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The Mediterranean Diet in the Treatment of Type 2 Diabetes

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Abstract. Type 2 diabetes mellitus (T2DM) is a major global public health crisis. It is featured by insulin resistance and chronic hyperglycemia, leading to serious complications, and current clinical treatments only relieve symptoms but cannot cure it. Recent research has shown that the Mediterranean diet (MD) is a promising way for T2DM prevention and management, and its role in regulating metabolic disorders has become a research focus. This review analyzes the core nutritional features of the MD and its regulatory effects on T2DM. It finds that the MD can balance gut microbiota, reduce chronic inflammation and oxidative stress, improve glycemic and lipid metabolism, and enhance pancreatic β-cell function and insulin sensitivity in T2DM patients. Clinical evidence also proves that the MD boosts patients' quality of life and has more advantages than conventional diabetic diets in long-term adherence and metabolic regulation. The MD provides a new nutritional intervention method for clinical T2DM management, offering evidence-based references for clinical practice. However, existing studies lack long-term follow-up data on diabetic complications and have insufficient research on the MD's cross-cultural adaptability and the synergy of its components. Future research should focus on personalized nutritional plans, long-term outcomes of complications and culturally adapted MD protocols. It is also necessary to explore the combined use of the MD with hypoglycemic drugs to better benefit T2DM patients worldwide.

Keywords: Mediterranean Diet, type 2 diabetes, insulin resistance

1. Introduction

Type 2 diabetes mellitus(T2DM) has now become a major global public health crisis. The disease is characterized by insulin resistance, relative insulin deficiency, and chronic hyperglycemia, with a complex pathogenesis and a prolonged, difficult-to-cure course [1]. This condition not only places a heavy burden on healthcare systems and social-economic development worldwide but also significantly increases the risk of patients developing serious complications such as cardiovascular disease, micro-vascular damage, and cognitive dysfunction, severely threatening their health and quality of life. Studies have found that the development of T2DM is mostly accompanied by obesity, which is closely related to unreasonable dietary patterns and excessive intake of carbohydrates or sugars [2]. At present, the main clinical measures for the treatment of T2DM include dietary pattern

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intervention, administration of weight-loss drugs, insulin injection, and surgery, all of which can only alleviate the condition but cannot cure it completely [3]. The Mediterranean diet (MD) has a rich history and is famous for originating in the Mediterranean region. As a widely studied and long-established dietary pattern, the MD has provided new insights for the treatment and prevention of T2DM. The MD is mainly based on grains, legumes, nuts and vegetables, with a diverse intake of foods including olive oil, fish, fruits and dairy products. Numerous studies have shown that the MD plays an important role in the management of diabetes, cardiovascular diseases and even cancer [4]. The pathogenesis of T2DM is complex and is usually associated with impaired pancreatic β-cell function, insulin resistance, and mitochondrial dysfunction. It can be seen that T2DM is mainly driven by environmental and genetic factors. This review will mainly explore the molecular mechanisms by which the MD pattern can improve diabetic conditions, such as how small organic molecules ingested affect islet function. By investigating the molecular mechanisms, this review aims to explore the clinical feasibility and limitations of the MD, so as to provide new insights for the treatment of T2DM.

2. Core characteristics of the MD

2.1. Features

The MD is rooted in the traditional eating habits of Mediterranean coastal populations, emphasizing a holistic lifestyle integrating nutrition, culture, and social interaction [5]. The composition of the MD can be viewed as a pyramid. The foods at the bottom of the pyramid are the daily staples consumed in the largest quantities, such as vegetables, fruits, and extra virgin olive oil. The next layer consists of whole grains, dairy products, and nuts. Whole grains are rich in carbohydrates and serve as the primary energy source, while nuts contain abundant vitamins, minerals, and unsaturated fatty acids. Cheese, a dairy product, can provide the human body with mineral salts and saturated fatty acids. The middle layer of the pyramid represents the two main sources of protein: legumes and fish. Further up are chicken, white meat, and potatoes. The foods at the top are those consumed only occasionally, such as hard cheeses. In addition, in the MD pattern, intake of salt, sugar, and alcohol should be as low as possible (Figure 1) [6].

