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Efficacy of Acupuncture for Treating Back Pain

By Yoon-Hang Kim, MD, MPH, DABMA

BACK PAIN IS THE FIFTH MOST COMMON REASON FOR ALL PHYSICIAN visits.¹ The direct health care expenditure for treating back pain is estimated to be more than \$20 billion annually and as much as \$50 billion per year when indirect costs are included.² In the United States, 90% of adults experience back pain at some time in their lives, and 50% of the working population complains of back pain annually.^{3,4}

Conventional medical approaches to back pain range from conservative management with non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy modalities to invasive interventions such as epidural steroid injection and back surgery.

Acupuncture is one of the most popular forms of complementary and alternative medicine and is rapidly gaining acceptance. In 1997, the NIH consensus panel concluded that acupuncture is effective for adult postoperative and chemotherapy-related nausea and vomiting and probably for the nausea of pregnancy.⁵ Furthermore, the panel concluded that there are reasonable studies showing relief with acupuncture on such diverse pain conditions as menstrual cramps, tennis elbow, and fibromyalgia.⁵

Mechanism of Action

Acupuncture analgesia is one of the most thoroughly researched physical modality in medicine and serves as a general model for basic science acupuncture research.⁶ Studies using animal and human subjects to evaluate acupuncture analgesia were started in China in 1965, and continue throughout the world to this day.

It is widely believed that acupuncture analgesia is initiated by stimulation of small diameter nerves in muscles, which send impulses to the spinal cord, midbrain, and pituitary gland, resulting in the release of neurotransmitters such as monoamines and endorphins, which in turn block pain signal transduction.⁶ The discovery of naloxone, an endorphin antagonist, helped elucidate the role of endorphins in acupuncture. Naloxone was shown to block acupuncture analgesia in human volunteers in a randomized, double-blind study.⁷ A subsequent study produced the same results, fashioned a

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dose-response curve for naloxone, and found that increasing doses created increasing blockade.⁸

In addition to endorphins, monoamines such as serotonin and norepinephrine have been shown to be involved in acupuncture analgesia. Microinjections of serotonin antagonists and norepinephrine antagonists have blocked the effect of acupuncture analgesia.^{9,10}

It is likely that endorphins and monoamines represent but two classes of molecules involved in acupuncture analgesia, and that other classes of molecules also may be linked to this cascade.

Systematic Reviews

In the West, acupuncture is most commonly used for the treatment of chronic pain, particularly musculoskeletal complaints. While there are many randomized controlled trials (RCTs) evaluating the effectiveness of acupuncture for back pain, the majority display poor quality, and provide conflicting evidence. One way to efficiently evaluate the confusing data is through the use of systematic review, applying scientific strategies in ways that limit bias. Two systematic reviews of acupuncture for back pain are summarized in Table 1.

Ernst and White selected 12 studies and pooled data from nine for meta-analysis.¹¹ The primary outcome

measure for the meta-analysis was numbers of patients whose symptoms were improved at the end of the treatment. The odds ratio of improvement with acupuncture compared with the control intervention was 2.30 (95% confidence interval [CI], 1.28-4.13). For sham-controlled, evaluator-blinded studies, the odds ratio was 1.37 (95% CI, 0.84-2.25). Ernst and White concluded that although acupuncture was shown to be superior to various control interventions, there was insufficient evidence to state whether it is superior to placebo.

van Tulder et al performed a qualitative review by assessing the methodological quality and outcome of the original studies and attributing levels of evidence to the effectiveness of acupuncture.¹² Eleven RCTs were included in the review, but only two were determined to be high quality. In eight of the 11 trials, the individual authors had concluded that acupuncture provided benefits beyond those noted for the control group. In the remaining three trials they had concluded that acupuncture's effectiveness was similar to the control group. By contrast, van Tulder et al disagreed with the original authors' conclusions in seven of the 11 studies, stating that there was no difference between acupuncture and control in seven trials and that acupuncture was superior in only two of the 11 trials. The results were unclear in the remaining two trials.

In summary, conclusions of the primary authors were positive for eight of 11 studies and the conclusions of van Tulder et al were positive for only two of the 11 studies. van Tulder et al concluded that they would not recommend acupuncture as standard treatment for patients with low back pain and that there is a need for high-quality RCTs.

Methodological Challenges of Systematic Reviews

Many challenges face acupuncture researchers including having a solid foundational research base, non-specific (placebo) effect of needle insertion, and a lack of reliable and valid research protocols. A wide range of acupuncture styles exists including microsystems acupuncture (i.e., auricular, scalp, and hand acupuncture), French energetics, neuroanatomic acupuncture, five elements acupuncture, and traditional Chinese approaches to acupuncture. The differences of these styles are understood by its practitioners, but rarely are taken into account in systematic reviews.

