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Standardization of Herbal Medicines

By Dennis V.C. Awang, PhD, FCIC

MANUFACTURERS OF HERBAL PRODUCTS COMMONLY PURVEY "standardized" extracts, often with the implied promise of guaranteed potency. Physicians who use botanical medicines want to be assured of consistent high quality, efficacious products, and comparable responses from the same dose of an herbal product.

However, ensuring the potency of herbal products is much more complicated than ensuring the potency of drugs. Standardization of conventional drugs normally indicates a guaranteed range of concentration of the known active ingredient, for which a clear dose-effect relationship has been established. After the expiration date for a given lot, the percentage of the active ingredient is expected to decline below a value sufficient to ensure a satisfactory therapeutic effect.

With herbal products, the identity of the plant's active constituent (or constituents) rarely is clearly established. Herbs contain hundreds of compounds, often ranging between extremes of hydrophilicity (water-solubility) and lipophilicity (fat-solubility). In herbal medicine, an herb's actions often are known long before a mechanism of action and the entities responsible for its activity are clarified. Often, numerous compounds are active to different degrees. There is relatively little research in this complex area; characteristically, advances in research cause emphasis to shift among the wide variety of classes of compounds, as well as their individual components.

Standardizing to known active compounds is sometimes impossible and may not always be necessary. Occasionally nature provides a plant with uniquely characterizing secondary compounds (e.g., ginkgolides in *Ginkgo biloba*), but this is an exception. The presence of "marker" compounds, even if they are known to be inactive, can be used to support botanical identity. Also, the presence of marker compounds (at levels consistent with those normally observed in efficacious preparations) can be a useful quality control parameter.

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INSIDE

Echinacea, St. John's wort, and ginseng are three of the most popular herbal preparations sold in "standardized" preparations. Echinacea is used to mitigate cold and flu symptoms; ginseng is used as a tonic/adaptogen; and St. John's wort is used to relieve mild or moderate depression. The cases of echinacea, St. John's wort, and ginseng serve admirably to illustrate the complexity of applying a drug-like standardization concept to herbal medications.

Echinacea[1,2]

Standardizing echinacea to an active compound or group of compounds is difficult because the claimed immunomodulatory effects of preparations of the three commercial echinacea species (*E. purpurea*, *E. angustifolia*, and *E. pallida*) have been said to reside in five classes of constituents, namely, caffeic acid derivatives ("total phenolics"), alkylamides, "polyacetylenes" (ketoalkenes/ketoalkynes), glycoproteins, and polysaccharides. Although alkylamides are widely regarded to be the most active chemical complement, it is unclear which of the alkylamides in echinacea root extracts should be used for standardization or whether (and how) the demonstrated in vitro activity of isolated alkylamides (phagocytotic or enzyme inhibitory effects) is related to the medicinal effect. In the language of Professor Rudolf Bauer (University of Dusseldorf), "the most effective constituent remains to be found." While it would be easy to standardize the extract to the most dominant alkylamide (the dodecatetraenoic acid isobutylamide 10-E/Z isomeric pair), that makes little sense because this compound exhibits only weak activity. In addition, the alkylamides of *E. purpurea* are structurally different from those in *E. angustifolia*. Lipophilic (chloroform) extracts of the three species exhibit identical activities to the granulocyte smear test, even though *E. pallida* root contains no alkylamides.

In Germany, most of the clinical research on echinacea has focused on the freshly expressed juice of aerial parts of *E. purpurea*, often administered parenterally. Other prominent commercial preparations include root extracts of *E. angustifolia* and *E. purpurea*. Cichoric acid, the caffeic acid derivative, is regarded as perhaps the most active constituent of fresh squeezed juice preparations (the predominant effect of caffeic acid derivatives appears to be antioxidant). Although it would be possible to standardize *E. purpurea* preparations to cichoric acid, it would be unsuitable for standardizing extracts made from the roots of *E. angustifolia* because cichoric acid is present only in trace amounts in the root extracts.