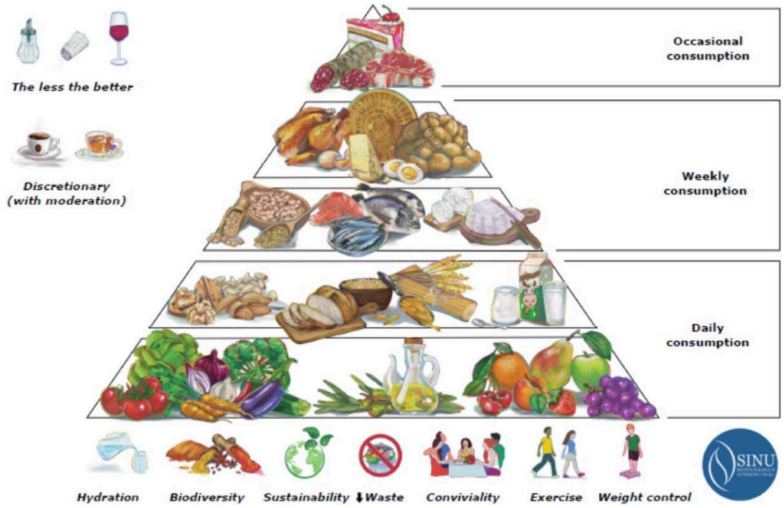

Figure 1. Schematic diagram of the MD structure [6]

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2.2. Nutrients contained

The MD, one of the most extensively studied and well-documented dietary patterns worldwide [7], is defined by a rich variety of whole, minimally processed foods that collectively deliver an exceptional breadth of essential nutrients, bioactive phytochemicals, and functional components, with each core food group contributing distinct and complementary nutritional elements as supported by robust scientific research; at the foundation of this dietary pattern is the regular consumption of extra-virgin olive oil (EVOO), its primary dietary fat source, which provides a balanced mixture of essential dietary fatty acids (predominantly unsaturated fatty acids) alongside fat-soluble vitamins, a diverse array of polyphenols including secoiridoid derivatives such as oleuropein, oleacein, and oleocanthal, simple phenols like tyrosol and hydroxytyrosol, as well as chlorophylls and phytosterols, all of which underpin many of the diet's well-documented bioactive effects, while complementing EVOO are whole-grain cereals such as rice and wheat (consumed in the form of pasta, bread, and couscous), which serve as the diet's main source of carbohydrates and energy while also supplying abundant dietary fiber, spermidine, ferulic acid, and other key micronutrients; legumes including beans, lentils, and chickpeas, a longstanding staple of the diet, are rich in flavanols (a subclass of polyphenols with a ketone group in their chemical structure) alongside other bioactive compounds that support endothelial function and metabolic regulation, and nuts such as hazelnuts, almonds, and pistachios, consumed daily across the Mediterranean region, offer a dense nutritional profile of vitamins, minerals, unsaturated fatty acids, and polyphenols including resveratrol, a well-characterized autophagy inducer. Fruits and vegetables, which form a major daily component of the MD supported by the region's favorable growing climate, contribute a vast array of antioxidant nutrients including vitamin E, β-carotene, vitamin C, and flavonoids, essential minerals such as selenium, natural folate, and a wide spectrum of specialized phytochemicals: lycopene from tomatoes, organosulfur compounds from onions and garlic, capsaicin from hot peppers, indol-3-carbinol, isothiocyanates, and sulforophane from cruciferous vegetables, monoterpenes from citrus fruits, polyacetylenes from pumpkins and carrots, and low-potency estrogenic molecules including biochanin A, formononetin, daidzein, coumestans, and genistein from beans and other legumes, all of which exert synergistic antioxidant and anti-inflammatory effects within the body. Moderate amounts of fermented dairy products, including yogurt and cheese derived primarily from goat and sheep milk, are also included in the dietary pattern, providing the human body with mineral salts and saturated fatty acids, while fish, a key protein source rooted in the Mediterranean region's rich fishing tradition, delivers critical omega-3 fatty acids and high-quality complete protein; moderate wine consumption, typically paired with meals as is traditional in European Mediterranean countries, adds additional polyphenolic compounds such as resveratrol, further enhancing the diet's phytochemical diversity. Additionally, the MD is naturally rich in oligosaccharides and resistant starch, which are metabolized by the gut microbiota to produce short-chain fatty acids that support gut barrier health and systemic metabolic regulation, and collectively, the diverse, complementary nutrient and phytochemical profile of the MD's core foods work in tandem to deliver its well-documented antioxidant, anti-inflammatory, and chronic disease-preventive properties across multiple bodily systems [8].

