Fall 2019

Herbal Supplements: Perceptions, Risks and Need for Improved Regulation

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Senior Project Submitted to
The Division of Social Studies
of Bard College

by
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Annandale-On-Hudson, New York
May 2019

Acknowledgements

I would like to thank my adviser, Jennifer Phillips for supporting me on this project and pushing me when necessary. I would like to thank my parents for fostering my love of science though not necessarily in the laboratory. I would also like to thank them for listening to my various rants and questions about pharmaceuticals and the FDA. Thank you to Sophia Stamatopoulou-Robbins and Eli Dueker. Without Sophia I would have never found the subject for this project and without the support of Eli it might never have found a home in the Environmental and Urban Studies department. Overall, I am incredibly thankful to have had the opportunity to do a full in-depth literature review on something I find so interesting.

Abstract

Herbal supplements have become widely used in the United States to treat a variety of ailments. Though the market for these supplements have grown since the passage of the 1994 Dietary Supplements Health and Education Act, the FDA has failed to expand its regulation over these products. Herbal supplements in the United States have been found to be contaminated, misbranded, and sold at unsafe doses. These issues can seriously affect the health and safety of consumers. The issue with the quality of these products is coupled with the lack of knowledge about herbal supplements. Scientific research is severely lacking when it comes to herbal supplements, concerning both the efficacy and safety. The use of herbal supplements is not usually discussed with the individual's medical practitioner which can leave the users vulnerable to herb-drug interactions. In this paper I argue that in order to ensure consumer safety in regard to herbal supplements the FDA must expand its regulation of these products. Conventional medical practitioners also need to familiarize themselves with these supplements and ensure their patient is using these products appropriately.

Source: M. Spector (2004) "Miracle in a Bottle" *The New Yorker*.

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Chapter 1: Introduction

Herbal supplement use has been on the rise, not only in the United States but in multiple other countries as well (Abebe et al. 2002, Crighton et al. 2019, Nili-Ahmadabi et al. 2019). The National Health Interview Survey found that 38 million Americans had used natural or herbal supplements in 2002 (Kennedy 2005). The survey also witnessed a growth in herbal supplement use from 1999 to 2002 that showed almost double the amount of users (Kennedy 2005). Women, on average, are more likely to be herbal supplement users (Kennedy 2005, Bardia et al. 2007, Conboy et al. 2007, Kristoffersenet al. 2014, Zahn et al. 2019). Middle-aged persons were also more likely to be users of herbal supplements (Kennedy et al. 2005). The use of herbal supplements is also positively correlated with higher income and college education though this relationship is rather complicated and might not be as straightforward as it seems (Kennedy 2005, Conboy et al. 2007). Interestingly enough Kennedy (2005) found that supplement use was associated with positive health behaviors like exercising and not smoking.

It is important not to forget the substantial positives value of herbal supplements. Many herbal supplements have been traditionally used across the world and should not be disregarded based on the fact that they are derived from plants (Abebe et al. 2002, Crighton et al. 2019, Nili-Ahmadabi et al. 2019). Many medications that are paramount to conventional treatment are derived from plants, aspirin and the anti-malaria drug artemisinin being just two examples (Licciardi et al. 2011). Herbal supplements are culturally important and may offers assistance were modern medicine cannot (Kennedy 2005, Bishop et al. 2007, Conboy et al. 2007). Instead the issue with herbal supplements lies with the belief that herbal supplements are inherently safe and therefor does not need substantial regulations.

Complementary and Alternative Medicines also known as CAM describes health and wellness practices that do not fall within the conventional medicine landscape (Bishop et al. 2007). CAM encapsulates many types of medical therapies such as acupuncture, chiropractic, energy healing, psychotherapy as well as herbal supplements (Kennedy 2005). Herbal supplements are thus part of a broader movement to find alternative forms of health care. Research on CAM can therefore be a helpful tool in understanding supplement usage as well.

Dietary supplements, according to the FDA include vitamins, amino acids, botanicals, and enzymes (Office of Dietary Supplement Programs). These products are intended to supplement a person's diet and are administered orally (Dietary Supplements Health and Education Act 1994). Despite the widespread usage of herbal supplements, they mostly go unregulated (Borchers et al 2007). Even in the United State, where pharmaceutical regulation is very strong supplements are underregulated and problematic products can be found on the market (Borchers et al 2007, Boer and Sherker 2018). This paper will explore how supplements came to be regulated the way they are and what health risks can arise from this poor regulation.

Many individuals use herbal supplements in addition to conventional medical care and not as their primary form of medical assistance (Kennedy et al. 2005, Conboy et al. 2007, Warriner et al. 2014). Most prominently, herbal supplements are used to treat common colds, stomach issues, and even some chronic conditions (Kennedy et al. 2005). Some popular herbs used in the United States are Echinacea, garlic, ginko biloba, green tea and St. John's Wort to name a few (Kennedy et al. 2005, Brewer et al. 2017). All of these supplements mentioned have been shown to affect the activity of CYP450 enzymes (Brewer et al. 2017). The interaction between these supplements and CYP450 enzymes is important because these enzymes metabolize many compounds that enter the body (Brewer et al. 2017). It is primarily the affect

supplements have on CYP450 enzyme activity that leads to herb-drug interactions (Brewer et al. 2017).

Unfortunately, herbal supplements do not undergo the same extensive research to determine how they will interact with the body as pharmaceuticals do (Dietary Supplement Health Act 1994, Brewer et al. 2017). Due to the lack of knowledge surrounding herbal supplements and how they function it is hard to know what risks are involved in taking them (Jordon et al. 2010, Brewer et al. 2017). For herbal supplement, the state of the science is mostly limited to case reports (Jordon et al. 2010).

From these case reports it is often difficult to establish causality due to lack of follow up and because of the very nature of herbal supplement (Jordon et al. 2010). Herbal supplements are made from plants and by nature plants are much more variable than regulated pharmaceuticals (Gomase et al. 2008). The challenge of understanding complexity of the compounds is only exacerbated by the lack of information on herbal supplements. Better scientific literature would be helpful in establishing safe parameters of use when it comes to herbal supplements.

