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INSIDE

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Progesterone Cream in Menopause

By Judith L. Balk, MD, MPH, FACOG

Dr. Balk is Assistant Professor, Magee-Womens Hospital, University of Pittsburgh; she reports no financial relationship to this field of study.

LAY BOOKS AND WEB SITES TOUT THE BENEFITS OF PROGESTERONE cream for use in menopausal women. A Google search reveals roughly 338,000 results when the term "progesterone cream" is entered. In contrast, when the term "progesterone" is combined with the term "cream" in Medline, 62 results are obtained. When the term "menopause" is added to the Medline search, only 11 articles remain, and when the term "perimenopause" is used, no articles appear.

The Google search reveals many sites that sell progesterone cream for use in menopause, with claims such as, "Many of the so-called 'modern' diseases can be prevented or overcome by progesterone therapy."[1] Thus, it is not surprising when our patients present either using or asking about progesterone cream. The purpose of this article is to review the use of progesterone transdermal cream in menopause. This review will not specifically address vaginal or oral progesterone, which are only available with a prescription.

Progesterone is produced from cholesterol by the ovaries, the placenta, the adrenal glands, the testes, and the central nervous system.[2,3] However, most of the associated research has focused on its pro-gestational effects, hence the name progesterone. With recent concern about menopausal hormone therapy, and specifically the progestin component, women are turning to progesterone as a possibly safe and effective approach to treat menopausal symptoms. The term progestin is used to signify a molecule that is chemically different from progesterone, but that has some similar effects. It is important to keep in mind that progesterone and synthetic progestins may induce different responses, such as on the breast.[4] It is likewise important to note that many authors use the term progesterone when what is being studied is actually a progestin-like medroxyprogesterone acetate. Progestagen is the term that encompasses both progesterone and progestins.

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Effects on Menopausal Symptoms

In one study, transdermal progesterone at 32 mg daily for 12 weeks did not affect vasomotor symptoms, mood, or sexual feelings in postmenopausal women. The authors postulate that insufficient hormone entered the body to achieve a biological effect.[5] Progesterone concentrations rose slightly, but in a statistically significant fashion, in the treatment group, demonstrating good absorption of the cream, although blood levels remained low. All women were mildly symptomatic at baseline with a Kupperman Index over 16 (out of 51). It is possible that perimenopausal women, or those who are more symptomatic, might have a different outcome.

A one-year randomized, placebo-controlled trial compared the effects of 20 mg of progesterone cream vs. placebo in postmenopausal women.[6] Only 55% and 69% of women had vasomotor symptoms at baseline in the placebo vs. progesterone group, respectively. Of those who had hot flushes, 83% experienced improvement in the progesterone group, compared to 19% in the control group ($P < 0.001$). Eight subjects in the progesterone group had vaginal spotting that was self-limited and resolved within 1-2 days.

An abstract described a study in which postmenopausal women received placebo or 20 mg of progesterone cream for 4 weeks, and then were crossed over to the opposite group.[7] The authors noted a decline in menopausal symptoms in the treatment group, but not in the placebo group. There is typically a large placebo response in short-term menopause studies.

Effects on the Cardiovascular System

The impact of progesterone on cardiovascular disease risk can include effects on lipids and on vascular function. In both non-atherosclerotic and pre-atherosclerotic surgically menopausal monkeys, progesterone cream prevented coronary hyperreactivity when compared to placebo cream.[8] In this study, progesterone cream protected against severe prolonged vasoconstriction from a challenge injection, in contrast to data indicating that oral medroxyprogesterone acetate adversely affects coronary reactivity and increases the risk of coronary vasospasm.[9] Route of administration and dosage may play a role in the effects seen. In another trial, 400 mg of vaginal progesterone acutely increased vascular resistance in 12 postmenopausal women at 3 hours post-administration, but after 8 hours a vasodilatory reaction was noted.[10] Transdermal progesterone in a dose of 32 mg daily for 12 weeks did not affect lipid levels in postmenopausal women; the authors postulated that insufficient hormone entered the body to achieve a biological effect.[5] Topical progesterone at 20 mg/d for 4 weeks did not increase thrombotic or inflammatory factors in postmenopausal women.[7]

Effects on Breast

Both progesterone and estrogen receptors exist in the breast, so it is possible that progesterone or estrogen or an interaction between the two, could have stimulatory or inhibitory effects on breast cells. The influence of progesterone on breast tissue has been debated for two decades, as results can differ based on the model used (animal vs. human, in vitro, or in vivo), the timing of progesterone administration, and the method of evaluation used (mitotic index, proliferating cell nuclear antigen, ^{3}H-thymidine labeling).[4] For instance, the mitotic index is highest in the midluteal phase in premenopausal women, which is when progesterone peaks[11]; however, in one study, the mitotic index declined with every decade of life, meaning that at the time of highest breast cancer risk, the mitotic index was lowest. The actions of progesterone on breast tissue are likely complex and dependent on many factors, including duration of exposure.[12]

