Botanicals As Therapeutics

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Many botanical compounds ("botanicals") have the potential to prevent, ameliorate, or even cure some common health perturbations. When the beneficial plant materials or extracts derived from those materials are directed toward specific therapies, they are frequently referred to as nutraceuticals. In most cases, the acceptance of their therapeutic value has taken an inordinately long time, even though the ratio of benefits to risks is often very high. Much of the delayed recognition of therapeutic potential can be attributed to poor physician training in the basic rudiments of nutrition. In addition, the emphasis among practitioners has consistently been on prescription pharmaceuticals, not on over-the-counter nutraceuticals. Accordingly, physicians offer statin-type drugs to lower cholesterol rather than non-prescription garlic and soluble fibers; sibutramine to aid weight loss rather than *Garcinia cambogia*. Moreover, vitamins and antioxidants to maintain good health do not achieve the desired professional appeal necessary for many practitioners. On the other hand, the exaggerated, often preposterous, beneficial claims of many in the natural products industry make it easier to comprehend why potentially useful plant products have been overlooked or even dismissed for far too many years.

However, the pendulum is gradually swinging in the other direction, as more and more patients are, through necessity, taking responsibility for their own health. The policy of "getting them in and out as fast as possible," emphasized by many large health organizations in order to increase profit margins, has made people aware that long-term health must, at least to some extent, become their own concern rather than that of the health professional. This coincides with a general recognition that, whereas modern medicine is good at treating acute and catastrophic illnesses, this does not hold for preventive measures. In certain vital areas of importance to health, such as obesity, where drug therapy has been less than satisfactory in its effects or has caused unacceptable side effects, natural products are fervently being sought as alternatives.

There are many other important health areas where botanicals have proven useful. In this discussion I will cite only some of the most promising of which I have first-hand knowledge.

Maitake Mushroom: Immunity Enhancer, Tumor Suppressor, Anti-Diabetic

Many natural compounds enhance nonspecific immunity, including biological agents of varied chemical structure. Herbs such as astragalus and echinacea have been documented to possess nonspecific immunity-modulating effects (Physicians' Desk Reference, 2000; Therapeutic Research Faculty, 2000). Medicinal mushrooms, such as reishi, shiitake, cordyceps, and maitake, show a common ability to enhance immune function by stimulating cell-mediated immunity (Lahnborg *et al.*, 1982). Quite simply, mushrooms seem to turn on cells in the immune system, including macrophages and T-cells, that appear to have significant cancer- and infection-fighting properties. This is primarily because some mushrooms are an excellent source of beta-glucans, which are non-digestible polysaccharides found in the cell walls (Borchers *et al.*, 1999). When beta-glucans are consumed prudently, significant benefits to immune health are common. The immune system is reactivated, regaining the ability to fight disease and to ward off infection. These complex sugars are the basis of multi-cellular immune intelligence—the ability of immune cells to communicate, cohere, and work together to keep us healthy and balanced.

Concentrating on the maitake mushroom, a logical question to ask is how does it work? Beta-glucans with certain molecular-branching configurations have been shown to dock onto receptors on the outer walls of macrophages and activate them, stimulating the immune response to pathogens (Brown and Gordon, 2001). Macrophages contain specific protein-based receptor complexes on their walls to which the β-1,3/1,6-D-glucan molecule readily attaches. The binding of β-1,3/1,6-D-glucan enhances the ability of macrophages to detect and scavenge a variety of health threats. Bacterial infections respond remarkably to these polysaccharides, as do many viral infections—from the common cold and influenza to herpes and HIV. Beta-glucans even mitigate the toxic effects of radiation and chemotherapy while augmenting their cancer-killing effects, resulting in prolonged survival and improved quality of life for cancer patients (Preuss and Konno, 2002).

It is now conclusive that the anti-tumor effects are the result of the activity of various beta-glucans located in the fruit body and mycelium (the mass of interwoven filaments that forms the vegetative portion of the mushroom in the soil) (Ohno *et al.*, 1985). Researchers have obtained various therapeutically useful fractions by continually refining the elements from the fruiting body of maitake. The results of much of this research were published in 1980s (Adachi *et al.*, 1987; Adachi *et al.*, 1989; Nono *et al.*, 1989; Ohno *et al.*, 1984; Ohno *et al.*, 1985; Suzuki *et al.*, 1984; Suzuki *et al.*, 1989). The D-fraction of the

maitake extract, obtained last, was found to possess the most potent anti-tumor activity, leading to the highest reduction rate in cancer proliferation (Preuss and Konno, 2002). Research on the specific beta-glucans found in the D-fraction has demonstrated effects not only on macrophages but also on natural killer cells and various T cells. Accordingly, the D-fraction demonstrates perhaps the highest cancer inhibition of any source of beta-glucans via oral administration (Adachi *et al.*, 1987; Nono *et al.*, 1989; Suzuki *et al.*, 1989).