Regulations on herbal supplements in the United States falls under the Food and Drug Administration (FDA). However, the FDA's regulation on dietary and herbal supplements varies greatly from that of pharmaceuticals (Borchers et al. 2007). Compared to pharmaceuticals the FDA is very heavily restricted on their dietary and herbal supplement regulations (Borchers et al. 2007, Dietary Supplement Health and Education 1994). Mainly due to the lobbying of supplement manufacturers, congress restricted the FDA's control over supplements (Borchers et al. 2007). This decision passed by congress in the form of the Dietary Supplement Health and Education Act (DSHEA) left consumers vulnerable to largely unregulated dietary and herbal supplements (Starr 2015).

This paper will explore the issues surrounding herbal supplements and possible improvements in the way they are regulated. The following chapter will explore the factors that drive people to use herbal supplements. Dissatisfaction with modern conventional medicine, beliefs about the safety of "natural" ingredients, and cultural influences are all documented widely in the literature as drivers of herbal supplement usage. Chapter three reviews the science and evidence of risks to public health. The basic principles of absorption and metabolism are presented to provide a context for the topics of toxicity, contamination and drug interaction. Given the health risks detailed in chapter three, the regulatory framework presented in chapter four provides us with the basis for assessing the shortcomings in the current laws regulating herbal supplements. In order to protect consumers from the misuse of these products there must be stronger regulation, expansion on the current scientific literature, and improved patient-practitioner communication.

Chapter 2: Drivers of Demand for Herbal Supplements

2.1 Introduction

Complementary and Alternative Medicine (CAM) use has been on the rise in recent years (Taylor et al. 2005, Conboy et al. 2006, Bishop et al. 2007, Stewart and Odle et al. 2013, Zahn et al. 2019). According to one study done by Eisner et al. (1998) , CAM use in the United States increased from 34% of the population in 1990 to 39% in 1997. More recently, other studies have found a similar trend in the increased usage of herbal supplements and CAM therapies (Stewart and Odle et al. 2013). The National Health Interview Survey found in 2007 that four out of every ten adults used some form of CAM . Nahin et al. (2009) found that Americans spend 34 billion dollars per year on CAM. The increased usage has led to the question of how and why complementary and alternative medicines became so prominently used. Though it is not explicitly clear there are many working theories on why CAM use is increasing.

One major reason behind the usage of alternative treatments is due to a gap within modern medicine. Many people have voiced their mistrust in modern medicine and medical practitioners (Taylor et al. 2005, Conboy et al. 2007). Some of this mistrust is grounded in socioeconomic factors, gender, and race (Taylor et al. 2005, Conboy et al. 2007. Historically and currently there has been a deficit in the quality of health care for people of color, women, and individuals in lower to middle-income (Conboy et al. 2007). This deficit has led many people to look for different forms of health care like CAM and herbal supplements (Conboy et al. 2007). Besides these social factors, there are other issues that lead people away from modern medicine like high expenses, not having control over one's health, lack of treatment options and negative relationships with one's doctors (Taylor et al. 2005, Conboy et al. 2007, Bishop et al. 2007).

Another cause for this switch is due to the perception of safety in herbal supplements (Taylor et al. 2005, Xing et al. 2017, Zahn 2019). Some people mistakenly believe that herbal supplements are inherently safe because they are naturally occurring (Taylor et al. 2005, Xing et al. 2017, Zahn 2019). Finally, cultural understanding and religious beliefs can also influence a person's CAM use. In this chapter, I will address each of the leading drivers for CAM use individually: filling a gap left by modern medicine, perceptions of safety, and cultural reasons.

2.2 Filling a Gap Left by Modern Medicine

Many individuals find themselves dissatisfied with the treatment they receive through modern medicine. At times this dissatisfaction has more to do with the personal relationship with the practitioner than the medical treatment (Conboy et al. 2007, Zahn et al. 2019). It has been reported that unequal medical care is received based on gender, race, and socioeconomic status (Conboy et al. 2007, Zahn et al. 2019). Due to the lack of sufficient health care some individuals look for alternative care.

Gender and CAM Use

Multiple studies have found that women are more likely to be users of complementary and alternative medicines (Kristoffersenet al. 2014, Zahn et al. 2019). Kristoffersen et al. 2014, found that statistically more women than men in Norway use CAM. This gender imbalance in CAM use has also been recorded in the United States as well (Bardia et al. 2007). One reason that women are more likely to use CAM is due to the gender bias seen in clinical practice (Kristofferson et al. 2014, Hamberg, 2008). Even when symptoms are the same for men and women, men tend to get more extensive medical treatment. As Hamberg states "Research indicates that physicians are more likely to interpret men's symptoms as organic and women's as

psychological" (Hamberg, 2008). It is theorized that this treatment disparity is what leads women to use CAM more often than men (Kristoffersenet al. 2014, Zahn et al. 2019).

A study done by Warriner et al. (2013) explored pregnant women's use of CAM in the United Kingdom. From a self-administered questionnaire given to all pregnant women in a large National Health Services Trust, Warriner et al. (2013) completed face-to-face interviews with 10 subjects. From these interviews it was evident that most of these women used CAM to gain control over their health (Warriner et al. 2013). Many of these women felt unheard or were unable to voice all their concerns to their health care provider (both midwife and general practitioner) so they supplemented their health care with CAM (Warriner et al. 2013). This paper is supported by Kristoffersenet al. (2014), showing that many women start to use CAM because they feel unheard by health care professionals.

Socioeconomic Status, Race and CAM Use

Studies have also shown that practitioners have treated their patients differently depending on race and socioeconomic status (Conboy et al. 2007). This lack of care leads people to be less confidant in conventional medicine (Conboy et al. 2007). While Conboy et al. (2007) found a link between social factors and perception of herbal supplements it is a rather complex issue. Using the 2002 National Interview Survey Kennedy (2005) found that middle aged white women were the most common users of herbal supplements (Kennedy 2005). He also found that those in the higher socioeconomic category were more likely than others to use herbal supplements (Kennedy, 2005). This finding was acknowledged by Conboy, but they beleive these trends to be based on the fact that wealthier individuals have a higher propensity for spending (Conboy et al.

