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DARKSIDE OF NUTRACEUTICALS

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Abstract:
The concept of "Let food be your medicine and medicine be your food," attributed to Hippocrates, has resonated through the ages, emphasizing the therapeutic potential of food. This philosophy finds parallels in Ayurveda and culminated in the term "nutraceutical," coined by Dr. Stephen De Felice in 1989. Nutraceuticals, a fusion of "nutrition" and "pharmaceuticals," encompass substances from food with perceived health benefits.
This paper presents a comprehensive classification of nutraceuticals based on chemical composition, source, and traditional or nontraditional nature. It explores their popularity, safety concerns, and the misconception that "all-natural remedies are beneficial." The list of marketed nutraceuticals illustrates their diversity, from appetite suppressants to immune boosters.

The analysis delves into potential health risks associated with nutraceuticals, focusing on vitamins, minerals, omega-3 fatty acids, soy protein, and botanicals. Adverse incidents, including liver damage and birth defects, are discussed. The paper highlights the lack of scientific consensus on the effectiveness of nutraceuticals in preventing diseases.

Specific attention is given to contaminants such as heavy metals, pyrrolizidine alkaloids, and mycotoxins found in nutraceuticals, emphasizing their potential harm. The significance of understanding and regulating nutraceuticals is underscored, given their increasing prevalence and the need for consumer awareness.

In conclusion, while nutraceuticals offer potential health benefits, their safety and efficacy are contingent on factors like purity, quality control, and accurate labeling. This paper contributes to the ongoing discourse on the integrity and security of nutraceutical products, urging a more informed and discerning approach to their consumption.

INTRODUCTION:

Hippocrates once advised, "Let food be your medicine and medicine be your food," highlighting the link between food and its potential therapeutic effects. This concept is also echoed in Ayurveda, an ancient Indian medical science, which places significant importance on the role of nutrition in maintaining health and managing illnesses.

In 1989, Dr. Stephen De Felice, Chairman of the Foundation for Innovation in Medicine, coined the term "nutraceutical." This term, formed by combining "nutrition" and "pharmaceutical," refers to a type of nutritional supplement that is marketed with the purpose of preventing or treating diseases. Despite lacking a clear regulatory definition, a "nutraceutical" essentially encompasses any substance found in or derived from food that offers medical or health advantages, including the potential to prevent and treat various ailments.[1]

CLASSIFICATION OF NUTRACEUTICALS:

Classification of nutraceuticals can be approached from different angles, including their chemical composition, the source of the ingredients, and their traditional or nontraditional nature.

1. Based on Food Items:

a. **Nutrients:** These are compounds with established nutrient functions. Examples include vitamins, minerals, and amino acids.

b. **Herbals:** Extracts or concentrates derived from herbs or botanical sources. Examples include aloe vera, ginger, and garlic.

c. **Dietary Supplements:** These are substances added to food for a specific purpose and taken orally. Examples include minimally refined grains and phytoestrogens (such as soy), as well as dairy foods.

2. **Traditional/Nontraditional:**

a. **Traditional:** Nutraceuticals that are consumed as whole foods or without significant alteration. This category includes fruits, vegetables, and dairy products.

b. **Nontraditional:** Nutraceuticals that are the result of agricultural breeding or the intentional addition of specific ingredients. Examples include the addition of folic acid to flour and calcium to juices.

This classification system provides a structured way to understand nutraceuticals based on their composition, source, and how they are used within the context of food.[1]

Nutraceuticals gained growing popularity among both humans and animals by the onset of the twenty-first century. This surge in popularity was attributed to their convenient availability, economical nature, and well-tolerated nature, accompanied by a substantial margin of safety.[2]

Many ordinary patients tend to lean towards nutraceuticals as they hold a mistaken belief that "all-natural remedies are beneficial." Consuming excessive amounts of certain ingredients can lead to side effects, such as headaches, liver damage, bone weakness, and birth defects, while excessive iron can cause nausea and liver damage.[3]

TABLE 1: List of marketed nutraceuticals.[4]

Category	Product	Claim	Manufacturer
Appetite suppressant	Appetite Intercept™	Caffeine, phenylalanine, and tyrosine	Natron, Chatsworth, CA, USA
	Metabolite Ultra Caffeine Free™	B-vitamins	Metabolite International, Inc., San Diego, CA
	Lumatol AC,	Cacti	Iron-Tek, Hauppauge, NY
Supplements for hangover	Chaser™	Activated calcium carbonate and vegetable carbon	Living essentials, Walled lake, MI, USA
Calcium supplement	Coral Calcium	Calcium and trace minerals	Nature's answer, Hauppauge, NY, USA
	Calcirol D-3®	Calcium and vitamins	Cadilla healthcare limited, Ahmedabad, India

