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REVIEW ARTICLE

Polyphenols as Suitable Control for Obesity and Diabetes

Dasha Mihaylova[1], Aneta Popova[2], Iordanka Alexieva[2], Albert Krastanov[1] and Anna Lante[3,*]

[1]*Department of Biotechnology, University of Food Technologies, 26 Maritza Blvd., Plovdiv 4002, Bulgaria*
[2]*Department of Catering and Tourism, University of Food Technologies, 26 Maritza Blvd., Plovdiv 4002, Bulgaria*
[3]*Department of Agronomy, Food, Natural Resources, Animals and Environment – DAFNAE, University of Padova, Viale Università 16, Agripolis 35020, Italy*

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Abstract:

Modern life is characterized by physical inactivity and poor food choices, which is often a prerequisite for unhealthy weight gain and overweight/obesity. These factors unlock the emergence of a number of diseases including diabetes, cardiovascular problems, different types of cancer, *etc*.

The pursuit of scientists to seek strategies to prevent, relieve and cure the patient leads to the usage of natural compounds of potential beneficial effect. Polyphenols are a large group of naturally occurring secondary metabolites mainly found in plants and beverages. The presence of these secondary metabolites seems to decrease the manifestation of miscellaneous disease-causing symptoms.

The purpose of this review is to synthesize information about polyphenols and their potential in controlling obesity and diabetes. Polyphenols are considered as health-beneficial sources and thus could be involved in novel strategies for preventing diabetes and obesity complications.

Keywords: Polyphenols, Diabetes, Obesity, Nutrition, Functional foods, Foods choices.

1. INTRODUCTION

Nutrition is an important health factor, as the main recommendations for achieving it include the consumption of a variety of foods. Nutritional knowledge is gained in the early years of development, thus promoting healthier choices at an early stage of habitual development may lead to minimizing the display of 21st century diseases *i.e.* diabetes type 2, obesity, heart complications, teeth decay, *etc*. with the help of adequate dietary assessment and food choices relevant to nutritional requirements.

A well-balanced diet usually means the provision of the required nutrients for the different physiological groups. People need a wide variety of nutrients in order to attain the anthropometric reference standards and lead an active life. Nutrient balance most often means an equilibrium of the input and output calories. In order to make recommendations, nutrient data is needed to propose a customary intake.

International experience has shown that food safety issues, as well as providing full and healthy food available to the general population, reducing nutrient deficiencies, morbidity and mortality from a number of Noncommunicable Diseases (NCDs) - cardiovascular disease, obesity, diabetes, hyperlipoproteinemias, certain cancers, *etc*., can be best addressed by implementing a unified national food and nutrition policy with coordinated cross-sectoral activities [1].

According to the WHO, noncommunicable diseases kill 40 million people each year, equivalent to 70% of all deaths globally. People of all age groups, regions and countries are affected by NCDs but raised blood pressure; overweight/obesity; hyperglycemia (high blood glucose levels); and hyperlipidemia (high levels of fat in the blood) are

* Address correspondence to this author at the Department of Agronomy, Food, Natural Resources, Animals and Environment – DAFNAE, University of Padova, Viale Università 16, 35020, Agripolis, Italy; Tel: +39 049 8272920; E-mail: anna.lante@unipd.it

the four key metabolic changes that increase the risk of NCDs [2]. Therefore the European Commission established a coherent and comprehensive Community Strategy to address the issues of overweight and obesity and related health issues [3] as well as the EU Action Plan on Childhood Obesity 2014-2020 [4].

2. DIABETES AND OBESITY

Diabetes (Diabetes *mellitus*) is a serious, lifelong, progressive endocrine disorder, which can influence the entire body. It is characterized by hyperglycemia (high blood sugar (glucose) levels in the body) due to absolute or relative insulin production dysfunction. Diabetes leads to serious consequences *i.e.* limb amputation, kidney failure, heart attack, stroke and blindness. In 2016, there are 3.7 million registered deaths due to diabetes. The three main types of diabetes are type 1 (10% of all diabetes), type 2 (85% of all diabetes) and gestational diabetes. 6th April 2016 was announced World Health Day: Beat diabetes, and according to the WHO global diabetes info gram, 422 million adults have diabetes, which means that every 11th person has diabetes [5].

