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Chapter 7 Ethics and Pseudoscience in Our Daily Lives: The Status of the Science Behind Dietary Supplements

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Chapter 7
Ethics and Pseudoscience in Our Daily Lives: The Status of the Science Behind Dietary Supplements

Abstract: In the age of clickbait and targeted marketing, we are constantly exposed to hype and misleading claims about dietary supplements. Many of us may need to take dietary supplements for various reasons (i.e., vitamin and mineral deficiencies). The goal of this chapter is not to advise against taking the dietary supplements that we need. The chapter will explore areas about which we all need to know: how to find what is scientifically known about supplements, where to look for the most rigorous studies, and how to assure the quality of a supplement in the absence of a formal FDA approval process. Although scientific certainty is the goal, high-quality botanical extracts that have worked for thousands of years to alleviate a variety of symptoms and improve human health are likely to continue working if used in the right context, science or no science.

Keywords: dietary supplements, misleading claims, scientific integrity

Investigation of dietary supplements, especially supplements that come from botanicals (of which there are tens of thousands), is truly the Wild West of pharmacological research. Universal research paradigms and standards are being developed, but the process is fraught with difficulty because the territory is so new, the variables are so many, and the funding is so scarce. I know about these challenges firsthand since I do research on botanical extracts in animal models such as fruit flies and mice. I will share a few of my own challenges with you in this chapter.

Inconsistency

Research efforts have thus far been plagued with inconsistency. The proper study of botanicals intended to treat specific conditions or alleviate specific symptoms, for instance, requires the same precision as studying pharmaceuticals but we also need to take into account the efficacy of a number of botanical remedies that

have been used for thousands of years in traditional medical practices around the globe. Studies often are not able to be repeated by other researchers or to be generalized, for a number of reasons, primarily because of the poor methodologies employed and failure to use standardized and high-quality botanical extracts. The majority of these studies did not properly describe the ingredients tested: what parts of the plant were used? What were the growth, harvest, and preparation methods? How was the plant product processed and manufactured? How was the plant extract standardized? For a study to be useful, it must be clear whether the tested substance was an extract, a raw ingredient, or a finished product (Swanson, 2002). In a review of 81 randomized clinical trials (RCTs) that evaluated echinacea, garlic, saw palmetto, ginkgo, or St. John's wort, only 12 (15%) of these studies performed tests to quantify the content of the herbal remedy that was studied (Wolsko et al., 2005).

Too often, these essential details are missing or vary so widely from study to study that it is impossible to draw firm and reliable conclusions. I personally know how inconsistency can present a major challenge to research. I endeavor to only test high-quality botanical extracts in my research laboratory, and I double-check their quality myself, even when the supplier's certificate of analysis for the botanical extract seems to be acceptable. In 2006, my laboratory tested an extract of *Rhodiola rosea* on the lifespan of fruit flies, and we observed a 7% increase in lifespan. Two years later, I tested another extract of *Rhodiola rosea* from another supplier and we observed a 25% increase in lifespan. We analyzed and compared the extracts and realized that the second extract contained more biomarker molecules than the first one, even though both products had been approved with the same certificate of analysis and were ostensibly rated as having the same quality level. After this experience, I started checking the quality of the botanical extracts that I work with using a third-party analytical lab such as Alkemist Labs (www.alkemist.com). Despite being very careful to only work with high-quality products, I have noticed that the harvest time and location can impact a botanical's quality, which may result in inconsistent outcomes.

Another challenge that leads to inconsistency in testing is regulatory issues. Each country has built its own classification system and corresponding regulation levels for dietary supplements, which means that the burden of proof for the supplements' effectiveness differs from place to place. Consider the common sleep aid melatonin. In the United States, melatonin is sold as a dietary supplement and does not require a prescription; in Europe and Canada, it is not sold as an over-the-counter substance and it requires a prescription (Riemann et al., 2017). Or the case of the hormone DHEA, which in many countries is treated as a controlled substance, as it was in the United States from 1985 to 1994: however, today the United States treats it as a dietary supplement that is available over the counter

(Kornblut & Wilson, 2005). In fact, a dear friend of mine took an over-the-counter DHEA supplement, believing it would increase her energy, and she developed DHEA-induced hypertension that went undiagnosed for months. Her physicians ran a number of tests to figure out why an otherwise healthy young female had developed hypertension. I was also concerned and asked her to send me a list of all the medications and supplements she was taking. As soon as I saw DHEA on her list, I became suspicious. She stopped taking DHEA, and her hypertension eventually disappeared.

