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Artemisinin-Based Combination Therapy: Emerging Evidence for Therapeutic Applications in Type 2 Diabetes Mellitus

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ABSTRACT

Artemisinin and its derivatives, traditionally employed as antimalarial agents, had demonstrated pleiotropic biological activities including anti-inflammatory, antioxidant, and metabolic regulatory properties. Recent preclinical investigations suggested potential therapeutic applications beyond parasitic diseases, particularly in metabolic disorders. This review critically evaluated the current evidence regarding the effectiveness of artemisinin-based combination therapies in managing type 2 diabetes mellitus in adult populations, examining molecular mechanisms, experimental findings, and clinical implications. A comprehensive literature search of PubMed, Scopus, and Web of Science databases was conducted for peer-reviewed studies published between 2014 and 2025 investigating artemisinin compounds and metabolic effects relevant to type 2 diabetes. Preclinical studies demonstrated that artemisinin derivatives modulate glucose homeostasis through multiple mechanisms including enhancement of pancreatic beta-cell function, improvement of insulin sensitivity via AMPK activation, reduction of hepatic gluconeogenesis, modulation of inflammatory pathways, and mitigation of oxidative stress. Animal models consistently showed reduced fasting glucose, improved glucose tolerance, and decreased insulin resistance following artemisinin administration. Limited human studies suggest potential glycemic benefits, though robust clinical trial data remain scarce. Combination approaches with conventional antidiabetic agents show synergistic effects in experimental models. However, significant gaps exist regarding optimal dosing, long-term safety, and translation of preclinical findings to clinical practice. While preclinical evidence supported potential antidiabetic properties of artemisinin-based therapies, current clinical evidence is insufficient to recommend routine use in type 2 diabetes management. Rigorous randomized controlled trials are urgently needed to establish efficacy, safety, and therapeutic positioning.

Keywords: Artemisinin, Type 2 diabetes mellitus, Glucose homeostasis, Insulin sensitivity, Metabolic therapy.

INTRODUCTION

Artemisinin, a sesquiterpene lactone endoperoxide isolated from *Artemisia annua*, represents one of the most significant pharmaceutical discoveries of the twentieth century, primarily recognized for revolutionizing malaria treatment [1, 2]. Beyond its potent antimalarial activity, artemisinin and its semisynthetic derivatives including artesunate, artemether, and dihydroartemisinin possess a unique endoperoxide bridge structure that mediates diverse biological effects through iron-dependent free radical generation and subsequent molecular interactions. Accumulating evidence demonstrates that artemisinin compounds exert anti-inflammatory, immunomodulatory, antioxidant, and metabolic regulatory activities independent of their antiparasitic mechanisms. These pleiotropic properties have stimulated investigation into novel therapeutic applications, particularly in chronic non-communicable diseases characterized by inflammatory and oxidative stress pathways. Recent molecular studies reveal that artemisinin derivatives interact with cellular energy sensors, lipid metabolism regulators, and glucose homeostatic machinery, suggesting potential relevance to metabolic dysfunction.

Type 2 diabetes mellitus constitutes a global pandemic affecting approximately 537 million adults worldwide, with projections indicating continued exponential growth driven by urbanization, dietary transitions, and sedentary lifestyles [3, 4]. The pathophysiology of type 2 diabetes involves complex interactions between insulin resistance in peripheral tissues, progressive pancreatic beta-cell dysfunction, chronic low-grade inflammation, oxidative stress, and dysregulated hepatic glucose production. Current pharmacological management includes metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists, yet many patients fail to achieve adequate glycemic control despite combination therapy.

Furthermore, existing antidiabetic medications are associated with limitations including hypoglycemia risk, weight gain, cardiovascular concerns, and progressive loss of efficacy due to declining beta-cell function. The persistent unmet need for novel therapeutic agents with complementary mechanisms, favorable safety profiles, and potential disease-modifying properties has intensified interest in repurposing established pharmaceutical compounds for diabetes management.

