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## Review Article



# A Comparative Review of Mediterranean, DASH, and Ketogenic Diets in Reducing Chronic Disease Risk

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## ABSTRACT

Dietary pattern is one of the modifiable factors for chronic non-communicable diseases (NCDs), which are the major contributors to morbidity and mortality around the world, including cardiovascular disease, type 2 diabetes mellitus, and several cancers. The current evidence base for dietary patterns associated with chronic disease prevention consists of three main diets: the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the ketogenic diet. A narrative review was conducted to compare the effectiveness, mechanisms, and safety of these three dietary patterns on cardiovascular, metabolic, and oncological outcomes, as well as long-term adherence and safety, with an emphasis on recent randomized controlled trials, prospective cohort studies, and systematic reviews and meta-analyses published primarily from 2021 to 2025 and using earlier studies when they provided foundational insights. The CORDIOPREV trial led updated secondary-prevention trial evidence that further consolidates the cardioprotective, cancer-risk-reducing, and mortality benefits of the Mediterranean diet. Recent meta-analyses have validated the blood pressure-lowering efficacy of the DASH diet while demonstrating concurrent effects on lipid profile and metabolic risk factors, and it remains the most consistent diet proven to lower blood pressure. Comparative and network meta-analyses indicate that carbohydrate restriction might provide metabolic benefits in the short term, but the Mediterranean and DASH diets have greater evidence for long-term hard clinical outcomes. Therefore, no one single pattern of diet should be recommended as the best, but should be tailored to each individual's metabolic profile, any comorbidities, and their capacity to follow it.

## INTRODUCTION

Noncommunicable diseases (NCDs) are responsible for the majority of deaths worldwide, with cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and cancer being the main conditions, and suboptimal diet is one of the biggest modifiable risk factors for these diseases. The contribution of diet-related risk factors to cardiovascular-, diabetes-, and neoplasm-related disability-adjusted life years (DALYs) is estimated to be an important proportion of all DALYs globally, and this varies by region and by sociodemographic development [1]. The dietary risks were estimated to be responsible for about a quarter of the cardiovascular disease burden and nearly 30% of the

combined diabetes and kidney disease burden in 2023 in the Nordic and Baltic countries [2]. Similar studies in China and Japan reveal that the burden of diabetes remains higher than ever despite the decrease in diet-attributable cardiovascular and cancer burden [3], indicating that the diet-chronic disease relationship is dynamic and not consistent across populations. In this context, the following three diet patterns have the largest and most extensively researched bases: the Mediterranean diet, the DASH diet, and the ketogenic diet. The Mediterranean diet is one of the best-studied diets in modern nutrition research, and it is defined by a high consumption of



vegetables, fruit, legumes, whole grains, nuts, and extra virgin olive oil, moderate fish and poultry consumption, and low consumption of red meat and processed foods [4, 5]. The DASH diet was created specifically as a diet to help lower blood pressure without taking blood pressure-lowering drugs, and is rich in fruit, vegetables, low-fat dairy, whole grains, and low in sodium, saturated fat, and added sugar. In contrast to this, the ketogenic diet is not based on a food-group plan, but based on macronutrient ratios: very low carbohydrate intake (usually <50 g/day), moderate protein and high fat, with a major aim to attain nutritional ketosis.

Although these three patterns are quite distinct in terms of mechanism, maturity of evidence and potential clinical use, they are all endorsed by clinicians, professional associations and popular media as approaches to chronic disease prevention and management. This results in a real need to compare evidence for each pattern, side by side, with similar outcome measures to allow informed decision-making by both clinicians and patients. This review aims to present a summary of the evidence for cardiovascular, metabolic, and oncological outcomes of each of the diets, and provides direct and indirect comparisons where

appropriate based on each trial, and takes into account long-term adherence and safety of each diet.

This is a narrative review and not a formal systematic review. Mediterranean diet, DASH diet, ketogenic diet, low-carbohydrate diet, cardiovascular disease, type 2 diabetes, cancer, and chronic disease risk were used in combination to identify relevant randomized controlled trials, prospective cohort studies, and systematic reviews/meta-analyses from targeted comprehensive searches conducted in PubMed, Google Scholar, and Scopus. Landmark randomized trials and umbrella reviews and meta-analyses were prioritized from 2021 to 2026, and where available, some key earlier trials were included as they remain the main source of evidence for a particular diet-outcome relationship (e.g. the original DASH trials and PREDIMED trials). Hand-searching of identified review reference lists was conducted to identify further relevant research, and searches were repeated in 2026 to ensure the timeliest evidence was retrieved. This study summarizes the landmark trials and meta-analyses that constitute the core evidentiary basis for this review (Table 1).