Immune Booster and immunomodulator	Celestial Healthtone	Dry fruit extract	Celestial Biolabs Ltd., India
	Chyawanprash	*Amla, Ashwagandha, Pippali*	Dabur India Ltd., India
	Amiriprash (Gold)	*Chyawanprash Avaleha, Swarnabhasma and RasSindur*	UAP Pharma Pvt. Ltd., India
	Immulina	Bioactive microalgae complex	Nordic Phytopharma Group, Havdrup, Denmark
	Emergen-C	Vitamin	Alacer Corp. California
	Ester C	Vitamin	Ester-C, Bohemia, NY
Prebiotics	Clif Bar	Fiber	Clif Bar Inc., Berkeley, CA, USA
	Cereals, drink mixes, and cereal bars	Fiber	Kashi Company, La Jolla, CA, USA
	Ensure Fiber	Fiber, digestive health	Abbott Nutrition, Columbus, OH, USA
	Builder's Bar	Fiber	Clif Bar Inc., Berkeley, CA, USA
	Helios Nutrition's Organic Kefir	Bifidogenesis, calcium absorption	Lifeway Foods, Morton Grove, IL, USA
	Low-fat ice cream sandwiches	Fiber	Skinny Cow, Nestle SA, Vevey, Switzerland
	Luna Bar	Fiber	Clif Bar Inc., Berkeley, CA, USA
	ZonePerfect Shakes	Fiber	Abbott Nutrition, Columbus, OH, USA
Probiotics	DanActive®	*L casei* DN114001	Danone Inc., Paris, France
	Danimals®	*L rhamnosus* GG (infant diarrhea)	Danone Inc., Paris, France
Nutritional supplement	Weight smart™	Vitamins and trace elements	Bayercooperation, Morristown, NL, USA
	GRD®	Proteins, vitamins, minerals, and carbohydrates	Zydus Cadila Ltd., Ahmedabad, India
	Proplus®	Soy proteins	Campbell soup company, Camden, NJ, USA
Immunity supplement	Immune Assist-complete	*Blend of A. blazei, C. sinensis, Coriolusversicolor, L. edodes, Grifola frondosa, and G. lucidum.*	Aloha Medicinals Inc., Carson City, NV, USA
	Mushroom optimizer™	Folic acid, mushrooms, and polysaccharides.	Jarrow formulas, Los Angeles, CA, USA
	Omega Women	Antioxidants, phytochemicals (*e.g.* Lycopene and resveratrol), and vitamins	Wassen, Surrey, U.K.
	Agaricus blazie	*A. blazei Murill*	Doctor's Best Inc.

(Table 1) Contd….

Category	Product	Claim	Manufacturer
Complete physical health supplement and immune supplement	Nutricafe -Organic performance coffee	*Cordyceps and Ganoderma*	EnerHealth Botanicals, Longmont, CO, USA
Dietary supplement	Olivenol™	Natural antioxidant hydroxytyrosol	Cre Agri, Hayward, CA, USA
Neuropathic pain supplement	PNer plus™	Vitamin and other natural supplement	NeuroHelp, San Antonio, Texas, USA
Protein supplements	Threptin® Diskettes	Proteina and Vitamin	Raptakos, Brett and Co. Ltd., Mumbai, India
	Proteinex®	Carbohydrates, minerals, pre-digested proteins, and vitamins.	Pfizer Ltd., Mumbai, India
Energy drink	Rox®	Caffeine, glucuronolactone, and taurine.	Rox America, Spartanburg, SA, USA
Meal replacement beverage	Snapple-a-day™	Vitamins and minerals	Snapple beverage group, White Plains, NY, USA
Amino acid supplement	WelLife®	Granulated-L-glutamine	DaesangAmerica Inc., Hackensach, NJ, USA
Neurotonic	Biovinca™	Vinpocetine	Cyvex nutrition, Irvine, CA, USA
Anti-depressant	Pure Red Reishi	*G. lucidum*	Terrasoul Superfoods, Fort Worth, TX, USA
Complete physical health supplement	Shiitake Gold	*L edodes*	Aloha Medicinals Inc., Carson City, NV, USA

