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RESEARCH PAPER REPORT

TABLE OF CONTENTS

Abstract:

Special plants have enjoyed the genuine trust of people around the world as being good for health, sometimes with special emphases on longevity. Ancient China, in particular, has lists of choice plants to maintain health. Herbal formulations have been listed for the treatment of various infections in epidemics, their indications of use, and ways of preparation, which are handed down to today to facilitate therapeutic and preventive measures. The rich collection of plant items used for infection control have been studied in the laboratory and clinically along the modern directions of immunological activities—first with reference to infection as described in the old days and later diversifying into other immunological areas, notably cancer. This review will first briefly explore medicinal herbs in traditional Chinese medicine that have been studied in modern research platforms to identify their unique influences in some specific cellular and serological tests related to immunological activities. Some of these herbs have been selected in our home-ground to serve our aspirations on cancer treatment and epidemics

Introduction:

Since the Han Dynasty (206 B.C.–220 A.D.) remarkable documentations are available. One special area of intense interest and wisdom is related to infections and epidemics: from clinical presentations and treatment choices to public health measures. When bodily defense was mentioned in those days, although no assumption needs to be raised about immunological activities, it is also clear that advocates' and narrators' line of thought could be very near the modern concept of immunology at its most primitive level [1,2]. Herbal formulations have been listed for the treatment of various infections in epidemics, their indications of use, and ways of preparation, which are handed down to today to facilitate therapeutic and preventive measures. The rich collection of plant items used for infection control have been studied in the laboratory and clinically along the modern directions of immunological activities—first with reference to infection as described in the old days and later diversifying into other immunological areas, notably cancer. This review will first briefly explore medicinal herbs in traditional Chinese medicine that have been studied in modern research platforms to identify their unique influences in some specific cellular and serological tests related to immunological activities.

Some of these herbs have been selected in our home-ground to serve our aspirations on cancer treatment and epidemics

Clinical Research

Numerous preclinical studies have demonstrated the antitumor activities of herbal medicines and their mechanisms of action. They may either directly inhibit the growth of tumors or indirectly exert an antitumor effect by enhancing the body's immune function [1]. Over the past 15 years or more, our institute has carried out many preclinical investigations on the antitumor and/or immunomodulatory activities of various Chinese medicinal herbs and mushrooms . For instance, in collaboration with the Memorial Sloan Kettering Cancer Center at New York, USA, the immunomodulatory activities of five medicinal herbs/mushrooms, namely Astragalus membranaceus, Coriolus versicolor, Curcuma longa, Echinacea purpurea, and Grifola frondosa, have been investigated using various types of preclinical models [3]. Promising results on Astragalus [4,5] and Curcuma longa [6,7] led to further investigations on these herbs in our institute. Furthermore, a panel of herbs, which are commonly prescribed to cancer patients according to traditional Chinese medicine (TCM) theory, have also been examined for their in vitro effects on cancer cells and/or on lymphocytes in our early screening program. Based on the results, seven medicinal herbs or mushrooms, namely Acanthopanax senticosus, Agaricus blazei, Curcuma longa, Ganoderma lucidum, Ganoderma sinense, Hedyotis diffusa, and Scutellaria baicalensis, with particular reference to their antiproliferative effects in cancer cells or immunomodulatory properties, have been further investigated for their mechanisms of action. In addition, since the establishment of our Partner State Key Laboratory in 2010, research collaboration with State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, has been focusing on several natural products, orchids as well as Yunnan wildly grown mushrooms. One of the edible mushrooms, Rubinoboletus ballouii, was shown for its immunomodulatory activities for the first time in our studies [8,9]. Hence, in this part of the review, the preclinical findings of the above-mentioned nine medicinal botanicals from our previous studies have been summarized. The clinical prospects of these individual botanicals, especially their potentials in cancer management with special focus on immunomodulation, have also been discussed.

Table 1. Medicinal plants and mushrooms with anticancer and immunomodulatory effects described in the text.

Name	Photos of Plants/Mushrooms	Main Habitat	Medicinal Use	Main Active Chemical Component	Our Main Research Findings	References
(1) *Agaricus blazei*		Brazil, East Asia	Cancer, inflammatory/allergy conditions	Crude extracts	Anti-cancer effects	[12,13]
(2) *Ganoderma lucidum*		China, East Asia	Longevity, cancer	Triterpenes, polysaccharides	Immunomodulatory effects	[18–24]
Ganoderma sinense						
(3) *Rubinoboletus ballouii*		Southwest China	Folk practice	Polysaccharides	Anti-inflammation, immunomodulatory effects	[8,9]