Type 1 diabetes is an auto-immune condition in which the cells that produce insulin are destroyed so lifelong treatment with insulin is required to prevent death. Type 2 diabetes, which may remain undetected for many years, occurs when the body either stops producing enough insulin for its needs or becomes resistant to the effect of insulin produced. The condition is progressive requiring lifestyle management (diet and exercise) at all stages. In this respect, functional foods may be a promising strategy to address this issue as reported by Tessari and Lante [6]. These authors studied the metabolic effects of a specifically designed functional bread, low in starch and rich in fibers in people with type 2 diabetes mellitus. Over time, most people with type 2 diabetes will require oral drugs and/or insulin. Obesity is only associated with type 2 diabetes and according to the WHO report every 3rd person is overweight and every 10th is obese. The physical inactivity and unhealthy diet are the main contributors to being overweight and obese.

Women with gestational diabetes are at an increased risk of complications during pregnancy and at delivery. It can occur at any stage of pregnancy, and does not usually cause any symptoms, but is more likely at 20 weeks or later. Screening for gestational diabetes is between weeks 8 to 12 when a doctor evaluates the risk of gestational diabetes. Women and their children are also at increased risk of type 2 diabetes in the future.

The likelihood and severity of type 2 diabetes are closely linked to Body Mass Index (BMI). A BMI above 30 is an alarming symptom. The epidemic of diabetes has major health and socioeconomic impacts, especially in developing countries. Obese people are seven times more likely to have diabetes, while overweight people are at only three times greater risk compared to those of healthy weight [7].

There are several theories of why obesity is linked to diabetes type 2. One of them states that abdominal obesity may cause fat cells to release pro-inflammatory chemicals, which lower the body sensitivity to insulin and disrupt its ability to properly respond to insulin [8]. Scientists claim that obesity is most likely to trigger changes to the body's metabolism that cause fat tissue to release increased amounts of fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors that are involved in the development of insulin resistance [9]. Studies with the skeletal muscle of type 2 diabetic humans demonstrate impaired insulin activation of the IRS-1/PI3K/Akt signaling pathway, which is a critical step in the regulation of glucose transport in response to insulin [10].

There is a clear association between increasing age and greater diabetes prevalence. In the UK, less than 2% of people aged 16-34 years are estimated to have diabetes compared to 5.1% of people aged 35-54 years, 14.3% of people aged 55-74 years and 16.5% of those aged over 75 years [11].

Both obesity and type 2 diabetes are strongly associated with an unhealthy diet and physical inactivity. Physical and social environments are important influences on diet and physical activity behavior along with interrelated economic, psychological and cultural factors [12]. Obesity and diabetes are characterized by both insulin resistance and endothelial dysfunction as increased artery intima-media thickness, and increased vascular stiffness leading to substantial increases in cardiovascular morbidity and mortality [13, 14].

Obesity is due primarily to an imbalance between caloric intake and activity. Obesity has rapidly become a serious public health concern. Obesity and overweight are different stages of unhealthy weight. Overweight people are those with BMI between 25 and 30, while obese ones are those with BMI over 30. This means that obese people have accumulated excessive fat tissues in their body. Social inequalities in overweight and obesity are strong, especially among women [15]. Absolute social inequalities were largest in Hungary (11.6% obese rates in men and 18.3% in women) and Spain (10% obese rates in men and 18.9% in women) across the education spectrum. Relative inequalities with poor education (largest in France and Sweden) showed that poorly educated men are 3.2 and 2.8 times more likely

to be obese than men with the higher education. According to Devaux and Sassi [15], USA and England had the highest rates of obesity and overweight. Obesity levels are expected to be particularly high in the United States (47%), Mexico (39%) and England (35%) by the year 2030.

On the contrary, the WHO foresees a weaker increase in obesity and overweight in Italy and Korea, with obesity rates projected to be 13% and 9% in 2030, respectively. The level of obesity in France is projected to nearly match that of Spain, at 21% in 2030. Obesity rates are projected to increase at a faster pace in Korea and Switzerland where rates have been historically low [16].