The convergence of artemisinin's molecular mechanisms with key pathophysiological targets in type 2 diabetes has prompted systematic investigation of its potential antidiabetic efficacy [5]. The objective of this review is to critically evaluate the current experimental and clinical evidence regarding the effectiveness of artemisinin-based combination therapies in adults with type 2 diabetes mellitus, examining molecular mechanisms, therapeutic potential, and translational challenges.

Molecular Mechanisms of Artemisinin Action on Glucose Homeostasis

Artemisinin derivatives exert multifaceted effects on cellular glucose metabolism through several interconnected molecular pathways that directly address core pathophysiological abnormalities in type 2 diabetes. The primary mechanism involves activation of adenosine monophosphate-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis that enhances insulin sensitivity and glucose uptake in peripheral tissues [6]. Experimental studies demonstrate that artesunate stimulates AMPK phosphorylation in skeletal muscle and adipose tissue, leading to increased glucose transporter type 4 (GLUT4) translocation to the plasma membrane and enhanced insulin-stimulated glucose uptake [7, 8]. This effect parallels the mechanism of metformin, suggesting potential synergistic applications. Additionally, artemisinin compounds suppress hepatic gluconeogenesis through AMPK-dependent inhibition of key gluconeogenic enzymes including phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, thereby reducing excessive hepatic glucose output characteristic of type 2 diabetes.

Beyond AMPK activation, artemisinin derivatives demonstrate significant anti-inflammatory properties relevant to diabetes pathogenesis [9]. Chronic low-grade inflammation mediated by pro-inflammatory cytokines including tumor necrosis factor-alpha, interleukin-6, and interleukin-1-beta contributes substantially to insulin resistance and beta-cell dysfunction [10]. Artemisinin compounds inhibit nuclear factor-kappa B signaling and reduce inflammatory cytokine production in adipocytes, hepatocytes, and immune cells, thereby ameliorating inflammation-induced insulin resistance. Furthermore, these agents exhibit potent antioxidant effects by enhancing endogenous antioxidant enzyme expression including superoxide dismutase, catalase, and glutathione peroxidase, while simultaneously reducing reactive oxygen species generation [11]. Oxidative stress plays a central role in beta-cell dysfunction and diabetic complications, making antioxidant properties therapeutically relevant.

Emerging evidence indicates that artemisinin derivatives directly support pancreatic beta-cell survival and function through multiple mechanisms. Studies demonstrate that dihydroartemisinin protects beta-cells against glucotoxicity and lipotoxicity-induced apoptosis by activating nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant pathways and inhibiting endoplasmic reticulum stress [12]. Additionally, artemisinin compounds enhance glucose-stimulated insulin secretion through modulation of calcium signaling and potassium channel activity in beta-cells. Interestingly, recent investigations reveal that artesunate influences incretin hormone secretion, potentially augmenting glucagon-like peptide-1 release from intestinal L-cells, which represents an additional mechanism for improving glycemic control. The multitargeted nature of artemisinin's molecular effects distinguishes it from conventional single-mechanism antidiabetic agents and suggests potential for addressing multiple pathophysiological defects simultaneously, though the relative contribution of each mechanism to overall glycemic improvement requires further elucidation.

Preclinical Evidence from Animal Models of Type 2 Diabetes

Animal studies utilizing diverse experimental models of type 2 diabetes provide substantial evidence supporting the antidiabetic potential of artemisinin-based therapies. Studies employing high-fat diet-induced diabetic rodent models consistently demonstrate that artemisinin derivative administration significantly reduces fasting blood glucose, improves oral glucose tolerance, and decreases glycated hemoglobin levels [13]. In streptozotocin-induced diabetic rats, artesunate treatment at doses ranging from 25 to 100 milligrams per kilogram body weight daily for eight weeks produced dose-dependent reductions in hyperglycemia accompanied by improved insulin sensitivity as measured by homeostatic model assessment of insulin resistance (HOMA-IR). These glycemic improvements were associated with enhanced hepatic glycogen storage, reduced hepatic lipid accumulation, and decreased circulating free fatty acid concentrations, indicating favorable effects on integrated metabolic function.

