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REVIEW ARTICLE

Multiple Therapeutic Applications of Metformin Moving Beyond Its Anti-Diabetic Role: A Systematic Review

Asif Jan,[1,2] Aftab Ullah,[2,3] Syed Shaukat Ali,[4] Rani Akbar,[4] Bushra Waheed[5]

[1]*District Headquarter Hospital (DHQH), Charsadda, Khyber Pakhtunkhwa, Pakistan*
[2]*Department of Pharmacy, University of Peshawar, Khyber Pakhtunkhwa, Pakistan*
[3]*Department of Pharmacy, Abasyn University Peshawar, Khyber Pakhtunkhwa, Pakistan*
[4]*Department of Pharmacy, Abdul Wali Khan University, Mardan, Khyber Pakhtunkhwa, Pakistan*
[5]*Department of Pharmacy, University of Swabi, Anbar, Swabi, Khyber Pakhtunkhwa, Pakistan*

Abstract

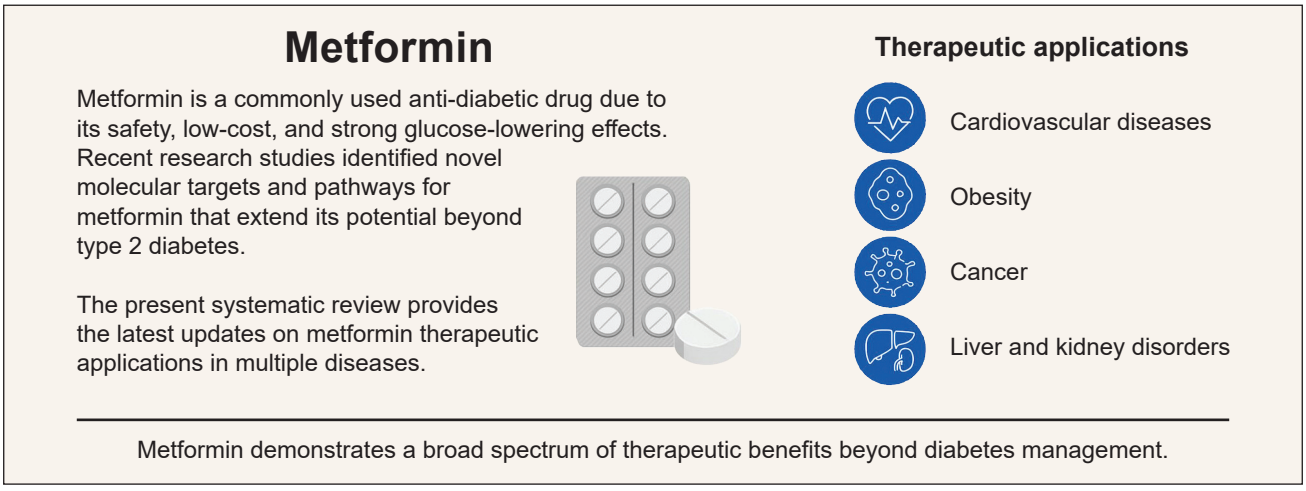
Introduction. Metformin is a commonly used anti-diabetic drug due to its safety, low cost, and strong glucose-lowering effects. Recent research studies have identified novel molecular targets and pathways for metformin, thereby expanding its potential beyond the treatment of Type 2 diabetes.

Methodology. This systematic review provides the latest updates on the therapeutic applications of metformin in multiple diseases. This systematic review follows the PRISMA guidelines, focusing on experimental studies systematic reviews and meta-analyses from PubMed, Scopus, Web of Science and Google scholar, the search terms ("Metformin"[MeSH] OR "Metformin") AND ("Cancer" OR "Cardiovascular Disease" OR "Neurodegenerative Disease" OR "Aging") AND ("Therapeutic Use" OR "Non-diabetic"). A comprehensive search yielded numerous studies, from which relevant and up-to-date papers were carefully selected.

Results. The review highlights the multifaceted applications of metformin in various diseases. Evidence demonstrates its positive effects on cardiovascular diseases, obesity, different types of cancer, and liver and kidney disorders. These findings suggest that metformin acts through diverse molecular mechanisms, exerting benefits that extend beyond glycemic control.

Conclusion. Based on the current literature, metformin exhibits a broad spectrum of therapeutic benefits, extending beyond its primary use in diabetes management. Its role in treating multiple diseases has marked it as a multifaceted agent in modern medicine. Further research is warranted to fully explore its capabilities and optimize its use in different clinical settings.

Key words: multiple therapeutic uses, metformin, cancer, obesity, cardiovascular diseases, anti-aging effect



Graphical Abstract

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Corresponding author: Asif Jan, PhD
Clinical Pharmacist, District Headquarter Hospital Charsadda
Peshawar Road, Tehsil Bazaar Chārsadda, 24430, Pakistan
Email address: Asif.research1@gmail.com
ORCiD: https://orcid.org/0000-0003-3880-5579

INTRODUCTION

Metformin, an oral antidiabetic agent, functions by enhancing insulin sensitivity, reducing hepatic glucose production and limiting intestinal glucose absorption. Due to its efficacious glycemic control and established safety profile, metformin is frequently prescribed as the initial pharmacological intervention for patients diagnosed with Type 2 Diabetes Mellitus (T2DM).[1]

Beyond its role in managing blood sugar levels in T2DM, metformin also provides health benefits in various other areas. A growing number of studies suggest that metformin lowers the risk of cardiovascular diseases (CVD), breast and endometrial cancers, obesity, liver and kidney conditions, and may also offer anti-aging effects.[2] Metformin exhibits a variety of biological effects, suggesting that it can influence different cellular processes. Studies have identified several cellular targets with which metformin interacts, resulting in its therapeutic effects. These interactions highlight the complex pathways by which metformin operates within the body, affecting not only blood sugar regulation but also other essential cellular functions that enhance its overall health benefits.[3-5]

Metformin suppresses high blood glucose levels mainly by two pathways: either through the AMPK (Adenosine Monophosphate-Activated Protein Kinase) dependent pathway[6] or the AMPK independent pathway.[7] In the case of the AMPK-dependent pathway, metformin works by blocking mitochondrial complex I in the liver, leading to the activation of AMPK. This activation enhances insulin sensitivity by modulating fat metabolism and reducing cAMP levels. The decreased cAMP levels have a negative/inhibitory effect on gluconeogenic enzymes involved in glucose synthesis in the liver. Recent studies suggest that metformin may also activate AMPK through a lysosomal pathway called the v-ATPase Regulator pathway.[5] This review article sheds light on the off-label uses of metformin, extending beyond its well-established role in the management of diabetes. It explores the drug's multifaceted impacts on various biological processes and its potential applications in areas such as cardiovascular health, cancer prevention, anti-inflammatory activities, weight management, and aging. By highlighting the multi-faceted pharmacological profile, offering insights into its mechanisms of action, and paving the way for future research into its use in non-diabetic conditions.

METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist is provided in Supplementary Table S1. Relevant studies were identified through a comprehensive search of PubMed, Scopus, Google Scholar and Web of Science databases. The search strategy included a combination of targeted keywords such as ("Metformin"[MeSH] OR "Metformin") AND ("Cancer" OR "Cardiovascular Disease" OR "Neurodegenerative Disease" OR "Aging") AND ("Therapeutic Use" OR "Non-diabetic"). The details of the MeSH terms searched across all databases are given in Supplementary Table S2. The inclusion criteria for the studies were: (1) studies investigated the effects of metformin beyond its primary use in diabetes management; (2) peer-reviewed articles published in English; and (3) studies providing details on metformin's role in cancer treatment, cardiovascular protection, obesity management and other non-diabetic conditions. Studies were excluded if they: (1) focused exclusively on metformin's role in glycemic control without addressing the additional therapeutic effects; (2) were conference abstracts, case reports, editorials or letters to the editor; or (3) lacked sufficient methodological details or relevance to the study objective. Eligible studies underwent a detailed data extraction process, focusing on key findings related to the multifaceted applications of metformin. The extracted data were then systematically analyzed and categorized to provide insights into the potential applications of the drug in cancer therapy, obesity management, cardiovascular protection and other non-diabetic conditions. The risk of bias was assessed using the Cochrane Tool for Randomized Controlled Trials (RCTs) and the Newcastle Ottawa Scale (NOS) for observational studies (Supplementary Table S1). The overall quality of evidence was moderate with heterogeneity in study designs. Findings were interpreted considering these limitations. Due to the significant heterogeneity in interventions (e.g., metformin dosages, combination therapies) and outcomes across studies, a meta-analysis was deemed inappropriate. A narrative synthesis was conducted to summarize key findings thematically.

Risk of bias assessment

Two reviewers (AU and AJ) independently assessed the risk of bias for each outcome measure using Cochrane RoB 2.0 (for RCTs) and NOS (for observational studies), with discrepancies resolved by a third reviewer (WAS). Rayan software aided the screening. Complete assessments are in Supplementary Table S1.

The PRISMA flowchart, shown in Figure 1, illustrates the detailed study selection process.

Metformin in obesity

A growing number of studies have reported the potential use of metformin in controlling obesity and associated comorbidities. Metformin has demonstrated modest yet significant effects on weight reduction in individuals without diabetes. In preclinical studies, metformin effectively mitigated obesity induced by high-fat diets. This effect is attributed to an increased expression of fibroblast growth factor 21 (FGF-21), a pivotal metabolic hormone that stimulates lipolysis in white adipose tissue, consequently reducing adipose accumulation.[8] Additionally, metformin enhances the brown adipose tissue (BAT) metabolic activity

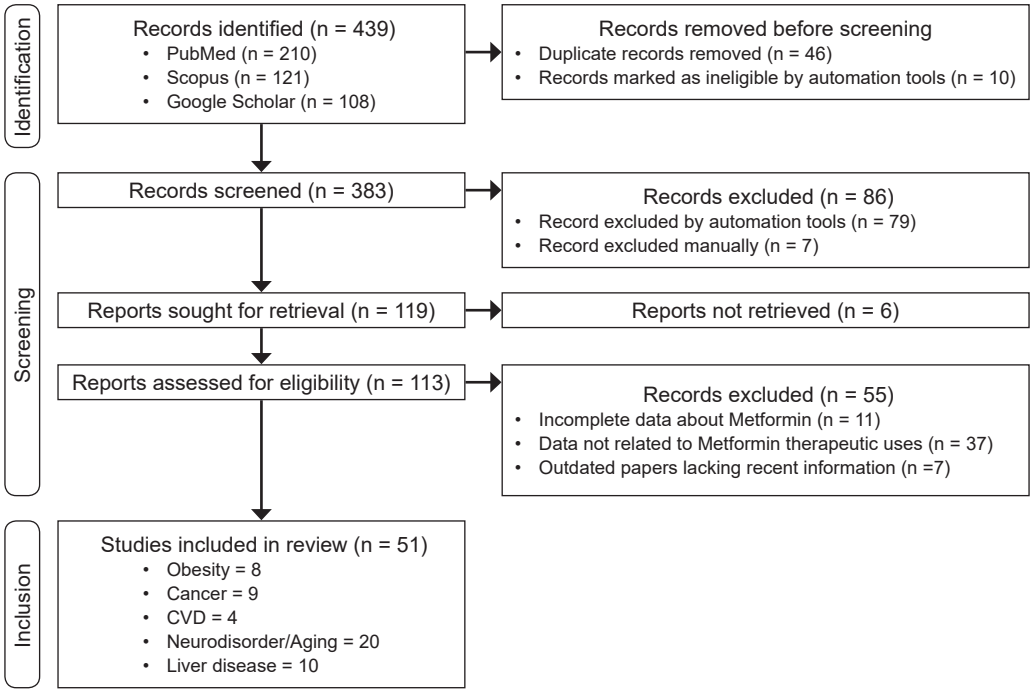

Figure 1. PRISMA flowchart.

Table 1. Detailed description of included studies

Author and publication year	Study type	Study duration	Study subjects	Age (years)	BMI (kg/m²)	Treatment groups
Jensterle et al. 2014[13]	RCT	15 weeks	32	27.6 ± 7.2	39.5 ± 6.2	Metformin 1000 mg BD (n = 15), Liraglutide 1.2 mg OD (n = 17)
Feng et al. 2015[14]	RCT	16 weeks	50	18–40	BMI ≥25	Metformin 500 mg TID or combination therapy
Nylander et al. 2017[15]	RCT	46 weeks	92	18–45	>30	Liraglutide 3 mg, Placebo
Kesavan et al. 2023[16]	Open-label RCT	22 weeks	176	18–40	>24	Exenatide 10 µg BD, Metformin 1000 mg BD
Ling et al. 2025[17]	RCT	36 weeks	72	29.9 ± 6.1	25	Liraglutide 1.8 mg OD, Placebo
Jensterle et al. 2016[18]	Prospective RCT	10 weeks	44	33.3 ± 4.4	37.2 ± 4.5	Combination therapy (Metformin 1g BD + Liraglutide 1.2 mg OD), Liraglutide 1.2 mg OD)
Jensterle et al. 2017[19]	Open-label RCT	26 weeks	30	33.1 ± 6.1	38.3 ± 5.4	Liraglutide 3 mg OD (n = 15), Combination therapy (Metformin 1000 mg BD + Liraglutide 1.2 mg OD, n = 15)
Salamun et al. 2018[20]	Open-label RCT	14 weeks	28	31.07 ± 4.75	36.7 ± 3.5	Metformin 1000 mg BD, Combination therapy (Metformin 1000 mg BID + Liraglutide 1.2 mg)