The fact that Ernst and White¹¹ and van Tulder et al¹² included almost the same studies, yet arrived at opposite conclusions, attests to the difficulty of evaluating the existing evidence. The major difference is that Ernst and White utilized a statistical approach

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Table 1 Systematic reviews of acupuncture for back pain				
Author	Comparisons	Studies	Results	Conclusion
Ernst and White ¹¹	Sham, other treatments, no treatments	12 RCTs	Odds ratio for improvement with all control interventions 2.30 (95% CI, 1.28-4.13), with sham acupuncture 1.37 (95% CI, 0.84-2.25). Majority of studies good quality.	Acupuncture superior to various control interventions, although insufficient evidence whether superior to sham acupuncture.
van Tulder et al ¹²	Sham, other treatments, no treatments	11 RCTs	Conclusions of primary authors positive in eight studies, by reviewers only two studies. Methodological quality judged as low. Conflicting evidence for acupuncture vs. no treatment. Acupuncture not more effective than trigger point injection or TENS. Acupuncture not more effective than placebo or sham acupuncture in most trials.	Acupuncture not recommended as standard treatment for low back pain. High-quality RCTs needed.

(meta-analysis) while van Tulder et al used qualitative analysis. Both authors agreed that more high-quality RCTs are needed.

Recent Clinical Trials

Several recent RCTs not included in the two systematic reviews are summarized below and in Table 2.

A study by Ghoname et al utilized percutaneous electrical nerve stimulation (PENS) acupuncture, a contemporary neuroanatomic style of acupuncture utilizing trigger points and electric stimulation.¹³ Ghoname et al demonstrated PENS acupuncture to be more effective in decreasing visual analog scale (VAS) pain score compared to sham, transcutaneous electrical nerve stimulation (TENS), and exercise. Additional benefits included decreased medication use and improved physical activity, quality of sleep, and sense of well-being ($P < 0.05$ for each). A weakness of the study is that the patients ($n = 60$) were divided into four groups leaving a small number of subjects for each treatment arm.

In a study published in 2004, Sator-Katzenschlager et al compared auricular acupuncture and auricular electro-acupuncture.¹⁴ Although both groups showed improvement during the observation period, the pain relief was significantly better in the auricular electro-acupuncture group than in the conventional auricular acupuncture group ($P < 0.001$). In addition, psychological well-being, physical activity, and quality of sleep during the six-week acupuncture treatment and follow-up were significantly improved in the auricular electro-acupuncture group compared to the conventional auricular acupuncture group ($P < 0.05$).

In another study, Meng et al compared medical treatment with acupuncture.¹⁵ The acupuncture group showed significant improvement in the Roland Disability Questionnaire ($P = 0.001$). Effects were maintained for up to four weeks after treatment ($P = 0.007$). Kerr et al conducted a similarly designed study comparing TENS and acupuncture.¹⁶ The result showed overall improvement of back pain in both groups; however, no differences between the two groups were observed. Both studies failed to control for potential placebo response resulting from needle insertion (by using sham acupuncture, for example). The fact that both acupuncture and TENS benefited back pain patients and no difference was observed between groups means both may be acceptable for treating back pain. Other studies document similar findings.¹⁷

In 2002, Leibing et al compared physical therapy, acupuncture, and sham acupuncture.¹⁸ At the end of the treatment phase, acupuncture was superior to the control intervention (physiotherapy) regarding pain intensity ($P < 0.001$), pain disability ($P < 0.001$), and psychological distress ($P = 0.020$). However, no differences were observed between sham acupuncture and acupuncture. The authors concluded that a non-specific or placebo effect had been shown through this trial.

Molsberger et al conducted a study comparing a combination of acupuncture and conservative orthopedic treatment (OT) vs. sham acupuncture + OT vs. OT.¹⁹ Percent improvements after three months appear below:

- Acupuncture + OT: 77% (95% CI, 62-88%);
- Sham acupuncture + OT: 29% (95% CI, 16-46%);
- OT: 14% (95% CI, 4-30%).