Table 1. *Cont.*

Name	Photos of Plants/Mushrooms	Main Habitat	Medicinal Use	Main Active Chemical Component	Our Main Research Findings	References
(5) *Astragalus membranaceus*		North China	Rejuvenation, infection	Polysaccharides	Immunomodulatory effects	[3–5]
(6) *Curcuma longa*		India, South China	Anti-aging, antioxidant, cancer	Crude extracts	Anti-inflammation, anti-angiogenesis, immunomodulatory effects	[6,7,33–38]
(7) *Hedyotis diffusa*		South China	Cancer	Crude extracts	Anti-angiogenesis, anti-cancer	[39–41]
(8) *Scutellaria barbata*		China	Infection, allergy	Crude extracts.Pheophorbide a	Anti-inflammation, detoxication, anti-cancer	[42–45]

2.4. Acanthopanax senticosus

Methods:

Bodily discomfort and fatigue are experienced by cancer patients undergoing treatment: from surgery and radiotherapy to chemotherapy, because of suppressed immunological functions.

Eighty-two patients who completed treatment for breast cancer were recruited to take Yun Zhi (50 mg/kg body weight, 100% polysaccharopeptide (PSP)) and Danshen (20 mg/kg body weight) capsules every day for a total of 6 months. Ethylenediaminetetraacetic acid (EDTA) blood samples were collected every 2 months for the investigation of immunological functions. Flow cytometry was used to assess the percentages and absolute counts of human lymphocyte subsets in whole blood. Plasma level of soluble interleukin-2 receptor (sIL-2R) was measured by enzyme-linked immunosorbent assay (ELISA). Results showed that the absolute counts of T-helper lymphocytes (CD4+), the ratio of T-helper (CD4+)/T suppressor and cytotoxic lymphocytes (CD8+), and the percentage and the absolute counts of B-lymphocytes were significantly elevated in the treatment group. The plasma slL-2R concentration was also significantly decreased (all $p < 0.05$) among these patients [72]. Cancer patients were given the Coriolus and Salvia capsules after they completed standard treatment. They were expected to enjoy better quality of life, and more specifically, we critically looked at the immunological effects, which would offer quantitative data on clinical benefits. The follow-up periods were short, which would not allow longer-term studies on clinical benefits.

Common Target Areas That Investigators Used to Study the Bioactivities Related to Immunological Properties of Medicinal Plants:

4.1. Organs Related to the Provision of Relevant Cells and Cellular Activities: [73]

a. bone marrow,

b. thymus,

c. lymph nodes and lymphatic system, and

d. spleen.

Hypertrophy of these organs with increased cell production must be the most accepted indications of a medicinal herb's immunological ability. Notable items in this group include Astragalus membranaceus, Angelica sinensis, and fungal varieties [2,73]. .

Activity of Macrophages: [74]

a. engulfing ability and

b. anticancer activities

Polysaccharides in medicinal plants have been of major interest, and many examples are related to fungal species. Triterpenes, saponins, and nucleotides are other components of great interests, exemplified by Panax ginseng. 4.3. Immune Cells—T Cells, B Cells, Natural Killer (NK) Cells: [75,76] a. T cells' responses give good pictures of anti-infection and anticancer influences, b. B cells could be studied on their responses to polysaccharide stimulation, and c. NK cell's direct cytotoxic effects have been observed. A large number of medicinal herbs, exemplified by Astragalus membranaceus, Hedyotis species, Acanthopanax senticosus, and Ledebouriella divaricata have been found influential. 4.4. Cytokines, Interleukin Production [77,78] Herbal extracts mainly act on the macrophages and related cells. Cellular activities, however, produce cytokines and chemokines, which have far-reaching immunological effects. Studies, therefore, include their productions accepted as extended cellular effects. Selected

herbs are those utilized in cellular studies . Other studies include analysis of interferons, TNF-α, etc.

Result:

The immunomodulating effects of PSP have been studied intensively from animal experiments to clinical trials, from in vivo studies to in vitro analysis, and from cell cultures to molecular and genomic explorations. The laboratory results greatly facilitated marketing, gaining substantial social and economic profits.Apart from anticancer effects, PSP was also found to be antiviral (human immunodeficiency virus, HIV) and hepatoprotective. Other studies showed significant analgesic effects of PSP on acute and chronic inflammatory pain induced in rats. Since this analgesic effect could be antagonized by the cerebral intraventricular injection of anti-IL-2 serum, the central analgesic activity of PSP may be mediated by the IL-2 receptor. Since the immune system and nervous system provide two major forces in the maintenance of the internal equilibrium of the whole body, through cellular and molecular networks, PSP is assumed to be influential in this process. One hundred healthy subjects were recruited to take Yun Zhi (50 mg/kg body weight) plus Danshen (20 mg/kg body weight) or placebo capsules daily for four successive months and, after a 2 month wash-out period, crossover to take placebo or Yun Zhi plus Danshen capsules for another four successive months. Flow cytometry was used to assess the lymphocyte subtypes and concentration of T helper (Th) cell cytokines in culture supernatant. Gene expression of cytokines and cytokine receptors of peripheral blood mononuclear cells (PBMCs) was analyzed by a cDNA expression array. Results showed that regular oral consumption of Yun Zhi–Danshen capsules could significantly elevate PBMC gene expression of interleukin (IL)-2 receptor, increase the percentage and absolute counts of T helper cell and ratio of CD4+ (T helper)/CD8+ (T suppressor and cytotoxic T) cell, and significantly enhance the ex vivo production of typical Th1 cytokine interferon-gamma from PBMCactivated by phytohemagglutinin and lipopolysaccharide. Common Target Areas:- abone marrow, b. thymus, c. lymph nodes and lymphatic system, and d. Spleen

