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REVIEW

Idebenone: Clinical Potential Beyond Neurological Diseases

Bin Yi[1–4,*], Jun Zeng[1–4,*], Jiashuo Li[1–4,*], Kunfeng Liu[1–4], Xiaocheng Zhu[4,5], Xiang Chen[4,5], Yang Gao[1–4]

[1]Department of Thoracic Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China; [2]Hunan Engineering Research Center for Pulmonary Nodules Precise Diagnosis & Treatment, Changsha, Hunan, People's Republic of China; [3]Xiangya Lung Cancer Center, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China; [4]National Clinical Research Center for Geriatric Disorders, Changsha, Hunan, People's Republic of China; [5]Department of Anesthesiology, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiang Chen; Yang Gao, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, 410008, People's Republic of China, Email chenxiangxt@csu.edu.cn; dr.gao@csu.edu.cn

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Abstract: Idebenone, a short-chain analog of coenzyme Q10 with a hydroxydecyl side chain, is known to activate mitochondrial function by transferring electrons to the electron transport chain complex III, thereby promoting adenosine triphosphate production. Numerous clinical trials have demonstrated the effectiveness of idebenone in the treatment of neurological diseases. Interestingly, emerging evidence suggests that idebenone may also have beneficial effects beyond neurological conditions through disrupting mitochondrial membrane potential, inducing mitochondrial apoptosis, promoting mitophagy attenuating ferroptosis, reducing reactive oxygen species and lipid peroxidation, etc. This study aims to comprehensively review the clinical potential of idebenone in various fields, including cancers (such as breast cancer, melanoma, glioblastoma, neuroblastoma, hepatocellular carcinoma, prostatic carcinoma and pancreatic carcinoma), cardiovascular diseases (including atherosclerosis, hypertension, myocardial infarction and heart failure), diabetes mellitus, liver diseases, urogenital diseases, sepsis, and other diseases. The findings highlight the potential of idebenone as a promising therapeutic option for the prevention and management of these condition, which need to be validated in more clinical trials.
Keywords: idebenone, antioxidant, mitochondria, electron carrier, non-neurological diseases

Introduction

Idebenone, a synthetic analogue of coenzyme Q10 (CoQ10) developed by Takeda Pharmaceuticals in Japan, serves as a lipophilic electron carrier and endogenous antioxidant within the mitochondrial respiratory chain.[1] Idebenone possesses a similar redox-active benzoquinone structure to CoQ10, but features a shorter lipophilic side chain and a terminal hydroxyl group to enhance its solubility[2] (Figure 1). Due to their structural similarities and variations, idebenone shares a redox-active benzoquinone core that enables it to act as an electron carrier in the respiratory chain to contribute to ATP production, and also function as a potent intramitochondrial antioxidant, which can cross the blood-brain barrier and biological membranes more readily and freely. Of note, it can shuttle electrons directly to complex III of the respiratory chain, thereby bypassing complex I.[3]

Given that microcirculatory changes in the central nervous system have been associated with reactive oxygen species (ROS) and lipid peroxidation, lipophilic antioxidants have shown promise for therapeutic effects.[4,5] In the 1980s, idebenone was first synthesized and introduced for the treatment of neurodegenerative disorders.[6,7] Clinical trials have demonstrated the safety and tolerability of idebenone, making it a commonly used drug to enhance brain metabolism and alleviate mental symptoms. A study published in Lancet Neurology reported that higher doses of idebenone were well-tolerated, and associated with improvements in neurological function and daily activities among patients with Friedreich's ataxia.[8] Additionally, a pilot open trial documented the visual function improvement in patients with OPA1-mutant dominant optic atrophy following idebenone therapy.[9] Furthermore, a double-blind randomized placebo-controlled Phase 3 trial published in Lancet found that

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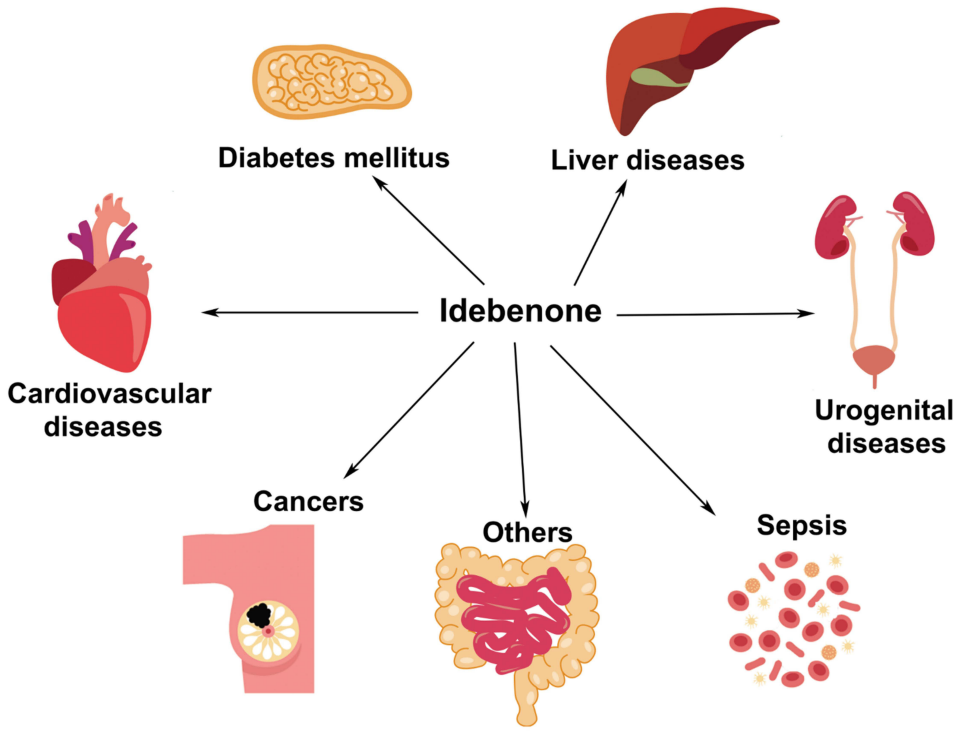
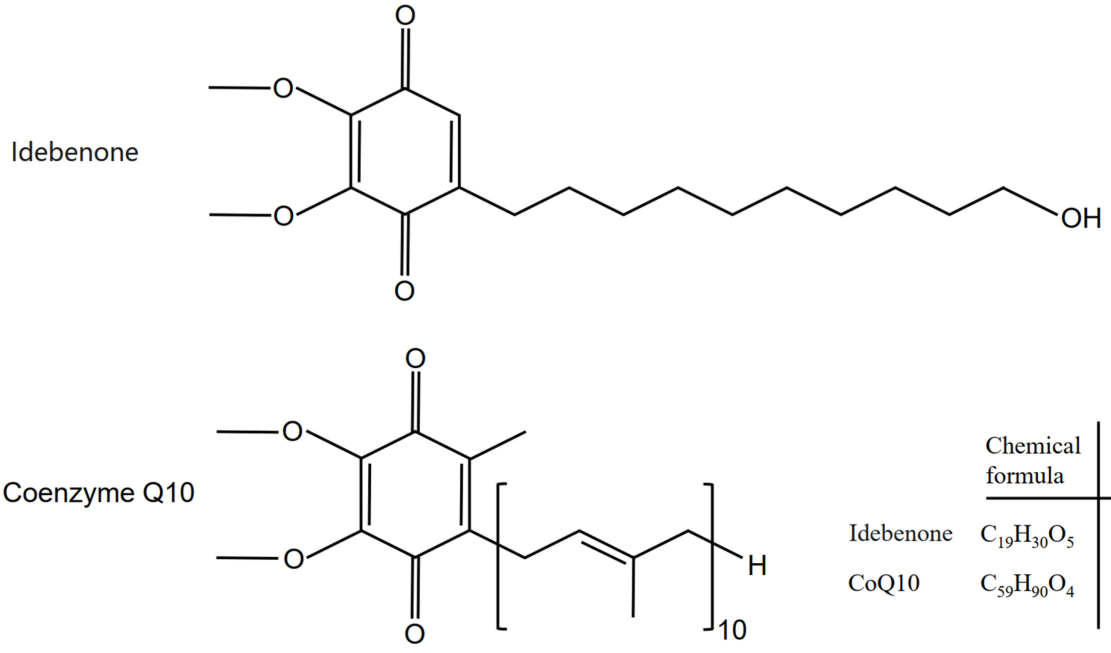
Graphical Abstract



