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## Herbs that Promote Cell Proliferation

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### ABSTRACT

Plants, herbs, and ethnobotanicals have been in use since the early days of mankind and are still used throughout the world for health promotion and treatment of disease. Around 75% of world population especially in the underdeveloped world and developing countries relies on natural pharmaceuticals for primary health care. However, in the last few years there has been a major increase in their use in the developed countries. In Germany, France and UK, many herbs and herbal extracts are used as prescription drugs. Herbal treatments are the most popular form of traditional medicine, and are highly lucrative in the international marketplace. Many herbs are active against neoplastic diseases by inhibiting cell growth and proliferation. They are also used to treat diseases that result from decline of stem cell proliferation and utilized for regeneration and rehabilitation of tissues by promoting cell proliferation. The aim of this paper is to review plants/herbs that have been shown to cause an increase in cell growth/proliferation and to discuss if there is a peril of an unwanted stimulation of cell proliferation.

**Keywords:** Cell, Proliferation, Herbs.

### 1. Introduction

Herbs and herbal extracts have long been utilized to control cell proliferation as a way of treating cancer cells. Cancer is a multistage disease that requires treatments targeting multiple cellular pathways. Drug toxicity and resistance to chemotherapeutic agents makes it arduous to treat cancer. Therefore, nontoxic dietary phytotherapy has been considered as a preventative and/or therapeutic method against cancer cells <sup>[1]</sup>. The field of ethnomedicine and ethno pharmacology is plenary of cases where herbs and plants are habituated to fight neoplastic diseases <sup>[2]</sup>. Traditional oriental herbal medicines have long been used and established for treatment of malignant cancers. Among these remedies, a number of herbal cocktails have been reported to have antitumor activities and some of them have already been utilized by cancer patients for some time <sup>[3-11]</sup>. Herbal cocktails consisting of various herbs could affect multiple cellular pathways, thereby modulating cellular activities during cancer progression. Interactions of phytochemicals present in different herbs may achieve more preponderant therapeutic efficacy than a single herb and abrogate deleterious side effects of single constituents <sup>[12-14]</sup>. Herbal formulations are the mundane form of administration in Chinese herbal practice, and herbal formulas are well documented in archaic and modern literature <sup>[15, 16]</sup>. Herbal chemoprevention and treatment is gaining a significant attention among both the public and the scientific communities <sup>[17]</sup>. On the other hand, the issue of enhanced cell proliferation needs to be addressed because there are some diseases that result from decline of stem cell proliferation and also in cases where increased cell proliferation is needed as in tissue regeneration, repair and aging. Here we review the herbs that promote cell proliferation and look for herbs that can promote categorical cell proliferation but at the same time not taking the peril of abnormal cell proliferation.

### 2. Herbs that promote cell proliferation.

Literature search about herbs that involve cell proliferation showed many research discussing the beneficial effects of herbs on stem cell proliferation, few reports focus on hair growth, stimulation of the immune system and other positive side of herbal remediation but there is lack of scientific research exploring possible deleterious effects of herbs on cell proliferation and possibly cancer development.

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### 3. Concerns about herbal therapy

Albeit herbal remedies are wide spread, well accepted and considered safe by many of us, there are many concerns that should be taken into consideration. There are few reports discussed possible carcinogenic ingredients in some well-known accepted herbal remedies [18, 19]. A series of kidney failure cases were reported in 1993 after the ingestion of the weight-loss herb *Aristolochia fangchi* [20] which had been found to possess some carcinogenic activity [21, 22]. A medicinal plant *Jussiaea repens* (L) that is widely used to treat many ailments in many Asian countries has been reported to cause adverse effects on male rat reproductive system [23].

### 4. Regeneration, repair and wound healing

Adult stem cells can be found in virtually all adult tissues. It is suggested that the utilization of herbal extracts to stimulate endogenous stem cells to promote rejuvenating and regeneration could be accommodated as an alternative to stem cell transplantation. Natural compounds known to promote rejuvenating can be investigated on stem cells. To advance the clinical utilization of herbal stem cell therapy in a kindred manner to stem cell transplantation, it is very consequential to find substances that promote endogenous stem cell proliferation and differentiation.