In a double-blind, randomized study, postmenopausal women scheduled for benign breast surgery applied either topical estradiol, progesterone, placebo, or a combination of estradiol and progesterone for the 14 days prior to surgery.[4] Estradiol induced cell growth based on the mitotic index, whereas findings for the progesterone and combined estradiol/progesterone groups did not differ from placebo. The authors concluded that the application of progesterone limited the estradiol-induced proliferation of normal breast cells. A similar design was

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Summary Points

- Progesterone cream is very popular among patients despite lack of scientific evidence.
- Progesterone cream is absorbed through the skin, but blood levels tend to rise only slightly.
- Progesterone cream is likely not sufficient to oppose the proliferative effect of estrogen on the endometrium, and should not be used as the progestagen in menopausal hormone therapy.

used for premenopausal women, and the findings were the same: Exposure to topical progesterone for 10-13 days reduced estradiol-induced cell proliferation.[13]

Luteal phase breast pain has no clear etiology, but an insufficiency of progesterone has been postulated.[14] A small randomized trial (n = 32) comparing luteal phase application of 5 g of cream containing either 1% progesterone (50 mg) or placebo found no improvement with progesterone.[14] In contrast, a larger study (n = 80) found that vaginal application of 4 g containing 2.5% progesterone (100 mg/application) improved breast pain and tenderness, while having no effect on breast nodularity.[15] No major side effects were seen. Possible differences between these studies could be the bioavailability of transdermal vs. vaginal cream, inadequate sample size for the first study, or dosage of progesterone.

Effects on Bone

The effects of progesterone cream on bone health are controversial. Bone mineral density was assessed in postmenopausal women in one trial before and after one year of 20 mg progesterone cream daily vs. placebo.[6] Both groups had small, nonsignificant decreases in mean bone mineral density at the post-treatment DXA scan. Bone turnover markers did not differ between 32 mg/d progesterone cream vs. placebo when given for 3 months in another trial.[5] However, a two-year study in postmenopausal women with either osteoporosis or three risk factors for osteoporosis found that progesterone cream at roughly 25 mg/d attenuated bone loss over a two-year period.[16] Interestingly, soy milk had the same effect, but when soy milk and progesterone cream were taken in combination, a negative interaction occurred, resulting in more bone loss than either treatment alone. A letter to the editor notes an increase in bone density as determined by dual photon absorptiometry with the use of 330-500 mg of transdermal progesterone monthly.[17] This study was a retrospective chart review, uncontrolled, and some of the patients were also on estrogen.

Effects on Endometrium

To be useful in postmenopausal estrogen-progestagen therapy, progesterone must protect the endometrium. Importantly, blood or salivary concentrations are not the best indicator; rather, tissue sampling must demonstrate endometrial protection. In one pilot randomized crossover trial, healthy menopausal women had a baseline endometrial biopsy, and then were randomized to 0.625 mg conjugated equine estrogen (CEE) daily and 2.5 mg medroxyprogesterone acetate or daily 0.625 mg CEE and twice daily transdermal cream containing 20 mg progesterone.[18] At the end of 6 months, a repeat endometrial biopsy was obtained, and the women were crossed over to other treatment. A final endometrial biopsy was performed after the final 6 months. Twenty-six women completed both arms of the study. Of the 52 post-treatment endometrial biopsies, 40 revealed atrophic endometrium and 12 proliferative endometrium (7 in the oral progestin group and 5 in the progesterone cream group). There was no evidence of endometrial hyperplasia in either group, and the incidence of vaginal spotting was similar in both groups.

Another study by the same investigative team was a 28-day randomized, double-blind, placebo-controlled trial assessing endometrial safety of various concentrations of progesterone cream.[19] The article notes that the pharmacy formulated the cream's concentration based on the patient's weight, but it is not clear how the progesterone cream concentrations of 0%, 1.5%, or 4.0% were adjusted based on patient weight when the subjects were randomized to one of these groups. Thus, it is not clear what the exact dosages of progesterone used were. Both dosages of progesterone cream decreased endometrial stimulation compared to placebo and to baseline.

