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The benefits of terpenoids as functional foods for the management of type 2 diabetes mellitus

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Millions of people worldwide are living with type 2 diabetes, and the numbers are rising at an unsustainable rate. Furthermore, many of those with type 2 diabetes suffer from micro and macrovascular complications that limit their quality of life and longevity as well as impose a significant financial burden on individuals and health systems worldwide. Many individuals living with type 2 diabetes are reliant on oral medications or a combination of oral and injectable insulin as treatment and for multiorgan complications from unregulated and prolonged states of high blood sugar levels. Many of these medications are an obstacle to adherence to treatment due to their side effects, which include but are not limited to gastrointestinal discomfort, headaches, urinary tract infections, and hypoglycemia. For many of the uninsured or underinsured in the United States and in developing countries, the cost of these medications is an additional burden that determines their treatment adherence and leads to undesirable complications. These drawbacks to current pharmacological treatments have led to interest and research into various bioactive compounds and phytochemicals such as alkaloids, polyphenols, flavonoids, and terpenoids to use as functional foods to mitigate the advance of type 2 diabetes. This editorial focuses on terpenoids and aims to review certain compounds within the subclasses of terpenoids that are being researched for their effectiveness in treating type 2 diabetes and, thereby, their potential use as a functional food product.

Type 2 diabetes is regarded as one of the leading causes of death, with high rates of morbidity and mortality worldwide. Due to its microvascular and macrovascular complications, diabetes contributes to multiorgan and multisystem dysfunction that include but are not limited to neuropathy, nephropathy, cerebrovascular, and cardiovascular disease. There are many drugs available for the treatment of diabetes that can be taken orally, such as metformin, the first-line drug used by many. Adherence to anti-diabetic drugs can be difficult due to their many side effects.

Type 2 diabetes is fast becoming highly prevalent in developed and underdeveloped countries. According to the Centers for Disease Control (CDC), about 422 million people worldwide have diabetes, with the majority living in low and middle-income countries [1]. As of 2019, the American Diabetes Association (ADA) estimates the prevalence of diabetes in the United States to be around 11% of the population [2]. In 2022, Diabetes was America's seventh leading cause of death [2].

The advances in genetics in the last 40-50 years have led to new advances in the genetic etiology of many diseases, primarily diabetes. Type 2 diabetes is a complex condition characterized by a combination of genetic and environmental factors leading to insulin insufficiency, though not a complete lack of insulin. Studies show that the genetic component of type 2 diabetes seems "to be the result of the interaction of multiple genes scattered all across the genome [3]." Two genes, the calpain 10 (*CAPN10*) and transcription factor 7-like 2 (T- (*TCF7L2*), are identified as being associated with T2D [3]. The close association between genetic predispositions to metabolic disturbances and environmental factors is being studied across multiple disease processes, from behavioral health and substance abuse to chronic conditions such as diabetes.

Epigenetics studies how our behaviors and environment change the chromatin structure and function but do not change the genetic sequence [4]. Epigenetics helps researchers understand the biological explanations for the long-lasting impact of metabolic changes, as metabolite levels change and are sometimes maintained during cell division [4]. The change in the chromatin structure and function results in the ability of the gene to be read or not by turning it "off" or "on" through DNA methylation, histone modification, and non-coding RNA [4]. Three environmental and behavioral factors that affect the epigenetics of type 2 diabetes are diet, physical activity, and obesity, all of which are known to be closely associated with the ability to reverse the disease and the severity of the disease. Environmental exposures in vitro or early in life can also influence epigenetic changes. Factors such as maternal diabetes, maternal over or undernutrition, maternal exposure to pathogens, and an infant's exposure to pathogens affect critical metabolic organ development, body composition, stem cell populations, and the tissue function of offspring [4]. While people with insulin-dependent diabetes may not start out being insulin-dependent, if their blood sugars are uncontrolled and the disease progression is not managed well, they eventually may become insulin-dependent.

Type 2 diabetes is more prevalent in adults, and obesity is a leading risk factor; however, with the increase in obesity rates among adolescents and children, the increase in type 2 diabetes is also becoming a common occurrence in these age groups. The predominant characteristic of type 2 diabetes is the inability of the tissues to use insulin and or the relative lack of insulin production. Many people with type 2 diabetes can avoid medication with early intervention through exercise, weight loss, and diet modification. However, to achieve optimal blood glucose levels to mitigate future complications, antidiabetic medication is required. Metformin is the most common oral antidiabetic medication used as the first line of therapy for type 2 diabetes in the past century [5, 6]. It is known to lower blood sugar levels but has side effects that impair the gastrointestinal system. Along with metformin, there are around eleven classes of oral and injectable antidiabetic drugs with different pharmacokinetics and adverse effects. The adverse effects of antidiabetic medications inhibit patient adherence and compliance to therapy, resulting in long-term complications of type 2 diabetes that affect multiple organ systems.

Research fueled by interest in medicinal herbs has shown that many plant alternatives can produce blood glucose-lowering or antihyperglycemic effects. These alternatives belong to a class of compounds known as secondary metabolites. Secondary metabolites, unlike primary metabolites such as carbohydrates, amino acids, and nucleic acids, function as protective agents for plants and manifest in producing various flavors, aromas, and colors. A class of secondary metabolites called terpenoids has been used since ancient times by people groups in China and India by extracting these compounds for medicinal purposes, flavorings, food colorings, and essential oils [7]. The medicinal functions of these secondary metabolites are being explored as an alternative to many of the current biosynthetic pharmacological medications used as antidiabetic agents while carrying fewer adverse effects. Terpenoids are quickly becoming promising for potential use as functional foods. Functional foods contain numerous bioactive compounds and provide a broad range of health benefits, including reducing the risk of chronic diseases such as type 2 diabetes [8].

Terpenoids are the largest compounds found in almost all natural foods. They are derived from terpenes, simple hydrocarbons that are the largest secondary metabolites [7]. Terpenoids are abundant, chemically diverse, and produced from flowering plants [9]. Terpenoids are differentiated into subclasses based on their isoprene structures and carbon molecules [9]. This review article aims to explore various subclasses and specific compounds of terpenoids, their bioavailability, and specifically their therapeutic effects on type 2 diabetes, and their potential to be introduced as a functional food product.

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