While the consumption of nutraceuticals is typically considered safe, it is not entirely devoid of potential risks. This analysis does not aim to present an exhaustive overview of every documented negative outcome related to all dietary supplements. Instead, we focus on exploring adverse incidents linked to frequently utilized supplements, including vitamins, minerals, omega-3 fatty acids (found in fish oil), soy protein, as well as plant-based nutraceuticals known for their antioxidant and anti-inflammatory properties. Additionally, we delve into supplements used for weight loss, bodybuilding, and a range of botanical products, which have been connected to more severe undesirable effects.
Nonetheless, given the rising prevalence of nutraceutical consumption within our aging population, it becomes imperative to place heightened emphasis on the calibre and safety of these products. Consequently, this manuscript undertakes a comprehensive examination and discourse on the prevalence of the most pertinent categories of impurities found in commercially available nutraceutical samples. Furthermore, it addresses the issues of Misleading Marketing and False Claims, along with the evident gaps in Regulation and Quality Control that surround the nutraceutical industry. These concerns, spanning the last two decades, are pivotal to the ongoing dialogue about the integrity and security of nutraceutical products.

- Health Risks Associated with Nutraceuticals :

- Nutraceuticals encompass items consumed alongside the regular diet to offer supplementary nutrients that contribute to enhanced health benefits. The primary motivations for using nutraceuticals were frequently cantered around enhancing overall well-being, sustaining health, and particularly in the case of women, promoting bone health. The most prevalent choices among

supplements included multivitamin and mineral variations, calcium additions, as well as omega-3 or fish oil products.[5]

Around a quarter of nutraceutical use was influenced by recommendations from healthcare professionals. Consequently, the majority of choices to incorporate supplements into one's routine are made autonomously by consumers. Despite their widespread popularity, the actual health advantages of nutraceuticals remain uncertain. The absence of essential vitamins can certainly lead to deficiency ailments such as scurvy, beriberi, pellagra, and rickets. Nonetheless, a well-balanced diet typically provides adequate vitamin content to prevent these conditions.

Research endeavours aimed at discerning the effects of nutraceuticals frequently yield contradictory outcomes. Presently, there exists no unanimous scientific agreement on whether vitamins or other dietary supplements are effective in preventing diseases or conferring health benefits to well-nourished individuals.[6]

The prevailing nutraceuticals frequently originate from fruits and vegetables. These substances often possess attributes like antioxidants or anti-inflammatory qualities, which are believed to offer safeguards against persistent ailments like cardiovascular issues, diabetes, and cancer.[7]

Limited evidence exists to indicate any toxicity from these compounds. Nevertheless, metabolites stemming from epigallocatechin gallate, the primary catechol present in green tea extract responsible for its antioxidant effects, are thought to potentially amplify oxidative stress. These metabolites have also been linked to instances of liver damage.[8]

1. Potential Side Effects of Vitamin and Mineral Supplements:

While vitamin and mineral supplements are often taken to support overall health and address nutritional deficiencies, it's important to recognize that excessive or improper use can lead to potential side effects. It's recommended to consult with a healthcare professional before starting any new supplement regimen. While it's necessary to consume sufficient amounts of these micronutrients to uphold good health, the potential for toxicity rises as the dosage increases.[9] Due to the declining occurrence of dietary micronutrient insufficiency in developed nations, a substantial number of supplement users are, in fact, surpassing their required intake of vitamins and minerals. Despite the prevalent notion that these supplements contribute positively to well-being, recent assessments of trials involving vitamin and mineral supplementation in adults residing within communities, who lack nutritional deficits, have reached the consensus that there is limited substantiation of advantageous health outcomes. These encompass the prevention of chronic ailments like cardiovascular conditions, cancer, and cognitive deterioration, as well as impacts on overall mortality.[10,11] In a controlled study involving individuals with head and neck cancer who underwent radiation therapy, the provision of vitamin E supplements was linked to heightened occurrences of cancer recurrence during the initial 3.5 years of post-treatment monitoring.[12] and A comprehensive analysis of multiple studies has indicated a rise in overall mortality following the consumption of high doses of vitamin E supplements.[13] Taking excessive amounts of vitamin A through supplementation has been proposed to have negative impacts on bone health, potentially leading to reduced bone mineral density and a higher likelihood of fractures. Moreover, pregnant women who heavily rely on vitamin A supplements have been noted to experience a greater occurrence of congenital abnormalities. [14] A patient with prolonged excessive vitamin A intake, spanning 12 years of supplementation, presented a case of intrahepatic cholestasis. This condition was resolved upon discontinuation of the supplements.[15] The consumption of minerals in excessive amounts, along with vitamins, can result in toxicity. Notably, there is an elevated likelihood of developing hyperchromatosis, a condition involving excessive iron storage that is linked to liver damage, when there's an overindulgence in iron or multimineral supplements. This risk can be further intensified by the consumption of alcohol.[16, 17]

2. Potential Side Effects of Probiotics:

Probiotics have the potential to cause four categories of adverse effects, which include:

a) Systemic infections.
b) Harmful metabolic actions.
c) Excessive activation of the immune system in people who are vulnerable.
d) Transfer of genes.[18]