idebenone could enhance respiratory function in glucocorticoid non-using patients with Duchenne muscular dystrophy.[10] An open-label, international, multicenter, natural history-controlled study confirmed the benefits of idebenone in patients with Leber hereditary optic neuropathy, even in the chronic phase.[11]



	Chemical formula	Molecular weight (g/mol)
Idebenone	$C_{19}H_{30}O_5$	338.44
CoQ10	$C_{59}H_{90}O_4$	863.49

Figure 1 Chemical structures of idebenone and CoQ10.

However, information regarding the clinical applications of idebenone beyond the neurological field remains limited and unclear. More importantly, there is a lack of articles to systematically summarize the research of idebenone in the non-neurological area. Therefore, our study aims to comprehensively review the potential therapeutic value of idebenone in various conditions with an analysis for the effects on health and living quality of patients.

Pharmaco-Chemical Properties of Idebenone

Idebenone, chemically known as 6-(10-hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone, is a yellow crystal or crystalline powder with a relative molecular weight of 338.44. It is relatively insoluble in water, but easily dissolved in organic solvents[1,12] (Table 1).

The half-life of idebenone varies with age, being approximately 9.4±0.5 hours for children, 10.4±1 hours for adolescents, and 12.7±2 hours for adults.[13] Following oral administration, idebenone is rapidly metabolized via oxidative shortening by various cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) to yield QS4, QS6, QS8 and QS10. Idebenone and these metabolites concomitantly undergo conjugation via glucuronidation and sulfatation to yield conjugated moieties represented as idebenone-C, QS4-C, QS6-C, QS8-C and QS10-C.[14]

Idebenone, a synthetic short-chain benzoquinone, is believed to possess superior pharmacological and chemical properties compared to CoQ10. It exhibits lower hydrophobicity than natural CoQ10 and has minimal toxicity.[15,16] Idebenone acts not only as an antioxidant but also participates in the electron transport chain at the mitochondrial membrane. Unlike CoQ10, which accepts electrons from complex I (nicotinamide adenine dinucleotide (NADH) dehydrogenase), idebenone effectively transfers electrons from complex II (succinate dehydrogenase) to complex III[17] (Figure 2). In the model proposed by King et al, idebenone is reduced at the hydrophobic quinone binding site within complex I but dissociates slowly due to its low lipophilicity. Consequently, it competitively inhibits endogenous CoQ10 function without substituting for its electron transfer function to mitochondrial complex III.[18] Despite early research confirmed that idebenone restored the oxidation of succinate in canine and rat CoQ10-depleted brain mitochondria, NADH oxidation in the presence of idebenone was independent of downstream components of the electron transport chain.[19] Experiments using fibroblasts, which oxidized mainly NADH-linked substrates, demonstrated that idebenone was not competent to replace CoQ10 in the mitochondrial respiratory chain under conditions of CoQ10 deficiency.[20]

Table 1 Pharmaco-Chemical Differences Between Idebenone and CoQ10

	Idebenone	**CoQ10**
Chemical formula	$C_{19}H_{30}O_5$	$C_{59}H_{90}O_4$
Molecular weight (g/mol)	338.44	863.49
Length of the sidechain	Short	Long
Water solubility	Low	Very Low
Liposolubility	High	High
In vivo t_{max}	1–3 h	6–8 h
In vivo $t_{1/2}$	10–15 h	About 33 h
Ability to cross membranes	Yes	No
Complex I inhibitor	Yes	No
Complex II substrate	Yes	Yes
Complex III substrate	Yes	Yes
Antioxidation	Extremely High	High

Abbreviation: CoQ10, Coenzyme Q10.

