REVIEW
Traditional Medicine Research 2023;8(5):30. https://doi.org/10.53388/TMR20220811001

Research progress of artesunate in diabetes and its complications

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Abstract

Diabetes is a metabolic disease characterized by abnormally elevated blood glucose levels. Persistent hyperglycemia leads to diabetic nephropathy, diabetic retinopathy, diabetes with periodontal disease and other diabetic complications. These diseases have become the main causes of disability and death in diabetic patients. Artesunate is well known as an antimalarial drug for controlling malaria symptoms. Current studies have shown that artesunate improves diabetes and its complications by protecting islet cells, improving glucose and lipid metabolism, anti-inflammatory and immune regulation. Based on the research status in recent years, this paper focuses on the mechanism of artesunate in diabetes and its complications, to provide a theoretical basis for future diabetes research.

Keywords: Artesunate; diabetes; diabetic complications; islet cells; glycolipid metabolism; anti-inflammatory; immunoregulation

Author contributions

Yuan-Hui Guo designed and wrote the manuscript. Lu-Lu Chen came up with this idea. Lu-Lu Chen, Ying Li, Jia-Jia Duan participated in the design and revision of the article. Chuan-Xin Liu and Hong-Wei Jiang strictly supervised and determined the final version. All authors read and agreed to the final manuscript.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

Special thanks to David Lubasi Nalisa for revising the language of this article. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Peer review information

Traditional Medicine Research thanks Ying-Ji Wang and other anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations

ART, artesunate; DHA, dihydroartemisinin; IL-1β, interleukin-1β; SIRT1, sirtuin1; DN, diabetic nephropathy; TLR4, toll-like receptor 4; NOD, non obese diabetes; DR, diabetic retinopathy; MMP-9, matrix metalloproteinase-9; AGEs, advanced glycation end products; MMP, matrix metalloproteinase; PI3K, phosphatidylin-ositol-3-kinase; TNF, tumor necrosis factor; PI3P, phosphatidylinositol-3-phosphate.

Citation

Guo YH, Chen LL, Li Y, Duan JJ, Liu CX, Jiang HW. Research progress of artesunate in diabetes and its complications. *Tradit Med Res*. 2023;8(5):30. doi: 10.53388/TMR20220811001.

Executive editor: Guang-Ze Ma.

Received: 11 August 2022; **Accepted:** 25 November 2022; **Available online:** 05 December 2022.

Highlights

Diabetes is a common metabolic disease characterized by continuous increase of blood glucose, which has become one of the chronic non-communicable diseases threatening human health. With the aggravation of the disease, it will induce complications such as diabetic nephropathy, diabetic retinopathy, diabetes with periodontal disease, which will seriously affect the life of patients. Artesunate, a common artemisinin derivative, has been shown to have a significant effect on malaria. Current research has confirmed that artesunate can effectively improve diabetes and its complications. This article systematically summarizes the effect and mechanism of artesunate in the treatment of diabetes and its complications, and provides reference for further research and clinical application of artesunate in the field of diabetes.

Medical history of objective

Artesunate is a derivative of artemisinin, which is derived from *Artemisia annua* of Asteraceae. *Artemisia annua* has a long history, first recorded in *Prescriptions for Fifty-two Diseases* (unknown author, 202 B.C.E.–8 C.E.). According to the records of *Pharmacopoeia of the People's Republic of China* (State Pharmacopoeia Committee, 2020 C.E.), *Artemisia annua* has the therapeutic effects of clearing "asthenic" fever, cooling off in summer, treating fever "from inside", treating jaundice, and malarial control. Modern pharmacological studies have shown that sesquiterpenes and flavonoids have good antimalarial, antiviral, anti-inflammatory, antipyretic, antibacterial and insecticidal effects. The volatile oil components can exert anti-tumor, antibacterial, insecticidal and anti-inflammatory activities.