Table 2

Randomized controlled trials of acupuncture for low back pain

Author	Design	Results	Conclusion
Ghonomie et al ¹³	RCT, n = 60 PENS acupuncture vs. sham acupuncture vs. TENS vs. exercise	PENS was significantly more effective in decreasing VAS pain score compared to sham acupuncture, TENS, and exercise. The average daily oral intake of non-opioid analgesics decreased from 2.6 ± 1.4 pills/d to 1.3 ± 1.2 pills/d (P < 0.008). The PENS therapy was more effective in improving physical activity, quality of sleep, and sense of well-being (P < 0.05 for each).	PENS was significantly more effective in decreasing VAS pain score compared to sham acupuncture, TENS, and exercise.
Sator-Katzenschlager et al ¹⁴	RCT, n = 61 Auricular electro-acupuncture vs. auricular acupuncture	Pain relief was significantly better in the auricular electro-acupuncture group vs. the conventional auricular acupuncture group (P < 0.001). Both groups showed some improvement; however, the improvement in psychological well-being, physical activity, and quality of sleep during the six-week acupuncture treatment and follow-up was significantly more in auricular electro-acupuncture group vs. the conventional group (P < 0.05).	Pain relief was significantly better in the auricular electro-acupuncture group vs. the conventional auricular acupuncture group.
Meng et al ¹⁵	RCT, n = 47 Acupuncture vs. medical treatment	Acupuncture group showed significant decrease in Roland Disability Questionnaire (P = 0.001). The effect was maintained for up to four weeks after treatment (P = 0.007).	Acupuncture is an effective, safe adjunctive treatment for chronic low back pain for older adults.
Leibing et al ¹⁸	RCT, n = 131 Acupuncture vs. sham acupuncture vs. physical therapy	Acupuncture was superior to the control intervention (physiotherapy) regarding pain disability (P < 0.001) and psychological distress (P = 0.020) at the end of treatment. However, no differences observed between sham acupuncture and acupuncture.	Both sham acupuncture and acupuncture showed superior results compared with the physical therapy.
Molsberger et al ¹⁹	RCT, n = 186 Acupuncture + OT vs. sham acupuncture + OT vs. OT	In the whole sample, pain relief of ≥ 50% on VAS was reported. The percentage improvements after three months were: Acupuncture + OT: 77% (95% CI, 62-88%); sham acupuncture + OT: 29% (95% CI, 16-46%), OT: 14% (95% CI, 4-30%). Effects are significant for acupuncture + OT over sham acupuncture + OT (P ≤ 0.001) and for acupuncture + OT over OT (P < 0.001).	Acupuncture can be an important complementary treatment to conservative OT in the management of chronic low back pain.
Cherkin et al ²⁰	RCT, n = 262 Acupuncture vs. massage vs. education	At 10 weeks, massage was superior to self-care on the symptom scale and disability scale (P = 0.01). The massage group used the least medications (P < 0.05) and had the lowest costs of subsequent care.	Therapeutic massage was effective for persistent low back pain. Traditional Chinese medical acupuncture was relatively ineffective.

The effects were significant for acupuncture + OT over sham acupuncture + OT ($P \leq 0.001$) and over OT ($P < 0.001$). While Leibing et al¹⁸ attributed the benefits of acupuncture to a non-specific effect, Molsberger et al¹⁹ and Ghoname et al¹³ demonstrated a difference between sham and true acupuncture.

Cherkin et al conducted a trial comparing acupuncture, massage, and self-education for treatment of lower back pain.²⁰ At 10 weeks, massage was superior to self-care on both symptom and disability scales ($P = 0.01$). The massage group used the least medications ($P < 0.05$) and had the lowest costs of subsequent care. The authors concluded that the therapeutic massage was effective for persistent low back pain and traditional Chinese medical acupuncture was relatively ineffective.

Gadsby and Flowerdew concluded that electroacupuncture and TENS reduce pain and improve range of motion in chronic back pain patients in their Cochrane Database System Review.²¹ Carlsson and Sjolund conducted a RCT comparing acupuncture and mock TENS, concluding that a significant decrease in pain intensities occurred at one and three months in the acupuncture group compared with the mock TENS group.²²

Another study by Giles and Muller compared acupuncture, medication, and spinal manipulation and concluded that manipulation results in greater short-term improvement than acupuncture or medication.²³

Cherkin et al performed a review of evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain utilizing existing systematic reviews and updated literature.²⁴ The conclusions reached by Cherkin et al are summarized in Table 3.

Notably, the review by Cherkin et al²⁴ left out at least four acupuncture RCTs documenting positive results and categorized Grant et al¹⁷ as a negative study when the results showed that both TENS and acupuncture showed positive effects.

Table 3 Conclusions of Cherkin et al ²⁴
<ul style="list-style-type: none"> • Massage is effective for persistent back pain. • Spinal manipulation has small clinical benefits. • The effectiveness of acupuncture remains unclear. • All of the treatments appear to be safe. • Preliminary evidence suggests that massage, but not acupuncture or spinal manipulation, may reduce the costs of care after an initial course of therapy.