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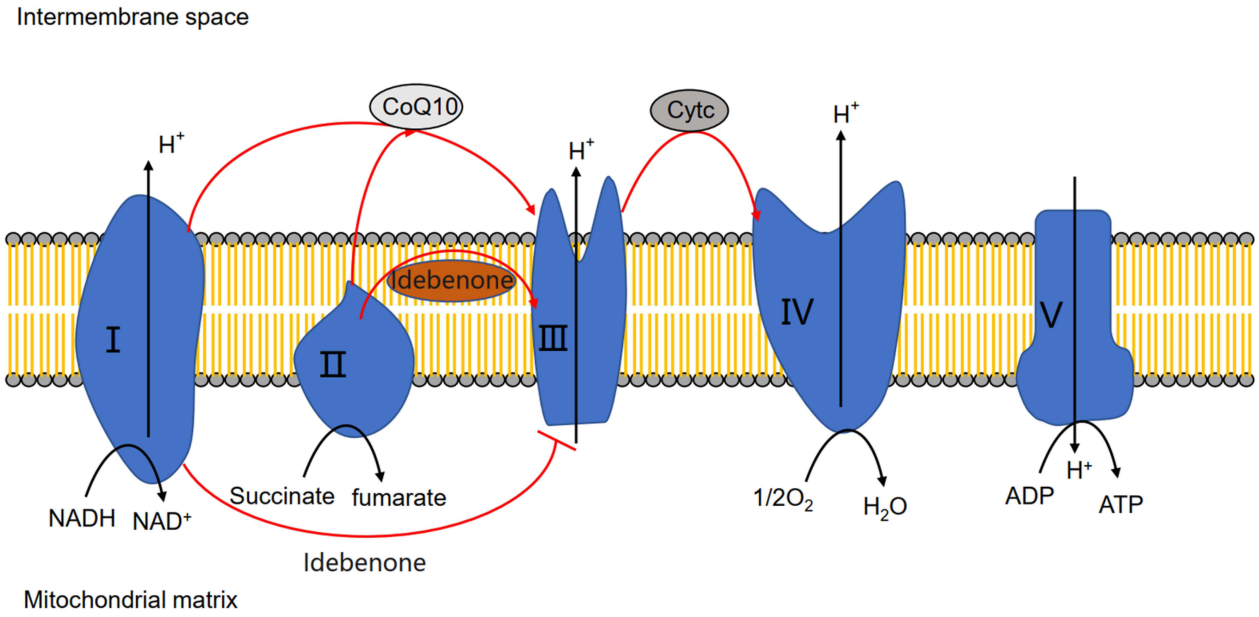

Figure 2 The role of idebenone and CoQ10 in mitochondrial electron transport chain.

Idebenone and Cancers

Idebenone and Breast Cancer

Breast cancer, one of the most prevalent cancers diagnosed globally, accounted for an estimated 2.3 million new cases in 2020.[21] With approximately 685,000 deaths, it was responsible for 16% of cancer deaths in female individuals.[22,23]

Among breast cancers, the triple-negative breast cancer (TNBC) stands out as a particularly aggressive form characterized by the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor 2 protein expression. TNBC often presents as one of high-grade tumors associated with elevated rates of relapse and mortality, making this disease subtype a clinical challenge to treat, and necessitating the development of novel and more effective targeted therapies or combinations.[24–27] A recent study conducted by a team of Chinese researchers investigated the potential therapeutic role of idebenone in TNBC. The results demonstrated that idebenone exerted inhibitory effects on TNBC through the GADD45/CyclinB/CDK1 signaling pathway, thus further impeded the proliferation, colony formation, migration, and invasion of TNBC cells, while halted the cell cycle in the G2/M phase. Additionally, idebenone disrupted mitochondrial membrane potential and promoted mitophagy, thereby activating cell autophagy via the AMPK/mTOR pathway and further suppressing TNBC cell proliferation[28] (Table 2).

Idebenone and Melanoma

Melanoma, characterized as a "ROS-driven" malignancy, represents the most fatal form of skin cancer originating from the malignant transformation of melanocytes. Melanocytes are pigment-producing cells primarily found in the skin, but can also be present in the eyes, ears, gastrointestinal tract, and oral and genital cavities.[34–36] Currently, early surgical intervention remains the optimal treatment for melanoma, with no established standard adjuvant therapy available for this cancer.[37,38]

In recent years, one of the most promising approaches in melanoma treatment involves utilizing the drug delivery systems as carriers capable of delivering therapeutic agents to the tumor microenvironment. This strategy aims to prevent degradation of the active ingredient, improve release kinetics, hinder premature drug metabolism before reaching the target site, and enhance the safety and efficacy profiles of adjuvant cancer therapy.[39] A noteworthy example is the utilization of microneedle-assisted topical delivery of idebenone-loaded bioadhesive nanoparticles, which has demonstrated a long-lasting protective effect against skin damage. This approach was shown to reduce levels of ROS and advanced glycation end-products in skin tissues, while also suppress melanogenesis.[40] Sonia Trombino et al designed microparticles using silk fibroin and epifibroin 0039, silk-derived

Table 2 The Anti-Tumor Effects of Idebenone

Author	Country	Models	Administration Route	Effects
Zhang (2024)[28]	China	TNBC cell lines and Xenograft mouse models	In vitro and in vivo experiments	Idebenone halted the cell cycle in the G2/M phase by GADD45/CyclinB/CDK1 signaling pathway, and promoted cell autophagy by disrupting the mitochondrial membrane potential and promoting mitophagy through the AMPK/mTOR pathway
Trombino (2024)[29]	Italy	COLO-38 cells	Cells culture in vitro	Idebenone reduced the proliferation of melanoma tumor cells
Damiani (2019)[30]	UK	U373MG and U87MG cells	Cells culture in vitro	Idebenone affected the clonogenic and migratory capacity of glioblastoma cell lines via inducing apoptosis and S-phase arrest
Tai (2011)[31]	USA	Neuroblastoma SHSY-5Y cells	Cells culture in vitro	Idebenone induced apoptotic cell death to reduce the viability of neuroblastoma cells
Tang (2024)[32]	China	HepG2 cells and nude mouse model	In vitro and in vivo experiments	Idebenone suppressed the proliferation and metastasis of hepatocellular carcinoma through regulating mitochondrial ROS and promoting apoptosis
Seo (2015)[33]	Korea	PC-3/CFPAC-1 cells	Cells culture in vitro	Idebenone impeded prostatic/pancreatic carcinoma cells proliferation and induced apoptosis by inhibiting ANO1/TMEM16A chloride channel

Abbreviations: TNBC, triple-negative breast cancer; ROS, reactive oxygen species.

proteins loaded with idebenone.[29] Efficacy studies revealed a decrease in the proliferation of COLO-38 melanoma tumor cells, and safety assessments confirmed that the microparticles were non-cytotoxic. Analysis of proinflammatory markers CD54 and CD86 indicated that the silk fibroin-based particles did not possess prosensitizing activity. These findings substantiated the effectiveness of idebenone-loaded silk protein microparticles in reducing the proliferation of melanoma cells without cytotoxicity (Table 2).

