In-depth multidisciplinary review of the usage, manufacturing, regulations & market of dietary supplements

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In-depth multidisciplinary review of the usage, manufacturing, regulations & market of dietary supplements

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Abstract
With dietary supplements usage growing exponentially, it is crucial to have a clear grasp of such products. This extensive review article aims to provide comprehensive information about dietary supplements from multidisciplinary perspectives from clinical to dosage form production and official regulations. It provides a crucial background of various topics relating to dietary supplements along with the corresponding key issues. The review article consists of four main sections. The first section gives the general background along with the usage and safety of dietary supplements. Here the article looks at the topic through a clinical lens. The second section focuses on the manufacturing aspect of dietary supplements. This section of the article is practical and provides an in-depth discussion of the issues revolving around dietary supplements, which range from extraction of active ingredients to stability and more. The third section provides comprehensive information with regards to the regulation of dietary supplements, which remains a crucial and evolving topic of discussion. The article goes into details about health claims, product labels and more. Finally, the fourth section brings forth the awareness of the global market trend of dietary supplements.

Keywords: Dietary Supplements; Nutraceuticals; Dietary Supplement Interactions; Dietary Supplement Manufacturing; Stability; Regulations on Dietary Supplements
1. Usage and safety of dietary supplements

1.2 A brief introduction to dietary supplements

To improve well-being and long-term health, food and appropriate supplementation are needed. Most of our energy and the necessary macro and micronutrients come from staple foods. Nowadays, staple foods are also considered as supplements. For example, turmeric is used as a dietary supplement and food. Dietary supplements are described in part by the policy as substances taken by mouth that contain a "dietary ingredient," which may include vitamins, minerals, amino acids, herbs or botanicals, and other substances used to complement the diet.

Dietary supplements are divided into three major categories based on their basis or function:

1) Botanical products and their essence, 2) Nourishing substances such as minerals, vitamins, amino acids, and fatty acids, 3) Other substances with a wide origin variation, such as steroid hormone procedures and pyruvate. Since people take dietary supplements for different aims, it can be said that some of the most important motivations are decreasing the risk of age-related diseases, adequate nutrition, protecting other body tissues. Dietary supplements' consumption has been widely growing, which resulted in rapid use expansion in botanical products, mineral and vitamin markets.

1.2 Dietary supplements and functional foods

It has been more than two decades since the term ‘nutraceuticals’ was first introduced by Stephen DeFelice (1991), founder of the Foundation for Innovation in Medicine [1]. His definition was quite broad: ‘A nutraceutical is any substance considered a food or part of food which provides medical or health benefits including the prevention or treatment of disease and includes isolated nutrients, dietary supplements, diets and dietary plans, genetically engineered foods, herbal products and processed foods such as cereals, soups and beverages [1]. These products are classified as nutraceuticals or dietary supplements. Despite the ongoing efforts to
reach a consensus over the definition, the term nutraceuticals has now captured the spirit of products at the food/drug interface. In a simpler form, any supplements or products that are derived from food and are often used for medicinal reasons are called nutraceuticals.

Similar to dietary supplements, functional foods are also another class of food additive, which are now gaining growing interest. Despite some overlaps between the regulations of these products, there are some differences between their entities from a regulatory and post labelling of safety perspective. Both are regulated as foods rather than drugs, but from a regulatory perspective, they are different. Quite often this confuses the consumers when pre-marketing versus post-marketing responsibilities for their safety is concerned. From a regulatory viewpoint, the law defines dietary supplements as products that are intended to supplement the diet and contain one or more “dietary ingredients”. These dietary ingredients may include but are not limited to vitamins, minerals, herbs or other botanicals, amino acids, or other dietary substances, which supplement the diet by e.g. increasing the total dietary intake, or concentrates, metabolites, etc [2]. In contrast, functional foods have no legal definition and the U.S. FDA does not recognise them as a unique category. Generally, the activity of enhancing or augmenting a food to result in some type of health benefit is referred to as functional foods [3, 4]. Section 201 (21 U.S.C. 321) states that “the term ‘nutraceutical’ means a dietary supplement, food, or medical food, as respectively defined in paragraphs (f) and (95) and section 5(h)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)), that- “(1) possesses health benefits; and “(2) is safe for human consumption in such quantity, and with such frequency, as required to realize such properties.” The term ‘health benefit’, when used with reference to a nutraceutical, means a benefit that prevents or reduces the risk of a disease or health condition, including the management of a disease or health condition or the improvement of health [5].
Until now, there is currently no consistency in the legal status of food supplements across the European Union (EU). However, to harmonize the regulatory status of food supplements in different EU countries, the EU has created a legal and regulatory framework for these dietary products with the Food Supplements Directive 2002/46/EC [6].

Article 2 of Directive 2002/46/EC defines food supplements, as “Foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drops dispensing bottles and other similar forms of liquids and powders designated to be taken in measures small unit quantities”. Examples include green tea extract or grape seed extract [7].

The Chinese Food Safety Law enacted in 2015 developed a new centralized system under the National Medical Products Administration (NMPA). Under this law, the natural products fall under either “Classified as Supplements” or “Classified as Medicines” where the latter has a strong presence in China and is generally referred to as Traditional Chinese Medicine (TCM). On the other hand, the former identified as “Classified as Supplements” is often called Health Foods which also includes products that are used in conjunction with the functional foods [8].

With few minor exceptions, Japan's recent legislation enacted in 2015 is largely adopted from the United States. Unlike those classified in Chinese Safety Law, foods in Japan are either regulated as "Foods in General" or "Food with Health Claims” [9].
Regardless of whether they are "Classified as Supplements" or "Classified as Medicines", in Australia, most natural products are treated as "complementary medicines" and termed as the "therapeutic goods," Likewise in Canada, most natural products are called natural health products (NHPs) and are regulated by Health Canada (HC) [10].

In New Zealand, dietary supplements are, however, regulated by the Dietary Supplements Regulations (DSR) of 1985. Dietary supplements in this country are supposed to be taken orally with a specific dosage provided on the drug label and should not be intended for therapeutic outcomes to keep them distinguished from the medicines [11].

1.3 The rise of dietary supplements

Dietary supplement usage among adult populations especially in the USA and Europe has grown significantly over the past few decades. Since the National Health and Nutrition Examination Survey (NHANES) initiated collecting data on the usage of dietary supplements in the early 1970s, it had reported that about 28% prevalence of dietary supplements among men and 38% among women aged 20 and older were found from 1971-1975. These numbers sustained for the follow on four years, however, a sharp rise was noted for the subsequent years where about 40% prevalence was found in US adults from 1988-1994. It is surprising that since 2003, these numbers have experienced steady growth as high as 50% [12]. A report on the study of the trends in alternative medicine use in the United States between 1990 and 1997 revealed that among other food additives, the use of herbal products such as nonvitamins or minerals had increased by many-fold, which reflected a staggering 480% overall growth [13]. Another study conducted by the National Institute of Health (NIH), released in December 2008, provided information for approximately 24,000 adults aged >18 and compared the results with the 2002 findings. There was a sharp rise in the numbers of food supplements usage recently
A recent report published by Zion Market Research in 2019 forecasted a significant rise in the global dietary supplements market between 2015 and 2021 where the global revenue is set to reach US$ 220.3 billion by the end of this forecast period. The major driving forces in this exponential rise includes botanical products, amino acids, vitamins, enzymes, and minerals.

