Review

Resveratrol as a Potential Therapeutic Strategy in Aspirin-Resistant Diabetic Patients: Focus on FoF1-ATP Synthase Inhibition

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Review

Resveratrol as a Potential Therapeutic Strategy in Aspirin-Resistant Diabetic Patients: Focus on F_oF_1-ATP Synthase Inhibition

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Abstract

Dysregulated platelet function contributes to various pathological conditions, including diabetes mellitus (DM), a metabolic disorder characterized by elevated blood glucose, due to impaired insulin action. In type 2 diabetes mellitus (T2DM), hyperglycemia, insulin resistance, oxidative stress, and inflammation impair endothelial function and platelet regulation, promoting a prothrombotic state. Platelet hyperreactivity is associated with T2DM cardiovascular complications, a leading cause of mortality in patients. Antiplatelet therapies often prove ineffective for a subset of T2DM patients due to aspirin resistance, necessitating alternative therapeutic strategies. Resveratrol, a natural polyphenol, is a potential therapeutic agent for T2DM, including inhibition of platelet aggregation. One of the pleiotropic actions of resveratrol is to modulate the F_oF_1-ATP synthase rotational catalysis. Platelet chemical energy demand during the activation phase is achieved through oxidative phosphorylation. Both mitochondrial and extra-mitochondrial oxidative phosphorylation drive aerobic energy production in activated platelets, utilizing fatty acids and glucose, respectively. Hyperglycemia can cause an overwork of the oxidative phosphorylation, producing oxidative stress. Targeting F_oF_1-ATP synthase with resveratrol may reduce platelet hyperreactivity in aspirin-resistant cases. This paper reviews the implications of resveratrol ability to inhibit platelet F_oF_1-ATP synthase on its potential as a novel alternative or synergistic antiplatelet strategy for aspirin-resistant T2DM patients.

Keywords: ATP synthase; aspirin resistance; oxidative stress; platelets; resveratrol

1. Type 2 Diabetes Mellitus (T2DM) and Its Complications

Diabetes mellitus is classified into type 1 and type 2. Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which autoreactive T lymphocytes mediate the destruction of pancreatic β-cells, resulting in an absolute insulin deficiency and dependence on insulin therapy [1]. Type 2 diabetes mellitus (T2DM), a metabolic disorder characterized by chronic hyperglycemia and an inadequate response to circulatory insulin by peripheral tissues (insulin resistance), accounts for approximately 90% of global cases [2]. The growing prevalence of T2DM and its complications worldwide, both in high-income and low-income countries, is a significant public health challenge [2,3]. The global number of people with diabetes (mostly T2DM) is projected to be more than 1,3 billion by 2050 [3]. Genetic predisposition and an unhealthy lifestyle are the main causes of T2DM, characterized by progressive loss of pancreatic β-cell function, determining hyperglycemia (Zheng et al., 2018). Chronic oxidative stress and low-grade inflammation activate kinases, including NF-κB, that worsen insulin resistance and trigger β-cell apoptosis [5]. Impaired insulin signaling is driven by defects in the insulin receptor substrate (IRS)–phosphatidylinositol-3-kinase (PI3K)-Akt pathway in tissues (skeletal muscle, liver and adipose tissue) and by mitochondrial dysfunction [6], and endoplasmic-reticulum stress [7,8]. T2DM is associated with both microvascular (diabetic retinopathy and nephropathy) and macrovascular (peripheral, coronary , and cerebral artery disease, atherosclerosis, and kidney disease) complications [9]. Cardiovascular complications are the leading

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cause of T2DM morbidity and mortality [4]. Increased cardiovascular risk in patients with T2DM is linked to platelet structural abnormalities and circulating immature platelets. In T2DM there is suppression of anticoagulant molecules, such as thrombomodulin, and impaired fibrinolysis increased levels of circulating pro-inflammatory cytokines (TNF-α, IL-1, IL-6), pro-coagulant factors (von Willebrand factor), plasma fibrinogen, and thrombin [10]. These factors along with hyperglycemia, hyperlipidemia, low-grade inflammation and oxidative stress determine platelet hyperreactivity, promoting a pro-thrombotic state in T2DM [11]. The inflammatory, pro-thrombotic environment heightens the cardiovascular risk observed in T2DM [12]. Therefore, in clinical practice, glucose-lowering, lipid-lowering drugs, and antiplatelet agents are employed [13,14]. By modulating platelet aggregation, it is possible to effectively prevent CVD [15].