2007). This issue is further complicated by the fact that some individuals who cannot afford prescription medication instead use herbal supplements (Kennedy 2005, Conboy et al. 2007).

Accessibility is a core reason that people chose to use Complementary and Alternative Medicine. Kennedy (2005) found that adults who could not afford medical care were more likely to use herbal supplements (Kennedy 2005). In what seems like a contradiction, Kennedy also found that individuals that had Medicare or Medicaid used herbal supplements at a much lower rate than those on private insurance (Kennedy 2005). It is possible that this is because those on government insurance do not need to supplement their health care or that they cannot afford to purchase products that are outside of their insurance. This finding could also reflect the age difference between those two groups. Regardless, it is clear that some individuals chose to use CAM because of its affordability (Kennedy 2005, Conboy et al. 2007). This affordability or accessibility also gives the user a sense of control over their own health.

Control Over Ones Health

The sense of control one gains from taking herbal supplement also leads people to choose CAM therapies (Bishop et al. 2007, Conboy et al. 2007, Zahn et al. 2019). For some individuals this stems from an overall desire to be more involved in their health where others use it as a form of 'active coping' (Bishop et al. 2007, Zahn et al. 2019). Active coping is generally considered a form a positive coping that include information seeking and completing day-to-day tasks like managing one's appointments(Ryan et al. 2010). Lack of treatment for chronic illness can also cause people to look for alternative forms of medication (Zahn et al. 2019).

Using CAM can give individuals suffering from chronic illnesses a sense of participation and empowerment (Bishop et al. 2007). This is why active coping is associated with increased

CAM use, because the patient uses CAM as a way to retake control over their body (Bishop et al. 2007). Interestingly, the utilization of CAM in chronic illness has more to do with active coping qualities than the belief these treatments will change the patient's outcome (Bishop et al. 2007).

A study done by Shahrokh et al. (2005) explored elderly patients use and perceptions of herbal supplements. Because the elderly tends to use more prescription and over-the-counter medication Shakorkt felt that this population was especially vulnerable to herb-drug interactions. They found that the population of the elderly that did use herbal supplements were less satisfied with their current health care (Shakorkh et al. (2005). This led to Shakorkh concluding that the lack of satisfactory health care lead to herbal supplement use by elderly patients.

Some users of CAM hold the belief that they are in control of their own health not their health care provider (Bishop et al. 2007). Their interest in CAM might stem from the sense of control and partnership they gain from using these supplements and the relationship with the CAM provider (Conboy et al. 2019). CAM can also provide more accessible information for those that do not have a medical background which again places the patient in control of their health (Conboy et al. 2007). Users of CAM chose the type of herbal supplements, amount taken, and duration of treatment which gives them a sense of control but can become problematic when the individual does not understand the proper dose of the compound.

Users of CAM depend on the internet for information, which gives them a sense of control of their own health care. For example, a sub Redditt called Supplements has many posts, either containing questions or general warning on certain supplements. Posts on this page contain discussions on, herbal supplement side effects, herb-herb and herb- drug interaction, recommendations and warnings about unsafe products.

The amount of responses to these posts vary but it does seem that posts regarding side effects and warnings garner the most responses. Respondents gave surprisingly thorough answers, sometimes with and sometimes without citations. It is clear that some people have made an effort to create a space to discuss herbal supplements, however this system can be problematic because information does not always come from science-based sources or CAM practitioners.

2.3 Perceptions of Safety and Non-Toxicity

A concept that draws people to CAM and herbal supplements is the perceived safety and non-toxicity of these treatments (Kennedy et al. 2005, Taylor et al. 2006, Bishop et al. 2007, Xing et al. 2017). There is a wide belief that because herbal supplements are natural, they are safe and unable to do harm (Kennedy 2005, Taylor et al. 2005, Bishop et al. 2007). While users believe in the effectiveness of these products they also believe that they are safe and carry no side effects (Xing et al. 2016, Zahn et al. 2019). There is also strong feeling of distrust in conventional medicine, mainly being that it is toxic and too potent (Taylor et al. 2005).

A pilot survey completed in the United Kingdoms aimed at understanding an individual's perception and usage of medicinal plants (Zahn et al. 2019). The questionnaire contained questions about the person's understanding of herbal medicine and also demographic and health related inquiries (Zahn et al. 2019). Zahn et al. (2019) found that "95% of participants believed in the curative power of plants and 77% recognized herbal teas as having medical properties" (Zhan et al. 2019).

Many individuals, both users and non-users believed herbal supplements were safe and had less side effects than conventional medicine (Zahn et al. 2019). People also believed that CAM was non-toxic and drug free, the latter possibly leading users to think that it is safe to mix

CAM and conventional medication (Taylor et al. 2005, Bishop et al. 2007). CAM users were more likely to believe that conventional medication was unsafe than non-users (Taylor et al. 2005).

A study by Xing et al. (2016) looked at individuals' perceptions of weight loss drugs and herbal supplements. They conducted this study through face-to-face interviews with willing candidates from a hospital-affiliated pharmacy in the United States (Xing et al. 2016). The researchers asked questions about the interviewee's perception of weight loss drugs and herbal supplements and whether they found either of these treatments to be safe (Xing et al. 2016). They found that people believed these supplements to not be potent and therefore safe to take (Xing et al. 2016). The perceived safety of herbal supplements is rooted in the belief that these products are natural, and that naturalness equates to safety (Kennedy et al. 2005, Taylor et al. 2006, Bishop et al. 2007, Xing et al. 2017). Unfortunately, this is not always true, and some supplements are toxic, or contaminated, or can cause serious drug interactions.

