Pharmaceutical Sciences Asia

Pharm Sci Asia 2025; 52(1), 30-43

DOI:10.29090/psa.2025.01.24.2456

Research Article

A Systematic Review of Antidiabetic Drug Benefits in Mitochondrial Dysfunction-Associated Cardiovascular Diseases

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ABSTRACT

Mitochondrial dysfunction is associated with the development of numerous cardiovascular diseases. Antidiabetic drugs are known to possess cardioprotective effects; however, mechanisms underlying their efficacies on mitochondrial dysfunction-associated cardiovascular diseases have not been systematically reviewed. A comprehensive literature search in the past five years from August 1, 2018, to July 31, 2023, from three electronic databases, including Pubmed, Embase, and Scopus, was carried out according to the defined inclusion and exclusion criteria. A total of 637 articles were identified, out of which 37 research articles were included in this study. We found that the sodium-glucose cotransporter 2 (SGLT-2) inhibitor was the most investigated class of antidiabetic drugs for alleviating cardiovascular diseases associated with mitochondrial dysfunction (16 articles, 43%). Focusing on the spectrum of cardiovascular diseases, the most extensively studied group was classified as other forms of heart disease (e.g., heart failure, myocardial abnormalities, etc.) with a total of 20 articles (56%). The impacts of antidiabetic drugs on mitochondrial structure included maintaining mitochondrial morphology (50%) as well as preserving mitochondrial dynamics via fission (35%) and fusion (15%) processes. For mitochondrial functions, antidiabetic drugs exerted several cardioprotective impacts via different mechanisms, including reducing oxidative stress (33%), decreasing apoptotic cell death (24%), promoting mitochondrial biogenesis (17%), preserving cellular respiration (11%), maintaining autophagy (6%), enhancing mitochondrial membrane potential (6%), reducing ferroptosis (2%), and preserving calcium homeostasis (1%). In conclusion, antidiabetic drugs provide benefits to cardiac defensive mechanisms by controlling biomarkers associated with mitochondrial structure and functions.

Keywords:
Antidiabetic drugs; Cardiovascular diseases; Mitochondrial dysfunction; Systematic review

1. INTRODUCTION

Cardiovascular diseases account for approximately one-third of all global mortalities, primarily from heart attacks and strokes, making them the leading cause of death worldwide[1]. Mitochondria play a crucial role in cardiovascular diseases by influencing energy production, oxidative stress, and apoptosis in cardiomyocytes and by affecting endothelial function and vascular integrity in coronary artery diseases[2]. Among a myriad of pathogenic mechanisms, mitochondrial dysfunction—characterized by impairment in the mitochondrial oxidative metabolism of substrates, including lipids and carbohydrates, resulting from a general decrease in oxidative phosphorylation—is closely related to the development of cardiovascular diseases[3].

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For example, heart failure occurs when mitochondria fail to produce sufficient energy in the myocardium, leading to an increased production of reactive oxygen species (ROS) and an imbalance of calcium homeostasis, thereby contributing to the progression of heart failure[4]. Although the pathophysiology of cardiovascular diseases is complex, targeting mitochondrial dysfunction to enhance cardiac function appears to be a promising strategy for both preventing and treating heart diseases[5].

Conventional classes of antidiabetic drugs, such as biguanides, thiazolidinediones (TZDs), and α-glucosidase inhibitors, have been reported to exhibit cardioprotective effects through various mechanisms that suppress mitochondrial dysfunction[6]. Metformin, a biguanide and the first-line treatment for type 2 diabetes mellitus (T2DM), promoted mitochondrial biogenesis through the activation of adenosine 5'-monophosphate-activated protein kinase (AMPK)[7]. Metformin also mitigated cardiac endothelial dysfunction caused by gamma radiation in rats by reducing oxidative stress, which involved decreasing cardiac biomarkers, lactate dehydrogenase (LDH) and creatine kinase MB (CK-MB), and enhancing activities of mitochondrial antioxidant enzymes, catalase and superoxide dismutase (SOD)[8]. Similarly, pioglitazone and rosiglitazone, members of the TZDs group, activated peroxisome proliferator-activated receptor-γ and reduced oxidative damage in the heart and aorta tissues in hypothyroid rats[9]. Additionally, miglitol, an α-glucosidase inhibitor, elevated plasma incretin level and mitigated cardiac hypertrophy and adverse remodeling in Dahl salt-sensitive rats fed a high-salt diet[10].

Recently, multiple lines of evidence have investigated novel classes of antidiabetic drugs, including glucagon-like peptide-1 receptor (GLP-1R) agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium-glucose cotransporter 2 (SGLT-2) inhibitors, reporting pronounced cardiovascular benefits by improving mitochondrial structure and functions[6]. GLP-1R agonists have expressed promising cardioprotective effects in various preclinical and clinical studies, irrespective of diabetes status[11]. In H9c2 cardiomyoblasts, activation of GLP-1R by exendin-4 inhibited methylglyoxal-induced mitochondrial dysfunction by exhibiting antioxidant and antiapoptotic effects, as well as improving mitochondrial functions through the cAMP/Epac/PI3K/Akt signaling pathway[12]. DPP-4 inhibitors represent another class of antidiabetic drug with significant therapeutic potential in treating cardiovascular disease[13]. In mice with diastolic dysfunction caused by a Western diet, linagliptin treatment prevented mitochondrial ultrastructural abnormalities in the heart, such as enlargement and fragmentation, and enhanced crista structure. This intervention alleviated disorganized cardiac remodeling and hypertrophy, ultimately improving both diastolic and systolic dysfunction in these mice[14]. SGLT-2 inhibitors were recently approved for the treatment of heart failure because of their cardiovascular benefits demonstrated in major clinical trials[15]. Dapagliflozin improved cardiac remodeling and reduced cardiomyocyte apoptosis in acute myocardial infarction rats induced by coronary artery ligation. Dapagliflozin also promoted mitochondrial structure and normalized mitochondrial fission via the activation of phosphoglycerate mutase 5 (PGAM-5)/dynamin-related protein 1 (Drp-1) signaling pathway, thereby suggesting the underlying mechanism of the drug's protective effect in the infarcted myocardium[16].

Although these antidiabetic drugs have demonstrated positive impacts on cardiac defense through various mechanisms, their potential benefits against mitochondrial dysfunction in cardiovascular diseases have not been comprehensively summarized. Therefore, this study aims to systematically review the mechanisms by which antidiabetic drugs exert cardioprotective roles against mitochondrial dysfunction in the heart.