Mechanistic animal studies have elucidated specific pathways underlying artemisinin's antidiabetic effects through targeted interventions and genetic approaches. Experiments using AMPK knockout mice demonstrated that the glucose-lowering effects of artesunate were significantly attenuated in the absence of functional AMPK, confirming the critical role of this pathway [14]. Similarly, studies examining pancreatic tissue from artemisinin-treated diabetic animals revealed preservation of beta-cell mass, reduced apoptosis markers, and enhanced insulin granule density compared to untreated controls. Immunohistochemical analyses showed decreased macrophage infiltration and inflammatory cytokine expression in adipose tissue and liver of treated animals, corroborating anti-

inflammatory mechanisms. Furthermore, artemisinin treatment ameliorated diabetic nephropathy and retinopathy in experimental models, suggesting potential benefits beyond glycemic control for preventing microvascular complications.

Combination therapy studies in animal models have explored synergistic interactions between artemisinin derivatives and established antidiabetic medications. Co-administration of artesunate with metformin produced superior glycemic control compared to either agent alone in diabetic rats, with lower doses of each drug achieving equivalent efficacy to higher monotherapy doses, suggesting dose-sparing potential [15]. Similarly, combination of artemisinin with dipeptidyl peptidase-4 inhibitors enhanced beta-cell function preservation and improved postprandial glucose control more effectively than monotherapy. However, critical evaluation of this preclinical evidence reveals several limitations including predominant use of chemically-induced diabetes models that may not fully recapitulate human type 2 diabetes pathophysiology, relatively short treatment durations typically ranging from four to twelve weeks, and absence of long-term safety data regarding potential toxicity with chronic administration. These experimental findings establish biological plausibility and mechanistic foundations but require validation through well-designed human clinical trials.

Clinical Evidence and Human Studies

Clinical evidence regarding artemisinin-based therapies for type 2 diabetes management remains limited but gradually accumulating. A small pilot study conducted in Vietnam examined the effects of artesunate supplementation in thirty-six adults with newly diagnosed type 2 diabetes over twelve weeks, reporting modest but statistically significant reductions in fasting plasma glucose (mean decrease 1.2 millimoles per liter) and HbA1c (mean decrease 0.6 percent) compared to placebo, with no serious adverse events reported [16]. However, methodological limitations including small sample size, short duration, and lack of standardized dietary control limit the generalizability of these findings. A retrospective cohort study from malaria-endemic regions comparing diabetic patients who received artemisinin-based combination therapy for malaria treatment with those receiving non-artemisinin antimalarials found improved glycemic metrics in the artemisinin-exposed group during the three-month follow-up period, though confounding variables including differential disease severity could not be adequately controlled [17].

Observational data from pharmacovigilance databases and malaria treatment registries provide indirect evidence regarding safety and potential metabolic effects in diabetic populations. Analysis of adverse event reports from millions of artemisinin-based combination therapy courses administered for malaria treatment revealed no increased risk of hypoglycemia or other metabolic complications in diabetic patients compared to non-diabetic individuals, suggesting acceptable safety profiles [18, 19]. Conversely, some case reports documented transient hypoglycemia in diabetic patients receiving high-dose intravenous artesunate for severe malaria, particularly when combined with oral hypoglycemic agents, indicating potential drug-drug interactions requiring careful monitoring. A small pharmacokinetic study demonstrated that diabetes per se does not significantly alter artemisinin derivative metabolism or clearance, suggesting standard dosing regimens may be appropriate, though this requires confirmation in larger populations.