Idebenone and Neural Tumors

Glioblastoma, previously known as glioblastoma multiforme, represents the most prevalent and aggressive form among infiltrative gliomas, a group of primary malignant tumors originating from the central nervous system.[41] Despite recent advancements in multimodality therapy for glioblastoma, which includes surgical resection, radiotherapy, chemotherapy, targeted therapy, and supportive care, the overall prognosis remains unfavorable, with long-term survival being rare.[42,43] Idebenone shows promise as a potential anti-cancer agent for glioblastoma.[30] In experiments conducted on two glioblastoma cell lines, U373MG and U87MG, idebenone demonstrated a time- and concentration-dependent decrease in cell viability. It also affected clonogenic and migratory capacity, and down-regulated p21 protein expression. Furthermore, idebenone enhanced the cytotoxic effects of two known anti-proliferative agents, temozolomide and oxaliplatin. Mechanistically, idebenone likely exerted its effects through cell cycle dysregulation, as evidenced by flow cytometric cell cycle analysis revealing S-phase arrest in U87MG cells. Additionally, the down-regulation of caspase-3 protein expression was observed in U373MG cells, indicating idebenone-induced apoptosis, which was confirmed by flow cytometric Annexin V/propidium iodide staining (Table 2).

Neuroblastoma is a malignancy that arises in the sympathetic nervous system, particularly sympathoadrenal progenitor cells, which differentiate into adrenal chromaffin cells and sympathetic ganglion cells.[44] As the most common extracranial solid tumor in children, neuroblastoma accounts for up to 15% of childhood cancer-related mortality. Unfortunately, it carries a poor prognosis, with 5-year event-free survival rates ranging from 50% to 60%.[45,46] The genetic, morphological, and clinical heterogeneity of neuroblastomas poses challenges for existing treatment modalities.[47] Kwok-Keung Tai et al discovered that idebenone, at high concentrations, induced apoptotic cell death in dopaminergic neuroblastoma SHSY-5Y cells.[31] Exposure of SHSY-5Y cells to idebenone for 72 hours at 25um or above concentration resulted in the reduced cell viability, as determined

by MTT assay, and induced significant amount of cell death revealed by extensive trypan blue-positive staining. Idebenone-induced cell death was apoptotic in nature, which was characterized by genomic DNA fragmentation and accumulation of cytochrome c in the cytosol. Through a series of experiments, idebenone was proven be a viable therapeutic option for neuroblastoma as it was capable of inducing apoptosis (Table 2).

Idebenone and Hepatocellular Carcinoma

Hepatocellular carcinoma, ranked as the sixth most prevalent malignancy and the fourth leading cause of cancer-related mortality worldwide,[48] commonly develops in individuals with chronic liver diseases such as viral hepatitis, alcohol-related liver disease (ALD), and nonalcoholic liver diseases.[49] The management of hepatocellular carcinoma patients typically involves a multidisciplinary approach, with collaboration among surgeons, medical oncologists, radiation oncologists, and interventional radiologists to ensure the optimal care.[50] However, the overall survival rate for hepatocellular carcinoma remains poor, with a median survival of 6–10 months, highlighting the urgent need for novel therapeutic options.[51,52]

Studies have reported that hepatocellular carcinoma progression and metastasis are closely associated with altered mitochondrial metabolism, encompassing mitochondrial stress responses, metabolic reprogramming, and mitoribosomal defects.[53] In a recently published study, researchers discovered that idebenone exhibited potent suppression of proliferation and metastasis in hepatocellular carcinoma by regulating mitochondrial ROS.[32] For one thing, idebenone effectively decreased the cell viability, inhibited the invasion and migration of HepG2 cells revealed by CCK-8, Wound-Healing and Transwell assays. Furthermore, intracellular ROS detection revealed that idebenone significantly reduced the total ROS level and mitochondrial ROS level, thereby alleviating oxidative damage. For another, the results indicated that idebenone promoted the apoptosis, while inhibited the tumorigenic and metastasis ability of tumor cells in vivo, according to the nude mouse model with HepG2 cells (Table 2).

Idebenone and Other Cancers

Oncogenes, which play a direct or indirect role in promoting cancer proliferation and progression, serve as drivers of tumorigenesis.[54,55] Numerous studies have described the correlation between the expression of ion channels and tumorigenesis.[56,57] Anoctamin 1 (ANO1), a calcium-activated chloride channel (CaCC) is frequently overexpressed in various cancer types and associated with poor prognosis.[58] In a study conducted by Yohan Seo et al, it was discovered that idebenone exhibited potent inhibition of the ANO1/CaCC channel activity in prostatic carcinoma PC-3 and pancreatic carcinoma CFPAC-1 cells. Furthermore, idebenone significantly reduced cell proliferation, inhibited cell migration, and induced apoptosis in these cells.[33] These findings suggest that idebenone, as a novel ANO1 inhibitor, holds promise as a potential candidate for the development of innovative therapeutic agents for the prevention and treatment of cancer (Table 2).