- **SYSTEMIC INFECTIONS:**

Several case studies recount instances of infections linked to microorganisms resembling probiotic strains in individuals who had taken probiotic supplements before experiencing symptoms. The most frequently documented individual occurrence involves fungemia. There have been a minimum of 33 accounts where blood cultures from patients who had ingested the S. boulardii probiotic showed the presence of Saccharomyces cerevisiae or Saccharomyces boulardii (these microorganisms are microbiologically identical).[18]

- **Harmful metabolic actions :**

A particular clinical trial raised notable apprehension regarding probiotic safety. The PROPATRIA study, designed as a double-blind, randomized, placebo-controlled trial, investigated the efficacy of a probiotic containing multiple strains in preventing infectious complications in 296 individuals diagnosed with severe pancreatitis.[19] Additional metabolic considerations involve the impact of D-lactate generated by probiotic strains and the breakdown of bile salts. There are five documented cases of D-lactic acidosis in existing literature, including one occurrence in a patient with short bowel syndrome.[20]

- **Excessive activation of the immune system in people who are vulnerable:**

Due to the demonstrated impact of probiotics on both the innate and adaptive immune systems, influencing factors like cytokine release and dendritic cell activity, there is apprehension about the likelihood of excessively stimulating the immune response in certain individuals. This heightened response could potentially trigger autoimmune reactions or inflammation. However, it's important to note that this theoretical concern has not been observed in any human subjects.[21]

- **Transfer of genes:**

Lactic acid bacteria carry plasmids containing genes that provide resistance to antibiotics such as tetracycline, erythromycin, chloramphenicol, lincomycin, macrolides, streptomycin, and streptogramins.[22] Leuconostoc species and Pediococcus species have shown indications of being able to receive antibiotic resistance plasmids with a wide host range from lactococcus species.[23] Transfer of genetic material through conjugation from enterococci to lactobacilli and lactococci is possible within the intestinal tracts of animals and also in laboratory settings. However, the occurrence of this transfer to lactobacilli is relatively uncommon.[24]While there exists a theoretical potential for lateral gene transfer between probiotic microorganisms and other entities within the gut or other locations, no clinical proof of antimicrobial resistance transfer has been observed. This is of significant importance, especially considering the frequent practice of using probiotics in conjunction with antibiotics.

Potential Side Effects of Protein Powders And Infant Formula:

Athletes and bodybuilders commonly use protein powders containing dairy proteins like casein and whey, as well as plant-based proteins such as soy protein isolate (SPI), as popular dietary supplements. Dairy proteins show minimal toxicity, except for those allergic to cow's milk protein; however, excessive intake could lead to ketosis. On the other hand, the safety of soy protein isolate (SPI) is a subject of ongoing discussion.[25]Numerous clinical investigations have been carried out to assess the toxicity of soy protein isolate (SPI) and soy formula. Epigenome-wide analysis of DNA methylation in vaginal cells from girls fed with cow milk formula and soy infant formula revealed varying DNA

methylation patterns linked to reduced expression of the estrogen-responsive gene known as proline-rich 5-like (PRR5L).[26] It was documented that rats exposed to soy-based diets during the perinatal period exhibited inhibited steroidogenesis, reduced secretion of testosterone, and heightened proliferation of Leydig cells. Likewise, Sharpe and his associates found similar results.[27,28] These investigations, combined with worries about estrogenic effects, prompted a recent assessment of the safety of soy infant formula. The evaluation was conducted by a panel from the Center for the Evaluation of Risks to Human Reproduction, established through collaboration between the National Toxicology Program and the National Institute of Environmental Health Sciences. Nonetheless, due to constraints in the existing human data, the committee faced challenges in providing a definitive recommendation concerning developmental and reproductive toxicity.[29]

4. Potential Side Effect of Botanical Supplement:

Traditional herbal medicine serves as the foundation for both modern pharmaceuticals derived from plant compounds (like aspirin and morphine) and present-day botanical dietary supplements. The continued appeal of herbal and botanical products is rooted in their status as one of the earliest forms of therapy, originating from natural sources such as plant roots, leaves, or bark.[30] Individually, the active components within botanicals can lead to immediate adverse reactions necessitating hospital care. This analysis outlines the acute negative effects and interactions with pharmaceuticals associated with the prevalent botanical and herbal supplements. Due to their origin from plants, botanical supplements comprise a blend of organic compounds. Among these, only a portion possess biological activity, and a smaller subset of these active compounds exhibit therapeutic and potentially harmful modes of action.[30] In the majority of instances, the effects tend to be mild, like nausea, fatigue, and headaches. Nonetheless, there have been instances of more severe clinical complications, typically connected to drug-induced liver injury and its underlying mechanisms, including mitochondrial dysfunction, oxidative stress, and disturbances in bile acid balance. For example, black cohosh (Cimicifuga racemosa) has been linked to cases of jaundice and liver failure in menopausal women.[31]