BMI: Body Mass Index; RCT: Randomized Controlled Trial; BD: twice daily; OD: once daily; TID: thrice daily

that prevents obesity in mice. BAT contributes to energy dissipation through thermogenesis, a process facilitated by the uncoupling protein 1 (UCP1). Using PET/CT imaging, researchers found that metformin accumulates in BAT likely due to increased expression of organic cation transporters (OCT).[9] Further studies have shown that metformin combats obesity effects by reducing fatty acid uptake, increasing mitochondrial biogenesis and stimulating thermogenesis.[10,11] Animal studies indicate that metformin influences gut microbiota, reducing fat uptake and decreasing the development of fat-induced obesity.[12] Table 1 illustrates an overview of different randomized clinical trials and other studies examining metformin as a treatment for obesity, including the study design, participant characteristics and interventions. The studies listed in Table 1 encompass a diverse range of study designs, including randomized, open-label and double-blind placebo-controlled trials. The study participants have met various diagnostic criteria, including the Rotterdam criteria for PCOS and the National Institutes of Health (NIH) 1990 criteria for obesity. The studies' duration spans from 12 to 32 weeks, with sample sizes ranging from 28 to 176 participants. The age range of the participants is 18 to 45 years, and the baseline BMI values generally fall within the range of 24 and 39 kg/m². Regarding interventions, metformin was evaluated both as monotherapy and in combination with other pharmacological agents such as Liraglutide, Exenatide or combinations thereof. The metformin dosage ranged from 500 to 1000 mg daily (BID, TID, or QD). Table 2 presents the clinical outcomes of the investigations listed in Table 1, with a focus on anthropometric measurements, including BMI, body weight, waist circumference (WC) and fat mass. In the study by Jensterle et al., patients receiving metformin 1000

mg BID exhibited a notable decrease in BMI (37.4 ± 6.4 to 36.5 ± 6.3) and body weight (103.6 ± 19.7 kg to 101.3 ± 19.8 kg) following a 12-week intervention.[13] Comparable results were observed by Ma et al. using metformin 500 mg TID, with reductions in BMI (30.8 ± 3.4 to 29.4 ± 3.3) and body weight (82.3 ± 11.4 kg to 78.6 ± 10.9 kg).[14] Elkind-Hirsch et al., reported that liraglutide 3 mg substantially reduced BMI and WC, while the control group receiving a placebo showed minimal changes.[15] Figure 2 depicts the comparative impact of metformin on body mass index (BMI) across different study groups. The data elucidate variations in BMI before and after metformin administration, demonstrating its potential for weight modulation. Error bars represent standard deviation.

Metformin in cancer

An increasing number of scientific studies suggest that metformin shows therapeutic potential for various cancer types, including breast cancer,[15] hematologic malignancies,[17] bone cancer,[18] colorectal cancer,[19] endometrial cancer, and melanoma[20] The anticancer effects of

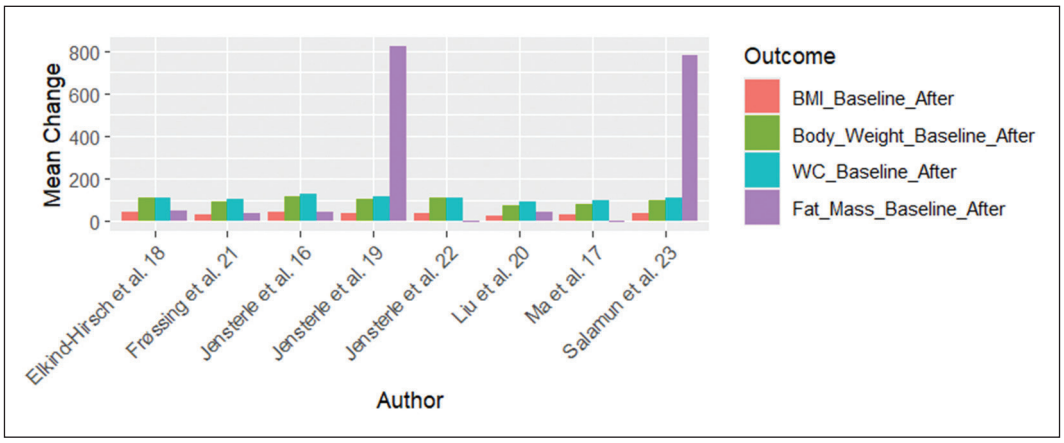

Figure 2. Effect of metformin on Body Mass Index (BMI).