Echinacoside, another caffeic acid derivative, is often used to "standardize" commercial echinacea preparations. However, although echinacoside is present in the roots of *E. angustifolia* and *E. pallida*, it is almost absent in the roots of *E. purpurea*. Also, it has been reported by Bauer and associates to lack immunostimulatory effect.

Other unsatisfactory options for standardizing echinacea include ketodialkenes and ketodialkynes; these dominate the lipophilic complement of *E. pallida* roots but are absent from the roots of *E. angustifolia* and *E. purpurea*. Hydrophilic polysaccharides and glycoproteins are present most prominently in echinacea-expressed juice, and in extracts of its aerial parts; lesser concentrations exist in the plant roots. These compounds would be unacceptable as marker compounds, however, because of the differences in preparations available in Europe and North America. These high molecular weight polymeric substances may only be bioavailable in parenterally administered preparations. (Parenteral preparations of echinacea have been common in Germany but are not available commercially in North America.) Oral administration would be expected to result in breakdown of these products. Also, athough extracts with a high alcohol content are popular in North America, high alcohol concentrations lead to appreciable precipitation and subsequent unavailability of these compounds.

In light of the above complexity, standardization of

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echinacea preparations for therapeutic effect appears to be a truly daunting proposition. Extensive chemical characterization of clinically efficacious preparations appears to be the only sensible path to pursue toward that objective.

Ginseng[3]

While the traditional Chinese preparation of ginseng (the root of *Panax* species) is a hot water infusion of ginseng, modern preparations of the plant are dominated by alcoholic root extracts. These alcohol-based extracts, relative to aqueous extracts, are richer in the characteristic triterpene saponins called ginsenosides, and deficient in more polar constituents such as polysaccharides, peptides, and other protein-like factors.

There are more than 30 of the so-called ginsenosides; there are eight major representatives, many of which have demonstrated some pharmacologic activity (for example, Rg1 has a mild CNS stimulant activity, while Rb1 demonstrates CNS depressant activity). Traditional Chinese Medicine practitioners have always held that North American and Asian species of *Panax* are very different and cannot be substituted for each other. In energetic terms Asian ginseng is perceived as hot (*yang*) and North American ginseng as cool (*yin*); differences may in fact be due to different ratios of these ginsenosides. Even without that controversy, commercial ginseng preparations do contain different components than traditional preparations. Some argue that the tonic benefit associated with traditional preparations (either a boiled infusion or mastication of the whole ginseng root) cannot be confidently expected from commercial alcohol ginseng root extracts enhanced for ginsenoside content.

St. John's Wort[4]

Hypericin has long been thought to be the main active compound in St. John's wort; however, recent research indicates that hyperforin may be the prime active principle. Most trials of St. John's wort have been done with extracts standardized to 0.3% hypericin. In fact, the 0.3% hypericin standard is less standard than it appears because analysis is done by several methods: "hypericin" may represent HPLC determination of hypericin (the gold standard) or the much less specific UV determination of total hypericins.

Hyperforin-standardized extracts are available and are usually standardized to a level of 3%. Hypericin-standardized extracts may contain hyperforin, and hyperforin-standardized extracts probably contain hypericin. In general, it is preferable to standardize to the currently recognized most active principles. Recently, flavonoids such as amentoflavone have received consideration as possible active compounds.

Conclusion

It seems clear that the promise of herbal standardization is very far from realization. As the respected Swiss researcher, Otto Sticher, has noted: "The standardization (chemical) of phytomedicines serves primarily as a precaution for the quality of medicinal plant extracts."[5] The worthy goal of standardization, i.e., to achieve a consistent level of the main therapeutically effective active plant constituent, remains remote. The only scientifically sound approach is to continually refine our efforts at chemical characterization, bioactivity assessment, and correlation with clinical end points.

Beyond all of this, there is a dire need, particularly in North America, for the establishment of certification processes for the assurance of the botanical identity of commercial plant products, and for a program of periodic analytical testing of marketed materials for quality and strength. ❖

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Cranial Sacral Treatment

By John M. McPartland, DO, MS

CRANIAL SACRAL TREATMENT (CST) IS A GENTLE FORM of body manipulation. Gentle manipulation of the cranium is said to serve many functions: disengagement of sutures jammed by trauma, releasing cranial nerves impinged within their foramenae, realigning dural membranes, reducing venous stasis, and improving the flow of cerebrospinal fluid.