Conclusion

An abundant amount of conflicting information exists on the efficacy of acupuncture for treating back pain. The waters are muddied further by systematic reviews that arrived at opposite conclusions while analyzing almost identical studies. Despite the lack of clear clinical evidence, basic science research shows plausible mechanisms of action for acupuncture with respect to reducing pain.

Recommendation

Back pain is a prevalent medical problem with huge social, economical, and medical implications. While most patients with back pain improve, a segment of the patient population requires intensive therapy or invasive procedures including surgery.

Given the low risk of acupuncture and existing range of therapeutic options, a trial of acupuncture should be considered a potentially useful option for some patients with persistent back pain. ❖

Dr. Kim is a Fellow in the Program in Integrative Medicine at the University of Arizona in Tucson.

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Green Tea and Breast and Prostate Cancer Chemoprevention

By Robert Krochmal, MD,
and Mary L. Hardy, MD

BREAST AND PROSTATE MALIGNANCIES ARE AMONG THE leading causes of cancer death in men and women in the United States.^{1,2} Despite advances in early detection and better initial treatments, each of these cancers still accounts for more than 200,000 newly diagnosed cases and up to 50,000 deaths per year. Given the reality of such numbers, it is imperative to develop prophylactic therapies with the potential to decrease cancer incidence. For cancers of the breast and prostate, which generally have a long latency period, there is ample opportunity to intercede preventively. In addition, patients who have survived an initial episode of cancer are very likely to be interested in dietary and lifestyle strategies to minimize risk of recurrence. For all of these reasons, there is a mandate to identify safe and effective therapies that may decrease the primary or secondary risk of cancer.

A chemopreventive agent is characterized by the ability to prevent or restrain the development of cancer. Since carcinogenesis is an extended process that can take up to 20-40 years to manifest as overt cancer, chemopreventive substances would necessarily need to be taken regularly over a long period of time. Therefore, it is essential that any agent being considered for chemoprevention have a high margin of safety and tolerability. Because a relatively low percentage of patients taking such a product would develop cancer without it, the incidence of toxic or adverse side effects must be small.

Green tea represents an ideal candidate for cancer chemoprevention. Derived from the evergreen *Camellia sinensis*, green tea is the most common chemopreventive drink in the world, popular for more than 4,000 years, and second only to water in worldwide consumption. It is safe, highly tolerable, and readily available in many forms, most commonly as a dried leaf for infusion. Epidemiological studies suggest a strong, dose-dependent preventive value of green tea consumption against development and recurrence of many forms of cancer, including cancers of the colon,³ prostate,⁴ ovary,⁵ and breast.⁶⁻⁸

Constituents and Chemistry

Green tea is grown for commercial use in more than 30 countries, and its harvest still depends on manual

techniques, given that the most palatable tea comes from the young, uppermost leaves of the plant. Original tea users in China exposed the leaves to hot steam immediately after harvesting, a process that is now known to inactivate polyphenol oxidase contained in the leaves, thus preventing the breakdown of catechins.⁹ When the leaves are not steamed, the oxidative enzymes convert the catechins to other polyphenols, such as theaflavine gallate and thearubigins.¹⁰ This process of oxidation and subsequent fermentation leads to black tea. Oolong is a type of tea that typically has been steamed about one hour after harvesting, creating an intermediate between green and black tea.

The major polyphenols found in green tea are epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate (EGCG) (see Figure 1). It has been estimated that up to 30% of the dry leaf weight of green tea consists of polyphenols.¹⁰ Other constituents include