**Table 1:** Key Landmark Studies and Clinical Trials

| Study/Trial                       | Design (Year)                                          | Population (N)                                             | Key Finding                                                                                                   | References |
|-----------------------------------|--------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------|
| PREDIMED                          | Multicenter RCT (2013; corrected republication)        | 7,447 adults at high cardiovascular risk                   | Mediterranean diet + EVOO or nuts significantly lowered major cardiovascular events vs. low-fat advice        | [6, 7]     |
| CORDIOPREV                        | Single-center RCT, 7-yr follow-up (2022)               | 1,002 patients with established coronary heart disease     | Mediterranean diet (EVOO-rich) reduced major cardiovascular events: 28.1 vs 37.7 per 1,000 person-years       | 7          |
| DASH meta-analysis                | Systematic review & meta-analysis of 54 RCTs (2021)    | Pooled RCT participants across chronic-disease populations | Significant reductions in SBP (-3.94 mmHg), DBP (-2.44 mmHg), weight, and LDL cholesterol                     | 8          |
| Low-carb vs low-fat meta-analysis | Meta-analysis of RCTs (2022)                           | Overweight/obese adults                                    | Low-carbohydrate diets produced greater short-term triglyceride reduction; effects narrowed over 10-30 months | 9, 10      |
| Ketogenic GRADE meta-analysis     | Systematic review & meta-analysis (2024)               | Patients with type 2 diabetes                              | Significant reductions in fasting glucose, HbA1c, HOMA-IR, and triglycerides; increased HDL                   | 11         |
| Look AHEAD (long-term follow-up)  | RCT, 12-yr intervention with extended follow-up (2024) | Adults with type 2 diabetes and overweight/obesity         | Diabetes remission during intervention associated with fewer later cardiovascular/microvascular events        | 12         |

## Cardiovascular Disease

The Mediterranean diet is the oldest of the three diets discussed in this report, and has seen an ongoing development of evidence in the last five years. In adults aged 60 years and older, the findings from a 2024 systematic review and meta-analysis of 28 observational and interventional studies showed that high adherence to the Mediterranean diet was associated with a 23% decreased risk of all-cause mortality and parallel decreases in cardiovascular morbidity (n=679,259) [5]. A separate meta-analysis of RCTs (the Lyon Diet Heart Study, the Indo-Mediterranean Diet Heart Study, PREDIMED and the more recent CORDIOPREV) that included all participants who were assigned to a Mediterranean style diet as opposed to control diets also found statistically significant lower composite cardiovascular events among the group consuming the Mediterranean diet [6]. The most recent contribution to this body of evidence has been the CORDIOPREV, a Spanish single-center randomized trial of 1,002 patients with known coronary heart disease. At seven years follow-up, those who were randomly allocated to a Mediterranean, extra-virgin olive oil (EVOO) diet experienced significantly fewer major cardiovascular

events (myocardial infarction, revascularization, ischemic stroke, peripheral artery disease, or cardiovascular death) than those allocated to a low-fat, high-complex-carbohydrate diet, with incidence rates of 28.1 versus 37.7 per 1,000 person-years, respectively. The PREDIMED is the primary-prevention evidence base for the Mediterranean diet, which remains unchanged despite the correction of the data and the republishing of the trial results, and has been confirmed by more recent trials and meta-analyses. Secondary prevention with a Mediterranean diet, without a specific caloric restriction, has been synthesized again in this decade, and results confirm lasting reductions in cardiovascular events and improvement of the cardiometabolic risk profile. The long-term sustainability of the intervention has also been shown: in the CORDIOPREV follow-up (follow-up for 7 years), the group that followed a Mediterranean diet significantly and consistently consumed more extra-virgin olive oil, nuts, and oily fish than the control group [7]. Mechanistic reviews have recently been published regarding the beneficial effects of the core components of the Mediterranean Diet on cardiovascular health, predominantly including the effects of EVOO on the gut microbiome, the production of short-chain fatty acids, and subsequent anti-inflammatory and endothelial effects, with the cardioprotective effects of increased adherence continuing to be supported by the latest evidence, including a reduced incidence of atrial fibrillation and other cardiovascular endpoints [13, 14].