5. Potential Side Effects Of Weight -Loss, Sport, Bodybuilding Supplements:

With the increasing prevalence of overweight and obese individuals worldwide, there is a significant demand for weight management products, which includes dietary supplements. Additionally, military personnel, athletes, and bodybuilders frequently consume sports supplements with the aim of enhancing fat metabolism and boosting their performance, muscle size, or strength.[32] For Example 64% of college students involved in sports turn to dietary supplements in order to boost their athletic performance.[33] According to a recent analysis, it was approximated that roughly 20% of drug-induced liver injuries are attributed to dietary supplements. Additionally, almost half of these injuries are associated with bodybuilding and weight-loss supplements.[34] Weight-loss products can lead to adverse effects in two main ways. First, supplements may contain ingredients, as stated in the product description, that can cause specific side effects. Second, supplements may be deliberately mixed with unlisted or illicit substances, such as anabolic steroids, which are referred to as adulterated supplements. Even supplements that contain declared compounds but haven't undergone sufficient safety testing can be labeled as adulterated by the FDA. Some researchers have contended that adulterated supplements should not be classified as legitimate dietary supplements.[35]

6. Potential Side Effects Of Omega 3 Fatty Acid And Fish Oil:

Omega-3 fatty acids are vital fats that cannot be naturally produced by the human body and must be obtained from dietary sources.[36] A connection between fish oil and ischemic heart disease was proposed through a widely circulated study conducted in 1971, which focused on Eskimos (Greenlanders) residing on the west coast of Greenland.[37] Greenlanders who followed a traditional diet consisting of meat and fish, which was abundant in polyunsaturated omega-3 fatty acids, exhibited notably lower levels of plasma total lipids, plasma cholesterol, plasma triglycerides, and pre β-lipoprotein (equivalent to very low-density lipoprotein) when compared to both Danes and

Greenlanders living in Denmark. The authors of the study theorized that this diet played a role in the low occurrence of ischemic heart disease and diabetes among Greenlanders. Subsequently, polyunsaturated omega-3 fatty acids, obtained from sources like fish oils, krill oil, or combinations of docosahexaenoic and eicosapentaenoic acids (referred to as DHA and EPA), which are purified from fish oils, have gained widespread use as dietary supplements. These fatty acids have metabolites that possess anti-inflammatory properties and contribute to electrical stability.[38]

- **Contaminants that are harmful in nutraceuticals:**

Several toxic contaminants and adulterants, including phytotoxins, metals, mycotoxins, pesticides, radiation, therapeutic drugs, and illicit drugs, can be found in both food and nutraceutical products. When individuals are exposed to these contaminants in higher concentrations, it can lead to severe adverse health consequences, and in some cases, even be fatal. It's important to note that specific population subgroups, such as pregnant women, children, and elderly adults, face a higher risk when the concentrations of these contaminants surpass acceptable levels. This heightened risk is due to their increased vulnerability to the harmful effects of these substances. ‘

Toxic Contaminants Reported in Nutraceuticals and Food Ingredients

1. Trace metals :

A. Heavy metals Al, Cd, Cr, Hg, Ni, Pb
B. Metalloids As
C. Oligoelements Cu, Zn, Mo, Se

2. Pesticides:

A. Organophosphorus pesticides Chlorpyrifos, methylchlorpyrifos, coumaphos, diazinon, dichlorvos, dimethoate, ethion, fenchlorphos, malathion, parathion, methyl-parathion propenophos
B. Organochlorine pesticides Hexachlorocyclohexane (HCH), lindane, dichlorodiphenyl trichloroethane (DDT), benzene hexachloride (BHC), pentachloronitrobenzene (PCNB), tecnazene (TCNB) Pyrethroid pesticides
C. Cypermethrin, esfenvalerate, fenvalerate, permethrin
D. Nitrogen-containing pesticides Atrazine

3. Mycotoxins:
Aflatoxin, ochratoxin A, fumonisins, citrinin

4. Radioactive contamination:
137Cs, 210Pb, 238U, 234U, 226Ra

5. Adulteration/ undeclared chemical substances:
6. Caffeine, ephedrine, norpseudoephedrine, synephrine, phosphodiesterase type 5 inhibitors[39]