3. Key regulatory pathways of the MD in T2DM

Gut microbiota imbalance, chronic low-grade inflammation, oxidative stress, glycemic and lipid metabolism disorders, insulin resistance, and pancreatic β-cell dysfunction are core pathological links in the occurrence and progression of T2DM. The MD exerts anti-diabetic effects through

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multiple synergistic pathways, forming a comprehensive regulatory network for T2DM management.

3.1. Modulation of gut microorganism

Intestinal flora dysbiosis is a key link in the pathogenesis of T2DM [8]. Specifically, it can down-regulate the expression of intestinal tight junction proteins, increase intestinal epithelial permeability, promote the accumulation of lipopolysaccharides, and further induce systemic chronic inflammation and the apoptosis of pancreatic β cells, which are important pathways leading to T2DM [8].The core microorganisms involved in this process are mainly divided into two categories: one is beneficial bacteria such as Bifidobacteria and Lactobacilli, and the other is conditionally pathogenic bacteria such as Escherichia coli and Enterococci. When the ratio of beneficial bacteria to pathogenic bacteria becomes imbalanced, it directly induces chronic inflammatory responses and insulin resistance, thereby forming a vicious cycle of 'gut microbiota imbalance — inflammatory response — insulin resistance' [8, 9].The Mediterranean diet is rich in dietary fiber, which can act as a prebiotic. A 3-month clinical study showed that in patients with type 2 diabetes, a high-fiber diet significantly increased the number of beneficial Bifidobacteria by 2.52 lg/g, while the number of pathogenic Escherichia coli decreased by 1.91 lg/g [8]; the levels of Lactobacillus and Enterococcus showed no significant difference between the intervention group and the control group [1]. These beneficial bacteria can produce short-chain fatty acids (SCFAs), such as butyrates, which help enhance intestinal barrier function, reduce systemic inflammatory reactions, and improve insulin sensitivity in patients with T2DM [9, 10]. This is because the dietary fibre in MD promotes the growth of beneficial bacteria, and the SCFAs metabolised by these flora can effectively regulate the intestinal microenvironment [9] It is worth noting that these microbial changes are not related to energy intake [10], which helps to break the cycle of "intestinal flora imbalance -inflammation-insulin resistance" [9].It can be seen that the imbalance of intestinal flora is closely related to T2DM. With its high fibre properties, MD can regulate the balance between beneficial bacteria and pathogenic bacteria, promote the production of short-chain fatty acids, improve insulin sensitivity, and alleviate inflammatory reactions, so as to break harmful cycles independently without relying on energy intake.

3.2. Reduction of chronic inflammation and oxidative stress

Chronic low-level inflammation and oxidative stress can damage insulin signalling and β-cell function. Relevant regulatory factors include C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α). Its core regulatory mechanism is to inhibit the inflammatory pathway and remove reactive oxygen substances. MD is rich in antioxidants: polyphenols (such as hydroxytyrosol) in olive oil, vitamins C and E in fruits and vegetables, and selenium in nuts, which can effectively remove reactive oxygen and inhibit inflammatory reactions. Long-term following this diet can reduce CRP by 0.8 mg/l, IL-6 by 0.2 pik/ml, and reduce the risk of T2DM by 21% in 20 years. Specifically, hydroxytyrosol in olive oil can inhibit the NF-κB inflammatory pathway and reduce the release of inflammatory factors, while omega-3 fatty acids in the diet can reduce the production of TNF-α and reduce the damage of inflammation to pancreatic islet function. A 16-week study showed that short-term adherence to this diet did not significantly reduce the level of inflammatory markers, but long-term adherence may have significant anti-inflammatory and antioxidant effects, thus improving insulin sensitivity [11].According to the literature, MD can target and regulate inflammatory factors such as CRP and IL-6, inhibit inflammatory pathways such as

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NF-κB, and remove reactive oxygen substances through its rich antioxidant ingredients. Long-term persistent use can effectively reduce chronic inflammation and oxidative stress, protect pancreatic islet function, and reduce the risk of T2DM. Although the short-term effect is not obvious, the long-term benefit is significant.