Background

Diabetes is a metabolic disease characterized by chronic hyperglycemia. Peripheral insulin resistance and pancreatic β-cell dysfunction are caused by environmental, genetic and other factors, leading to chronic low-grade inflammation and glucose metabolism disorders [1]. The global incidence of diabetes increased year by year, is expected to 2,045 global diabetes patients reached 693 million, the incidence of diabetes in China is 11.6%, the country with the largest number of diabetic patients [2, 3]. Long-term hyperglycemia and persistent metabolic disorders lead to a variety of tissue and organ damage, complicated by diabetic nephropathy, diabetic retinopathy, diabetic cardiovascular disease and other chronic diseases. Comparatively, diabetes itself has lower mortality and disability rate than its related complications, which seriously threaten the life and property safety of people all over the world. Therefore, it is urgent to develop drugs to prevent and intervene in diabetes and its complications. Artesunate (ART) is a semi-synthetic artemisinin derivative widely known for its significant efficacy against malaria. ART exerts its biological activity by regulating certain biological pathways. It has been found that ART has anti-diabetic, anti-inflammatory, immunosuppressive, anti-atherosclerotic, anti-cancer, anti-viral and other effects. In the course of administration, ART can be loaded into liposomes alone or in combination with other therapeutic agents. The routes of administration include oral, intravenous, intragastric and parenteral administration [4].

Overview of artesunate

ART, also known as dihydroartemisinin-12-α-succinate, is a semi-synthetic peroxide-bridged sesquiterpene lactone compound. The production of ART from artemisinin involves a two-step reaction of reduction and esterification using diisobutylaluminum hydride and succinic anhydride [5]. The biological activity of ART is closely related to its 1,2,4-trioxane core containing endoperoxide bond [6]. When administered orally, ART has a half-life of about 20 to 45 minutes and is metabolized by esterase-catalyzed hydrolysis to dihydroartemisinin (DHA), a metabolite of ART that exerts antimalarial activity [7]. Due to the short half-life of ART, its bioavailability and pharmacological activity are relatively low, so repeated administration is required to cure, but this may lead to drug resistance [8].

Trimeric ART derivative TF27 shows that ART interacts with human cytomegalovirus through export protein, mitochondria and nuclear factor-κB (NF-κB) pathway [9, 10]. ART exerts anti-tumor activity by affecting non-apoptotic cell death, such as autophagy, oncosis and ferroptosis [11–14]. ART also affects multiple landmark events in cancer development by inhibiting cancer cell proliferation and invasion, disrupting cancer signaling pathways, inducing cell cycle arrest, causing oxidative damage, and inducing apoptosis [4]. In addition, ART has anti-atherosclerosis, treatment of lupus, anti-inflammatory and immunosuppressive activity, can also inhibit angiogenesis or as a transfer agent [15–20].We have drawn the structure diagram of artesunate, see Figure 1.

Effect and mechanism of artesunate in treating diabetes

Protecting islet cells

Insulin secreted from islet β cells is critical for maintaining the normal physiological range of blood glucose, especially for islet cell survival and functional integrity. The survival and function of islet β cells are impaired, resulting in decreased insulin secretion, which is the main cause of diabetes. Therefore, protecting islet β cells and promoting insulin secretion are effective methods for treating diabetes [21]. Interleukin-1β (IL-1β) has been found to play an important role in the early damage of β cells, and β cells themselves produce IL-1β under high glucose stimulation [22, 23]. Studies have found that by activating the NF-κB pathway, IL-1β independent factors can cause glucose-stimulated insulin secretion dysfunction [24]. Inhibition of NF-κB pathway can protect human and rodent islets from IL-1β-stimulated β-cell damage [25]. Sirtuin1 (SIRT1) is a nicotinamide adenine dinucleotide-dependent deacetylase that regulates a variety of cellular activities, including cell survival, anti-stress ability, and cell autoregulation [26]. Studies have shown that SIRT1 plays a role in reducing insulin resistance and protecting islet β cells [27]. In addition, SIRT1 can protect islet β cells by deacetylating p65 [28]. Therefore, SIRT1 is expected to become a new target for the treatment of diabetes. Yu et al found that, ART inhibited the activation of the NF-κB pathway induced by IL-1β and alleviated insulin secretion dysfunction [29]. ART reversed IL-1β-induced islet β cell injury and decreased SIRT1 expression. The protective effect of ART on islet β cells was partially eliminated after SIRT1 inhibition. In conclusion, ART fully activates SIRT1 expression in islet β cells, inhibits the NF-κB-iNOS-NO signaling pathway, promotes insulin secretion and down-regulates apoptosis. In addition, ART enhances the viability of streptozotocin-treated mouse islet β cells, reduces the number of late apoptotic cells and pyroptosis cells, and down-regulates the expression of proteins related to the pyroptosis pathway, thereby protecting islet β cells [30].

