Herbal Antioxidants in Clinical Practice

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Presented at the 23rd Annual Nutritional Medicine Today Conference, May 1, 1994, Vancouver, Canada.

Antioxidant. The word itself is magic. Suggesting some type of all-encompassing protection against cellular wear and damage, the scientific-medical community has now embraced a once reviled theory. Using the antioxidant concept as a spearhead in proposed mechanisms for staving off so-called "free-radical" reactions, the rush is on to mine claims for the latest and most effective combination of free-radical scavenging compounds.

Without disputing or supporting the concept that aggressive oxygen species are the new culprit for most illnesses (superseding the microbial causative drama of the 19th century), we must acknowledge that such "radicals" have definitively been shown to damage all biochemical components such as DNA/ RNA; carbohydrates; unsaturated lipids; proteins; and micronutrients such as Carotenoids (alpha and beta carotene, lycopene), vitamins A, B_6, $B_{]2}$, and folate.

Defense strategies against such aggressive radical species include enzymes, antioxidants that occur naturally in the body (glutathione, uric acid, ubiquinol-10, and others) and radical scavenging nutrients, such as vitamins A, C, and E, and Carotenoids.

This paper will present a brief discussion of some well- and little-known phytopharma-ceuticals (i.e., herbs) that may add to the optimization of antioxidant status and therefore offer added preventive values for overall health.

It is important to state at the outset that antioxidants vary widely in their free-radical quenching effects and each may be individually attracted to specific cell sites. Further evidence of the specialized nature of the Carotenoids is demonstrated by the appearance of two Carotenoids in the macula region of the retina where beta-carotene is totally absent (Handelman, 1988). These two retina specific Carotenoids are *zeaxanthin* (a yellow pigment found in corn seeds, sweet red pepper, bitter orange peel, and in green algae) and *lutein* (found in the green leaves of all higher plants, also in algae, in citrus rind, in apricot, peach, plum, apple, and cranberry).

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How the Antioxidants Complement Rather Than Compete with One Another

As scientific inquiry proceeds we will likely learn of other site-specific attractions and functions of the Carotenoids. This will help us understand why we need not reject one class of antioxidant compounds to accept another. They each may accumulate in specialized cells and tissues, with some overlapping protection, but a variety of them is required to give us the best protection possible.

Interestingly, just as foods work together so do the antioxidants. Professor Lester Packer of the University of California at Berkeley is one of the world's pre-eminent antioxidant researchers. He and coworkers recently demonstrated how Carotenoids interact with vitamins E and C. Beta-carotene, it was shown, can protect LDL against oxidative damage even when vitamin E levels are low (Packer, 1993).

In this regard, antioxidants act synergis-tically, offering a rainbow of protection rather than a single band of the spectrum. Moreover, plant antioxidants such as phenols and bioflavonoids may potentiate vitamin antioxidants. For example, rutin, a bioflavonoid, potentiates vitamins C and E when taken in combination, yielding a *more potent* radical scavenging action. That is, adding a *third* antioxidant (rutin) creates a combined effect greater than the sum of the parts (Negre-Salvayre, 1991).

Some Major Antioxidant Herbs

Antioxidant factors found in plants are based upon constituent nutrients with demonstrated radical-scavenging capacities as well as upon non-vitamin or mineral substances. So, in addition to alpha-tocopherol, ascorbate, Carotenoids, and zinc, plant-based medicines may contain flavonoids, polyphenols, and flavoproteins. Further, some plants or specific

combinations of herbs in formulations may act as antioxidants by exerting superoxide scavenging activity (Pronai, 1991) or by increasing superoxide dismutase (SOD) activity in various tissue sites (Liu, 1990). Each of these groups of compounds are substances that may exert that cell-protective action by more than one biochemical mechanism (Dragsted, 1993).

In addition to antioxidant properties per *se*, cancer-protective factors are found in many plants, including some fruits, vegetables, and commonly used spices and herbs.

They can be divided into several different groups, based on their chemical structure, e.g., polyphenols, thiols, Carotenoids and retinoids, carbohydrates, trace metals, terpenes, tocopherols and degradation products of glucosinolates (i.e., isothiocyanates, indoles and dithiothiols) and others. Among each of these groups of compounds are substances, which may exert their cancer-protective action by more than one biochemical mechanism. The biochemical processes of carcinogenesis are still not known in detail and probably varies with the cancer disease in question. Accordingly, the description of the biochemical backgrounds for the actions of cancer-protective factors must be based on a simplified model of the process of carcinogenesis. The model used in this presentation is a generalized initiation-promotion-conversion model, in which initiators are thought to be directly or indirectly genotoxic, promoters are visualized as substances capable of inferring a growth advantage on initiated cells and converters are believed to be genotoxic, e.g. mutagens, clastogens, recombinogens or the like. Experimental evidence for the mechanisms of action of cancer-protective agents in fruits and vegetables that protect against initiation include the scavenging effects of polyphenols on activated mutagens and carcinogens, the quenching of singlet oxygen and radicals by Carotenoids, the antioxidant effects of many compounds including ascorbic acid and polyphenols, the inhibition of activating enzymes by some flavonols and tannins, the induction of oxidation and of conjugation (protective) enzymes by indoles, isothiocyanates and dithiothiones, the shielding of sensitive structures by some polyphenols and the stimulation of DNA-repair exerted by sulphur-containing compounds. Mechanisms at the biochemical level in antipromotion include the antioxidant effects of Carotenoids and the membrane stabilizing effects reported with polyphenols, the inhibition of proteases caused by compounds from soybeans, the stimulation of immune responses seen with Carotenoids and ascorbic acid, and the inhibition of ornithine decarboxylase by polyphenols and Carotenoids. A few inhibitors of conversion have been identified experimentally, and it can be argued on a theoretical basis, that many inhibitors of initiation should also be efficient against conversion. The mechanisms of anticarcinogenic substances in fruits and vegetables are discussed in the light of cancer prevention and inhibition (Dragsted, 1993).