3.3. Improvement of glycemic control

Multiple clinical studies consistently indicate that the Mediterranean diet (MD) has a stabilizing effect on blood glucose in patients with type 2 diabetes (T2DM). For example, a three-month randomized controlled trial involving 110 patients showed that compared with the conventional treatment group, the intervention group adopting the Mediterranean diet combined with aerobic exercise had significantly lower levels of fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), and glycated hemoglobin (HbA1c), with the three indicators being 6.58 vs 7.43 mmol/L, 8.15 vs 9.21 mmol/L, and 6.55% vs 7.36%, respectively [1].

Another study on patients with type 2 diabetes combined with abdominal obesity found that after 3 months of Mediterranean diet combined with insulin pump therapy, the decrease in patients' HbA1c levels was more significant (6.55% vs 7.36%) [10]. In addition, a 16-week Mediterranean diet intervention study showed that patients who adhered to this dietary pattern had a fasting blood glucose decrease of 19.6 mg/dL and a reduction in glycated hemoglobin of 0.8% [11].

Long-term cohort studies have further confirmed the sustained benefits of the Mediterranean diet in blood sugar control and the prevention of type 2 diabetes. For example, a 20-year follow-up study reported that long-term adherence to the Mediterranean diet could reduce the risk of developing type 2 diabetes by 21% (RR = 0.79, 95% CI 0.47–0.86). The landmark PREDIMED study in this field demonstrated that a Mediterranean diet supplemented with extra-virgin olive oil or nuts could reduce the risk of type 2 diabetes in high-risk individuals by 52%, and this protective effect was independent of weight loss.

The aforementioned benefits of the Mediterranean diet mainly stem from the following key mechanisms: first, the complex carbohydrates and dietary fiber in the diet can delay gastric emptying, thereby stabilizing the absorption rate of carbohydrates [12]; second, monounsaturated fatty acids help improve insulin sensitivity [2]; third, various bioactive components work synergistically to collectively protect and enhance the function of pancreatic β-cells.

In summary, a large number of clinical studies have confirmed that the Mediterranean diet can effectively regulate blood glucose levels in patients with type 2 diabetes. Long-term cohort studies have further validated its sustained protective effects, being able to reduce the overall incidence of type 2 diabetes and lower the risk of disease in high-risk populations. These benefits stem from the unique nutritional composition of the Mediterranean diet, whose core components can slow carbohydrate absorption, improve insulin sensitivity, and protect pancreatic β-cell function.

3.4. Regulation of lipid metabolism

Patients with type 2 diabetes often have dyslipidemia, which can exacerbate metabolic abnormalities and is also an important risk factor for cardiovascular diseases. Clinical data show that the Mediterranean diet can reduce triglycerides (TG) by 0.86 mmol/L, low-density lipoprotein cholesterol (LDL-C) by 0.55 mmol/L, while increasing high-density lipoprotein cholesterol (HDL-C) by 0.36 mmol/L [1]. In type 2 diabetes patients with abdominal obesity, treatment with the Mediterranean diet combined with continuous subcutaneous insulin infusion (CSII) can increase HDL-C to 1.47 mmol/L and reduce LDL-C to 2.80 mmol/L; repeated measures variance analysis

