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The Use of Medical Foods to Fight Chronic Diseases: A Narrative Review

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ABSTRACT
Chronic diseases cannot be treated completely, and, therefore, often require repeated treatments. This issue leads to long-term drug utilization. However, medical foods can offer alternative natural drugs in the management and treatment of chronic diseases. Medical foods are specially formulated food to meet the particular nutritional requirements of patients affected by certain diseases. They play an important role in nutritional support for patients in clinical applications such as deglutition, dyspepsia or eating disorders. Moreover, they considerably enhance the quality of living of patients by reducing drug usage, preventing complications that may arise through the overreliance of drugs, and reducing the expenses of treatments. The nutritive value of medical foods can be regulated and personalized depending on the disease. Since they are not drugs, they exempt from regulations applying to drugs. Each medical food is formulated specifically for the relevant chronic disease. However, there are no studies in the literature that provide examples of medical foods for different diseases available in the market. The examination and compilation of medical foods, including examples from the market, is vital both in terms of creating new products and filling the gap in the relevant literature. Consequently, the aim of this review is to explain the use of medical foods for Alzheimer's, Parkinson's, anxiety and sleep disorder, pain syndrome, cancer, congenital metabolic disorders, diabetes mellitus, and indicate why should be used as a nutritional supplement for these chronic diseases.

Keywords: Food, Medical nutrition therapy, Disease, Treatment, Dietary management

1. Introduction

Today, the world is facing a notable increase in the number of people suffering from complex and chronic diseases such as diabetes, Alzheimer's, cancer, and autism. An examination of the existing medical research shows a noticeable shift, where the primary objective of treating patients has evolved into a pursuit of comprehensive healing. This paradigm shift implies that while patients' symptoms may persist, they can be managed over the course of their lives with an escalating regimen of drugs. What patients truly require is a therapeutic approach that aims to promote healing by addressing the root cause of their diseases. It is in this context that the significance of functional medicine becomes apparent. Functional medicine adopts an individualized and integrative methodology, encompassing the understanding and exploration of preventive measures and the management of chronic diseases. Functional medicine does not refuse conventional medicine, but it uses conventional medicine as a basis on which to add new aspects in the consideration, prevention, and management of chronic disease (Nikogosian 2022). One specific aspect investigated within the realm of functional medicine is the dietary pattern of a patient. At this point, the importance of the term of "medical food" in the treatment of chronic diseases emerges.

Medical foods first entered the market under the regulatory oversight of the Food and Drug Administration (FDA) in the United States in 1972. One of the first examples of medical foods was "Lofenalac", which was used for the dietary management of patients in the treatment of phenylketonuria (PKU), an inborn disease of metabolism. In 1988, the Orphan Drug Act was rearranged to create a legal definition for the term medical food (Holmes et al. 2021). In 1990, the Nutritional Labeling and Education Act (NLEA) exempted medical foods from the health claims and nutrition labeling requirements. The legal definition refers to the "specific dietary management of a disease or condition" whereas the NLEA refer to the "dietary management of a patient with a specific disease or condition". This distinction is important as not all food produced for patients is medical food (Bagchi 2019). In 1996, the FDA reevaluated the regulatory norms of medical foods and published an announcement with a detailed definition for the term "medical food" (Parker 2005). After the FDA withdrew the announcement in 2004 due to constraints in resources, it released a final guide in 2016 to ensure that manufacturers better understood the regulations concerning medical foods (Lewis & Jackson 2019). The document "Guidance for Industry: Frequently Asked Questions About Medical Foods, Second Edition" clarifies the term "medical food" via a question-and-answer format (FDA 2016).

Medical foods are produced for special medical purposes according to a particular recipe to address the specific dietary needs of patients suffering from metabolic disorders or other chronic diseases. According to the FDA's definition, medical food is a "food formula generated for the specific dietary management of a disease or condition for which distinctive nutritional needs have been determined by medical evaluation that has been formulated for consumption or enteral administration under the supervision of a physician" (Lange et al. 2019a; FDA 2022). Most foodstuffs are grouped, whether they are "sugar-free", "low fat", "lactose-free", "gluten-free" or "organic" produced. However, uncertainty remains regarding the differences of health-related foods from dietary/nutritional supplements and conventional foods in the market, throughout various medical disciplines and especially among consumers (Markowitz et al. 2020). For a better understanding of the differences, commonly known food terms using for different food stuffs and their definitions are provided in the Table 1. Although all the food items can be used to improve health conditions, medical foods must be consumed under medical supervision in the specific dietary management of certain diseases (Shi et al. 2020).

The current review aims to elucidate the definition of medical foods, highlight their distinctions from pharmaceutical drugs, and provide illustrative examples of medical food applications in conditions such as Alzheimer's, Parkinson's, anxiety and sleep disorders, pain syndromes, cancer, congenital metabolic disorders, and diabetes mellitus.