Other studies have not found adequate endometrial protection. When postmenopausal women used transdermal estrogen and a cream containing 16 mg, 32 mg, or 64 mg of progesterone, endometrial biopsies did not demonstrate a change from baseline after 14 days of progesterone.[20] In a different study, a combination of 40 mg progesterone cream and 1 mg estradiol, given transdermally for 48 weeks in 54 postmenopausal women, did not prevent endometrial stimulation.[21] Thirty-two percent of subjects had either proliferative or hyperplastic endometrium at 48 weeks. Researchers have recommended that transdermal progesterone not be used for endometrial suppression at the current time.[18,19,21]

Absorption, Distribution, and Measurement of Progesterone

Ideally, topical progesterone will distribute to the organs where it has beneficial effects, such as the uterus.

An experimental rat model demonstrates that progesterone cream is absorbed transdermally and then distributed and metabolized in the same manner as progesterone that enters the blood directly.[22] Progesterone accumulates in progesterone target areas, such as the uterus, lung, and saliva, at concentrations in excess of plasma levels.

The measurement of progesterone concentrations when using the cream remains controversial. An editorial in *Menopause* discusses the issues of salivary vs. serum testing of progesterone.[23] On one hand, salivary progesterone measurements confirm that progesterone cream is absorbed.[24] Also, due to the lipophilic nature of progesterone, it is not thought to be absorbed into plasma, but rather into red blood cells, which deliver progesterone to target tissues and to saliva, making salivary concentrations more relevant for measurement than blood levels[25]; but even so, salivary levels can be so variable that some investigators found the levels to be completely unreliable.[20] In addition, it is not clear what salivary concentration of progesterone is sufficient to protect the endometrium or bone, and thus salivary measurement is less clinically useful. No empirical association between progesterone dosage and salivary concentrations exists that can be used to treat menopausal symptoms.[24] Salivary measurements of progesterone were found to be inaccurate in one study, due to contamination from cream on the subjects' fingers.[14]

Serum concentrations did not change when women applied a single dosage of 64 mg of topical progesterone.[24] However, serum concentrations did increase somewhat after 10 days of progesterone cream use,[26] and luteal phase concentrations were obtained in some women after 4 weeks of 30-60 mg/d application of progesterone.[27] Whole blood progesterone concentrations, as opposed to serum concentrations, demonstrate significant absorption, with a dosage of 40 mg twice daily being roughly equivalent to the prescription 200 mg oral dosage of progesterone.[28]

Safety

No studies have specifically addressed the safety of progesterone cream, but in the clinical trials noted above, no adverse events were noted. Given what appears to be minimal absorption of the cream, especially at dosages available over the counter (up to 30 mg/mL), the most significant risk may be when patients use the cream assuming it is protective of the endometrium. Given that it is most likely not protective, the use of the cream instead of a well-studied medication places the patient at risk for endometrial cancer. Also, in women with hormonally dependent cancers such as breast cancer, the use of progesterone cream is likely premature until more research is done on its safety.

Conclusion

Transdermal progesterone administration may be useful when subphysiological levels are required, such as for mastodynia.[29] The literature supports that some women may achieve relief from menopausal symptoms with progesterone cream, but it is likely that only a subset of women will respond. We currently do not know who will respond to transdermal progesterone for symptom relief; it is possible that those with elevated endogenous estrogen, like obese women, would benefit more from progesterone.

Recommendation

Given the available literature, I would recommend that transdermal progesterone not be used for endometrial protection, osteoporosis, or in breast cancer patients. It is possible that progesterone may be helpful with symptoms of menopause, but more research is necessary to delineate the ideal clinical scenarios in which transdermal progesterone is most effective. ❖

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Imported Fruits: Drink Their Juices?

By David Kiefer, MD

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IN THE POPULAR PRESS, THERE HAS BEEN A RECENT FOCUS on "superfoods," or foods that contain high levels of nutrients that some people feel have the best evidence for the prevention or treatment of various medical conditions.[1,2] Examples are avocado, blueberries, dark chocolate, oats, olive oil, salmon, and yogurt. Along the same vein, juices from imported, often tropical, fruits are mentioned as being "healthy" and are now common on the shelves of health foods stores, pharmacies, and most of our refrigerators; for example, recent sales show double-digit growth in juices from açaí (pronounced "ah-sai-EE"), mangosteen, and pomegranate.[3] In most cases, these fruits have a long history of traditional use as foods and medicines, and laboratory and clinical trials are starting to elicit their mechanisms of action, clinical

Summary Points

- Açaí, mangosteen, and pomegranate each have a rich tradition of use as food and medicine.
- These three plants contain a variety of phytochemicals, some of which have been shown to have antioxidant effects, the primary mechanism of action.
- Pomegranate is the only one of these plants with significant human clinical research; the focus has been on antioxidant effects, and benefits for diabetes and cardiovascular disease.