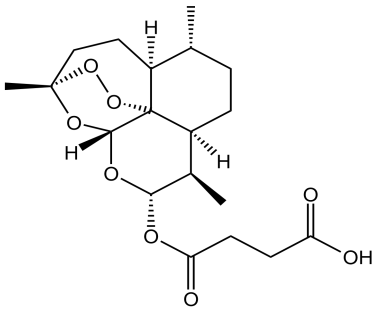

Figure 1 Structure of artesunate

Improved glucose and lipid metabolism

The characteristic disease of diabetes is the abnormal increase in blood glucose level. The disorder of blood glucose metabolism can lead to abnormal lipid metabolism, which in turn causes the increase of plasma cholesterol, triglyceride and low-density lipoprotein cholesterol, and the decrease of high-density lipoprotein cholesterol [31]. ART reduces fasting blood glucose in type 2 diabetic mice, improves insulin sensitivity and glucose tolerance, and improves islet morphological damage and insulin resistance [32]. ART up-regulated apolipoprotein-A1 levels and significantly down-regulated serum cholesterol, low-density lipoprotein and triglyceride levels in golden hamsters. In addition, ART can also down-regulate blood lipid levels in golden hamsters, reduce the accumulation of cholesterol in RAW264.7 cells and the accumulation of free fatty acids in HepG2 cells. It is worth noting that ART can also inhibit fatty acid synthesis, promote fatty acid β-oxidation and reverse cholesterol transport outflow through related signaling pathways, thereby completing the lipid-lowering process [33]. Some researchers have found that there may be gender differences in the hypoglycemic effect of ART [34]. ART reduces blood glucose by down-regulating glucagon concentration in plasma and inhibiting G6Pase activity in both sexes to inhibit hepatic glycogen decomposition. In addition, the increase in insulin concentration was beneficial to the hypoglycemic process of ART in male rats but had no effect on female rats. Moreover, ART-induced G6P increase enhanced antioxidant enzyme activation and nicotinamide adenine dinucleotide phosphate production in male rats. Pu et al. found that, ART by affecting lipid metabolism, energy metabolism, amino acid metabolism and other metabolic pathways, plays a significant lipid-lowering effect [35].

Anti-inflammation

Type II diabetes has been shown to be a chronic low-grade inflammation [36]. The inflammatory response activates a variety of pro-inflammatory mediators, such as IL-1β, IL-6, tumor necrosis factor (TNF), etc. by various transcription factors-mediated oxidative stress and molecular pathways, and leads to insulin resistance by interfering with insulin signaling pathways [37]. An inflammatory response is the key cause of insulin resistance in diabetes, and pancreatic dysfunction is closely related to the inflammatory response of islet cells [38]. Pancreatic damage caused by inflammation is thought to be an important cause of worsening diabetes [39]. ART has been shown to play a significant anti-inflammatory effect in infectious inflammation, allergic inflammation and autoimmune diseases by inhibiting inflammatory factors and their related pathways, which may be beneficial to alleviate pancreatic pathological changes and diabetic insulin resistance [40]. The levels of IL-6, C-reactive protein and adiponectin in patients with type 2 diabetes are abnormal, and the correlation is obvious. Therefore, the detection of serum IL-6, high-sensitivity C-reactive protein and adiponectin levels may become the core indicators of type 2 diabetes symptom assessment and treatment effect evaluation [41]. IL-6 is considered to be a cytokine with significant endocrine characteristics, which can be produced by adipocytes or immunocompetent cells, acting on the body's energy metabolism and inflammatory response, and can be an important reference for predicting the occurrence and development of diabetes [42]. ART can effectively down-regulate the level of IL-6, and the effect is comparable to artemisinin, which is better than another artemisinin derivative artemether. However, whether the hypoglycemic effect of ART is related to IL-6 level needs further study [43].

Immunoregulation

Type 1 diabetes is an organ-specific autoimmune disease caused by immune cells infiltrating islets and attacking β cells, leading to β cell destruction and insulin deficiency. Studies have shown that IFN-γ plays an important role in driving the disease, and the tissue-specific expression of IFN-γ in the pancreas is sufficient to cause type 1 diabetes [44]. Therefore, the elevated level of IFN-γ is associated with the pathogenesis of type 1 diabetes, and accordingly blocking the abnormal increase of IFN-γ may become a potential method to prevent type 1 diabetes. Recombinant IL-4 administration or IL-4 expression in the pancreas may be beneficial to the prevention of autoimmune diabetes in non obese diabetes (NOD) mice [45]. Changes in cytokine production in T cells were observed in transgenic NOD mice receiving anti-CD20 depletion antibodies, revealing the importance of IFN-γ and IL-4 in the pathogenesis of type 1 diabetes [46]. ART administration can prevent the development of type 1 diabetes in NOD mice, reduce the frequency of T cells producing IFN-γ in peripheral immune tissues, increase T cells producing IL-4, and promote the functional maturation of islet β cells [47]. In addition, IFN-γ decreased and IL-4 increased during the production of cytokines in $CD4^+$ and $CD8^+$ T cells after ART administration [47].

