

Review Article

Nutritional Supplements from Medicinal Plants - Industrial Hemp, Flax, and Ashwagandha

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Received: October 19, 2021; Accepted: November 12, 2021; Published: November 19, 2021

Abbreviations

FDA: Food and Drug Administration; DSLD: Dietary Supplement Label Database; THC: Tetrahydrocannabinol; CBD: Cannabidiol; SDG: Secoisolariciresinol Diglucoside

Introduction

Dietary supplements have gained popularity through the years, and their use has been increasing even further due to the aging population, increased tendency to use natural products, and increased cost of synthetic pharmaceuticals [1]. The dietary supplement market was valued at USD 101.38 billion in 2018, and the market revenue is set to reach USD 220.3 billion by 2030 [2]. Commodities with claimed health benefits are referred to as nutraceuticals (including dietary supplements), nutritional foods, functional foods, etc. [3].

Though popular, dietary supplements have been subject to debate as they occupy an awkward place in terms of regulation. The Food, Drug, and Cosmetics Act (FDCA) was passed in 1938 by the US Congress, which provided the US Food and Drug Administration (FDA) the authority to regulate products classified as foods, drugs, or cosmetics [4]. The FDA initially attempted to regulate some dietary supplements by treating them as drugs; however, this method did not succeed, and in response, the Congress passed a law in 1976 prohibiting the FDA from treating dietary supplements as drugs [4]. After failing to regulate dietary supplements as drugs, the FDA tried to regulate them as food additives, but this also did not come to fruition [4].

In 1990, the Nutrition Labelling and Education Act was passed that required all packaged foods to provide nutrient information on the label; this act also gave the FDA the authority to regulate the health claims [4]. In 1992, the Dietary Supplement Act was passed due to FDA's rejection of most health claims made for dietary supplements. The debate about FDA's authority led to the passage of the Dietary Supplement Health and Education Act of 1994 [4], which defined a dietary supplement as a product (other than tobacco) intended to supplement the diet and that bears or contains one or more of the following dietary ingredients: vitamins, minerals, herbal ingredients, amino acids, proteins, and other substances that provide

Abstract

Plants have been long used in nutritional supplements due to their natural therapeutic properties. The recent increase in the use of nutritional supplements has increased the need to establish the scientific basis of nutritional supplements and their regulation. Industrial hemp, flax, and ashwagandha have long been used in traditional herbal medicine. Along with their role in herbal medicine and supplements, they have gained popularity due to their therapeutic and nutritional values.

Keywords: Dietary supplement; Industrial hemp; Flax; Ashwagandha

a nutritional or physiological effect; most such products fell under the category of "herbal" medicines [5-7]. Dietary supplements can be classified as follows: 1) substances with established nutritional function; 2) botanical products, their concentrates, and extracts; and 3) other substances with a plethora of origins and physiologic roles [8]. Botanical products are primarily responsible for the expansion and growth of the dietary supplements market [8].

Advantages of Nutraceuticals Over Pharmaceutical Drugs

There is still much debate surrounding the efficacy, safety, and quality of nutritional supplements. However, the main advantage of nutritional supplements over pharmaceutical drugs is that they may cause little or no adverse effects, which is why they may be preferred over conventional therapies [9]. The largest argument making the case for nutritional supplements is the association because diet is largely associated with chronic diseases including cataract, obesity, cardiovascular diseases, diabetes, gallstones, inflammatory diseases, cancer, and neurodegenerative diseases, nutritional supplements are becoming more popular as preventive agents [9]. In addition to their safety, nutritional supplements are more affordable and have multiple therapeutic benefits while increasing health value [9-11]. Their ability to act via multiple pathways make them favorable for pathologic conditions arising due to neuronal cell death and neurodegenerative diseases [9]. As another major advantage of nutritional supplements over pharmaceutical drugs, nutritional supplements provide a high concentration of nutrients in a small amount of supplement dosing [12,13]. Additionally, plant-based nutritional supplements are environmentally friendly and obtained from renewable sources [11,14].