From country to country, there is great variation even when it comes to the most basic questions about dietary supplements, like recommended dosages and intended use. This poses a significant challenge to conducting research with universal reliability.

Bad "Science" and Overstretched Claims

But in its own way, perhaps the greatest challenge for good science is just overcoming the existing body of poorly done bad supplement "science." When used in the right context, high-quality dietary supplements, including botanicals, could enhance our health.

And there is a lot of bad supplement science out there. *Natural Products INSIDER*, which provides information on sales trends to dietary supplement manufacturers, performed an online survey among their readers. The survey asked whether the company participates in clinical research, and if so in what way. More than 100 dietary supplement companies responded, and two-thirds of those respondents reported that their companies were funding and/or supporting such research. This, as *Natural Products INSIDER* wrote, seemed like very "good news" (Myers, 2015).

Upon further investigation, however, I realized that the commonly accepted definition of research by the scientific community is different from the way that most of these companies define it. For instance, testing the impact of a supplement with claims to enhance memory and cognition on only 10 subjects in a non-controlled and observational study using memory tests that are not validated by the research community is not considered research – it is called marketing. Also, the results obtained from testing a dietary supplement in an in vitro cell culture experiment cannot be presented as a scientific study applicable to humans. As we have seen in the previous chapters, many companies have very little incentive to research their products' effectiveness and safety before putting them on the market, but they have every incentive to market and sell them with extraordinary

health promises afterward. This practice has led to a cultural oversaturation of bad science, especially online, where fairytales and outright fraud are pervasive.

This chapter will explore how to find what is scientifically known about supplements, explaining where to look for the most rigorous studies and how to evaluate their meaning. In the age of clickbait and targeted marketing, we will learn how to cut through the hype and avoid falling for misleading claims.

But first, we will put on our lab coats and (theoretically) do a little science ourselves. How do scientists test for supplements' safety and efficacy? What happens behind the scenes?

The Science Behind Dietary Supplements

I have written quite emphatically that most supplements require greater research before we should trust their claims. But what exactly does that entail? What kinds of tests should be performed, and how much can they tell us about what a supplement can or cannot do?

For instance, how can we prove whether docosahexaenoic acid (DHA), found in fish oil, can prevent Alzheimer's disease; whether coenzyme Q10 is able to lower blood pressure; or whether turmeric and curcumin, long used in traditional Ayurvedic medicine in India, can fight cancer? For those supplements that make condition-specific health claims, there is in fact a series of methods to scientifically test whether or not such claims are true. Or, if a substance's exact properties and effects are inconclusive, we can at least test for whether or not they are likely to do harm. I firmly believe that research on safety issues is as important as research on efficacy issues. In the following sections, I will describe various scientific experiments that are often used to make scientific claims. These studies vary from in vitro (in a test tube) to in vivo (animal studies) to clinical trials (human studies).

In Vitro Experiments: Studies Performed in an Artificial Environment Such as a Test Tube or a Petri Dish

The simplest, safest, and often the least expensive way to test the effect of any substance is in vitro: put it in a test tube, a flask, or a petri dish and evaluate it. Under a microscope and through other experiments, a scientist examines what happens when the substance encounters a tiny culture of cells that have been isolated from

living organisms such as humans, organs, microorganisms, or molecular entities such as enzymes and genes. These in vitro studies provide researchers with their first insights into a compound's efficacy, safety, and mechanisms of action.

As a trial run for supplements, these studies are essential, but a positive effect in a petri dish does not equate with definitive science nor does it warrant recommendations for humans. In vitro studies only serve as a foundation for further studies: based on the results of an in vitro study, scientists can ask if there is enough potential to consider the expense and risk involved in further trials on live subjects (study participants). Since what happens in an *in vitro* environment does not mirror what happens in an *in vivo* environment (i.e., inside a living organism), the in vitro studies' results cannot be directly extrapolated to humans.

Why am I talking about in vitro studies here? Because significant and unwarranted health claims about dietary supplements are sometimes made based on in vitro studies. Curcumin (the active ingredient in the spice turmeric), for example, has been studied in vitro with specific types of cancer cells to great effect (Hatcher et al., 2008), but as we will see, these findings have not been as easily replicated in human studies.

