Willow Bark versus NSAID

Given the safety concerns over the COX-2 inhibitor drugs, it is interesting to find that standardized willow bark compared well with a conventional treatment for arthritis. In a randomized, double-blind, parallel group trial, the therapeutic efficacy and tolerance of standardized willow bark extract was compared with diclofenac sodium (a conventional NSAID, nonsteroidal anti-inflammatory drug) on patients with knee or hip arthritis.1 From the 79 patients enrolled, 59 completed the study. The patients were allocated randomly to one of three groups, receiving either 150 mg/day of diclofenac sodium or willow bark extract in two different doses (corresponding to 90 or 180mg/day salicin, respectively). During the study period lasting over 3 weeks, no additional analgesic NSAID medication was allowed. The outcome measures were evaluation of pain intensity by a visual analogue scale (VAS), evaluation of functional capacity, evaluation of pain intensity during different activities, impairment of daily activity, estimation whether pain was localized or diffuse, stage of edema and intensity and time of stiffness of the observed joint. The results indicated a good tolerance of the willow bark extract and demonstrated, statistically supported, its therapeutically relevant analgesic activity. In terms of pain intensity an effect comparable to diclofenac sodium was demonstrated.

Specific results for the trial included the following:

- Pain intensity (VAS) was reduced by 48.0% for the NSAID and by 39.5% and 31.3% for the two willow bark groups.
- Functional capacity was significantly improved (p < 0.05) in all groups (after NSAID treatment 100% of patients were grouped in the lowest ratings of 1 or 2 compared to 90% for the higher dose of willow bark).
- The percentage of symptom-free patients (with various daily activities) increased by similar amounts for all groups.

Commentary

Previous comparative trials on standardized willow bark in osteoarthritis used Vioxx as the reference treatment. This drug has now been recalled so it is useful to understand the value of willow bark treatment when compared to a conventional NSAID. The results of this trial are very promising. It not only demonstrates that willow bark is as effective as the NSAID, but also demonstrates that for osteoarthritis of the knee or hip the lower dose of willow bark (corresponding to 90 mg of salicin) can achieve good clinical results. This outcome is therefore useful in terms of reducing the cost to patients and improving their compliance.

It should also be noted that the dose of diclofenac sodium used in the trial was (at 150 mg) at the high end of the normal use of this drug for osteoarthritis.

Reference


Sage is Well Named

A team of British scientists has undertaken a series of investigations on plants which may improve memory and might therefore be relevant to the treatment of Alzheimer's disease (AD). One of the herbs they chose for investigation was sage, because of its traditional reputation as a tonic for the nervous system and memory. For example, the 16th century English herbalist John Gerard wrote about sage: "It is singularly good for the head and brain and quickeneth the nerves and memory." Culpeper stated: "It also heals the memory, warming and quenching the senses." From the writings of Hill in 1756 we find a possible reference to AD: "Sage will retard that rapid progress of decay that treads upon our heels so fast in latter years of life, will preserve faculty and memory more valuable to the rational mind than life itself."

The scientists' initial findings were that sage extracts possessed significant antioxidant, anti-inflammatory and cholinesterase-inhibiting activities.1 (Current conventional drugs for the treatment of AD are acetylcholinesterase inhibitors.) Much of this activity appeared to reside in the essential oil.1

The next step in their research was a clinical trial in healthy young volunteers.2 Two experiments utilized a placebo-controlled, double-blind, crossover methodology. In the first trial, 20 participants received 50, 100 and 150 μL of a standardized essential oil extract of Salvia lavandulaefolia and placebo. In the second trial, 24 participants received 25 and 50 μL of a standardized essential oil extract of S. lavandulaefolia and placebo. Doses were separated by a 7-day washout period. Assessment was undertaken using the Cognitive Drug Research computerised test battery prior to treatment and 1, 2.5, 4 and 6 hours thereafter. The primary outcome measures used were immediate and delayed word recall. The 50L dose of sage essential oil significantly improved immediate word recall in both studies. These results were the first systematic evidence that sage was capable of enhancing cognition in healthy young adults.