Table

Latin binomials, pharmacology, and traditional use(s) of açai, mangosteen, and pomegranate

Plant	Genus Species (Family)	Traditional Use(s)	Pharmacology
Açaí	*Euterpe oleracea* (Arecaceae)	Food, diarrhea	Anthocyanins, lignans, polyphenols
Mangosteen	*Garcinia mangostana* (Clusiaceae)	Food, abdominal pain, cough, cystitis, diarrhea, eczema, fever, gonorrhea, pruritis, stomatitis, thrush, wounds	Xanthones (mangostins), tannin, garcinone, gartanin, chrysanthemin
Pomegranate	*Punica granatum* (Punicaceae)	Food, diarrhea, parasites, apthous ulcers, contraception, HIV, allergies, cardiovascular protection, "blood tonic"	Polyphenols (anthocyanidins and hydrolysable tannins)

uses, and other effects. This review will detail some of this research, helping health care practitioners guide their patients' choice of refreshing drinks.

History, Traditional Use, and Botany

Each of these plants has a rich history of traditional use as foods and medicines *(see Table, above)*. For example, açaí is a palm widely distributed in northern South America, especially important economically in the Brazilian state of Pará, and considered abundant in eastern Amazonian estuary floodplains.[4,5] The trees produce a dark, purple-colored fruit, yielding a viscous juice for use in energy drinks, jellies, ice cream, and to mix with other juices[4]; açaí is also mentioned as a treatment for diarrhea.[6] The immature fruits are green, though if they remain green in the mature state the fruits are called white açaí. The pulp is approximately 50% lipid and 10% protein, and is said to taste like a mix of beets and carrots.[5] One example of an açaí juice blend studied in a recent clinical trial is Mona Vie Active®.[7]

Another "exotic" fruit is mangosteen. Mangosteen, locally known in Thai as mangkhut, is a tree thought to be native to Indonesia or Southeast Asia, and has been cultivated for centuries in tropical areas such as Indonesia, Malaysia, Thailand, and the Philippines.[8,9] It is considered by some to have the best tasting fruit in the world. The fruit, roughly the size of a tangerine, contains a white inner pulp that is divided into 4-8 segments, and a non-edible, tough, bitter pericarp (or peel, rind, or fruit hull) that contains a yellow resin with physiologically active phytochemicals, xanthones.[8] The pericarp has been used for treating cough, cystitis, diarrhea and other intestinal ailments, eczema, fever, pruritis, and various skin conditions, whereas the leaves have traditionally been used in teas and for diarrhea, dysentery, fever, and thrush, and the bark can be used for genitourinary complaints and stomatitis.[8]

The pomegranate is a small tree or large shrub originating from the Middle East, but now found throughout the Mediterranean, and in China, India, Mexico, and the American Southwest.[10] The pomegranate fruit, botanically considered a berry, contains, by weight, 3% seeds (20% of which is oil), 30% juice, and the rest pericarp, including the inner network of membranes.[10] The pomegranate plant is a prominent part of many religions and societies, dating back centuries, and its fruit, bark, roots, and flowers have had a wide variety of medical uses, including for diarrhea, parasites, apthous ulcers, contraception, HIV, allergies, cardiovascular protection, and as a "blood tonic."[10]

Pharmacology and Mechanism of Action

The phytochemical constituents of these plants have mostly been determined, and numerous in vitro and animal studies have begun to elucidate their mechanism of action. An analysis of açaí pulp showed the presence of anthocyanins such as cyanidin and pelargonidin, and polyphenols such as ferulic acid, catechin, epicatechin, gallic acid, and homoorientin.[4,11,12] Açaí oil is also being studied; it contains 60% oleic acid, 22% palmitic acid, 12% linoleic acid, and other fatty acids in trace amounts, as well as numerous phenolic compounds, such as procyanidins and phenolic acids, but not anthocyanins.[11,13]

Most mechanistic studies have focused on the anticancer and antioxidant effects of açaí. For example, one analysis using the total oxidant scavenging capacity (TOSC) placed açaí in the top class of oxidant-scavenging juices, except for white açaí which was in the lowest class along with tomato and sauerkraut juices; the researchers attributed this high TOSC capacity to as-yet-unidentified compounds other than the known anthocyanins.[5] Another research group using a different antioxidant assay (Trolox equivalents per milliliter) found the antioxidant level of açaí was comparable to

cranberries, and approximately double the levels for blueberries, raspberries, strawberries, blackberries, and muscadine grape juice.[4] Methanol extracts of the seeds appear to be the most effective antioxidants, partially due to the oligomeric procyanidins,[14] and methanol extracts of the fruit also show antioxidant effects.[6]

