The Pomegranate: Nature’s Power Fruit?

Robert Longtin

Mention pomegranates to Ephraim Lansky, M.D., and he will gladly offer you his opinion, though he probably won’t mention whether he likes to eat the seed-filled fruit. What interests Lansky about pomegranates is, in his words, the "extraordinary" medicinal properties of the tree itself, an idea that dates to Biblical times and which, he says, has been oddly overlooked by Western medicine.

Reports of the pomegranate’s medicinal qualities have echoed throughout the millennia. Several Middle Eastern, Asian, and South American peoples continue to chew small bits of its bark, petals, and peel to treat ailments ranging from dysentery to diseases of the mouth and gums.

So bullish is Lansky on the health-promoting properties of the pomegranate tree—fruit, leaves, bark, and all—that he launched a start-up company 3 years ago in Israel to move his idea into the
marketplace. Already, the company has created a fermented, antioxidant-rich juice supplement that it promotes for better cardiovascular health, and Lansky said that other products and markets await.

Among them is a special blend of pomegranate juice, seed, and peel that, according to published results, potently and reproducibly kills prostate and breast cancer cells in culture. Lansky said he hopes to move his extract into clinical trials as quickly as possible. If the initial data establish the efficacy of the product, he envisions additional human trials and ultimately regulatory approval.

Although Lansky’s drug development strategy seems to cover most of the scientific bases, it still leaves wide open one fundamental question: In a world of reductionist science, where researchers study single compounds as new therapeutic agents, is it possible to rationally develop a botanical drug that consists of hundreds of distinct molecules? According to several experts, though the idea remains a huge challenge scientifically, it may not be as farfetched today as it once seemed.

**Back to the Future**

Reports of the pomegranate’s medicinal qualities have echoed throughout the millennia. In addition to Biblical references, the Romans mention the tree’s unique healing powers, and several Middle Eastern, Asian, and South American peoples continue to chew small bits of its bark, petals, and peel to treat ailments ranging from dysentery to diseases of the mouth and gums.

The echoes have been slow to interest Western scientists, however. Some say the indifference may owe to geography. Because the pomegranate is native to the Middle East and a rare item in Western diets, the tree may have simply fallen through the cultural cracks. In fact, a Medline search reveals that just 38 papers were published on pomegranates from 1975 to 1999, many of questionable quality.

By the late 1990s, the West slowly began to take more notice, thanks in part to a wave of interest in the pomegranate among Israeli scientists. Lansky became interested in the fruit during the early 1990s and eventually founded his company, Rimonest, a linguistic marriage of the Hebrew word "rimon," or pomegranate, and the English superlative "-est." Then, in 2000, Michael Aviram, D.Sc., and colleagues at the Rambam Medical Center in Haifa reported that people who supplemented their diets with pomegranate juice, which is high in antioxidants, seemed to improve some key indicators of cardiovascular health.

For those scientists who have examined the pomegranate, most say they are impressed. "In general, I would say the pomegranate is ‘extraordinary’ and offers the opportunity to find new substances with health promoting properties," said Ivo Feussner, Ph.D., a scientist at University of Goettingen’s Albrecht von Haller Institute for Plant Sciences in Germany, who has studied the chemical composition of pomegranate oil. "Therefore, this fruit needs to be studied more intensely."

What particularly intrigues these scientists is the unique biochemistry of the pomegranate tree. In addition to the high levels of antioxidant-rich tannins and flavonoids in the juice and peel, researchers crush and dry the seeds to produce a unique oil, about 80% of which is a very rare 18-carbon fatty acid, or punicic acid. Also present in the oil is the isoflavone genistein, the phytoestrogen coumestrol, and the sex steroid estrone. In fact, the pomegranate is one of the only
plants in nature known to contain estrone.

"All of this chemical peculiarity may be related to the fruit’s botanical isolation," noted Lansky. "The pomegranate sits alone in its own botanical family, accompanied by its rare genetic forebear, whose habitat is restricted to the Yemeni island of Socotra."

**Seeds of a Cure?**

Lansky, in particular, has championed the hypothesis that the plant’s chemical peculiarity might be effective in treating cancer, an idea that, he said, was supported in his initial *in vitro* work. Rather than take the standard reductionist step of sifting through his fruity mixture to isolate one ingredient that inhibits the tumor cells, Lansky went in the other intellectual direction. Trained as a homeopathist, Lansky argued that the whole worked better than the one active ingredient, a concept known as "herbal synergy."