2. MATERIALS AND METHODS

2.1 Search strategy

A five-year comprehensive literature search from August 1, 2018, to July 31, 2023, was conducted using three electronic databases, including Pubmed, Embase, and Scopus. The search was carried out using the following search terms: "cardiovascular diseases" OR "heart diseases" AND "antidiabetic" OR "hypoglycemic" OR "metformin" OR "dipeptidyl peptidase-4 inhibitors" OR "sodium-glucose cotransporter 2 inhibitors" OR "thiazolidinediones" OR "glucagon-like peptide-1 receptor" AND mitochondri* OR "mitochondrial respiration" OR "mitochondrial biogenesis" OR "mitochondrial dynamic" OR "reactive oxygen species" OR "oxidative stress" OR "mitophagy".

2.2 Study selection

All obtained articles were screened based on their titles and abstracts to ensure they met all of the inclusion criteria: (1) studies conducted with clinically approved antidiabetic drugs, (2) studies that mitochondrial outcomes were measured, (3) studies conducted *in vitro* or *in vivo* and have been completed, (4) studies that were published in English language, and (5) studies that published in the last 5 years (from August 1, 2018, to July 31, 2023). Following the initial screening, selected articles underwent a full-text analysis to exclude articles meeting any of the exclusion criteria: (1) studies that investigated non-FDA-approved or off-labeled antidiabetic drugs, dietary supplements (e.g., coenzyme Q_{10},linoleicacid), vitamins (e.g., vitamin E, ascorbic acid), herbs, phytotherapies, and other non-drugs, (2) studies that were

not research articles (review articles, case reports, dissertations, book chapters, conference abstracts, or protocols), (3) studies that full-text was not available, (4) studies that published in non-English languages, and (5) studies that published outside of the period August 1, 2018, to July 31, 2023. Duplicate articles were removed using the Endnote reference manager software. Furthermore, the quality of the included articles was assessed based on the CONSORT-Outcomes 2022 Extension for *in vitro* studies[17] and the ARRIVE guidelines 2.0 for *in vivo* studies[18].

2.3 Data extraction

The following data parameters were extracted from included articles: citation (author and year of publications), study design (*in vitro* or *in vivo*), cardiovascular classifications, antidiabetic drugs and their classes, study models and inducers, and main findings on biomarkers related to mitochondrial structure and functions.

3. RESULTS

3.1 Selected studies

Following a literature search, a total of 637 articles were identified, of which 265 were from Pubmed, 74 from Embase, and 298 from Scopus. After the removal of duplicates and the screening of titles and abstracts based on inclusion and exclusion criteria, 596 articles were excluded, leaving 37 articles included in the study (**Figure 1)**.

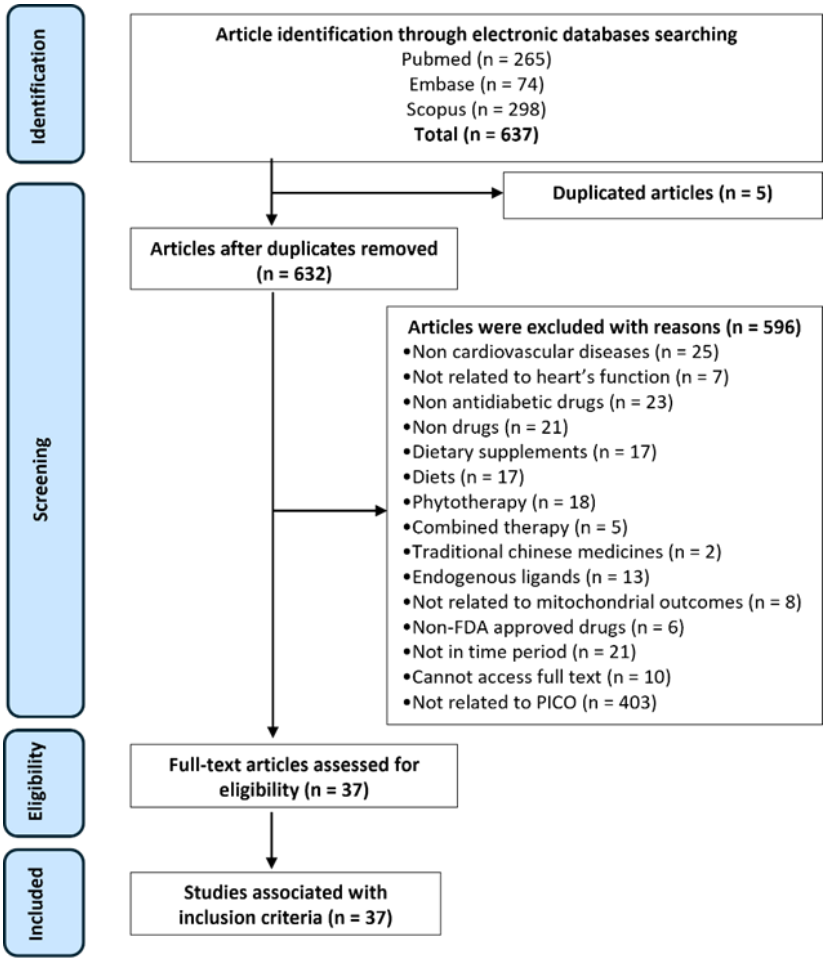

Figure 1: Prisma flow diagram illustrates the screening strategy for the selection of the articles included in this systematic review. After searching the literature, 637 articles were identified: 265 from PubMed, 74 from Embase, and 298 from Scopus. After removing duplicates and screening, 37 articles were included in the study.

3.2 Study characteristics categorized by study design and types of cardiovascular diseases

Among the 58 experiments from 37 studies, 26 experiments (52%) were *in vitro* studies and 23 experiments (48%) were *in vivo* studies **(Figure 2, left panel)**. After classifying all of cardiovascular diseases into 4 categories using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) by the World Health Organization (WHO)[19], the most extensively studied group was in the category of "other forms of heart disease" (e.g., heart failure, myocardial abnormalities,cardiac valve disorders, cardiac arrhythmias, diseases of pericardium,

cardiac arrest, etc.), with a total of 20 studies (56%), followed by 8 studies (22%) focused ondiseases of arteries, arterioles, and capillaries, 7 studies (19%) on ischemic heart disease, and 1 study (3%) on hypertension **(Figure 2, right panel)**.