Table 2. Clinical studies with anthropometrical outcomes

Author and publication year	Group for intervention	Baseline for BMI after	Baseline for body weight after	Baseline for WC after	Baseline for body mass after	Baseline after
Jensterle et al. 2015[13]	Liraglutide (1.2 mg)	41.6 ± 5.3 / 40.5 ± 5.1	113.7 ± 18.7 / 110.7 ± 18.1	128.5 ± 13.9 / 124.1 ± 11.7	42.5 ± 2.8 / 40.8 ± 3.2	−3.0 / −2.3
	Metformin (1000 mg BID)	38.4 ± 6.4 / 36.5 ± 6.3	103.6 ± 19.7 / 101.3 ± 19.8	121.6 ± 17.1 / 119 ± 18	43.3 ± 6.4 / 45.2 ± 4.2	−6.2 ± 2.4 / −3.8 ± 3.5
Ma et al. 2021[14]	Metformin (500 mg TID) + Exenatide 2 mg	30.8 ± 3.4 / 29.4 ± 3.3	82.3 ± 11.4 / 78.6 ± 10.9	97.3 ± 9.6 / 92.7 ± 8.7	−3.8 ± 2.4 / −2.1 ± 3.0	−5.7 ± 0.75 / −3.8 ± 3.5
	Metformin (500 mg TID)	32.4 ± 3.2 / 29.6 ± 2.8	79.1 ± 10.8 / 77.0 ± 9.7	96.6 ± 9.1 / 95.0 ± 8.1	(p < 0.01) / (p = 0.008)	−4.3 ± 1.3 / −2.3 ± 0.6
Elkind-Hirsch et al. 2022[15]	Liraglutide (3 mg)	41.6 ± 1.1 / 39.1 ± 1.1	111 ± 2.8 / 104.7 ± 2.9	111 ± 2.2 / 101 ± 2.0	47.6 ± 0.8 / 46.0 ± 0.9	−7.0 ± 6.0 / −7.5 ± 3.9
	Placebo	43.9 ± 1.7 / 43.4 ± 1.8	119 ± 4.7 / 117.9 ± 5	116 ± 3.3 / 110 ± 3.3	48.2 ± 0.8 / 47.9 ± 0.9	−7.0 ± 6.0 / −7.5 ± 3.9
Liu et al. 2017[16]	Exenatide (10 µg)	29.1 ± 3.1 / 26.0 ± 3.5	72.9 ± 9.8 / 68.7 ± 9.7	92.9 ± 10.1 / 83.9 ± 9.7	44.1 ± 3.8 / 39.4 ± 3.7	−7.0 ± 6.0 / −7.5 ± 3.9
	Metformin (1000 mg BID)	27.3 ± 1.8 / 27.2 ± 1.8	70.4 ± 4.6 / 68.2 ± 4.6	89.4 ± 6.6 / 84.4 ± 5.3	41.3 ± 2.7 / 40.2 ± 2.9	−7.0 ± 6.0 / −7.5 ± 3.9
Frøssing et al. 2018[17]	Liraglutide (1.8 mg)	33.3 ± 5.1 / 33.3 ± 4.6	94.2 ± 15.4 / 91.3 ± 13.6	102.6 ± 10.8 / 102.6 ± 11.1	35.9 ± 8.5 / 35.7 ± 7.2	NA
	Placebo	33.3 ± 4.6 / 33.3 ± 4.6	91.3 ± 13.6 / 91.3 ± 13.6	102.6 ± 11.1 / 102.6 ± 11.1	35.7 ± 7.2 / 35.7 ± 7.2	NA
Jensterle et al. 2017[18]	Metformin (1000 mg BID) + Liraglutide (1.2 mg)	37.7 ± 4.0 / 35.5 ± 4.2	105.8 ± 15.8 / 99.6 ± 15.9	117.2 ± 14.5 / 105.2 ± 27.0	824.2 ± 254.7 / 735.3 ± 227.5	−5.2 / 0.2
	Liraglutide (1.2 mg)	36.7 ± 5.1 / 35.3 ± 5.1	102.6 ± 17.9 / 98.8 ± 17.6	113.0 ± 13.9 / 107.5 ± 15.4	−6.2 ± 2.4 / −3.8 ± 3.5	−6.3 ± 3.7 / 3.6 ± 2.5
Jensterle et al. 2015[19]	Liraglutide (3 mg)	39.2 ± 5.5 / 37.0 ± 5.5	111.1 ± 14.8 / 104.7 ± 14.8	110.1 ± 12 / 105.9 ± 12.8	−6.3 ± 3.7 / 3.6 ± 2.5	NA
	Liraglutide (1.2 mg) + Metformin (1000 mg BID)	37.5 ± 5.3 / 36.2 ± 5.5	102.5 ± 9 / 98.9 ± 10.3	105.2 ± 10.7 / 103.0 ± 8.2	−5.2 ± 2.5 / −4.4 ± 3.2	NA
Salamun et al. 2018[20]	Metformin (1000 mg BID)	35.5 ± 4.9 / 33.0 ± 3.3	99.6 ± 17.8 / 92.6 ± 18	108.8 ± 14.5 / 97.5 ± 11	779.4 ± 247.3 / 698.1 ± 292.8	NA
	Metformin (1000 mg BID) + Liraglutide (1.2 mg)	NA	NA	NA	NA	NA

BMI: Body Mass Index; BID: twice daily; TID: thrice daily; NA: Not Applicable WC: waist circumference

metformin stem from its capacity to directly and indirectly modulate cellular metabolism. It exerts its influence through two primary signaling pathways: the AMPK-dependent and the AMPK-independent. In the AMPK-dependent pathway, metformin triggers AMPK activation, which subsequently suppresses the mTOR (mammalian target of rapamycin) signaling pathway. This interference with mTOR activity impacts protein synthesis, consequently decelerating cell growth and division.[21]

Table 3 presents an overview of the studies examining metformin's role in cancer treatment, highlighting various treatment protocols, patient profiles and dosing strategies. The studies encompassed prospective cohort, randomized clinical, and retrospective designs with diverse sample sizes and treatment approaches, including MPA, MA and LNG-IUD in conjunction with metformin. Treatment efficacy, measured by complete response (CR) and partial response (PR), differed across studies, with the majority demonstrating favorable outcomes for the progestin-metformin combination. BMI and age information were also documented, revealing comparable baseline values among groups. Table 4 outlines the diagnostic and reproductive outcomes for patients in studies investigating metformin usage. These investigations compared progestin monotherapy to progestin-metformin combination therapy, assessing outcomes such as complete response (CR), partial response (PR), non-response (NR) and pregnancy rates. Reproductive outcomes varied, with some studies reporting pregnancy and live birth rates, while others omitted reproductive data. In general, the progestin-metformin combination showed promising results regarding response rates, although reproductive outcomes were not consistently reported across studies.

Metformin in cardiovascular diseases

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity worldwide. Multiple factors contribute to the development of CVDs, including lifestyle choices and medical conditions such as tobacco use, diabetes mellitus, obesity, hyperlipidemia and hypertension. Among these risk factors, diabetes mellitus demonstrates a strong association with CVDs (including coronary artery disease, atherosclerosis and heart failure) and frequently presents as a comorbid condition.[31] Elevated blood glucose levels (hyperglycemia) induce oxidative stress, which can lead to endothelial dysfunction and a lipoprotein imbalance, thereby increasing the risk of CVDs. Metformin has demonstrated efficacy in reducing CVD incidence among individuals with diabetes. Metformin prevents deleterious modifications of apolipoprotein residues caused by alpha-dicarbonyl compounds through the activation of AMPK. This mechanism contributes to the restoration of high-density lipoprotein (HDL) function and mitigates alterations in low-density lipoprotein (LDL). Enhanced HDL function facilitates cholesterol transport and diminishes the risk of cardiovascular disorders. Furthermore, metformin attenuates oxidative stress in blood vessels and mitigates inflammation induced by hyperglycemia, further reducing the risk of CVDs. Type 2 diabetes mellitus (T2DM) elevates the risk of heart failure, with approximately one-third of heart failure cases reported in patients with diabetes. Metformin has been shown to enhance cardiac energy metabolism, which is necessary for normal heart function, by improving lipid and glucose metabolism through AMPK activation.[32] Table 5 presents an overview of the study characteristics included in the review, evaluating incident heart failure outcomes in patients with preserved left ventricular ejection fraction (LVEF ≥50%). The table outlines the study design, demographic details of the populations and follow-up durations. Figure 3 illustrates a forest plot summarizing the effect of metformin treatment across four studies on HFpEF. Individual effect sizes ranged from 0.68 (95% CI: 0.51, 0.85) to 0.88 (95% CI: 0.83, 0.93), with a pooled random-effects model estimate of 0.82 (95% CI: 0.74, 0.90), demonstrating a statistically significant beneficial effect.