1. Heavy Metals:

Generally, nutraceuticals are perceived as being safe for consumption. However, their safety can be compromised when they become tainted with specific metals. In reality, there is ample documented evidence of heavy metal contamination in traditional medicinal products.[40] Due to their ability to accumulate in organisms and their toxic nature, heavy metal levels have the potential to reach concentrations that pose risks to the health of both humans and animals. Cadmium (Cd), mercury (Hg), lead (Pb), and arsenic (As) are particularly worrisome nonessential toxic elements because they can have harmful effects even when present in small amounts.[41] Research has revealed that some traditional Chinese medicines (TCM) have been extensively polluted with arsenic (As), lead (Pb), and mercury (Hg). Such alarming discoveries can expose consumers to the potential danger of severe, or in extreme cases, lethal heavy metal or metalloid poisoning due to the consumption of these herbal remedies. Consequently, it is crucial to analyse metal levels in nutraceuticals and food ingredients to

evaluate their safety and potential toxicity.[42] Exposure to lead has been linked to various health issues, including renal tumours, impaired cognitive development, elevated blood pressure, and cardiovascular problems. In a recent retrospective observational study, it was discovered that traditional and folk remedies contained hazardous levels of lead, leading to symptoms such as abdominal pain, constipation, hypertension, anaemia, neurological symptoms, and dysfunction of the kidneys and liver.[43]

2. Pyrrolizidine Alkaloids:

Among plant toxins, pyrrolizidine alkaloids (PAs) are the most potent and can be found in various plant species, including Crotalaria, Senecio, Heliotropium, Symphytum, Cynoglossum, Amsinckia, and Echitum. Over 150 pyrrolizidine alkaloids (PAs) have been identified, and certain PAs are frequently found as contaminants in food and herbal nutraceuticals. These PAs share a common pyrrolizidine nucleus and can be characterized by fundamental structures like senecionine and heliotrine. The toxic effects of PAs are somewhat similar, although their potency can differ due to their conversion in the liver into toxic metabolites known as pyrroles.[44] The toxicity of pyrrolizidine alkaloids (PAs) can also interfere with various hepatic functions, including copper metabolism, clotting factors, ammonia (NH3) metabolism, and protein metabolism. Research has shown that the extended presence of DNA adducts derived from pyrrolizidine alkaloids (PAs) in living organisms indicates their role as mechanism-based biomarkers of both PA exposure and its associated toxicity.[45]

3. Mycotoxins:

Mycotoxins are substances generated by fungi as secondary metabolites, posing a risk of contamination in herbs and dietary supplements. Frequently encountered mycotoxins in nutraceuticals and dietary ingredients comprise aflatoxins, ochratoxin A, citrinin, and various others. [46] Ochratoxin A (OTA), generated by Penicillium verrucosum, Aspergillus ochraceus, A. carbonarius, and A. niger, is another mycotoxin posing health risks. It is recognized for inducing nephrotoxic, hepatotoxic, embryotoxic, teratogenic, neurotoxic, immunotoxic, genotoxic, and carcinogenic effects through various mechanisms.[47] Aflatoxin B1 contamination has been identified in diverse varieties of spices, aromatic herbs, and medicinal plants originating from Italy. Aflatoxin B1 is predominantly produced by the fungus Aspergillus flavus, and its adverse effects include liver toxicity, hepatocarcinogenicity, as well as mutagenic, teratogenic, and immunosuppressive outcomes.[48]

- Nutraceutical: fact from fiction

The scientific community is presently exploring the impact of nutraceuticals on human nutrition, with a primary emphasis on functions that hold significant potential and diverse applications for consumers, healthcare professionals, food regulation authorities, as well as producers and distributors within the food industry. The current landscape recognizes nutraceuticals as crucial for maintaining optimal health, yet the surge in their widespread and uninformed use has become a notable trend. These products are sometimes perceived as substitutes for a balanced diet, even replacing traditional dietary items in certain cases. However, the dearth of comprehensive information about nutraceuticals contributes to uncertainty, apathy, and confusion among consumers. This lack of clarity has created an environment where numerous companies are entering the market, producing nutraceuticals that may pose potential risks to the health of millions who rely on them without question.

A significant concern arises from the production practices of many brands, which often involve the creation of synthetic products containing oxide minerals and other chemical substances. These formulations are frequently augmented with harmful additives, including preservatives, fillers, binders, coal tar, bitumen, gelatin, and waste products. The overarching worry is centered on how effectively the human body assimilates these products, as there is a potential for them to accumulate in body tissues, potentially leading to the onset of diseases or exacerbating existing health conditions.