It is important for us to understand that we cannot assume that an in vitro experiment's positive outcomes can be duplicated in a human body. As consumers, we need to remember that companies often leave out this critical piece of information as they try to sell us their products. Here, I will review just a few examples of unwarranted health claims promoted by businesses hoping to boost their bottom line. In these cases, manufacturers magically transformed the in vitro test results into solid "scientific evidence" for how their supplement would affect humans. Such small-scale exploratory studies, which might be a good beginning for scientists, are treated as the full story.

About a decade ago, marketers fell in love with the idea of antioxidants. Whether it was juices, cosmetics, supplements, or fortified snacks, many new products trumpeted their cleansing, antioxidant properties. For the first time, companies began advertising the "antioxidant levels" in their food products. The numbers were meant to impress consumers, and they certainly did: in 2011, sales of products advertising their antioxidant levels reached $65 million dollars (Berkeley Wellness, 2012). But what were these numbers representing? No in vitro measurement technique can tell us how much of the antioxidants in food are absorbed into our body and then remove potentially harmful oxidation products (free radicals) from our system. Whatever numbers we see on food packaging only reflect what happened in a test tube (and different tests seem to yield very different results). Yet, consumers' obvious assumption is that those numbers do reflect something meaningful about the actual health benefits of the products they are stamped on. The FDA chased down some of the worst offenders of over-

stretching antioxidant claims, including the manufacturers of Lipton Green Tea and Canada Dry Sparkling Green Tea Ginger Ale. Both companies received warning letters over their antioxidant claims and the purported corresponding health benefits that were used to market their products (FDA, 2010a, 2010b; Zajak, 2010).

Another hot product line seen by many as having health superpowers was the pomegranate juice product marketed by POM Wonderful, which was censured by the Federal Trade Commission (FTC) in 2010. The company's advertisements implied that its juices were able to prevent heart disease, prostate cancer, and even erectile dysfunction. When the FTC stepped in, the company was outraged, claiming to have spent more than $34 million in private research. After a fascinating court battle, the judge ruled that there was insufficient scientific evidence for the level of health claims being made. At the time, our local newspaper, the *Orange County Register*, called me to ask for a statement for an article that the paper was preparing about POM's health claims. The reporter asked my opinion about these claims and the science behind them. I told the reporter that people trust labels, especially health product labels, and that when companies are using scientific claims to sell a product they should have scientific evidence to back it up (Hall, 2010).

One more intriguing example of the gap between marketing promises and scientific research is supplements that are derived from the spice turmeric. This golden root related to ginger was one of the top 10 trending supplements of 2017 and indeed the range of promises attached to it are spectacular. A CNN report published in 2018 goes down the list of enthralling claims: "Alzheimer's disease. Diabetes. Arthritis. Unwanted hair growth. Baldness. Infertility. Erectile dysfunction. Hangovers. Glaucoma. Cancer." If you have an ailment, there is a good chance that someone, somewhere, is studying whether turmeric can treat it. The report goes on to say that "there are more than 15,000 manuscripts published about curcumin, the active ingredient in turmeric, and about 50 manuscripts added to this collection each week" (Moulite, 2018).

How do we sort through the many studies and the barrage of speculation related to turmeric? Often, the first place that people turn to is a general internet search. If you look up "cancer and turmeric," for instance, the search will immediately yield a few dozen articles, blogs, and websites celebrating the discovery of a "natural cure for cancer." One turmeric website confidently touts the claim: "Research proves that turmeric and curcumin have natural anti-cancer, chemopreventive, and radio-protective properties." The site proceeds to list many studies that seem to showcase why curcumin will revolutionize cancer care (Turmeric for Health, 2016). Of course, a closer look shows that the majority of the studies listed were conducted in vitro, outside of human beings, which we know means that they do not account for problems such as the limited bioavailability (absorp-

tion) of curcumin when ingested by humans. There is no way to guarantee similar results when curcumin is tested in a living organism versus a petri dish (Meyerowitz-Katz, 2017). So what can curcumin actually do? Internet summaries are not enough. We need to dig deeper and find the scientific studies themselves. And, out of all those studies, we need to look for human clinical trials if we want hard evidence of the effect curcumin (or any other supplement) is proven to have on the human body.

So what happens when curcumin is tested on human beings? A host of interesting findings emerge that highlight the complexity of supplement science.

Several human trials on curcumin's impact on colorectal cancer have been completed with conclusive results. Based on a recently published double-blind RCT funded by the National Institutes of Health (NIH), there was no difference found in the mean number or size of lower intestinal tract adenomas (polyps, which are the precursor to colon cancer) between groups of patients who received curcumin versus the group who took a placebo. When it comes to the development of colorectal cancer, the ultimate outcome of these intestinal adenomas, this clinical trial showed that curcumin had no effect in slowing or reversing its spread (Cruz-Correa et al., 2018).