With respect to cancer, an in vitro study on a human leukemic cell line showed that the polyphenolics in açaí induced apoptosis in a dose-dependent and time-dependent fashion.[15] In addition, in vitro inhibition of human colon carcinoma cell growth was observed for both the pulp and phytochemically enriched açaí oil, though more so for the oil, probably due to different concentrations of the relevant phytochemicals.[11]

Finally, extracts (hydro-alcoholic more so than water) of açaí fruit stone (or "pit") and skin causes a dose-dependent vasodilation of rat mesenteric vascular bed, possibly through an antioxidant effect that increases the bioavailability of nitric oxide (NO).[12]

Some of these same themes continue with mangosteen. Mangosteen pericarp contains a variety of compounds, including the xanthones alpha-, beta-, and gamma-mangostin, methoxy-beta-mangostin, tannin, garcinone, gartanin, polyphenolic acids such as phenols, and chrysanthemin.[8] Mangosteen pericarp extracts have shown anti-inflammatory and antioxidant effects, inhibitory effects against skin and gastrointestinal bacteria, and antitumor effects.[9] The xanthones have been shown to have antibacterial, antifungal, and antitumor activity, and cancer cell toxicity effects against human leukemia and colon cancer cell lines in vitro, mainly due to apoptosis.[8,16]

Methanol extracts of mangosteen pericarp have a dose-dependent inhibition of breast cancer cells in vitro comparable to the controls quercetin and paclitaxel, and there are indications of an apoptotic effect; morphological changes in those cells at several concentrations; and, a suppression of intracellular reactive oxygen species, consistent with an antioxidant effect.[9] Alpha- and gamma-mangostin have anti-inflammatory activity in some in vitro models.[17] When alpha- and gamma-mangostin were studied in an in vitro human adipocyte model, they were found to decrease the induction of inflammatory genes related to insulin resistance.[17] In vitro and in vivo models show anti-inflammatory effects of gamma-mangostins greater than alpha-mangostins, via NO and prostaglandin-E2 (PGE2), but not via inhibition of the COX-2 enzyme system.[16] In another in vitro study, however, a mangosteen extract was found to have neither antitumor nor antihelmintic effects.[18] Researchers have found that mangosteen pericarp has an antioxidant effect in in vitro neuron models.[19] Finally, an in vitro study showed potent anti-inflammatory effect for the pericarp extract, as well as the alpha-mangostin and gamma-mangostin fractions, related to inhibition of NO and PGE2 release, as well as TNF-alpha and IL-4 levels.[20] Inhibitory effects against acne-causing skin bacteria (*Propionibacterium acnes*, *Staphylococcus epidermidis*) were also identified.[21]

Pomegranate juice contains the antioxidant flavonoids anthocyanins and proanthocyanidins, which provide its dark red color, as well as pentose glycosides such as malvidine and pentunidin, catechins and epicatechins, as in green tea and dark chocolate, and quercetin; the pericarp also contains anthocyanins, in addition to tannins.[10] There are numerous in vitro trials documenting the antitumor effects of extracts from different parts of the pomegranate; apparent mechanisms and actions include increased apoptosis, decreased inflammation, decreased metastasis, and decreased drug resistance. The anti-inflammatory and antioxidant effects of pomegranate juice and its individual components have been well-established, affecting several different enzyme systems, including lipoxygenase and cyclooxygenase.[10,22] Pomegranate juice has been shown to have in vitro antiplatelet activity,[23] and anti-anxiety effects in mice.[24]

With respect to antioxidant effects there are many assays, and although the oxygen radical absorbance capacity (ORAC) is most commonly mentioned in the literature, there are others, such as TEAC, FRAP, and DPPH, that can estimate a given compound's antioxidant effect. One group compared juices by creating a composite index score (100 = best) using seven antioxidant tests, and found pomegranate juice to score 95.8, red wine 68-72, Concord grape juice 57-70, açaí juice 44-54, iced green tea, 17-29, apple juice 14-15, and iced white tea 5-24.[25] Other groups found that purple (Concord) grape juice had the highest level of phenolics and antioxidant effect (using ORAC and FRAP tests), followed by apple juice, pomegranate juice, and cranberry juice drink.[26]