Effect and mechanism of artesunate in treating diabetic complications

Diabetic nephropathy

Diabetic nephropathy (DN) is a microvascular complication associated with disorders of glucose metabolism, oxidative stress and changes in renal hemodynamics [48]. The early pathological features of DN include podocyte loss, glomerular hypertrophy, mesangial matrix expansion and glomerular basement membrane thickening. The late pathological features include nodular glomerulosclerosis, mesangial dissolution and tubulointerstitial fibrosis. The activation of inflammatory response is the main pathological damage mechanism [49]. Although current strict glycemic control and renin-angiotensin system blockade can slow the progression of DN, many diabetic patients eventually develop end-stage renal disease. Relevant studies have shown that ART can effectively intervene DN and provide a theoretical basis for clinical DN prevention and treatment. ART can effectively reduce the apoptosis rate of rat renal tubular epithelial cells induced by high glucose, inhibit the expression of IL-8, TNF-α, NF-κB and toll-like receptor 4 (TLR4), and improve the inflammatory response of rats. The intervention effect is dose-dependent [50, 51]. ART can also increase the level of renal autophagy and alleviate the progression of renal fibrosis in diabetic rats by up-regulating AMPK expression and interfering with TGF-β1/Smad2 pathway [52]. ART alleviates the occurrence and development of DN, promotes the proliferation and apoptosis of glomerular mesangial cells induced by high glucose in a dose-dependent manner, and down-regulates the expression levels of inflammatory factors such as NF-κB and MCP-1 [53]. Sun et al. confirmed that ART protects rat mesangial cells induced by high glucose by inhibiting inflammatory response, oxidative stress and extracellular matrix accumulation [54]. TLR4/NF-κB/NLRP3 inflammasome pathway is involved in the protective effect of ART, indicating that ART may be a potential drug for the treatment of DN.

Diabetic retinopathy

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes, which is the main cause of visual disability and blindness in diabetic patients [55]. About 75 % of DR patients have irreversible visual loss [56]. The early pathological features of DR are vascular cell loss, vascular leakage and blood-retinal barrier damage [57]. Related studies have shown that inflammation and oxidative stress are crucial in a series of pathological changes of DR [58]. Enhancing autophagy can reduce inflammation and oxidative stress in the heart of diabetic mice, which indicates that regulating autophagy may provide a reference for the prevention and treatment of DR [59]. Li et al. found that ART inhibited the increase of retinal thickness, vascular leukocyte adhesion, microglial activation, production of inflammatory cytokines and reactive oxygen species in the retina of diabetic rats [60]. In addition, ART enhanced the level of autophagy in the retina of diabetic rats by up-regulating Beclin-1 expression and LC3II/I ratio and down-regulating p62. ART can protect the blood-retinal barrier and retinal tissue structure of diabetic rats, reduce inflammation and oxidative stress in retinal tissue, up-regulate the activation level of AMPK/SIRT1 pathway, and

enhance autophagy. In addition, ART can also use SIRT1 to activate autophagy, alleviate the release of pro-inflammatory factors and oxidative stress in retinal pigment epithelial cells under high glucose conditions, and then protect cells [61]. The angiogenesis of DR patients is closely related to matrix metalloproteinase-9 (MMP-9). Studies have confirmed that ART can inhibit the expression of MMP-9, angiogenesis factors VEGF and ANG in DR patients [62, 63]. After ART administration, the expression of Hsp27 and Bcl-2 in the retinal tissue of diabetic rats was up-regulated, and the apoptosis of diabetic retinal cells was reduced, which had a protective effect on nerve cells [64]. ART inhibited the expression of MMP-9 and ICAM-1 protein in vascular endothelial cells under high glucose, and the inhibitory effect was dose-dependent [65].