However, even nutritional supplements must be used in moderation. Overuse and abuse of nutritional supplements may lead to health risks [9,13]. The human body can absorb only a certain amount of nutrients at a time or for a duration of time; the excess unabsorbed nutrients become toxic to the body and do more harm than good, similar to pharmaceutical drugs. Therefore, careful regulation of nutritional supplements is essential to prevent the overconsumption of these potentially beneficial products. Overall,

nutraceuticals are more cost-effective, safer, and have a nutritional value, all of which are advantages over pharmaceutical drugs, as long as these products are regulated to avoid misuse and overconsumption.

Dietary supplements are used for various reasons. According to the FDA, three out of four adults consume supplements regularly to improve overall health, maintain health, meet nutritional needs, and/or increase immunity [15-17]. Despite their popularity, few studies have been conducted to assess their efficacy, effectiveness, and safety. The FDA regulates dietary supplements in an evidently different manner than it does pharmaceuticals. While it is mandatory for the manufacturer of a pharmaceutical drug to document its effectiveness and safety before it can be marketed, the safety requirements for dietary supplements are much less stringent [16]. Post-market surveillance is primarily followed for dietary supplements, along with some premarket checks [18]. A dietary supplement when manufactured must hold evidence that is in support of the claims (i.e., the supplement provides nutritional support); however, specific disease treatment claims cannot be made [18]. These products must also have a disclaimer on the label stating that the claims have not been reviewed by the FDA [18].

The increasing use of nutraceuticals has also raised concerns for public health. The less stringent regulatory requirements have led to the introduction of several dietary supplements for disease prevention, for health benefits, or for enhancing physical performance, and monitoring these products has become a great challenge mainly because these dietary supplements contain multiple ingredients, their composition can vary over time, or they are used intermittently [1]. The use of dietary supplements is not without risks. A study had revealed that 59% of the dietary supplements contained ingredients that were not listed on the label [19]. Another risk is that dietary supplements can interact with commonly used pharmaceutical medications [18,19].

Nutritional or dietary supplements have various modes of delivery depending on the product. Nutritional supplements are most commonly formulated as capsules or tablets, liquids, or powders for oral consumption, but other forms such as bars also exist. A database has been created by the National Institute of Health known as the Dietary Supplement Label Database (DSLDB), which allows keyword

searches for what is printed on the label. In this case, some overlap may exist as certain labels may use capsules and tablets interchangeably. Additionally, the whole database can be searched and filtered if needed. The database has labels for supplements that are on market and off market. On market supplements can readily be found and sold commercially, whereas off market supplements are not found commercially [20]. The following table (Table 1) characterizes the labels found in the database that are on market and off market and the mode of delivery of the supplement.

The information in Table 1 was obtained by searching the whole database and filtering by supplement form and market status. The most common supplement form was capsules (37.2%), whereas the least common supplement form was bars, which only consists of 42 labels in the DSLDB and makes up <1% of the whole database.

The use of plant-based supplements, commonly referred to as botanical dietary supplements, has become increasingly popular worldwide as a means of maintaining or improving health. According to the Office of Dietary Supplements, botanicals or the plants used as the basis of the supplements, are sold as fresh or dried plant material. The supplements are prepared by isolating either a single chemical or a group of chemicals from within the botanical compound and are usually sold as a tablet or capsule. The safety and strength of the botanicals used in the supplements depend on their chemical composition, their effects on the body, and the method and amount used during preparation [21]. Furthermore, since botanical dietary supplements do not require proof of efficacy or premarketing approval by the FDA, the quality and safety of these supplements in the United States are heavily dependent on the manufacturer [22]. As such, the FDA has recently established a policy that requires all manufacturers to produce botanical dietary supplements following the Good Manufacturing Practice (GMP) guidelines to ensure that consumers buy products that have been accurately labeled [22]. Moreover, concrete scientific evidence backing the health effects and safety of botanical dietary supplements is lacking. Black cohosh, for instance, has been studied in depth as a treatment for menopausal symptoms, while the efficacy and safety of other botanical ingredients, such as astragalus, are not extensively known. The complexity and disparities of the composition of botanical dietary supplements give

Table 1: Mode of Delivery of Supplements as per the DSLDB.

