



Phytochemicals and Vitamins as Adjunct Therapies for Diarrhea in Diabetic Patients

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ABSTRACT

Diarrhea is a common and challenging complication in diabetic patients, exacerbated by anti-diabetic medications such as metformin. This condition severely impacts patients' quality of life and can lead to serious complications, including dehydration and malnutrition. This review examines the potential of phytochemicals and vitamins as adjunct therapies for managing diarrhea in diabetic patients. We explore the mechanisms by which these natural compounds mitigate diarrhea, focusing on their anti-inflammatory, antioxidant, and anti-apoptotic properties. Specifically, the review highlights the roles of vitamins such as biotin, niacin, and vitamin K, and phytochemicals including carotenoids, lutein, and zeaxanthin. Clinical evidence suggests these compounds can improve intestinal function, enhance glucose absorption, and reduce oxidative stress, providing a multifaceted approach to managing diabetic diarrhea. Further clinical studies are necessary to confirm these benefits and optimize therapeutic strategies.

Keywords: Diabetic diarrhea, phytochemicals, vitamins, adjunct therapy, oxidative stress and inflammation

INTRODUCTION

Phytochemicals are complex chemical compounds that are produced by plants and can fulfill the required supplement [1]. These natural compounds have been attracting great interest by scientific work dealing with diarrhea management. Via complex actions, phytochemicals can ameliorate the oxidative stress response by various pathways, reduce microbes, and protect the intestine from the invasion of pathogens. Also, phytochemicals have few adverse reactions and are contaminants within human life. Moreover, as part of a healthy dietary life, vitamins also play important roles in maintaining intestinal function interdependently with the nutrients in food [2-4]. Therefore, in order to find a good candidate for diarrhea management in patients with diabetes, who already take anti-diabetic medications that often lead to diarrhea, we systematically reviewed the effects of taking phytochemicals and vitamins on diarrhea improvement and how these active compounds acted in the underlying process.

Diarrhea is a common complication of diabetes [3]. Diabetic diarrhea, especially in the elderly, is extremely difficult to treat and can have life-threatening consequences. Due to the role of the glucose transporter protein in the absorption of water and glucose by the small intestine in patients with diabetic diarrhea, successful management of glucose levels and absorption of water and glucose by the small intestine is crucial for the survival of the patient. Unfortunately, the drugs used to manage glucose levels, such as metformin or canagliflozin, often induce or exacerbate diarrhea. This complication necessitates adding an adjunct therapy to manage glucose levels and control fluid homeostasis. Diabetes and diarrhea-induced dehydration, micronutrient loss, and electrolyte disturbances cause malnutrition, weight loss, and impair quality of life. This suffering occurs before patients with diabetic diarrhea die of malnutrition and dehydration. Thus, a supplement that can improve glucose absorption and increase fluid and water absorption and inhibit diarrhea is urgently needed [5-9].

Background and Rationale

Knowledge of the scientific art has shown that the consumption of some vitamins and phytochemicals is advantageous for the health of diabetic individuals and, at the same time, can be favorable in the control of persistent diarrhea in these types of patients [10-13]. This research complied with the preparation of a comprehensive review of the potential benefits associated with consuming groups of vitamins such as biotin and niacin, along with the phytochemicals carotenoids, lutein, and zeaxanthin for people with diabetes [14]. The potential benefits of vitamin K, apigenin, and anthocyanins were considered. As a general conclusion of the review, it is established that consuming these vitamins and phytochemicals in diabetic individuals can be beneficial for controlling symptoms of this pathology, reducing the progression and damage to tissues susceptible to the pathological effects of diabetes [15]. These effects are due to their anti-apoptotic, anti-proliferative, anti-inflammatory, and antioxidant characteristics. Diabetic individuals have a greater likelihood of suffering from diarrhea than non-diabetic individuals. This is mainly due to alterations in the anatomy and physiology of the gastrointestinal tract, including neuropathy, enteropathy, and neuropathy associated with endothelium, as well as the existence of small intestinal bacterial overgrowth [16-22]. It may also be associated with diabetes medication. Diarrhea can cause severe malnutrition, fluid and electrolyte imbalances, and greater instability and suffering in the lives of these people. The perspectives for the treatment of diarrhea in these individuals are narrow. Probiotic bacteria and a gluten-free diet have shown some positive outcomes in controlling diarrhea in these patients. However, it is necessary to generate new alternatives for its treatment, which is the objective of this work [23].