Plant antioxidants are more than mere supporting players in the battle against cellular damage and disease. As folklore has long instructed, certain plants play specific roles in disease prevention and treatment. A well known hepatic antioxidant, *silymarin*, from the milk thistle *(Silybum marianum)*, for example, inhibits liver damage by scavenging free radicals among other mechanisms (Hikino & Kiso, 1988). This powerful antioxidant protects the liver against alcohol and pharmaceutical injury and even poisoning from extremely toxic compounds found in the Deathcap mushroom, *Amanita phalloides*. Interestingly, the *Amanita* toxins are *not* thought to be neutralized via any free-radical scavenging effects. Rather, it is theorized that silymarin competes with the *Amanita* toxins for the identical receptor on cell membranes (Hikino & Kiso, 1988). Here again, contemporary laboratory science confirms and elucidates the liver-protecting attributes of milk thistle, well known to folk medicine for 2,000 years.

GINGER

Scientific Name: *Zingiber officinale* **Parts Used:** Rhizome

Dosage: 1 ounce of rhizome to 1 pint of water. Boil the water separately, then pour over the plant material and steep for 5 to 20 minutes, depending on the desired effect. Drink hot or warm, 1 to 2 cups per day.

Recent Scientific Findings

Currently, Ginger has received new attention as an aid to prevent nausea from motion

sickness. Ginger tea has long been an American herbal remedy for coughs and asthma, related to allergy or inflammation; the creation of the soft drink ginger ale, sprang from the common folkloric usage of this herb, and still today remains a popular beverage for the relief of stomach upset. Externally, Ginger is a rubefacient, and has been credited in this connection with relieving headache and toothache.

The mechanism by which Ginger produces anti-inflammatory activity is that of the typical NSAID (non-steroidal anti-inflammatory drug). This common spice is a more biologically active prostaglandin inhibitor (via cyclo-oxygenase inhibition) than onion and Garlic. By slowing associated biochemical pathways an inflammatory reaction is curtailed. In one study, Danish women between the ages of 25 to 65 years, consumed either 70 grams raw onion or 5 grams raw ginger daily for a period of one week. The author measured thromboxane production and discovered that ginger, more clearly than onion, reduced thromboxane production by almost 60%. This confirms the Ayurvedic "prescription" for this common spice and its anti-aggregatory effects.

By reducing blood platelet "clumping," Ginger, Onion and Garlic may reduce our risk of heart attack or stroke. In a series of experiments with rats, scientists from Japan discovered that extracts of Ginger inhibited gastric lesions by up to 97%. The authors conclude that the folkloric usage of Ginger in stomachic preparations were effective owing to the constituents zingiberene, the main terpenoid and 6-gingerol, the pungent principle.

In an earlier look at how some of the active components of Ginger (and onion) act inside our cells, it was found that the oils of these herbs inhibit the fatty acid oxygenases from platelets, thus decreasing the clumping of these blood cell components.

A 1991 double-blind, randomized crossover trial involved thirty women suffering from hyperemesis gravidarum. Ginger was alternated with a placebo. Seventy percent of the women confirmed they subjectively preferred the period in which they took the Ginger. More objective assessment verified the subjective reactions, as significantly greater relief was found after the use of the Ginger. In a series of experiments with rats, scientists from Japan discovered that extracts of ginger inhibited gastric lesions by up to 97%. The authors concluded that the folkloric usage of Ginger in stomachic preparations was effective due to the constituents zingiberene, the main terpenoid, and 6-gingerol, the pungent principle.

GINKGO

Scientific Name: *Ginkgo biloba* **Parts Used:** Leaves

Dosage: Approximately 1/2 ounce of leaves to 1 pint of water. Boil water separately and pour over the plant material and steep for 5 to 20 minutes, depending on the desired effect. Drink hot or warm, 1 to 2 cups per day, at bedtime and upon wakening.

Recent Scientific Findings

The free-radical scavenging properties of *Ginkgo biloba* extract have been demonstrated as being at least as effective as uric acid, a potent, naturally occurring antioxidant. The plant extract has the further capacity to inhibit the formation of radicals that uric acid does not effect (Pincemail, 1988, in E.W. Funfgeld, 1988),

Ginkgo research has proceeded in many other areas. The most interesting and important relate to vascular diseases, brain function, impotency, dopamine synthesis, inflammation, and asthma.