3. POLYPHENOLS AND HUMAN HEALTH

Polyphenols are a large group of naturally occurring secondary metabolites mainly found in plants (fruits, vegetables, cereals *etc*.) and beverages. They have a wide variety of diverse structures, which belong to two main classes: non-flavonoids (particularly phenolic acids, stilbenes and lignans) and flavonoids, which are characterized by the basic C_6-C_3-C_6 skeleton (Fig. **1**). The two aromatic rings within the flavonoid structure are linked by a heterocyclic ring, which differs in the degree of oxidation and leads to the following sub-classifications: flavones, flavonols, isoflavones, flavanones, anthocyanins and flavanols, usually called catechins. Some of the widespread representatives of natural phenolic compounds are kaempherol (flavonol), quercetin (flavonol), luteolin (flavone) and resveratrol (stilbenoid) (Fig 1). Both luteolin and quercetin are associated with their protective effects on diabetic nephropathy and retinopathy [17, 18]. Treatment with quercetin has the ability to abrogate hypertension progression induced by diabetes together with amelioration of the exaggerated contractile responses of aorta. Studies have confirmed the efficacy of resveratrol in type 2 diabetes. Furthermore, *in vitro* and *in vivo* studies have described resveratrol as a potent activator of histone deacetylase Sirtuin1 (Sirt1) [19].

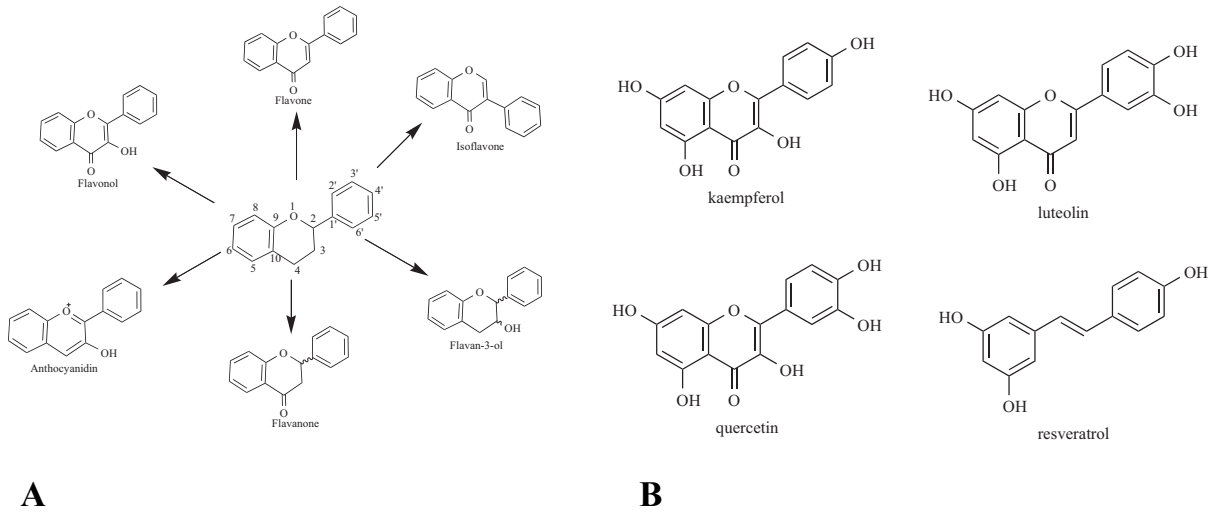

Fig. (1). Structure of flavonoid: **A** – structure of flavonoid skeleton; **B** – chemical structures of some dietary flavonoids.

Polyphenols are generally involved in defense against ultraviolet radiation or aggression by pathogens. In food, they may contribute to the bitterness, astringency, color, flavor, odor and oxidative stability. Because of their possible beneficial effects on human health, polyphenols and other food phenolics are still increasing their scientific interest. Studying the dietary polyphenol intake in Europe, Zamora *et al*. [20] reported a large number of dietary individual polyphenols consumed and high variability of their intakes between European populations, in particular between Mediterranean (MED) and non-MED countries. The main polyphenol contributors were established to be phenolic acids (52.5-56.9%), except in men from MED countries and in the UK health-conscious group where they were flavonoids (49.1-61.7%). Coffee, tea, and fruit were the most important food sources of total polyphenols. Zamora *et al*. [20] reported that the consumption of 437 different individual polyphenols (including 94 consumed at 1 mg/day) had health-promoting properties. The most abundant ones according to the above-mentioned authors were caffeoylquinic acids and the proanthocyanidin olygomers and polymers [20].