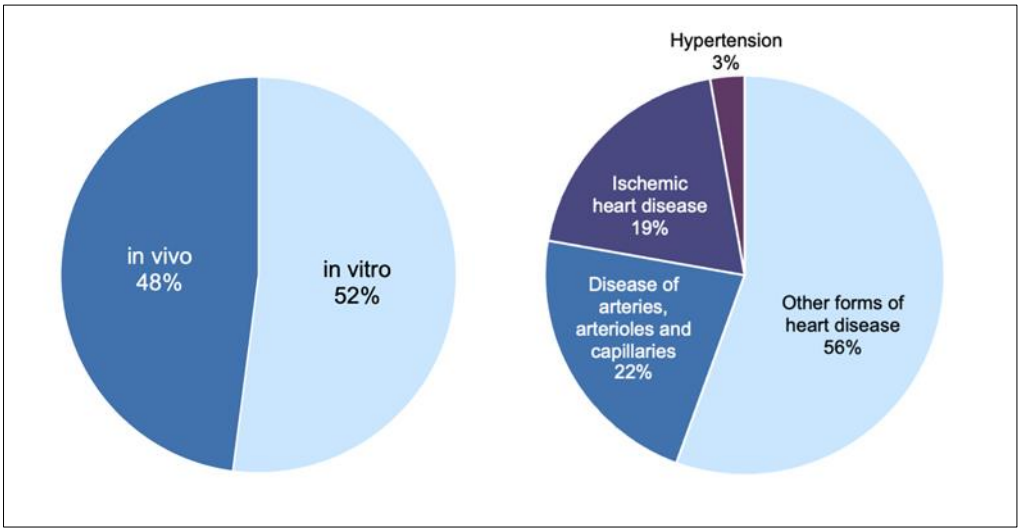

Figure 2: Characteristics of the study classified by study design and cardiovascular disease classification. Of the 58 experiments across 37 studies, 52% were in vitro, and 48% in vivo. The review classified 56% under "other forms of heart disease," 22% focused on arterial diseases, 19% on ischemic heart disease, and 3% on hypertension.

3.3 Characteristics of the studies sorted by antidiabetic drug classes

From a total of 37 studies, six classes of antidiabetic drugs were examined according to their mechanisms of action. An antidiabetic drug class known to alleviate mitochondrial dysfunction in cardiovascular diseases was the SGLT-2 inhibitors with 16 studies (43%), biguanides with 12 studies (32%), GLP-1R agonists with 4 studies (11%), and DPP-4 inhibitors with 3 studies (8%) **(Figure 3).** For SGLT-2 inhibitors, a total of 16 studies found that three drugs were studied, including empagliflozin (10 studies, 55%), canagliflozin (5 studies, 28%), and dapagliflozin (3 studies, 17%). For biguanides, only metformin was investigated (12 studies, 100%). A total of 4 studies investigated GLP-1R agonists, with exenatide being the focus of 3 studies (75%) and liraglutide being examined in 1 study (25%). Among 3 studies regarding DPP-4 inhibitors, linagliptin, sitagliptin, and alogliptin, were investigated with one study for each drug. For the TZD and alpha-glucosidase inhibitor classes, one study each (3%) on rosiglitazone and miglitol was included in the systematic review.

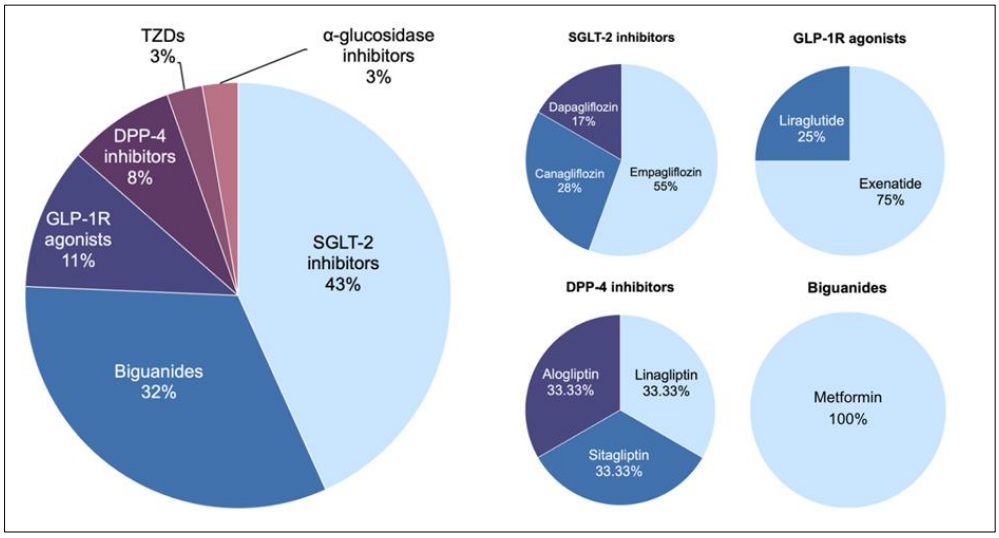

Figure 3: Characteristics of the study classified by antidiabetic drug classes. The SGLT-2 inhibitors accounted for 43% of studies on antidiabetic drugs that alleviate mitochondrial dysfunction in cardiovascular diseases, followed by biguanides at 32%, GLP-1R agonists at 11%, and DPP-4 inhibitors at 8%.

3.4 Effects of antidiabetic drugs on mitochondrial structure

According to the review, antidiabetic drugs conferred cardioprotective benefits to mitochondrial structure through various mechanisms, including maintaining mitochondrial morphology in 10 experiments (50%), reducing mitochondrial fission in 7 experiments (35%), and promoting fusion processes in 3 experiments (15%) **(Figure 4)**. Antidiabetic agents preserved mitochondrial morphology by improving mitochondrial ultrastructure, ensuring that mitochondria maintained their integrity and functionality. These drugs increased the number and mass of mitochondria and optimized their size, thereby promoting energy production and ultimately contributing to overall cellular health. Additionally, various antidiabetic drugs minimized the mitochondrial fission process by lowering the levels of fission markers, including dynamin-related protein 1 (Drp1) and phosphoglycerate mutase 5 (PGAM5). They also increased mitochondrial fusion by boosting the levels of fusion markers, such as optic atrophy-1 (Opa1) and mitofusin 1 and 2 (Mfn1 and Mfn2). The effects of antidiabetic agents on biomarkers associated with mitochondrial fusion and fission are summarized in **Table 1** for *in vitro* studies and **Table 2** for *in vivo* studies.