On the other hand, clinical studies on curcumin's anti-inflammatory abilities have shown promising results in small-scale trials. In one of these trials, 367 people with knee osteoarthritis were divided into two groups, one taking ibuprofen and the other taking curcumin. After four weeks, the researchers concluded that on every scale of pain measurement the curcumin supplements "were as efficacious as ibuprofen in pain reduction and functional improvement" (Daily et al., 2016). A related study on osteoarthritis tested curcumin's impact on biomarkers in the blood that indicate degeneration of collagen and inflammation. In an exploratory study, qualifying osteoarthritis patients were invited to take curcumin and then their blood was periodically tested to evaluate their biomarkers. There was no control group taking a placebo or other intervention to compare to those taking curcumin. The results were positive: curcumin did seem to contribute to improved biomarkers. But the researchers were appropriately cautious because of the limitations of their research design. They concluded that the results were "encouraging" and a good indicator that more research should be done in this area (Henrotin et al., 2014).

Another recent human trial was conducted to test whether or not curcumin could improve memory, or slow memory loss, in aging adults. Though earlier trials in this area were inconclusive, this study, completed with 40 middle-aged adults over an 18-month period, found that curcumin did improve memory and possibly also aided in brain health. The authors also openly acknowledge that Theracumin, a curcumin manufacturer, helped to fund the study, though there

were many other supporters, from Alzheimer's disease organizations to the NIH (Small et al., 2018).

I personally have no doubt that curcumin has biological activities. I tested this compound in my laboratory and reported that it can increase fruit flies' lifespan and improve their healthspan by targeting longevity pathways. After the publication of my research in a peer-reviewed journal, I was approached by news media outlets asking me whether people should take curcumin in order to live longer. My answer was consistent with all the other answers I have given when asked this question about other natural products that I have worked with that have been shown to improve lifespan and healthspan: "If you are a fruit fly, curcumin can extend your lifespan." Of course, since we share about 75% of our disease genes with fruit flies, my hope is to eventually test my findings in mammalian model systems, such as mice, and ultimately humans. But as of now, I have not tested curcumin on mice or people – the jury is still out on whether it will lengthen human beings' lives or health spans.

So, what should we learn from all this? Curcumin shows many potential benefits when observed in vitro, but well-designed and replicable clinical studies are the only way to determine how curcumin affects (or fails to affect) a specific health concern. Each trial's design and size matter, giving us indicators of how much credence we should give to the results. Again, in vitro studies provide valuable information, but their main disadvantage is that it is often challenging to extrapolate their outcomes to humans. In the end, no matter what the internet's many voices are telling us, there is no surefire link between what happens in a petri dish and what will happen in the human body.

In Vivo Experiments: Studies Performed in Animals

Only through in vivo studies – those on living organisms – can it be determined how a whole living system, not just a small culture of cells, responds to the treatment. Many in vivo experiments are performed in so-called animal "model systems," including worms, insects such as fruit flies, and mammals like mice. Animal model studies are important and useful because researchers' overarching concern is to protect human beings from unintended negative effects; thus, efficacy and safety tests often do not begin with human populations but instead with animal models. But we need to keep in mind that animal models are simply "models": they are not humans.

In my own work, I conduct efficacy and safety tests on the insect model *Drosophila melanogaster* – better known as fruit flies. Since 2005, my research has focused on evaluating the impact of dietary supplements, including plant extracts, on the lifespan and health span of fruit flies with the goal of eventually testing them in mammalian models. My lab has extensively studied five plant extracts that we identified after screening hundreds of compounds and natural products with potential properties to slow the aging process: *Rhodiola rosea*, *Rosa damascena*, curcumin, cinnamon, and *Angelica keiskei*. This process began with prior in vitro research and then graduated to whole system studies on fruit flies, which, as mentioned above, share about 75% of disease genes (i.e., genes whose function has been directly implicated in specific diseases) with humans. About half of their protein sequences have mammalian counterparts or homologues. We developed an algorithm to evaluate the impact of dietary supplements and botanical extracts on fruit fly lifespan and healthspan and then identify their mechanism of action. We have started experiments in mice and tested the impact of *Rhodiola rosea* in a severe mouse model of diabetes (leptin-deficient mouse) and observed that this plant extract improved biomarkers of diabetes (Jafari et al., 2022). We are now in the process of developing additional studies testing the impact of *Rhodiola rosea* in pre-diabetes.