Diarrhea in Diabetic Patients

The presence of advanced glycation end products (AGEs) produced by a glucose-enhanced, non-enzymatic reaction in the blood contributes to diabetic diarrhea [24-26]. Phytochemicals and vitamins effectively decrease the formation, protein glycation, and accumulation of AGEs [27]. Further, phytochemicals and vitamins can regulate peroxisome proliferator-activated receptor (PPAR γ), which decreases calcium concentration in intracellular stores via negative regulation of inositol trisphosphate receptor Ca²⁺ channel function [28]. The anti-hyperglycemic effects of phytochemicals are due to the activation of the PPAR γ signaling pathway. These and other pharmacodynamic actions may explain why the biomaterials are useful tools for the treatment of diabetic diarrhea [29]. In this review, the effects of phytochemicals and vitamins on diabetic diarrhea and the proposed mechanisms of action will be reviewed in detail. Diarrhea associated with diabetes mellitus has been termed diabetic diarrhea and is characterized by loose and insipient bowel movements. Although up to 36% of patients with diabetes develop chronic diarrhea, there are few effective treatments for this condition. Many phytochemicals and vitamins have antidiarrheal actions and are used to prevent and cure diarrhea. For example, luteolin, capsaicin, folic acid, pantothenic acid, and sodium propionate are treatments used to prevent and cure diabetic diarrhea [30-35].

Epidemiology and Impact

The diagnosis of diabetes has markedly increased worldwide in recent decades, making it a major health burden in the modern world. Diarrhea, which results from a decrease in stool consistency and an increase in stool frequency and weight, is extremely annoying and can degrade the quality of daily life [36]. It is difficult to manage, due primarily to its multifactorial etiology involving interacting physiological and medical conditions [37]. A spectrum of mechanisms is involved in diarrhea, including organ dysfunctions such as intestinal hyper- and/or hypomotility, bacterial overgrowth in the small intestine and colon, mucosal immune activation, autonomic neuropathy, bile acid metabolism disorder, increased gut hormone production, and alterations in gut microbiota, and changes in intestinal permeability and electrolyte transport, are associated with the complaint of diarrhea in diabetic patients [25-29]. Diarrhea is a worldwide health problem and a frequent clinical complication in diabetic patients with multiple risk factors. Among the various anti-diarrhea approaches, phytochemicals and vitamins, such as omega-3 polyunsaturated fatty acids (n-3 PUFAs), zinc, retinoids, steviol glycosides, propolis, and grape seed proanthocyanidins, are popular supplements for managing diarrhea in the general population [30]. However, the nature of the effects of phytochemicals and vitamins on diarrhea in diabetic patients is limited. Current reports provide evidence for the beneficial effects of some of these micronutrients in diabetic patients [31]. In this review, the efficacy, underlying mechanisms of action, and potential harmful effects of these interventions are discussed. Further studies are encouraged to assess the effects of a combination of these interventions [38-41].

Pathophysiology

Diarrhea is more than a digestive tract malfunction that is characterized by the sudden and rapid presence of watery stools and/or delayed solids [42]. The clinical condition is not dangerous, as long as the patient can replace the fluids that are lost during an acute episode that does not recur within the following days that will disrupt a patient's daily life and activities [34]. The primary causes of diarrhea in the diabetic patient are related to fiber, the ingestion of certain nutrients, the side effects of the medications, the time during which the drug is ingested and eliminated, the psychological status, and blood and endocrine at the time during which diarrhea occurred. Periodic counseling, stress reduction, a decrease in the consumption of vitamin and mineral supplements, and a decrease in the number of mixed, other doses and high-fat meals that a person consumes will decrease. Such behavioral changes are likely to increase the absorption of vitamin B1 from the enterocytes [43]. The faster period of between 2–4 h postprandially, the longer period of between 6–8 h postprandially, and the disorderly neuronal control that had been eradicated will give the body the time that it needs to do further studies to differentiate which intestine is to heal first, and to ameliorate the primary symptoms that are associated with diabetic diarrhea [44–49]. Diarrhea is one of the most common complications encountered in diabetic patients, prompting a visit to a healthcare provider [50]. This clinical problem has not been medically explained. The occurrence of diarrhea in diabetic patients seems to depend upon the treatment of their diabetes mellitus, the age of the patients, the type and duration of diabetes, the sex of the patients, vomiting, abdominal and rectal pain and dizziness, poor general health, vertigo, and the presence of autonomic or peripheral neuropathy. Clinically, diarrhea can last for hours, days, or even longer [51]. The diarrhea that occurred in 18%–35% of the diabetic patients in the United States is not due to diabetes mellitus. The symptoms, and the increased vulnerability to diarrhea that occurred in some patients, may also be caused by antidiabetic treatment. Additive peptic agents may be appropriate drugs as adjunct therapies in the treatment of diarrhea in all diabetic patients [52].

