18
	Liver		16	15
	Stomach		15	14
	Other		10	12
Efficacy[a]	CR		3 (4%)	1 (1%)
	PR		25 (32%)	14 (18%)
	NC		29 (37%)	36 (47%)
	PD		21 (27%)	25 (33%)
	KPS ↑ or no change		45 (58%)	30 (40%)
	KPS ↓		33 (42%)	46 (61%)
Adverse effects[b]	WBC decrease	0	5	1
		I	36	19
		II	30	36
		III	6	15
		IV	1	5
	Nausea	0	29	1
		I	11	17
		II	23	23
		III	13	26
		IV	2	9
	Vomiting	0	6	1
		I	33	23
		II	25	18
		III	10	20
		IV	4	14

[a] According to WHO efficacy categories of solid tumor treatment. CR: complete response, KPS: Karnofsky performance status, NC: no change, PD: progressive disease, PR: partial response
[b] According to WHO adverse event categories of anticancer drugs

the efficacy rate (complete and partial relief rate) from 20% to 60% ($P<0.05$), and significantly reduce the white blood cell decrease ($P<0.01$) and gastrointestinal adverse effect ($P<0.001$) caused by the chemotherapies. It could also achieve significantly more pain relief than the chemotherapy alone ($P<0.01$), and provide better life quality than the latter ($P<0.05$). Similar results were also observed by Luo et al. (2002) in the treatment of late-stage digestive and lung cancer.

9.3.6 Clinical Applications and Representative Formulas

Spreading hedyotis is widely used in various cancer treatments, in combination with other herbs or chemo-therapeutics. In the following, several representative formulas are listed.

Formula 1: fresh spreading hedyotis 70 g, *Scutellaria barbata* 20 g, *Cortex phellodendri* 10 g, *Coptis chinensis* 10 g, *Achyranthis bidentatae* 10 g, *Rhizoma atractylodis* 10 g, *Atractylodis macrocephalae* 10 g, *Panax notoginseng* 10 g, *Cortex moutan* 10 g, *Paeoniae rubra* 10 g, *Semen coicis* 10 g, *Rhizoma sparganii* 10 g, *Curcumae aeruginosae* 10 g, *Panax ginseng* 10 g, *Astragalus membranaceus* 10, *Radix bupleuri* 10, *Rehmanniae preparata* 10 g. Take one dose per day for the treatment of late-stage ovarian cancer. Extract with boiling water and divide the extract into 3 portions for drinking (Wu 2009).

Formula 2: spreading hedyotis 30 g, *Dioscoreae bulbiferae* 10 g, *Paeoniae rubra* 10 g, *Rhizoma homalomenae* 15 g, *Radix aristolochiae* 7 g, *Fructus trichosanthis* 30 g, *Herba prunellae* 10 g, *Bulbus fritillariae thunbergii* 10 g, *Concha ostreae* 15 g, *Alga sargassi fusiformis* 12 g, *Radix scrophulariae* 15 g, *Radix glehniae* 30 g, *Radix ophiopogonis* 10 g. Take one dose per day for the treatment of late-stage thyroid cancer. Extract with boiling water and divide the extract into 3 portions for drinking (Wang 2009).

Formula 3: *Radix adenophorae* 15 g, *Radix polygonatae* 15 g, *Radix asparagi* 15 g, *Flos inulae* 3 g (wrapped separately with cloth), *Rhizoma dioscoreae* 24 g, *Rhizoma imperatae* 60 g, spreading hedyotis 120 g. Take one dose per day for the treatment of esophagus cancer. Extract with boiling water, mix with suitable amount of honey, and divide the extract into 3 portions for drinking (Chang 1987).

Although these three formulas were used for the specific cancer in the original publications, the authors believe, based on our experience and knowledge, that indications of these formulas can be expanded to other cancers as well.

9.3.7 Dosage Forms and Doses

Spreading hedyotis is available in the form of a dried herb. In most cases, the dried herb is extracted with water and taken orally. Injections made of its extract are also available commercially for intramuscular and intravenous injection. The common

daily dose is around 30 g, and 60 g is also used in many formulas. The highest daily dose recorded is 120 g (Chang 1987).

9.4 Concluding Remarks and Perspectives

Spreading hedyotis is one of the most widely used herbs for cancer treatment in TCM practice. Pre-clinical and clinical studies have established its effectiveness and safety in treating various cancers. It has been proven that the combination of spreading hedyotis with chemotherapies can result in higher efficacy and less adverse effects than the chemotherapies alone. Compared to the chemotherapies, spreading hedyotis provides better life quality to patients and usually does not cause any noticeable side effects based on currently commonly used doses. It seems that there is a possibility to increase the dose above the commonly used level (30–60 g/day) in order to achieve higher efficacy. In another word, there is a need to establish the appropriate doses through well-controlled clinical trials in order to render the best efficacy with the balance of acceptable adverse effects. In conclusion, spreading hedyotis is an effective anticancer herb with minimum adverse effects.

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