1.4 Interactions

1.4.1 Drug-Nutrient Interactions

It has been reported that in the modern era, approximately 80% of adults older than 50 years take at least 1 prescription medicine, whereas more than 20% take 5 or more prescription medications in the USA [16]. The analysis of these prescription medication users showed that more than 50% of these consumers also use dietary supplements [17] but this may be more in recent years due to COVID-19. For those who are on food or special therapy treatments such as complementary and alternative medicine (CAM), more than 77% concurrently use 1 or more prescription medications. These growing numbers indicate that the use of both prescription medications and dietary supplements may lead to possible interactions between them [16-18].

It has been reported that the potential for clinically significant interactions between medications and dietary supplements ranges between 21%-46%, of which about 30% are confirmed clinically significant [19]. The possible interactions between drugs and herbs can both be pharmacokinetic and pharmacodynamic. When it is pharmacokinetic, the absorption and metabolism are affected, whereas for pharmacodynamic, the effect is antagonistic. It is shocking that approximately 80% of the dietary supplements that are currently available globally for intake likely interact with the cytochrome P450 enzyme system (CYP) in the human body. The CYP system plays a pivotal role in the metabolism prior to the absorption of many medications. In addition, dietary supplements can have adverse effects on some other
enzymes of the CYP system such as CYP3A4, CYP2C19, CYP2C9, CYP2D6, CYP1A2, including inhibition of drug metabolism [19]. Study shows that garlic has a moderate to major effect on CYP3A4 substrates such as simvastatin, verapamil, amlodipine, diazepam, and the drug effect. In another study, it was demonstrated that kava and valerian inhibited the enzyme and increase the drug effect of CYP3A4 substrates [19]. Therefore, the possible drug-nutrient interactions have to be carefully considered before taking any dietary supplements.

1.4.2 Nutrient-Nutrient Interactions

In general term, dietary supplements are taken to supplement the diet and provide an additional source of vitamins, phytonutrients and minerals to the diet. Upon the administration of the dietary supplements, it is likely that any nutrients coming from the diet may interfere with that of the supplements. There are various possibilities of interactions between the dietary supplements and medications and even between two different dietary supplements or with the nutrients coming from food intake. It can be assumed that a safe dietary supplementation requires adequate knowledge and a robust dietary plan detailing the safe and healthy levels of intake of all nutrients. Particular care should be given to those nutrients being supplemented, as any nutrient over its toxicity level can be very dangerous and sometimes life-threatening. Many nutrients supplemented can also compete for receptor sites and can appear as the main cause for an imbalance of other nutrients. It is advised that robust Dietary Reference Intakes (DRIs) is fully implemented to assess dietary food and supplement intake for all age groups. It is common in Europe and the USA that some specific vulnerable groups are often recommended with some specific food supplements. Examples include pregnant women being encouraged to take folate, and breastfed infants to be supplemented with vitamin D or formula milk fortified with vitamin D, which is recommended for bottle-fed infants in the first year of life [20, 21]. Though in most of these cases, recommended food supplements prove beneficial
and seem to work, however, at the same time, it is also important to be aware that nutrient excesses can also pose a health threat. For example, excess folic acid may influence vitamin B12 deficiency and mask its possible effects whereas high doses of iron supplements can reduce the rate of absorption of zinc in the body [22].

1.5 Safety

It is a common misperception in society even in this current modern era that dietary supplements are safe since they come from natural sources. Not all natural supplements can be considered risk free and completely safe. For example, kava is a natural product but its regular consumption may have a negative impact on the liver [23]. Unlike prescribed or non-prescribed medications, for safety and effectiveness, the government bodies for almost all countries where dietary supplements are recognised do not approve dietary supplements before they are made available to consumers. For this reason, an extra consideration and safety management plan have to be imposed prior to taking food supplements.

Figure 1. The 10 most common natural products used by adults [percentages based on adults who responded to the 2007 National Health Interview Survey (NHIS) and reported their use of natural (nonvitamin, nonmineral) products in the past 30 days] [24, 25].
1.6 Commonly used dietary supplements

Despite the lack of data supporting therapeutic efficiency, over one-third of the adults in the US or Europe take a daily multivitamin/mineral (MVM) supplement. The main reason for the popularity of multivitamin/mineral supplementation is due to the prevention of developing chronic diseases, including cancer. Now, a variety of MVM supplements are available in the marketplace and still, their numbers are significantly rising with varying concentrations and compositions of vitamins and minerals (Figure 1). Though there are several MVM products currently available in the market that contain up to 100% of the recommended dietary allowance (RDA) for one or less vitamins and some for minerals, no supplement is currently available that contains 100% of RDA for calcium, magnesium, phosphorus, or potassium. MVM supplements are produced specifically for individual segments of the population. Often, these supplements are designed to provide higher or lower amounts of a particular vitamin and/or mineral for that niche market segment. For example, supplements manufactured for women typically contain more iron than those developed for men. Some commonly used supplements are summarized in Table 1 below whereas some commonly used dietary supplements and their properties in Table 2.

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin/mineral Supplements</td>
<td>Multivitamin/mineral (standard or speciality; age-related or sex-specific)</td>
</tr>
<tr>
<td></td>
<td>Vitamin C</td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
</tr>
<tr>
<td></td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Botanical supplements</td>
<td>Astragalus</td>
</tr>
<tr>
<td></td>
<td>Milk thistle</td>
</tr>
<tr>
<td></td>
<td>Turmeric</td>
</tr>
<tr>
<td></td>
<td>Resveratrol</td>
</tr>
<tr>
<td></td>
<td>Ginger</td>
</tr>
<tr>
<td></td>
<td>Ginseng</td>
</tr>
<tr>
<td>Other</td>
<td>β-carotene</td>
</tr>
<tr>
<td></td>
<td>ω-3 fatty acids</td>
</tr>
<tr>
<td></td>
<td>Glutamine</td>
</tr>
<tr>
<td></td>
<td>Melatonin</td>
</tr>
</tbody>
</table>
### Table 2. Most commonly used non-vitamin, non-mineral, natural products by adults