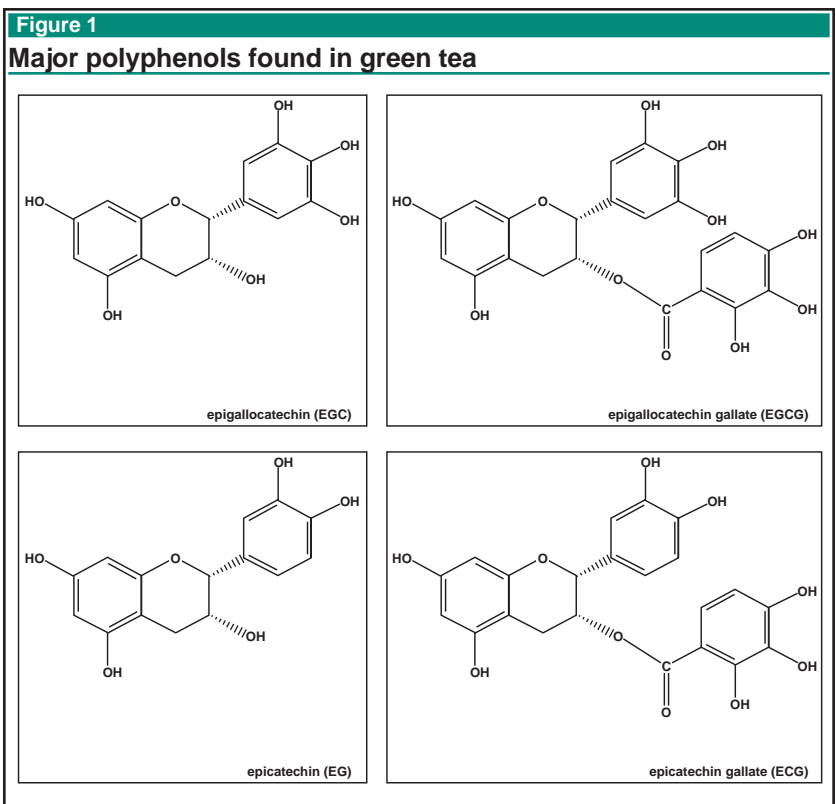
caffeine (1%-4%) and related methylxanthines, fiber, sugars (5%), protein (15-20%), and various micronutrients. All of these constituents have been shown to vary significantly with different commercial samples of green tea.^{11,12} In addition, levels of EGCG and other catechins vary according to age of the leaf and method of processing in the following order: green tea (old leaves) > green tea (young leaves) > oolong tea > black tea.¹³

Bioavailability

A number of Phase I trials have documented the absorption of flavonoids, leading to enhanced blood antioxidant potential.¹⁴ Upon ingestion, two kinds of transformations can occur that affect flavonoid bioavailability. First, large complex molecules may be broken down by stomach acid and digestive enzymes into smaller phenolic acids that are absorbed more easily. Then, compounds can be either absorbed and modified by the liver or further degraded by gut microflora. Therefore, the bioavailability and pharmacokinetics of green tea polyphenols represent a complex process, and their activity results not only from the parent molecules, but also from their metabolites.

Mechanism of Action

Consistent with other botanicals, green tea is distinguished by its diversity of composition compared with pharmaceutical agents that act upon a single target. Not



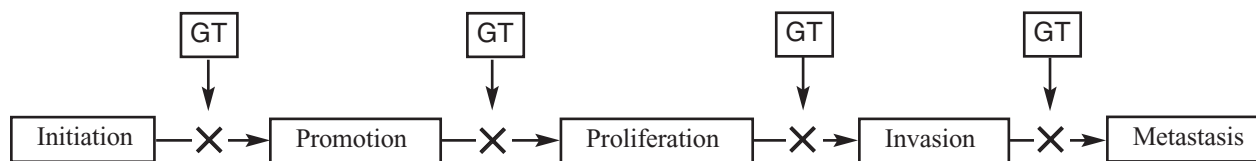
surprisingly, studies with green tea in recent years have demonstrated an assortment of mechanisms against tumorigenesis. This multidimensionality makes green tea unique as a chemopreventive agent, since it has the ability to act upon multiple stages of cancer progression. It takes many years from the initial insult leading to malignant transformation until the ultimate progression to metastasis. As shown in Figure 2, various steps are necessary for this to occur, and there is evidence to support the role of green tea in the suppression of each of them.

Through its antioxidant capacity,^{12,15,16} green tea can block the initiation of malignancy by neutralizing reactive oxygen and nitrogen species that promote mutagenicity and genotoxicity. Green tea's capacity for this action is apparent in the images of the major catechins in Figure 1, with multiple hydroxyl moieties poised to scavenge. It has been shown that the catechin content of green tea correlates with its antioxidant capacity.¹² Indirectly, green tea also may exhibit antioxidant effects through inhibition of pro-oxidant enzymes, such as cyclooxygenase and nitric oxide synthase.¹⁷

A study in IL-2 deficient mice given green tea polyphenols found a decrease in interferon-gamma and tumor necrosis factor-alpha, which corresponded with lower colitis scores for the treated mice compared with placebo.¹⁸ This anti-inflammatory potential also may contribute to an ability to reduce tumorigenesis.