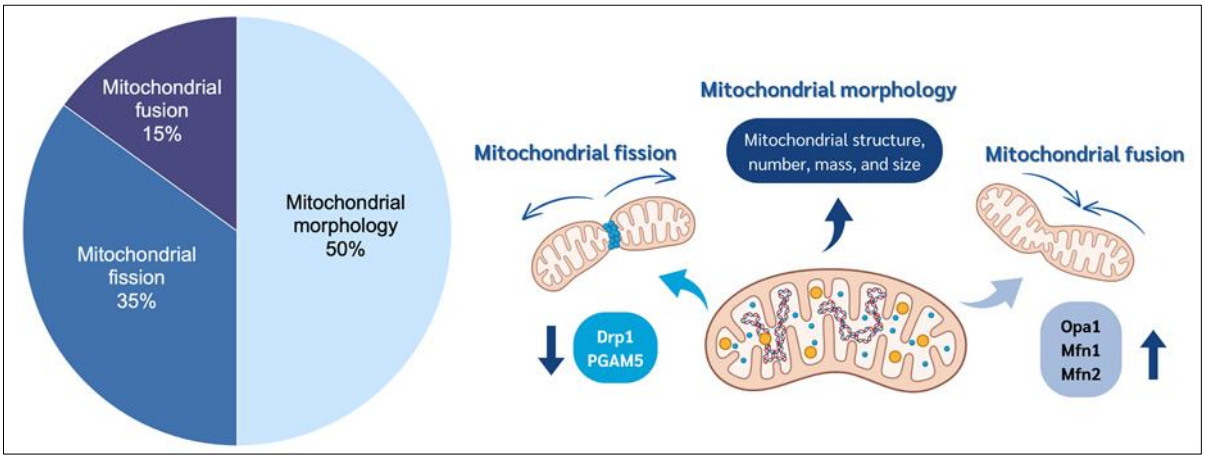

Figure 4: Influence of antidiabetic drugs on mitochondrial structure. Antidiabetic agents preserved mitochondrial morphology by increasing their number and mass and optimizing size. They reduced fission by lowering markers like Drp1 and PGAM5, while promoting fusion by enhancing levels of markers such as Opa1, Mfn1, and Mfn2.
Abbreviations: Drp1, dynamin-related protein 1; Mfn, mitofusin; Opa1, optic atrophy-1; PGAM5, phosphoglycerate mutase 5.

3.5 Impacts of antidiabetic drugs on mitochondrial functions

Regarding mitochondrial functions, antidiabetic drugs primarily enhanced mitochondrial functions by mitigating oxidative stress, as demonstrated in 35 studies (33%) by suppression of ROS generation and upregulation of antioxidant enzyme SOD level **(Figure 5)**. These drugs reduced apoptotic cell death, as shown in 26 studies (24%) by lowering levels of proapoptotic proteins (such as caspase-3 and Bax) while increasing the level of the anti-apoptotic protein, Bcl-2. Additionally, cardiac defensive mechanisms were supported by antidiabetic agents through various mechanisms, including promoting mitochondrial biogenesis, demonstrated in 18 studies (17%), preserving cellular respiration in 12 studies (11%), maintaining autophagy in 7 studies (6%), enhancing mitochondrial membrane potential (MMP) in 6 studies (6%), reducing ferroptosis in 2 studies (2%), and preserving calcium homeostasis in 1 study (1%) **(Figure 5)**. The influences of antidiabetic agents on mitochondrial function-related biomarkers are shown in **Table 1** and **Table 2** for *in vitro* and *in vivo* studies, respectively. Taken together, the cardioprotective effects of antidiabetic drugs are primarily due to their antioxidative and anti-apoptotic properties, with additional benefits from enhanced mitochondrial function, including promoted biogenesis and maintained respiration.

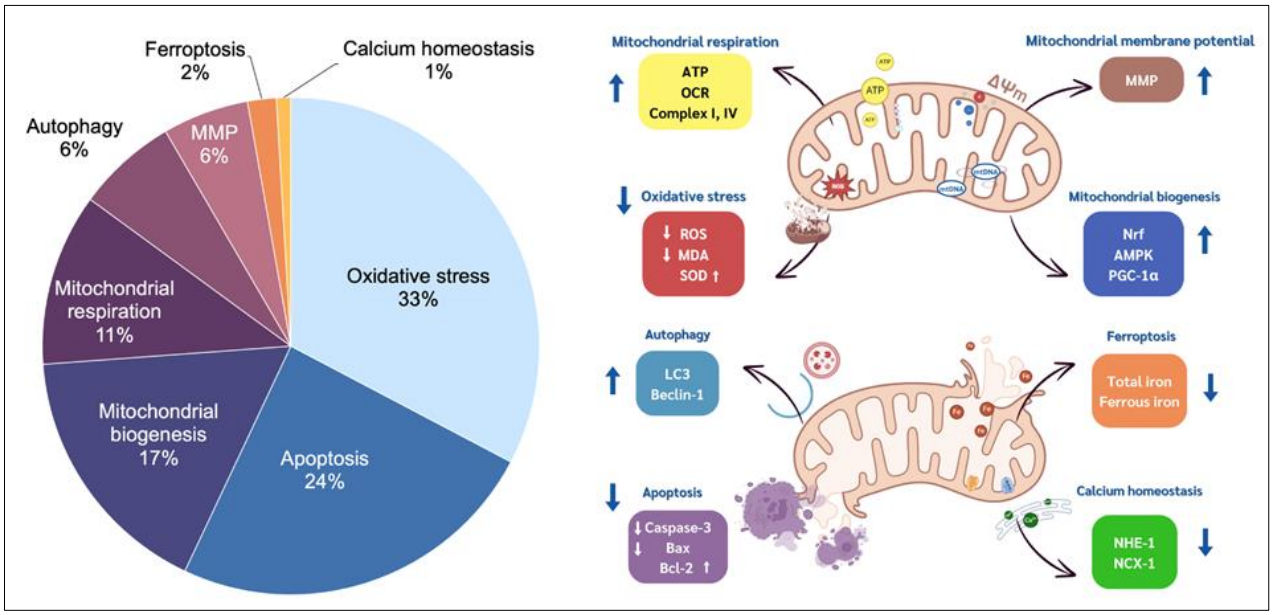

Figure 5: Role of antidiabetic drugs in mitochondrial functions. Antidiabetic drugs improved mitochondrial function by reducing oxidative stress through lower ROS production and increased SOD levels. They decreased apoptosis by lowering proapoptotic proteins like caspase-3 and Bax, while boosting the anti-apoptotic Bcl-2. Additionally, these drugs supported cardiac protection by promoting mitochondrial biogenesis, maintaining respiration, autophagy, and MMP, reducing ferroptosis, and preserving calcium homeostasis.
Abbreviations: AMPK, adenosine 5'-monophosphate-activated protein kinase; Bax, Bcl-2 associated X; Bcl-2, B-cell lymphoma 2; MDA, malondialdehyde; MMP, mitochondrial membrane potential; NCX-1, sodium-calcium exchanger 1; NHE-1, sodium-hydrogen antiporter 1; Nrf, nuclear respiratory factor; OCR, oxygen consumption rate; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; ROS, reactive oxygen species; SOD, superoxide dismutase

Table 1: Summary of *in vitro* studies examining the effects of antidiabetic drugs on biomarkers related to mitochondrial structure and functions.