An extract from Ginkgo leaves is marketed as Tebonin. Clinical research has shown that Tebonin achieves vasodilation and improved blood flow, especially in deeper-seated medium and small arteries. The flow rate in capillary vessels and end arteries is increased. In elderly subjects, Tebonin alleviated dizziness and loss of memory. Ginkgo has proven to be a particularly valuable geriatric drug.

Mild memory loss continues to be one of humankind's tragedies and one of medicine's greatest challenges. Interestingly, ginkgolides and a bilobalide possess a structure that is unique in the vegetable kingdom. A double-blind, placebo controlled study shows yet another powerful benefit from this ancient Chinese herbal medicine.

Thirty-one patients showing mild to moderate memory impairment were followed for six months while taking a standardized extract of *Ginkgo biloba* extract (GBE). (All were over the age of 50.) The extract con-

tained 24% flavonoid glycosides and 6% terpenes. The results show that GBE "has a beneficial effect on mental efficiency in elderly patients showing mild to moderate memory impairment of organic origin."

Sixty patients suffering from arterial erectile dysfunction received a daily treatment with 60 mg. of an extract of *Ginkgo biloba.* After 6 months, 50% of the subjects once again were able to achieve penile erections. Upwards of 45% of the remaining subjects showed some improvement.

Another study found that *Ginkgo biloba* extract (GBE) might prevent radical mediated human kidney and liver damage caused by Cyclosporin A, an immunosuppressive drug used in transplants. This herbal product was found to as be as effective as vitamin E and glutathione in protecting against such damage, adding to our understanding of the value of incorporating nutritional and herbal supplements in modern medicine. The protective effects of GBE were diminished in the presence of iron, owing to the limits imposed by this powerful oxidant.

Ginkgo's effect as an anti-allergic, anti-asthmatic agent has also been demonstrated. The platelet activating factor (PAF) has been implicated in pathophysiological states including allergic inflammation, anaphylactic shock, and asthma. One study concluded that Gingkolide B is the most active PAF antagonist found in this class of gingkolides. It appears that Ginkgo relieves broncho-constriction due to its PAF antagonist activity. A randomized, double-blind, placebo-controlled crossover study in 8 atopic asthmatic patients showed that Ginkgo achieved significant inhibition of the bronchial allergen challenge compared to placebo.

LICORICE

Scientific Name: *Glycyrrhiza glabra*
Parts Used: Root
Dosage: 1 teaspoon of the root or subterranean stem, boiled in a covered container with 1 -1 /2 pints of water for about 1 /2 hour, at a slow boil. Allow liquid to cool slowly in the *closed* container. Drink cold, 1 swallow or 1 tablespoon at a time, 1 to 2 cups per day.

Recent Scientific Findings

The multitude of pharmacological effects of Licorice rhizomes and roots are practically all attributed to the presence of a triterpene saponin called *glycyrrhizin,* which is about fifty times sweeter than sugar, and has a powerful cortisone-like effect. Several cases have been reported in medical literature in which humans ingesting 6-8 ounces (a very large amount) of licorice candy daily for a period of several weeks are "poisoned" due to the cortisone- like effects of licorice extract in the candy. Proper treatment restores patients to normal. The above amount of this compound is very large compared with the relatively small amount found in supplements.

In addition, Licorice rhizomes and roots have a high mucilage content. When mixed with water, the resulting preparation has a very pleasant odor and taste, and acts as an effective demulcent on irritated mucous membranes, such as accompany a sore throat. One study found that glycyrrhizin was as effective a cough suppressant as codeine. A 1991 experiment with mice found that glycyrrhizin protected against skin cancer. The authors speculated that it might prove useful in protecting against some forms of human cancer as well.

It is not surprising that Licorice and glycyrrhizin have such wide applications. It should be noted that this chemical constitutes only 7 to 10% of the total root (on a dry weight basis). Glycyrrhetic acid (G.A.) is obtained when acid hydrolysis is applied to the main component of licorice. This compound is extensively used in Europe for its anti-inflammatory properties, especially in Addison's disease and peptic ulcer. Some European researchers concluded that G.A. may be preferred to cortisone because it is safer, especially when prolonged treatment is required.

A recent study (1990) demonstrated that G.A. exerts its activity *not* as a *direct effect* but by reducing the conversion of Cortisol to cortisone, its biologically inactive product. The authors concluded that hydrocortisone, a "weak anti-inflammatory agent," can be greatly potentiated (i.e., made more powerful) by the addition of 2% GA. To lessen the toxic effects of corticosteroids, the authors suggested that patients use hydrocortisone *together* with GA. Here is another example of the growing marriage between prescription pharmaceuticals and herbal preparations.

Glycyrrhizin has also exhibited anti-viral activity. A 1979 study demonstrated that

glycyrrhizin inhibited Epstein-Barr Virus (EBV), cytomegalovirus (CMV), and hepatitis B virus. In Japan, glycyrrhizin has long been successfully used to treat chronic hepatitis B. This has led to speculation that glycyrrhizin holds promise in the treatment of HIV.

A note of caution: Side effects from the ingestion of large amounts of Licorice have been reported. Glycyrrhizin in very large amounts can promote hypokalemia and hypertension. For these reasons people with heart problems and high blood pressure are advised to avoid consuming large quantities of Licorice or its components.