Figure 2

Possible effects of green tea (GT) on the progression to metastasis



Another biological effect of green tea is its ability to induce apoptosis (programmed cell death) and cell cycle arrest in cancer cells.¹⁹ Apoptosis is involved in maintaining mammary epithelial cell homeostasis, thereby inhibiting the initiation, progression, and metastasis of breast cancer.²⁰ Green tea-induced apoptosis has been found to affect the breast cancer cell lines MCF-7 and MDA-MB-231, but not normal breast epithelial cells.²¹ Telomerase, a factor which is elevated in more than 90% of breast cancers, has been found to be down-regulated by EGCG, leading to induction of apoptosis in MCF-7 cells, with no adverse effect on normal mammary cells.²² In prostate cancer, both androgen-sensitive and androgen-insensitive cells appear to be susceptible to EGCG-induced apoptosis.^{4,23}

Angiogenesis (the process leading to the formation of new blood vessels) also has been proposed as a factor in tumor development and proliferation.²⁰ Green tea extract has been shown to reduce vessel density and tumor size in breast cancer xenographs,²⁴ which appears to be mediated through an inhibition of vascular endothelial growth factor (VEGF).²⁵ Inhibition of VEGF also has been found in prostate cancer cells.²³ Components of green tea not only decrease VEGF-promoter activity, but also epidermal growth factor receptor (EGFR)-signaling pathways.²⁶

Various other cell-signaling pathways are affected by the constituents in green tea. For example, green tea polyphenols have been found to inhibit Her-2/neu signaling,²⁷ a factor in breast cancer cell proliferation. In addition, EGCG appears to synergize with growth factor-dependent signals to induce p21 and impair cell cycle progression.²⁸ A study in rats found green tea extract to decrease mammary tumor burden, potentially through induction of p27 (kip1) cyclin-dependent kinase (CKI) inhibitor expression.²⁹ Green tea's effects on ornithine decarboxylase also appear to play a role in decreased cellular proliferation,³⁰ particularly in the prostate, which has the highest concentration of this enzyme.

In addition to its antioxidant, anti-inflammatory, antiangiogenesis, and antiproliferative activities, green

tea may also be useful in the inhibition of metastasis through its anti-invasive actions. EGCG has been shown to be a natural inhibitor of metallo and serine proteases.³¹ In TRAMP mice, a model for prostate prevention, green tea at a dose equivalent to six cups per day was able to significantly inhibit metastasis to lymph nodes, liver, lung, and bone.³² Strikingly, distant metastases were reduced by fourfold compared with mice on placebo. Green tea polyphenols thus appear to suppress factors required for tumor invasion and metastasis.

Clinical Studies

Breast Cancer. Although there have been no direct clinical trials to date, epidemiologic studies have found the relative risk of breast cancer in women who are consistent tea drinkers to be as low as half that of women drinking less than one cup per month.⁶ A follow-up to one study found that women with a low-activity allele for catechol-O-methyltransferase (COMT), an enzyme that rapidly methylates tea polyphenols, had the highest risk reduction for breast cancer.³³ This suggests that tea catechins are an active chemopreventive constituent of green tea, and that women less efficient in eliminating these compounds derive the most benefit from their consumption.

A study of breast cancer recurrence found that risk was decreased significantly among women drinking three or more cups of green tea per day.⁷ The highest risk reduction was found in women with earlier stages of cancer at time of initial diagnosis.

Previous studies by Fujiki et al have found that a history of consuming more than 10 cups of green tea per day led to delayed cancer onset, and that high consumption of green tea is associated with decreased axillary lymph node metastases among premenopausal women.³⁴ Fujiki also found that stage I and II breast cancer patients consuming more than five cups per day experienced a lower recurrence rate and longer disease-free period than those consuming fewer than four cups per day.³⁵ This led Fujiki to propose a two-stage approach to the analysis of green tea cancer prevention, namely prevention prior to cancer development and

prevention following cancer diagnosis and treatment. It is possible not only that green tea can prevent the onset of cancer, but also that it can protect against recurrence, especially in the early stages.

The broad ability for green tea to be effective at both primary and secondary prevention, while exhibiting extremely low toxicity, is remarkable. Future studies should evaluate both of these potential mechanisms.

Prostate Cancer. For prostate cancer, risk appears to decrease with increasing frequency, duration, and quantity of green tea consumption. One study found a relative risk for the development of prostate malignancy to be 0.27 for those men drinking more than three cups daily.⁴ This risk dropped as low as 0.12 for those drinking tea for more than 40 years, and was 0.09 for those consuming more than 1.5 kg of green tea leaf per year.

As stated previously, a number of Phase I trials have documented the absorption of flavonoids leading to enhanced blood antioxidant potential,¹⁴ suggesting that orally consumed green tea components are indeed bioavailable. Henning et al recently demonstrated that green tea polyphenols were detectable in prostate tissue of men who consumed five cups daily prior to radical prostatectomy.³⁶ It was further shown that LNCaP prostate cell proliferation was decreased when grown in a medium containing patient serum collected after green tea consumption, as compared with serum collected prior to consumption.