Clinical Trials

Açaí and mangosteen have limited human research associated with them, whereas pomegranate juice has been more extensively studied. A study of 7 mL/kg of clarified açaí juice as a one-time dose in 12 human subjects showed plasma, but not urine, antioxidant effects after the ingestion of both açaí pulp and juice (but pulp more than juice) when compared to a control beverage.[27] The researchers also demonstrated that açaí anthocyanins are bioavailable. For mangosteen, an extract of alpha- and gamma-mangostin (150 mg daily for 7 days)

was found to upregulate natural killer cell activity in a pilot human study.[8]

Some examples of the type of clinical research performed on pomegranate juice follows:

Pomegranate juice (250 mL daily for 4 weeks) was administered to 13 elderly subjects and, compared to a control group consuming apple juice, improved antioxidant function in the pomegranate group was found.[28]

Another study of 30 people with type 2 diabetes compared 10 men and 10 postmenopausal women ingesting 50 mL of pomegranate juice (from a variety called Wonderful) daily for 4 weeks with 10 men ingesting 5 mL of a pomegranate polyphenol extract daily for 6 weeks.[29] When compared to baseline levels, all groups demonstrated serum antioxidant effects and an increased affinity of paraoxonase-1 with HDL-cholesterol, two effects which could be of significance in decreasing atherosclerosis in diabetics. In another study, 10 people with type 2 diabetes drank 50 mL of pomegranate juice daily for 3 months, and baseline and follow-up laboratory analyses were done, comparing the results to 10 healthy subjects who also drank the same amount of pomegranate juice.[30] The baseline labs were predictable, with the diabetes group showing elevated triglycerides, lower HDL-cholesterol, increased hemoglobin-A1c, and elevated lipid peroxides, a measure of serum oxidative status. After the pomegranate treatment, there was no change in hemoglobin-A1c (an interesting result given that pomegranate juice contains 10% total sugars), a decrease in lipid peroxidation, a decrease in in vitro oxidative status, as well as a decrease in oxidized LDL-cholesterol uptake by macrophages, which the authors interpret as showing an anti-atherogenic effect.

Other clinical trials have examined the effect of pomegranate on hypertension and atherosclerosis, documenting such results as lower systolic blood pressure and decreased thickness of the carotid artery.[22] Pomegranate juice in higher doses (240 mL daily) may decrease myocardial ischemia, as demonstrated in a 3-month, randomized, placebo-controlled trial.[31]

Other Berries

There are many other berries containing antioxidant phytochemicals similar in structure and physiological effect as the three fruits reviewed in this article. Native to North America, of course, are blueberries, cranberries, blackberries, and strawberries, among others, which have various polyphenols such as anthocyanins *(see* Alternative Medicine Alert *October 2008 for a review of cranberry, blackberry, and grapes)*.[32] Also readily available in many grocery stores, health foods stores, and online, are juices from the fruits of noni (*Morinda citrofolia*), goji (*Lycium chinense*), and a fermented tea beverage purportedly high in B vitamins, kombucha.

Dose and Administration

The plants are often recommended as juices, occasionally a single juice extract, but more often as a mixture with other juices. It is not immediately obvious what an adequate daily dose of these juices should be. If there were large epidemiological studies available, it would be possible to extrapolate from populations that ingest a given amount of juice on a regular basis and possibly identify an improvement in disease outcomes, and make a recommendation to a given patient or patient population; these data do not exist at this point. Some indication of possible dosing comes from the clinical trials as mentioned above. For example, in clinical trials pomegranate juices have been dosed at approximately 50-240 mL (4 Tbsp to 1 cup) daily.

Adverse Effects

Polyphenol-enriched extracts of pomegranate juice have been found to be safe in humans and animals, but the lack of definitive data makes it difficult to comment on the safety of pomegranate juice in high doses or in specific clinical situations.[22] The same can be said for açaí and mangosteen. For example, researchers and experts have debated in the medical literature the pros and cons of antioxidant ingestion during cancer treatment; until this issue is resolved, caution, or better yet, avoidance of strong antioxidant foods and supplements is recommended in this clinical setting.

Conclusion

Açaí, mangosteen, and pomegranate are each plants with a rich history of traditional use as both foods and medicines. The most commonly used parts are the fruit pulp for açaí, the fruit rind (pericarp) for mangosteen, and the fruit juice of pomegranate. All of these plants contain phytochemicals that have shown primarily antioxidant, but also anti-inflammatory, and antitumor effects: anthocyanins (açaí, pomegranate), catechins (açaí, pomegranate), xanthones (mangosteen), and polyphenols (açaí, mangosteen, pomegranate). There is only one clinical trial each for açaí and mangosteen, demonstrating antioxidant and immune system effects, respectively. There are many, mostly small, clinical trials for pomegranate juice, showing serum antioxidant effects, and improvements in cardiovascular parameters.