Discussion:

Medicinal plants have been used for centuries for the treatment of various diseases in many parts of the world. The utility of natural products as important resources for the discovery of new and safe drugs for human healthcare apparently is still important and is ongoing. It has been estimated that about 65% of the world's population relies on plant-derived medicines for treating various diseases [81]. The demand for natural products has been growing during the past few decades. Herbal dietary supplements continued to experience strong sales growth in the United States in 2019, with an increase by 8.6% [82]. While a recent pilot survey in the UK showed that over 80% of participants used medicinal plants for multiple health benefits [83]. Cancer is one of the leading causes of death in the world, and it has caused the death of 9.9 million people in 2020 [84]. Cancers of the lung, breast, colorectum, liver, stomach, and prostate were listed as the top six cancers in causing mortality [84]. The use of complementary and alternative medicines (CAMs) by patients suffering from cancers is quite well documented [85]. Nowadays, many cancer patients use herbal medicines and natural products derived from plants or mushrooms to combat cancer, to strengthen the immune system, and to counter some possible side effects of the conventional treatment [86]. Approximately 60% of the anticancer agents that are currently available for clinical use or are

in late stages of clinical trials are derived from natural products [87]. According to previous reviews, the most frequently used CAM modalities in Europe are herbal medicines [88]. In fact, herbal medicine is at the forefront of traditional medicine in Germany and Western Europe [89]. An Italian survey revealed that herbal medicine is frequently employed to improve quality of life [90]. Recent studies also showed that dissatisfaction with conventional medicine is the most important reason for the preferred use of herbal medicine in Germany [91]. In fact, a similar scenario has occurred with cancer patients worldwide. The use of Chinese herbal medicines (CHMs) as an adjuvant to cancer treatment is more frequent among cancer patients in Chinese communities, such as in China, Hong Kong, and Taiwan [59,92–94]. Plentiful clinical studies can be found on the efficacies of traditional Chinese medicines (TCMs), either combined with conventional cancer therapies or used alone, in cancer patients. The conclusions drawn from most of these studies suggest that, for cancer patients, TCM can be useful and effective, helping to control the disease, prolonging survival time, alleviating side effects of chemotherapy and radiotherapy, and improving the quality of life [95]. One systematic review summarized that traditional Chinese medicine preparations, combined with chemotherapy, may improve the objective response rates and disease control rates more than chemotherapy alone [96]. Throughout these years, pharmacognosists, pharmacologists, and biochemists Molecules 2021, 26, 2173 11 of 15 are anticipating more and more scientific evidence on the efficacies of medicinal herbs, to be gained through modern pharmacological research approaches. This is also the mission of our institute. In this review, the preclinical studies of several medicinal herbs and mushrooms are chosen as examples. Their applications as adjuvant therapeutic agents in the management of cancer, particularly in the areas related to immunological support, are expected to gain increasing enthusiasm in future. During the current COVID-19 pandemic, our research interests on the immunomodulatory effects of medicinal herbs have shifted to include their use as immuno-boosters for innate-immunological defense. Our efforts could be discussed in subsequent reports. The academic editor of this journal, while reviewing this manuscript, brought forward the concern about the quality issues of the herbal materials and the methodological challenges associated with clinical studies. Indeed, the two issues deserve a separate review to reach a thorough recommendation. We tackle the quality issue through a stringent process: consisting of firstly acquiring the selected herbs from the most reliable seller, followed by comprehensive authentications, from gross examinations to chemical scrutiny; then storing the information in our regional herbal data authority to ensure that future repeated research material could be cross matched to prove identical criteria. With regard to clinical studies, we insist on taking reference from the clinical trial procedures so that safety comes first, followed by dosage identifications before the proper clinical trial could be planned.

Conclusion:

The dosages of the A. blazei extracts in these studies have not clearly reported. On the other hand, health supplements containing A. blazei were also shown to be effective in improving symptoms in inflammatory or allergic conditions. consumption had no adverse effects on the liver and renal functions and the biochemical profile. Herbal extracts mainly act on the macrophages and related cells. Cellular activities, however, produce cytokines and chemokines, which have far-reaching immunological effects. The

immune modulating effects of selected herbs were carefully studied to gain insight into their immunomodulatoty effects relevant to cancer treatment. There was no discussion of clinical significance

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