Idebenone and Cardiovascular Diseases

Idebenone and Atherosclerosis

Atherosclerosis, a progressive inflammatory disease triggered by excessive oxidized low-density lipoprotein (ox-LDL), underpins various cardiovascular diseases, such as peripheral artery disease, acute coronary syndrome, and stroke.[59,60] Its development involves a complex interplay of abnormal lipid transport and metabolism, impaired endothelial function, inflammation, and oxidative stress.[61]

One of studies investigating idebenone supplementation in atherosclerotic disease focused on cultured vascular endothelial cells from fetal bovine aorta. The study revealed that incubation with idebenone inhibited the toxicity of oxLDL, without affecting copper-induced modification of LDL. These findings suggested that the protective effects of idebenone against oxLDL-induced endothelial toxicity could be beneficial in inhibiting atherosclerosis development.[62] More recent studies have delved into specific signaling pathways or mechanisms associated with atherosclerosis. Through the experimental model using oxLDL-induced human umbilical vein endothelial cells (HUVECs), Pengfei Lin et al demonstrated that idebenone showed promise as a treatment or preventive agent for atherosclerosis. Idebenone not only inhibited apoptosis induced by oxLDL through the mitochondrial-dependent apoptotic pathway but also protected against oxLDL-mediated cytotoxicity via GSK3β/β-catenin signaling pathways.[63] Subsequently, researchers further confirmed that idebenone held therapeutic potential for

patients with atherosclerosis by improving mitochondrial dysfunction and inhibiting oxidative stress through the inhibition of NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) activation via the SIRT3-SOD2-mtROS pathway. On the one hand, idebenone significantly regulated the expression of SIRT3, SOD2, and NLRP3 both in vivo and in vitro. On the other hand, idebenone protected against endothelial cell damage and inhibited the production of mtROS in cholesterol-treated HUVECs[64] (Table 3).

Statins are the first-line choice for protecting against atherosclerosis due to their LDL-lowering and anti-inflammatory effects.[72] Statin-mediated inhibition of the NLRP3 inflammasome has been observed both in vivo and in vitro.[73,74] Min Tong et al aimed to investigate the anti-atherosclerotic effect of combining idebenone with statins, which could offer an improved therapeutic option. Their study suggested that the combination of idebenone and rosuvastatin appeared to be a promising strategy for further preventing atherosclerosis by suppressing oxidative stress and NLRP3 inflammasome activation in both in vivo and in vitro settings.[65] Furthermore, another study from the same team reported that idebenone ameliorated simvastatin-induced myotoxicity in atherosclerotic ApoE-/- mice by reducing oxidative stress and improving mitochondrial function[66] (Table 3).

Table 3 The Cardioprotective Effects of Idebenone

Author	Country	Diseases	Models	Effects
Naito (1993)[62]	Japan	Atherosclerosis	Vascular endothelial cells from fetal bovine aorta	Idebenone inhibited of the development of atherosclerosis by reducing oxLDL-induced endothelial toxicity
Lin (2015)[63]	China	Atherosclerosis	Human umbilical vein endothelial cells	Idebenone inhibited mitochondrial dysfunction induced by oxLDL through the mitochondrial-dependent apoptotic pathway and GSK3β/β-catenin signalling pathways
Jiang (2021)[64]	China	Atherosclerosis	Human umbilical vein endothelial cells and apoE-/- mice model	Idebenone acted as a mitochondrial protective agent by inhibiting the activation of NLPR3 via the SIRT3-SOD2-mtROS pathway
Yu (2023)[65]	China	Atherosclerosis	Human umbilical vein endothelial cells and apoE-/- mice model	Idebenone suppressed oxidative stress and NLRP3 inflammasome activation
Yu (2024)[66]	China	Atherosclerosis	Human umbilical vein endothelial cells and apoE-/- mice model	Idebenone ameliorated simvastatin-induced myotoxicity in atherosclerotic apoE-/- mice by reducing oxidative stress and improving mitochondrial function
He (2024)[67]	China	Hypertension	Two-kidney one-clip rat model of renal hypertension	Idebenone provided the protective effect on renovascular arterial hypertension by inhibiting inflammation, oxidative stress, and apoptosis
Shimamoto (1982)[68]	Japan	Hypertension	Spontaneously hypertensive rat model	Idebenone had a mild antihypertensive effect and improves the myocardial energy state in the hypertrophied heart
Li (2023)[69]	China	Myocardial infarction	Myocardial infarction cells and animal model	Idebenone attenuated ferroptosis by inhibiting excessive autophagy via the ROS-AMPK-mTOR pathway to preserve cardiac function after myocardial infarction
Buyse (2009)[70]	Belgium	Heart failure	Dystrophin deficient mdx mouse model	Idebenone treatment significantly corrected cardiac diastolic dysfunction and prevented mortality from cardiac pump failure induced by dobutamine stress testing in vivo, significantly reduced cardiac inflammation and fibrosis, and significantly improved voluntary running performance in mdx mice
Sagie (2001)[71]	Israel	Heart failure	A woman with severe combined right and left heart failure	Following idebenone treatment there was a dramatic improvement in the clinical status with resolution of the heart failure

Abbreviations: oxLDL, oxidized low-density lipoprotein; NLPR3, NOD-, LRR-, and pyrin domain-containing protein 3; ROS, reactive oxygen species.

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Idebenone and Hypertension

Hypertension, defined as persistently elevated systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure of at least 90 mmHg according to the guidelines of the International Society of Hypertension, affects approximately 33% of the global population of 8 billion individuals.[75–77] It represents a significant risk factor for cardiovascular events, including heart attack, stroke, myocardial infarction, heart failure, and renal failure. The risk of mortality from these conditions increases twofold with every 20 mmHg rise in systolic blood pressure and every 10 mmHg increase in diastolic blood pressure.[78,79]

As the most influential modifiable risk factor for overall morbidity and mortality, several studies have explored the use of idebenone in hypertension (Table 3). By employing the two-kidney one-clip rat model of renovascular arterial hypertension, it was demonstrated that idebenone exerted protective effects on the kidneys through its suppressive actions on inflammation, oxidative stress, and apoptosis. These findings might offer potential guidance for the use of idebenone in managing renovascular arterial hypertension.[67] N. Shimamoto et al also confirmed that idebenone exhibited a mild antihypertensive effect and improved the myocardial energy state in hypertrophied hearts during the sustained phase of hypertension in spontaneously hypertensive rats.[68]

Idebenone and Myocardial Infarction

Myocardial infarction, one of the life-threatening coronary-associated pathologies, is characterized by sudden cardiac death, and carries a high mortality rate.[80,81] Regardless of whether the culprit coronary artery undergoes prompt revascularization, millions of cardiomyocytes die from persistent ischemia and hypoxia following myocardial infarction.[82] Residual ischemia in the peri-infarct border zone leads to further damage to cardiomyocytes, resulting in a progressive decline in contractile function.[83] Currently, no treatment has successfully increased vascularization in the infarcted heart.