The polyphenol content of foods is strongly influenced by the methods of culinary preparation. The process of

peeling of fruits and vegetables, for example, can significantly reduce polyphenol content, not only because these substances are often present in high concentrations in the outer parts, but also due to enzymatic browning which occurs after the breakdown of plant cell structure and the subsequent interaction between enzyme Polyphenol Oxidase (PPO) and substrate during post-harvest stages leading to color alteration and antioxidant degradation as a consequence of the phenolic oxidation. For this reason, the research of new eco-friendly systems for controlling PPO activity is focused on innovative non-thermal technologies and bioactive compounds to replace the conventional thermal treatments and traditional additives which could impair the sensory, nutritional and health properties of food products [21 - 26].

The process of heating, also, has an outstanding effect. About 75% of the initial quercetin content in tomatoes and onions is lost after boiling for 15 min, 65% after cooking in a microwave oven, and 30% after frying. Potatoes contain up to 190 mg chlorogenic acid/kg mainly in the skin [27]; so, an extensive loss occurs during culinary processes, and as a result, no remaining phenolic acids are found in French fries [28]. Also, extraction by heating or boiling of green tea leaves seems to increase the epimerization of tea catechins and therefore a lower recovery of bioactive compounds [29].

Polyphenols, of natural origin, are potential sources of various beneficial effects - anti-obesity, anti-diabetic, antihypertensive, anti-hyperlipidemic and anti-inflammatory effects [30]. Commonly consumed polyphenols such as green tea catechins, especially epigallocatechin gallates, as well as resveratrol and curcumin are considered to impact obesity and obesity-related inflammation. Dietary polyphenols are demonstrated to reduce viability of adipocytes and proliferation of preadipocytes, suppress adipocyte differentiation and triglyceride accumulation, stimulate lipolysis and fatty acid β-oxidation, and reduce inflammation. Furthermore, polyphenols can modulate signaling pathways including the adenosine monophosphate-activated protein kinase, peroxisome proliferator-activated receptor γ, CCAAT/enhancer binding protein α, peroxisome proliferator activator receptor gamma activator 1-alpha, sirtuin 1, sterol regulatory element binding protein-1c, uncoupling proteins 1 and 2, and nuclear factor-κB that regulate adipogenesis, antioxidant and anti-inflammatory responses [31]. Black tea polyphenols inhibit the emulsion of droplets and the activity of pancreatic lipase, α-amylase and glucosidases [32]. Green tea was reported to reduce significantly body mass index and waist circumference. Furthermore, Vernarelli and Lambert [33] compared the intake of flavonoids with the Body Mass Index (BMI) and waist circumference. The authors established that higher flavonoid intake influenced lower BMI and waist circumference, which could contribute to the health issues associated with obesity as a higher risk for many chronic diseases. Cocoa supplementation and cinnamon reduce blood glucose. Soy isoflavones, citrus products, hesperidin and quercetin improve lipid metabolism [34].

Increased consumption of polyphenol-rich foods and beverages was associated with a reduction of cardiovascular diseases [35 - 37]. Furthermore, among polyphenol-rich foods and beverages, Arab *et al*. [38] associated a higher intake of green or black tea with a lower risk of stroke and type 2 diabetes [39]. Increasing flavonoid intake also appeared to be a way to reduce moderately the risk of disease as stroke [40]. Additionally, flavonoids have been reported to provide both antioxidant and antithrombotic properties [41, 42].

Some of the most common sources of dietary polyphenols are given in Table **1**.

Table 1. List of some major polyphenol compounds of plant origin.