Author, year	Drugs	Study model (Inducer)	Mitochondrial Structure or Function	Main findings
SGLT2 inhibitors				
Behnammanesh, G., et al., 2020 [20]	Canagliflozin	**Rat aortic smooth muscle cells**	Apoptosis Biogenesis Oxidative stress	- ↓ Apoptotic cells - ↑ Nrf2 - ↑ Antioxidant (HO-1)
Dasari, D., et al., 2023 [21]	Canagliflozin	**H9c2 cells** (High glucose + Palmitic acid)	Morphology MMP	- ↑ Mitochondrial mass - ↑ MMP
Du, S., et al., 2022 [22]	Canagliflozin	**H9c2 cells** (High glucose)	Apoptosis Ferroptosis MMP Respiration Oxidative stress Morphology	- ↑ Cell viability - ↓ Total iron and Fe^{2+} levels - ↑ MMP - ↑ ATP production - ↓ Oxidative markers (ROS, MDA) - ↑ Antioxidants (SOD, CAT, GSH) - ↑ Number of cristae, ↓ swollen mitochondria - ↑ Inner and outer mitochondrial membrane
Fan, Z. G., et al., 2022 [16]	Dapagliflozin	**H9c2 cells** (Hypoxia)	Fission Apoptosis	- ↑ Drp1 and PGAM5 - ↓ Caspase-3
Hsieh, P. L., et al., 2022 [23]	Dapagliflozin	**H9c2 cells** (Doxorubicin)	MMP Oxidative stress	- ↑ MMP - ↓ Oxidative marker (ROS) - ↑ Antioxidants (SOD, HO-1, NQO1)
Dogan, Z., et al., 2023 [24]	Empagliflozin	**H9c2 cells** (Methotrexate)	Apoptosis Oxidative stress	- ↑ Cell viability - ↓ Oxidative markers (HIF-1α, MDA, XO) - ↑ Antioxidants (TSH, CAT)
Kolijn, D., et al. 2021 [25]	Empagliflozin	**LV biopsies from HFpEF patients**	Oxidative stress	- ↓ H_2O_2 level and lipid peroxidation - ↑ Antioxidant (GSH)
Lascu, A., et al. 2023 [26]	Empagliflozin Metformin	**Human internal mammary arteries**	Oxidative stress	- ↓ Oxidative markers (ROS, H_2O_2) - ↓ MAO-A and MAO-B

Author, year	Drugs	Study model (Inducer)	Mitochondrial Structure or Function	Main findings
		(High glucose +Angiotensin II)		
Li, X., et al., 2021 [27]	Empagliflozin Dapagliflozin Canagliflozin	**Coronary artery endothelial cells** (Cyclic stretch)	Oxidative stress	- ↓ Oxidative marker (ROS)
Park, S. H., et al., 2021 [28]	Empagliflozin	**Endothelial cells from porcine coronary arteries** (Angiotensin II)	Apoptosis Oxidative stress	- ↓ p53, p21, and p16 - ↑ eNOS
Soares, R. N., et al., 2022 [29]	Empagliflozin	**Vascular smooth muscle cells** (Aged human)	Respiration Fission	- ↑ OCR (baseline and maximal respiration) - ↓ F-actin and P-cofilin content
Song, Y., et al., 2021 [30]	Empagliflozin	**H9c2 cells**	Biogenesis Respiration	- ↑ TOM40 - ↑ OCR (baseline and maximal respiration)
Biguanides				
Chen, Y., et al., 2023 [31]	Metformin	**H9c2 cells** (Ethanol)	Apoptosis Biogenesis Oxidative stress	- ↓ Bax and c-Caspase-3, ↑ p-Akt/Akt - ↑ Nuclear accumulation of Nrf2 - ↓ Oxidative marker (ROS) - ↑ Antioxidants (CAT, HO-1, SOD2)
En, Q., et al., 2021 [32]	Metformin	**Human aortic valve interstitial cells** (Phosphate medium)	Apoptosis Biogenesis Oxidative stress	- ↓ Bax and c-Caspase 3, ↑ Bcl-2 - ↑ AMPK - ↓ Oxidative marker (ROS) - ↑ eNOS
Fei, Q., et al., 2022 [33]	Metformin	**Mouse macrophages** (H_2O_2 + ATP)	Apoptosis Autophagy Oxidative stress	- ↓ p62 - ↓ NLRP3, ↑ LC3 - ↓ Oxidative marker (ROS)
Jia, W., et al., 2021 [34]	Metformin	**H9c2 cells** (Palmitic acid)	Apoptosis Biogenesis MMP	- ↓ Cell apoptosis - ↑ p-AMPK/AMPK, ↑ Sirt1 - ↑ MMP
Johnson, R., et al., 2019 [35]	Metformin	**H9c2 cells** (High glucose)	Apoptosis Biogenesis MMP Respiration Oxidative stress	- ↓ Caspase 3/7 - ↑ p-AMPK - ↓ Mitochondrial membrane depolarization - ↑ ATP level - ↓ Oxidative markers (ROS, MDA) - ↑ Antioxidants (SOD, GSH)
Merce, A., et al., 2022 [36]	Metformin	**Human internal mammary arteries** (Angiotensin II)	Oxidative stress	- ↑ eNOS and nNOS - ↓ Oxidative marker (H_2O_2)
Sun, C. C., et al., 2020 [37]	Metformin	**HUVEC cells** (High glucose)	Apoptosis Biogenesis Oxidative stress	- ↓ p65 - ↑ Nrf2 - ↑ Antioxidant (HO-1)
Sun, Q., et al., 2022 [38]	Metformin	**HUVEC cells** (Epirubicin)	Fission Fusion Autophagy Biogenesis Oxidative stress	- ↓ Drp1 and Mff - ↑ Mfn1 and Opa1 - ↑ TFEB - ↑ PGC-1α and TFAM - ↓ Oxidative marker (ROS)
Wang, G., et al., 2022 [39]	Metformin	**HUVEC cells** (Methylglyoxal)	Morphology Apoptosis Biogenesis MMP Oxidative stress	- ↓ Mitochondrial outer membrane and cristae - ↓ Cell apoptosis, ↓ c-Caspase-3 - ↑ Bcl-2 and p-Akt/Akt, ↓ Bax - ↑ Nrf2 - ↑ MMP - ↓ Oxidative markers (ROS, MDA) - ↑ Antioxidants (SOD, CAT, GPx, HO-1)
Wang, Z., et al., 2019 [40]	Metformin	**Rat aortic smooth muscle cells** (Angiotensin II)	Apoptosis Autophagy	- ↓ p-PI3K/PI3K, p-Akt/Akt - ↓ p-mTOR/mTOR - ↓ LC3B and Beclin1
GLP-1 analogs				
Ding, W., et al., 2019 [41]	Exenatide	**H9c2 cells** (High glucose)	Apoptosis Oxidative stress	- ↓ Cell apoptosis, ↓ p53 - ↓ Oxidative marker (ROS) - ↑ Antioxidants (MnSOD, CAT)