Mode of Delivery of Supplements	Overall		On Market		Off Market		Source No.
	Number of Labels	Percentage of Database	Number of Labels	Percentage of Database	Number of Labels	Percentage of Database	
Capsules	48,320	37.2%	28,753	22.1%	19,567	15.1%	[20]
Tablets and Pills	24,034	18.5%	13,936	10.7%	10,098	7.8%	
Powders	18,352	14.1%	13,047	10.0%	5,305	4.1%	
Liquids	17,731	13.6%	11,426	8.8%	6,305	4.9%	
Softgel Capsules	13,942	10.7%	7,650	5.9%	6,292	4.8%	
Other	4,385	3.4%	2,822	2.2%	1,563	1.2%	
Gummies and Jellies	2,103	1.6%	1,308	1.0%	795	<1%	
Lozenges	669	<1%	370	<1%	299	<1%	
Unknown	365	<1%	206	<1%	159	<1%	
Bar	42	<1%	40	<1%	2	<1%	

Other includes less common supplement forms such as tea bags. Unknown includes supplements that the DSLDB was not able to determine its form.

Table 2: Mode of Delivery of Industrial Hemp Supplements as per the DSLD.

Mode of Delivery of Supplements	Overall	On Market	Off Market	Source No.
	Number of Labels	Number of Labels	Number of Labels	
Capsules	74	70	4	[20]
Softgel Capsules	97	80	17	
Tablets and Pills	1	1	0	
Gummies and Jellies	24	22	2	
Liquids	274	257	17	
Powders	256	185	71	
Other	2	2	0	

Other includes less common supplement forms such as tea bags.

Table 3: Intended Target Group of Hemp Supplements as per the DSLD.

Intended Target Group	Overall	On Market	Off Market	Source No.
	Number of Labels	Number of Labels	Number of Labels	
All Adults and Children 4 years and above	728	617	111	[20]

Table 4: Mode of Delivery of Flax Supplements as per the DSLD.

Mode of Delivery of Supplements	Overall	On Market	Off Market	Source No.
	Number of Labels	Number of Labels	Number of Labels	
Powders	1,051	658	393	[20]
Softgel Capsules	712	391	321	
Capsules	540	340	200	
Tablets and Pills	399	204	195	
Other	122	77	45	
Liquids	104	74	30	
Gummies and Jellies	42	20	22	
Unknown	23	9	14	
Bars	2	2	0	

Other includes less common supplement forms such as tea bags. Unknown includes supplements that the DSLD was not able to determine its form.

rise to two limitations: difficulties in comparing test articles across studies and reproducibility of botanical research [23].

Industrial hemp, flax, and ashwagandha are three plants commonly used in dietary supplements today for their health and nutritional benefits. Industrial hemp, characterized by reduced levels of the psychoactive compound Tetrahydrocannabinol (THC), is rich in non-psychoactive Cannabidiol (CBD), which has been shown to have anxiolytic, spasmolytic, and anticonvulsant effects [24]. Flax, commonly sold in the form of flaxseed or flaxseed oil, is high in omega-3 fatty acids, alpha-linolenic acid, the lignan secoisolariciresinol diglucoside, and fiber, all of which exhibit anti-inflammatory, antioxidant, and lipid-modulating properties [25]. Ashwagandha has primarily been used in dietary supplements for patients with arthritis, diabetes, infertility, fatigue, anxiety, stress, and cognitive deficits [26].