2. Platelets

Platelets are anucleate cell fragments generated by the megakaryocyte in the bone marrow (BM), abundant in the bloodstream (150–400 × 109/L) [16]. Platelets express diverse receptors and ligands and contain several organelles (mitochondria, lysosomes, and alpha and dense granules) and specialized canalicular systems. As key players in hemostasis, upon vascular injury, platelets transition from a quiescent to an activated state and adhere to the exposed subendothelial matrix through a multistep process related to the shear conditions of blood flow [17]. Under high (arterial) shear, adhesion to the exposed subendothelial matrix is mediated by glycoprotein (GP) Ib–IX–V binding to the plasmatic von Willebrand factor (vWF). At low shear rates, platelets adhere to exposed subendothelial collagen through the GPVI and integrin $\alpha 2\beta 1$ receptors [18]. Following adhesion, inside-out signaling triggered by agonists such as thrombin, ADP, and thromboxane A_2 (TXA_2) or adhesive proteins drives platelet aggregation by the conformational activation of GPIIb/IIIa (integrin $\alpha IIb\beta 3$ [19]. Upon activation, $\alpha IIb\beta 3$ shifts from a low- to high-affinity state that binds fibrinogen, VWF, and other ligands (e.g., vitronectin, fibronectin), cross-linking adjacent platelets that assemble to coagulation factors, forming stable platelet plugs. Platelet indices such as mean platelet volume (MPV), platelet distribution width (PDW), platelet-large cell ratio (P-LCR), and plateletcrit (PCT) are altered in T2DM, and have been proposed as biomarkers of poor glycemic control [20].

3. Platelet Hyperactivation and Aspirin Resistance in T2DM

In T2DM, platelets are hyperreactive, compared to controls, basal platelet activation is similar, thrombin stimulated activation is enhanced, limiting aspirin effectiveness [21,22]. Aspirin irreversibly blocks COX-1 by acetylating its serine-529 [14] preventing the conversion of arachidonic acid (AA) to thromboxane A2 (TXA2), a potent platelet aggregation agonist. Aspirin resistance (AR) in patients with diabetes is a clinical phenomenon empirically defined as a condition where the conventional dose of aspirin does not sufficiently suppress platelet aggregation [22]. Although AR can be due to other factors, such as lack of adherence to therapy, reduced bioavailability, or interactions with medications, A systematic review discussed AR prevalence in diabetic patients, higher than other populations at cardiovascular risk [22]. AR has been studied more in T2DM than in T1DM. A classic ambulatory study characterized platelets in T1DM patients and found a lab-defined AR phenotype in T1D associated with female sex, corresponding to a maladaptive phenotype with increased basal activity and hyperactivation upon stimulation [23]. Different direct and indirect laboratory assays are utilized to measure platelet functional AR. Serum thromboxane B_2 ($sTXB_2$) is the most specific pharmacodynamic marker of platelet COX-1 activity. High serum $sTXB_2$ levels suggest inadequate platelet inhibition [24]. Test of urinary 11-dehydro-TXB_2 reflects TXA_2 but is less specific. Point-of-care test VerifyNow® Aspirin measures platelet response to aspirin using an arachidonic acid agonist to measure their ability to aggregate (results are expressed in Aspirin Reaction Units) [25]. The PFA-100 Indirect assay is another point-of-care assay that evaluates platelet reactivity in high-shear flow by measuring the time it takes for a platelet plug to occlude a small aperture in a membrane-coated cartridge (Closure Time CT) [26]. Concordance of assays is low, due