History

CST was originally developed by William Sutherland, an American osteopath. Sutherland began studying cranial anatomy in 1899, and began teaching "cranial osteopathy" in 1929.[1] Sutherland developed his methods de novo, apparently unaware that ancient Greeks practiced therapeutic cranial manipulation.[2] Recent authors[3] have claimed that cranial manipulation was also practiced in Asia, but this claim has been disputed.[4] CST remained the esoteric tool of osteopaths for many decades, but CST is now used by MDs, chiropractors, physical therapists, and massage therapists. This sudden surge in interest and utilization is primarily due to the Upledger Institute, which has taught CranioSacral Therapy™ to more than 25,000 people since 1985.[5]

Theory

Most anatomy courses teach that sutures between skull bones ossify in childhood. In fact, recent histological studies have shown that most cranial sutures never obliterate.[6] One review of cranial bone motion found that published research is "scant and inconclusive" but concedes that "animal and human studies demonstrate a potential for small magnitude motion."[7]

Living sutures contain ligaments, blood vessels, and nerves. Collagen fibers traverse sutures, connecting the external periosteum with the internal dura mater. In other words, the dura is directly accessible to external forces. In the suboccipital region, for instance, the outer surface of the dura attaches to the inner surface of the posterior atlanto-occipital membrane (PAOM) via a fine connective tissue bridge.[8] The outer surface of the PAOM, in turn, is fused to the deep surfaces of the paired rectus capitis posterior minor muscles (RCPMs), near their conjoined origin upon the atlas.

Thus, the RCPMs have fascial continuity with the dura via the PAOM. Whiplash injuries of the RCPMs often result in dural headaches and neck pain. In one study, whiplashed individuals with chronic pain exhibited atrophy of the RCPMs (seen by magnetic resonance imaging); this led to a loss in postural balance, as measured on a force platform (a plate mounted flush with the floor that tracks forces moving upon it, such as gravity, torque, and shear).[9]

Within the skull, the dura infolds upon itself, forming an internal support for brain tissue, called the "reciprocal tension membrane,"[1] but better known as the falx and the tentorium. The dura also forms a sleeve running down the spinal column and attaches to the sacrum. The entire system is interconnected.

CST theory holds that distortion of any part of the dura transmits forces across the whole. Contours of the 22 cranial bones, their interlocking articulations, and the reciprocal tension membrane limit cranial motion to specific directions. These movements may become dysfunctional, which forces the skull, its connective tissue, and the brain itself into strain patterns. Causes of dysfunction may be external, such as trauma, or internal, such as sinus infections. Malaligned temporal bones, for example, are said to give rise to temporomandibular joint syndrome, headache, and dizziness, and to predispose children to otitis.[10] Many cranial nerves exit the skull at sutures; if restricted they may vitiate distal tissues, including all the organs innervated by the vagus.

Treatment

CST is usually performed with the patient supine. The practitioner sits at the head of the examination table and carefully palpates cranial bones for mobility, motion tests for strain patterns, and checks sutures for tenderness. Treatment is applied with the hands, using very light pressure. The technique does not involve the quick thrusts and "popping" noises characteristic of thrust-style manipulation. CST movement is very slow and gentle, similar to what some practitioners call "indirect myofascial release."

Craniosacral Rhythms

CST practitioners take another step away from conventional medicine by describing a phenomenon called the "cranial rhythmic impulse" (CRI). The CRI is a palpable pulsation, much like the respiratory excursion of the chest, but sensed as a broadening and narrowing of the head. Clinical studies report a palpable CRI rate of 6-12 cycles/min in healthy humans, independent of cardiac or diaphragmatic rhythms.[10,11] This rate has been corroborated by CRI studies using mechanical and electronic devices.[12,13] However, two small studies (each utilizing two practitioners of craniosacral therapy) found little interexaminer reliability (meaning that the two practitioners did not agree on the rate).[14,15] These studies also looked at intraexaminer reliability (meaning the consistency of one examiner's findings in the same patient); one found good intraexaminer reliability[14] and the other (which compared examiner ratings of the CRI at the head and at the feet) did not.[15]