Table 1- Food Terms and Definitions (Markowitz et al. 2020)

Term	***Definition***
Functional Food	Products used in combination with enhanced, fortified or enriched foods that offer health benefits when consumed in a certain diet.
Fortified Food	A conventional food which is enriched by adding extra micronutrients to it.
Enriched Food	Food product in which essential nutrients lost during processing are added back.
Dietary Supplements	A product which is manufactured to support the diet with components like plant extracts, vitamins, amino acids, minerals, various dietary fiber and/or a combination of these components. Unlike medical foods, it is not used under physician supervision or for the treatment of any specific disease.
Food for Special Dietary Use (FSDU)	A product used to meet dietary needs due to a physiological, pathological or other condition, including disease, pregnancy etc. It is not used under medical supervision, and it does not make health claims.
Drug	Any substance (except food) which is used to treat, prevent, or cure a disease.
Medical Food	Food formulated for consumption under the supervision of a physician to meet nutritional needs which are identified by a clinical study of patients.

2. The Differences Between Medical Foods and Drugs

Medical foods have an important place in enteral nutrition but are not defined as drugs. Enteral nutrition supplemented with medical foods can reduce the adverse effects of long-term drug utilization, incidence of some complications, shorten the length of hospital stay, and decrease the economic losses resulting from illness (Seron-Arbeloa et al. 2013; Przyrembel et al. 2015). Healthcare professionals do not desire the depletion of certain nutrients when considering the long-term health consequences of prescription drugs continuously used by patients for the treatment of chronic diseases (Meletis & Zabriskie 2007). Vitamin B_{12} deficiency caused through the use of an oral hypoglycemic agent, coenzyme Q_{10} deficiency that occurs through the use of statins, vitamin B, calcium and magnesium deficiencies arising from the frequent use of antibiotics are some examples of loss of nutrients due to drug use. Consequently, the use of medical foods and dietary supplements is thought to be effective in prohibiting drug-related nutritional losses (Valuck & Ruscin 2004).

Medical foods are exempt from FDA laws and requirements for drugs. However, medical foods are liable to all the FDA requirements determined for conventional and functional foods, such as good manufacturing practices. There is a misunderstanding that medical foods can only be given to patients through prescriptions; unlike medical drugs, over the counter delivery of medical foods is not prohibited. It is forbidden to include the inscription "*Rx*" in prescription medical drugs on the label of a medical food. In addition, medical foods produced for dietary management should be labeled to indicate that they are specific to the relevant patient or disease and meet the nutritional requirements necessary for managing that disease. All ingredients used in the formulation of medical foods should meet FDA requirements and be generally recognized as safe (GRAS). Medical foods are exempt from nutritional content and health claims requirements (Fung et al. 2018; Markowitz et al. 2020; Li et al. 2021).

While foods for special medical purposes (FSMPs) are expressed as medical foods in some non-European Union (non-EU) countries (e.g., USA, Argentina), they are also expressed as enteral nutrition in some countries (e.g., Brazil). Since the 1970s, these specialty medical foods or FSMPs, were subject to drug regulations due to the lack of advanced regulatory rules. However, in recent years, medical foods have been characterized in more detail within the scope of food laws (Domínguez Díaz et al. 2020). The re-evaluation of medical food regulations has allowed for a new phase of development in medical food industry. In China, however, medical foods are not subject to the FDA regulations that apply to drugs (Bagchi 2019). Products regarded as medical foods in the USA are regulated as FSMPs in the EU (Domínguez Díaz et al. 2020). In Turkey, the registration,

permission, import procedures, control, and inspection of establishments for producing and selling medical foods are carried out by the Ministry of Health and the Ministry of Agriculture and Forestry, in accordance with the provisions of the "Turkish Food Codex Regulation on Dietary Foods for Special Medical Purposes". As per the regulations (Official Gazette No. 24640), the product should be used under the supervision of a physician, and the target consumer group for the product should be stated on the packaging. In addition, packaging information should be created without using nutrition and health claims (TFC 2001; Domínguez Díaz et al. 2020).

3. Medical Foods Treatment on Different Diseases

Simple dietary changes can be effective in the management of many chronic diseases. In this narrative review, we will emphasize neurodegenerative diseases (Alzheimer's & Parkinson), anxiety & sleep disorders, pain syndromes, cancer, congenital metabolic disorders, and diabetes mellitus. These are chronic diseases where diet and medical food use have proven effective, and they affect a significant number of patients.

3.1. Neurodegenerative diseases

Alzheimer's disease (AD), a multifactorial neurodegenerative disease, is the most common cause of dementia in the world. The greatest known risk factor for the disease is old age, and most Alzheimer's patients are over the age of 65. Treatments to prevent or delay disease progression are not yet available that provide a significant improvement in the condition of patients. The current treatment options are primarily aimed at treating clinical symptoms that only offer symptomatic relief and promote healthy brain aging (Ohnuma et al. 2016).