Diabetes with periodontal disease

Chronic periodontal disease is the inflammatory state of gums, periodontal tissue and alveolar bone, caused by anaerobic gram-negative microorganisms. The inflammatory response of patients with diabetes mellitus complicated with periodontal disease is stronger than that of patients with periodontal disease. Periodontal disease can cause cardiovascular disease, obesity, pregnancy complications and so on [66]. Periodontal disease is becoming a risk factor for chronic complications in diabetic patients. The inflammation caused by it will not only occur locally in the oral cavity but also circulating inflammatory mediators can lead to systemic reactions, which aggravate microvascular damage caused by chronic hyperglycemia [67]. High levels of glucose metabolism can also promote inflammation, aggravate periodontitis symptoms and affect oral health [68]. ART inhibits mTOR/LC3 gene expression, regulates autophagy in the aorta of type 1 diabetic rats with periodontal disease, reduces blood glucose levels, and alleviates periodontal conditions [69]. ART improves the inflammatory response in the motor area of the cerebral cortex of rats with type 1 diabetes mellitus and periodontal disease by down-regulating the expression of Caspase-3 and TNF-α, and inhibits neuronal apoptosis [70]. Liang Chen confirmed that ART intervention can inhibit the expression of TNF-α in gingival tissue, regulate periodontal flora and OPG, ALP and RANKL expression, improve alveolar bone tissue reconstruction; in addition, ART can also reduce the content of SUN and Scr in serum of type 1 diabetic rats with periodontal disease, inhibit renal inflammation and fibrosis, enhance autophagy and improve renal injury [71]. In addition, ART can alleviate gingival inflammation in diabetic rats, partially restore the impaired osteogenic ability of jaws, and improve the osteogenic differentiation ability of human bone marrow mesenchymal stem cells under high glucose conditions [72]. Chen Yi found that ART intervention can regulate periodontitis-related pathogenic bacteria, inhibit cardiovascular complications related pathways NF-κB/p38/MAPK/TGF-β and NF-κB/TLR4, improve myocardial apoptosis, fibrosis and vascular inflammatory changes, relieve periodontitis symptoms and type 1 diabetes with periodontal disease complicated by cardiovascular complications [73].

Diabetic skin ulcer

Diabetic skin ulcers is one of the common complications of diabetes. Due to peripheral neuritis, peripheral vascular lesions, abnormal collagen and other vascular lesions and complications, it is difficult for diabetic patients to heal skin wounds and then develop into chronic ulcers. The healing process involves inflammatory response, wound proliferation, remodeling regulation and stem cell control. In addition, under high glucose conditions, white blood cell function is impaired and immune function is weakened, resulting in insufficient immune response in related parts, making diabetic foot more difficult to heal [74]. Persistent infection, tissue ischemia, necrosis, exudation and excessive expression of inflammatory factors, matrix metalloproteinases (MMPs), different growth factors, nitric oxide, reactive oxygen species, endothelial progenitor cells, microRNA and other factors are closely related to delayed healing of diabetic wounds [75, 76]. High glucose conditions can stimulate the formation of advanced glycation end products (AGEs), which bind to monocyte-macrophage cell surface receptors and induce excessive inflammatory response. In addition, AGEs bind to their specific immune superfamily AGEs receptors, up-regulate the high expression of TNF-α, IL-6 and MMPs, so that the wound healing process is in a state of inflammation for a long time, and the use of extracellular matrix collagen cleavage slows wound healing [77]. After the intervention of ART on the back wound of diabetic rats, the wound area was reduced and the healing rate was accelerated. The appropriate dose of ART reduced the expression of MMP-2 and MMP-9 in the wound skin of rats and promoted the expression of transforming growth factor-β1 and epidermal growth factor, thereby promoting wound healing [78]. ART can also down-regulate the expression of TNF-α, inhibit the inflammatory response and accelerate wound healing [79].