Metformin in neurodegenerative disorders

Neurodegenerative disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD), are characterized by progressive neuronal loss and cognitive or motor impairments. Parkinson's disease primarily affects the dopaminergic neurons in the substantia nigra, resulting in tremors, bradykinesia, and rigidity. Genetic and environmental factors contribute to its pathogenesis.[33,34] Metformin has been demonstrated to decelerate the progression of neurodegenerative disorders, mitigate age-related diseases, and extend lifespan.[35-39] Table 6 summarizes the characteris-

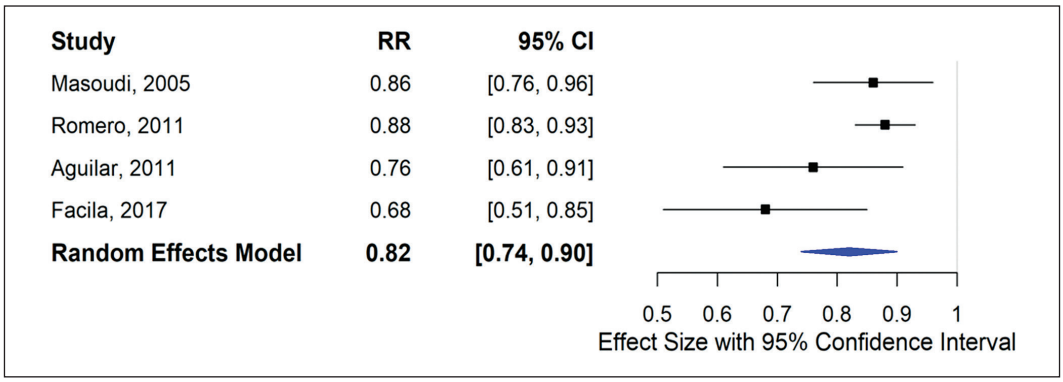

Figure 3. Effect of metformin in patients with heart failure with preserved ejection fraction (HFpEF).

Table 3. Overview of studies on metformin use in cancer treatment, including patient demographics, treatment methods and outcomes

Author and publication year	Study Type	BMI (mean, baseline)	Number of patients (groups)	Treatment methods	Diagnosis groups	%	Age (mean, baseline)
Shao et al et al. 2023[22]	Prospective cohort study	PROG: 26.33 ± 4.30 / PROG + MET: 27.01 ± 4.43	Total = 219, PROG = 138, CAH = 81	MPA or MA + Metformin	CAH+PROG = 35.5, MET+PROG = 35.8	PROG: 35.05 ± 5.14, PROG + MET: 32.00 ± 4.58	PROG: 32.00 ± 4.58
Janda et al. 2021[23]	3 arm open-label RCT	3-arm: 48.0 ± 9.7, 2-arm: 43.1 ± 9.6	Total = 165, PROG = 118, Met = 47	LNG-IUD + Metformin	EAC = 58%, EHA = 42%	3-arm: 51.5 ± 14.1, 2-arm: 60.6 ± 13.8	3-arm: 51.5 ± 14.1, 2-arm: 60.6 ± 13.8
Acosta-Torres et al. 2020[24]	Retrospective study	PROG: 34.7 (26.9–45.3) / PROG + MET: 41.5 (32.7–53.1)	Total = 92, PROG = 58, PROG + MET = 34	MPA or MA or Prometrium or LNG-IUD + Metformin	AH/EIN: 54 (59%), EC: 38 (41%)	PROG: 36.0 (30.0–38.5), PROG + MET: 32.0 (29.0–35.0)	PROG: 32.0 (29.0–35.0)
Mandelbaum et al. 2020[25]	Retrospective study	PROG: 38.3 (31.2–45.0), PROG + MET: 37.1 (32.7–46.3)	Total = 245, CAH = 176, Local progestin group = 69	MPA or MA or norethindrone or depo-medroxyprogesterone acetate (systemic); LNG-IUD (local) + Metformin	CAH: all patients	PROG: 32.9 (32.2–46.3), PROG + MET: 42.0 (38.0–60.5)	PROG: 42.0 (38.0–60.5)
Factor et al. 2024[26]	Randomized, single-center	PROG: 24.6 ± 4.1 / PROG + MET: 24.7 ± 5.2	Total = 150, PROG = 74, PROG + MET = 76	MA + Metformin	PROG: 62 (AEH) + 12 (EEC), PROG + MET: 61 (AEH) + 15 (EEC)	PROG: 34.4 ± 5.2, PROG + MET: 32.0 ± 4.5	PROG: 32.0 ± 4.5
Yuan et al. 2022[27]	No data	PROG: 33.37 ± 4.49, PROG + MET: 34.43 ± 4.24	All = 120, EAC: all patients	MPA + Metformin	EEC: all patients	PROG: 36.12 ± 8.41, PROG + MET: 33.73 ± 7.47	PROG: 33.73 ± 7.47
Shan et al. 2014[28]	Controlled, single-blind	No data	All = 16, PROG = 8, PROG + MET = 8	MA + Metformin	EAH: all patients	All patients: 35.2 ± 5.8, PROG: 34 ± 7.1, PROG + MET: 36.4 ± 4.2	PROG + MET: 36.4 ± 4.2
Shiwani et al. 2024[29]	Retrospective study	All patients: 26.7 (17.6–36.0)	All = 32, PROG = 23, PROG + MET = 32	MPA or MA + Metformin	AH: 13/32 (40.6%), G1EC: 19/32 (59.4%)	All patients: 30.4 (20–40)	All patients: 30.4 (20–40)
Mitsuhashi et al. 2019[30]	Retrospective study	PROG: 23.3 (21.6–27.1), PROG + MET: 29.7 (27.3–32.0)	All = 63, PROG = 23, PROG + MET = 42	MPA + Metformin	AEH/CAH: 21/63, EC: 42/63	All patients: 35 (26–44)	All patients: 35 (26–44)

BMI: Body mass index; EAC: endometrial adenocarcinoma; EIN: endometrial intraepithelial hyperplasia; M: oral metformin; WL: weight loss intervention; CR: complete response; PROG: progestin; MA: megestrol acetate; PROG+MET: Progestin+Metformin; CH: complex hyperplasia; AH: atypical hyperplasia; AEH: Atypical Endometrial Hyperplasia; CAH: Complex Atypical Hyperplasia

Table 4. Reproductive and treatment outcomes comparing progestin + metformin versus progestin alone across different studies