One of the common questions that I am asked about my findings from my fruit fly experiments (especially from the media) is, "Will this have the same effect on humans as it does on fruit flies?" (in particular, there was a lot of concern when we found that large doses of green tea extract harmed male fruit flies' reproductive systems!). I always provide the same answer: "If you are a fruit fly, this plant extract will have this impact. Beyond that, we don't know. Our findings need to be replicated in mammalian model systems and eventually humans." Lab tests on fruit flies provide us with a useful screening process; we can identify which plants may positively impact lifespan and healthspan or which plants may have negative side effects. Due to similarities between genes and proteins of fruit flies and mammals, we can also identify the potential mechanism of action of the extracts and compounds we are testing. But there is no way to extrapolate these results directly to humans without performing human testing.

Another commonly used in vivo model system to study dietary supplements is rodents. Mice and rats have played a critical role in biomedical research, from discovering drugs to testing dietary supplements. Although working with rodents is more expensive and labor-intensive than working with fruit flies, they are more convenient and less expensive than conducting studies on human beings. They have a shorter lifespan and can be housed and maintained easily, and their genetic, biological, and behavioral characteristics closely resemble those of humans. In addition, the use of "transgenic mice" – mice that have been manipu-

lated to carry genes that are similar to those that cause human diseases – has created a new research platform to evaluate the efficacy and toxicity of drugs and dietary supplements.

In the case of both pharmaceuticals and dietary supplements, pre-clinical animal studies, using insects and mammals, that have sound methodologies are very useful for shedding light on the mechanism of action and screening for safety and efficacy. Often, after observing a positive effect in a study involving insects, the experiment is repeated in a rodent model, perhaps using mice. For instance, in my lab, after observing that a plant extract changed the microbiome (the microbiome is the community of all microorganisms that resides in living organisms) of fruit flies, we tested the impact of the same plant extract on the microbiome of a genetically engineered mouse model of obesity and diabetes (leptin-deficient mice) to see if the plant extract changed the microbiome of these mice. We observed that this plant extract did change the microbiome of these mice (Jafari et al., 2022). Since the modulation of the microbiome appears to be conserved (in other words, to be maintained the same way) between two species, insects and mammals, we hypothesize that the plant extract may have the same effect on the microbiome of humans.

Animal studies may be useful in biomedical research, and it is fascinating to watch these studies evolve, but the bottom line is that they do not present a complete picture of whether or not the intervention will have preventive or therapeutic effects in humans.

Clinical Research and Clinical Trials: Studies Performed in Humans

According to the NIH, "Clinical research includes all research involving human participants. Clinical trials are clinical research studies involving human participants assigned to an intervention in which the study is designed to evaluate the effect(s) of the intervention on the participant and the effect being evaluated is a health-related biomedical or behavioral outcome" (http://www.nih.gov/). This broad description of NIH research reminds us that not all clinical studies have the same explanatory value; rather, there are many kinds of studies, each with different goals and levels of value.

Some clinical studies are observational: a researcher tracks what happens over time to a group of people. For instance, it has long been noted that people who eat Mediterranean diets have less heart disease (Hamblin, 2014). It also has been observed that India has a lower incidence of cancer than elsewhere. In ob-

servational studies like these, the observed fact is used as a springboard to theorize the cause but does not prove any cause conclusively. Could low cancer rates in India be explained by diet – turmeric, perhaps? Or do they have to do with a lack of detection? While cancer rates may appear low in India, a larger percentage of diagnosed cases are fatal, which may point to a problem with early-stage identification of cancers rather than a truly lower incidence of the disease (Dhillon, 2018). Observational studies identify interesting patterns, and we may speculate about their causes, but they do not provide us with a definite answer.

In addition to observational studies, there are other types of experimental clinical studies. For instance, a researcher may introduce a new factor and record the result. These experimental trials on humans provide us with different levels of evidence depending on their design, whether they are "controlled" or "uncontrolled." For example, if a group of people are all given a supplement said to improve mood and are then asked after a fixed amount of time if their mood improved, they may all say yes. But how do we know that the weather didn't change for the better, lifting everyone's spirits? Or perhaps it was a placebo effect: people believe the pill will make them feel better and in turn do feel better. This hypothetical experiment may show us something important – perhaps the supplement does improve mood – but because the experiment does not control for the influence of other possible explanations (known as confounding factors) other than the effect of the pill, its value is limited.