Study on pharmacokinetics and drug resistance of artesunate

Study on the pharmacokinetics of artesunate

ART pharmacokinetic studies mainly use plasma samples, a few use whole blood, serum, saliva, or other biological samples. ART has excellent physical and chemical properties and can be made into injection, suppository, tablet, liposome microcapsules and other preparations for intravenous injection, intramuscular injection, oral administration, rectal administration and other ways [80]. After oral administration, ART tablets need to be disintegrated and dissolved in the gastrointestinal tract before being absorbed. The main absorption site is the small intestine. Some ART is absorbed into the blood after forming DHA by chemical hydrolysis of acid in the intestine. The untransformed part enters the liver directly through the portal vein, and some are converted to DHA through liver metabolism. If ART in the blood is directly measured, the proportion of drugs absorbed into the blood is small and the bioavailability is low. If ART bioavailability is evaluated by measuring DHA in blood, its bioavailability is higher. The elimination half-life of ART in major tissues and organs is not the same. Bone marrow and spleen have the longest elimination half-life, about 140–222 h, followed by lung (105–123 h), heart (91–109 h), muscle tissue (96–106 h), kidney (94–102 h), blood (82–99 h) [81]. The plasma protein binding rate of ATR prototype form or its active metabolite DHA was higher after entering the blood through different routes of administration. The plasma protein binding rate of ART in human and rat plasma was 73%–81%, and the DHA binding rate was 76%–82% [82, 83]. The plasma protein binding rate of DHA in patients infected with malaria parasites is 93% [84]. The absorption rate of ART by intramuscular injection is faster than that by oral administration, and the peak time is shorter. The absolute bioavailability is 86.4% in adults with falciparum malaria and 88% in children calculated by the concentration of DHA [85]. The absolute bioavailability of ART after oral administration was 61% (95% confidence interval: 52%–70%) [86]. After oral administration, part of ART is absorbed into the blood and converted into DHA, and its bioavailability is 80%–85%. Another part of ART is absorbed into the liver through the hepatic portal vein and metabolized into DHA in the liver [87, 88].

Study on drug resistance of artesunate

Artemisinin and its derivatives are effective in the treatment of malaria, but there are still some difficulties and challenges, among which drug resistance is particularly critical. The mutation of K13 gene on chromosome 13 of *Plasmodium falciparum* is most closely related to artemisinin resistance. Nine loci including F446I, N458Y, M476I, Y493H, R539T, I543T, P553L, R561H, and C580Y have been proven to be related to artemisinin resistance by WHO [89]. The C580Y, R539T, Y493H, I543T mutations directly affect drug resistance [90, 91]. However, ART resistance is still observed in malaria parasites without K13 mutations [92]. In a study, four Plasmodium isolates with wild-type K13 protein but ring stage survival assays ≥ 0.8 % were identified. The results showed that K13 had independent resistance to ART. The subsequent genomic analysis

identified 37 new mutations in 19 non-K13 genes in sensitive and resistant strains, 11 of which were present in strains without K13 mutations. Phosphatidylin-ositol-3-kinase (PI3K) and multidrug resistance protein mutations are the most intensive [93]. After C580Y site mutation, its polyubiquitination and binding affinity with K13 decreased, up-regulated PI3K levels, resulting in phosphatidylinositol-3-phosphate (PI3P) content increased, but artemisinin and its derivatives can inhibit PI3K, down-regulated PI3P levels. This abnormal change in kinase levels explains the generation of artemisinin resistance in mutant parasites, and PI3P levels can be used as predictors of artemisinin resistance [94, 95].

Conclusion

Research on diabetes and its complications has always been the focus of researchers around the world, and its cutting-edge achievements emerge in endlessly. The pathogenesis and progression of diabetes mellitus and its complications are complex and changeable. Therapeutic drugs with one-way effect and single target have been difficult to adapt to the current medical status. Nowadays, natural drugs have attracted much attention from scholars because of their small side effects. ATR, as an artemisinin derivative, has been proven to have significant effects on malaria, tumor, inflammation, angiogenesis, fibrosis and other aspects. Its multi-channel, multi-process and multi-target characteristics have a good therapeutic effect on the occurrence and development of diabetes and its complications. By acting on bioactive substances such as interleukin, TNF-α, IFN-γ, SIRT1, TLR4, AMPK, MMP-9, and pathways such as NF-κB-iNOS-NO, TGF-β1/Smad2, TLR4/NF-κB/NLRP3, AMPK-SIRT1, ART plays a role in the treatment of diabetes and its complications based on biological processes such as inflammatory response, immune regulation, autophagy, oxidative stress, and apoptosis. However, there are still many problems to be solved in the process of ART in-depth research and clinical new drug development. For example, there are few studies on the effect of ART on other pathogenic mechanisms of diabetes, such as insulin receptor, oxidative stress, intestinal flora, hemodynamics, or other complications of diabetes, such as diabetic cardiomyopathy, diabetic peripheral neuropathy, diabetic heart disease, and diabetic foot. In addition, most studies of ART are limited to in vitro cell and animal levels, and clinical applications are less involved. In short, ART, as a new drug, has broad prospects. With the deepening of research, it is believed that in the future, it will receive more attention and application not only in the field of diabetes but also in the entire medical and health field, contributing to human health.

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