### Type 2 Diabetes

In addition to cardiovascular outcomes, a recent dose-response meta-analysis of prospective cohort studies in 2022 revealed that every additional point on the adherence score was linked to a significantly reduced risk of incident T2D, further strengthening previous subgroup analysis data from PREDIMED [15]. This aligns with a recent 2023 systematic review and meta-analysis of 23 observational studies that concluded that adherence to a higher, as opposed to lower, Mediterranean diet was significantly associated with a lower risk of developing type 2 diabetes in a variety of populations, regardless of whether the emphasis was on weight loss or physical activity [16].

### Cancer and Mortality

New evidence also suggests that anti-inflammatory and antioxidant food items in the Mediterranean diet can lower the risk of cancer. In a dose-response meta-analysis of 11 studies and more than 1.3 million participants, the highest adherence to the Mediterranean diet was linked to a 29% lower risk of gastric cancer, and each additional point on the Mediterranean diet score was linked to a 5% decrease in risk [17]. Likewise, a 2022 meta-analysis has identified a significant inverse link between adherence to the Mediterranean diet and risk of lung cancer (HR 0.82, 95% CI

0.74–0.92) that was apparent across studies in a dose-response fashion [18]. More recent syntheses that have included randomized and observational evidence that are broader in scope continue to confirm the death-saving and cancer-preventing effects of the Mediterranean dietary pattern for the total cancer burden and for certain site-specific cancers in high adherers to the pattern, further supporting the findings of the earlier Cochrane-level evidence of cardiovascular and mortality benefits [6]. The cardioprotective and anticarcinogenic properties of this diet have been mechanistically explained by the high ratio of monounsaturated to saturated fats, the presence of polyphenols, fiber-mediated alterations of the gut microbiome, and its net anti-inflammatory activity [4].

### Blood Pressure and Cardiovascular Risk

The DASH diet was specially designed and tested for blood pressure reduction, and this is the best-supported blood pressure-lowering effect of the DASH diet in new evidence syntheses. The DASH diet had significant effects on systolic blood pressure (–3.94 mmHg), diastolic blood pressure (–2.44 mmHg), body weight (–1.59 kg), and waist circumference (–1.93 cm) compared to control diets in a systematic review and meta-analysis of 54 RCTs conducted in 2021 across various chronic-disease populations [8]. The same synthesis concluded that these blood-pressure benefits were also observed in trials with different amounts of sodium restriction, which confirms the original dose-response relationship between sodium intake, dietary pattern, and blood pressure [19]. In this 2021 meta-analysis, DASH-style eating was also shown to significantly lower total cholesterol (–5.12 mg/dl) and LDL cholesterol (–3.53 mg/dl) without significant decrease in HDL cholesterol, and there was consistent improvement of other cardiovascular risk factors in the 54 pooled trials [20].

### Cancer Risk Factors

In addition to blood pressure, the same set of updated evidence also shows that the DASH pattern results in more overall benefits in terms of other metabolic risk components across the randomized trials – particularly in weight and waist circumference, and lipid profile, with effect sizes tending to be stronger the higher the baseline cardiometabolic risk of the participants [8].

### Type 2 Diabetes

In a 2023 dose-response meta-analysis of prospective cohort studies that included combinations of low-risk lifestyle behaviors, a DASH-style dietary pattern (in addition to other healthy lifestyle behaviors) was shown to be associated with a meaningfully reduced risk of incident type 2 diabetes, with each additional low-risk behavior resulting in an increasingly lower risk of incident type 2

diabetes [8]. This is generally in line with the dietary-pattern literature, as both Mediterranean and DASH-type diets are associated with reduced future risk of type 2 diabetes compared to poorer quality diets [8, 21].