A literature review on maitake confirms that its natural polymer is an important adjuvant in cancer therapeutics, for mitigating the damaging side effects of chemotherapy and radiation, as well as for improving the body's innate defenses and improving the chances of living cancer-free. Another way that beta-glucans may add therapeutic benefit is by stimulation of tumor inhibitors. In certain experimental models, systemic macrophage activation and certain cytokine releases seem to be critical for clearing tissues of tumor cells and inhibiting metastasis. In 1995, Dr. Mitsuhiro Okazaki and co-researchers (1995) demonstrated that the maitake mushroom stimulates release, or, rather, "primes" the body to release tumor-necrosis factor-alpha. Additional studies have corroborated that maitake is a potent, broad-spectrum cytokine inducer. In other words, maitake D-fraction exhibited an anti-tumor effect on tumor-bearing mice through both enhanced cytotoxic activity and stimulation of macrophages—helping the macrophages to function to their fullest potential. This enhanced activity of macrophages invariably results in elevated production of interleukin-1, thereby activating cytotoxic T lymphocytes and many additional cytokines. Finally, maitake has also been described as possessing anti-angiogenic (Matsui *et al.*, 2001) and apoptotic potential (Konno, 2001).

In a non-randomized clinical study, 165 patients, aged 25 to 65, diagnosed with various stages of cancers (III-IV) were given maitake D-fraction plus crude maitake powder tablets alone without chemotherapy or this same combination along with chemotherapy (Nanba, 1995). Tumor regression or significant improvements were observed among eleven out of fifteen breast-cancer patients, twelve out of eighteen lung-cancer patients, and seven out of fifteen liver-cancer patients. If taken with chemotherapy, these response rates improved further by 12 to 28%. In several cases with both liver and lung cancer, the patients went from dangerous stage III status to more manageable stages.

Recent studies in our laboratory using diabetic mice and rats further suggest that maitake mushroom favorably affects diabetes mellitus and hypertension (Manohar *et al.*, 2002; Talpur *et al.*, 2002). A group of eight diabetic Zucker fatty rats given a fraction of maitake designated SX showed significantly decreased systolic blood pressure and fasting blood-glucose levels when compared to eight rats in a control group. At the end of six weeks, the differences in systolic blood pressure between the two groups exceeded

20 mm Hg; and the differences in fasting blood-glucose levels exceeded 60 mg/dL (218 mg/dL±18.3 (SEM) vs. 151 mg/dL±11.2). It is believed that the specific beta glucans in the water-soluble fraction SX were responsible for these effects. Interestingly, the previously discussed fraction D, unlike fraction SX, did not affect either of these parameters.

Defined Pollen Extract (Cernitin)

Compared to another natural plant product, *Serenoa repens* (saw palmetto), a defined flower pollen extract commonly called cernitin has received, up to now, little recognition in the United States concerning its potential to benefit various perturbations of the prostate. Ironically, it may be the best natural product for this condition currently available. In 1950, a Swedish beekeeper found a way to collect pollen artificially (Preuss and Adderly, 1998). Since it seemed good for bees, his hypothesis was that the defined pollen extract would be good for humans. Initially, the flower pollen was used as a prophylactic agent against infections. The extraction process was eventually modified so that the active pollen was released and was non-allergenic. A water-soluble and an oil-soluble fraction were deemed therapeutically useful. Oily cernitin GBX and water-soluble cernitin T60 are a mixture of three different pollens—rye, timothy, and maize. Whatever the original hypothesis concerning overall health, the defined pollen extract (cernitin) has proven useful specifically in treating benign prostatic hyperplasia (BPH) (Loschen and Ebeling, 1991).

Leander (1962) published results of a carefully controlled clinical trial of cernitin. He compared placebo with cernitin pollen extract in 179 cases. Using defined pollen extract, he found a 60 to 80% improvement over placebo in symptoms of obstruction, probably occurring through elimination of inflammatory edema. In various subsequent clinical studies, a standardized, allergen-free whole extract of selected *Graminaceae* pollen was found to be suitable in the long-term treatment of prostatic congestion in BPH, chronic prostatitis, and prostadynia (Leander, 1962; Ebeling, 1986; Becker and Ebeling, 1988). The usual dose in clinical studies is four to six tablets per day in divided doses. Each tablet contains an average of 63 mg of *Graminaceae* pollen.

In 1986, a field study of 2,289 patients being treated by 170 urologists was undertaken (Ebeling, 1986). The investigators examined the effectiveness of cernitin pollen extracts on chronic prostatitis and/or BPH. Improvement of symptoms was reported in 64 to 82%, in contrast to a low rate of adverse reaction found only in 2.9 per cent of cases. In the same year, Brauer (1986) compared the effects of cernitin and beta-sitosterol in thirty-nine patients. A significant reduction in circulating levels of prostate specific antigen (PSA) with cernitin therapy indicated a reduction of cell lesions in BPH. In contrast, no such change occurred with beta-sitosterol treatment. Although flower-pollen extract proved superior to beta-sitosterol in many respects, the mean values for residual volume fell under 15 mL for both at the end of treatment.