Emerging evidence suggests that ROS-induced lipid peroxidation contributes to autophagy and ferroptosis, leading to the loss of healthy myocardium and subsequent dysfunction of cardiac tissue.[84,85] Therefore, it is crucial to identify drugs that can alleviate autophagy and ferroptosis while providing cardioprotection after myocardial infarction. Demin Li et al confirmed that idebenone effectively prevented excessive autophagy and subsequent ferroptosis through modulation of the ROS-AMPK-mTOR pathway axis.[69] More importantly, idebenone demonstrated its cardioprotective function by regulating ROS-dependent autophagy and inhibiting ferroptosis in a mouse model of myocardial infarction. These findings paved the way for future clinical translation of idebenone in the management of myocardial infarction (Table 3).

Idebenone and Heart Failure

Heart failure, characterized by a complex and life-threatening clinical syndrome involving structural and/or functional impairment of cardiac blood ejection, is associated with substantial morbidity and mortality, reduced functional capacity and quality of life, and high economic burden.[86,87] It affects a staggering population of over 64 million individuals worldwide,[88] making efforts to alleviate its social and economic impact a critical global public health priority.

In a long-term blinded placebo-controlled study, idebenone treatment demonstrated notable benefits. It effectively corrected cardiac diastolic dysfunction, prevented the development of lethal acute heart failure induced by dobutamine stress protocol, reduced cardiac inflammation and fibrosis, and improved voluntary running performance in dystrophin-deficient mdx mice.[70] Furthermore, T. Lerman-Sagie et al reported a case of a woman with severe combined right and left heart failure caused by mitochondrial cardiomyopathy. Remarkably, her clinical condition experienced a remarkable improvement, with resolution of heart failure following idebenone treatment[71] (Table 3).

Idebenone and Diabetes Mellitus

Diabetes mellitus, an irreversible and chronic metabolic disorder indicated by hyperglycemia, arises from insufficient insulin levels that impede the physiological disposal of glucose and hinder energy storage in adipose tissue, muscle, and liver. This condition leads to complications affecting multiple organs and systems, reducing quality of life and increasing mortality rates.[89,90] Diabetes mellitus is traditionally classified into various clinical categories, including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus, and other specific types resulting from genetic causes, exocrine pancreatic disorders, or medications.[91] As a global pandemic now, our understanding of the

pathophysiology, treatment, and prevention about diabetes mellitus has significantly expanded. It is noteworthy that idebenone has emerged as a novel clinical drug for diabetes mellitus (Table 4).

In a diabetic rat model, it was demonstrated that the administration of insulin and idebenone reduced blood-brain barrier permeability by upregulating protein expressions of occludin, claudin-5, and ZO-1, suggesting that the combined therapy exerted a synergistic or enhanced effect.[92] The ROS/AGE/RAGE/NF-κB signaling pathway might be involved in the regulation of blood-brain barrier permeability by insulin and idebenone in diabetes mellitus.

Table 4 The Pharmacological Effects of Idebenone in Diabetes Mellitus, Liver Diseases, Urogenital Diseases, Sepsis and Other Diseases Beyond Neurological Fields

Author	Country	Models	Effects
Sun (2015)[92]	China	Diabetic rat model	The combination of insulin and idebenone could decrease the blood-brain barrier permeability in diabetic rats by upregulating the expression of occludin, claudin-5, and ZO-1 and the ROS/AGE/RAGE/NF-κB signal pathway might be involved in the process.
Jintao (2022)[93]	China	Diabetic rat model	Idebenone-loaded wound dressings promoted diabetic wound healing through downregulation of Il1b, Nfkb genes and upregulation of Fgf2 gene
Tomilov (2018)[94]	USA	FL83B cells and ShcKD mice model	Idebenone acted as a cytoprotective insulin sensitizer whose mechanism was Shc inhibition
Hui (2020)[95]	USA	HEK 293 and FL83B cells, and C57BL/6 mice model	Idebenone blocked Shc's access to insulin receptor to improve insulin sensitivity
Zhao (2024)[96]	China	HEK 293 cells, Wistar rat and C57BL/6 mice models	Idebenone enhanced glucose-stimulated insulin secretion via agonism of GLP-1R
Higa (2017)[97]	Argentina	Albino Wistar rat model	Pro-oxidant/pro-inflammatory alterations in the offspring´s heart of mild diabetic rats were regulated by maternal treatments with idebenone
Higa (2018)[98]	Argentina	Albino Wistar rat model	Maternal idebenone treatment ameliorated parameters related to the prooxidant-proinflammatory environment found in embryos from mild diabetic rats
Linenberg (2021)[99]	Argentina	Albino Wistar rat model	The maternal treatment with idebenone in pregestational diabetic rats alleviated placental alterations in proteins related to inflammation, and regulated the intergenerational placental nitrative damage
Tiefenbach (2018)[100]	Canada	Transgenic zebrafish, C57BL/6 *db*/*db* mice model, murine 3T3-L1 cells	Idebenone was novel PPARα/γ ligands, with potential treatment options for fatty liver diseases
Han (2024)[101]	China	C57BL/6J mice models	Idebenone inhibited the activation of hepatic stellate cells through its antioxidant activity to suppress EphB2-mediated FAK/MAPK pathway
Jiang (2021)[102]	USA	Fibrotic methionine-choline deficient diet and the metabolic fast food diet mouse models of nonalcoholic steatohepatitis	Idebenone blocked Shc activation to ameliorate liver injury and fibrosis.
Yoladi (2024)[103]	Turkey	Abino Wistar rat model	Idebenone prevented the hepatotoxicity caused by ethanol by inhibiting the NLRP3/caspase-1/IL-1 pathway

(*Continued*)

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Table 4 (Continued).