The paucity of robust randomized controlled trials specifically designed to evaluate artemisinin as an antidiabetic therapy represents a major evidence gap. Currently, no phase 3 clinical trials have been completed examining artemisinin derivatives as primary diabetes treatments in non-malaria populations. Several challenges impede clinical translation including uncertainty regarding optimal dosing strategies, concerns about developing artemisinin resistance in malaria-endemic regions if used for non-malarial indications, regulatory complexities surrounding repurposing established antimalarial drugs, and limited pharmaceutical industry investment in generic compound development. Nonetheless, ongoing phase 2 trials registered in clinical trial databases are investigating artemisinin derivatives combined with metformin in Asian populations, with preliminary results expected within the next two years [20]. These studies will provide critical data regarding efficacy, safety, and appropriate patient selection for potential therapeutic applications, though their outcomes remain uncertain pending completion.

Combination Therapy Strategies and Synergistic Approaches

The concept of artemisinin-based combination therapy for diabetes draws inspiration from successful antimalarial treatment paradigms where combination approaches prevent resistance and enhance efficacy through complementary mechanisms. Rational combination strategies pair artemisinin derivatives with conventional antidiabetic agents targeting different pathophysiological pathways to achieve synergistic glycemic control. Metformin represents the most extensively studied combination partner, given overlapping AMPK-activating mechanisms that may produce amplified insulin-sensitizing effects while allowing dose reduction of either agent to minimize adverse effects [21]. Preclinical models demonstrate that artesunate-metformin combinations produce greater reductions in fasting glucose, HOMA-IR, and inflammatory markers compared to equivalent doses of either drug alone, suggesting genuine pharmacodynamic synergy rather than simple additive effects.

Combination of artemisinin derivatives with incretin-based therapies including dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists presents another promising strategy. Given emerging evidence that

artemisinin compounds may enhance endogenous incretin secretion while DPP-4 inhibitors prevent incretin degradation, this combination theoretically addresses both incretin production and preservation [22, 23]. Experimental studies combining artesunate with sitagliptin demonstrated superior postprandial glucose control and beta-cell function preservation compared to monotherapy, with enhanced glucose-stimulated insulin secretion and reduced glucagon levels. Similarly, artemisinin-thiazolidinedione combinations leverage complementary insulin-sensitizing mechanisms, with thiazolidinediones activating peroxisome proliferator-activated receptor-gamma pathways while artemisinin activates AMPK signaling.

From a safety perspective, combination approaches must carefully consider potential drug-drug interactions and cumulative toxicity risks. Artemisinin derivatives are metabolized primarily by cytochrome P450 2B6 and 3A4 enzymes, raising concerns about interactions with antidiabetic medications sharing these metabolic pathways [24]. However, clinical pharmacokinetic studies have not identified significant interactions between artemisinin compounds and metformin, sulfonylureas, or DPP-4 inhibitors at therapeutic doses. The primary safety consideration involves hypoglycemia risk when combining multiple glucose-lowering agents, necessitating careful dose titration and glucose monitoring during combination therapy initiation. Additionally, artemisinin compounds may rarely cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, requiring screening before treatment initiation [25, 26]. Future combination therapy development should prioritize fixed-dose combination formulations to improve adherence, optimize pharmacokinetics, and facilitate clinical implementation, though such formulations require substantial pharmaceutical development investment and regulatory approval processes that present significant barriers to clinical translation.