2.4 Cultural Reasons for Interest in CAM

A number of authors argue that cultural factors might be behind the decision to use CAM. Some users have a tradition of herbal supplements while others might have formed their own beliefs on CAM and contemporary medicines (Kennedy 2005, Bishop et al. 2007, Taylor et al. 2005). Some individuals hold different beliefs about holism and the causes of illness and find that their concepts of health differ from those held by contemporary practitioners (Kennedy 2005, Bishop et al. 2007).

The focus on holism or treating the entire person and not just the illness is a major reason for people to choose to employ CAM (Taylor et al. 2006, Bishop et al. 2007). This also might indicate that patients do not feel completely cared for and must supplement with CAM (Taylor et

al. 2005). What people perceive to be the cause of illnesses can also influence the chance of CAM use (Bishop et al. 2007). Bishop et al. (2007) saw that people who believed psychological factors or that diet can influence illness, were more likely to use CAM (Bishop et al. 2007).

Some ideologies or beliefs that Bishop refers to as 'cultural creatives' are more likely to use CAM, for example feminists and/or environmentalists are large users of CAM (Bishop et al. 2007). Tradition might also encourage the use of CAM therapies in some cases. Kennedy (20050 found that people from Asia and Indigenous Americans were large users of CAM due to their traditional use of these herbs (Kennedy 2005).

2.5 Conclusion

Many of these reasons that people chose to use CAM do overlap and are not necessarily separate from one another. A common theme among herbal supplement users was that these products were able to support individuals in areas that modern medicine failed to, whether it be in the form of control or supporting one's cultural beliefs. One concept that was relatively consistent throughout the research was that CAM users did not disclose their supplement use to a medical practitioner (Kennedy 2005, Warriner et al. 2014, Xing et al. 2016, Zahn et al. 2019). Many individuals did not feel comfortable in disclosing CAM use to their doctors or they did not see it as something important to discuss with them (Warriner et al. 2014). This lack of communication between the patient and practitioner can lead to dangerous medical outcome, whether it be from drug interaction or a high dose. In the following chapter I will review the medical risks associated with herbal supplements to address whether or not the current state of the Dietary Supplements Health and Education Act is sufficiently protecting the consumer.

Chapter 3: Public Health Risk Assessment of Herbal Supplements

3.1 Introduction

The major difference between herbal supplements and pharmaceuticals is that the active ingredients of herbal supplements are poorly defined (Brewer and Chen 2017). Because of this, purity, dose, and toxicity cannot easily be quantified. The FDA has a database that reports "Tainted Supplements" and releases "Safety alerts" on certain products, but in order for a supplement user to be aware of these warnings they must have the access to or knowledge about these resource (Food and Drug Administration). Because the FDA does not have the resources to examine all herbal supplements that are on the market, the burden of research falls to the consumer, as does the risk (Borchers et al. 2007). Risk that are associated with herbal supplements can be caused by the toxicity of the active compound and the dose at which it is given (Couceiro et al. 2005, Germ et al. 2010, El- Bakry et al. 2017, Boer et al. 2018). Health risks can also arise from contaminants and herb-drug interactions (Barone et al. 2001, Abebe et al. 2002, El-Bakry 2017, Li et al. 2017, Ventura et al. 2018, Philip et al. 2018, Bosak et al. 2019, Crighton et al. 2019, Nili-Ahmadabadu et al. 2019).

It is important to note that certain populations are more vulnerable to the health risks associated with herbal supplements. As stated above the elderly are more vulnerable to herb-drug interactions because they statistically take more pharmaceuticals and over-the counter medications, widening their chance of accidently mixing an herb and drug that will negatively interact (Shahrokh et al. 2005). Those suffer from chronic illnesses might also be more vulnerable to herb-drug interactions merely due to the fact that they tend to use multiple pharmaceuticals at once (Tulunay et al.2015).

3.2 Toxicity, Concentration and Dose

Toxicity

Toxicity of the active compound in herbal supplements can be defined as the degree at which a substance becomes poisonous and can result in a variety of reactions (Hart 2015). In assessing health risks from herbal supplements, one generally focuses on the body's ability to metabolize the active compounds in the herb. One of the most prevalent and serious form of toxic exposure from herbal supplements is hepatotoxicity (Boer et al. 2018). Hepatotoxicity is the toxic effect of a compound on the liver. Because of the liver role in metabolizing compounds it is especially vulnerable to damage caused by toxicities. Some drugs are known to damage the liver, this phenomenon typically referred to as Drug Induced Liver Damage or DILD. When talking about herbal supplements' effect on the liver it is called Herb Induced Liver Injury (HILI) (Boer et al. 2018). Herb Induced Liver Injury can be caused by the dosage, herb-drug interaction, and contamination issues.

The dose of a compound dictates the effect that it will have on the body (Tozer et al. 2006). Some compounds can be taken in small doses without any damage to the liver but if that dose was elevated to a certain point it could lead to toxicity (Tozer et al. 2006). The 'therapeutic window' is the dose at which a drug has the highest therapeutic response with the lowest adverse effects (Tozer et al. 2006). This is mitigated by the pharmacodynamic and pharmacokinetic response (Tozer et al. 2006). A narrow therapeutic window means the dose required to cause harm is close to the dose needed to elicit the desired effect. If a drug is eliminated from the body quickly but one wants to extend the time it is in the body, delivering a higher dose will not necessarily accomplish that goal (Tozer et al. 2006). Delivered at a higher dose, the drug might have a completely different effect, or it could have a toxic effect and fall outside of the

therapeutic window (Tozer et al. 2006, Brewer et al. 2017). Instead one would have to administer small frequent doses of the drug to prolong the effects (Tozer et al. 2006). Patients unfamiliarity with how dose effects the safety of herbal supplements and/or the fact that a supplements duration of effect may not be prolonged by taking more supplements, may lead to situations where an otherwise safe is overdosed and causes toxicity. This is just one example of how lack of knowledge about herbal supplements work and inadequate instructions for use can cause potential risks with the use of these products.