Industrial Hemp

Industrial hemp, also known as *Cannabis sativa* L. of the Cannabaceae family, is an ancient plant that originated from Central Asia. Cultivated for its various uses in food and medicine, industrial hemp is a great source of fiber and oilseed [27]. Hemp is a close relative to medical marijuana. The difference between the two lies in the concentration of the psychoactive compound THC. In North

America and most European countries, industrial hemp is classified as having THC concentrations of 0.3% or less in dried herbage, while medical marijuana is classified as *Cannabis sativa* with THC concentrations that exceed 0.3% [27,28]. Besides THC, hemp flowers and herbage contain other valuable cannabinoids with the most prominent one being CBD. There has been a growing interest in CBD as recent studies have shown that CBD may have therapeutic properties such as antiepileptic, anxiolytic, antipsychotic, and neuroprotective properties [27].

An ingredient search of the DSLD found that 728 labels listed hemp as an ingredient, which makes up less than 1% of the database. Of these, 617 labels in the database are on market and 111 labels in the database are off market [20]. The following table (Table 2) provides a breakdown of the supplement forms that list industrial hemp as an ingredient.

Of all supplement forms, there were no hemp products as Lozenge, Bar, or Unknown forms. The DSLD also categorizes the labels by target age group [20]. The following table (Table 3) provides details on the intended target group breakdown for industrial hemp products. There are no hemp supplements that are intended for infants, children of ages one to four, or pregnant and lactating women according to the DSLD [20].

Table 5: Intended Target Group of Flax Supplements as per the DSLD.

Intended Target Group	Overall	On Market	Off Market	Source No.
	Number of Labels	Number of Labels	Number of Labels	
Children 1-4 years	34	17	17	[20]
Pregnant and Lactating	17	13	4	
All Adults and Children 4 years and above	2,982	1,767	1,215	

Table 6: Mode of Delivery of Ashwagandha Supplements as per the DSLD.

Mode of Delivery of Supplements	Overall	On Market	Off Market	Source No.
	Number of Labels	Number of Labels	Number of Labels	
Capsules	3,378	2,281	1,097	[20]
Tablets and Pills	1,266	768	498	
Powders	976	784	188	
Liquids	841	563	262	
Other	432	282	133	
Softgel Capsules	195	98	88	
Unknown	31	20	11	
Lozenges	5	4	1	
Gummies and Jellies	2	2	1	

Other includes less common supplement forms such as tea bags. Unknown includes supplements that the DSLD was not able to determine its form.

Table 7: Intended Target Group of Ashwagandha Supplements as per the DSLD.

Intended Target Group	Overall	On Market	Off Market	Source No.
	Number of Labels	Number of Labels	Number of Labels	
Infants	2	2	0	[20]
Children 1-4 years	28	22	6	
Pregnant and Lactating	9	4	5	
All Adults and Children 4 years and above	7,146	4,844	2,302	

As an easily extractable, plant-based, biologically active compound with numerous medicinal uses, CBD can be found on the market as hemp-derived dietary supplements or as drugs such as Epidiolex. CBD nutritional supplements account for one-third of the 1.34-billion-dollar global industry for CBD [24]. However, despite its widespread use as a nutritional supplement, evidence from studies investigating the effects of hemp-derived CBD as an ingredient in dietary supplements is scarce. For instance, in a small interventional trial, 12 individuals received up to 90 mg of single oral doses of CBD and were observed for changes in cardiovascular and cognitive functions after CBD consumption; in participants who received 90 mg of CBD, cerebral perfusion increased and blood pressure decreased without any clinically evident adverse events or changes in blood count, inflammation, or metabolic markers [24]. Hence, the little clinical evidence for the effects of CBD as a dietary supplement only allows researchers to hypothesize that the optimal dose range for supplementation in adults is 5-10 mg/day [24].

Flax

Flax, also known as *Linum usitatissimum L.* of the Linaceae family, is one of the oldest crops and has been cultivated for thousands of years. There has been a renewed interest in the crop due to its perceived health benefits from some of its biologically active compounds including alpha-linolenic acid, linoleic acid, short-chain

polyunsaturated fatty acids, and secoisolariciresinol diglucoside (SDG; phytoestrogenic lignan) [29,30]. Flax-derived metabolites protect against diabetes and certain cancers [31,32]. These health benefits and additional protective effects against mental stress have been attributed to the antioxidant properties of SDG [33]. These biologically active compounds contribute to the nutraceutical properties of flax.