<table>
<thead>
<tr>
<th>Name of supplement</th>
<th>Commonly reported uses</th>
<th>Proposed mechanism of action</th>
<th>Clinical implications: interactions, side effects and cautions</th>
</tr>
</thead>
</table>
| Fish oil/Omega-3 (ω-3)   | • To lower blood pressure  
• To prevent heart disease and stroke | ω-3 essential fatty acids reduce the build-up of cholesterol and triglycerides and decrease the risks for heart attack by exerting anti-thrombotic and anti-inflammatory effects. | Fish oil/ω-3 supplements appear to be safe.  
In large doses, fish oil may increase the risk of bleeding.  
Fish oil may also reduce immunity.  
**Side effects:** belching, bad breath, heartburn, nausea, loose stools, rash, and nosebleeds. |
| Glucosamine and chondroitin | • To reduce pain from osteoarthritis. | Glucosamine cushions the joints. Chondroitin helps cartilage retain water. | Glucosamine and chondroitin sulfate are likely safe for most adults.  
It increases the risk of bleeding. Chondroitin may worsen asthma and may be associated with the spread of prostate cancer.  
Glucosamine may raise blood sugars in individuals with diabetes and trigger allergy.  
**Side effects:** mild GI pain, nausea, diarrhea, constipation, and heartburn. |
Echinacea
- To prevent cold, flu, and other infections
  Inulin may activate the alternative complement pathway of the immune system, increasing phagocytosis and lymphocyte activity.
  Echinacea appears to be safe for most adults. Echinacea may have an antagonistic effect on immunosuppressing medications.

Side effects: Rashes, asthma, and anaphylaxis and allergies to daisies.

Flaxseed and fiber/psyllium
- To lower serum cholesterol levels and as a laxative
  May have a laxative effect. Fiber also binds with cholesterol in the gut, preventing it from being absorbed. Flaxseeds reduce platelet aggregation, lower blood cholesterol, and reduce inflammation, which may lower atherogenic risks and protect against heart disease.
  Appear to be safe for most adults. The high fiber content may lower the body’s capacity for absorption.

Side effects: May cause diarrhea and should be taken with ample water to prevent constipation and intestinal obstruction.

Ginseng
- To increase vitality and energy
  Stimulate the CNS, and natural killer cell activity, and may inhibit
  Appears to be safe for most adults.
platelet aggregation. It may also lower postprandial blood glucose levels. Ginseng may lower blood glucose levels and may have an antagonistic effect on immuno-suppressing medications.

**Side effects:** headaches, sleep disturbances, GI upset, allergic reactions, breast tenderness, menstrual irregularities, and high blood pressure (may be due to a nonpure preparation).

<table>
<thead>
<tr>
<th>Ginkgo biloba</th>
<th>To improve memory and prevent or treat Alzheimer and other dementias.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>It contains flavonoids, terpenoids, and organic acids.</td>
</tr>
<tr>
<td></td>
<td>Flavonoids have antioxidant properties that may protect cells from oxidative damage. They may also inhibit platelet aggregation.</td>
</tr>
<tr>
<td></td>
<td>Appear to be safe. Raw ginkgo seeds contain ginkgotoxin, which can cause serious adverse reactions, including seizures and death.</td>
</tr>
<tr>
<td></td>
<td>It may increase bleeding risk and should therefore be taken with caution before or after surgery and dental work.</td>
</tr>
<tr>
<td></td>
<td><strong>Side effects:</strong> Headache, nausea, GI upset, diarrhoea, dizziness, or allergic skin reactions.</td>
</tr>
</tbody>
</table>
Green tea

- To prevent cancers, including breast, stomach, and skin cancer.
- To improve mental alertness, lower cholesterol levels, and promote weight loss.

It contains catechins and polyphenols to prevent inflammation and swelling, protect cartilage between the bones, and lessen joint degeneration. Polyphenols appear to have antimutagenic effects and may protect DNA and prevent cancer. Antioxidants protect the heart and blood vessels.

Appears to be safe for most adults.

It should be used with caution or discontinued in the presence of liver disease symptoms, including abdominal pain, dark urine, or jaundice.

Green tea contains small amounts of vitamin K.

Side effects: Caffeine may cause insomnia, anxiety, irritability, GI upset, nausea, diarrhoea, and frequent urination. Concentrated green tea may cause liver problems.

Side effects: Caffeine may cause insomnia, anxiety, irritability, GI upset, nausea, diarrhoea, and frequent urination. Concentrated green tea may cause liver problems.

2. Formulation and manufacturing issue on dietary supplements

2.1 A brief overview of formulation and manufacturing problems

The issue regarding formulation and manufacturing of dietary supplements cannot be applied broadly due to the array of variations on the dietary supplement in source, physicochemical properties and dosage form. Dietary supplement encompasses a broad spectrum of products such as botanicals, algae, fungi, bacteria, vitamins, minerals, synthetic products, animal-derived products, amino acid, metabolites and so forth [26–28], with different dosage forms.
such as a tablet, capsule, powder, liquid, bars and so forth [27, 28]. Hence, there is a degree of complexity in the issue revolving around formulation and manufacturing especially if these products are a combination of the mentioned above. The formulation and manufacturing challenges should be acknowledged via case by case product. However, there are some key formulation and manufacturing issues which will be highlighted in this review, particularly source, availability, dose, bioavailability, stability, compatibility, flow property, particle size, compressibility, coating and quality control test.

2.2 Source and availability

In the perspective of dietary supplements formulation and manufacturing, the initial key issue to look into is the supply and possibly the extraction process of the bioactive compounds. Since dietary supplement encompasses biological extracts, herbals, minerals, vitamins and amino acids [29], the sustainability of the source and supply is an important factor. A large portion of the dietary supplement comes from botanical products or their extracts, thus, the content of active compounds may vary, which could be dependent on season, climate, temperature, humidity, soil, storage condition and other factors [26]. Hence, a method to identify the bioactive compounds (i.e macroscopic examination, microscopic examination, Fourier Transform Infrared Spectroscopy, thin layer chromatography etc.) along with maintenance of uniform quality, bioavailability, safety, efficacy, metabolite profiling and regulatory consideration should be taken on board for a large portion of dietary supplements [26].

To exemplify the importance of identity tests, dietary supplements such as ginseng will be discussed. This identity test is to ensure true species are used to maintain uniform quality. True ginseng is the roots of Panax ginseng C. A. Meyer (Araliaceae), also known as Asian or Korean ginseng, whilst the roots of Panax quinquefolius L. (American ginseng) and Eleutherococcus
senticosus (Rupr. & Maxim.) Maxim. (Siberian ginseng) are also known and substituted to true ginseng, whose pharmacological profiles are more or less similar [30]. Although there are similarities, only the marker compound has been established as Rf, which is found only in P. ginseng (Korean ginseng) and not present at all in P. quinquefolius (American ginseng) [30]. Also, the roots of Mandragora officinarum L. (Solanaceae) might be adulterated again with Panax ginseng, which it resembles closely. However, M. officinarum, also known as a toxic plant species, has completely different pharmacological effects and phytochemistry [30]. Hence, it is prudent to identify and use the true medicinal species with the highest pharmacological and phytochemical quality in the preparation of dietary supplements. Such identification and assurance of pharmacological and phytochemical quality may be a challenge to achieve.