One important risk factor for Alzheimer's is nutrition. Current evidence suggests that embracing prudent dietary patterns may be linked to a decelerated cognitive decline and a reduced risk of AD and related dementias, even though the precise mechanisms remain unclear. One potential mechanism involves the impact of specific dietary constituents on neural resources, thereby enhancing cognitive health and resilience. For instance, adopting healthier dietary patterns has been associated with the homeostatic formation of hippocampal neurons - an impairment often observed in the early stages of Alzheimer's dementias (Ellouze et al. 2023). An unhealthy diet, like a high-fat, low protein intake, high glycemic load, and high cholesterol or Western diet, is a significant risk factor for neurodegeneration, increasing Aβ peptide stores and neurodegeneration biomarkers in AD. Conversely, adopting a healthy diet like Dietary Approaches to Stop Hypertension (DASH), Mediterranean, or low-fat diets has neuroprotective effects, reducing oxidative stress, inflammation, and Aβ peptide accumulation. The Mediterranean and DASH diets, rich in potassium, calcium, magnesium, and fiber, with low sodium and saturated fat, exhibit anti-inflammatory effects and help protect against AD (Hoscheidt et al. 2022). The Mediterranean diet (MD) benefits cerebral perfusion, especially in early AD stages, while the Western diet heightens AD risk, impacting metabolic health, reducing cerebral perfusion, and impairing cognition (Xu et al. 2023). Therefore, by fortifying cognitive resilience over time, these dietary elements may contribute to enhanced cognitive trajectories in later life. Various dietary approaches provide symptomatic benefits for AD and fulfill the criteria for approval as medical food by providing components that meet the special nutritional needs of the patients. When considering the developments in symptomatology and regional brain atrophy in Alzheimer's disease (AD), studies have accelerated on various types of medical foods. These include products that provide ketone bodies as an alternative energy source for neurons, contain precursors believed to improve synaptic function, and address oxidative stress associated with memory loss (Atri 2019; Lange et al. 2019a). In a study conducted on Alzheimer's disease patients, it was determined that the medical food called *Axona*, which contains medium chain fatty acids, yielded positive results in patients with mild AD (Sharma et al. 2014). Another medical food that has shown success in treating the disease is *Souvenaid*, which improves memory efficiency in Alzheimer's patients. *Souvenaid* contains phosphatide precursors and other cofactors such as eicosapentaenoic acid (EPA), phospholipids, vitamin E, vitamin C, selenium, vitamin B_{12} (Scheltens 2010). Many other methodological shortcomings complicate the interpretation of the current findings of medical food trials in AD (Table 2). In addition, dietary patterns such as the Mediterranean diet show promise in the prevention of AD, but large-scale clinical studies using valid, sensitive and reliable assessment tools are needed to determine the efficiency of them (Morley et al. 2018; Omar 2019).

The second most common neurodegenerative illness is Parkinson's disease (PD), a slowly progressing disorder in the brain linked to the loss of dopaminergic neurons, resulting in involuntary movements, balance disorders, and ataxia. Non-motor symptoms in PD patients include anosmia, autonomic disorders, cognitive deficits, psychological disorders, and sleep disturbances (Postuma et al. 2012; Lange et al. 2019a). Various genetic and environmental factors contribute to the occurrence of PD (Simon et al. 2020; Gonzalez-Latapi et al. 2021), with age being the most significant and well-established factor in its development. The brain, particularly susceptible to oxidative stress in old age, is believed to play a crucial role in the dysfunction of the dopaminergic system (Aslan et al. 2019; Kaya & Soyukibar 2022; Özdemir 2022). Neuropathological clinical trials reveal the accumulation of α-synuclein proteins, known as Lewy bodies, in the central, autonomic, and peripheral nervous systems of PD patients. These bodies destroy relevant nerve cells and intercellular junctions, halting the exchange of neurotransmitters (Armstrong & Okun 2020). There is still no definitive treatment for PD, but the basis of treatment is the administration of drugs that increase dopamine levels or directly stimulate dopamine receptors (Aarsland et al. 2021; Bloem et al. 2021). Specific macronutrients and micronutrients, which are environmental factors in the etiology of PD, are an effective parameter in the management and progression of the disease and therefore in its treatment. In a study on potential nutritional risk factors in PD,