Food Group	Some Major Sources of Polyphenols
Fruit	oranges, apples, grapes, peaches, grapefruit juice, cherries, blueberries, pomegranate juice, raspberries, cranberries, black elderberries, blackcurrants, plums, blackberries, strawberries, apricots
Vegetables	spinach, onions, shallots, potatoes, black and green olives, globe artichoke heads, broccoli, asparagus, carrots
Whole grains	whole grain wheat, rye, and oat flours
Nuts, seeds, and legumes	roasted soybeans, black beans, white beans, chestnuts, hazelnuts, pecans, almonds, walnuts, flaxseed
Beverages	coffee, tea, red wine
Fats	dark chocolate, virgin olive oil, sesame seed oil
Spices and seasonings	cocoa powder, capers, saffron, dried oregano, dried rosemary, soy sauce, cloves, dried peppermint, star anise, celery seed, dried sage, dried spearmint, dried thyme, dried basil, curry powder, dried ginger, cumin, cinnamon

Numerous scientific reports give evidence regarding the intake of polyphenols (and their food sources) and the influence on related-diabetes risk factors. Several studies highlight the anti-obesity effects of polyphenol-rich diets affecting the ability of polyphenols to interact, directly or indirectly, with adipose tissues (preadipocytes, adipose stem cells, and immune cells). However, obesity and diabetes nowadays are among the major diseases of health concern, which provoke the scientific interest. Obese individuals are at a greater risk for the development of several pathologies

including diabetes *etc*. [43], which show the relationship between both.

Polyphenols (p-coumaric acid, m-coumaric acid, ferulic acid and hydroxyhippuric acid) could boost insulin sensitivity, slow down the rate, the digestion, and absorption of sugar [44]. Recent studies associate the decrease of the insulin resistance to type of flavonoid (flavan-3-ols) and revealed the flavonoids as the type of polyphenols most often associated with a lower risk for type 2 diabetes [45, 46]. Unfortunately, in order to state concrete flavonoids conducting large-scale, well-designed, and population-based studies is required in the future [47].

Lambert *et al*. [48] evaluated a synergistic effect of grape polyphenols supplementation combined with the exercise by increasing muscle lipid oxidation and sparing glycogen utilization, which resulted in enhancement of endurance capacity based on the intensification of their individual metabolic effects. The reported, underlined the importance of both dietary and physical training recommendations in insulin resistance condition. Furthermore, the use of a combination of polyphenols is proposed to treat diabesity complications in view of reported synergisms of resveratrol when combined with quercetin or resveratrol plus quercetin and genistein in *in vitro* studies [49, 50].

However, it is difficult such beneficial effects to be proven in *in vivo* experiments. Bruckbauer *et al*. [51] stated synergisms during *in vitro* and *in vivo* approaches with other compounds, such as a leucine metabolite, methylxanthines and metformin as potential therapeutic agents in obesity and diabetes prevention and management.

Resveratrol, commonly found in grapes, berries, and some nuts, is one of the most commonly used nutritional supplement polyphenolic compound with potent antioxidant activity. Resveratrol is particularly interesting to the scientific field because of its health benefits associated with diseases such as cancer, type 2 diabetes, cardiovascular disease, and neurological conditions [52]. This polyphenol gains worldwide interest when reports of its cardio protective effects originating from red wine become available [53]. Resveratrol was reported as a potential obesity treatment as it can lead to lowering body weight [54]; reducing the fat mass by inhibiting adipogenesis. However, the data on long-term resveratrol toxicity is contradictious [55, 56] even though clinical trials proved a well-tolerated and pharmacologically safe dosage of up to 5 g/day [57]. Yet, the research of its bioavailability and effectiveness *in vivo* is essential thus, the current data are still insufficient.

Retinopathy, nephropathy and neuropathy are only some of the serious health concern problems diabetes can cause in the long term. Various anthocyanins, flavonoids and other polyphenolic compounds have been found with potential preventive effects for improving the quality of life in the patients. Anthocyanins and anthocyanins-rich extracts have been reported as potential to alleviate some pathologic conditions because of diabetes [58]. Flavanols, on the other hand, were assumed as potential to improve cognitive disorders and cholinergic dysfunction related to diabetes and other secondary consequence of changes in the nervous system induced by hyperglycemia and diabetes oxidative stress and, as for example, quercetin was reported to improve mental function and memory in rats with diabetes [59].

Numerous literature data support the natural phenolic compounds as health-beneficial sources, furthermore, functional foods and dietary supplements containing phenolic compounds gain extensive publicity and interest as a contemporary inexpensive therapeutic approach [60]. Based on the increased scientific interest, various research studies are involved in the evaluation of the polyphenol dietary sources potential of fruit, vegetables, herbs and spices [61 - 64]. All this is a prerequisite polyphenols to be involved in novel strategies for preventing diabetes and obesity complications [65].