The Gold Standard of Research: Randomized Clinical Trials (RCTs)

The pinnacle of clinical trials on human beings is the RCT. These studies can yield the most meaningful data and are designed to prevent ambiguous and misleading outcomes. In an RCT, at least two groups of participants are necessary, one of which is given a placebo (the control) while the other is given the substance being studied (the intervention). In a "blinded" study, the participants don't know which group they are in. In a so-called double-blinded study, the researchers evaluating the outcomes of the study also don't know which group a patient is in until the results are finalized. The study participants need to be matched for all relevant characteristics (e.g., sex, age, race/ethnicity, and other medical conditions) and are then randomized to either the control or the intervention group. The control group is the standard by which the researcher measures the effect of the intervention. The researchers measure and record the impact of control and intervention on outcomes that were hypothesized beforehand. After a given period, the researcher stops the

experiment and analyzes the data. They may replicate the experiments to assure that their results are valid. The design of an RCT eliminates the possible interference of a placebo effect and controls for external and confounding factors that might skew the results.

What does a well-designed RCT look like, and what kinds of things can we learn from them?

One landmark RCT was conducted in 2005 on the long-term effects of vitamin E supplementation on heart problems. In a seven-year study, a Canadian research team followed nearly 10,000 adults over the age of 55 who were considered at high risk for heart attack or stroke. Half of the participants were given high doses of vitamin E every day, and the other half took a placebo pill. After seven years, there was no reduction in heart attacks, stroke, or cancer for the group taking vitamin E. There was, however, a 13% increased risk of heart failure in the group taking vitamin E (Lonn et al., 2005). Other studies have had similar results. In a study that evaluated the impact of selenium and vitamin E for cancer prevention, researchers found an increased incidence of prostate cancer in healthy men consuming these supplements (Klein et al., 2011). Despite the promising in vitro, animal and observational studies on vitamin E, clinical trials in humans show no benefits and actually some risk (Vivekananthan et al., 2003).

In 2018, another significant study was published on the impact of dietary supplements on heart disease. Multiple researchers worked together to compile and analyze the results of over 1000 RCTs completed between 2012 and 2017. The RCTs included in this compilation, known as a "meta-analysis," were all testing for a relationship between particular supplements and the prevention of cardiovascular disease. The results of their meta-analysis are fascinating: first, there was no discernable effect on cardiovascular health found in the trial populations taking multivitamins, vitamins C or D, beta-carotene, calcium, or selenium. There was, however, some evidence of preventive benefits for the heart health of those who took folic acid, and fewer incidences of stroke for those who took B vitamins. Finally, there was increased risk for overall mortality found in studies of those taking antioxidant mixtures and niacin. Even with such an overwhelming wealth of studies to draw from, the authors acknowledge that much remains unknown. Depending on an individual's age, health, and dietary background, the benefits or potential dangers of taking any supplement will vary (Jenkins et al., 2018).

Studies like this one are a good place to start. Such studies provide us with the best summary of what is presently known about supplements and what they can and cannot do.

A Grain of Salt: Young Science, Old Earth

Ideally, every supplement and its health claims would go through the appropriate progression of scientific studies, establishing if there is any benefit or risk, and what the level of efficacy is. But, of course, this process is rarely so clean-cut. In the case of botanicals, only a fraction of the properties of the hundreds of thousands of plants that exist have been tested for. For vitamins and minerals, an important part of future testing, in addition to efficacy, is to establish safety and dosage limits. We largely know what deficiency looks like for essential vitamins and minerals, but in cases where additional vitamin doses are theorized to help with specific health problems, there is still much left to learn. In relation to supplements and their potential, the science is still very young.

Having said that, although scientific certainty is the goal, high-quality botanical extracts that have worked for thousands of years to alleviate a variety of symptoms and improve human health are likely to continue working if used in the right context, science or no science.

Choosing Supplements Wisely

Unlike pharmaceuticals, the major driver behind supplement use is personal choice rather than a prescription from a physician. Most people who are using supplements do so based on their own research, faith in advertising claims, or others' recommendations. Very few people are aware of the results of human RCTs like the ones discussed above. Instead, anecdotes ("My friend's sister started taking this and now her skin is perfect!") and endorsements are key motivators and clues that point people toward products. But these anecdotes, whether from friends, celebrities, or personal testimonies found on blogs, are not science.