The determination of CRI is said to decrease in a variety of conditions, including coma,[11] traumatic brain injury,[16] psychological disturbances,[10] emotional exhaustion,[11] malnutrition,[11] and many other maladies. CRI is said to accelerate in cases of acute fever,[10] and in hyperkinetic and autistic children.[11]

If it does exist, what is its origin? The functional origin of the CRI remains unknown but fluctuations are

usually attributed to pulse waves of cerebrospinal fluid (CSF). Magoun first suggested that rhythmic variations of CSF production by the choroid plexus may generate the CRI.[10] However, the rate of choroid plexus pulsations is much faster than the CRI and appears to be synchronous with cardiac systole.[17] An alternative theory is that CRI is due to glial cell pulsations (these pulsations were observed in a 1951 study often quoted by CRI proponents).[18] But glial cells pulsate at a completely different rhythm than the CRI.

A new theory suggests that CRI represents a summation signal, a "harmonic frequency" of many palpable biological pulsations, including the cardiac pulse, diaphragmatic respiration, waves of CSF produced by the choroid plexus, pulsating glial cells, oscillations in cerebral blood velocity, Traube-Hering modulations (change in cerebral blood pressure that varies on a beat-to-beat basis), rhythmically contractile lymphatic vessels, and many other oscillations.[19] Furthermore, the CRI may not be the fundamental harmonic. Sutherland alluded to deeper, slower, more subtle rhythms around 1948. He poetically described ocean waves moving rhythmically through water (the CRI), and deeper tides moving through water and waves, "the Breath of Life, a fluid within a fluid."[1] Incidentally, Sutherland borrowed these seaside metaphors from Rachel Carson, and quoted her.

Some CST practitioners wander yet further afield from the physical realm and attribute the CRI to patterns of electromagnetic energy. Indeed, electrical fields generated by cortical neurons exhibit rhythmicity.[20] These rhythms may be linked to cortical oxidative metabolism, which oscillates at 9 cycles/min.[21] Others claim the source of this "subtle energy" is an external, universal energy matrix, organized in the body by fluid forces (perhaps electromagnetic water hydrogen bonds).[22] This idea is similar to the "water imprint" theory of homeopathic researchers. Practitioners of this lysergic school of osteopathy apparently palpate bioenergetic fields with "an undefined seventh sense," as described by yoga practitioners.[11]

Clinical Trials

Although heavy on theory, CST is light on evidence; no randomized controlled clinical trials of CST were identified. Those critical of CST claim it lacks efficacy,[23] and it is true that the two main texts[10,11] in the field refer mainly to anecdotal reports. Studies do exist, although these mainly consist of case series and uncontrolled studies (and most of these have been published only as abstracts).

One pilot study, reported only in abstract form, found that CST induced uterine contractions in post-term pregnancies;[24] another descriptive study, also published as an abstract, reported a similar effect.[25] A retrospective, case-control study sought to determine whether women who received chiropractic and craniosacral therapy during pregnancy had fewer obstetric interventions.[26] No difference in rates of obstetric intervention were found in 35 women who received chiropractic care and craniosacral therapy (for any reason during pregnancy) and a matched sample within the same county.

An uncontrolled pilot study of infants with suckling dysfunctions found a positive effect of CST.[27] A controlled trial found a positive effect of CST on neurological development in children, as measured with Houles Profile of Development scale.[28]

Several controlled (open or single-blind) trials found a beneficial effect of CST on autonomic function.[29-31] Uncontrolled studies that found a benefit of CST include a study of trigeminal neuralgia[32] and one of torticollis.[33] Other uncontrolled studies reported only as abstracts include two studies on headache;[34,35] a study of tinnitus;[36] and a study of Bell's palsy:[37] all found a benefit for CST.