Certain dietary components and over 800 plants were claimed to help prevent or moderate metabolic syndrome by assisting the body homeostasis mechanism [66]. Phenolic beneficial effects are exacted from plants belonging to taxonomic families such as Moraceae, Fabaceae, Asteraceae, Pyrus, Lauraceae, Lythraceae, and Malvaceae [67].

Possible pathways of polyphenol metabolism by intestinal bacteria [68] have been investigated in several research projects, highlighting the significant evidence of the diet-derived bioactive metabolites produced by gut microbiota, with a particular emphasis on polyphenols and their potential impact on human health. In this regard, the characterization of microbial strains, suitable for the fermentation process of plants historically recognized by folk medicine, could be used to design new functional food with added beneficial attributes [69, 70]. Furthermore, other health beneficial functions associated with obesity symptoms improvement have been associated with maintaining normal gut microbiota [71 - 73].

Microbial engineering is one of the alternative approaches, which can meet the global demand for natural products in an eco-friendly manner [74]. Metabolic engineering of microorganisms could provoke microbial synthesis of many plant polyphenols. However, recent technological innovations such as the development of biosensor-driven directed

evolution approaches could enable the rapid engineering of microbial host strains for providing more precursor molecules to increase polyphenol synthesis [75, 76]. New molecular techniques, as well as approaches and concepts from synthetic biology, could be also employed to harmonize endogenous and heterologous pathways for maximizing product titers and host could improve rerouting of carbon fluxes to and through polyphenol-providing pathways of interest [77, 78].

In particular, nanotechnological approaches could help to overcome the pharmacokinetic issues of bioactive compounds by providing improved bioavailability, overcoming the first-pass metabolism and trounce enterohepatic recirculation, by protection against degradation, enhancement in intracellular penetration and control delivery, and by reducing potential toxicity [79]. Stilbenes can be therefore used in a natural form for prevention or in their pure form of therapy, for which large doses or nanoformulations are recommended [80].

4. FUTURE INSIGHT AND PERSPECTIVE

An intake of above 600 mg/d of polyphenols within a healthy dietary pattern, rich in fruits and vegetables has been recommended. Future clinical and epidemiological studies are warranted to replicate these associations, especially using biomarkers, in other populations. The advances in polyphenols research will be important to make dietary recommendations for developing effective public health policies and for improving the autonomy and quality of life of older people [81].

In addition, epidemiological studies and associated meta-analyses recommended the long-term consumption of rich in plant polyphenols diets as significant protection against the development of cancers, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases [34, 82].

The measurement of phenolic metabolome in humans would point out which phenolic molecules are present in the plasma/urine of humans followed the intake of polyphenol-rich foods (green tea, cocoa, citrus, apple) and should facilitate the provision of clearer evidence on the relations between food composition and risk of major chronic diseases such as cancer, cardiovascular diseases or diabetes and shed new light on the causes of such diseases [83]. The future research in this field should focus on the actual contribution of dietary polyphenols, new cellular and molecular targets and on clarification of *in vivo* biotransformation processes, including analyses of the biological effects of each single metabolite.

Applying good practices for health promotion and disease prevention through conscious nutritious choices and fostering a positive attitude towards nutrition. Sustainable diets are a key factor to long-term wellbeing and healthy lifestyle. Deepening consumer's knowledge will create healthy eating patterns and therefore promote personalized nutrition.

CONCLUSION

Promoting healthier choices at an early stage of human development may lead to minimizing the display of 21st-century diseases (*i.e.* diabetes type 2, obesity, heart complications, teeth decay, *etc*.) based on adequate dietary assessment and food choices relevant to nutritional requirements.

Diabetes and obesity are issues among serious health concern. Both conditions are strongly associated with an unhealthy diet and physical inactivity. Several recent studies on plant deriving polyphenols revealed their possible beneficial effects on human health. Developing efficient public health policies and improving people's quality of life by personalized nutrition, based on the recommendation of polyphenol intake, would enhance consumer's trust in sustainable dietary choices lying on a sound scientific basis.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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