Even what appear to be scientific studies are not always trustworthy: sources matter. Because supplement manufacturers can only make very limited claims on their products' packaging or they will be in trouble with the FTC or the FDA, websites and social media outlets are the perfect place to informally drum up enthusiasm for their products. Marketing and self-promotion are often presented as "research" and "science."

Studies can also be purposely designed with bias, guaranteeing that companies or individuals get the results they want rather than presenting the full picture. This is easy to see in the growing market for weight-loss supplements. Each and every company hustling to sell their natural weight-loss aid will tell consum-

ers that there is scientific evidence that their weight-loss supplement works (and, no doubt, will flash dramatic before-and-after pictures to prove it).

But science tells another story. One research team reviewed the results of nine different sets of clinical trials on human beings, all of which sought to test whether or not a given dietary supplement could help with weight loss. Each of the experiments lasted for at least 12 weeks, and they covered a wide range of dietary supplements: guar gum, chromium, ephedra, *Citrus aurantium*, conjugated linoleic acid, calcium, glucomannan, chitosan, and green tea. What was the conclusion? Based on the studies' results and quality, the reviewers wrote that these clinical trials "fail to provide good evidence that any of these preparations generate clinically relevant weight loss without undue risks" (Pittler & Ernst, 2004).

The fine print revealed that several of the supplements, such as chromium, might show potential for a very small increase in weight loss, but that the trials conducted thus far were not robust enough to be considered strong evidence. Ephedra was the only one that truly showed a significant effect on weight loss, but the serious risks, such as heart disease, of taking ephedra are also well known and that is why ephedra is no longer on the market. Based on this review, there are no safe and effective weight-loss supplements on the market, and most of the studies that claim otherwise are poorly constructed and untrustworthy (Pittler & Ernst, 2004).

In addition, even well-designed studies may be cherry-picked or abused; numbers do not simply speak for themselves. You don't have to be a science professor to know that any kind of data can easily be manipulated. Interpreting the meaning of quantitative results is the art of good science, but all too often misconstruing data is part of effective (if immoral) marketing campaigns. A good scientific publication presents its findings but also states the study's limitations and encourages the reader to do their homework prior to extrapolating these findings to their own life. A good scientific study will also inform the reader about who funded the study and if the authors and investigators had any potential conflict of interest with the supplement's manufacturer. An analysis of the press releases and news stories that were generated in response to clinical studies of dietary supplements revealed that 100% of the industry press releases hyped results or de-emphasized negative findings compared to 55% of the non-industry press releases. The authors concluded that the press releases of the dietary supplement industry emphasize results that are favorable to supplement use and downplay results that are not (Wang et al., 2014).

Where to Find Good Science on Dietary Supplements

So where should we look for the scientific studies on supplements, and how can we read them well?

Studies that showcase true scientific research will show up in professional and peer-reviewed journals, which mean that other experts in the field reviewed the data's quality before the study was published. Fortunately, independent organizations like US Pharmacopeia and federal research institutions like the NIH's ODS provide user-friendly compendiums of the latest research on supplements. The goal is to link the public to the scientific community, making the best research available to all. Having said that, not all the studies that have been published in scientific peer-reviewed journals are solid and can be replicated. A survey of 1576 scientists conducted by one of the most prestigious scientific journals, *Nature*, reported, "70% of researchers have tried and failed to reproduce another scientist's experiments, and more than half have failed to reproduce their own experiments" (Baker, 2016). I have personally failed to reproduce the results of natural product studies published by others. If I fail to reproduce the results of my own experiments, then I present the data as negative unless additional replications (at least two more positive studies) point to the contrary. The NIH recently developed guidelines to address the so-called rigor and reproducibility in NIH-funded studies. Future surveys and studies that attempt to reproduce experiments will test the impact that these guidelines might have on the quality of scientific studies. Science-based medicine has improved human health over the last 150 years, and I certainly believe that it will continue to do so.

Despite concerns regarding reproducibility of studies on drugs and dietary supplements, here are the places to find the very best science on supplements:

National Institutes of Health's Office of Dietary Supplements Evidence-Based Review Program

Since 2001, the NIH ODS (2001) has been part of a large-scale project to review the existing scientific studies related to supplements and to create recommendations for further areas of investigation. Draining one little corner of the swamp at a time, they are encouraging the science behind supplements to catch up to their claims (and sales!). Through the ODS Evidence-Based Review Program, peer-reviewed journal articles that examine the effects of vitamin D, soy, B vitamins,

omega-3 fatty acids, multivitamins, and several other common supplements are made accessible to the public. Information on various dietary supplements may be found at http://www.ods.od.nih.gov/.