those who consumed foods rich in vegetables, seeds, nuts, xanthophylls, xanthine, and lutein had a lower frequency of the disease compared to the control group (Ishihara & Brayne 2005; Gaenslen et al. 2008). It was determined in a similar study conducted with a group of 4,524 individuals aged 40-79 years without a diagnosis of PD that the consumption of milk had a positive effect on the progress of the disease, while the consumption of niacin-rich meat and meat products had a negative effect (Sääksjärvi et al. 2013). Dietary polyphenols which have antioxidant and anti-inflammatory properties, such as resveratrol, anthocyanins, catechins, theaflavins, and curcumin may have neuroprotective potential in PD (Farooqui & Farooqui 2017; Singh et al. 2020; Giuliano et al. 2021). Omega-3 polyunsaturated fatty acids that allow for the continuation of neurobiological functions, play an important role in the neurodegenerative process in PD with actions that alleviate oxidative stress and neurotrophic factors. Studies have shown that docosanoids and elovanoids from omega-3 fatty acids contribute to inflammatory responses and neuroprotection (Bazan 2018; Lange et al. 2019b). Considering potential mechanisms leading to neurodegeneration in PD oxidative stress, antioxidant components such as vitamins C, D, E and carotenoids can prevent oxidative stress and act as a neurotrophic factor. A study has shown that a diet rich in vitamin D, in particular, can induce an increase in dopamine levels in the brain. This is achieved by facilitating the transition of the dopamine precursor, tyrosine, into the cerebrospinal fluid and by stimulating the expression of tyrosine hydroxylase, a key enzyme in dopamine synthesis (Yeshokumar et al. 2015; Hughes et al. 2016; Bivona et al. 2019; Miclea et al. 2020). In this sense, preliminary tests of medical foods in PD are based on a ketogenic diet (KD) composition. The KD is defined by its emphasis on high fat intake and low carbohydrate consumption, encouraging the production of ketones for energy. A high-carbohydrate diet can induce dopamine increase in the brain by facilitating the transition of dopamine precursor tyrosine into the cerebrospinal fluid (Yeshokumar et al. 2015). In addition, a KD contributes positively to PD by improving the energy metabolism of central neurons and mitochondrial biogenesis and by controlling neurotransmitters (Rudy et al. 2020). Studies have indicated a significant association between high adherence to the MD and overall reductions in the mean age of onset, incidence, progression, and motor symptom manifestations of PD, along with an increase in cognitive function (Bianchi et al. 2023). MD is a diet rich in olive oil, unrefined cereals, fruits, and vegetables; a moderate to high intake of fish; a moderate consumption of dairy products, predominantly cheese and yogurt; moderate wine consumption; and a low consumption of red meat products. The MD exerts an anti-inflammatory effect by reducing oxidative stress, C-reactive protein (CRP), fasting insulin, adiponectin levels, and neuroinflammation. Additionally, it improves gut microbiota and metabolic syndrome, leading to a reduction in α-synuclein aggregation and early neuronal degeneration. This improvement is presumed to occur both in the gut and various areas of the brain (Molsberry et al. 2020).

3.2. Anxiety & Sleep disorder

Sleep, a highly regulated function in which different groups of neurons are affected, is necessary for the normal and healthy functioning of the human body and is associated with the regulation of learning, memory and emotional state. Sleep disorders can be seen as a disease on their own or as a symptom of another physical or mental illness. One of these mental illnesses is anxiety (Adell 2004; Arenas et al. 2019), a psychological disorder which includes symptoms such as irritability, difficulty concentrating, sensitivity to sound, and restlessness. Anxiety and sleep disorders have long been known to be interrelated. The majority of those suffering from anxiety disorders have chronic or periodic sleep problems. At this point, it is important to emphasize the necessity of restorative sleep for central nervous system disorders, including anxiety, as it significantly influences feelings of depression (Groff et al. 2022). Sleep is regulated by several neurotransmitters, including serotonin and acetylcholine, which are released sufficiently and at appropriate times. Agents and drugs used for anxiety and sleep disorders interfere and regulate neurotransmitters. However, they may cause side effects such as lethargy, depression, and dysmnesia. Therefore, in recent years, medical foods for anxiety and sleep disorders have been introduced in the market. Medical foods formulated for anxiety and sleep disorders consist of serotonin and acetylcholine precursors that increase amino acid intake and neurotransmitter release. The produced serotonin and acetylcholine commence sleep and support delta sleep. Firstly, 5-hydroxytryptophan is converted to serotonin to induce sleep, then choline is converted to acetylcholine for delta sleep (España & Scammell 2004). In a study conducted by Md et al. (2012), 111 subjects using *Sentra*, a medical food formulated for anxiety, were monitored for 30 days. The subjects provided informed consent and completed an initial sleep survey. Their study found that medical food reduces the time to fall asleep, reduces drowsiness in the morning and improves sleep quality. Therefore, the study has proven that the use of Sentra contributes positively to depression and anxiety. A similar study utilized various ingredients including Ginkgo biloba as an uptake stimulator, choline, glutamic acid as a precursor of glutamate, cocoa as an adenosine antagonist, and grape seed extract as a source of polyphenols. These ingredients were used in the production of a medical food called *GABADone*, which is a combination of amino acids. It has been indicated that the produced medical food decreases the sleep latency and increases the duration and quality of sleep (Shell et al 2010). In summary, studies in the literature show that some amino acids affect sleep cycles and therefore central nervous system functions, including depression and anxiety (Glenn et al. 2019; Zhao et al. 2020).