This was followed up by a pilot, open-label study in patients with AD.3 The trial, conducted in 1999 but only recently published, included 11 patients aged 76 to 95 years with mild to moderate AD who received capsules containing

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50 μL of S. lavandulaefolia essential oil (building from 1 to 3 capsules per day during the 6 weeks of the trial). No patient experienced any adverse physical or neurological effects during the study, except possibly an unrelated increase in blood pressure in two patients with a history of hypertension. Over the 6 weeks there were some promising indications of a therapeutic effect, specifically statistically significant differences for neuropsychiatric symptoms (reduced) and attention (improved). The authors now intend to confirm such benefits in a placebo-controlled trial.

Commentary

While the clinical trials used silymarin essential oil, it is conceivable that other components in sage might have therapeutic value in the context of AD. For example sage contains diterpenes which can interact with the GABA-benzodiazepine receptor and two diterpenes from dan shen (Salvia miltiorrhiza) have recently been shown to inhibit acetylcholinesterase. (Dan shen has been used in China for at least a thousand years to treat age-related cognitive degeneration.)

References

Does Milk Thistle Increase Hepatic Clearance of Drugs?

A common misconception concerning milk thistle (Silybum marianum) is that, since it is a liver herb, it is likely to increase the metabolism and clearance of many drugs due to enhanced hepatic detoxification. This is certainly fueled by in vitro studies showing this effect and an in vivo study in rats where high doses increased phase I hepatic metabolism. Oral administration of silymarin (100 mg/kg/day) to rats resulted in a significant increase in the activity of the mixed-function oxidation system (cytochrome P450; aminopyrine demethylation, p-nitroanisole demethylation). However, an experimentally-induced reduction in activities of the mixed-function oxidation system and glucose-6-phosphatase could not be prevented by pretreatment with silymarin.

In human volunteers, treatment with silymarin (210 mg/day for 28 days) had no influence on the metabolism of aminopyrine or phenylbutazone. Concentrated milk thistle (silymarin) extract at commonly administered doses did not interfere with indinavir therapy in patients with HIV. In other words, despite the findings of in vitro and in vivo studies, there was no evidence from clinical studies that milk thistle extract increases phase I/II liver metabolism. The reason behind this discrepancy is probably that normal clinical doses are not high enough to achieve the effects shown at the artificially high doses used in experimental models.

But a study has recently been published which, on the face of it, appears to challenge this position. A clinical study was undertaken in 12 healthy volunteers. At first, subjects received metronidazole (Flagyl; a substrate for cytochrome CYP3A4 and CYP2C9) alone at a dose of 400 mg every 8 h for 3 days. On day 4, blood and urine were collected at different time points and metronidazole levels were measured. After a washout period of one week silymarin was given at a daily dose of 140 mg for 9 days. From day 7 both silymarin (140 mg/day) and metronidazole (3 x 400 mg/day) were given till the 9th day. On day 10, blood and urine were collected as above and the levels of metronidazole and its metabolite were measured. Administration of silymarin increased the clearance of metronidazole and its major metabolite, hydroxy-metronidazole (HM) by 29.51% and 31.90% respectively, with a concomitant decrease in half-life and maximum concentration. Urinary excretions of acid-metronidazole, HM and metronidazole were all decreased.

Commentary

The key to understanding this recent study is the decreased levels of metronidazole and its metabolites in serum and urine. This suggests reduced absorption into the bloodstream via the induction of the drug transporting P-glycoprotein (P-gp), particularly at the level of the intestine. P-gp is a molecule that acts as a drug efflux pump at epithelial cells, especially the intestinal wall. In other words, induction of P-gp results in less absorption of any drug which is subject to its effects. So the most likely explanation of the findings is a reduced uptake due to P-gp induction, rather than increased clearance resulting from the induction of hepatic phase I cytochrome P450 enzymes such as CYP 3A4. Nonetheless, it is possible that silymarin could reduce the oral bioavailability of other drugs susceptible to P-gp, which include paclitaxel and digoxin.

References

Phytotherapy Review

Fragrance free?
I'm sorry, I thought you said fragrance please!
Phytotherapy Review

Ginkgo in Down Syndrome

The drug donepezil, which is used in Alzheimer’s disease (AD), recently achieved good results in four adults with Down Syndrome (DS). Similarities between the neurobiology of AD and DS have also been noted. This prompted two Italian scientists to investigate the value of the standardized extract of Ginkgo biloba in two young patients with DS.