Author, year	Drugs	Study model (Inducer)	Mitochondrial Structure or Function	Main findings
Fang, J., et al., 2019 [42]	Exenatide	**H9c2 cells** (Doxorubicin)	Apoptosis Oxidative stress	- ↑ Bcl-2, ↓ Bax and p53 - ↓ Oxidative markers (LDH, MDA, ROS) - ↑ Antioxidant (SOD)
Chen, P., et al., 2021 [43]	Liraglutide	**Cardiac fibroblasts** (Angiotensin II)	Oxidative stress	- ↓ Oxidative marker (ROS)
DPP-4 inhibitors				
Li, Y., et al., 2020 [44]	Linagliptin	**Mice blood** (Thrombin)	Morphology Respiration	- ↑ Mitochondrial number - ↑ OCR, ↑ Intracellular cAMP level

Abbreviations: AMPK, adenosine 5'-monophosphate-activated protein kinase; Bax, Bcl-2 associated X; Bcl-2, B-cell lymphoma 2; CAT, catalase; Drp1, dynamin-related protein 1; GSH, glutathione; H_2O_2, hydrogen peroxide; HIF-1α, hypoxia-inducible factor-1α; HO-1, heme oxygenase 1; LDH, lactate dehydrogenase; MDA, malondialdehyde; Mfn, mitofusin; MMP, mitochondrial membrane potential; NOS, Nitric oxide synthase; Nrf, nuclear respiratory factor; OCR, oxygen consumption rate; Opa1, optic atrophy-1; PGAM5, phosphoglycerate mutase 5; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; ROS, reactive oxygen species; SOD, superoxide dismutase; XO, xanthine oxidase.

Table 2: Summary of key findings from *in vivo* studies examining the effects of antidiabetic drugs on biomarkers associated with mitochondrial structure and function.

Author, year	Drugs	Study model (Inducer)	Mitochondrial Structure or Function	Main finding
SGLT2 inhibitors				
Dasari, D., et al., 2023 [21]	Canagliflozin	**Wistar rats** (High-fat diet and streptozotocin)	Apoptosis Ca^{2+} homeostasis	- ↓ Caspase-3 - ↓ NHE-1 and NCX-1
Du, S., et al., 2022 [22]	Canagliflozin	**C57BL/6J mice** (Streptozotocin)	Ferroptosis Respiration Oxidative stress	- ↓ Total iron and Fe^{2+} level - ↑ ATP level - ↓ Oxidative marker (MDA) - ↑ Antioxidants (CAT, GSH)
Wang, X., et al., 2022 [45]	Canagliflozin	**C57BL/6J mice** (High-fat diet)	Morphology Biogenesis Oxidative stress	- ↓ Mitochondrial cristae damage - ↓ Fat drops in mitochondria - ↑ pAMPK/AMPK - ↑ Antioxidants (SOD, GPx, HO-1) - ↓ Oxidative marker (MDA)
Fan, Z. G., et al., 2022 [16]	Dapagliflozin	**Sprague Dawley rats** (Coronary artery ligation)	Fission Morphology	- ↑ Drp1 and PGAM5 - ↑ Mitochondrial area ratio and number
Chen, M., 2023 [46]	Empagliflozin	**Sprague Dawley rats** (Doxorubicin)	Biogenesis Respiration Oxidative stress	- ↑ p-AMPK, Sirt1 and PGC-1α - ↑ ATP level and ATP/ADP value - ↓ Oxidative marker (MDA) - ↑ Antioxidants (CAT, SOD)
Kolijn, D., et al. 2021 [25]	Empagliflozin	**Zucker diabetic fatty obese rats**	Oxidative stress	- ↓ H_2O_2 level and lipid peroxidation - ↑ Antioxidant (GSH)
Li, X., et al., 2022 [47]	Empagliflozin	**C57BL/6J mice** (Transverse aortic constriction)	Morphology Apoptosis Autophagy Biogenesis Respiration Oxidative stress	- ↑ Mitochondrial number and size - ↓ c-Caspase-3 and Bax/Bcl-2, ↑ p-Bad/Bad - ↓ Cytochrome C release, ↓ p-mTOR/mTOR - ↑ Autophagosomes number - ↑ Beclin-1, Atg7, LC3, and LC3 II/I - ↑ PGC-1α, TFAM, COX-1, Nrf1 and Nrf2 - ↑ p-AMPK/AMPK - ↑ OCR (baseline and maximal respiration) - ↓ Oxidative markers (H_2O_2, ROS) - ↑ Antioxidant (HO-1)
Soares, R. N., et al., 2022 [29]	Empagliflozin	**C57BL/6J mice** (Aging)	Fission Oxidative stress	- ↓ F-actin and P-cofilin content - ↓ Oxidative marker (MDA) - ↑ p-eNOS/eNOS
Song, Y., et al., 2021 [30]	Empagliflozin	**C57BL/6J mice** (Coronary artery ligation)	Fusion Biogenesis Respiration	- ↑ Mfn2 and Opa1 - ↑ TOM40 - ↑ OCR (baseline and maximal respiration) - ↑ COX-IV and OXPHOS levels