SCHIZANDRA
Scientific Name: *Schizandra chinensis*
Parts Used: Berry
Dosage: 1 to 2 grams per day in tablet or capsule form.

Recent Scientific Findings

This interesting plant has many biological activities including: anti- bacterial (equivocal results), sympatho-mimetic (stimulant), resistance stimulation, liver-protective, anti-toxic, anti-allergenic, antidepressant, glycogene-sis stimulant, and antioxidant effects.

In addition, and perhaps most interesting from the point of view of it being a folkloric "tonic," this herb protected against the narcotic and sedative effects of alcohol (ETOH) and pentobarbital (PB) and exposure to the highly toxic ether, in mice. As a result of these data, the authors concluded that Schizandra may be a useful clinical agent for reversal of CNS depression.

They based this antidepressant activity on the reasoning that depression may be due, in part, to adrenergic exhaustion following severe psychogenic stress. It is known that MAO (monoamine oxidase) inhibitors, as well as other selected compounds that increase noradrenergic neurotransmission within the CNS (such as imipramine), have proven benefit in depression.

This herb is also being promoted for its stimulating effect on the nervous system without being excitatory like amphetamine or caffeine. There are some proponents who claim "the higher the degree of exhaustion, the greater is the stimulating effect."

A very interesting study on performance in race horses tends to confirm the folkloric
claims. Polo horses given the berry extract of this species showed a lower increase in heart rate (during exercise), a quicker recovery of respiratory function, a reduction of plasma lactate, and improved performance.

A 1990 study reported that a lignan component of Schizandra fruit *suppresses* the arachidonic (AA) cascade in macrophages. The AA cascade pushes the production of leukotrienes, which may play a role in inflammatory diseases. By inhibiting the arachidonic acid cascade, Schizandra both protects the liver and stimulates the immune system—two key roles of an ideal adaptogen.

An interesting non-Western 1991 study tested the "tonifying and invigorating yang" powers of Schizandra and other herbs in mice. The researchers measured the animals body weight, thymus weight, leukocyte count, and other parameters of "yang." They observed a direct correlation between the amount of herb ingested (as hot water extracts) and improved immunocompetence. They also noticed a distinct anti-fatigue quality, which was measured by reduced excitability of the parasympathetic nervous system. No toxicity was reported. The antioxidant activity of dibenzo-cyclo-octene lignans isolated from species found in the Schizandra family were reported in a 1992 study (Lu, 1992).
It appears that this creeping herb from the Far East has valid claims to the title of a "new" anti-fatigue agent which possibly helps to accelerate restorative processes within the human body. Traditional Chinese Medicine continues to offer new candidates to the annals of World Medicine. As we in the West are slowly learning, "traditional" or "folk" medicine really is the medicine of the people. *Caution:* While Schizandra is a very safe herb with much historical usage one supplier of a standardized extract recommends that this herb be avoided by: epileptics, those with high intracranial pressure or severe hypertension, and those with "high acidity."

TURMERIC
Scientific Name: *Curcuma longa*
Parts Used: Rhizome
Dosage: 1 to 2 grams per day in food or take capsules/tablets.

Recent Scientific Findings

Currently, Turmeric is used in India to treat anorexia, liver disorders, cough, diabetic

wounds, rheumatism, and sinusitis. In one study Turmeric extract was tested for its anticarcinogenic and antimutagenic properties. Laboratory (non- human) experiments it was found that this ancient spice reduced both the number of tumors in mice and the mutagenicity of benzo(a)pyrene (BP) and two other potent mutagens, NPD and DMBA.

Preventing cancer now receives the attention it has long deserved. Numerous biochemical and epidemiological studies have demonstrated diet's role in modulating the development of cancer. Laboratory experiments have established that the active principle of Turmeric (curcumin) is a potent antimutagenic agent.

For those interested in *how* curcumin may act to prevent cancer we turn again to the by-now all pervasive theory of free-radical inac-tivation. The test carcinogens BP and DMBA are metabolically activated to proximate mutagenic/carcinogenic epoxides, which then bind to macromolecules. One study's authors concluded that since curcumin is a potent antioxidant, it may scavenge the epoxides and prevent binding to macromolecules. In other words, this spice's cell-protective properties are similar to nutrient antioxidants, vitamins C and E, which inhibit free radical reactions.

This type of herb is known as a non-steroidal anti-inflammatory (NSAID). Curcumin inhibits cycloxygenase and lipoxygenase enzymes. Curcumin has three main mechanisms of action: 1) antioxidant activity; 2) lipoxygenase inhibitor; and 3) cycloxygenase inhibition. By inhibiting the associated biochemical pathways, inflammation is curtailed. Modern science thus confirms what traditional healers have known for centuries. Namely, that the fresh juice from the rhizome will reduce swelling in recent bruises, wounds and insect bites; and that the dried powdered root kills parasites, relieves head colds and arthritic aches. (Interestingly, this spice has sometimes been used to adulterate ginger.)