It has been found that Aconiti Lateralis Preparata Radix (ALR) promoted the proliferation rate of mouse bone marrow mesenchymal stem cells (mBMMSCs) up to 122.24% compared to untreated cells [24]. A dose-related effect of blueberry, green tea, catechin, carnosine, and vitamin D3 was observed on proliferation of human bone marrow as compared with human granulocyte-macrophage colony-stimulating factor (h GM-CSF). Furthermore, it has been shown that coalescences of nutrients engender a synergistic effect on hematopoietic progenitors by enhancing cell proliferation. This shows that nutrients can act to promote rejuvenating via an interaction with stem cell populations [25].

Poon and colleagues studied the effect of herbal extracts on bone fracture and osteoporosis, ethanol extracts of *Gendarussa vulgaris* and *Drynaria quercifolia* were investigated on rat bone marrow stromal cells and they found that *Gendarussa vulgaris* could enhance bone-cell proliferation [26]. Osteoblast-like cell proliferation was also been found to be stimulated by herbal extracts [27]. The *C. brasiliense*, *I. pes-caprae* and *M. elaeagnoides* extracts significantly increased cell proliferation in a dose-dependent induction of cell proliferation suggesting T-lymphocyte stimulation [28]. Numerous studies showed that herbal extracts can be used in the management of wound healing. A polyherbal formulation consisting of extracts of *Wrightia tinctoria*, *Aloe vera*, *Curcuma longa* and *Terminalia chebula* was used to study the fibroblast cell migration and proliferation using scratch wound assay technique. The results of this study indicate that the polyherbal formulation may be useful in effective management of superficial wounds [29]. Herbal extracts were also found to stimulate growth of skin cells. The polysaccharides of St. John's herb were found to stimulate keratinocyte differentiation [30]. It has also been reported that hyperforin which is found in significant amounts in *Hypericum perforatum* (St. John's wort) induced keratinocyte differentiation *in vitro* and skin hydration *in vivo* [31, 32]. Polysaccharides from Kiwi fruit (*Actinidia chinensis* L.) were also found to have a stimulating effect on human keratinocytes [33]. A mixture of herbal extracts and platelet rich plasma was found to

induce dermal papilla cells proliferation [34, 35]. Other herbal extracts can stimulate keratinocyte cell proliferation and avail in wound rejuvenating [35, 36].

### 5. Immunomodulatory activities

Ethanol extracts of *Allium sativum* (garlic), *Glycyrrhiza glabra* (licorice), *Plantago major* (plantain) and *Hippophae rhamnoides* (sea buckthorn) were assessed for their effects on cellular immunity in laying hens. Certain extracts definitely enhanced the fowl innate and/or specific cell immunity and may therefore amend host resistance in poultry. Considering the chicken as an important non-mammalian model that also serves as an available laboratory approach for some human diseases, herbs exerting immunomodulatory properties may find pertinent clinical applications [37].

### 6. Radioprotection

Many herbal extracts have been reported to have a radio protective potential. The results obtained from an *in vitro* and *in vivo* studies indicate that several botanicals such as *Ginkgo biloba*, *Centella asiatica*, *Hippophae rhamnoides*, *Ocimum sanctum*, *Panax ginseng*, *Podophyllum hexandrum*, *Amaranthus paniculatus*, *Emblia officinalis*, *Phyllanthus amarus*, *Piper longum*, *Tinospora cordifolia*, *Mentha arvensis*, *Mentha piperita*, *Syzygium cumini*, *Zingiber officinale*, *Ageratum conyzoides*, *Aegle marmelos* and *Aphanamixis polystachya* protect against radiation-induced lethality, lipid peroxidation and DNA damage [38]. Sah and colleagues showed that some herbal extracts exhibitant thermo-radiation properties. It was found cells exposed to *Selaginella* extract (SE) for 1 h afforded complete protection against heat-induced growth suppression. SE may possess anti-stress and antioxidant activities that could be responsible for the observed effects. Chemical analysis shows that (SE) contains hexoses and proteins. Taken together, *S. bryopteris* extract may help in stress-induced complications including those due to heat shock [39].