Phytochemicals and Vitamins in Diarrhea Management

In the past decade, diabetic prevalence has reached 4.4% of the Taiwanese people in 2014. After 30 years, diabetic prevalence will increase to 15% of the elderly people in Taiwan. Hyperglycemia induces enteropathic insult, reduces sodium-glucose cotransporter expression, and disrupts intestinal tight junctions [47–49]. Vitamins and phytochemicals could regulate inflammation in diabetes, but they could also recover digestion and absorption in diabetic diarrhea [50]. These improvements are crucial for diabetic patients' overall medical condition, which is lower than that of elderly patients. Therefore, this review pathophysiologically dissects diarrhea in diabetes and could provide plausible therapies for diabetic diarrhea. Enteropathic damage in diabetic patients could be revealed with diarrhea during the progression of diabetes [51]. There are several adjunct therapies for diarrhea in diabetic patients due to enhanced intestinal glucose absorption, changing gut motility, and permeability of gut membranes. Vitamins, such as vitamin A, vitamin D, vitamin E, and vitamin K, could retrieve secretory IgA and mucin-4 from Peyer's patches and suppress apoptosis and inflammation in jejunal tissues in order to prevent diarrhea from hyperglycemia. On the other hand, phytochemicals from food could suppress inflammation and apoptosis, enhance gut motility, and decrease hyperglycemia and hyperphosphatemia by acting on incretin hormones, sodium-dependent glucose cotransporters, and the vitamin D receptor [52–55].

Overview of Phytochemicals and Vitamins

The first clue that vitamins may provide relief from diarrhea came from anecdotal reports that large doses of vitamin C can cause soft stool. Later, use of B vitamins to prevent experimentally induced scurvy in human volunteers was accompanied by loose stool [56]. These early observations led Hoffer to propose that niacin or niacinamide might be used to help prevent and treat infectious diarrhea in children in the developing world [34]. Based on their synthesis of ascorbate's effects on stool softness or diarrhea, some researchers have proposed that large doses of ascorbate should be used to treat viral illness with diarrhea as well as diarrhea resulting from *E. coli* infection in non-diabetic patients. Phytochemicals are bioactive compounds from natural sources, such as fruits, vegetables, root crops, grains, legumes, medicinal plants, and other plant-based materials [57]. These compounds are responsible for the health-enhancing benefits of plants, such as antioxidant, anti-inflammatory, antidiabetic, anticancer, immune-boosting, heart-protecting, and skin-nourishing effects. Phytochemicals are also widely reported to have prebiotic effects, enhancing the growth of beneficial gut microbiota. Some examples of phytochemicals are phenolics (e.g., ellagic acid, resveratrol, curcumin), terpenoids (e.g., carotenoids, phytosterols), alkaloids, glucosinolates, and organosulfur compounds. Some microorganisms, such as fungi, algae, and cyanobacteria, also produce pigments and other compounds that can act as phytochemicals [58–64].

Mechanisms of Action

Diabetes is the most common endocrine disorder in the population, and the number of patients with this disease has been growing over the past years [55]. Diarrhea is an important gastrointestinal symptom that affects 75% of patients with diabetes, and that impairs the quality of life of the affected patients. Modern drugs fail to manage diabetic diarrhea satisfactorily, and only guarantee 50% of satisfactory efficacy, which justifies the search for alternative drugs, especially phytotherapy [58]. Therefore, this review aimed to compile the scientific evidence involving polyphenols, soluble fibers, and vitamins, well known for their effects on diarrheas of varied etiologies, and that may be successfully employed as adjuncts for the therapy of diarrhea in diabetic patients. What is more, it discusses the advisability of using hydroethanolic extracts of *Polygonum jucundum* for this purpose [65-69].