This complex scenario highlights the need for a more informed and discerning approach to the consumption of nutraceuticals to ensure both their efficacy and safety.[49]

- The Significance of Nutraceuticals in Preventing and Treating Health Conditions :

Nutraceuticals and dietary bioactive components are not classified as pharmaceutical drugs; instead, their purpose is to address nutritional gaps in a balanced diet. These compounds offer advantages in fulfilling daily nutritional needs, particularly when it becomes challenging to meet these requirements solely through food intake. In certain physiological conditions, there is an elevated demand for specific nutrients that surpasses normal limits. For example, Vitamin D supplements are utilized to meet the daily nutritional needs of individuals. For the elderly, it is advisable to enhance calcium intake to prevent bone weakness, while antioxidants are recommended to alleviate the emergence of aging marks on the skin. While supplements may play a role in preventing disease and supporting overall health, they do not have a role in directly treating diseases. Consequently, the assertion that supplements and nutraceuticals can effectively treat health disorders is entirely unfounded.[50,51]nn

REFRENCE:

1. Dudeja P, Gupta RK. Nutraceuticals. In Food safety in the 21st century 2017 Jan 1 (pp. 491-496). Academic Press.
2. Gupta RC, Srivastava A, Lall R. Toxicity potential of nutraceuticals. Computational toxicology: methods and protocols. 2018:367-94.
3. Kalra EK. Nutraceutical-definition and introduction. Aaps Pharmsci. 2003 Sep;5(3):25.
4. Sachdeva V, Roy A, Bharadvaja N. Current prospects of nutraceuticals: A review. Current pharmaceutical biotechnology. 2020 Aug 1;21(10):884-96.
5. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. JAMA internal medicine. 2013 Mar 11;173(5):355-61.
6. Moyer MW. Vitamins on trial. Nature. 2014 Jun 26;510(7506):462.
7. Weaver CM, Alekel DL, Ward WE, Ronis MJ. Flavonoid intake and bone health. Journal of nutrition in gerontology and geriatrics. 2012 Jul 1;31(3):239-53.
8. Oketch-Rabah HA, Roe AL, Rider CV, Bonkovsky HL, Giancaspro GI, Navarro V, Paine MF, Betz JM, Marles RJ, Casper S, Gurley B. United States Pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. Toxicology reports. 2020 Jan 1;7:386-402.
9. Mulholland CA, Benford DJ. What is known about the safety of multivitamin-multimineral supplements for the generally healthy population? Theoretical basis for harm. The American journal of clinical nutrition. 2007 Jan 1;85(1):318S-22S.
10. Guallar E, Stranges S, Mulrow C, Appel LJ, Miller III ER. Enough is enough: stop wasting money on vitamin and mineral supplements. Annals of internal medicine. 2013 Dec 17;159(12):850-1.
11. Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: an updated systematic evidence review for the US Preventive Services Task Force. Annals of internal medicine. 2013 Dec 17;159(12):824-34.
12. Bairati I, Meyer F, Gélinas M, Fortin A, Nabid A, Brochet F, Mercier JP, Têtu B, Harel F, Abdous B, Vigneault É. Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. Journal of clinical oncology. 2005 Aug 20;23(24):5805-13.
13. Miller III ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Annals of internal medicine. 2005 Jan 4;142(1):37-46.
14. Rothman KJ, Moore LL, Singer MR, Nguyen US, Mannino S, Milunsky A. Teratogenicity of high vitamin A intake. New England Journal of Medicine. 1995 Nov 23;333(21):1369-73.