Author, year	Drugs	Study model (Inducer)	Mitochondrial Structure or Function	Main finding
Tan, Y., et al., 2021 [48]	Empagliflozin	**Sprague Dawley rats** (Cardiac arrest)	Morphology Fission Respiration Oxidative stress	- ↓ Lipid droplets number - ↑ Intermitochondrial junction number - ↓ Drp1 - ↑ ATP level and NAD^+/NADH ratio - ↑ Complex I activity - ↓ Oxidative markers (4-HNE, lactate, ROS)
Biguanides				
Fei, Q., et al., 2022 [33]	Metformin	**C57BL/6J mice** (Coronary artery ligation)	Apoptosis Autophagy	- ↓ p62 - ↑ LC3 and LC3 II/I ratio, ↓ NLRP3
Jia, W., et al., 2021 [34]	Metformin	**C57BL/6 mice** (db/db mutation)	Biogenesis Oxidative stress	- ↑ p-AMPK/AMPK - ↓ Oxidative marker (ROS)
Karam, H. M., et al., 2021 [8]	Metformin	**Albino rats** (γ-radiation)	Oxidative stress	- ↓ LDH activity - ↑ Antioxidants (SOD, CAT)
Wang, G., et al., 2022 [39]	Metformin	**C57BL/6 mice** (Methylglyoxal)	Apoptosis Biogenesis Oxidative stress	- ↓ Cell apoptosis, ↓ c-Caspase-3 - ↑ p-Akt/Akt ratio - ↑ Nrf2 - ↑ Antioxidants (SOD, CAT, GPx) - ↓ Oxidative marker (MDA)
Wang, Z., et al., 2019 [40]	Metformin	**C57BL/6 mice** (Abdominal aortic aneurysm)	Apoptosis Autophagy	- ↓ p-PI3K, p-Akt, and p-mTOR - ↓ LC3B and Beclin1
GLP-1 analogs				
Ding, W., et al., 2019 [41]	Exenatide	**C57BL/6J mice** (High-fat diet or Streptozotocin)	Apoptosis Oxidative stress	- ↓ p53 - ↓ Oxidative marker (ROS) - ↑ Antioxidants (MnSOD, CAT)
Fang, J., et al., 2019 [42]	Exenatide	**C57BL/6 mice** (Doxorubicin)	Apoptosis Oxidative stress	- ↑ Bcl-2, ↓ Bax - ↓ Oxidative markers (LDH, MDA) - ↑ Antioxidant (SOD)
Wang, D., et al., 2020 [49]	Exenatide	**Sprague Dawley rats** (Streptozotocin)	Morphology Apoptosis Oxidative stress	- ↓ Mitochondrial damage - ↓ Caspase-3 level, ↓ p-mTOR-S2448/mTOR - ↓ Oxidative marker (ROS)
DPP-4 inhibitors				
Zhang, X., et al., 2018 [50]	Alogliptin	**White rabbits** (5% alloxan monohydrate)	Apoptosis Biogenesis MMP Respiration Oxidative stress	- ↓ NF-kB p65 - ↑ PGC-1α, TFAM, and Nrf1 - ↑ MMP - ↑ Respiratory control ratio - ↓ Oxidative markers (ROS, MDA) - ↑ Antioxidant (SOD)
Li, Y., et al., 2020 [44]	Linagliptin	**C57BL/6J mice** (High-fat diet and streptozotocin)	Respiration	- ↓ OCR
Gu, Y., et al., 2018 [51]	Sitagliptin	**C57BL/6 mice** (Streptozotocin)	Apoptosis Autophagy	- ↓ p62 - ↑ LC3-II
Alpha-glucosidase inhibitors				
Naruse, G., et al., 2019 [10]	Miglitol	**Dahl salt-sensitive rats** (High-salt diet)	Fission Fusion Morphology Respiration	- ↑ p-Drp1 - ↑ Mfn1 and Opa1 - ↓ Swollen mitochondria and damaged cristae - ↑ ATP level
Thiazolidinediones				
Zhang, L., et al., 2020 [52]	Rosiglitazone	**Wistar rats** (Doxorubicin)	Apoptosis Biogenesis Oxidative stress	- ↓ Caspase-3 and Bax, ↑ Bcl-2 - ↑ Nrf2 - ↓ Oxidative markers (LDH, MDA, NO) - ↑ Antioxidants (SOD, CAT, HO-1, GPx)

Abbreviations: AMPK, adenosine 5'-monophosphate-activated protein kinase; Bax, Bcl-2 associated X; Bcl-2, B-cell lymphoma 2; CAT, catalase; Drp1, dynamin-related protein 1; GSH, glutathione; H_2O_2, hydrogen peroxide; HIF-1α, hypoxia-inducible factor-1α; HO-1, heme oxygenase 1; LDH, lactate dehydrogenase; MDA, malondialdehyde; Mfn, mitofusin; MMP, mitochondrial membrane potential; NCX-1, sodium-calcium exchanger 1; NHE-1, sodium-hydrogen antiporter 1; NOS, Nitric oxide synthase; Nrf, nuclear respiratory factor; OCR, oxygen consumption rate; Opa1, optic atrophy-1; PGAM5, phosphoglycerate mutase 5; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; ROS, reactive oxygen species; SOD, superoxide dismutase; XO, xanthine oxidase.

4. DISCUSSION

Mitochondrial dysfunction is implicated in the development and progression of cardiovascular diseases. Recent research has highlighted the significant role of antidiabetic drugs in the treatment of patients with cardiovascular diseases irrespective of diabetes. In this review, we performed a five-year systematic search of thirty-six literature to gather evidence of how antidiabetic agents preserve mitochondrial structure and function in association with their cardioprotective effects. Based on the data obtained in this systematic review, antidiabetic drugs preserved mitochondrial homeostasis by improving their functions through various mechanisms, including suppressing oxidative stress, apoptosis, and ferroptosis, while increasing mitochondrial biogenesis, MMP, calcium homeostasis, cellular respiration, and autophagy processes. Moreover, antidiabetic drugs improve mitochondrial structure by maintaining mitochondrial morphology, reducing mitochondrial fission, and promoting fusion processes.

Currently, SGLT-2 inhibitors, dapagliflozin and empagliflozin, are recommended for patients with heart failure to reduce the risk of hospitalization due to heart failure or cardiovascular death[53]. Numerous clinical trials have demonstrated that treating patients with T2DM and cardiovascular risk using empagliflozin, canagliflozin, and dapagliflozin reduces hospitalizations due to heart failure[54-56]. Dapagliflozin exerted cardioprotective benefits in both diabetic rats and high glucose-induced primary cardiac fibroblast cells by activating the AMPK-α and transforming growth factor-β (TGF-β)/Smad signaling pathway, which suppresses fibroblast activation and endothelial-to-mesenchymal transition, thereby reducing cardiac fibrosis[57]. Since empagliflozin has the additional benefit of decreasing the mortality rate, most studies focus on the effects of empagliflozin in reducing mitochondrial dysfunction in cardiovascular diseases (**Figure 3)**. In methotrexate-induced cardiac injury H9c2 cells, empagliflozin alleviated cellular damage by suppressing oxidative stress and apoptosis, which was achieved through increasing antioxidant parameters such as thyroid-stimulating hormone and catalase, while decreasing oxidative markers, particularly hypoxia-inducible factor-1α (HIF-1α) and xanthine oxidase[24]. Likewise, empagliflozin maintained mitochondrial homeostasis by reducing oxidative stress, attenuating apoptotic cell death, increasing autophagy, enhancing mitochondrial biogenesis and respiration, and preserving the mitochondrial structure in mice with heart failure induced by transverse aortic constriction, highlighting its cardioprotective roles[47].

Metformin, the only biguanide antihyperglycemic agent used in the treatment of T2DM, lowered the incidence of cardiovascular diseases in patients with or without diabetes by activating AMPK, which enhanced mitochondrial biogenesis and reduced mitochondrial fission, thereby improving overall mitochondrial homeostasis[58]. In H9c2 cardiomyoblasts treated with high glucose, metformin has been reported to reduce cardiac injury by activating mitochondrial biogenesis through an increasing level of AMPK and preserve mitochondrial activities by upregulating antioxidant markers such as SOD and glutathione, while reducing malondialdehyde (MDA), a potent oxidative stress marker[35]. An impairment of MMP is one of the key events in apoptosis that contributes to the release of cytochrome c, a main component of the apoptosome complex [3]. Interestingly, metformin treatment prevented mitochondrial membrane depolarization and improved ATP production of cardiomyoblasts exposed to high glucose, indicating that metformin could restore MMP and prevent an apoptotic process[35].