2.3. Extraction process

After determining the source and supply of the raw material, extraction or other processes may be required. Such a choice of method may be crucial in determining yield, contamination or may induce desirable or non-desirable chemical/biological transformation. This can ultimately affect the formulation. If the extraction process is insufficient to prevent contamination with other botanical species (including fake species), microbes, fungi, insects and toxins, it can lead to major formulation safety issues [30], which applies particularly to herbal products. It may be the case that the extraction process is inadequate and need to be optimized before formulation design and manufacturing can proceed.

2.4. Regulatory issues

Another important aspect to consider which may challenge dietary supplement production is the regulatory issue. The regulatory issue will only be explained briefly as different countries
have different regulations regarding dietary supplements. The regulatory issues will be discussed further in later sections in detail. In some cases, it is difficult to categorize drugs and dietary supplements depending on regulatory issues [30]. For example, cholestin is a cholesterol-lowering supplement made from red yeast rice, is actually a supplement identical to a drug called lovastatin. According to regulatory issues i.e. health claims and dosage, cholestin can be either categorized as a dietary supplement or drug [30]. In fact, some dietary supplements in the United States are categorized as medicines in other countries [28], adding to the complexity of the regulatory issue.

The increasing health risk with herbal formulations marketed as dietary supplements, throughout the world due to adulteration of synthetic drugs, contamination or fake species [30] put the dietary supplement in the spotlight for regulatory bodies. Although dietary supplements in the United States can be marketed without the full FDA scrutiny on safety, and the manufacturer can avoid investing the time and money on safety, U.S. FDA has the authority to remove any dietary supplement from the market for phase IV post-marketing surveillance adverse event reports, adulteration, contamination, misidentification, mislabelling or false claims, and not meeting good manufacturing practices (GMP) [31]. Thus, to avoid being removed from the market, dietary supplement manufacturing companies should first ensure the initial challenges regarding safety and quality to be satisfied and that they comply with GMP [32,33]. Hence, it can be seen that the regulatory body may pose challenges to the manufacture of dietary supplements, especially for those with limited studies.

2.5 Dose

The determination of a suitable dose of a dietary supplement is another challenge, particularly a plant-based product. This is due to the problem mentioned earlier regarding the source of raw
material, the environmental condition, contamination, reliability of extraction process and the reliability of identification of bioactive substances. All of this influences the dose of the formulation to ensure acceptance in efficacy and safety. In many cases, clinical studies influence the determination of a suitable dose. In some cases the determined dose may lead to the end product being too bulky which may not be practical for swallowing. This is especially a problem for tablet and capsule dosage forms. Also, since a dose with acceptable efficacy and safety is the target, it may be difficult to determine such dose as this is influenced by age, sex, size, activity and state of health, which is another challenge to address when formulating dietary supplement [27].

2.6 Bioavailability

It is apparent that some dietary supplements have poor bioavailability. This can affect the dose and efficacy of the product. One of the major reasons for poor bioavailability is due to poor water solubility. Such a challenge is also apparent in orthodox drugs. In fact, the mechanism of poor bioavailability of dietary supplements due to poor water solubility can be explained in a similar manner to orthodox drugs. Drug’s dissolution rate is often the rate-limiting step for absorption for such drug [34].

In order for an active ingredient in a solid dosage form to be available for absorption in the gastrointestinal tract (GIT), it must undergo dissolution [35]. Ultimately this means a poor water-soluble dietary supplement will have poor absorption, naturally leading to poor bioavailability. Examples of dietary supplements such as turmeric [36], resveratrol [37] and more are poorly water-soluble, affecting its efficacy as a dietary supplement. There is a demand to overcome such challenges through chemical and physical modification.
2.7 Stability

The stability of dietary supplements can be a major challenge for formulation scientists to overcome. The factor from the environment needs to be considered, for example, the storage conditions of the product should be designed such that minimizes degradation and micro-contamination that would spoil the product. The degradation is heavily dependent on the chemical and physical properties of the dietary supplement. Bioactive compounds can degrade through photodegradation, oxidation, storage material interaction, moisture, temperature, pH and catalytically active components [38, 39]. The mechanism of degradation of dietary supplements is very similar to the degradation of orthodox drugs, thus, through understanding the degradation of orthodox drugs, one can understand the degradation of dietary supplements. Table 3 describes the different forms of degradation.

Table 3. Details of key types of degradation [40]

<table>
<thead>
<tr>
<th>Type of degradation</th>
<th>Details of the degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrolysis</td>
<td>Hydrolysis is a process where a molecular bond is broken via a reaction with water. It is the most common cause of chemical degradation. In most cases, hydrolysis involves derivatives of carboxylic acids, such as acid and amides. Note that hydrolysis reaction can be catalysed by acid or base</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Oxidation reaction is usually complex and produces a variety of products. Auto-oxidation is termed when oxidation occurs at ambient temperature and involves molecular oxygen. This usually involves free radicals (chemical species with an unpaired electron).</td>
</tr>
<tr>
<td>Isomeric changes</td>
<td>Different isomers of active ingredients usually have different pharmacological activity or toxicity. This may also be the case for some dietary supplement bioactive components. Isomeric change can occur as a result of racemization or epimerization, or the formation of geometrical or structural isomers.</td>
</tr>
<tr>
<td>Photodegradation</td>
<td>Photolysis may occur in molecules that absorb the wavelength of light from sunlight or artificial light. Apparently, wavelength between 300 to 400 nm tends to be most damaging. Although shorter wavelengths are also damaging, it is not present in sunlight or artificial light, thus not of practical concern.</td>
</tr>
<tr>
<td>Interaction with other</td>
<td>Other components in the formulation may interact with the active component and cause degradation.</td>
</tr>
<tr>
<td>components</td>
<td></td>
</tr>
</tbody>
</table>
It should be noted that amino acids may undergo hydrolysis, oxidation, deamidation or racemization, causing potential conformational changes of protein and aggregation [40]. This may apply to amino acid-based dietary supplements.

To exemplify the stability issue in the dietary supplement, the stability profile of vitamins will be discussed due to their highly reactive nature. Different vitamins are degraded to a different extent under a particular condition. Vitamin C is rapidly degraded by oxygen, whereas vitamin A (retinol) is rapidly degraded under sunlight [38, 41].