15. Ramanathan VS, Hensley G, French S, Eysselein V, Chung D, Reicher S, Pham B. Hypervitaminosis A inducing intra-hepatic cholestasis—a rare case report. Experimental and Molecular Pathology. 2010 Apr 1;88(2):324-5.
16. Barton JC, Lee PL, West C, Bottomley SS. Iron overload and prolonged ingestion of iron supplements: Clinical features and mutation analysis of hemochromatosis-associated genes in four cases. American journal of hematology. 2006 Oct;81(10):760-7.
17. Swanson CA. Iron intake and regulation: implications for iron deficiency and iron overload. Alcohol. 2003 Jun 1;30(2):99-102.
18. Doron S, Snydman DR. Risk and safety of probiotics. Clinical Infectious Diseases. 2015 May 15;60(suppl_2):S129-34.
19. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Rosman C. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. The Lancet. 2008 Feb 23;371(9613):651-9.
20. Munakata S, Arakawa C, Kohira R, Fujita Y, Fuchigami T, Mugishima H. A case of D-lactic acid encephalopathy associated with use of probiotics. Brain and Development. 2010 Sep 1;32(8):691-4.
21. Vaarala O. Immunological effects of probiotics with special reference to lactobacilli. Clinical & Experimental Allergy. 2003 Dec;33(12):1634-40.
22. Lin CF, Fung ZF, Wu CL, Chung TC. Molecular Characterization of a Plasmid-Borne (pTC82) Chloramphenicol Resistance Determinant (cat-TC) fromLactobacillus reuteriG4. Plasmid. 1996 Sep 1;36(2):116-24.
23. Dessart SR, Steenson LR. High frequency intergeneric and intrageneric conjugal transfer of drug resistance plasmids in Leuconostoc mesenteroides ssp. cremoris. Journal of Dairy Science. 1991 Sep 1;74(9):2912-9.
24. Morelli L, Sarra PG, Bottazzi V. In vivo transfer of pAMβ1 from Lactobacillus reuteri to Enterococcus faecalis. Journal of Applied Bacteriology. 1988 Nov;65(5):371-5.
25. Fang N, Yu S, Badger TM. Comprehensive phytochemical profile of soy protein isolate. Journal of agricultural and food chemistry. 2004 Jun 16;52(12):4012-20.
26. Harlid S, Adgent M, Jefferson WN, Panduri V, Umbach DM, Xu Z, Stallings VA, Williams CJ, Rogan WJ, Taylor JA. Soy formula and epigenetic modifications: analysis of vaginal epithelial cells from infant girls in the IFED study. Environmental health perspectives. 2017 Mar;125(3):447-52.
27. Tan KA, Walker M, Morris K, Greig I, Mason JI, Sharpe RM. Infant feeding with soy formula milk: effects on puberty progression, reproductive function and testicular cell numbers in marmoset monkeys in adulthood. Human Reproduction. 2006 Apr 1;21(4):896-904.
28. McCarver G, Bhatia J, Chambers C, Clarke R, Etzel R, Foster W, Hoyer P, Leeder JS, Peters JM, Rissman E, Rybak M. NTP-CERHR expert panel report on the developmental toxicity of soy infant formula. Birth Defects Research Part B: Developmental and Reproductive Toxicology. 2011 Oct;92(5):421-68.
29. Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, Betz JM, Sempos CT, Picciano MF. Dietary supplement use in the United States, 2003–2006. The Journal of nutrition. 2011 Feb 1;141(2):261-6.
30. Enbom ET, Le MD, Oesterich L, Rutgers J, French SW. Mechanism of hepatotoxicity due to black cohosh (Cimicifuga racemosa): histological, immunohistochemical and electron microscopy analysis of two liver biopsies with clinical correlation. Experimental and molecular pathology. 2014 Jun 1;96(3):279-83.
31. Lieberman HR, Stavinoha TB, McGraw SM, White A, Hadden LS, Marriott BP. Use of dietary supplements among active-duty US Army soldiers. The American journal of clinical nutrition. 2010 Oct 1;92(4):985-95.

32. Hoyte CO, Albert D, Heard KJ. The use of energy drinks, dietary supplements, and prescription medications by United States college students to enhance athletic performance. Journal of community health. 2013 Jun;38:575-80.
33. Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. Hepatology. 2017 Jan;65(1):363-73.
34. 45. Raman P, Patino LC, Nair MG. Evaluation of metal and microbial contamination in botanical supplements. J Agric Food Chem. 2004 Dec 29;52(26):7822-7. doi: 10.1021/jf049150+. PMID: 15612762.
35. 46. Gan F, Hou L, Zhou Y, Liu Y, Huang D, Chen X, Huang K. Effects of ochratoxin A on ER stress, MAPK signaling pathway and autophagy of kidney and spleen in pigs. Environmental toxicology. 2017 Oct;32(10):2277-86.
36. 47. Prado G, Altoé AF, Gomes TC, Leal AS, Morais VA, Oliveira MS, Ferreira MB, Gomes MB, Paschoal FN, Souza RV, Silva DA. Occurrence of aflatoxin B1 in natural products. Brazilian Journal of Microbiology. 2012;43:1428-35.
37. 48. Sharif MK, Khalid R. Nutraceuticals: myths versus realities. InTherapeutic foods 2018 Jan 1 (pp. 3-21). Academic Press.
38. 49. Nikolić G, Marković D. MISCONCEPTIONS ABOUT NUTRITIONAL SUPPLEMENTS AND MODERN DISEASES. Hrana u zdravlju i bolesti [Internet]. 2015 [cited 2023 November 28];4(1):34-47.
39. 50. Isidoro C, Huang CC, Sheen LY. Report from the second international conference of traditional and complementary medicine on health 2015. Journal of traditional and complementary medicine. 2016 Jan 1;6(1):5-9.
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