The patients were not affected by cardiac or other malformations and did not have any other significant medical or psychiatric problems. The Ginkgo was given over their summer holidays.

The first case study was a boy aged 10 years 11 months who had an IQ of 40 (Wechsler Scale) and a Vineland score of 455 (a measure of mental impairment). He was given a daily dose of 80 mg of Ginkgo extract (corresponding to 4 g of leaf) for 11 weeks. Retesting the Vineland score showed an improvement to 497. The child also exhibited major improvements in personal autonomy and social behavior (he began to make new friends spontaneously).

The second patient (age 17 years 8 months) had an IQ of 44 and a Vineland score of 721. He received 120 mg of Ginkgo extract for 13 weeks. His Vineland score improved to 758 with improvements in memorizing, writing and self control.

Commentary

The results from these two case studies are very encouraging and hopefully will be confirmed by a properly designed clinical trial. They also suggest a potential role in Down Syndrome for other herbs which have been proven to enhance cognitive processes such as Bacopa, sage, Korean ginseng, Schisandra and Eleutherococcus.

Reference


Licorice and Testosterone Revisited

A previous article in this column (No. 205/206 August-September, 2000) examined an Italian pilot study that claimed to demonstrate licorice consumption lowered testosterone in men and asserted that licorice should be avoided by men with low libido. During the period of licorice administration (0.5 g of glycyrrhizin, around 10 g of licorice root) there was a substantial (around 35%) and significant drop in the men’s serum testosterone and a (smaller) significant increase in 17α-hydroxyprogesterone (p<0.001). Serum androstenedione was also raised, but the difference did not achieve statistical significance, possibly because of the small size of the experimental group.

The authors concluded their results demonstrated that licorice inhibits the enzymes involved in the production of testosterone, namely 17α-hydroxysteroid dehydrogenase and 17,20-lyase. They suggested that men with decreased libido or other sexual dysfunction, as well as those with hypertension, should be questioned about their intake of licorice confectionery.

Attempts at replicating the results of this trial were tried twice by a different research team using the same dosage of glycyrrhizin. An insignificant decrease in testosterone, as measured in saliva, was observed in both studies. The authors therefore disagreed with the above recommendation that men with low libido should avoid licorice consumption. Normal values of salivary testosterone during licorice ingestion were found, but as a result the trial methodology may not have been suitable accurately.

The Italian research group subsequently demonstrated that licorice decreased plasma testosterone in healthy women (22-26 years old) during the luteal phase of the menstrual cycle. The women received licorice containing 250 mg of glycyrrhizin daily for 2 cycles. At pretreatment the mean plasma testosterone was 27.8 ng/dL, which reduced to 19 ng/dL after the first cycle and 17.5 ng/dL after the second cycle, and returned to the pretreatment value one month after discontinuation of licorice. The reduction at both cycles was statistically significant (p<0.05).

This finding could certainly justify the current use of licorice in PCOS (polycystic ovarian syndrome).

Now, new findings have reopened the licorice and testosterone debate for men. In the new research, a team from Iran investigated the effect of licorice root extract in 20 healthy male volunteers. The group took 1.3 g of dried extract (containing around 400-500 mg glycyrrhizin) daily for 10 days. Blood samples were collected before the study and then for 20 days to measure testosterone levels.

A significant (p<0.05) decrease in serum testosterone levels of around 35% after 10 days of licorice consumption was observed. The effect on testosterone was believed to relate to interference of the active agent glycyrrhizin with 17α-hydroxysteroid dehydrogenase, the enzyme that catalyzes conversion of androstenedione to testosterone.

Commentary

Both the Italian and Iranian studies used relatively high doses of licorice over a short period of time. A daily dose of around 500 mg of glycyrrhizin corresponds to at least 10 g of licorice root. The long-term use of such doses would invariably result in the well-known side effects of licorice, namely potassium loss, hypertension and eventually fluid retention. Normal therapeutic doses of licorice root (between the equivalent of 2 to 3 g per day) are likely to cause only a modest reduction in serum testosterone in men, which is probably not clinically significant. However, women have considerably lower serum testosterone levels than men, and it is quite possible that therapeutic doses of licorice could reduce normal testosterone levels in women, albeit to a minor extent (around 10 to 20%).

The clinical significance of such a decrease is uncertain.

References