In a double-blind, placebo-controlled study performed in 1988 in collaboration with six practicing urologists, Becker and Ebeling (1988) compared forty-eight patients taking cernitin with an equal number of patients receiving placebo over a 12-week period. Patients were classified as having stage II/III BPH. Nocturia was claimed by 97% of the patients as a symptom. The results showed that there was a significant improvement using cernitin compared to placebo on nocturia, i.e. 69% vs. 37% (P <0.005). Not only the sensation of residual urine but the actual volume of residual urine was significantly reduced by flower-pollen extract. Mild nausea was reported in one patient. All in all, the "superiority of the active therapy is documented in the symptomatology, the results of the urodynamic investigations and by the global evaluation of the therapy by both doctor and patient."

In conjunction with two other clinical centers, we conducted a study using a combination of cernitin and saw palmetto to treat the symptoms of BPH. In a randomized, double-blind, placebo-controlled study of 127 subjects (fifty-seven placebo and seventy verum), we found statistically significant improvement in nocturia, frequency, and overall prostate score by the American Urological Association Symptom Index (Preuss *et al.*, 2002).

A major mechanism behind the beneficial action of pollen extract is believed to be inhibition of edema formation and prevention of inflammation in the prostate. Inflammation of the prostate can cause edema of the interstitial tissue surrounding the acini and ducts of the glands leading to poor drainage. This, in turn, creates difficult voiding, dysuria, frequency, and nocturia—symptoms that have been shown to improve with defined flower-pollen extract usage. In addition, pollen extract has been reported to reduce prostatic volume and residual volume, to improve voiding difficulties and increase urinary flow rates of patients with BPH. Obviously, pain may result from such processes and will remit to some extent if these perturbations are overcome. It is believed that the anticongestive action is based upon the inhibition of prostaglandin and leukotriene biosynthesis. The activities of 5-lipoxygenase and cyclo-oxygenase enzymes are markedly reduced and the arachidonic cascade is interrupted (Loschen and Ebeling, 1991). Additional pharmacological effects reported for the pollen are: inhibition of prostate-cell growth in animals, influences on contractility of bladder and urethral smooth muscle as well as diaphragms of animals, and effects on metabolism of dihydrotestosterone (Loschen and Ebeling, 1991). In conclusion, the combined mechanisms behind the beneficial effects of cernitin pollen extract will go a long way toward ensuring overall prostate health.

Essential Oils (Cidal to *Candida* and *Staphylococcus*)

It has been recognized for centuries that meat and fish can be preserved in oils obtained from various spice plants. In our laboratory, we examined the ability of essential oils to kill the fungus *Candida albicans*, and the bacterium

Staphylococcus aureus (Manohar *et al*., 2001). The experiments were carried out both *in vitro* and *in vivo*. The spices examined included oregano, cinnamon/cassia, myrtle, bay leaf, lavender, and cumin. Oregano and cinnamon were found to be the most potent based on their ability to kill both *Candida* and *Staphylococcus in vitro* at the lowest dilutions. When prevention of death of mice infected with *Candida* was subsequently examined, a reasonable dose of oregano was found to save all the mice—similar to the effect of nystatin. Carvacrol, believed to be the major active constituent in oregano, was also shown in the same study to have therapeutic effects on the fungus. When the mice were sacrificed after 30 days of daily treatment, they were found to be clear of fungus with both nystatin and oregano.

In a second group of investigations, a dose of *Staphylococcus* was given that killed all control mice within a 5-day period. All the mice receiving carvacrol died eventually, but survived much longer, averaging 17 days. In contrast, half (3/6) of the test mice survived for 30 days while taking daily doses of oregano. Two of those receiving daily oral doses of vancomycin (2/6) survived the full 30 days and were free of *Staphylococcus* judged by postmortem examination and by kidney cultures.

Miscellaneous Useful Botanicals

Other useful botanicals examined in our laboratory include:

- Wild garlic—a potential antihypertensive that works, at least in part, through its inhibitory effects on angiotensin converting enzyme (ACE) in rats (Mohamadi *et al*., 2000; Preuss *et al*., 2001).
- Grape-seed extract—a powerful antioxidant that can reduce circulating levels of the really bad cholesterol, oxidized LDL (Preuss *et al*., 2000).
- Cinnamon—a potential anti-diabetic and anti-hypertensive agent and potentially fungicidal and bactericidal based on rodent studies (Berrio *et al*., 1992).

Conclusion

Many nutraceuticals offer a reasonable approach to prevent, ameliorate, or cure chronic debilitating disorders safely and effectively.

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