### **The Ketogenic Diet: Weight Loss and Glycemic Control**

The keto diet differs from the Mediterranean and DASH patterns, which are based on foods grouped by their composition, in that it is based on macronutrient restriction (fewer than 50 g of carbohydrate per day) and has been most widely studied for short- to medium-term weight loss and glycemic control. In obese and overweight adults, a 2022 meta-analysis of randomized controlled trials (RCTs) that included 20 studies with 762 participants showed that low-carbohydrate diets resulted in significantly greater decreases in triglycerides, as well as generally similar or greater weight loss over the short-term, but with somewhat smaller differences seen during longer periods of follow-up [9]. The same pattern was observed in a 2022 meta-analysis of 25 RCTs studying long-term (10–30 month) efficacy of low-carbohydrate diets, which revealed that there was significant weight loss benefit at 3–8 months which decreased in significance after 10 months of follow-up [10]. Patients with type 2 diabetes specifically: updated GRADE-assessed evidence indicates that very-low-carbohydrate ketogenic diets significantly lower fasting blood glucose, HbA1c, HOMA-IR, and triglyceride levels and raise HDL cholesterol levels compared with control diets [11]. A second umbrella review that focused on multiple health outcomes also found positive short-term outcomes of the KD on weight, glycemic markers, and a few cardiovascular risk factors, with less consistent and less comprehensive evidence regarding cancer- and neurology-related outcomes [22, 23]. Further, controlled feeding studies have compared the effects of dietary fat restriction to carbohydrate restriction, and, on a calorie-per-calorie basis, results on the metabolic ward for short-term feeding do not necessarily translate to free-living results over longer periods, making direct comparison of the effects of dietary fat restriction and other strategies for sustained diabetes management difficult [9].

### **Cardiovascular Risk Factors**

The profile of the cardiovascular risk factors associated with the ketogenic diet is still more varied than with the Mediterranean or DASH patterns. The meta-analysis of low carbohydrate versus low fat diets in overweight and obese adults published in 2022 showed that, while triglycerides decreased significantly with low carbohydrate diets, LDL cholesterol had an inconsistent response and in a meaningful subset of individuals, LDL actually increased significantly [9]. This variability has been described in

detail in the recently described "lean mass hyper-responder" (LMHR) phenotype: lean individuals with low triglyceride levels and high HDL levels who have very high levels of LDL when following a carbohydrate-restricted ketogenic diet [24]. In a clinical commentary on this phenotype in 2022, this elevation of LDL was deemed worthy of 'urgent individual clinical attention, closer lipid monitoring and further research regarding implications for cardiovascular disease' as the authors were unclear whether such dyslipidemia carries the same atherogenic risk as LDL elevation due to other causes [25].

### **Long-Term Safety, Adherence, and Sustainability**

The evidence base for the ketogenic diet is most divergent from that of the Mediterranean and DASH diets in terms of long-term sustainability and safety. A narrative review of the benefits and risks of KDs for chronic disease applications found that the benefits of KDs were generally outweighed by the negative aspects, including the often-short-term nature of metabolic effects, the poor overall dietary quality, and the lack of long-term safety data, while long-term adherence was limited by limited food choice and common adverse effects [26]. In keeping with this, a systematic review of long-term (12+ months) weight loss interventions in T2DM showed that diabetes remission rates decreased from as high as 62% at 1 year to 13% at 5 years after the intervention, after which there was partial weight regain, although average metabolic parameters generally remained improved compared with baseline [27]. Even in the cohorts that have been followed prospectively with the ketogenic diet, there was significant attrition over the course of 3–9 months, with some structured programs dropping by over 90% [22] as the weight-losing group achieved significant anthropometric improvements. A review of Ketogenic Diets in Cancer patients also reports that although ketogenic diets have shown promising results in the body composition of patients, the results in terms of treatment compliance are limited due to the short follow-up periods and small sample sizes of the trials [28].

### **Comparative Analysis**

A few direct comparisons of these three diets can still be found, but the evidence from comparative trials is still mainly two-arm evidence versus a single comparator or arm, and not three-arm evidence. A meta-analytic review of low-carbohydrate versus low-fat diets shows that triglyceride reductions are generally larger in LCHF diets in the short term, and that weight loss is slightly larger in LCHF diets over the first 10–30 months of follow-up, but that these differences tend to diminish during the 10–30 months follow-up, whereas the effects on lipids and lipid profile and on the development of metabolic syndrome tend to be more variable [9, 29]. Recent mechanistic

studies on the benefits of both Mediterranean and ketogenic diets show that both can have beneficial effects on cardiometabolic risk factors, but there are significant differences in the gut microbiota profile that they produce, suggesting that the metabolic effects of the two dietary patterns may be mediated in part by different biological pathways [30, 31].