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to lack of standardization, therefore it is recommended to use at least one direct and a functional test to investigate AR in T2DM [27] Several are the T2DM features that can impair aspirin ability to suppress platelet aggregation. A systematic review and meta-analysis comparing the characteristics of AR versus non-AR T2DM patients reported that AR is associated with younger age, fasting glucose and HbA1c levels, dyslipidemia, BMI, and smoking habit, but not with gender, comorbidities and concurrent medications [22]. Hyperglycemia induces nonenzymatic glycation of surface platelet proteins decreasing membrane fluidity, and increases protein kinase C Activation [11]. In T2DM, inflammation increases platelet phosphatidylserine (PS) exposure, and expression of the surface glycoproteins Ib and IIb/IIIa [28], of Fcγ receptor type IIa (FcγRIIa) and factor V^a binding [29]. Patients with T2DM show constitutively activated $P2Y_{12}$ receptor expression, linked to ADP-induced platelet hyperreactitiy [30]. Hypertriglyceridemia (common in T2DM), due to elevated VLDL, also correlates with AR due in part to apolipoprotein E. Diabetes is associated with systemic inflammation and oxidative stress that may contribute to increased platelet reactivity [31]. Guidelines still recommend low-dose aspirin (75–100 mg daily) for secondary prevention in diabetes, but individualized use for primary prevention; none recommend routine platelet-function testing or routine BID dosing for all T2D patients because outcome evidence is lacking (Diabetes Care 2024 guidelines) [32]. A small PD trial showed that BID low-dose aspirin suppresses platelet reactivity better than QD in T2D. Participants with Type 2 diabetes (n = 24) but without known cardiovascular disease were randomized in a three-way crossover design to 2-week treatment periods with aspirin 100 mg once daily, 200 mg once, or 100 mg twice daily. In T2DM, aspirin 100 mg twice daily reduced platelet reactivity more effectively than 100 mg once daily, and numerically more than 200 mg once daily. Clinical outcome trials evaluating primary cardiovascular disease prevention with aspirin in Type 2 diabetes may need to consider using a more frequent dosing schedule [33]. No large randomized outcomes trial yet demonstrates that BID (or higher dose) improves ASCVD endpoints in T2D compared with standard QD dosing. The Ongoing ANDAMAN trial on adult (type 1 or type 2) patients with DM or AR admitted to intensive cardiac care unit, plans to evaluate the superiority of twice-daily compared to once-daily aspirin in patients with DM or AR during a follow-up of 18 months after acute coronary syndrome (ACS) [34]. The ADAPTABLE study, a large open-label, multicentric trial, enrolled patients with DM and concomitant CVD and randomized them to 81 mg or 325 mg of daily aspirin. No difference was found for the daily aspirin dosing strategies for patients with DM in the primary outcomes (death, myocardial infarction, or hospitalization for stroke) or safety outcomes (major bleeding) [35].

3.1. Endothelial Dysfunction in Type 2 Diabetes

In T2DM, AR is the result of an interplay among extrinsic metabolic factors, and intrinsic platelet modifications, rising the thrombotic risk [12,16]. In the T2DM dysmetabolic and pro-oxidant milieu, hyperreactive platelets establish a cross-talk to endothelial cells [21] causing endothelial dysfunction, a hallmark of T2DM. The intact endothelium, a monolayer lining the inner surface of the vascular lumen, maintains an antithrombotic condition by producing nitric oxide (NO) and prostacyclin (PGI_2), which retard platelet activation by increasing intraplatelet concentrations of cyclic guanosine- and adenosine-monophosphate [36]. Vascular oxidative stress reduces NO and PGI_2 availability [37]. contributing to platelet hyperreactivity and endothelial activation [38], increasing the release of vWF, which promotes platelet adhesion and enhanced platelet consumption and turnover. The latterkl in turn causes newly formed immature platelets with uninhibited COX-1 to enter the circulation [22]. The American Diabetes Association (ADA), which provides the current clinical practice recommendations for DM care [32], recommends standard low-dose aspirin for secondary prevention, but individualized use for primary prevention, as the bleeding risk may outweigh the cardiovascular benefit of aspirin, and also because T2DM patient platelets may not respond adequately to aspirin therapy [39]. Antiplatelet bioactive compounds in food may represent and early intervention to prevent AR and thus may preventing T2DM significantly impacting T2DM complications [40].