GLP-1R agonist exerts cardioprotective effects by acting through its receptor, which is abundantly expressed in various cardiovascular cells, including vascular smooth muscle cells, endothelial cells, and cardiomyocytes [11]. The cardioprotective effects of GLP-1R agonists are mainly attributed to their antioxidative and anti-apoptotic properties[59]. Liraglutide attenuated angiotensin II-induced ROS production in cardiac fibroblast cells [43]. In both streptozotocin-induced T1DM and high-fat diet-induced T2DM mice, exenatide protected against cardiac injury from ischemic reperfusion by suppressing ROS generation via upregulation of antioxidant enzymes, manganese-dependent SOD and catalase[41]. Furthermore, exenatide exhibited anti-apoptotic effects by reducing p53 expression in doxorubicin-induced cardiac injuries of H9c2 cells[41]. Exenatide counteracted the cardiotoxic effects of adriamycin in mice by improving cardiac function as determined by echocardiography. In addition, productions of oxidative stress-related parameters (ROS, LDH, and CK-MB), apoptosis-related genes (Bax and p53), and inflammation-related molecules (tumor necrosis factor-α, interleukin-6, nuclear factor-κB) were blunted by the impact of exenatide[42]. Likewise, exenatide suppressed oxidative stress and apoptosis by reducing caspase-3 activity in rats with cardiac remodeling induced by streptozotocin,[49]. Altogether, these data emphasize the cardioprotective impacts of GLP-1R agonists in cardiovascular diseases

DPP-4 inhibitors, such as alogliptin, have been shown to increase the risk of hospitalization for heart failure in patients with diabetes at high cardiovascular risk[60]. Furthermore, the clinical practice guideline advises against the use of DPP-4 inhibitors in patients with heart failure, as the drug's mechanism of action stimulates the sympathetic nervous system, resulting in an increased heart rate[61]. However, the toxicological mechanisms inducing heart failure at the molecular level remain unclear, and animal studies have yielded

results that contradict clinical findings. In diabetic rabbits treated with 5% alloxan monohydrate to induce ventricular dysfunction, alogliptin alleviated ventricular hypertrophy, interstitial fibrosis, and diastolic dysfunction by reducing p65 apoptotic protein and decreasing ROS and MDA levels[50]. Additionally, mitochondrial functions were enhanced by treatment with alogliptin, as indicated by increased cellular respiration, sustained MMP, and elevated levels of biogenesis markers such as peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), mitochondrial transcription factor A (TFAM), and nuclear respiratory factor 1 (Nrf1)[50]. Furthermore, DPP-4 inhibitors express antithrombotic effects by inhibiting platelet aggregation through decreasing plasminogen activator inhibitor (PAI-1) and von Willebrand factor (vWF) levels in mice[62]. Linagliptin attenuated oxygen consumption rate (OCR), which serves as an indicator of mitochondrial respiration, in thrombin-induced platelets and mice subjected to high-fat diet and streptozotocin-induced metabolic stress[44]. Although suppression of mitochondrial respiration adversely impacts mitochondrial function, arterial thrombosis is widely acknowledged as a precursor to ischemic heart disease[62]. Thus, the reduction in OCR inhibits platelet aggregation, highlighting linagliptin's cardioprotective effects.

Nevertheless, not all antidiabetic drugs exert beneficial effects on cardiovascular diseases; some can exacerbate the condition. For example, TZDs like pioglitazone and rosiglitazone may elevate the risk of heart failure in patients with cardiovascular risks. Hence, these drugs are not recommended for heart failure patients due to their potential to increase sodium and water reabsorption in renal tubules, resulting in dose-dependent fluid retention and elevated blood pressure[63]. In doxorubicin-treated rats, rosiglitazone mitigated cardiotoxicity by enhancing antioxidant markers (SOD, GSH, catalase, and heme oxygenase-1), decreasing oxidative stress markers (MDA and nitric oxide), boosting expression of anti-apoptotic Bcl-2, and reducing expression of apoptotic Bax and caspase-3[52], demonstrating its cardioprotective properties, findings that contrast with those observed in humans using TZDs. However, it is assumed that variations in rosiglitazone dosage and study duration, compared to the lower doses typically administered to diabetes patients, may have influenced its pharmacological effects in humans.

To evaluate the research quality in *in vitro* studies, we use the CONSORT-Outcomes 2022 Extension, which provides a comprehensive evaluation including randomization, an aspect often lacking in detailed reporting[17]. However, certain aspects, such as sample size, criteria for inclusion and exclusion, randomization, and allocation concealment, were not reported, potentially impacting statistical power and introducing selection bias into the study. Additionally, regarding blinding procedures, researchers need to disclose who was blinded after assignment to interventions to mitigate potential performance, attrition, and detection biases[17]. These factors collectively impact the reliability of the research. Hence, we recommend that future studies rigorously conduct experiments and report findings to minimize potential biases.

5. CONCLUSIONS

In conclusion, preclinical studies have demonstrated that six classes of antidiabetic drugs—SGLT-2 inhibitors, biguanides, GLP-1R agonists, TZDs, DPP-4 inhibitors, and α-glucosidase inhibitors—exert positive effects on cardiovascular diseases by modulating mitochondrial structure and functions. Nevertheless, the consistency of cardioprotective effects observed with TZDs and DPP-4 inhibitors in preclinical studies did not translate consistently into clinical trials. It is recommended that future research should expand clinical studies to investigate particularly the cardioprotective effects of antidiabetic drug classes. In addition, it's important to note that each antidiabetic class offers cardioprotective effects through several mechanisms beyond mitochondrial actions, such as lowering blood glucose, pressure, and volume; enhancing insulin secretion and sensitivity; reducing appetite; improving endothelial function and lipid profiles; and decreasing inflammation.

Author contributions:

Conceptualization, W.P.; Methodology, P.W., P.S., S.P., and W.P.; Visualization, P.W. and P.S.; Validation, W.P.; Formal analysis and interpretation, P.W., P.S., and W.P.; Investigation, P.W., P.S., and W.P.; Resources, W.P.; Data curation, W.P.; Writing - original draft preparation, P.W. and P.S.; Writing - review & editing, S.P., L.T.T.P., T.L., and W.P.; Supervision, T.L. and W.P.; Project administration, W.P.; Funding acquisition, W.P. All authors have read and agreed to the published version of the manuscript.

Fundings:
This research was supported by grants from the National Research Council of Thailand (NRCT) and Mahidol University [N42A650352] (to W.P.), and the Strategic Research Fund: Fiscal year 2024 from Mahidol University [MU-SRF-RS-05A/67] (to W.P.).

Conflicts of interest:
None to declare

Ethics approval:
None to declare

Article info:
Received June 26, 2024
Received in revised form August 18, 2024
Accepted August 21, 2024

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