Author	Country	Models	Effects
Shivaram (1998)[104]	USA	Isolated rat hepatocytes and in isolated hepatic mitochondria from Sprague-Dawley rats	Idebenone functioned as a potent protective hepatocyte antioxidant during hydrophobic bile acid toxicity, perhaps by reducing generation of oxygen free radicals in mitochondria
Wieland (1995)[105]	Germany	Rat liver microsomal models	Idebenone had the potential to protect hepatic microsomes against oxygen radical-mediated damage during liver transplantation
Fadda (2018)[106]	Saudi Arabia	Abino Wistar rat model	Idebenone ameliorated oxidative stress, inflammation, DNA damage, and apoptosis induced by titanium dioxide nanoparticles in rat liver
Schreiber (2019)[107]	Germany	Tissue samples from patients with autosomal dominant polycystic kidney disease, embryonic kidney cultures	Idebenone might delay cyst development in polycystic kidney disease, by largely reducing activation of TMEM16A
Rasheed (2013)[108]	Saudi Arabia	Abino Wistar rat model	Idebenone took prophylactic role on the toxic impacts of titanium dioxide nanoparticles on rat kidneys, by alleviating immuno-inflammatory and oxidative renal damage
Blanco (2020)[109]	USA	MRL/*lpr* mice model	Idebenone improved kidney damage, vascular dysfunction, inflammatory cascades, neutrophil dysregulation and mitochondrial metabolism
Lone (2019)[110]	India	Ram semen samples	Idebenone mitigated oxidative stress to improve quality of ram semen during cryopreservation
Eslami (2019)[111]	Iran	Ram semen samples	Idebenone ameliorated nitrosative and peroxidative stress to improve quality of ram semen at 4°C
Nikitaras (2021)[112]	Australia	Sperm from men aged >40 years and older CBAF1 mice (12–18 months)	The addition of idebenone to sperm culture media reduced sperm ROS concentrations associated with advanced paternal age
Abdelzaher (2022)[113]	Egypt	Juvenile rat model	Idebenone regulated Sirt1/Nrf2/TNF-α pathway with inhibition of oxidative stress, inflammation, and apoptosis in testicular torsion/detorsion
Choi (2024)[114]	Republic of Korea	Murine macrophage cell lines RAW 264.7 and J774A.1, C57BL/6 mice models of sepsis and systemic inflammation	Idebenone treatment suppressed inflammatory responses in macrophages, inhibited the NF-κB signaling pathway, reduced reactive oxygen species and lipid peroxidation, and normalized the activities of antioxidant enzyme
Gou (2022)[115]	China	Sprague-Dawley rat model	Idebenone attenuated cell viability injury, apoptosis, oxidative stress, and inflammatory damage in sepsis-induced hepatocytes via RAGE/p38 signaling.
Akpinar (2022)[116]	Turkey	Abino Wistar rat model	Idebenone mitigated the inflammatory response in sepsis-induced lung injury by decreasing free radicals and preventing lipid peroxidation
McDaniel (2005)[117]	USA	A clinical trial involving 41 women	Idebenone could be an anti-aging cosmetic by improving skin roughness/dryness, skin hydration, fine lines/wrinkles, and overall global assessment of photodamaged skin

(*Continued*)

Table 4 (Continued).

Author	Country	Models	Effects
Shastri (2022)[118]	Australia	*Winnie* mice model	Idebenone protected against spontaneous chronic colitis by alleviating inflammatory response and endoplasmic reticulum stress
Qiu (2024)[119]	China	C57BL/6J mice model	Idebenone alleviated doxorubicin-induced cardiotoxicity by stabilizing FSP1 to inhibit ferroptosis
Suno (1989)[120]	Japan	Rat and human platelet samples	Idebenone suppressed platelet aggregation by regulation of thromboxane B2 synthesis
Sugizaki (2019)[121]	Japan	A549 cell or LL29 cell lines, ICR mice model	Idebenone had preventative and therapeutic effects on pulmonary fibrosis via preferential suppression of fibroblast activity

Abbreviations: ROS, reactive oxygen species; NLPR3, NOD-, LRR-, and pyrin domain-containing protein 3.

Diabetic wounds pose challenges due to various pathophysiological factors involved in their development and progression. Consequently, researchers are continuously seeking alternative solutions. Recent research using a rat model of diabetic wounds showed that idebenone-loaded wound dressings promoted diabetic wound healing by reducing oxidative stress, modulating inflammation, and promoting the formation of granulation tissue during the wound healing process.[93]

As for T2DM, Gino Cortopassi et al reported that idebenone dose-dependently decreased the interaction between SHC and the insulin receptor at pharmacologically relevant concentrations at which it sensitized cells and animals to insulin, indicating that idebenone should be considered for the treatment of insulin resistance and T2DM, particularly in patients receiving corticosteroids.[94,95,122] Additionally, Xin Zhao et al identified, for the first time, that idebenone promoted glucose-dependent insulin secretion through agonism of GLP-1R, leading to the reduced blood glucose levels in mice. This discovery offered a potential therapeutic strategy for the prevention and treatment of metabolic diseases such as T2DM.[96]

Maternal diabetes has implications for the metabolic and cardiovascular health of offspring. A team from the University of Buenos Aires investigated the effect of idebenone on the intergenerational programming of gestational diabetes mellitus. Their initial study revealed evident cardiac alterations in the offspring of mild diabetic rats, while maternal treatment with idebenone prevented these alterations in the offspring's hearts.[97] Another study found that the antioxidant properties of idebenone inhibited the increases in markers of prooxidant and proinflammatory processes in embryos from mild diabetic rats during organogenesis.[98] Furthermore, it was reported that idebenone alleviated placental alterations in proteins related to inflammation and regulated intergenerational placental nitrative damage.[99]

Idebenone and Liver Diseases

Liver disease is responsible for two million deaths annually, accounting for 4% of all deaths.[123,124] Numerous studies have reported on the liver-protective effects of idebenone (Table 4).