An ingredient search of the DSLD found that 2995 labels listed flax as an ingredient, which makes up 2.3% of the database. Of these, 1775 labels or 1.4% of the database are on market and 1220 labels or less than 1% of the database are off market. The following table (Table 4) provides a breakdown of the supplement forms that list flax as an ingredient.

Of all supplement forms, there were no flax products as a Lozenge. The following table (Table 5) provides details on the intended target group breakdown for flax products. There are no flax supplements that are intended for infants according to the DSLD [20].

Flax has many nutritive properties, making them an increasingly popular addition to the diets of many consumers. The compounds found in flax have shown to be useful in the prevention and management of chronic conditions such as type 2 diabetes, kidney disease, rheumatoid arthritis, hypertension, coronary heart disease, stroke, Alzheimer's disease, alcoholism, and certain types of cancers

[34]. A study found that adding SDG to an atherogenic diet reduced total cholesterol and low-density lipoprotein while increasing high-density lipoprotein; when the researchers of that study examined the extent of atherosclerosis in the aorta, they found that the SDG-treated groups had significantly smaller plaques, and the lesions were distributed over a smaller area [35]. Dietary supplementation with flax has been shown to have beneficial cardiovascular effects through several studies, both preclinical and clinical [36].

Ashwagandha

Ashwagandha, also known as *Withania somnifera L.* of the Solanaceae family and as the Indian Ginseng, is an ayurvedic plant grown traditionally in central and northwestern India. The plant is resistant to drought and is often grown on land not suitable for food crops [37]. Similar to other plants used in herbal medicine, ashwagandha contains many biologically active compounds such as flavonoids and natural antioxidants [38-40]. Ashwagandha was also found to contain steroidal lactones [41]. Withanolides, the active class of compounds in this plant, have antibacterial, antitumorogenic, anxiolytic, and antidepressant activities [40]. A recent study has also demonstrated their efficacy against SARS-CoV-2 activity [42].

An ingredient search of the DSLD found 7158 labels listing ashwagandha as an ingredient, which makes up 5.5% of the database. Of these, 4851 labels or 3.7% of the database are on market, and 2307 labels or 1.8% of the database are off market. The following table (Table 6) provides a breakdown of the supplement forms that list ashwagandha as an ingredient.

Of all supplement forms, there were no ashwagandha products that could be found as a Bar. The following table (Table 7) provides details on the intended target group breakdown for ashwagandha products.

Ashwagandha is known to promote balance in different body systems i.e., it acts as an adaptogen. The supplements and the plant are also known to reduce stress and increase immunity [43]. Ashwagandha supplements increased stamina in a swimming endurance test in rats and prevented swimming stress-induced changes in cortisol and ascorbic acid content in the adrenal glands of the rats [44]. The anxiolytic effect of ashwagandha makes it suitable for treating depression [44]. The root of the plant can act as a tonic, narcotic, diuretic, astringent, aphrodisiac, anthelmintic, thermogenic, and stimulant [43]. Ashwagandha supplements promote brain health [43]. The plant also significantly increased body weight in rats [44]. In a clinical study, ashwagandha supplements increased muscle mass and strength [45,46]. Overall, ashwagandha is primarily used as an adaptogen and for its anti-stress activity as it helps different body processes return to homeostasis.

Conclusion

Industrial hemp, flax, and ashwagandha all have nutritive value and are available as supplements on the market. These plant-based supplements are potentially driving the market for nutritional supplements. With a rise in the use of nutritional supplements, the need for proper regulations to ensure their safe use has also risen.

Acknowledgments

The authors would like to acknowledge the School of Science,

Engineering, and Technology at Penn State Harrisburg.

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