3.3. Pain syndromes

Chronic pain syndrome is defined as pain in which the etiology is not very clear, and which usually lasts longer than 6 months or that relapses frequently (Martikainen et al. 2018). Chronic pain, unlike acute pain, may not derived from damaged tissue. It is thought to be associated with pain memory in the related centers of the brain and sensitive areas around the backbone. In other words, nerve cells can send pain signals without the presence of tissue damage in the affected area (Martikainen et al. 2018). In this type of pain, besides biological approaches, psychodynamic perspectives are also crucial. Therefore, some chronic pain may

be psychological in origin. Although chronic pain treatment methods vary according to the type and location of the pain, the use of medication is usually recommended at the first stage (Shim et al. 2019). In addition to drug use, psychological and physiotherapeutic methods are also frequently used chronic pain treatment methods. However, chronic pain syndrome, which usually does not completely respond medical treatment, can best be treated with a multidisciplinary approach (manual therapy, physical therapy, aqua therapy, occupational therapy, psychotherapy, and certain new therapies). Physical therapy and other approaches may increase treatment costs (Shim et al. 2019). In this multidisciplinary approach, nutrition and medical foods in the specific dietary management of the patients plays an important role. The production of medical foods containing specific amino acids and neurotransmitters required to reduce chronic pain syndrome, which occurs depending on the frequency and volume of the pain signals in the nervous system, has increased in recent years. One of these medical foods currently available is *Percura* which formulates with biogenic amins, amino acids, and botanicals inducing the production of neurotransmitters to decrease signals throughout the pain pathways. The key ingredients of this medical food are choline bitartrate as a precursor of acetylcholine, inositol for the development and functioning of peripheral nerves, osteogenesis, and reproductive functions, L-arginine as an ingredient for producing nitrite oxide a neurotransmitter substance, L-ornithine for improving the sympathetic nerve outflows, and creatine monohydrate as a source of intracellular energy. In a clinical outcome study of *Percura*, it was found that patients with peripheral neuropathy experienced a reduction in pain and numbness at a rate of 82-89% over a 21-day period (Shell et al. 2016). *Trepadone* is another medical food specifically designed to address the specific amino acid requirements needed in the reduction of chronic pain syndromes associated with joint disorders. It contains chondroitin sulfate, glucosamine sulfate, L-histidine, and whey protein, which stimulate the production of serotonin, γ-aminobutyric acid (GABA), nitric oxide, glutamate and histamine neurotransmitters. It has been scientifically proven that these ingredients support the cellular or physiological activities needed to restore metabolic balance (Shell et al. 2016; Taylor et al. 2021). Although there are examples of medical foods on the market, there are limited studies showing the effectiveness of medical foods containing specific amino acids and neurotransmitter precursors on chronic pains. For this reason, further studies on the subject are required.

3.4. Cancer

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Nutrition plays a crucial role as a risk factor in the deaths of cancer patients, accounting for 20-40% of direct causes of death. Therefore, enteral nutrition therapy is an important part of cancer treatment (Mao et al. 2018). The primary nutritional problem, and likely also the most impactful on prognosis, is myolysis. Myolysis in cancer patients may lead to cachexia and anorexia over time. Cachexia is characterized by involuntary weight loss and anorexia on top of skeleton mass loss (Arends et al. 2017; Muscaritoli et al. 2021). Several studies have shown that muscle mass can be improved and losses can be reduced with a daily protein intake of >1.5 g/kg body weight in patients with cancer cachexia, and this effect may be more significant when combined with exercise. In this sense, protein-enriched medical foods such as *ProtiMedic Amino Plus* can be used in the dietary management of cancer patients (Blasiak et al. 2020).

Medical foods designed for cancer patients are widely used nutritional agents and have an important place in medical nutrition therapy. For example, to maintain the nitrogen balance, the protein content of medical foods for cancer patients may be increased and thus cachexia can be prevented. Antioxidants such as vitamin E, vitamin C and selenium can retard the formation and development of cancer by preventing lipid peroxidation. Since the cancer disease weakens the immune system of patients, immunomodulatory agents such as arginine, glutamine, n-3 fatty acids, and nucleotides can be used in medical food formulas (Rosenthal et al. 2016; Xu et al. 2016).

3.5. Medical foods for congenital metabolic disorders

Congenital Metabolic Disorders (CMD) are expressed as inherited disorders that occur in carbohydrate, protein or fat metabolism due to a particular enzyme defect. CMD is divided into three categories as intoxication disorders, energy metabolism disorders and disorders of complex molecules. Treatment methods for this disease are determined by considering the defective enzyme and the damaged metabolic reaction. Although the most effective treatment modalities for CMD are organ transplantation and gene therapy, their applicability is more difficult due to immune rejection issues, donor availability, and immature gene therapy. At this point, medical foods produced specifically for CMD can be effective in relieving the symptoms and reducing their incidence by limiting the uptake and accumulation of the relevant reaction substrate (Camp et al. 2012).

A common CMD is phenylketonuria (PKU), which is one of the most common congenital metabolic diseases requiring nutritional therapy. PKU is an amino acid metabolism disorder that occurs as a result of the inability to break down phenylalanine due to the deficiency of the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine. Since the accumulation of phenylalanine in blood and tissue causes permanent damage to the nerves, reducing its level is crucial, especially for children (Camp et al. 2012). Medical foods used in the treatment of PKU are divided into two groups according to their differences based on components. While one group contains all other nutrients, foods that do not contain phenylalanine at all or contain negligible amounts; the other group can be expressed as foods that have been modified to be low in protein. Various studies on the subject have shown that medical foods with a low phenylalanine formula can improve the health status of children with PKU (Chen et al. 2015; MacDonald et al. 2020; Mtewa et al. 2020). Specified medical food formulas that do not contain

disease-causing protein derivatives should be used in other amino acid metabolism disorders such as non-ketonic hyperglycinemia, tyrosinemia, and maple syrup urine disease (McCandless et al. 2021; Chong et al. 2022).