A 1991 pharmacological review confirmed many of Turmeric's folkloric effects, including wound healing, gastric mucosa protection, antispasmodic activity, reduction of intestinal gas formation, protection of liver cells, increasing bile production, diminishing platelet aggregation (i.e. blood clumping), lowering serum cholesterol (at very high doses), antibacterial properties, antifungal properties, and potential antitumor activity. While most of the above effects were demonstrated with intravenous extracts in animals, they do parallel folkloric claims in humans and are not to be dismissed as "experimental" or "trivial." Turmeric's benefits for arthritis treatment have been demonstrated in human clinical trials. A herbal formula of Turmeric, Ashwagandha, and Boswellin was evaluated in a randomized, double-blind, placebo-controlled study. After a one-month evaluation period 12 patients with osteoarthritis were given the herbal formula or placebo for three months. The patients were evaluated every two weeks. After a 15 day wash-out period, the treatment was reversed with the placebo patients receiving the drug and vice versa. Again results were evaluated over a three month period. The patients treated with the herbal formula showed a significant drop in severity of pain and disability score.

QUERCITIN

(A natural flavone derivative widely distributed in the plant world.)

Quercitin is the commonest flavonoid in higher plants. It is usually present as a glycoside (example: rutin, isoquercitrin, quercitrin, hyperin, and quercimeritrin), but is also isolated in the free state from the families *Compositae, Passiflorae, Rhamna-ceae,* and *Solanaceae* (where it mainly occurs on leaf surfaces, in fruits, and in bud extracts) (Harborne & Baxter, 1993).

Quercitin is a powerful antioxidant that decreases the concentration of superoxide anions in enzymic and nonenzymic systems. A recent animal study demonstrated antiulcer and gastroprotective effects, especially against ethanol injury. The cyto-protective activity was effected through several interacting pathways involving stimulation of prostaglandin and inhibition of leukotriene production and through Quercitin's antioxidant properties. Pretreating the experimental animals with 200 mg/kg (a very high dose!) 120 minutes before administering ethanol was found to be the most effective dosage in prevention necrosis (Alarcon de la Lastra, 1994).

Commonly Known Antioxidant Plants

Hundreds of plants have been studied and found to possess antioxidant properties. The following list consists of the English names of

some you may be familiar with.

plantain	cumin	American
leek	turmeric	ginseng
onion	lemongrass	opium poppy
garlic	Siberian	beans (green,
angelica	ginseng	kidney,
celery	eucalyptus	pinto, etc.)
peanut	licorice	allspice
bearberry	ivy	anise
areca nut	elecampane	betel leaf
horseradish	nettle	black pepper
tarragon	bay laurel,	evergreen
mugwort	avender	oak
oats	motherwort	rosemary
borage	hoarhound	blackberry
frankincense	balm	raspberry
tea (black	mint	sage
and green)	pennyroyal	schizandra
bell peppers	bergamot	saw palmetto
(green, red,	mace	sesame
cayenne,	nutmeg	spinach
paprika,	myrtle	betony
pimento,	catnip	boneset
chile, etc.)	basil	cloves
papaya	olive	cocoa
cinnamon	marjoram	thyme
citrus	oregano	cranberry
coriander	rice	ginger
dogwood	ginseng	

General References

1. Dragsted, L.O., Strube, M., & Larsen, J.C. Cancer-protective factors in fruits and vegetables biochemical and biological background. Pharmacology and Toxicology, 72(1): 116-135, 1993.
2. Handelman, G.J., Dratz, E.A., Reay, C.C., & van Kuijk, F.J. Invest. Ophthalmology Vis. Science, 29:850-855, 1988.
3. Harborne, J.B. & Baxter H. (Eds.). Phyto-chemical dictionary: A handbook of bioactive compounds from plants. Washington, DC: Taylor & Francis, 1993.
4. Liu. j., Edamatsu, R., Kabuto, H., & Mori, A. Antioxidant action of guilingji in the brain of rats with FeC 13-induced epilesy. Free Radical Biology and Medicine, 9(5):451-454. 1990.
5. Negre-Salvayre, A., Affany, A.. Hariton. C. & Salvayre, R. Additional antilipoperoxidant activities of alpha-tocopherol and ascorbic acid on membrane-like systems are potentiated by rutin. Pharmacology, 42:262-272, 1991.
6. Niwa. Y. Miyachi, Y, Ishimoto, K... & Kanoh T. Why are natural plant medicinal products effective in some patients and not in others with the same disease? Planta Medica, 57(4):299-304,1991.
7. Packer, L. Interaction of carotenoids with vitamins E and C. New York Academy of Sciences Conference, February 6-9, 1993.
8. Pronai,L. & Arimori, S. BG-104 enhances the decreased plasma superoxide scavenging activity in patients with Behcet's disease, Sjogren's syndrome or hematological malignancy. Biotherapy, 3(4):365-371, 1991.

Ginger

1. Fischer-Rasmussen, W., Kjaer, S.K., Dahl, C, & Asping, U. Ginger treatment of hyperemesis gravidarum. European Journal of Obstetrics, Gynecology, and Reproductive Biology, 38(1): 19-24, 1991.
2. Srivastiva. K.C. Effect of onion and ginger consumption on platelet thromboxane production in humans. Prostaglandins, Leukotrienes and Essential Fatty Acids, 35:183-185, 1989.
3. Vane, J.R. Nature, 231:232, 1971.
4. Yamahara, J., et al., The anti-ulcer effect in rats of ginger constituents. Journal of Ethnopharmacology. 23:299-304, 1988.