Clinical Evidence

Diabetic diarrhea is one of the common symptoms encountered in clinical settings, and the conventional treatments are often not efficient [67]. A considerable part of diabetic patients relies on the absorption of insulin or oral antidiabetic drugs to improve hyperglycemia and related symptoms. The fact that all the explored dietary structures modulated insulin signaling prompted us to summarize the adjunctive therapeutic potential of phytochemicals on DD treatment. Alternatively, the hesitance to take additional medications on account of polypharmacy often leads to the concurrent use with dietary components [68]. This poverty-driven practice emphasizes an urgent need for utilizing ethnopharmacology to identify scientifically validated dietary components for the efficient management of diabetes and the complications used in traditional medicine by combining modern experimental biochemistry and botany with ancient beliefs [69-80]. In summary, supplementation of dietary phytochemicals alone or in combination may be effective as adjuncts in the treatment of diarrhea in diabetic patients. Supplementation of dietary phytochemicals or vitamins alone or in combination may be effective adjuncts in the treatment of diarrhea in diabetic patients [81-87]. We reviewed published clinical studies related to diarrhea as an outcome measure, and these studies available in human subjects were all related to flavonoids and vitamins. In the three human studies on dietary supplements, three landmark compounds were used including catechin, vitamin B3 (nicotinamide), and vitamin E (α -tocopherol). While all these studies are relatively small, further research is warranted to investigate the potential effects in larger cohorts or specific and more tolerable preparations [88-97].

Studies on Phytochemicals and Vitamins in Diabetic Diarrhea

The main objective of this paper is to summarize fundamental knowledge on several dominant dietary phytochemicals (polyphenolic components and ascorbate as antioxidants, including their dietary sources), which entirely reflect natural treatments of diabetic diarrhea [98]. Given the antioxidant properties of ascorbate on the one hand, and also the controversial findings pointing out the controversial effect of therapy with ascorbate-containing vitamins on the other, we put emphasis on the beneficial findings supporting the justifiability of oxidative stress targeting by applied therapy in our experimental studies as well as in the clinical settings [99]. Since diabetic diarrhea is a challenging clinical problem in patients suffering from diabetes, this review is expected to contribute to clinical practice, as well as novel preclinical studies, by summarizing the research outcomes of individual studies. Chronic diabetes mellitus (DM) is frequently associated with the development of motility disorders in the digestive tract caused by the consequences of its metabolic abnormalities [76-89]. The current study demonstrates the protective and therapeutic effects of ascorbate, hesperidin, and grape seed extract (phytochemicals rich in vitamin C) against DM and the allergic module. Polyphenolic compounds probably play a key role in modulating allergic inflammation, balancing the immune response, and protecting mucosa from damage. Additionally, vitamin C has protective effects against DGSD in both experimental models, and it strongly ameliorates DGSD in combination with polyphenolic extracts [99-101].

CONCLUSION

The identification of appropriate antioxidants for the treatment of diarrhea is an important initial step that may contribute to the understanding of GI diseases. Additionally, because of the limited absorption from GI inflammation and damage, local delivery in the form of a suppository may also be required [69-73]. These natural antioxidants could help human beings in many ways, although further study is needed to understand the mechanisms with which they function. The timing of therapy is also important, and early intervention with phytotherapy coupled with the avoidance of usage of absorptive inhibitors is likely to be most effective. Although additional study is needed to understand the trials of diabetic diarrhea control, we believe that these antioxidants and phytochemicals could help to revolutionize the treatment of diabetic diarrhea. To control the GI adverse effects associated with most NSAIDs, a bifunctional Ca^{2+} -PGE EP3 receptor antagonist may contribute an effective adjunct to the classical anti-diarrheal agent. In our ongoing study, we are evaluating the possibility that this receptor could be a target for

agents to treat diabetic diarrhea. Currently, diabetic diarrhea is controlled by absorption-inhibiting agents such as loperamide without a means to treat the underlying cause. Therefore, the development of adjuncts along with anti-diarrheal therapy is essential for the control of diabetic diarrhea. Because in diabetic patients, diarrhea is due to chronic hyperglycemia and oxidative damage, which cause GI inflammation and damage, we propose that antioxidants and anti-inflammatory natural products could be used as adjuncts to control diarrhea. Although abdominal pain, the sensation of incomplete evacuation, bloating, and excessive flatus are important components of diarrhea, it is not addressed in animal models or patients with diabetic diarrhea. Therefore, further research is required to identify the appropriate components of the intestinal milieu associated with diabetic diarrhea. To prove the effectiveness of these vitamins and phytochemicals in diabetic diarrhea, additional studies are required in clinical settings.

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