Another CMD is lactose intolerance. Lactose is a disaccharide found in both cow and human milk and is the primary energy source that supports growth in infants. But in some cases, lactase deficiency causes problems in the digestion of lactose. For this reason, medical food product prescriptions are designed to be lactose-free. The main difference between lactose-free infant formulas and standard infant formulas is that lactose-free formulas have glucose instead of lactose as the source of the carbohydrate (Lynch et al. 2020). Medical foods are produced for infants in the case of special disorders or conditions according to their nutritional requirements. Therefore, infant formulas are designed to provide ease of administration to infants for nutritional and medical purposes (Mtewa et al. 2020). Medical foods are widely used for premature infants as well as lactose intolerance. According to a statement made by the World Health Organization (WHO), infants born before 37 weeks are defined as premature (Chen et al. 2020; WHO 2022). These infants need a special diet because they have an immature gastrointestinal system due to preterm birth. Premature infant formulas are created to support the growth and development of preterm newborn and low birth weight babies (babies' weight <1500 g). Formulas containing cow's milk protein in their composition contain very high amounts of calcium and phosphorus. They are designed to match the higher calcium and phosphorus levels children need as they grow, similar to the levels found in whole milk (Chen et al. 2020; Sanadgol Nezami et al. 2021).

3.6. Diabetes mellitus

Diabetes Mellitus (DM) is a chronic metabolic disease characterized by persistent hyperglycemia, resulting from the insufficient or decreased effectiveness of insulin. The disease can be classified into two groups: Type-1 (insulin-dependent) and Type-2 (insulin-independent). Type-1 involves the complete destruction of pancreas β-cells, leading to an absolute insulin deficiency, while Type-2 is characterized by chronic hyperglycemia due to impaired insulin secretion or receptor function (Li et al. 2018; WHO 2022). The incidence of diabetes is rising globally, with approximately 592 million estimated cases by 2035. Type-2 diabetes accounts for 90% of all diabetes cases (Atkinson et al. 2014; Guariguata et al. 2014). The disease poses a significant economic burden and, if untreated, can lead to life-threatening complications affecting various organs. Treatment approaches include hypoglycemic drugs, insulin therapy, and surgical procedures. Ideal treatment focuses on achieving good glycemic control and correcting accompanying metabolic conditions (Tümer & Çolak 2012; Kaur et al. 2017). The American Diabetes Association (ADA) recommends a balanced diet, incorporating oral antidiabetic drugs and insulin, if necessary, along with regular exercise for Type-2 diabetes management. Medical foods are attracting more attention in diabetes treatment, as they offer nutritional support to help control blood sugar levels, and clinical trials exploring the use of medical foods in diabetes treatment are on the rise (ADA 2018). Representative examples of medical food products produced for DM patients are provided in Table 2.

When examining the compositions of medical foods produced for diabetes patients, healthcare professionals encourage individuals to consume various fiber-containing foods such as whole grains, fruits, and vegetables, since these foods provide vitamins, minerals, fiber, and other substances considered important for health. Studies conducted on the use of fibrous foods with patients with Type-1 diabetes show that fibrous structure has a positive effect on glycemia. In Type-2 diabetes patients, it has been determined that high fiber intake provides metabolic benefits on glycemic control, hyperinsulinemia and plasma lipids (Gao et al. 2020). For this reason, there is no harm in consuming fructose, which is naturally found in fruits, vegetables and other foods, depending on the level of intake, and the consumption of products rich in dietary fibers is encouraged (Satija et al. 2016; Torres et al. 2020). Agrawal et al. (2014) reported an association between vegetarian diet consumption and the occurrence of Type-2 diabetes in a nationally representative sample of 156 participants aged 20-49 years. It has been determined that the risk of diabetes in individuals who adhere to any vegetarian diet is statistically significantly lower. The similar results obtained in this study was found to be consistent with another study conducted by Chiu et al. (2014). Epidemiological studies comparing the prevalence of Type-2 diabetes among vegetarians and non-vegetarians have shown that vegetarians have a lower risk of Type-2 diabetes. This can be partially explained by lower weight, higher intakes of dietary fiber and plant-derived protein, lower intakes of saturated fat and a lack of protein from meat and eggs in the diet. Studies have shown that vegetarian diets, especially vegan diets, are effective tools in glycemic control and these diets are traditionally recommended for patients with diabetes (Pawlak 2017).

4. Medical Foods on Different Diseases in Global Market

The global medical foods industry is experiencing sustained growth due to the increasing recognition of the significance of nutrition in maintaining health and overall well-being. The market size of medical foods was assessed at $21.38 billion in 2022 and is anticipated to increase from $22.62 billion in 2023 to $35.3 billion by 2032. The higher prevalence of chronic diseases, the aging global population, and a growing demand for customized nutrition are driving the market growth (Gotadki 2023). Representative examples of medical food products commercially available for different chronic diseases are given Table 2.