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confirmed a significant interaction between group and time [2]. Another 6-month intervention study found that compared with the conventional diabetes diet group, patients in the Mediterranean diet group showed a more significant reduction in TG (1.88 vs 2.13 mmol/L) and LDL-C (2.81 vs 3.27 mmol/L), mainly due to the abundant dietary fiber in the Mediterranean diet promoting cholesterol excretion [12]. There is ample evidence supporting the lipid-lowering mechanism of the Mediterranean diet: Omega-3 polyunsaturated fatty acids in fatty fish can reduce levels of pro-inflammatory factors, plant sterols in nuts can inhibit cholesterol absorption, and dietary fiber can promote cholesterol excretion; together, these three maintain the body's lipid metabolism balance. It is worth noting that the ATTICA cohort study provides further population-based evidence for the lipid-lowering effects of the Mediterranean diet: long-term adherence to this dietary pattern can significantly reduce total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, while increasing high-density lipoprotein cholesterol levels. This finding is highly consistent with the results of several independent meta-analyses, and existing data indicate that the Mediterranean diet shows even stronger lipid-improving effects in patients with type 2 diabetes.

Existing evidence indicates that the Mediterranean diet has a definite effect in improving dyslipidemia in patients with type 2 diabetes. Compared to conventional dietary regimens, significant reductions in triglycerides and low-density lipoprotein cholesterol can be observed even with a short-term intervention of just six months. It is noteworthy that for diabetic patients with abdominal obesity, combining continuous subcutaneous insulin infusion (CSII) treatment with the Mediterranean diet can further enhance lipid control. Long-term follow-up data from the ATTICA cohort study also support this point—people who adhere to the Mediterranean diet are more likely to maintain their lipid levels within the ideal range. Mechanistically, this is mainly attributed to the synergistic effects of active components such as omega-3 fatty acids, plant sterols, and dietary fiber, providing strong evidence for the clinical use of the Mediterranean diet in the management of diabetic dyslipidemia.

3.5. Improvement of insulin resistance and β-cell function & enhancement of quality of life

Insulin resistance has always been a key link in the pathological chain of type 2 diabetes. Fortunately, an increasing amount of clinical data supports the view that adjusting dietary structure, especially switching to a Mediterranean diet, can indeed bring substantial metabolic improvements for these patients. For those with both abdominal obesity and type 2 diabetes, studies have recorded a rather remarkable change—after adhering to the Mediterranean diet, their insulin resistance index (HOMA-IR) decreased on average by 3.20, while the HOMA-β index, representing pancreatic β-cell function, increased by 55.17 [10].There are actually several mechanisms at play behind this improvement. The reduction of visceral fat is probably the most direct one; with less fat, the chronic damage of lipotoxicity to β-cells is reduced, and insulin resistance naturally is less likely to worsen [10]. At the same time, the overall body's lipid metabolism tends to normalize, and ectopic fat deposits in key organs like the pancreas and liver will gradually be cleared. Additionally, since the Mediterranean diet has a high proportion of fruits and vegetables, with sufficient intake of antioxidants like polyphenols, it is comparable to giving β-cells an extra 'protective layer' to resist damage caused by oxidative stress. A 16-week intervention study provided more direct evidence: after participants strictly followed the Mediterranean diet, their BMI dropped by 3.0 kg/m², and researchers found that as weight decreased, the ability of muscles and tissues to uptake glucose improved, and insulin sensitivity also improved [5]. If diet is combined with exercise, the effect can be even greater—a 3-month clinical trial showed that the Mediterranean diet combined with aerobic exercise can lead to a larger reduction in HOMA-IR [8].Metabolic indicators have improved, and

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patients can go about their daily lives much more easily. Using the Diabetes-Specific Quality of Life Scale (DSQL) for measurement, those who adhere to a Mediterranean diet score generally 15% to 20% higher than the conventional diet group in the four dimensions of treatment compliance, psychological state, physiological function, and social relationships [8]. A three-month controlled trial also confirmed this trend, with the Mediterranean diet group outperforming the traditional diabetes diet group in all dimensions [10].When it comes to specific life experiences, smaller fluctuations in blood sugar significantly reduce bothersome symptoms like frequent nighttime urination and overall fatigue [12]; sufficient intake of whole grains, high-quality protein, and healthy fats can gradually restore a person's physical strength and endurance. Another often overlooked point: the Mediterranean diet fundamentally encourages families to sit down and have meals together, and this socially engaging approach to eating unconsciously helps relieve the long-term psychological burden of managing the disease, allowing patients to breathe easier both physically and emotionally [8].