Herbalists argue that this chemical synergy can be transferred in its entirety to people. Take a complex botanical therapy, they say, and it will have a multifactorial effect that influences multiple cellular pathways at once. Take a standard, one-compound agent, they counter, and it generally will influence a single pathway, meaning cells can more readily switch to a backup pathway and become resistant to the drug, a common problem with chemotherapy.

"Our studies show that combinations of compounds act differently than single compounds in two ways," said David Heber, M.D., Ph.D., a scientist at the University of California at Los Angeles Center for Human Nutrition. "One is enhanced action. The other is they are metabolized differently."

For Lansky, who combines chemicals from a single plant, unusual in herbal and botanical medicine, the great leap of faith is that the pomegranate has evolved a potent synergism. That is, Mother Nature has evolved an unusual plant that punches all of the right mechanistic buttons to kill a tumor cell.

To build support for this idea, Lansky reported last year in *Breast Cancer Research and Treatment* that his pomegranate extracts selectively inhibited the growth of breast cancer cells in culture. According to Lansky, his currently unpublished data on *in vitro* work with prostate cancer cells are even more impressive.

"We feel our basic research is broad and clearly shows the efficacy of the product in repeatable, statistically significant ways and in a variety of settings," he said. "We’ve also shown that the mode of inhibition is varied, including programmed cell death, invasion inhibition, proliferation inhibition, and angiogenesis. So, it’s a broad effect that consistently shows synergy."

**Going Mainstream**

Assuming Lansky is correct, how then does he translate the synergy of his extract to the clinic and ultimately mainstream medicine?
For Andrew Vickers, Ph.D., a scientist in the Integrative Medicine Service at Memorial Sloan-Kettering Cancer Center in New York, one key is to be open minded about the concept of herbal synergy. "The lack of scientific attention given to whole botanicals, compared with single compounds extracted from plants, is arguably not because the former are known to be ineffective or unsafe," he wrote recently, "it is because they are difficult to study." The point being, the difference between developing a single-compound drug and a botanical is the difference between juggling one ball and having hundreds of balls in the air. The variables are overwhelming.

He said another key is getting past the traditional division between "mainstream" and "alternative" medicine. "I don’t like that kind of language because it promotes a kind of ‘us’ and ‘them,’” he said in an interview. "The ‘us’ has to prove to the skeptical and cynical ‘them’. I think the point is, not to get the ‘establishment’ to buy in [to alternative medicine], the challenge is just to do good science, and good science is all about reproducibility, and that’s an inherent problem with botanicals."

Vickers and others say that, as more "mainstream" cancer centers have invested in offices of integrative medicine, the necessary funding and multidisciplinary give and take have allowed herbalists to think more carefully about tackling the problem of reproducibility. "Fifty years ago, someone would say huang lian [an extract from a plant root] seems to work," said Vickers. "They would look at it under the microscope, see it contained all of this different stuff, and they would say, ‘How are we going to look at it? It’s just too complicated to take forward rationally as an agent.’"

"But now we’re saying that we’ve got all these techniques," he continued. "We’ve got massive computer power, we’ve got pretty good analytical techniques in terms of chemistry, we have good biological assays. Let’s see if we can take this thing forward."

Vickers and others noted that several groups have begun to think more systematically about standardizing the quality of botanical extracts, validating the presence of their active ingredients, and establishing objective standards to gauge their efficacy. Many say they are also studying possible cross reactivity among approved chemotherapeutic agents and alternative medicines.

Heber, for instance, noted that UCLA’s Center for Human Nutrition is trying to improve quality control, a major issue in botanical medicine, in that different batches of the same extract may have different chemical profiles and levels of activity. "We’re going at the belly of the beast," he said, noting the center’s efforts to genotype and molecularly fingerprint botanicals, standardize plant growing conditions, and develop bioassays to test the actual activity levels of key compounds in the mixtures.

"Now is definitely the time to do it," he said. "What we’re seeing is a merging of basic biological mechanisms, such as inflammation and oxidative stress, in cancer, heart disease, diabetes, and many other conditions, and I think metabolics is just as important as genomics in understanding these issues."

In the meantime, Lansky said he would like to move his extract into clinical trials. Lansky said his animal data show his product has essentially no toxicity, and he noted that his patented extraction method can reproducibly yield a high quality extract for clinical trials. "All of the components of the extract are there for a reason," he said. "...You know, I believe in synergy. It just really makes sense.
to me."