In their mechanisms, the diets still vary significantly. Polyphenols, the high monounsaturated fat content, and the gut-remodeling effect of the Mediterranean diet due to fermentable fibre are among the main mechanisms by which this diet exerts its cardioprotective effect [4]. Blood-pressure lowering by virtue of increased potassium, calcium and magnesium consumption and a reduction in sodium is the main principle of the DASH diet, and recent large-scale meta-analysis [14] suggests that secondary lipid-modulating effects are also present. The benefits of the keto diet are believed to be largely due to the significant reduction in glycemic and insulin levels after meals and swift short term calorie deficit, with the risks being directly attributed to the macronutrient content of the diet, such as elevation of LDL in some individuals (including the lean mass hyper-responder phenotype), low dietary fiber and micronutrient consumption, and loss of lean body mass without concurrent resistance training [13, 25].

The latest (2026) scientific statement from the American Heart Association, which supersedes and updates its

previous dietary-fat recommendations, reiterates the importance of unsaturated fat sources as a focus of heart-healthy dietary patterns, rather than saturated fat, less processed foods and less sodium intake, and states this represents a level of hard-outcome cardiovascular evidence that is not matched by ketogenic interventions [25, 32]. The randomized evidence regarding the effects of carbohydrate restriction on metabolic syndrome components in the short- to medium-term is still positive, although only a few trials have been followed long enough or with enough patients to allow the ability to confidently assess hard cardiovascular endpoints [19, 33]. Interestingly, in an updated long-term follow-up of the intensive lifestyle-intervention Look AHEAD trial whose dietary approach was similar to calorie-restricted DASH and Mediterranean dietary patterns, the trial primary cardiovascular endpoint was not significantly reduced over the original 12-year follow-up, however, those who achieved and maintained diabetes remission throughout the intervention experienced a significantly lower incidence of cardiovascular and microvascular events post intervention, suggesting that longevity of improvement – rather than diet type – may be a determinant of hard outcome benefit [31]. The findings present a comparative summary of the three dietary patterns across composition, mechanism, and major chronic disease outcomes (Table 2).

**Table 2:** Comparative Summary of the Mediterranean, DASH, and Ketogenic Diets Across Chronic Disease Outcomes

| Feature                    | Mediterranean Diet                                                                                                   | DASH Diet                                                                                       | Ketogenic Diet                                                                                                                            | References |
|----------------------------|----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Primary composition        | High vegetables, fruit, legumes, whole grains, nuts, extra-virgin olive oil; moderate fish/poultry; limited red meat | High fruit, vegetables, low-fat dairy, whole grains; reduced sodium, saturated fat, added sugar | Very low carbohydrate (<50 g/day), moderate protein, high fat                                                                             | [8, 19]    |
| Primary mechanism          | Anti-inflammatory, high MUFA polyphenol content, favorable gut microbiome remodeling                                 | Reduced sodium with increased potassium, calcium, magnesium intake                              | Reduced postprandial glycemic/insulin excursions; rapid caloric deficit via nutritional ketosis                                           | [11, 22]   |
| Cardiovascular disease     | Strong: reduced composite cardiovascular events and mortality (PREDIMED, CORDIOPREV)                                 | Strongest evidence for blood pressure reduction; parallel lipid improvements                    | Mixed: triglyceride benefit, but variable/inconsistent LDL response                                                                       | [23, 25]   |
| Type 2 diabetes            | Reduced incidence with higher adherence; supportive dose-response evidence                                           | Associated with lower incident risk, especially combined with other healthy behaviors           | Fastest short-term glycemic improvement; remission rates decline substantially by 5 years                                                 | [24, 27]   |
| Cancer risk                | Reduced risk of gastric and lung cancer with high adherence; reduced overall cancer mortality                        | Limited direct evidence                                                                         | Limited and inconsistent evidence                                                                                                         | [17, 18]   |
| Long-term adherence/safety | High sustainability; durable dietary changes over 7-yr follow-up                                                     | Generally well-tolerated and sustainable long-term                                              | High short-term efficacy but steep attrition; limited long-term safety data, possible LDL elevation (lean mass hyper-responder phenotype) | [25, 26]   |