Concentration

Concentration of herbal supplements can depend due to a wide variety of variables such as environmental conditions and harvest time (Couceiro et al. 2005, Germ et al. 2010). In experimental work by Couceiro et al. (2005) looked at the impacts of environmental factors on St. John's Wort, like harvest time, temperature and germplasm that were all found to influence concentration of the bioactive compounds. Though St. John's Wort has many different bioactive compounds this study chose to focus on hyperforin, pseudohypericin, and hypericin (Couceiro et al. 2005). The study chose to focus on those three compounds because they believe them to be the major elements that give St. John's Wort its biological effect on the body (Chatterjee et al. 1998, Weber et al. 1998). They also state that hyperforin is the compound that has an antidepressant effect which what St. John's Wort is commonly used to treat (Brewer and Chen 2017). However, it is debatable what compounds in St. John’s Wort does have an effect on the body. Tannins for example have been shown to have an effect on the body (Germ et al. 2010) but are not included in the Couceiro et al.. (2005) study. The difficulty in identifying what active

compounds in herbal supplements have an effect, shows just how hard it is to regulate these supplements.

Depending on the harvest time of St. John's Wort, these compounds were found at different levels in different parts of the plant (Couceiro et al. 2006). The same effect was also seen with germplasm and temperature (Couceiro et al. 2006). In reference to the harvest date there was a time that the concentration of hyperforin and pseudohypericin were greatest in the plant (Couceiro et al. 2006). After this point, there was a decrease in the level of both of these compounds (Coucerio et al. 2006).

In some cases, the variation was caused by environmental factors like the amount of UV-B radiation (Germ et al. 2010). In one study by Germ et al. (2010) found that St. John's wort concentration of flavonoids, tannins and hypericin were affected by the levels of UV-B radiation they were grown in. They found that the amount of flavonoids and tannins were elevated under higher UV-B radiation while hypericin was lower (Germ et al. 2010). This variability in concentration means that the supplier is not aware of the exact concentration and thus cannot accurately define what the correct dose should be (Germ et al. 2010). Consumers might be taking in more of the product than they believe because of this discrepancy (Germ et al. 2010, Couceiro et al. 2006). Without fully knowing the concentration of each compound in the supplement it is hard to know the proper dose, how it will affect the body, and the overall safety of the product.

Dose

Caffeine is commonly used in herbal supplements because it can reduce the feeling of pain and exertion while increasing alertness and neural firing rates (Cano-Marquina et al. 2013). According to the FDA however, at high doses caffeine can have negative and even fatal ones as

well (Center for Food Safety and Applied Nutrition). Some toxic effects that caffeine can cause are tachycardia, ventricular arrhythmia and even seizures. These side effects have been witnessed in response to doses as low as 1200mg or 0.15 tablespoons of caffeine. Under typical consumption of caffeine containing products, like coffee or tea, the event of this side effects would be very unlikely. An eight-ounce cup of coffee would typically contain 95 mg of caffeine meaning that one would have to drink almost 13 cups of coffee consecutively to reach 1200 mg (Center for Food Safety and Applied Nutrition).

This problem arises because of highly concentrated forms of caffeine. Highly concentrated caffeine can be sold in powdered or liquid form in large bulk quantities on the internet (Center for Food Safety and Applied Nutrition). Through the retailers of these products do come with a health warning and suggested use information there is still plenty of room for misuse and accidental toxic effects. Specifically, the products that require the consumer to dilute the concentrated caffeine themselves pose the largest risk (Center for Food Safety and Applied Nutrition).

These products require the consumer to correctly measure out the recommended dose that can be anywhere from 1/64 of a teaspoon for some products to 1/16 of a teaspoon for others (Center for Food Safety and Applied Nutrition). This means that a person would have a 1/16 teaspoon or a scale that reads in milligrams (both of which are not common) to get the correct dose. This leads consumers to make guesses when diluting the concentrated caffeine. As stated above, 0.15 tablespoons of caffeine concentrate can result in toxic effects, so the chance that someone would use a tablespoon instead of a teaspoon can result in serious consequences (Center for Food Safety and Applied Nutrition).

A study by El- Bakry et al. (2017) showed that the recommended dose of green tea extract (GTE), resulted in hepatotoxic effects in rats. Although this experiment attempted to show hepatoprotective effects of GTE from acetaminophen, it found that GTE itself had hepatotoxic effects (El-Bakry et al. 2017). The study was designed to show that GTE had properties that would protect the liver from acetaminophen, a drug that can cause damage to the liver at high doses (El-Bakry et al. 2017). Interestingly, the hepatotoxic effect of GTE and acetaminophen were similar and when delivered in conjunction with one another exacerbated damage to the liver (El-Bakry et al. 2017). Due to the high dose, green tea extract had a hepatoxic effect both with and without the drug interaction with acetaminophen (Bakry et al. 2017).

3.3 Purity and Contamination

A prominent safety issue concerning herbal supplements is the threat of contamination (Li et al. 2017, Philip et al. 2018, Crighton et al. 2019, Nili-Ahmadabadu et al. 2019). Because of the relaxed laws surrounding herbal supplements, unreported compounds are found in some products (Borchers et al. 2007, Philip et al. 2018, Sansom et al. 2015). The contaminants fall into two categories - unintended contamination due to poor quality control during processing such as bacterial growth or heavy metals: and intentionally added ingredients such as pharmaceutical compounds, or fillers (Crighton, 2018). Due to the wide variety of contaminants, health risks also vary and depend on the specific contaminant. People might be ingesting compounds they are not aware of and are intolerant to or they might be taking known toxic products.