Ginkgo

1. Barth, S.A., Inselmann, G., Engemann, R., & Heidermann, H.T. Influences of Ginkgo biloba on cyclosporin A induced lipid peroxidation in human liver microsomes in comparison to vitamin E, glutathione and N-acetylcysteine.
2. Braquet, P. & Hosford, D. Ethnopharmacology and the development of natural PAF antagonists a therapeutic agents. Journal of Ethnopharmacology, 32(1-3): 135-139, 1991.
3. Chung, K.F., et al. Effect of a ginkgolide mixture (BN 52063) in antagonizing skin and platelet responses to platelet activating factor in man. *The Lancet,* January 31, 1987.
4. Funfgeld, E.W. (Ed.). *Rokan (Ginkgo biloba), recent results in pharmacology, and clinic.* Berlin: Springer-Verlag, 1988. '
5. Massoni, G.. Piovella, C, & Fratti, L. Effects microcirculatoires de la *Ginkgo biloba* chez les personnes agees. *Gioren. Geront.,* 20:444, 1972.
6. Peter, H. Vasoactivity of *Ginkgo biloba* preparation. 4th Conf. Hung. Ther. Invert. Pharmacol. Soc. Pharmacol. Hung. (Edited by Dumbovitch, B.). 177, 1968.
7. Pincemail, J., & Deby. C. The antiradical properties of *Ginkgo biloba* extract. In E.W. Funfgeld (Ed.), *Rokan (Ginkgo biloba), recent results in pharmacology, and clinic.* Berlin: Springer-Verlag, 1988, pp. 71-82.
8. Rai, G.S., Shovlin, C, & Wesnes, K.A. A double-blind, placebo controlled study of *Ginkgo biloba* extract ("tanakan") in elderly

outpatients with mild to moderate memory impairment. *Current Medical Research and Opinion, 12(6):* 350-355, 1991.
9. Sikora, R., et al. *Ginkgo biloba* extract in the therapy of erectile dysfunction. *Journal of Urology, 141:188A,* 1989.
10. Warot, D., et al. Comparative effects of *Ginkgo biloba* extracts on psychomotor performances and memory in healthy subjects. *Therapie,* 46(1): 33-36, 1991.

Milk Thistle

1. Campos, R., Garrido, A., Guerra, R. & Valenzuela, A. Silybin dihemisuccinate protects against glutathione depletion and lipid peroxidation induced by acetaminophen on rat liver. *Planta Medic, 55:* 417-419, 1989.
2. Chander, R., Kapoor, N.K., & Dhawan, B.N. Hepatoprotective activity of silymarin against hepatic damage in Mastomys natalensis infected with Plasmodium berghei. *Indian Journal of Medical Research, 90: All-All,* 1989.
3. Ferenci, P, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *Journal of Hepatology,* 9(1): 105-113, 1989.
4. Hikino H. & Kiso, Y. Natural products for liver disease. In H. Wagner, H. Hikino, & N.R. Farsworth (Eds.), *Economic and medicinal plant research,* Vol. 2, New York: Academic Press, 1988, pp. 39-72.
5. Kalmar, L., et al. Silibinin (Legalon-70) enhances the motility of human neutrophila immobilized by formyl-tripeptide, calcium ionophore, lymphokine and by normal human serum. *Agents and Actions,* 29(3-4): 239-246, 1990.
6. Mereish, K.A., Bunner, D.L., Regland, D.R., & Creasia, D. A. Protection against microcystin-LR-induced hepatotoxicity by Silymarin: biochemistry, histopathology, and lethality. *Pharmaceutical Research, 8(2):* 273-277, 1991.
7. Valenzuela, A., Aspillaga, M., Vial, S., & Guerra, R. Selectivity of silymarin on the increase of the glutathione content in different tissues of the rat. *Planta Medica, 55(5):* 420-422, 1989.