Fat-soluble vitamins such as vitamin A, D, E and K1 may be degraded to a different extent under different conditions from each other. Vitamin E (or tocopherol) degrades via oxygen in a reaction catalysed by light. Both amount of oxygen and light intensity and wavelength influence tocopherol degradation [42]. Vitamin K1 is sensitive to photodegradation [39].

Water-soluble vitamins such as vitamin C (or ascorbic acid), B2 (or riboflavin), B6 (or pyridoxine) and folic acid degrade to a different extent under different conditions from each other. As mentioned, vitamin C is rapidly degraded by oxygen; it is a strong antioxidant and quenches reactive oxygen and nitrogen species [43]. Vitamin B2 degrade in the presence of light and oxygen [39]. Pyridoxine is sensitive to light and folic acid mainly degrade through changes in pH [38]. Table 4 summarize the stability of various vitamins under specific condition [38].

There is also physical instability of products caused by impurities and contaminants. Since herbal medicine has numerous active components, it is difficult to determine optimal storage conditions.
Table 4. Summary of reference of known physical vitamin sensitivities [38, 39, 41, [42, 43]

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Light</th>
<th>Oxygen</th>
<th>pH</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Vitamin K</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Thiamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riboflavin</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotinamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biotin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridoxine</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Cyanocobalamin</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folic acid</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

One of the main issues with supplement products is the absorption of moisture over time, which compromise the stability of the finished products. A certain coating can be applied to protect the finished products against moisture such as Nutrafinish produced by Colorcon and this coating formulation can reduce moisture uptake to improve final product quality and increase in-use shelf life [44]. Colorcon showed that their film coating formulation can protect a highly hygroscopic herbal extract by drug layering and film coating. Other than Nutrafinish, there are other commercial coating products offering protection from moisture such as Sepifilm LP by Seppic [45] and VIVACOAT® M neo by JSR Pharma [46].

2.8 Compatibility

As mentioned earlier, some components in the dietary supplement may interact with each other and promote degradation. Another serious issue of such interaction is the potential for adverse reaction either by producing harmful by-products, biotransformation, chemical transformation, synergistic or antagonistic action. Therefore, understanding such interaction in the dietary supplement will aid safe formulation design. An example of positive interaction between
components is curcumin (the key bioactive component in turmeric) and piperine (from black pepper). Peperine can increase curcumin absorption by 2000% [47].

2.9 Manufacturing aspect

The manufacturing aspect of the dietary supplement may face many similar issues as in orthodox drugs, particularly solid oral dosage forms such as tablets and capsules. In such cases, properties such as flow properties, particle size, compressibility, ease of coating and stability during processing time, all should be optimized to ensure smooth manufacturing of a product. Also, as mentioned in an earlier section, the initial extraction of bioactive compounds should be in such a way that ensures high quality and low risk of contamination.

2.10 Flow properties, particle size and compressibility

The flow property is of critical importance in terms of manufacturing, particularly tablets, capsules or free powders/granules form, as flow property determines uniform feed and reproducible filling. Factors such as particle size, particle morphology and surface properties can influence the flow rate and behaviour. The flow may be variable and unpredictable [40]. Generally speaking, fine particles with a high surface to mass ratio have more adhesive/cohesion force than coarser particles, resulting in poorer flow properties [40]. Shapes of a particle can also influence flow properties i.e. needle shape particle may form an interlocking structure, giving rise to poorer flow property than spherical particles. If moisture or liquid is incorporated into the powdered formulation, this will increase adhesive/ cohesive force at the surface of the particle and the opposite is true if a glidant/anti-tack agent is used. As mentioned earlier, particle size can influence the flow property, but it can also contribute to the uniformity of content. For example, if an admixture of the powdered component in a
formulation is of different sizes, this can lead to segregation phenomena which may result in uniformity of content issues when processed [48]. Other than the particle size of the dietary supplement component, the final dosage form size is also important to consider. It should be of reasonable size and weight for swallowing.

In order to for a quality tablet or caplet to achieve suitable robustness, the compressibility property is an important factor to consider. The compressibility is mostly dependent on the properties of the components in the formulation. In case of poor compressibility of solid oral dietary supplement products, excipients with better compressibility such as microcrystalline cellulose or lactose should be selected in the design of the finished products such as tablets or capsules.

2.11 Coatings

The application of polymeric coating can be applied to dietary supplements for various reasons. This may include modifying the release of the active ingredient, taste masking, improved appearance, improved stability (i.e. enteric coating) and improved mechanical integrity [49]. Colorcon provides a wide range of coatings that could be suitable for the coating of tablet or capsule-based dietary supplement products. These include Nutrafinsih and Nutrapure which are immediate release coating formulations and can be used to add benefits such as aesthetic appearance and makes tablets easier to swallow. The film coating can be applied to tablets, caplets or pellets (or granules). The key issue with such coating is whether it will rupture during processing or transportation, which may result in loss of function. A plasticizer is often incorporated in the film coating to improve flexibility, which in turn reduces the likelihood of film rupturing [50]. As it was mentioned earlier, there are other commercial coating products
offering protection from moisture such as Sepifilm LP by Seppic [45] and VIVACOAT® M neo by JSR Pharma [46].

The polymeric film coating for the sustained release can be categorized into two main groups, 1) cellulosic polymer and 2) acrylic polymer [51, 52]. The main cellulosic polymer used in the sustained release includes Ethocel (ethylcellulose), and the main acrylic polymers include Eudragit and Kollicoat [49]. It has been stated that among these two types of polymer, acrylic polymer is more flexible; thus, it is more suitable for coating [53]. As we can see, there are various challenges to overcome in dietary supplements in terms of formulation and manufacturing.

2.12 Potential solution to the formulation and manufacturing issues in solid oral nutraceuticals

Table 5 elucidate the potential approach to solve the discussed formulation and manufacturing issues involved in solid oral dietary supplement production.