Recommendation

There is an allure of exotic fruits and the possibility of improving certain medical conditions with their

ingestion. For açaí, mangosteen, and pomegranate, phytochemical analyses, in vitro studies, and some clinical trials (the latter primarily for pomegranate) support antioxidant and other effects that may correlate with improvements in some disease outcomes. The ideal doses, possible side effects, and identification of people most likely to benefit from specified juice ingestion, if any, have yet to be determined. It probably isn't worth spending the significant dollars these juices usually command when there are other fruits and juices that have been better studied. Perhaps future data will provide more to recommend açaí, mangosteen, and pomegranate than antioxidant potential, but until that time there is little clinical reason to use them, with the possible exception of pomegranate juice. ❖

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Systematic Reviews Reveal Benefits of Acupuncture for Prevention of Migraines and Tension-type Headaches

ABSTRACT & COMMENTARY

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Synopsis: *Two systematic reviews concluded that acupuncture is somewhat beneficial in the prophylactic treatment of both migraine and tension-type headaches. The results of additional, recently published randomized trials provided more evidence of benefit compared to studies available for a 2001 version of these reviews.*

Source: Linde K, et al. Acupuncture for migraine prophylaxis. *Cochrane Database Syst Rev* 2009;(1):CD001218.

THIS SYSTEMATIC REVIEW INVESTIGATED WHETHER acupuncture is more effective in reducing the frequency and intensity of migraine headaches in migraine patients than three other comparison groups: a) no treatment or routine care; b) placebo or "sham" acupuncture; or c) other treatments. Only randomized trials were included that had a post-randomization observation period of 8 weeks or longer. Trials with clinical outcomes such as headache frequency, pain intensity, analgesic use, etc., were included, but not those reporting only physiological or laboratory parameters. The main outcome measure was the proportion of responders during the 3-4 month period after randomization as measured by patient diaries. This outcome was selected because it was available for most studies. The meta-analysis used a random effects model due to the large clinical heterogeneity.

A total of 22 trials met the inclusion criteria, involving 4,419 participants. Twelve of these were not available at the time of the 2001 systematic review,[1] of which this review was an update. Some trials compared acupuncture to more than one other intervention. Six trials compared acupuncture to no treatment or routine care in which acute treatment was given during a migraine attack. Much clinical heterogeneity existed in these trials, leading the reviewers to place little weight on pooled effect size measures. However, "the findings clearly show that response, headache frequency, headache days, and headache scores 3-4 months after randomization are more favorable in patients receiving acupuncture." Only one trial involved long-term follow-up (9 months after treatment stopped) and those who received acupuncture did significantly better than those on routine care.

Fourteen trials had a placebo or "sham" acupuncture group. The techniques varied widely, but included using needles without penetrating the skin or inserting needles at irrelevant needle points. The outcomes did not show statistical differences between the two groups.

Four trials compared acupuncture to pharmaceutical treatment, one to a relaxation program and one to combined relaxation and massage therapy. For the trials comparing acupuncture with pharmaceuticals, acupuncture was significantly more effective on almost all outcome measures. In all four trials, patients reported fewer adverse effects following acupuncture compared to the pharmaceuticals. The two trials involving relaxation groups were small and of low quality providing little useful data, although in both cases the results favored the relaxation group.

Overall, the authors concluded that acupuncture is more beneficial than routine care or treatment of acute migraines only, and that it is at least as beneficial as pharmacological treatments. However, an apparently contradictory finding is that true acupuncture is as effective as "sham" acupuncture for migraine.

Source: Linde K, et al. Acupuncture for tension-type headache. *Cochrane Database Syst Rev* 2009;(1):CD007587.

THIS SYSTEMATIC REVIEW USED THE SAME METHODOlogy as the above except that it searched for trials involving patients with episodic or chronic tension-type headaches. Randomized trials were examined where acupuncture was compared against the same three types of controls: a) no prophylactic treatment or routine care; b) placebo or "sham" acupuncture; or c) other interventions.

Eleven trials involving a total of 2,317 participants met the inclusion criteria, of which six were published since the earlier version of the review.[1] Two large trials in which acupuncture was added to routine care and acute treatment found statistically significant and clinically relevant benefits in the acupuncture groups. The benefits were found up to 3 months, but were not investigated beyond this. Six trials compared acupuncture treatment with a "sham" acupuncture intervention. A meta-analysis found small but statistically significant benefits of acupuncture over "sham" on a number of outcomes. Four trials compared acupuncture with physiotherapy, massage, or relaxation. Three had significant methodological limitations and their results were difficult to interpret. The results with acupuncture tended to be less beneficial than with the other interventions.