Adverse Effects

Because its manipulations are very gentle, CST has been applied to patients where more aggressive manipulation may not be indicated, e.g., pregnant women, newborns, and hospitalized patients in critical care units. Contraindications to CST include recent skull fractures, acute intracranial hemorrhages, and intracranial aneurysms.[11]

Significant side effects from CST, however, have been described in the literature. Rare complications include headache, dizziness, emotional swings, psychiatric disturbances, nausea, vomiting, diarrhea, cardiac palpitations, and a case of opisthotonos (tetanic spasm in which the head and feet are bent backward and the body bowed forward).[16] Breaking the opisthotonos required paralysis with intravenous pancuronium bromide, supported by mechanical ventilation. Another series of nine case reports described depression, confusion, diplopia, vertigo, loss of consciousness, trigeminal nerve damage, hypopituitarism, brainstem dysfunction, opisthotonos, tonic-clonic seizure, and miscarriage of a 12-week pregnancy.[5] Two-thirds of the cases involved women. More than half of the cases involved patients with recent trauma (usually car accidents) or serious diseases (e.g., brain cancer), which may have predisposed them to side effects. A majority of cases involved lay practitioners.

Summary

There is scant clinical trial evidence supporting the use of craniosacral therapy, although there are some intriguing results from uncontrolled studies. While double-blind studies of any hands-on therapy (including surgery) are difficult to perform, well-designed, single-blind, controlled trials should certainly be conducted in craniosacral therapy. There is evidence that CST can cause significant physiological changes, and also that the therapy can cause complications if poorly performed. ❖

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CME Questions

1. **The presence of "marker" compounds, even if they are known to be inactive, can be used to support botanical identity.**
   a. True
   b. False
2. **Recent research indicates that the prime active compound in St. John's wort is:**
   a. hypericin.
   b. hyperforin.
   c. amentoflavone.
3. **The goal of standardization is to achieve a consistent level of the main therapeutically effective active plant constituent.**
   a. True
   b. False
4. **CST theory holds that distortion of any part of the dura transmits forces across the whole.**
   a. True
   b. False
5. **Writing about which of the following was shown to reduce chronic symptoms in asthma or rheumatoid arthritis patients?**
   a. Stressful events of the past week
   b. The most stressful event ever experienced
   c. Any subject of the patient's choosing
   d. A time management exercise

Clinical Abstracts

With Comments from Adriane Fugh-Berman, MD

Vitamin B_6 and PMS

Source: Wyatt KM, et al. Efficacy of vitamin B_6 in the treatment of premenstrual syndrome: A systematic review. *BMJ* 1999;318:1375-1381.

Summary: This systematic review identified 25 published trials of PMS and vitamin B_6. Studies of cyclical mastalgia were included, and studies of multivitamins were included if the treatment contained at least 50 mg of vitamin B_6. Ten randomized, placebo-controlled, double-blind, parallel or crossover studies were included. Two analyses were conducted—one of 10 trials and one of nine trials (one trial was excluded because of "statistical heterogeneity").

Results: Only three of 10 trials scored >3 on the Jadad scale (a measure of methodological quality). None of the trials included a power calculation; and only three of 10 trials noted the number of and reasons for withdrawals. Using a random effects model, the overall odds ratio (OR) in favor of vitamin B_6 in the analysis of all 10 trials was 1.57 (95% confidence interval 1.40-1.77). The analysis of nine trials (934 patients) resulted in an OR of 2.32 (1.95-2.54) in favor of vitamin B_6. Data on depressive symptoms were extracted from five trials; the overall OR in favor of vitamin B_6 was 2.12 (1.80-2.48). There was no dose-response effect. One patient taking 600 mg/d of vitamin B_6 reported neurological side effects.

Comment: This is a difficult subject for meta-analysis. No consensus exists on criteria for diagnosing or treating PMS, and the B_6 trials demonstrate little consistency in inclusion criteria, doses, formulations, and use of concurrent medications. Only two studies enrolled more than 55 people; the largest study (434 women) included those on psychotropics, analgesics, diuretics, and oral contraceptives (at least two other trials also included oral contraceptive users); vitamin B_6 doses ranged from 50-600 mg/d; and outcome measures included the vague ("tiredness") and the strange ("violence," "stomach ache," "coordination"). The authors kept dropping inclusion criteria in order to have anything to analyze. After creating a quality screen based on both the Jadad criteria and their own scale, they write "as none of the trials met both our and the Jadad quality criteria, we did not take the quality score into account when considering trials for inclusion."