Author (year)	Diagnostic method	Patients (total)	Groups (PROG + MET vs. PROG)	Intervention	Comparison	Treatment outcomes	Reproductive outcomes
Shao et al et al. 2023[22]	Hysteroscopic surgery	219	Group 1: 81, Group 2: 138	MPA or MA + MET, MPA or MA	Group 1: MET + PROG, Group 2: PROG	CR: 93.8% (Group 1), 84.1% (Group 2); PR: 3.7% (Group 1), 3.6% (Group 2); NR: 2.5% (Group 1), 11.6% (Group 2)	Pregnancies: Group 1: 37%, Group 2: 36.8% Live births: Group 1: 22.2%, Group 2: 23.7% Abortions: Group 1: 40%, Group 2: 35.7%
Janda et al. 2021[23]	Endometrial biopsy or D&C	165	Group 1: 47, Group 2: 118	LNG-IUD + MET, LNG-IUD	Group 1: PROG + MET, Group 2: PROG	CR: 61% (Group 1), 67% (Group 2); PR: 6% (Group 1), 12% (Group 2); NR: 24% (Group 1), 18% (Group 2)	No data on pregnancies, abortions, or live births
Acosta-Torres et al. 2020[24]	Endometrial biopsy or D&C	92	Group 1: 34, Group 2: 58	MPA/MA/Prometrium/ LNG-IUD + MET	Group 1: PROG + MET, Group 2: PROG	CR: 68% (Group 1), 69% (Group 2); Relapse Rate: 4 cases on treatment, 10 off treatment	Pregnancies: Group 1: 6%, Group 2: 24% Live births: Group 1: 6%, Group 2: 24%
Mandelbaum et al. 2020[25]	Endometrial biopsy	245	Systemic Progestin Group: 176, Local Progestin Group: 69	MPA or MA + MET	Systemic Progestin: Group 1 + MET, Group 2: PROG	CR: 34.1% (Systemic), 84.1% (Local); PR: 10.2% (Systemic), 1.4% (Local)	No data on pregnancies, abortions, or live births
Factor et al. 2024[26]	D&C +/− hysteroscopy	150	Group 1: 76, Group 2: 74	MA + MET	Group 1: PROG + Metformin, Group 2: PROG	CR at 16 weeks: 34.3% (Group 1), 20.7% (Group 2) CR at 36 weeks: 74.3% (Group 1), 68.2% (Group 2)	Pregnancies: Group 1: 51.3%, Group 2: 48.4% Live births: Group 1: 21.6%, Group 2: 41.9%
Yuan et al. 2022[27]	Histopathological exam	120	Group 1: 60, Group 2: 60	MPA + MET	Group 1: PROG + MET, Group 2: PROG	CR: 26.7% (Group 1), 20% (Group 2); PR: 45% (Group 1), 33.3% (Group 2)	Pregnancies: Group 1: 81.7%, Group 2: 61.7% ART: Group 1: 32.7%, Group 2: 37.8%
Adamyan et al. 2024[28]	D&C	16	Group 1: 8, Group 2: 8	MA + MET	Group 1: PROG + MET, Group 2: PROG	CR: 75% (Group 1), 25% (Group 2); NR: 37.5% (Group 1), 67.7% (Group 2)	No data on pregnancies, abortions, or live births
Zhou et al. 2015[29]	Hysteroscopic biopsy or D&C	32	Group 1: 9, Group 2: 23	MPA or MA + MET	Group 1: PROG + MET, Group 2: PROG	CR: 88.9% (Group 1), 84.4% (Group 2)	Pregnancies: Group 1: 55.6%; ART: Group 1: 88.9%
Mitsuhashi et al. 2019[30]	D&C	63	Group 1: 42, Group 2: 23	MPA + MET	Group 1: PROG + MET, Group 2: PROG	CR: 97% (Group 1), 61% (Group 2); Relapse: 13.1%	Pregnancies: Group 1: 45%; ART: 83% of pregnancies occurred within 12 months

PROG: Progesterone; MET: Metformin; MPA: Medroxyprogesterone Acetate; MA: Megestrol Acetate; D&C: Dilation and Curettage; CR: Complete Response; PR: Partial Response; NR: Non-Response; ART: Assisted Reproductive Technology

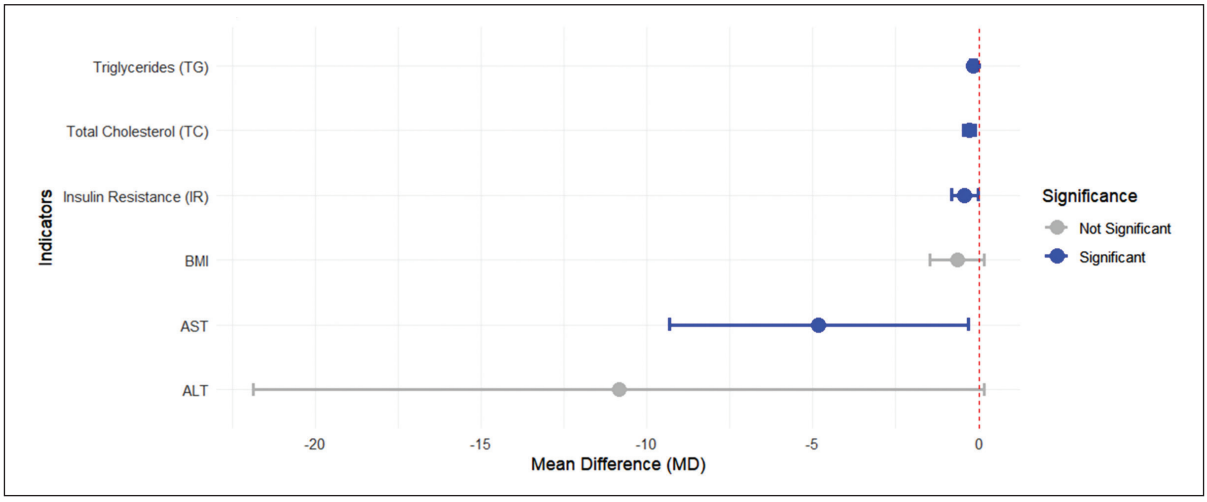

Figure 4. Impact of metformin on clinical and biochemical indicators in MASLD patients.