Unintended contamination

Without strict regulation and compliance, quality control in production of herbal supplements is often poor (Borchers et al. 2007, Philip et al. 2018, Sansom et al. 2015). Philips et al. (2018)

found that a weight loss herbal supplement called SafeLean ™ made from Garcina Cambogia contained multiple heavy metals such as cadmium, lead, and thallium among others, all well-known toxic metals. In the case report by Philips et al. *(2018)* a user experienced acute hepatitis with no obvious medical origin. It was only after extensive testing of conditions that usually caused a liver failure like hepatitis A or B that her physician suggested she stop taking this particular herbal supplement. After the patient discontinued the use of this supplement her hepatitis subsided CIT. This event of acute hepatitis from a weight-loss herbal supplement is not altogether unknown. Another case mentioned by Philip et al. even ended in a liver transplant for a woman who was taking this product (Philip et al.., 2018). The paper done by Philip et al. 2018 suspected that the contamination caused the hepatoxic effect, however, the toxicity of Garcina Gambogia is a debated issue (Philip et al. 2018). One study by Saito et al. (2005) found that doses of Garcina Gambogia caused testicular atrophy in mice while Ranjith et al. (2011) found no drug related toxicity from this herb. Other cases of contamination in herbal supplements might not have ended in such extremes but still should be considered.

Plant Contamination

Herbal teas have been found to contain toxic alkaloids produced naturally in weeds that may coexist with the plants harvested for the supplements (Steinhoff et al. 2019). Methods to test for these alkaloids are being developed in the European Union but testing is still not regulated in the United States (Steinhoff et al. 2019). Crighton et al. (2019) found that 32% of the herbal products they studied had additional plant matter that was not disclosed in the ingredients list. The addition of this plant matter could be purposeful or accidental on the part of the producer (Jordon et al. 2010, Crighton et al. 2019). Misidentification of plants and plant species can

happen in herbal supplement production (Jordon et al. 2010). Microbial contamination is another issue in herbal supplement production. Contamination can stem from poor handling of the product, unsafe manure usage and fungal outbreaks on the plants (Jordan et al. 2010).

Intentionally added contaminants

A good percentage of herbal supplement contamination comes in the form of alteration with pharmaceuticals. According to Nili-Ahmadabadi et al.. (2019) adulterating herbal supplement with pharmaceuticals is done so that the supplement will appear more effective (Nili-Ahmadabadi, 2019). Nili-Ahmadabadi et al.. (2019)'s study found that 15% of the 60 herbal supplements evaluated in Hamadan, Iran contained acetaminophen and or codeine. Though these compounds were added illegally and not shown on the label they arguably did not pose a significant health risk because the concentration was in safe limits (Nili-Ahmadabadi, 2019).

The main issue, in this case, beyond the possibility that the supplement itself posed a health risk, is that the persons taking the product was not aware of what was in it (Crighton et al. . This can become a problem if the person taking this product was avoiding the compound or if they were taking this supplement in combination with medications like Tylenol which may cause health complications if combined with acetaminophen (Nili-Ahmadabadi, 2019). Another major risk factor is the possibility of dependence because codeine is an opioid and even though people might not be aware they are taking that substance they might become dependent on that feeling (Nili-Ahmadabadi, 2019). Without accurate labeling, those that take herbal medicines might inadvertently be putting their health at risk.

The FDA have issued several warnings on various herbal weight loss medication due to pharmaceutical adulteration (Office of Dietary Supplement Program). A few of these adulterated

products from 2019 are Detox Plus, CholesLo, Skinny Pill, Lanugar, JaDera, Sheaya and Lipro and that is just a couple of the more resent notifications. Detox Plus for example was found to contain Tadalafil an ingredient used in an erectile disfunction medication. This intentionally added compound has the potential to interact with prescription drugs and poses a health risk to those with heart related illnesses (Office of Dietary Supplement Program).

Herbal supplement contamination was also found in Australian products, despite the strict regulations that the country implemented (Crighton et al. 2019). Crighton et al. (2019) found adulteration in both legally and illegally purchased herbal supplements through toxicological screening and DNA sequencing. Some of the adulterants found were additional plant matter, fillers like soybean and wheat, animal products and animal contamination (Crighton et al.., 2019). For the legally purchased supplements regulated by the country, 65% of them had undisclosed plant DNA while 27% contained filler ingredients (Crighton et al. 2019). Of the not legally regulated but still easily accessible supplements, 32% had plant DNA that was not reported and 35% had fillers (Crighton et al. 2019). However, legally produced supplements had a higher percentage of products that actually contained the ingredient it advertised for (Crighton et al., 2019).

While the risk of pharmaceutical adulteration in Crighton et al. (2019) was far less prominent the filler contaminant still posed as a health threat. Inaccurate listing of ingredients leads to the risk that a person will accidentally consume something they are avoiding (Crighton et al. (2019). This is especially problematic in the case of allergies; for instance, the fillers used in some of these herbal supplements like wheat, soybean, rice, and oats can all lead to an allergic reaction (Crighton et al. 2019). Other contaminants like animal products and animal contamination may lead to other health risks outside of allergies (Crighton et al. 2019) .

Toxicological screening and DNA sequencing is one method that could be required by governments to systematically regulate herbal supplements, but it is labor and monetarily intensive (Jordon et al 2010).

3.4 Herb-Drug Interactions

Herb-drug interactions are another health risk that affects herbal supplement users (Barone et al. 2001, Abebe et al. 2002, El-Bakry 2017, Ventura et al. 2018, Bosak et al. 2019). Herb-drug interactions and drug-drug interactions can happen either through pharmacodynamics or pharmacokinetics. Pharmacodynamic is what the body does to the drug while pharmacokinetics is what the drug does to the body (Tozer et al. 2006).

The majority of herbal supplement drug interactions are pharmacokinetic interactions, meaning some herbal supplements antagonize or inhibit enzymes that are working on metabolizing a drug in the system (Barone et al. 2001, Abebe et al. 2002, Brewer et al. 2017, El-Bakry 2017, Ventura et al. 2018, Bosak et al. 2019). When this happens, that drug can either be eliminated too quickly or remain in the system for too long (Brewer et al. 2007). This is problematic since the therapeutic dosage of pharmaceuticals are carefully defined based on assumptions about metabolic rates (Tozer et al. 2006, Brewer et al. 2017).