A zebrafish screen identified idebenone as a novel ligand for PPARα/γ, suggesting its potential as a treatment option for fatty liver diseases.[100] In two mouse models of liver fibrosis, idebenone decreased hepatic injury through its antioxidant activity and inhibition of EphB2 function.[101] Additionally, as the first small-molecule SHC inhibitor drug,[94] idebenone ameliorated liver injury and fibrosis in two mouse models of nonalcoholic steatohepatitis.[102] By inhibiting the NLRP3/caspase-1/IL-1 pathway, idebenone also prevented ethanol-induced hepatotoxicity in rats.[103] Moreover, idebenone acted as a potent protective hepatocyte antioxidant during hydrophobic bile acid toxicity, perhaps by reducing the generation of oxygen free radicals in mitochondria.[104] Additionally, during liver transplantation, idebenone showed potential in protecting hepatic microsomes against oxygen radical-mediated damage.[105]

Nano-sized titanium dioxide, a commonly used metallic nanoparticle, can accumulate and cause toxicity in human and animal organs. Excess oral administration of titanium powder induces liver damage, leading to an increase in the ALT/AST ratio, lactate dehydrogenase activity, liver weight, and hepatocyte necrosis.[125–127] Evidence suggested that

idebenone could improve liver injury induced by nano-sized titanium dioxide, given idebenone had antifibrotic and angiostatic potential, and reduced oxidative stress, inflammation, DNA damage, and apoptosis in rat liver.[106,128,129]

Idebenone and Urogenital Diseases

Urogenital diseases are the result of an imbalance of the normal homeostasis of the urinary and reproductive tracts brought about by hormonal, environmental, and management-related stress factors. With the increasing number of elderly patients with comorbidities, the prevalence of these diseases is projected to rise in the coming decades.[130] Therefore, it is crucial to ensure widespread access and affordability of new-generation protective drugs to prevent the development and delay the progression of urogenital diseases.

It was demonstrated that idebenone might be powerful therapeutic approaches to delay cyst development in polycystic kidney disease, by largely reducing activation of TMEM16A.[107] Meanwhile, idebenone had the potential to take prophylactic role on the toxic impacts of titanium dioxide nanoparticles on rat kidneys, by alleviating immuno-inflammatory and oxidative renal damage.[108] Also, idebenone was found to mitigate kidney damage, improve vascular dysfunction, inflammatory cascades and neutrophil dysregulation, suggesting the therapeutic potential in systemic lupus erythematosus.[109] Moreover, idebenone was reported to improve quality of ram semen by mitigating oxidative stress.[110,111] For another, the addition of idebenone to sperm culture media reduced sperm ROS concentrations associated with advanced paternal age, thus further improved fertilization rates, embryo quality and implantation rates after in vitro fertilization.[112] Furthermore, idebenone reduced testicular ischemia-reperfusion injury in the juvenile rat testicular torsion/detorsion model by limiting oxidative stress, inflammation, and apoptosis through modulation of the Sirt1/Nrf2/TNF-pathway[113] (Table 4).

Idebenone and Sepsis

Sepsis is a life-threatening condition characterized by the dysregulation of the host response to infection, resulting in organ dysfunction and failure.[131,132] Despite advances in clinical recognition and management, sepsis remains a global health concern and a major contributor to mortality.[133,134] Increasing studies have succeeded to confirm efficacy of intervention therapies amid sepsis, including precision medicine and personalized therapies.[135]

Idebenone exerted therapeutic effects in mice models of cecal ligation puncture-induced sepsis and lipopolysaccharide-induced inflammation. Meanwhile, in vitro experiments showed that idebenone treatment ameliorated inflammatory responses in macrophages, inhibited the NF-κB signaling pathway, reduced ROS and lipid peroxidation, and normalized the activities of antioxidant enzyme.[114] Moreover, in vivo and in vitro experiments revealed that idebenone alleviated cell viability injury, apoptosis, oxidative stress, and inflammatory damage in sepsis–induced liver injury via the RAGE/p38 signaling pathway,[115] and against sepsis-induced lung injury by decreasing free radicals and preventing lipid peroxidation[116] (Table 4).

Idebenone and Other Diseases

Idebenone has also shown potential in various other diseases. A clinical trial involving 41 women showed that skin roughness/dryness, skin hydration, fine lines/wrinkles, and overall global assessment of photodamaged skin were improved after six weeks of using 0.5% and 1.0% idebenone, suggesting the great potential of idebenone to be anti-aging cosmetics.[117] In Winnie mice, idebenone could represent a potential therapeutic approach against spontaneous chronic colitis by alleviating inflammatory response and endoplasmic reticulum stress.[118] Besides, it was proposed that idebenone attenuated doxorubicin-mediated cardiotoxicity by inhibiting ferroptosis via stabilizing of FSP1, making it a promising clinical drug for patients treating with doxorubicin.[119] In addition, idebenone suppressed platelet aggregation by regulation of thromboxane B2 synthesis,[120] and exerted inhibitory activity on the function of lung fibroblasts[121] (Table 4).

Limitations

There are some limitations to be pointed out. On the one hand, the vast majority of the included studies are in vivo and in vitro experiments, absent of enough human studies on the effects of idebenone on diseases beyond neurological conditions. On the other hand, clinical studies often lack controlled groups with homogeneous patients in terms of gender, age, or idebenone used.

However, according to the broadness of the theme, we have covered all the aspects regarding the pharmacological effects of idebenone beyond neurological diseases as comprehensive as possible.

Conclusions

Although numerous and encouraging findings in the neurological field, in particular for mitochondrial optic neuropathies, with idebenone being the only currently approved therapy into clinical practice across Europe, data about idebenone among other pathological disorders are still limited, with unknown challenges in clinical translation of idebenone beyond neurological diseases. Consequently, the objective of this study is to comprehensively review and explore the potential therapeutic uses of idebenone in various non-neurological disorders, including cancers, cardiovascular diseases, diabetes mellitus, liver diseases, urogenital diseases, sepsis, and other diseases. Firstly, idebenone acts as an electron carrier in the respiratory chain, that promotes the production of ATP. In addition to impairing lipid peroxidation, idebenone, as a powerful antioxidant, is capable of detoxifying a wide variety of free radicals, including peroxyl and tyrosyl radicals and peroxynitrite. Moreover, idebenone also functions as a novel anti-inflammatory agent in protecting against tissue damage, and decreased the expression of inflammatory enzymes and cytokines. Therefore, idebenone possesses potential therapeutic application in cancers, cardiovascular diseases, diabetes mellitus, liver diseases, urogenital diseases, sepsis, and other diseases. Despite these findings are based on cell and animal experiments, the preclinical data not only pave the way for the early human trials which have confirmed the feasibility and safety of idebenone, but remind that the further validation is crucial and necessary, through well-designed, long-term follow-up clinical trials in the future.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no known conflicts of interests or personal relationships that could have appeared to influence the work reported in this paper.

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