Table 5. Study characteristics on the incident heart failure outcomes in patients with left ventricular ejection fraction ≥50%

Study	Design	Sample size	Mean age (years)	% of Patients with LVEF ≥50%	Follow-up duration (years)
Lupon et al. 2018[33]	Retrospective study	13,930	76	23%	1.0
Ziao et al. 2024[34]	Prospective study	1,519	72	51%	4.7
Lee et al. 1993[35]	Retrospective study	835	72	49%	2.4
Ohno et al. 2025[36]	Retrospective study	6,185	68	45%	2.2

LVEF: Left Ventricular Ejection Fraction

Table 6. Characteristics and quality of included studies assessing the risk of neurodegenerative diseases with metformin use

Study	Design	Study period	Outcome	Sample size (exposure vs control)	Adjusted OR (95% CI)	Quality score
Wang et al. 2024[41]	Cross-sectional	2008–2012	Cognitive dysfunction (FAB)	2304 (318 vs 1986)	1.29 (0.96 – 1.74)	7/11 (AHRQ)
Laurie-Anne et al. 2023[42]	Cohort	2004–2009	Dementia (ICD-9-CM)	1829 (1033 vs 796)	0.82 (0.52 – 1.28)	7/9 (NOS)
Fang et al. 2023[43]	Cohort	1996–2007	Parkinson's Disease (ICD-9-CM or A-code)	3758 (1879 vs 1879)	1.30 (0.69 – 2.46)	7/9 (NOS)
Villani et al. 2022[44]	Cohort	2000–2007	Dementia (ICD-9-CM or A-code)	12,383 (1864 vs 10,519)	0.76 (0.58 – 0.98)	7/9 (NOS)
Garcia-Ptacek et al. 2016[45]	Cohort	2000–2010	Parkinson's Disease (ICD-9-CM)	9302 (4651 vs 4651)	2.27 (1.68 – 3.07); Dementia: 1.66 (1.35 – 2.04)	7/9 (NOS)
Emre et al. 2003[46]	Cohort	2003–2005	Cognitive dysfunction (MMSE)	365	0.49 (0.25 – 0.95)	5/9 (NOS)
Canet et al. 2003[47]	Case-control	1998–2008	Alzheimer's Disease	14,172 (7086 vs 7086)	1.73 (1.11 – 2.68)	7/9 (NOS)
Armstrong et al. 2019[48]	Cohort	2004–2010	Dementia (ICD-10)	5332 (1478 vs 3854)	0.96 (0.89 – 1.03)	7/9 (NOS)
Gorelick et al. 2010[49]	Case-control	2006	Alzheimer's or Cognitive Dysfunction	126 (35 vs 91)	1.75 (0.81 – 3.78)	8/9 (NOS)
Bamford et al. 2021[50]	Cohort	2005–2014	Parkinson's Disease (ICD-10)	102,745 (94,349 vs 8396)	1.39 (1.06 – 1.82)	7/9 (NOS)
Connor et al. 2020[51]	Cohort	2001–2012	Dementia (ICD-9)	14,562 (10,437 vs 4125)	<75 yrs: 0.89 (0.79–0.99); ≥75 yrs: 0.96 (0.87 –1.05)	8/9 (NOS)
Ruan et al. 2025[52]	Cross-sectional	2014	Cognitive dysfunction (RCS)	198	0.52 (0.24 –1.00)	5/11 (AHRQ)
Silvija et al. 2025[53]	Cross-sectional	2012	Cognitive dysfunction (MMSE)	1323	0.59 (0.35 – 0.99)	4/11 (AHRQ)
Ordoobadi et al. 2024[54]	Cohort	2004–2012	Dementia (ICD-10)	22,841 (NA)	0.58 (0.39 – 0.88)	8/9 (NOS)
Negru et al. 2025[55]	Cohort	1998–2011	Alzheimer's (NINCDS-ADRDA)	5894 (2120 vs 3774)	1.60 (0.87 – 2.93); Dementia: 1.42 (1.02 – 1.98)	8/9 (NOS)
Friedman et al. 2011[56]	Cohort	2011–2014	Cognitive dysfunction (MMSE)	757	2.47 (1.10 – 5.57)	6/9 (NOS)
Riedel-Heller et al. 2001[57]	Case-control	2013–2017	Dementia (ICD-10)	16,522 (8276 vs 8276)	0.96 (0.88 – 1.04)	8/9 (NOS)
Du et al. 2023[58]	Cohort	1997–2007	Alzheimer's (ICD-9)	30,170 (4978 vs 25,192)	Mono: 0.69 (0.28 – 1.71); Combo: 0.57 (0.26–1.26)	7/9 (NOS)
Hsiao et al. 2015[59]	Cohort	1999–2011	Dementia (ICD-9)	31,352 (15,676 vs 15,676)	0.71 (0.63–0.79)	7/9 (NOS)

SU: sulfonylurea; MET: Metformin; AD: Alzheimer's disease; FAB: Frontal Assessment Battery; FBG: Fasting blood glucose; RCS: Rapid cognitive screen; RCS: Rapid cognitive screen; AHRQ: Agency for Healthcare Research and Quality; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; NOS: Newcastle–Ottawa Scale; MMSE: Mini-Mental State Examination; AHRQ: Agency for Healthcare Research and Quality; NA: Not Applicable; Mono: monotherapy; Combo; combination therapy

tics and quality of studies assessing the association between metformin use and the risk of neurodegenerative diseases, including dementia, Alzheimer's disease (AD), and Parkinson's disease (PD). It elucidates variations in study design, population demographics, outcome measurements, and quality scores. The findings demonstrate heterogeneous results, with some studies suggesting that metformin has protective effects, while others report an increased risk or no significant association.[40]

Metformin in liver diseases

Table 7 summarizes the characteristics of studies evaluating the effects of metformin on liver health, highlighting the diverse study designs, diagnostic methods and covariate adjustments employed. The varied metformin doses administered (ranging from 500 mg to 3000 mg) reflect individualized treatment approaches. Figure 4 illustrates the effects of metformin on key clinical and biochemical indicators in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Metformin significantly reduces Triglycerides (TG), Total Cholesterol (TC) and Insulin Resistance (IR), as indicated by the blue markers. Non-significant changes are observed for BMI, AST and ALT as indicated by gray markers with confidence intervals crossing the line of no effect.[60-62] These findings elucidate the role of metformin in improving metabolic parameters in patients with MASLD.