4. Discussion

In this review, we present a detailed analysis of how the Mediterranean diet functions in clinical management of type 2 diabetes, supported by specific data from recently published trials. Available clinical evidence unequivocally indicates that this dietary pattern effectively optimizes multiple metabolic markers in patients and improves their long-term prognosis.

Compared with the various dietary patterns widely used in current clinical interventions for type 2 diabetes, the Mediterranean diet demonstrates irreplaceable advantages, mainly due to its balanced nutritional composition based on natural, minimally processed foods. Some clinical dietary programs have strict restrictions, making it difficult for patients to adhere to them long-term, whereas the Mediterranean diet is closer to the daily eating habits of the general population, resulting in significantly higher long-term compliance. At the same time, interventions with single nutrients can only act on a single metabolic pathway, whereas the Mediterranean diet can exert multi-target, holistic regulatory effects on the complex metabolic disorders associated with type 2 diabetes.

Although multiple studies have fully confirmed that Mediterranean diet interventions have clear clinical value for type 2 diabetes, existing related research still has certain limitations. First, the design schemes of various studies are not yet uniform, including both retrospective analyses and prospective trials, and the differences in research paradigms can easily lead to heterogeneity in conclusions. Second, studies on the adaptability of the Mediterranean diet in special populations are still insufficient. For example, there is a lack of in-depth exploration of applicable programs for elderly patients with underlying diseases, as well as for different regional and ethnic groups, making it difficult to form a comprehensive clinical application guidance system.

From the perspective of future clinical application prospects, the Mediterranean diet is expected to be gradually incorporated into the routine clinical management system of type 2 diabetes, with individualized health management plans developed based on patients' physical characteristics, lifestyle, and metabolic traits. Subsequent research can focus on the long-term molecular mechanisms by which the Mediterranean diet regulates type 2 diabetes and conduct stratified studies to optimize its suitability for different populations. Through the above explorations, more practical reference evidence can be provided for the clinical prevention and treatment of type 2 diabetes.

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5. Conclusion

The Mediterranean diet is supported by sufficient research evidence and has a balanced nutritional structure, playing multiple positive roles in the prevention and clinical intervention of type 2 diabetes.The Mediterranean diet targets key pathological pathways in type 2 diabetes, improving glycemic control, reducing inflammation and oxidative stress, enhancing insulin sensitivity, protecting β-cell function, and correcting lipid disorders. High-quality data from landmark trials and long-term cohort studies confirm that sustained adherence significantly lowers HbA1c, fasting and postprandial glucose, and improves overall patient quality of life. Compared with standard diabetes dietary approaches, the Mediterranean diet has clear advantages: it provides better glycemic control and cardiovascular protection than traditional low-fat diets (which often cause refined carbohydrate overconsumption), and has superior long-term patient adherence.At the same time, unlike highly restrictive very low-carbohydrate diets, it can maintain long-term stable blood glucose levels without placing excessive metabolic burden on the liver and kidneys.Additionally, compared with pro-inflammatory Western diets, the Mediterranean diet can reduce the risk of developing type 2 diabetes by more than 20%; and compared with nutritionally unbalanced unhealthy plant-based diets, its whole-food balanced nutritional structure effectively prevents an increased risk of insulin resistance.

Nevertheless, existing studies still have significant limitations: most intervention studies are short- to medium-term in design and lack long-term follow-up data on diabetes-related microvascular complications and cognitive comorbidities; research on its cross-cultural adaptability (especially among Asian populations with unique staple food structures) is still insufficient; the mechanisms of synergistic effects among the different components of the Mediterranean diet, standardized protocols for combined use with hypoglycemic drugs, and key factors affecting patient adherence have not been fully explored.

In the face of the global prevalence of type 2 diabetes, incorporating the Mediterranean diet into clinical guidelines and developing individualized dietary plans that fit different cultural contexts have become urgent issues. Future research should focus on precision nutrition, long-term complication outcomes, and cross-cultural validation to maximize its clinical value for patients with type 2 diabetes worldwide.

Author contribution

All the authors contributed equally and their names were listed in alphabetical order.

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