### 7. Herbal and plant extracts that might cause cancer.

Some herbs and plants have been found to have deleterious effects on certain cancer cell lines. Croton oil has been long known to induce inflammation and carcinogenesis in different types of cells [40-42]. Moreover, herbal extracts such as *Lycium shawii* leaves extract was found to possess proliferative, anti-inflammatory and cytotoxic activity. Pure ingredients of these extracts were found to have significant proliferative activity when human embryonic kidney cells were used (HEK-293) [43]. It has also been reported that some herbal extracts can stimulate cancer cell proliferation while others can inhibit it. The proliferation of MCF7 cells was significantly increased following treatment with ecdysterone, saffcomin A, psoralen or isopsoralen [44]. Astragalus plant, which has been consumed by humans for over a thousand years and is available in any vitamins shop, has a single molecule called TA-65 which has been found to activate the telomerase enzyme hence stimulating proliferation and fighting aging [45]. Therefore, theoretically, TA-65 could stimulate unwanted growth and cell overpopulation. It is also reported that Chinese herbal extracts showed neuro proliferation properties *in vitro* and *in vivo* [46]. More specifically, Rhizome Chuanxiong, Radix Scutellaria and Radix Phellodendri could promote the proliferation of neural stem cells (NSCs) in a concentration-dependent manner. Danggui Buxue Tang (DBT), a Chinese herbal decoction used to treat ailments in

women, contains Radix Astragali (Huangqi; RA) and Radix Angelicae Sinensis (Danggui; RAS). When DBT was applied onto cultured MG-63 cells (osteosarcoma cell line), an increase of cell proliferation and differentiation was noticed [47]. Aristolochic acids (AAs) are primarily found in different species of the genus *Aristolochia* (e.g. *Aristolochia clematidis*, *Aristolochia fangchi* and *Aristolochia manshuriensis*), but have also been described in certain *Asarum* species (International Agency for Research on Cancer (2002)).

### 8. Angiogenesis/immune system

Natural and plant concentrates can likewise impel angiogenesis and fortify the immune system. Peripheral lymphocyte proliferation was found to be stimulated after treatment with Chinese medicinal herbal extracts (CHME). Nine CHMEs were experimentally tested; Astragalus polysaccharide (APS), *Isatis* root polysaccharide (IRPS), *Epimedium flavone* (EF), *Propolis flavone* (PF), Astragalosides (AS) and Ginsenosides (GS) were found to promote lymphocyte proliferation and antibody titer, while *Epimedium* polysaccharide (EPS) mainly stimulated cellular immune responses [48]. The results also suggested that *Angelica* and *ChuanXiong* have angiogenic effects, and may provide some mechanisms for the treatment of myocardial infarction and peripheral ischemia [49]. On the other hand, concanavalin significantly stimulated proliferation of mice spleen cells from fed with 100 mg rosemary extract compared to control animals [50, 51]. Anther herbal extract, *Hemidesmus indicus* extract was found to significantly stimulate lymphocyte cell proliferation at 1 mg/ml concentration. The extract increased the IgG production from cultured PBLs, when used at 1 mg/ml concentration. It also increased the ADA activity of PBLs after 72 h in culture [52].

### 9. Specific nutrients found in plants and herbs that can Promote Stem Cell Proliferation.

When bone marrow stem cell activity is interfered with, diseases such as anemia (red blood cell deficit), neutropenia (specialized white blood cell deficit), or thrombocytopenia (platelet deficit) are often diagnosed. Scientists have long known that folic acid, vitamin B12, and iron are required for bone marrow stem cells to differentiate into mature red blood cells [53, 54]. Vitamin D has been shown to be crucial in the formation of immune cells, where bas carnosine has demonstrated a remarkable ability to rejuvenate cells approaching senescence and extend cellular life span [55, 56].

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