A Phase II trial conducted by the North Central Cancer Treatment Group at the Mayo Clinic among patients with androgen-independent prostate cancer found that green tea consumption was able to significantly decrease PSA values, while the placebo group sustained a PSA increase of 43%.³⁷

Safety

Historical use of green tea demonstrates exceptional safety of the hot water infusion,⁹ and clinical trials have shown no adverse effects with concentrated, decaffeinated formulas of green tea extract equivalent to 8-16 cups per day.^{34,38} Most reported toxicity has been due either to temperature of the green tea taken as an infusion (increased incidence of esophageal cancer in China) or to its caffeine content (tachycardia, irritability, insomnia). Both problems are eliminated with standardized, decaffeinated capsules.

The only herb-drug interaction reported in the literature with green tea is a single case study regarding its potential inhibitory effect on warfarin.³⁹ Warfarin produces its effect by inhibiting the production of vitamin K, and green tea may contain significant amounts of vitamin K. It is therefore advisable that any patient

requiring warfarin therapy undergo close monitoring and be questioned routinely about their intake of vitamin K-containing products.

Dosage and Administration

Green tea most commonly is encountered as a dried leaf used to prepare an infusion. An average cup of green tea contains between 50 mg and 150 mg of polyphenols, depending on the amount of leaves used and the length of time they are steeped. Most of these polyphenols become available in the hot water infusion within minutes of preparation. A general rule of thumb is that 1 g of soluble components will yield about 100 mg of polyphenols in the infusion.

For those who prefer not to drink tea, given the large amount of green tea needed to demonstrate most epidemiological effects, green tea extracts have been developed for convenience and phytochemical control. Decaffeinated products prioritize the polyphenol fraction, and concentrate this component to between 60% and 89% of the weight of the extract. Three cups of green tea per day or 400 mg of standardized extract (80% total polyphenols) would supply approximately 300 mg of polyphenols. This generally is the minimum dosage that has been studied in epidemiological trials, and higher dosages appear to be well tolerated.

Conclusion

Epidemiological data suggest a clear benefit in cancer chemoprevention with green tea taken as a beverage. Although amounts of green tea consumption are not consistent among epidemiological studies, as little as 2-3 cups/d appears to be effective in some cases. Prospective, randomized, double-blind trials with green tea could provide more definitive insight into the potential of this agent against breast and prostate malignancies. Such trials will necessarily be time-consuming (generally they have a duration of five years or more); however, given the wealth of background data, they are warranted.

In any such trial, to standardize the intervention and ensure an adequate dose, utilization of a well-characterized, standardized supplement would be advisable. Furthermore, elimination of the caffeine component would not only minimize potential side effects (thus allowing higher doses), but also would strengthen the role of the polyphenol fraction of green tea as the active principle, should those studies be positive. Further studies might determine whether green tea may be used along with or as an adjuvant to chemotherapy, or whether it can be combined with other chemopreventive compounds. There is ample evidence that green tea is safe and non-toxic for most patients.

Recommendation

Given the growing data supporting the antitumor properties of green tea, the use of this botanical in the treatment and prevention of breast and prostate cancer should be strongly considered, especially as a beverage. Incorporating this drink into a daily routine is a sensible option, given its reasonable cost, palatability, and rich composition of antioxidants. The dried leaf is widely available in both loose leaf and convenient tea bag form, and the infusion is becoming more and more popular at coffee and tea shops as an alternative to coffee. For those wishing to avoid caffeine, decaffeinated forms are available.

Given that many studies show dose-dependent preventive effects, supplementation with a standardized, concentrated product is recommended for those wishing to secure a more powerful breast or prostate cancer chemopreventive regimen. This option would likely be the most beneficial for those with an environmental or familial predisposition for either disease. Since green tea is safe, readily available, effective, and relatively inexpensive, it should be considered one of the top dietary choices for patients concerned about breast or prostate cancer prevention. ❖

Dr. Krochmal is a Fellow and Dr. Hardy is Associate Director, UCLA Center for Dietary Supplement Research: Botanicals; Dr. Hardy also is Medical Director, Cedars-Sinai Integrative Medicine Program, Los Angeles, CA.