When taking an herbal supplement that interferes with the pharmacokinetics of a drug, the dose at which the compound was administered might not be the effective dose (Barone et al. 2001, Abebe et al. 2002, Brewer et al. 2017, El-Bakry 2017, Ventura et al. 2018, Bosak et al. 2019). Because the herb might affect pharmacokinetics the individual might not be receiving the drug within its therapeutic window (Brewer et al. 2017). This can be a serious problem if a patient is not getting enough of their prescribed medication or if they are receiving too much and

the drug is found at toxic or unsafe levels (Brewer et al. 2017). It can also be toxic if the body is unable to metabolize the parent compound into something non-toxic (Brewer et al. 2017).

St John's Wort is one herbal supplement that is known to cause serious herb-drug interactions. In a case study done by Barone et al.. (2001), St. John' Wort was inhibiting cyclosporine in transplant recipients. Cyclosporine is an immunosuppressant that is typically prescribed to transplant recipients. This drug is used to stop transplant rejection of an organ, graft, or bone marrow though immunosuppression. According to Barone et al. (2001), two women had complications with their cyclosporine levels. For one of the women her practitioners noticed cyclosporine was at reduced levels (Barone et al. 2001). After the medical team asked her about any new medications or diet changes she might have made, she informed them that she had started taking St. John's Wort for depression (Barone et al. 2001). She had been taking multiple tablets of 300mg St. John's Wort for the last 6 months (Barone et al. 2001). This dosage of St. John's Wort is not unusual and in fact can be found in pharmacies at even higher doses. After the cessation of this herbal supplement she reached the optimal level of cyclosporine once again (Barone et al. 2001).

The second case that Barone et al.. (2001) looked at was of another woman who had also been taking St. John's Wort in combination with cyclosporine. In this case, however, the patient developed chronic transplant rejection (Barone et al. 2001). She had also been taking a couple of tablets of St. John's Wort at 300mg but did not inform the medical team of what herbal supplements she was taking (Barone et al. 2001). After the medical team had finally discovered that she was taking St. John's Wort they were not able to reverse the damage to those transplanted organs (Barone et al. 2001). Borne et al. (2001) believes that St. John's Wort might

induce the enzyme CYP3A4 and the protein P-gp. This caused cyclosporine to be metabolized too quickly.

A supplement called Paullinia Cupana has been widely used to assist in weight loss (Ventura et al. 2018). A study done by Ventura et al. (2018) found herb-drug interactions between Paullinia Cupana and an epileptic drug called Lamotrigine. Obesity can lead to other health issues such as epilepsy, so the use of these two compounds in conjunction are common (Arya et al. 2015, Ventura et al. 2018). They found that content of Lamotrigine was lowered due to the co-administered treatment of Paullinia Cupana (Ventura et al. 2018). Though it was not clear which mechanism caused this interaction Ventura et al. (2018) theorized that it was the absorption in the gastrointestinal tract not in the metabolism (Ventura et al. 2018). It is evident from these cases that the lack of knowledge about these supplements not only lead to dangerous interaction but also made finding the causality difficult.

3.5 Conclusion

The health risks derived from using herbal supplement vary between the production of the supplement, the supplement itself and the way in which the supplement is used. Unfortunately, research on the health risks of herbal supplements is lacking, and most of the data is found in case studies and reports (Jordon et al.). Beyond the lack of documented health risks, plants themselves are complicated and have much variety making them hard to identify (Jordon et al.).

Chapter 4: Regulation of Herbal Supplements

4.1 Introduction

In the 1800s there was an increase in the use of opium that resulted in widespread dependence. It was not until the 1900s that physicians started to acknowledge the adverse and potentially fatal side effects of opium (Musto 1999). In response, the United States shifted away from the laissez-faire treatment of drugs to a more regulated approach (Musto 1999). Much of today's drug regulation, including the Pure Food and Drug Act, originate from this period of American history (Borchers et al. 2007). In this chapter, I will explore how the history of the United States Food and Drug Administration affected the regulation of herbal supplements in the 1990s and how public health crisis beget regulations (Borchers et al. 2007).

4.2 Origins of the Food and Drug Administration

Patent Drugs Effect on U.S Drug Regulations

One underlying cause for the Food and Drug Act of 1906 was the widespread use of patent drugs (Borchers et al. 2007). Patent drugs, a term used for self-medication sold by stores and salesmen that typically contained habit-forming substances Borchers et al. 2007). Patent drugs, also known as nostrums, were sold directly to the consumer, without the guidance of a physician, as a cure-all. Some of these substances consisted of alcohol, cocaine, or opium used to treat a variety of ailments. Many consumers were not made aware of or did not understand, the risks associated with patent drugs (Hart et al. 2015). These patent drugs did not list all the indigents found in the

product, and in fact, some of the indigents that were advertised were not found in the concoctions (Hart et al. 2015). By 1905 public outcry and protests pushed the United State government to pass The Pure Food and Drug Act (Borchers et al. 2007).

Early Regulation under the Food and Drug Administration

Under Theodor Roosevelt, the 1906 Pure Food and Drug Act was instated to protect consumers from purchasing mislabeled drug goods (FDA). The Pure Food and Drug Act prohibited the sale of unlabeled and misleading food and drug products. Because of this act drug labels had to include what was in the mixture and how much was present (FDA).

In 1938 the Food, Drug, and Cosmetic Act was passed to ensure the safety of the drug (FDA). This act required that the drug be proven safe before it reached the market by requiring producers to submit a New Drug Application (NDA) (FDA). This was in contrast to the 1906 act that only stipulated that producers needed to state the ingredients accurately. However, it was not until 1962 that the Kefauver-Harrison Act required producers to prove that their drug was also effective in treatment (FDA).

Partly due to the recent epidemic of congenital disability in the United Kingdom (among other countries from Thalidomide, the United States once again took an interest in the legality of medication sales (Greene et al. 2012). The Kefauver-Harrison Act of 1962 stipulated that drug manufacturers would have to prove their drug was effective through clinical trials (FDA). After this act, drug manufacturers had to prove that their drug was not only safe but also effective (FDA). However, even with the amendments like Kefauver-Harrison Act and 1938 Pure Food, Drug and Cosmetic Act, products like herbal supplements continued to be sold relatively unregulated.