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4. Resveratrol

Resveratrol (RSV) (3,4′,5-trihydroxy-*trans*-stilbene) is a polyphenolic phytoalexin structurally related to stilbenes consisting of two phenolic rings bonded by a double styrene bond, which is synthesized in considerable amounts in grapes, peanuts, berry fruits and a variety of medicinal and edible plant species in response to stress condition [41]. The low RSV solubility affects absorption that differs according to the dietary source. After oral RSV intake, resveratrol is readily absorbed in the small intestine by passive diffusion and binding to transporters such as multidrug resistance–associated proteins MRP2 and MRP3, members of the ATP-binding cassette (ABC) transporter family, integrins and others [42]. In humans about 70% of orally administered RSV is absorbed and rapidly metabolized (less than 30 min), with a half-life of about 10 h [43]. RSV undergoes extensive phase I and phase II metabolism in the liver and intestinal epithelial cells, resulting in glucuronic acid and sulfate conjugation metabolites that keep biological function [44]. In human studies using a single oral dose (25 mg) the free RSV blood peak was around 10 ng/mL within maximum 2 h, whereas metabolite concentrations reached 500 ng/mL suggesting that also conjugates have biological effects [45]. RSV phase I hydroxylation by CYP1B1 produces piceatannol, characterized by higher antioxidant properties [45]. Phase II metabolic reactions include sulfation, via cytosolic sulfotransferase enzymes and glucuronidation catalyzed by uridine 5′-diphospho-glucuronosyltransferase enzymes [45]. In the bloodstream RSV is found in its glucuronide or sulfate conjugated forms, or free, which is about 90 % bound to plasma proteins, representing a reservoir [42] Trans-RSV is well tolerated by healthy subjects, and its use in humans is safe in vivo [46]. In humans RSV has numerous promising therapeutic properties as antioxidant, anti-inflammatory, endothelial protective, antitumor, anti-adipogenic, antioxidant, antiaging, and antidiabetic, and has been suggsetd to have a complementary action to modulate AR states affecting glucose metabolism [44,47–49]. RSV also displays antibacterial effects against various food-borne pathogens (*Campylobacter*, *Staphylococcus aureus*, and others), that have been related mostly on its ability to inhibit the F_oF_1-ATPase and consequently the electron transport chain (ETC), decreasing the production of cellular energy [50].

4.1. Clinical use of Resveratrol in Diabetes

Since antiplatelet drugs such as aspirin are not recommended in primary prevention, natural polyphenols, such as RSV may represent a viable alternative particularly for T2DM patients with AR. RSV is well tolerated, and its pleiotropic actions can favorably affect endothelial function, and diabetic AR [47,51]. The Mediterranean diet (MD) is recommended in DMT2 for its antioxidant activity, which is attributed to the presence of antioxidants in foods, such as polyphenols [52]. RSV and other flavonoids demonstrated therapeutic activities on diabetes-associated macrovascular complications [53,54]. It inhibits platelet aggregation by suppressing TXA_2 synthesis through cyclooxygenase-1 (COX-1) inhibition [55]. RSV improves glucose homeostasis, decreases insulin resistance, diminishes AR, protects pancreatic β-cells, and increases GLUT4 and GLUT2 levels. Such effects are associated with RSV ability to stimulate Silent Information Regulator 1 (SIRT1), 5′ AMP-activated protein kinase (AMPK), and nuclear factor erythroid 2–related factor 2 (Nrf2), with antioxidative and anti-inflammatory effects across various diabetic complications [48], Diabetic Retinopathy (DR) [56]. A meta-analysis showed that, in patients with T2DM, RSV supplementation reduced C-reactive protein levels, lipid peroxidation markers, oxidative stress, and increased antioxidant enzyme activity (glutathione peroxidase and catalase) levels exerting beneficial effects on inflammation and oxidative stress [57]. A randomized, double blinded placebo-controlled trial studied the effect of daily RSV supplementation (200 mg) for 24 weeks in T2DM patients, reporting improvement of glycemic control, and oxidative stress [58]. A single-blind, randomized controlled clinical trial on elderly T2DM patients, assessing a 6-month treatment period with RSV, reported improved blood glucose control, inflammation, insulin resistance, and renal function [59] The modulation of the same molecular targets, including also endothelial nitric oxide synthase (eNOS)

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exerts protective effects of RSV on the endothelium [60]. In parallel, resveratrol enhances endothelial release of nitric oxide (NO) and prostacyclin (PGI_2), two potent endogenous inhibitors of platelet adhesion and aggregation. Furthermore, it attenuates platelet adhesion to the vascular wall by disrupting interactions with von vWF and collagen. Specifically, RSV reduces vWF secretion and impairs binding of platelet glycoprotein Ib (GPIb) to vWF, a critical interaction under high shear stress that initiates platelet adhesion and thrombus formation. RSV also improves mitochondrial biogenesis by activating SIRT1 [54].