Safety, Limitations, and Future Research Directions

Critical evaluation of artemisinin-based therapies for diabetes management must address several important safety considerations and knowledge gaps that currently limit clinical implementation. While artemisinin compounds demonstrate excellent safety profiles in short-term antimalarial use, long-term chronic administration for diabetes management requires more comprehensive toxicology data. Animal studies examining chronic artemisinin exposure over six to twelve months have generally not revealed significant organ toxicity, mutagenicity, or carcinogenicity concerns at therapeutic doses. However, some investigations report potential neurotoxicity manifesting as brainstem damage in animal models receiving very high doses, though relevance to human therapeutic dosing remains unclear. Additionally, artemisinin derivatives cross the placental barrier and are contraindicated in first-trimester pregnancy due to embryotoxicity concerns, necessitating careful counseling for women of reproductive age with diabetes [27]. Methodological limitations in existing research substantially constrain confidence in therapeutic recommendations. The majority of supporting evidence derives from animal studies employing experimental diabetes models that incompletely replicate the complex, multifactorial pathophysiology of human type 2 diabetes characterized by prolonged development, genetic heterogeneity, and comorbid conditions [28]. Translation of preclinical findings to clinical efficacy remains uncertain, as numerous promising experimental diabetes therapies have failed to demonstrate meaningful benefits in human trials. Furthermore, existing human studies suffer from small sample sizes, short follow-up durations inadequate to assess long-term efficacy and safety, heterogeneous patient populations, and insufficient control for confounding variables including diet, exercise, and concomitant medications [29]. Publication bias favoring positive results may inflate perceived efficacy while underreporting negative or null findings.

Several critical research priorities must be addressed to advance the therapeutic potential of artemisinin-based diabetes treatments. First, well-powered, multicenter, randomized, double-blind, placebo-controlled trials examining artemisinin derivatives as add-on therapy to standard antidiabetic regimens are essential, with primary endpoints including HbA1c reduction, achievement of glycemic targets, and cardiovascular outcomes over minimum twelve-month durations [30, 31]. Second, dose-finding studies must identify optimal dosing regimens balancing efficacy and safety, as current dosing proposals extrapolate from antimalarial protocols without diabetes-specific optimization. Third, pharmacogenomic investigations should examine whether genetic polymorphisms in drug-metabolizing enzymes or target pathways predict therapeutic response, enabling personalized treatment approaches. Fourth, mechanistic studies using advanced techniques including metabolomics, proteomics, and single-cell analyses could elucidate precise molecular targets and identify biomarkers predicting treatment response. Finally, health economic analyses must evaluate cost-effectiveness compared to existing therapies, particularly relevant given artemisinin's generic availability and low production costs, which could facilitate accessibility in resource-limited settings where diabetes burden is rapidly increasing.

CONCLUSION

Current evidence regarding artemisinin-based combination therapies for type 2 diabetes management reveals substantial preclinical promise but insufficient clinical validation for routine therapeutic application. Mechanistic studies demonstrate that artemisinin derivatives modulate multiple pathophysiological targets relevant to diabetes including AMPK activation, inflammatory pathway inhibition, oxidative stress reduction, and beta-cell function preservation. Animal models consistently show glycemic improvements, enhanced insulin sensitivity, and metabolic

benefits following artemisinin treatment, with synergistic effects when combined with conventional antidiabetic agents. However, human clinical evidence remains limited to small pilot studies and observational data lacking the rigor necessary to establish therapeutic efficacy and safety definitively. The multitargeted mechanisms of artemisinin compounds distinguish them from existing single-pathway antidiabetic medications and suggest potential for addressing multiple pathophysiological defects simultaneously, which may prove particularly valuable for patients inadequately controlled on standard therapies. Nevertheless, significant knowledge gaps regarding optimal dosing strategies, long-term safety profiles, patient selection criteria, and comparative effectiveness against established treatments prevent premature clinical adoption. The favorable safety record from extensive antimalarial use provides reassurance, though chronic administration for diabetes requires more comprehensive toxicology evaluation. Given the substantial global diabetes burden and persistent therapeutic limitations of current pharmacological options, artemisinin-based therapies warrant serious consideration as potential novel treatment modalities, but this promise must be validated through rigorous clinical investigation before evidence-based implementation can be recommended. Large-scale, multicenter, randomized controlled trials examining artemisinin derivatives combined with metformin versus standard care in adults with inadequately controlled type 2 diabetes should be prioritized as the most critical next step to establish clinical efficacy, safety, and appropriate therapeutic positioning.

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