There is a discrepancy between the text and a table; although it is stated that only double-blind trials are included in this review, a table notes that one study was "blinded to patient only."

As Alvin Feinstein wrote about meta-analysis, "Among the many virtues that have been extolled for meta-analysis, the main appeal is that it can convert existing things into something better."[1] An aggregation of data from flawed trials cannot be used to draw conclusions. ❖

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Prevention of recurrence

Insert 1 suppository once per day at bedtime, during menstruation for four months.

Additional naturopathic care

Avoid fermented foods such as cheese, vinegar, beer, and wine. Avoid simple carbohydrates such as sugar, fruit, white and flour products(sic). Avoid foods with baker's yeast. Increase dietary intake of active yogurt and garlic.

Do not use this product if pregnant without consulting a health care practitioner.

Keep this product out of reach of children.

Store in a cool, dry place.

Supplement Facts

One suppository contains:

Boric acid	600 mg
Hydrastis canadensis—goldenseal root	100 mg
Calendula officinalis—calendula flowers	50 mg
Berberis aquifolium—Oregon grape root	50 mg

Suggested use: insert one suppository in vagina morning and evening.

"Formulated by Dr. Tori Hudson, a naturopathic physician specializing in women's natural health care"

Yeast Arrest™ is a trademark of Vitanica™, P.O. Box 1285, Sherwood, OR 97140.

Price: $11.49, 14 suppositories

Comments from Adriane Fugh-Berman, MD

The suppositories (actually large clear capsules filled with powdered light-brown material) could easily be mistaken for oral medication; however, the lid of the plastic container is clearly marked "Suppositories: Do Not Ingest."

Boric acid clearly has antifungal properties, has been tested as a treatment for both acute[1] and chronic[2] vulvovaginal candidiasis, and is quite safe (occasional burning at the introitus has been noted in those using boric acid for more than two weeks[1]). Although not widely used, boric acid is an inexpensive and apparently effective therapy for treating *Candida* infections. Doses used in studies were usually 600 mg bid, which this formula provides.

Although there are no published clinical trials for the use of the herbs in this formula for vaginitis, there is some evidence for anti-inflammatory and antifungal activity. Calendula reduces inflammation, and antifungal activity of a 10% methanol extract of calendula has been demonstrated.[3] Goldenseal contains alkaloids (including hydrastine and berberine) and has been used in Native American Indian medicine for oral sores and irritation. Oregon grape root also contains berberine, but in lesser amounts than other *Berberis* species, especially *B. vulgaris*. Berberine has broad-spectrum antibacterial and antifungal activity.

The package insert is referenced, which is unusual and commendable for an OTC product. Most women are quite familiar with symptoms of *Candida* overgrowth and self-treatment is fine. However, OTC products that include directions for chronic use are worrisome. Dosing instructions for "mild cases," "resistant cases," and "chronic yeast vaginitis" could encourage consumers to continue using this product when they should consult a health care provider. Triggers for recurrent yeast infections should be identified: possibilities include irritant exposure (soap, bath oil); labial occlusion/irritation (swimsuits, bicycle pants); or immunosuppression. And of course another diagnosis may be in order. The insert does state "…for symptoms other than those related to yeast infections, or persistent or recurring symptoms, consult a health care practitioner." However, it would be more useful to specify a time frame of one or two weeks.

In summary, this product should be effective in treating a yeast infection, although boric acid alone may work as well and would be a less expensive option. It does not appear to be more convenient or less expensive than generic antifungal suppositories.

References

1. Van Slyke KK, et al. Treatment of vulvovaginal candidiasis with boric acid powder. *Am J Obstet Gynecol* 1981;141:145-148.
2. Jovanovic R, et al. Antifungal agents vs. boric acid for treating chronic mycotic vulvovaginitis. *J Reprod Med* 1991;36:593-597.
3. European Scientific Cooperative on Phytotherapy. *Calendula monograph*. Exeter, UK; 1997.