<table>
<thead>
<tr>
<th>Formulation and manufacturing issues</th>
<th>Details of how the issue may be overcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contamination</td>
<td>As mentioned earlier, extraction and identity test are important factors to consider at the beginning. Both processes should be optimized early on to prevent contamination of fake species, toxins and unwanted contaminants.</td>
</tr>
<tr>
<td>Compliance to regulations</td>
<td>To ensure the product meets the GMP and safety standard for consumers, identifying active and toxic compounds as well as determining safety dose is prudent. Regulatory body such as U.S. FDA is able to remove any dietary supplement product if they are deemed unfit for purpose.</td>
</tr>
<tr>
<td>Dose</td>
<td>In order to determine a safe dose, consideration of reliable analytical screening of bioactive substance and pharmacokinetic should be studied. With a reliable analytical method to identify active and toxic substances, it is possible to reduce the risk of a sub-therapeutic or toxic dose.</td>
</tr>
<tr>
<td>Stability</td>
<td>It can be appreciated that there are various factors determining stability. The following are methods that can improve the stability of the product:</td>
</tr>
</tbody>
</table>
- Desiccant can reduce humidity, which can prevent degradation via hydrolysis
- Amber glass bottle or bottle that prevent light passing through can be used to prevent degradation via photolysis
- Excipient that can modify pH for a product that is sensitive to pH
- Process in such a way that minimise microbial contamination
- Screen for catalytically active component and take appropriate measure
- Investigate for polymorphism and isomer changes then take appropriate action

| Compatibility | In cases where it is undesirable for different bioactive components to interact, these different components can be made into separate pellets and coated. The polymeric coating can prevent undesirable interaction. |
| Flow property | This applies specifically to formulations such as tablets, caplets, hard-shell capsules and free pellets/granules. Excipients such as glidant, lubricant and anti-tack agents can improve the flow of formulation. Aside from excipients, the manipulation of physical properties such as granulation and pelleting can improve flow properties. |
| Particle size | Since segregation phenomena can occur when an admixture of powdered formulation has a component of different sizes, particle size manipulation can be useful to prevent this. Methods such as granulation, pelleting, milling, etc can aid in obtaining excipient of the desired size [50]. |
| Compressibility | Choice of excipients can affect compressibility property, which is important in tabletting. A bulking agent such as microcrystalline cellulose and lactose tends to have good compressibility. Careful choice of excipients can overcome poor compressibility properties. In addition, processes like granulation may affect compressibility properties. |
| Coating rupturing | Excipients such as plasticizers mixed in the coating solution before applying the coating to dosage form can increase the film flexibility, reducing the risk of film rupturing. With a pellet-based tablet, the addition of cushioning excipients can reduce the risk of film rupturing during the compaction stage [49]. |
| Bioavailability | One of the major causes for poor bioavailability is due to active substance being poorly water-soluble. This causes the dissolution to be the rate-limiting step for absorption. Hence, techniques can be applied to enhance water solubility to improve bioavailability. In this regard, a dietary supplement can be very similar to an orthodox drug. By understanding how dissolution rate is enhanced in orthodox drug, we can understand how this can also work for a dietary supplement. There are various techniques that include conversion of crystalline drug into its amorphous state [54], micronization [55-58], solid dispersion [59], co-grinding [60-62], nanosuspension [63, 64], self-
emulsifying drug delivery system [65, 66] and inclusion of drug solution in soft gelatin capsule [67].

3. Regulators and claims

3.1. Regulations on dietary supplements

Clinton approved the Dietary Supplement Health and Education Act (DSHEA) as the United States President on October 15, 1994, pursuant to which the FDA regulates dietary supplements. According to the DSHEA, dietary supplement regulation is not like a medicine or food additive but the same as food products [68, 69]. When the dietary supplement was regulated as the foodstuff category, consequences such as marketing rules were created: manufacturers were not obliged to prove the safety and effectiveness of dietary supplements before it was marketed. Inevitably this led to a step-down of the FDA's direction of such products [70, 71]. There are conjointly some other data in the DSHEA, such as the precise definition of dietary supplements and dietary ingredients, the frameworks for the GMP, labeling and its rules, and the respective regulations of new dietary ingredients [72].

According to DSHEA, ingredients that existed before October 15, 1994, are considered safe, and ingredients supplied after this date are introduced in the terms of "new dietary ingredients" [73]. The manufacturer is duty-bound to inform the FDA of this substance's existence, the amount of its use in the past, and all information indicating that this substance is safe 75 days before the marketing of the mentioned dietary supplement [74]. Despite the increasing growth of supplements and increasing people's interest in the use of dietary supplements, only 170 new dietary ingredients have been received by December 2012, since it had been initially registered in 1995 [75]. Hence, the FDA led to the regulation of new dietary ingredients (NDI) guidance in August 2016 to extend the understanding of companies and people about notification NDI and improve the quality of NDIs sent by the companies [76]. It is notable that according to the
DHSEA, dietary supplements cannot be regarded as a conventional food or meal replacement in any form, and all of them should be labeled as dietary supplements [77]. DHSEA collectively has data on the labeling rules, details, and relevant claims. The details and rules on the claims are briefly explained in the Claims section.

According to the European Union, food supplement regulation is the same way for food regulation, but a great deal of variation and expansion can be observed in the food supplements legislation among different countries. However, this legislation relies on native regulation [78]. The variation is so broad that the same product is considered medicine or food in different countries. It may even be possible that the same product is regulated as a botanical product in the dietary supplement’s group or food [79]. Thus, a product considered medication or food hugely depends on its use and what country’s market it was being sold.

For example, 2002/46/EC is one of the regulatory policies in Europe that determines a list of vitamins and minerals allowed in dietary supplements plus their specific usage limit in food supplements (Listed in Annex II of EU Directive 2002/46/EC) [80]. Such regulations aim to provide health and prevent the risk of harmful substances and adverse effects to consumers [81].

Codex Alimentarius Commission or Codex was designed collectively by some organizations in June 1962. The organizations included the U.S. FDA, the European Commission, the World Trade Organization, and United Nations' two organizations: World Health and Food and Agriculture [82]. The Codex contains the highest safety standards on food and food production [83]. In addition to the standards mentioned, the practice codex contains different guidelines and instructions with the primary objective of protecting consumer health and establishing a
fair practice in the global food trade [84]. Vitamin Guideline and Mineral Codex contain data on packaging, labeling, and at last composition, content, and source of choice of vitamins and minerals [85].

3.2 Claims

In general, there are various regulations and criteria for classifying claims related to dietary supplements. For example, according to the U.S. FDA regulations, claims are divided into structure/function claims, health claims, and nutrient content claims [86]. However, in Europe, there are two main categories: 1. Nutrition claims: almost similar to the nutrient content claim in U.S. FDA, and 2. Health claims: Children's development and health claims, Reduction of disease risk claims, and General function health claims, [87]. The former and latter cases are almost similar to the structure/function claims in the US. However, reducing disease risk claims are almost similar to the Health claims in the US regulations [88]. The following section investigates different types of claims by the FDA regarding regulations and definitions in detail.

3.2.1 Health claims

There is a specific relationship between dietary supplements (product) or their constituents and reduced risk of a disease or overall health condition. The details have been precisely studied in the FDA (CFR 101.14) [89]. FDA is responsible for reviewing and determining the existence of a significant scientific agreement to authorize the claim [90]. That is the reason behind why all of these claims must be confirmed by the FDA.
Two examples of health claims that may be used in labeling are listed below to explain the effects of vitamin D and calcium on osteoporosis, which is a condition where bones become brittle and fragile [91]:

- Adequate calcium and vitamin D as part of a healthy diet, along with physical activity, may reduce the risk of osteoporosis in later life [92].