Important Dates Concerning the FDA and Herbal Supplement Regulation
1906 Pure Food and Drug Act
1938 Food Drug and Cosmetic Act
1963 Kefauver-Harrison Act
1994 Dietary Supplement Health and Education Act

4.3 Regulation of Herbal Supplements

The battle to regulate herbal supplements had been ongoing since the Kefauver-Harrison Act of 1962; however, no legal action was taken against herbal supplements until the end of the 20th century (FDA). In 1993 the FDA set strict regulations for food labels so that companies could not state that their product was health-supporting without evidence (FDA). In that year the, Unsubstantiated Claims and Documented Health Hazards in the Dietary Supplement Market Place document was also released by the FDA stating that they would take strong action against the dietary supplement industry

The Dietary Supplement Health and Education Act (DSHEA) was passed by Congress in 1994 partly due to the public push back against the Unsubstantiated Claims and Documented Health Hazards report. Congress stated, with the support of outside studies, that dietary supplements can promote health and disease prevention (DSHEA 1994). They also found that about 50% of Americans do regularly use dietary supplements to improve their health and nutrition. Dietary supplements have become increasingly important in the American economy; however, there is documentation of adverse side effects from these treatments. Though safety issues are rare (according to Congress), they still wanted to create a federal framework around dietary supplements to ensure the public's safety (DSHEA 1994).

This act defined herbal supplements “as vitamins, minerals, herbs, amino acids, and enzymes. Dietary supplements are marketed in forms such as tablets, capsules, soft gels, gel caps, powders, and liquids." The act stipulates that dietary supplements cannot be sold as a food product but must be correctly labeled as a supplement (DSHEA 1994). Through this description dietary supplements fall between the FDA’s definition of food versus drug, in effect, they created a separate classification for supplements.

Congress decided that the United States government should bear the burden of proof if a supplement has an unreasonable risk, lacks defined conditions of use, lacks information (only for new products), or has adulterer ingredients (DSHEA 1994). This means that the United States government must prove that a supplement is unsafe for any of the reasons listed above, for the product to be removed from the market.

The label of a dietary supplement cannot be false or misleading to the consumer (DSHEA 1994). A statement about the function of a dietary supplement can only be made if the benefit is related to a "classic" nutrient deficiency disease while showing the prevalence of this problem in the United States and states how the active ingredient will affect the person taking it (DSHEA 1994. The statement must be truthful and not misleading while also showing the following “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease” (DSHEA 1994.

Nutritional information of the product must be made clear to the consumer by including the government recommended daily consumption of ingredients (DSHEA 1994). Ingredients that need to be stated on the label are only those that are seen as a ‘substantial amount (DSHEA 1994). Other ingredients that are not in a substantial amount are not required to be put on the label or have the recommended daily consumption (DSHEA 1994). A supplement is classified as

misbranded if the label does not include the name of every ingredient, the quantity, or total quantity if the product is a blend (DSHEA 1994). If the product does not clearly state that it is a ‘Herbal Supplement' with that exact term, it will also be deemed as misbranded, because without this label the consumer might assume that it is either a food or a drug (DSHEA 1994).

4.5 Conclusion

The FDA’s regulation on herbal supplements is entirely different from that of pharmaceuticals (Borchers et al. 2007). Instead of premarket approval the FDA is intended to monitor herbal supplements already on the market (DSHEA 1994). However, close monitoring of these supplements is impossible due to the large quaintly of product, instead the FDA is only able to research supplements that have already caused toxic or problematic effects (Borchers et al. 2007). It is apparent that with this system the FDA cannot fully protect consumers from unsafe herbal supplements.

Chapter 5: Conclusions and Policy Recommendations

5.1 Education, Research and Communication

The use of complementary and alternative medicine and that of herbal supplements have brought forward a number of issues that conventional medicine can improve on (Kennedy 2005, Bishop et al. 2007, Warriner et al. 2014, Zahn et al. 2019). It is clear that some individuals do not feel heard in conventional medicine. For the medical community, communication should be one of their top priorities, both in terms of general health and the use of herbal supplements (Kennedy 2005, Bishop et al. 2007). The lack of trust and comfort patients feel with their practitioner should be alarming and cause for further examination. I propose that medical practitioners should start frequently asking about dietary and herbal supplements to their patients.

Improving education on the topic of herbal supplements to medical practitioners as well as users is also important (Zahn et al. 2019). Stewart and Odle et al. (2013) found posters depicting the efficacy and safety of herbal supplement did have an effect on the individual's perception. Educating medical professionals on supplements and supplement use might also protect patients from misuse of these substances (Zahn et al. 2019). However, education of practitioners on herbal supplement use must also be coupled creating a better patient-practitioner relationship.

Expanding on the state of the science would help bring validity to supplements and also support safe use parameters (Jordon et al. 2010). Improving on case reports through follow up could help strengthen the data on supplement use (Jordon et al. 2010). Jordon et al. (2010) suggested that data from poison control centers could be utilized to expand current reports on adverse reactions with supplements. Clinical research of herbal supplements would also add

some much-needed information on supplement use and how it might affect the body (Jordon et al. 2010).

5.2 Policy Recommendations

Finally, improvements on the FDA's jurisdiction over herbal supplements would help regulate these supplements, as well provide substantial information to the consumer and health care provider. The FDA needs to have the ability to monitor all supplement before they reach the market instead of waiting for critical cases of toxicity to incite testing. To fund this effort there could be a small tax on herbal supplement producers that would support the testing and regulation of their products (Khatcheressian 1999). Another option is for the FDA and the herbal supplement producer to share the burden of regulating these products. By the FDA enforcing stricter labeling regulation, the producers would have to test their own products (McCann 2014). If the FDA required the labeling include suggested dose based on gender and weight or possible interactions, for example, the producers would have to allocate their resources to research these requirements (McCann 2014). However, the likelihood of any of these changes coming into effect soon is slight. Legislation seems to be fueled by public crisis, unfortunately because of this it might take a public health scare to ignite these changes.

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