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CME Questions

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 certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

29. Which of the following has been shown to be involved in acupuncture analgesia?
 - a. Endorphins
 - b. Serotonin
 - c. Norepinephrine
 - d. All of the above

30. The systematic reviews of acupuncture conducted by Ernst and White and van Tulder et al arrived at similar conclusions.
 - a. True
 - b. False
31. Despite the lack of clear clinical evidence of acupuncture's efficacy, basic science research shows plausible mechanisms of action for acupuncture with respect to pain reduction.
 - a. True
 - b. False
32. An effective chemopreventive agent:
 - a. is characterized by the ability to prevent or restrain the development of cancer.
 - b. would necessarily need to be taken regularly over a long period of time.
 - c. would have a high margin of safety and tolerability.
 - d. All of the above
33. The minimum daily dosage of polyphenols used in epidemiological studies of green tea is 300 mg. This equates to:
 - a. 1 cup of tea per day
 - b. 2 cups of tea per day
 - c. 3 cups of tea per day
 - d. 4 cups of tea per day
34. Epidemiological data suggest a clear benefit in cancer chemoprevention with green tea taken as a beverage.
 - a. True
 - b. False

Answers: 29. d, 30. b, 31. a, 32. d, 33. c, 34. a.

With Comments from Russell H. Greenfield, MD

Oral Vitamin C

Source: Padayatty SJ, et al. Vitamin C pharmacokinetics: Implications for oral and intravenous use. *Ann Intern Med* 2004;140:533-537.

Goal: To determine whether route of administration has a significant impact on plasma levels of vitamin C.

Design: Depletion-repletion, with dose concentration studies and pharmacokinetic modeling.

Subjects: Seventeen healthy volunteers (7 men, 10 women, aged 19-27 years) hospitalized for 3-6 months at an academic medical center.

Methods: Subjects adhered to a diet containing < 0.005 g vitamin C; once a state of depletion had been assured, vitamin C was administered orally in a dose of 0.015 mg twice daily. After a steady state was attained, subjects received successive oral daily vitamin C doses of 0.03 g, 0.06 g, 0.1 g, 0.2 g, 0.4 g, 1.0 g, and 2.5 g until a steady state was achieved for each dose. Bioavailability sampling was conducted at various doses, with blood samples obtained almost hourly. Intravenous administration of similar doses of vitamin C occurred at 250 mg/min, again with frequent blood sampling during the first hour following administration, and then over the subsequent 10 hours. Plasma vitamin C concentrations were calculated for a dose range of 1-100 g.

Results: Plasma concentrations of vitamin C were significantly higher over all

dosages with intravenous administration. At the largest vitamin C dose used, mean peak serum values were 6.6-fold higher with intravenous administration. Peak plasma vitamin C levels increased with increasing dosages when administered intravenously, but reached a plateau with increasing oral dosages. Urine levels of vitamin C also were higher with intravenous administration across all doses.

Conclusion: Only intravenous vitamin C produces high plasma and urine levels. When ingested orally, plasma concentrations of vitamin C are tightly controlled, even at very high dosage.

Study strengths: Controlled setting with precise intakes of vitamin C; diligent blood sampling.

Study weaknesses: The conditions used for the study severely limit generalizability; very small sample size and no mention of race; only male subjects were used to construct the pharmacokinetic model.

Of note: In vitro data suggest that vitamin C in an extracellular concentration > 1,000 $\mu\text{mol/L}$ kills cancer cells via oxidative damage that normal cells may be able to repair; using their pharmacokinetic model, the authors suggest that a single oral dose of 3 g vitamin C will produce a peak plasma level of 206 $\mu\text{mol/L}$ and that repeated administration every four hours will result in almost no increase in plasma concentration, whereas intravenous administration of 3 g vitamin C will produce a peak plasma level of 1,760

$\mu\text{mol/L}$; some CAM practitioners use intravenous vitamin C in a dose of 60 g daily; how did they identify volunteers to spend 3-6 months in the hospital?(!)

Did you know?: Retrospective, non-blinded trials of oral and intravenous high-dose vitamin C (10 g daily) have shown clinical benefits for people with terminal cancer; placebo-controlled trials of patients with cancer using a daily oral dose of 10 g of vitamin C found no benefit to patients; vitamin C-rich foods often contain up to 200 mg of vitamin C.

Clinical import: This is one of the first papers to evaluate the difference in plasma vitamin C levels obtained with intravenous vs. oral administration. Whether there is clinical import to this finding, or therapeutic efficacy in the setting of cancer or wound healing as has been proposed, is yet to be proven. Of note, the authors suggest that plasma vitamin C concentrations from food intake compare favorably with those associated with oral supplemental vitamin C. It is already well-established that regular consumption of fruits and vegetables confers significant health benefits above and beyond vitamin C content.

Together, these statements speak against the need for vitamin C supplementation if fruits and vegetables are enjoyed on a frequent basis. Intravenous vitamin C and the resultant high plasma levels obtained, however, may have clinical implications.

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