In September 2018, I presented in a workshop organized by ODS titled "Enhancing Natural Product Clinical Trials." The workshop's goal was to develop and publicize good practices for various stages of research on natural products, including dietary supplements, from in vitro assays to clinical trials. Concentrated efforts such as this by the NIH are a significant step toward assuring the quality of research and publications on dietary supplements. The recommendations from this workshop were published in a paper titled, "Improving Natural Product Research Translation: from Source to Clinical Trial" (Sorkin B. et al., 2020).

National Institute of Health Consortium for Advancing Research on Botanical and Other Natural Products (CARBON) Program

The CARBON program was initiated by the NIH ODS to promote collaborative research on the efficacy, safety, and mechanism of action of botanical dietary supplements with high potential to benefit human health. Other centers and institutes at NIH, such as National Center for Complimentary and Integrative Health and National Institute on Aging (NIA), collaborate with this program and award funding to research centers and academic institutions with the goal of advancing research on botanical dietary supplements.

National Institutes of Health Clinical Trials

Anyone can find out if a supplement's efficacy and safety has ever been systematically tested on humans. All clinical trials on human beings, whether publicly or privately funded, must be approved by institutional review boards at each research institution, and every study is then registered with the federal government. Fortunately, these studies are available to the public through a federal website, www.clinicaltrials.gov/. However, we need to remember that just because a clinical trial is listed on this website, it does not mean that the clinical study is high quality. In the next section of this chapter, I will give you some basic questions to ask when assessing clinical studies.

The Food and Drug Administration

Another way to learn whether a product's health claims have any basis is to search the FDA catalog of investigations. If the FDA sent a letter of injunction or seizure concerning a supplement, often it is because a company was caught making a false scientific claim or the product was harming the public. By typing the name of the company in the search box of www.fda.gov/, anyone can access warning letters that the FDA has sent to that company. We need to remember that in most cases, by the time the FDA starts investigating a company, that company's products have already harmed the public.

Good Questions to Ask

We need to remember again that only the results of clinical studies can be extrapolated to humans. In vitro and animal studies are useful, but their results do not transfer into prescriptions for human health.

Without having to become an expert in research methodologies, consumers can still look for several key markers in clinical studies to interpret a particular study's meaning. Here are the questions that you should ask:

1. First, research methodology is important. How many participants were there? Was this a small study of a 100 people or less? Or was it a large study? The study's size and length can help us see whether it was exploratory in nature or if the findings are well-established. Was the study controlled, randomized, and blinded (i.e., the patients or subjects don't know what treatment they're receiving)? It is important that the dietary supplement being tested is compared to a placebo or an established intervention in a randomized and blinded manner. If not, the significance of the study's findings is greatly diminished.
2. Next, where did the funding come from? Sound research can of course come from private sources, but we should be extra careful if a supplement manufacturer or another party financially vested in the outcome is funding the project. As we saw in Chapter 1, the funding for research on the effectiveness of dietary supplements is sparse overall. The NIH and ODS are the primary sources of federal research dollars on dietary supplements, but many independent foundations also fund research on dietary supplements. The source of funding for the study should appear in the paper under the acknowledgments section.
3. Where was the study published? Was it in a peer-reviewed journal, where reviewers had access to the primary data underlying the study? Or was it

published in a newsletter, online blog, or website that is sponsored directly or indirectly by the dietary supplement manufacturer?

4. Finally, when it comes to supplements that come from botanicals, considering the challenges to perform scientific studies on them, we need to make sure that the supplement has high-quality botanical ingredients. Was the supplement manufactured by a reputable source? Is there a clear statement on the label of the supplement that the claims have not been approved by the FDA? Was the quality verified by a neutral third-party organization such as USP?

Conclusion

The science behind dietary supplements is still young, working against a tidal wave of conjecture. We must be careful about so-called scientific claims and adopt the mentality of a skeptical investigator as we approach supplements. Companies that sell dietary supplements should be transparent about research findings related to their products, information about the source and the quality of the ingredients and the botanicals in their products, and their manufacturing practices. Spending some time on finding answers to these questions may not only save you a lot of money but can also ensure the efficacy and safety of the supplement you are taking. After all, we all need to learn to make informed decisions about our health.

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