Licorice

1. Abe, N., Ebina, T., & Ishida, N. Interferon induction by glycyrrhizin and glycyrrhetinic acid in mice. *Microbiology and Immunology, 26:* 535, 1982.
2. Agarwal, R., Wang, Z. Y., & Mukhtar, H. Inhibition of mouse skin tumor-initiating activity of DMBA by chronic oral feeding of glycyrrhizin in drinking water. *Nutrition and Cancer, 15(3-4):* 187-193, 1991.
3. Baba, M. & Shigeta, S. Antiviral activity of glycyrrhizin against varicella-zoster virus in vitro. *Antiviral Research,* 7: 99-107, 1987.
4. Borst, J.G.G., ten Holt, S.P., de Vries, L.A., & Molhuysen, J.A. Synergistic action of liquorice and cortisone in Addison's and Simmonds's disease. *Lancet, 1:* 657-668, 1953.
5. Baker, M.E. & Fanestil, D.D. Licorice, computer-based analyses of dehydrogenase sequences, and the regulation of steroid and prostaglandin action. *Molecular and Cellular Endocrinology, 78(1-2):* C99-102, 1991.
6. Baltina, L.A., et al. Synthesis and antiphlogistic activity of protected glycopeptides of glycyrrhizic acid. *Pharm. Chem. J.,* 226:460-462, 1989.
7. Finney, R.S.H., Somers, C.F., & Wilkinson, J.H. Pharmacological properties of glycyrrhetinic acid—a new anti-inflammatory drug. *J. Pharm. Pharmacol., 10:*687, 1958.
8. Fujisawa, K., Watanabe, Y., & Kimura, K. Therapeutic approach to chronic active hepatitis with glycyrrhizin. *Asian Medical Journal, 23:* 745-756, 1981.
9. Fujita, H., Sakurai, T., Yoshida, M., & Toyoshima, S. Anti-inflammatory effects of glycyrrhizinic acid. *Oyo Yakuri,* 79:481-484, 1980.
10. Gijon, J. R. & Murcia, C. R. Estudio farmacologico comparativo de la actividad anti-inflammatoria local del acido glicirretinico con la de la cortisona. *An. Real Acad. Farm. ,26:5,* 1960.
11. Hatano, T., et al. Phenolic constituents of licorice. IV. Correlation of phenolic constituents and licorice specimens from various sources and inhibitory effects of licorice extracts on xanthine oxidase and monoamine oxidase. *Journal of the Pharmaceutical Society of Japan, 111(6):* 311-321, 1991.
12. Kiso, Y., Tohkin, M,, & Hikino, H. Assay method for antihepatotoxic activity using carbon tetrachloride induced cytotoxicity in primary cultured hepatocytes. *Planta Medica, 49:* 222-225, 1983.
13. Kitagawa, K., Nishino, H., & Iwashima, A. Inhibition of the specific binding of 12-0-tetradecacanoylphorbol-13-acetate to mouse epidermal membrane fractions by glycyrrhetic acid. *Oncology, 43:* 127-130, 1986.
14. Kraus, S.D. The anti-oestrogenic action of glycyrrhetic acid. *Experimental Medicine and Surgery, 27:* 411-420, 1969.
15. Segal, R., Pisanty, S., Wormser, R., Azaz, E.. & Sela, M.N. Anticarcinogenic activity of liquorice and glycyrrhizin I: Inhibition of in vitro plaque formation by *Streptococcus mutatis. Journal of Pharmaceutical Sciences, 74:* 79-81, 1985.'
16. Sugishita, E., Amagaya, S., & Ogihara, Y. Studies on the combination of glycyrrhizae radix in shakuyakukanzo-to. *J. Pharmacobio*

Dyn, 7: 427-435, 1984.
17.Tanaka, S., Kuwai, Y., & Tabata, M. Isolation of monoamine oxidase inhibitors from *Glycyrrhiza uralensis* roots and the structure-activity relationship. *Planta Medica:* 5-7, 1987.
18.Teelucksingh, S., et al. Potentiation of hydrocortisone activity in skin by Glycyr-rhetinic acid. *The Lancet, 335:* 1060-1063, 1990.

Quercitin

1. Alarcon de la Lastra, C, martin, M.J., & Motilva, V. Antiulcer and gastroprotective effects of quercetin: A Gross and Histologic Study. *Pharmacology, 48:56-62,* 1994.