The widespread use of metformin for non-diabetic purposes has gained significant attention in recent years. This shift in usage patterns reflects the drug's potential therapeutic benefits across various medical domains. Among these non-diabetic applications, liver disease stands out as the most prominent, accounting for 30% of the non-diabetes indications of metformin use. This suggests a growing recognition of metformin's hepatoprotective properties and its potential role in managing liver disorders. Following closely, cognitive dysfunction represents 15% of non-diabetes indications of metformin use, indicating an emerging interest in the drug's neuroprotective effects and its potential to mitigate cognitive decline. While cancer treatment and prevention still represent a significant area of research and clinical interest, they account for only 5%. The timeline plot presented in Figure 5 provides a chronological perspective on the evolution of metformin research across these different applications. This visual representation enables a comprehensive understanding

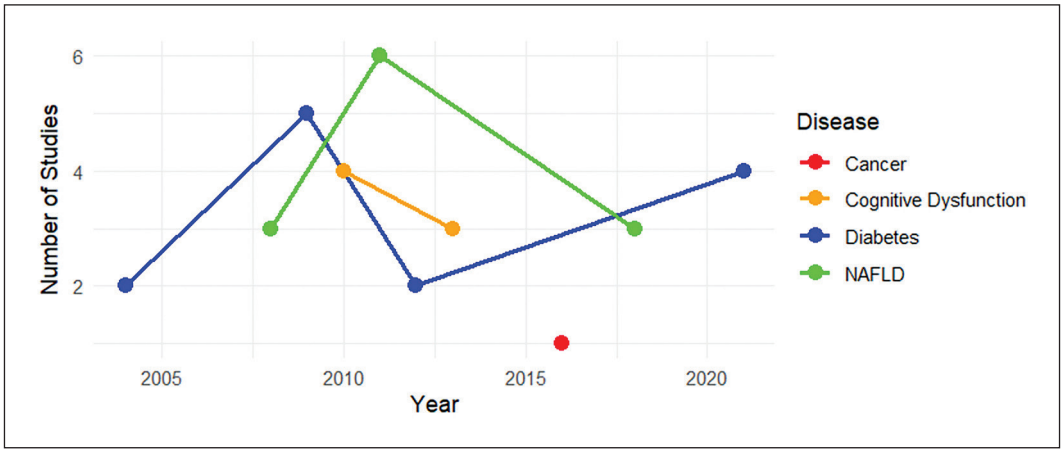

Figure 5. Timeline of research on metformin by disease.

Table 7. Characteristics of studies evaluating the effects of metformin on liver health

Study	Study Design	Case Count	Study Duration (Months)	Diagnostic Method	Metformin Dosage (Treatment Group)	NOS
Brackett et al. 2010[63]	RCT	93	24	Ultrasonography	250 mg first week, 500 mg second week, and 1000 mg third week	8
Pinyopornpanish et al. 2021[64]	Prospective cohort	50	6	Ultrasonography	1000 mg/day	7
Federica et al. 2024[65]	RCT	42	6	Ultrasound	500 mg first week, 2000 mg second week	8
Idilman et al. 2008[66]	Cohort	44	6	Biopsy	500 – 3000 mg/day	7
Ramanathan et al. 2022[67]	Prospective	129	6	Biochemical, radiological, and histological criteria	850 mg/day	9
Nar et al. 2008[68]	Open label RCT	28	12	MRI, CT, imaging, and liver biopsy	500 mg once daily (first week), 500 mg twice daily (second to third weeks), 1000 mg twice daily thereafter	8
Lee 2020[69]	Prospective cohort study	34	6	Ultrasonography	850 – 1700 mg/day	7
Woo et al. 2014[70]	Prospective	57	24	Biopsy and ultrasonography	1.5 g/day	8
García-Compeán et al. 2022[71]	RCT	36	6	Ultrasonography	850 mg/day	7
Hesen et al. 2017[72]	Cohort	63	4	Ultrasonography	850 – 1700 mg/day	8

of how scientific interest in metformin's non-diabetes indications has evolved over time. The timeline likely reveals key milestones, breakthrough studies, and shifting trends in research focus, offering valuable insights into the drug's expanding therapeutic potential. By examining this timeline, researchers and clinicians can better appreciate the progression of metformin's applications, from its traditional role in diabetes management to its current status as a multifaceted therapeutic agent with diverse clinical implications.

CONCLUSION

The findings of this systematic review underscore the multifaceted therapeutic potential of metformin, extending well beyond its established role in managing type 2 diabetes. The analysis of recent literature reveals a growing body of evidence supporting metformin's efficacy in various health conditions, including cardiovascular diseases,[73] different types of cancers,[74] neurodegenerative diseases, and obesity. This review aims to synthesize these findings, explore the implications for clinical practice, and highlight areas for future research. The positive effects of metformin on cardiovascular health are significant. Multiple studies have demonstrated that metformin not only improves glycemic control but also exerts beneficial effects on lipid profiles and blood pressure, thereby reducing cardiovascular risk factors. The drug's ability to enhance insulin sensitivity and exert anti-inflammatory effects may contribute to these cardiovascular benefits. Given the high prevalence of CVD among diabetes patients, the integration of metformin into CVD management protocols could be a valuable therapeutic strategy. Metformin's cardiovascular benefits extend beyond diabetes management, suggesting potential applications in non-diabetic populations for the prevention and treatment of heart disease. Long-term studies show reduced cardiovascular events and mortality in type 2 diabetes patients using metformin. The drug's diverse effects on metabolic pathways make it promising for further cardiovascular medicine research.

Evidence suggests that metformin inhibits cancer cell proliferation and induces apoptosis through various mechanisms, including activation of the AMP-activated protein kinase (AMPK) pathway. This review elucidates that metformin has demonstrated efficacy in treating several types of cancer, including breast, colorectal, and endometrial cancers. These findings indicate that metformin may be considered an adjunctive therapy in oncology, particularly for patients with insulin resistance or metabolic syndrome.

Emerging research suggests that metformin may play a potential role in reducing the risk of neurodegenerative diseases. The reviewed data suggest a potential association between metformin use and improved cognitive function, particularly in individuals with hyperglycemia. The neuroprotective effects of metformin can be attributed to its ability to mitigate oxidative stress and inflammation, which are critical factors in the pathogenesis of neurodegenerative disorders. However, additional longitudinal studies are necessary to establish causality and elucidate the underlying mechanisms involved.

Metformin's role in obesity management represents a further area of research interest. The medication has demonstrated efficacy in promoting weight reduction and enhancing metabolic parameters in overweight and obese individuals, particularly those exhibiting insulin resistance. Looking at the fact that obesity increases risk for diabetes and cardiovascular problems, the application of metformin in obesity for weight management could have significant public health implications.

In summary, metformin demonstrates a broad spectrum of therapeutic benefits that extend well beyond diabetes management. Its roles in treating cardiovascular diseases, various cancers, neurodegenerative diseases, and obesity position it as a multifaceted agent in modern medicine. As research continues to evolve, it is essential to optimize the use of metformin in clinical settings and explore its full potential in improving patient outcomes across a range of health conditions.

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CRediT Author Statement
AJ: Conceptualization, Methodology, Validation, Formal analysis, Data Curation, Writing – original draft preparation, Writing – review and editing; **AU:** Methodology, Writing – original draft preparation, Writing – review and editing; **SSA:** Methodology, Data Curation; **RA:** Formal analysis, Investigation.

Data Availability Statement
The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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