Overall, the authors concluded that acupuncture could be a valuable non-pharmacological intervention for patients with frequent episodic or chronic tension-type headache.

■ COMMENTARY

Most people who get migraine headaches can manage them with acute treatment at the onset of the attack. However, some migraine patients get attacks so frequently or respond so inadequately to acute treatment that prophylactic treatment is desirable. Drugs such as propranolol, valproic acid, topiramate, and others are available and effective at reducing migraine frequency, but many patients discontinue them because of their side effects. Relaxation and biofeedback can help some people, but other non-pharmacological interventions would be welcome. In the same way, tension-type headaches can be treated acutely. However, for people experiencing these headaches chronically (defined as more than 15 days per month) prophylactic therapy would be desirable.

Acupuncture is a popular complementary therapy for the relief of migraine and other headaches. This review team published a systematic review of acupuncture for idiopathic headache in 1999[2] and updated it in 2001.[1] That review concluded that while the evidence was supportive of acupuncture as an effective treatment for idiopathic headache, the quality and amount of evidence was not convincing. Within the Cochrane Collaboration,

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

27. Progesterone is produced by the:
a. ovaries
b. adrenal glands
c. central nervous system
d. all of the above

28. Transdermal progesterone is consistently protective of the endometrium.
a. True
b. False

29. Salivary concentrations demonstrate an increase when transdermal progesterone is used.
a. True
b. False

30. Which of the following has been established with the use of açaí, mangosteen, and pomegranate?
a. Ideal dosage
b. Side effect profile
c. Patient population that benefits from use
d. None of the above

Answers: 27. d, 28. b, 29. a, 30. d.

authors are expected to update their systematic reviews regularly to take account of new studies. For this update, the authors decided to split their original review in two because of the number of new studies that had become available.

Systematic reviews have been criticized for combining high- and low-quality studies. These two systematic reviews included only studies in which randomization was appropriately carried out. They also used the new risk of bias approach developed by the Cochrane Collaboration.[3] Rather than giving a single quality score, this approach examines study quality on the basis of sequence generation, allocation concealment, blinding, incomplete outcome data, incomplete follow-up outcome data, and selective reporting. The methodological quality of the trials varied considerably, with newer trials tending to be of higher quality than older ones.

One of the main limitations with both reviews was the heterogeneity of the studies. Some studies included patients with various types of headaches. Therefore, for the migraine review, the included studies were only those involving migraine patients or where data for migraine patients could be separated from all other data. In the other review, only studies in which data were available for episodic or chronic tension-type headache were included. The adequacy of the acupuncture intervention in the trials was assessed by members of the review team who were experienced acupuncturists. Only needle acupuncture in which the needles were inserted at acupuncture points, pain points, or trigger points were included. Methods such as laser acupuncture were not included. However, acupuncture is practiced differently in different countries and trials came from several countries. Curiously, none of the studies included in either review were conducted in China. The most frequently represented country was Germany, where acupuncture is most often practiced by physicians trained according to traditional Chinese medicine. The next most commonly represented country was the United Kingdom, where acupuncturists are usually not physicians and are trained in a more Western approach. The impact of these differences is not known.

While some benefit can be seen in some of the comparisons made in the two reviews, the size of the effect is difficult to establish because of the study heterogeneity. Explanations for the apparently contradictory findings in the migraine review were proposed. First, acupuncture might have a particularly strong placebo effect so that even "sham" acupuncture elicits a relatively large clinical effect. Second, the "sham" acupuncture often used acupuncture points believed to be irrelevant for migraine. However, some of the proposed mechanisms of action for acupuncture do not involve these points and instead suggest that the needles act through a more nonspecific mechanism. These theories would suggest that "sham" acupuncture would be as effective as "true" acupuncture. The third explanation is that since participants were blinded only in the "sham" acupuncture trials, bias was introduced into the other trials. In addition, acupuncturists often question the appropriateness of acupuncture in clinical trials because of highly restrictive protocols that do not support individualization of therapy. This is particularly the case in trials involving "sham" acupuncture.

While many issues regarding acupuncture trials for migraine or tension-type headaches remain unresolved and require further research, these systematic reviews show that the evidence of benefit from acupuncture has become stronger in recent years. For prophylactic treatment of migraines and chronic tension-type headaches, acupuncture can be considered a treatment option for patients interested in trying it. Migraine patients who have experienced adverse effects from pharmaceutical treatments might be particularly interested. ❖

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