3.2.2 Qualified health claims

Compared to the health claims that require a significant scientific agreement, qualified health claims relish less scientific evidence, so manufacturers who associate this type of claim with their product should provide FDA with acceptable reports of not misleading customers by their claim and provide proof [93]. An example of the qualified health claims that shed more light on the descriptions above would be Diabetes Psyllium Husk & Diabetes Docket No. FDA-2013-Q-016706/24/2014.

Claim Statements of this one are:

- Psyllium husk may reduce the risk of type 2 diabetes, although the FDA has concluded that there is very little scientific evidence for this claim [94].
- Psyllium husk may reduce the risk of type 2 diabetes [95]. FDA has concluded that there is very little scientific evidence for this claim [96].

3.2.3 Nutrient content claims

These kinds of claims focus on the nutrients level's specifications on the product labels. These regulatory rules are based on the resources needed for the body using terms as Free, High, or Low, each representing a certain level of the product's intended substance [97]. Another category of the same family of claims, which is used explicitly for dietary supplements, is the Percentage claims, which indicates the percentage of that substance in the intended dietary supplements [98]. For example, vitamin C from the family of antioxidants is usually found in
a specific interval in most products, but if it is more than usual, the phrase "high in vitamin C"
should be inserted on the label of that product in the case of observing the allowable range [99].

3.2.4 Structure and Function Claims

Structure and function claims are one category of the claims that examine the effects of the
nutrient or dietary ingredients on the body's structure and function, and these nutrients and
dietary ingredients are characterized based on what function and mechanism they have on the
structure and function of the body [100].

Examples of structure and function claims abound: "fiber maintains bowel regularity" and
"calcium builds strong bones."[101]

Two other common types of this category are general well-being claims and Nutrient
Deficiency Disease Claims to examine how nutrient or dietary ingredients contribute to the
improved overall well-being. Nutrient deficiency disease claims also deal with their benefits
over nutrient deficiency diseases. However, this type of disease is generally rare in the United
States, and this claim can be used when we have data on the prevalence of the disease. For
instance, the relationship between vitamin C and scurvy (general fatigue and skin hemorrhage
syndrome reflecting a lasting deficit of vitamin C in nutrition) can be noted in this type of claim
[99].

As the FDA does not approve all three of the claims mentioned above, manufacturers are the
ones who are responsible for the accuracy and validity of the claims. Therefore, these claims
should not be ambiguous so that consumers consider those supplements as medicines approved
by the FDA [102, 103]. In simple terms, a "disclaimer" must also be put for this purpose in
using these types of claims. It should be noted that "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" [104] because only orthodox drugs/medicines can legally use this claim.

3.3. Comparison between food and drug clinical trial

Various research trials, each having a specific characteristic to determine manufactured products' efficacy (whether foodstuff or medicine), are done by manufacturing firms. In general, a clinical trial on pharmaceuticals is conducted on a patient or healthy population over four phases. All clinical trials are required to observe the GCP and HSP principles and clearly define their executive and research protocols. Moreover, the study investigators must also ensure that the staff involved in the process are trained, and their behaviour with humans should be according to the specified allowable protocols [105, 106]. Despite the similarities mentioned above, there are differences between the clinical trial for food and drug. The most apparent difference between these two is total expenditures per patient, equal to 150,000 euros for medicine and; 2,000 euros for food per patient. Besides, the medicines have more serious adverse effects than food, and, hence, monitoring the population under study in terms of the medicine is much more important than the food [107, 108].

In contrast, foods are used at high rates due to their natural properties and exhibit lower adverse effects. However, this is not true for medicines due to their potency and high efficacy. Moreover, because these products' target populations are normal and healthful, the tested population in food trials should be healthy [109].
3.4. Regulatory issues with dietary supplements

As mentioned in the Government Accountability Office (GAO) report in 2009, it was found that consumers do not have much information about dietary supplements' safety and efficacy. Indeed, they miss a complete understanding of the instructions on the product labels [110]. The consumer's misunderstanding of the phrases inserted on the label for marketing and unique sentences inserted on the label leads to the misuse of the dietary supplements. According to the GAO's report (2010), this mistake is terrible to the degree to which people take them as medicines. The probable reason for this issue could be vendors' attempts to deceive consumers into buying dietary supplements instead of physicians' prescribed drugs. This effort negatively affects people's decisions regarding buying the appropriate choice for their health [111].

Another regulatory issue of dietary supplements is the maladaptation of existing formulations with the substances inserted on the label, which can be attributed to the high cost and time required to achieve appropriate formulation through research [112]. According to the report made in consumer lab 2011, the amount of curcuminoid in curcumin supplements and their release rate significantly differ from the information inserted on the label [1113]. The other safety issue is related to dietary supplements because there are no supervisory rules on dietary supplements' efficacy and safety, such as food additives, although both enter the body and affect the body's functional system. Before October 15, 1994 (before DHSEA), all the supplements referred to the so-called grandfather are considered safe based on the law and do not require FDA re-monitoring [114]. When dietary supplements are not printed in the history of the patient's medication use, the physician cannot track any of his patients' supplements intake, which can decrease the quality of medical care. For example, the medicine and supplement intervention in terms of pharmacology can be one of the unexpected adverse effects of supplementary dietary lack on the patients' history [115]. More interestingly, if the same supplement alone results in any adverse effect, these reports are not publicly observable.
Failure to supervise the FDA on the raw materials of supplements, particularly the herbal ones, might be another problem in this area. A lot of these raw materials originate from Traditional Chinese Medicines (TCM) are not necessarily risk-free, and some are potent, hence requiring further studies [116]. The same lack of supervision on the raw materials is also true in excipients, which can be problematic [117]. One of the severe regulatory issues is online sales of dietary supplements because there is minimal monitoring on the sale of such products through the internet, which can give misleading claims [118].

It is notable that with the increase in the size of the market, the problems mentioned above are more likely to occur. Placing a more stringent regulation may offer an approach to prevent the occurrence of such problems. Also, changing the content of product labels to increase detail and accuracy increases consumer awareness [119].

Not all countries will have effective regulations in place to tackle such problems. Having a monitoring system in place for the dietary supplement internet market could be another potential approach in responding to misleading claims and safety-related issues [120].

4. The global dietary supplements market

Today, increasing awareness and interest of consumers (especially those in the middle-class economy) in the supplements and the tendency to use a healthier diet have doubled the use of supplements. People consuming dietary supplements are mainly divided into two groups; The first group wants to insure themselves against future illnesses, and the second are those who seek treatment for their current state of health. The major causes of using dietary supplements include improving well-being, treating and preventing diseases. Therefore, it can be expected
that dietary supplements will be equally crucial to the pharmaceutical market, given the increased awareness of consumers [121, 122].