Table 2- Medical Foods in Global Market

Medical Food	*Composition*	*Efficacy*	*Findings*	*Reference*
ALZHEIMER				
Axona	Caprylic triglyceride (Medium chain triglycerides), caseinate, maltodextrin, whey protein, soy lecithin, magnesium phosphate.	Provides an energy source that the brain can use as an alternative to glucose to support the formation and function of synapses in the brain.	Ketone bodies occurring from the metabolism of medium chain triglycerides induce hyperketonemia, and thus ensure an alternate glucose substrate.	Sharma et al. 2014
Souvenaid	Omega-3 fatty acids, vitamin B_{12}, vitamin C, uridine monophosphate, choline, phospholipids, vitamin E, vitamin B_6, and folic acid.	The components in Souvenaid are effective in forming synapses between cell membranes.	Souvenaid has been scientifically proven to lead to improvements when taken daily for 3 years in the early diagnosis of Alzheimer's disease.	Soininen et al. 2021
Prevagen	Apoaequorin, vitamin D_3, microcrystalline cellulose, maltodextrin, magnesium stearate, salt, sugar, soy peptones, and modified corn starch.	Apoaequorin is a photoprotein naturally found in jellyfish. It improves memory, thinking speed, and overall cognition	It is thought that the calcium-binding ability of Prevagen is beneficial in preventing forgetfulness. This is because calcium disorder plays a part in the onset and progression of AD.	Grossman et al. 2022
Cerefolin	L-methylfolate calcium (Metafolin), methylcobalamin, algae powder, N-acetylcysteine.	L-methylfolate, an activated folate, influence memory, and protecting cognitive health.	Cerefolin is a prescription dietary supplement containing B vitamins. It is aimed at preventing and/or treating memory issues and forgetfulness caused by vitamin B12 and/or folate deficiency.	Spence et al. 2017
CANCER				
Nutrisource® Fiber	Partially hydrolyzed guar gum, soy, milk, and egg products.	It ensures soluble fiber to support digestive health and intestinal system and can be mixed with pudding, yoghurt, juices etc.	It should be used under the supervision of a physician to ensure that the ingredients do not affect the patient's health or cancer treatments.	Ravasco 2019
Medtrition ProSource	Water, protein (from collagen hydrolysate and whey isolate), maltodextrin, fructose, phosphoric acid, natural flavors, L-tryptophan, and milk.	The product, which is lactose-free and gluten-free, and contains 10 grams of protein, can be consumed orally or by tube.	Enriched medical foods as nutritional content are important for patients who have difficulty in swallowing in the last stages of cancer.	Liu et al. 2018
Boost® Nutritional Pudding	Maltodextrin, canola, high oleic sunflower and corn oil, milk protein concentrate, modified cornstarch, riboflavin, ß-carotene, other vitamins and minerals.	It is produced to supply energy with 230 nutrients to facilitate the conversion of food into energy. It does not contain any artificial sweeteners.	Antioxidants, such as vitamins C and E, bind free radicals and prevent them from reacting with healthy cells. Therefore, antioxidant-rich formulas are recommended for cancer patients receiving chemotherapy.	Imran et al. 2020
Impact Advanced Recovery®	Water, sugar, calcium caseinate (milk), fish oil (anchovy, sardine), citric acid, maltodextrin, ß-carotene, vitamin K_1, biotin, vitamin D_3, vitamin B_{12}, riboflavin.	This formula can help patients recover quickly after surgery and prevents the harmful effects that may occur due to malnutrition.	The importance of medical foods and supplements that strengthen the immune systems of cancer patients during the difficult treatment process is increasing.	Chen et al. 2021