### Clinical and Public Health Implications

Several practical conclusions follow from this updated evidence synthesis. First, for cardiovascular risk reduction with the strongest and most current hard-outcome evidence, the Mediterranean diet now has both a mature primary-prevention trial base and a decisive, modern secondary-prevention trial (CORDIOPREV), particularly for high-risk populations with established coronary disease [6, 7]. Second, for patients whose principal risk factor is hypertension, the DASH diet remains

the most extensively validated dietary intervention, with updated meta-analytic effect sizes for blood pressure reduction that remain clinically comparable to some first-line antihypertensive approaches [8]. Third, for patients requiring rapid weight loss or urgent glycemic control for example, those with poorly controlled type 2 diabetes or severe obesity – a ketogenic or low-carbohydrate approach may offer the fastest short-term metabolic improvement, but should be implemented with baseline and follow-up lipid monitoring given the variable, sometimes marked, LDL response now well documented in the lean mass hyper-responder literature, and ideally under professional supervision given the diet's restrictiveness and the well-documented difficulty of long-term adherence [25, 27].

Given the divergent adherence profiles of the three diets – the Mediterranean and DASH patterns are generally rated as more palatable and sustainable over years, and now carry updated long-term secondary-prevention trial data to support this, while ketogenic diets show high short-term efficacy but steep long-term attrition [34, 35] – dietary counselling should weigh not only theoretical or short-term efficacy but also the likelihood that a given patient will sustain the pattern long enough to realize its benefits. A pragmatic, patient-centered approach might therefore favor Mediterranean- or DASH-style eating as a default, long-term foundation for chronic disease prevention, reserving ketogenic approaches for defined, time-limited therapeutic goals with appropriate clinical monitoring.

### Limitations and Future Recommendations

This is a narrative review with a few limitations. First, it is a narrative and not a systematic literature search and therefore has no formal, predetermined search protocol, quality assessment of the individual studies included or quantitative synthesis of effect sizes for all outcomes; second, as a narrative review and not a systematic search of the literature, no formal search protocol was used; third, there was no quality assessment of the individual studies included and no quantitative synthesis of effect sizes for all outcomes. Second, the review focused on landmark trials and recent meta-analyses, which may lead to selection bias and may fail to include smaller or negative trials. Future studies should focus on large, multicenter, randomized controlled trials with longer follow-up duration (≥5 years) and direct comparison of the Mediterranean, DASH and ketogenic diet head-to-head, to measure hard clinical endpoints, such as cardiovascular events, duration of diabetes remission, incidence of cancer, and all-cause mortality.

### CONCLUSIONS

The evidence base for each diet has also evolved since 2021, and the mechanisms by which the three diets reduce risk of chronic disease differ. The evidence base for each

diet has also changed since 2021, and the evidence base for each has evolved meaningfully since that time, though there are different levels of strength and maturity of evidence for each. The Mediterranean diet has the widest and newest evidence base in the field of cardiovascular disease, cancer and diabetes, with a modern secondary-prevention trial (CORDIOPREV) supporting the collective primary-prevention basis. The DASH diet continues to be unequalled in terms of blood pressure lowering and, according to recently updated large-scale meta-analyses, the diet provides strong secondary evidence of lipid and wider metabolic benefit. The short-term benefit of the ketogenic diet is the most dramatic improvement in weight and blood sugar control, but the long-term effect of the diet on lipids is inconsistent and sometimes significant, and long-term cardiovascular safety is unclear, as is adherence. In fact, the evidence remains as it is: there is nothing one-size-fits-all, but rather individualized dietary prescription – Mediterranean and DASH diets as long-term foundations and the ketogenic diet as best suited to specific, monitored, shorter-term therapeutic applications.

### Authors' Contribution

Conceptualization: WW

Methodology: MS

Formal analysis: WW

Writing and Drafting: MS

Review and Editing: WW, MS, MFG

All authors approved the final manuscript and take responsibility for the integrity of the work

### Conflicts of Interest

All the authors declare no conflict of interest.

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