Schizandra

1. Ahumada, F., et al. Studies on the effect of *Schizandra chinensis* extract on horses submitted to exercise and maximum effort. *Phytotherapy Research,* 3(5): 175-179, 1989.
2. Chang, I. H., Kim. J. H., & Han, D. S. Toxico-logical evaluation of medicinal plants used for herbal drugs (4). Acute toxicity and antitumor activities. *Korean J. Pharmacog, 13(2):62-69,* 1983.
3. Chen, Y. Y., Shu, Z., & Li, L. N. Studies of *Fructus shizanorae.* IV. Isolation and determination of the active compounds (in lowering high SGPT levels) of *Schizandra chinensis. Chung-Kuo K. O. Hsueh, 19:216-,* 1976.
4. Hancke, J. L., Wikman, G., & Hernandez, D. E. Antidepressant activity of selected natural products. *Planta Med.,* 7986(6):542-543, 1986.
5. Hendrich, S. & Bjeldanes, L. F. Effects of dietary cabbage, brussels sprouts, illicium verum, *Schizandra chinensis* and alfalfa on the benzopyrene metabolic system in mouse liver. *Food Chem. Toxicol,* 21(4):479-486, 1983.
6. Hendrich, S. & Bjeldanes, L. F. Effects of dietary *Schizandra chinensis,* brussels sprouts and illicium verum extracts on carcinogen metabolism systems in mouse liver. *Food Chem. Toxicol., 24(9):903-9\2,* 1989.
7. Hernandez, O. E., Hancke, J. L., & Wikman, G. Evaluation of the anti-ulcer and antisecretory activity of extracts of aralia elata root and *Schizandra chinensis* fruit in the rat. *J. Ethnopharmacol.,* 25(1):109-114, 1988.
8. Hikino, H., Kiso, Y., Taguchi, H., & Ikeya, Y. Antihepatotoxic actions of lignoids from *Schizandra chinensis* fruits. *Planta Med.,* 50(3):213-218, 1984.
9. Kim, M. S., Lee, M. G.. Lee, J. H., Byun, S. J., & Kim, Y. C. Immunopotentiating activity of water extracts of some crude drugs. *Korean J. Pharmacolog. 19(3):* 193-200, 1988.
10.Koda, A.. Nishiyori, T., Nagai. H.. Matsuura, N., & Tsuchiya, H. Anti-allergic actions of crude drugs and blended Chinese traditional medicines. Effects on Type I and Type IV allergic reactions. *Nippon Yakurigaku Zasshi,* 80:31-41, 1982.
11. Liu, G. T., Wang, G. F., Wei, H. L., Bao, T. T., & Song, Z. Y. A comparison of the protective actions of biphenyl dimethyl-dicarboxylate trans-stilbene, alcoholic extracts of fructus schizanorae and ganoderma against experimental liver injury in mice. *Yag Hsueh Hsueh Pao,* 74:598-604, 1979.
12.Liu, G. T. & Wei, H. L. Protection by fructus schizanorae against acetaminophen hepatotoxi-city in mice. *Yao Hsueh Hsueh Pao,* 22(9):650-654, 1987.
13.Lu, H. & Liu, G. T. Antioxidant activity of dibenzocyclooctene lignans isolated from Schisandraceae. *Planta Medica,* 58(4):311-13, 1992.
14. Nishiyori, T., Matsuura, N., Nagai, H., & Koda, A. Anti-allergic action of Chinese drugs. *Jap. J. Pharmacol. Suppl.,* 31:115-, 1981.
15.Pao, T.T., Liu, K.I., Hsu, K.F., & Sung, C.Y. Studies on schizandra fruit. I. Its effect on increased SGPT levels in animals caused by hepatotoxic chemical agents. *Natl. Med. J. China, 54:215-,* 1974.
16. Shin, K. H. and Woo, W. S. A survey of the response of medicinal plants on drug metabolism. *Korean J. Pharmacog, 11:*109- 122,1980.
17.Shipochliev, T. & Ilieva, S. Pharmacologic study of Bulgarian *Schizandra chinensis. Farmatseyacsofia, 17*(3):56-, 1967.
l8.Volicer, L., Srahka, M., Jankumi, Capek, R., Smetana, R., & Ditteova, V. Some pharmacological effects of *Schizandra chinensis. Arch. Int. Pharmacodyn Ther., 163:249-,* 1966.
19.Wahlstrom, M. *Adaptogens,* Utgivare, Gote-borg, 1987.
20.Woo, W. S., Shin, K. H., Kih, I. C, & Lee, C. K. A survey of the response of Korean medicinal plants on drug metabolism. *Arch. Pharm. Res.,* 7:13-19, 1978.
21.Yin, H. Z. A report of 200 cases of neurosis treated by "shen wei he ji" (decoction of ginseng, schisandra fruit and others). *Zhejiang-Zhongyi Zazhi,* /7(9):411-, 1982.
22.Yu, J. & Chen, K. J. Clinical observations of AIDS treated with herbal formulas. *Int. J. Oriental Med., 14(A):* 189-193, 1989.

Turmeric

1. Amnion, H.P. & Wahl, M.A. Pharmacology of *Curcuma longa. Planta Medica.* 57(1): 1-7, 1991.
2. Chandra, D. & Gupta, S. S. Anti-inflammatory and anti-arthritic activity of volatile oil of *Curcuma longa* (haldi). *Indian J. Med. Res., 60.* 1972.
3. Donatus, I.A., Sardjoko. & Vermeulen, N.P. Cytotoxic and cytoprotective activities of

curcumin. Effects on paracetamol-induced cytotoxicity, lipid peroxidation and glutathione. *Biochemical Pharmacology,* 39(12): 1869-1875.

4. Kulkarni, R.R., et al. Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study. *Journal of Ethnopharmacology,* 33(1-2): 91-95, 1991.
5. Nagabhushan, M. & Bhide, S. V. Antimutagenicity and anticarcinogenicity of turmeric
6. *(Curcuma longa). Journal of Nutrition, Growth and Cancer,* 4:83-89, 1987. Polassa, K., Sesikaran, B., Krishna, T.P.. & Krishnasawan, K. Turmeric *(Curcuma longa)*-induced reduction in urinary mutagens. *Food and Chemical Toxicology,* 29(10): 699-706, 1991.
7. Rafatullah, S., et al. Evaluation of turmeric *(Curcuma longa)* for gastric and duodenal antiulcer activity in rats. *Journal of Ethnopharmacology,* 29(l):25-34, 1990.
8. Shalini, V.K. & Srinivas, L. Fuel smoke condensate induced DNA damage in human lymphocytes and protection by turmeric *(Curcuma longa). Molecular and Cellular Biology,* 95(1): 21-30, 1990.
9. T0nnesen, H. H. Studies on curcumin and curcuminoids. XIII. Catalytic effect of curcumin on the peroxidation of linoleic acid by 15-lipoxygenase. *International Journal of Pharmaceutics,* 50:67-69, 1989.