The worldwide market for dietary supplements is projected to rise from $132.8 billion in 2016 to $220.3 billion in 2022, according to zion market research [123]. This illustrates the massive market for supplements and its estimated growth in the future. Aging of the population and increased consumer awareness are the main reasons for the advancement of this market as follows:

1. Aging of the population: The increased sales of dietary supplements could be justified by the aging of the population and increasing problems related to their health, especially in areas such as bone, joint, and eyes [124].

2. Increased consumer awareness: Increasing consumer awareness, especially in the field of preventive health care, is another reason why the market is growing, which results from digital media, such as television advertising, science news, and popular websites. The media provides various information about healthy diets, healthy lifestyles, and maintaining fitness, emphasizing prevention rather than treatment [125].

4.1 Different components of the dietary supplement’s market

The dietary supplement’s market can be divided into type, dosage form, geographical regions, and end-user insights.

4.1.1 Type

The dietary supplements market can be studied based on their types. For instance, vitamins and botanicals are considered two types of dietary supplements. The vitamins market makes up a large part of the dietary supplement market with around 31.4% share of the total market
in 2020. This is followed by botanicals, which is the second largest in terms of market share in 2020, and are projected to see substantial growth over the coming years due to the rising trend of conscious diets such as plant-based diet and the implication it has on the climate and environment [126].

One factor that makes the vitamin category of dietary supplements attractive is that they are easily eliminated from the kidneys and the body. Vitamin D has experienced faster growth than others in this category [122]. Another part of the supplements in terms of type is botanical extracts. Botanical or herbal supplements are dietary supplements that are utilized for restorative reasons [127]. Due to their effectiveness in both physical and mental health, significant growth is predicted. This category of supplements contributes to a particular group of organs such as liver, bone, and skin health. Botanical supplements accounted for the largest share of the dietary supplement’s market in 2013 [128]. The value of the global markets for botanical supplements was estimated to be more than 40 billion dollars in 2017 and is predicted to reach 65 billion dollars by the end of 2025 [129].

4.1.2 Dosage form

The dietary supplements market is divided into various parts based on the dosage form, including tablets, powders, and liquids. It is predicted that the tablet dosage form market's revenue will exceed 100 billion dollars by 2025, so among all the types mentioned above, it can be said that the tablet form could account for a large part of the market [130]. However, due to the broader research and development projects on the powder form, it is expected that this form of dietary supplements can grow significantly compared to the rest of the dosage forms. One underlying reason for conducting an investigation focusing on the powder form is the popularity of energy mix powders between athletes [131].
4.1.3 Geographical regions

Currently, the world dietary supplements market is divided into five main geographical sectors: Asia, Latin America, North America and Europe, Middle East, and Africa. Asia has succeeded to account for the largest market for dietary supplements in terms of the geographic region, which can be attributed to the increased awareness of Asian consumers in dietary supplements’ benefits, methods of personal care, and the increased purchasing power of this region population [123, 132]. The sizeable middle-class population in Asian countries such as China, India, Pakistan, and Bangladesh encourage nutraceutical manufacturers to invest in these financially attractive regions. North American market is considered the second largest marketplace for various reasons, including the increased use of low-calorie products and high nutrients, increasing the aging population, and prevalence of life-threatening diseases [133].

The third-largest market in terms of the geographic region belongs to the European market because of the increasing medical costs and the aging of targeted consumers, the same as the United States. On top of that, the consumers' tendency has recently changed to be more health-conscious. With the expansion of the nutraceutical distribution channel and higher access to nutraceuticals, it could be expected that this share of the market will experience a fair growth process in the future. Western Europe has a larger market than other parts of Europe, and it has tremendous potential for dietary supplement growth according to researches on this market [134, 135]. In addition to the mentioned markets, relatively suitable growth has been planned for Latin America, the Middle East, and Africa. One solution to improve the market growth in these regions is educating consumers about dietary supplement products and their health benefits. The increase in the population, modernization of retail sectors, and higher incomes of middle-class consumers are the reasons for the Latin American market's expected growth over the next few years.

4.1.4 End-user insights
An analysis of the supplements market from the end-user perspective is done by categorizing into groups of adults, children, and pregnant women. Adults' share in the entire market was slightly more than half representing the more significant segment. The reasons behind this trend would be increased interest in taking supplements by both professional athletes and ordinary people. The next group is children, which is expected to see a significant share increase in the following years. The reason lies in the fact that parents have been increasingly gravitating to nourish their children with vitamins and tissue/bone repair supplements in recent years.

Last but not least, the importance of the pregnant women group in the market shall not be overlooked. Supplements such as folic acid and B12 play a crucial role in developing and delivering healthy babies by pregnant women [136]. Besides, governments have made efforts to raise awareness in pregnant women to prevent nutrient deficiencies. As a result, it makes sense that this segment is projected to grow in the future.

5. Conclusion

Dietary supplements are sold and supplied by multimillion-dollar companies. It is quite clear that with the global exponential growth of dietary supplement usage and demands there need to be more thorough studies from multiple angles. Some of the key areas that require further investigation includes understanding the efficacy and safety of dietary supplements, and the way it interacts in the human body along with other orthodox drugs, supplement and food. It is clear that the current wealth of knowledge in this matter is lacking. The safety and efficacy are also linked to the manufacturing process of dietary supplements. It was revealed that such a process is complex with numerous factors to consider particularly for a natural-product-based supplement such as plants. The season, climate, soil, extraction process and so forth need to be considered even before the manufacturing of the dosage form begins. Contamination and
degradation are some of the key aspects to investigate along with optimizing the formulation to increase manufacturing feasibility. In the article, it is learnt that many manufacturing issues can be overcome. Despite the mentioned complexity, a dietary supplement is relatively simple to manufacture with minimal regard to quality, efficacy and safety as current regulations in many countries view such product as ‘dietary ingredient’, thus is omitted from the stringent regulation as is seen with orthodox drugs. What is concerning is that this lack of regulation could have a serious effect on consumers, particularly because some supplements are considered as a drug in some countries but not in others. Although there is a lack of regulations, major regulators such as U.S. FDA still have the authority to remove dietary supplements from the market. The complexities in supplementing research and its regulations provide scientists and regulators new opportunities to collaborate both domestically and globally, learn from one another, and co-operate and harmonize public health approaches where possible. The judgement on efficacy and safety is more difficult in products with limited studies. It was also learned that health claims and labeling of dietary supplements can be considered a challenging area, however, there are some regulatory forces and standards at work. Overall, such product is becoming increasingly used in society, thus investigation of key aspects that were discussed needs to match up with the ever-growing dietary supplement. Dietary supplements are best advised only for particular cases of medical or public health needs. A diet of nutritious foods which meets both macro and micronutrient necessities is the most beneficial choice for public health. Education programs to eliminate supplementary consumption are desirable, but it is impossible to cope with an enormous industry with large profits at risk.

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