Table 2(Continued)- Medical Foods in Global Market

Medical Food	*Composition*	*Efficacy*	*Findings*	*Reference*
CMD				
Vitabite	Lactose (milk), vegetable oil (fractionated palm kern oil), sugar, natural and artificial flavoring, carob flour, soy lecithin, and nuts.	A chocolate with high energy and low protein content is preferred for patients who require a protein-restricted diet due to an IEM.	The consumption of Vitabite, whose compositions are appropriately formulated for the disease, positively affects the course of the disease.	Rocha et al. 2021
PKU Start™	Carbohydrate, fat, essential and non-essential amino acids, trace elements, vitamins, arachidonic acid, docosahexaenoic acid, and minerals.	It is phenylalanine free formula food for PKU and must be used under doctor's supervision.	It is very important to use specially formulated medical foods that do not contain phenylalanine in order to prevent neurological diseases that may occur due to disease.	Van Calcar 2022
SMA LF®	Glucose, sunflower oil, soya lecithin, citric acid, phenylalanine, antioxidants (tocopherol-rich extract, ascorbyl palmitate), and L-carnitine	It is a lactose-free medical formula for babies with lactose intolerance. It is suitable for babies up to 18 months.	Lactose-free formulas are available to meet health and nutritional needs lactose intolerant. Reduced-lactose and lactose-free formulas can affect the course and reduce the duration of diarrhea.	Dipasquale et al. 2020
Similac NeoSure	Non-fat milk, corn syrup solids, lactose, soy oil, whey protein concentrate, coconut oil, ß-carotene, lutein, potassium citrate, inositol, calcium carbonate, and soy lecithin.	It provides comprehensive nutrition for babies born prematurely (<37 weeks). This special formula has increased protein, vitamins, and minerals.	Nutrition can be difficult for many premature babies. At this point, it is crucial to produce medical food that babies can easily consume with premature formulas.	Lubbe 2018
DIABETES				
Diabetisource® AC	Water, corn syrup, soy protein, canola oil, green pea, green bean puree, and less than 2% of fructose, peach puree, FOS (soluble fiber), orange juice, refined fish oil, guar gum (soluble fiber), and soy fiber (insoluble fiber)	It is a tube feeding mixture that includes pureed fruits and vegetables to provide a source of carbohydrates for the diet management of diabetes.	In recent years, has become a growing global concern. The use of formulas rich in omega-3 fatty acids in diabetes reduces the risk of complications and prevents the occurrence of side effects that may arise with the use of medical drugs	Gao et al. 2020
Glytrol®	Water, maltodextrin, calcium-potassium caseinate (milk), modified corn starch and less than 2% of canola oil, safflower oil, pea fiber, FOS, soy lecithin, inulin (from chicory), L-carnitine, vitamins and minerals.	Glytrol® is medical food including easily digestible carbohydrate mixtures to regulate blood glucose. It contains soluble prebiotic fiber admixtures to promote a healthy digestive system.	Research studies show that the high fiber content of the diet has a high potential for preventing Type-2 diabetes. Therefore, this medical food is effective in diabetes management.	Torres et al. 2020
Boost Glucose Control® Max	Water, milk protein isolate, and less than 2% of sunflower oil, vitamins and minerals, cellulose gel, inulin, salt, calcium caseinate, whey protein concentrate, sucralose, carrageenan, and vanilla extract.	It contains 30 g of protein. For this reason, it is effective in preventing muscle weakness and keeping the fasting glucose level in balance.	It is clinically proven to produce a lower blood sugar response as a normal nutritional drink in patients with Type-2 diabetes.	Moore 2018
Betacell Glucofix	Cinnamon, gymnema, berberine, bitter melon and turmeric.	Glucofix is designed to regulate glucose metabolism, to provide ideal sugar values and to create an antioxidant source for the body.	Glucofix consists of a mixture of natural herbal ingredients that are effective on blood sugar. It is stated in various studies that the herbal materials in the product composition are effective in the treatment of diabetes	Awuchi 2019

CMD: Congenital metabolic disorder.

4. Conclusions

Chronic diseases last for an extended period of time, cannot be completely treated and, therefore, often require repeated treatments, and the extended use of pharmacological drugs. Standard treatments, while effective, come with a high financial cost and a range of side effects, including weight gain, hypertension, peripheral edema, anemia, nephropathy, and gastrointestinal issues. As an alternative approach, medical foods appear to be a promising avenue in the management and treatment of chronic diseases. Medical foods, formulated specifically for the treatment of certain diseases or disorders, offer a distinct advantage over conventional diets. When the nutritional requirements of a disease or condition cannot be adequately met through a regular diet alone, the use of medical foods becomes imperative. Despite their potential, the awareness of medical foods in society remains insufficient, emphasizing the need for further research to bridge this knowledge gap. This review has aimed to elucidate the term of medical food and underscore its importance by providing illustrative examples of its application in the treatment of various chronic diseases, including neurodegenerative diseases, anxiety and sleep disorders, pain syndromes, cancer, congenital metabolic disorders, and diabetes. The need remains to develop new medical food prescriptions and increase commercial production as natural alternatives to costly pharmaceutical products for both public health and the current gaps in literature. It is evident that more comprehensive studies are required to raise societal awareness regarding the vital role of medical foods in treating chronic diseases effectively through dietary intervention. The recommendation from the authors is to prioritize future exploratory and meta-analysis studies in this field. This approach aims to achieve a more precise estimation of the global impact on the health of patients and individuals. In addition, legal procedures for the production, distribution and processing of medical foods need to be detailed and there is a pressing need for specialized training programs to cultivate expertise in the field. These initiatives will not only ensure the adherence to regulatory standards but also contribute to the proficiency of professionals involved in the medical food industry.

Abbreviations

AD	Alzheimer's disease
ADA	American Diabetes Association
DASH	Dietary approaches to stop hypertension
DM	Diabetes mellitus
FDA	Food and Drug Administration
FSMPs	Foods for special medical purposes
GABA	γ-aminobutyric acid
CMD	Congenital metabolic disorders
KD	Ketogenic diet
MD	Mediterranean diet
PD	Parkinson's disease
PKU	Phenylketonuria
WHO	World Health Organization

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