5. The F_1Fo-ATP Synthase

The F_1Fo-ATP synthase (ATP synthase) is a key enzyme of the oxidative phosphorylation (OxPhos) pathway [61]. The ATP synthases are protein complexes found in the membranes of bacteria, chloroplasts and mitochondria, that couple the proton gradient generated by the electron-transport chain (ETC) Complexes I–IV to ATP production [62]. ATP synthase employs a transmembrane protonmotive force, as a source of energy to drive a mechanical rotary mechanism that leads to the chemical synthesis of ATP from ADP and Pi. The overall ATP synthase structure comprises a Fo moiety, constituted by a membrane-embedded rotor ring comprising 8-14 c-subunits and the a-subunit that allows protons to flow down their electrochemical gradient, and a catalytic F_1 moiety protruding into the matrix ($\alpha_3\beta_3$ hexamer with central γ, δ, ε subunits). The small ATPase inhibitory factor 1 (IF1) binds the F_1 domain to prevent wasteful ATP hydrolysis when the mitochondrial membrane potential collapses [63]. Genetic defects of ATP synthase are linked to Mitochondrial disorders [64]. Besides the inner mitochondrial membrane, ATP synthase is expressed in ectopic locations (extra-mitochondrial membranes). Biochemical, proteomic, and imaging studies have demonstrated that the ATP synthase is expressed also ectopically [65]. An ecto-ATP synthase was found expressed on the plasma membrane of cancer cells [66–69]. Experimental evidence shows that the ETC complexes and ATP synthase are fucntional in the plasma membrane of human umbilical vein endothelial (HUVEC) cells [69,70], cancer cells [68], hepatocytes [71], exosomes and microvesicles [72,73], myelin sheath and rod outer segment (OS) disks [74], and platelets [75].

5.1. Resveratrol Inhibition of ATP Synthase and Its Relevance in AR

Platelets display a unique metabolic plasticity which enables them to adapt to changing conditions, in terms of substrate availability and metabolic capacity [76]. While resting platelets mainly utilize anaerobic glycolysis, activated platelets also rely on an extra-mitochondrial OxPhos that utilizes on glucose [77], and a mitochondrial OxPhos utilizing fatty acids. The platelet metabolic microenvironment influences multiple physiological and pathological conditions [76]. OxPhos over functioning, such as in case of chronic hyperglycemia, can lead to excess reactive oxygen species (ROS) generation. Hyperglycemia-induced oxidative stress plays a pivotal role in the development of diabetes complications [78]. Intraplatelet glucose concentration mirrors the blood concentrations, and hyperglycemia is an AR cause factor. Notably, platelet activation promotes rapid uptake of exogenous glucose, through glucose transporter 3 (GLUT3) whose absence blocks activation [79], and OxPhos activation. The ETC is the main source of ROS [80]. Overwork of OxPhos can conceivably cause excess Reactive Oxygen Species (ROS) production, inside the mitochondrial matrix but also in the cytosol, due to the extra-mitochondrial OxPhos, producing oxidative stress. Elevated ROS and inflammation cause a pro-thrombotic environment. RSV has been reported to inhibit the activity of mitochondrial ATP synthase, as shown by structural and biochemical studies [81], suggesting a direct interaction with the enzyme that may underlie some of its bioenergetic and signaling effects. In line with the complex of these findings, the modulation of the ectopic OxPhos by RSV, thank to its inhibition of ATP synthase inside the platelets would play a pivoalt role in alleviating the ROS production, the oxidative stress, ultimately counteracting AR. It is tempting to widen the concept of the causative role of mitochondrial dysfunction to the extra-mitochondrial OxPhos overwork in the promotion of the micro- and macrovascular complications of diabetes [82]. This hypothesis is consistent with the data showing that the ATP synthase as the molecular target if Chromium (III), a

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nontoxic form of chromium. In hepatic cells (HepG2), Cr3+ binds the ATP synthase β subunit, the catalytic subunit of the ATP synthase, abolishing its catalytic activity in a dose-dependent manner, which ameliorates hyperglycemia [83]. Also, it was shown that IF1, the physiological inhibitor of ATP synthase, can ameliorate metabolic disorders. Elevated serum IF1 was protective against CVD. It was proposed that circulating IF1 might inhibit the ecto-ATP synthase [84]. These data suggest that the inhibition of ATP synthase by RSV might be important in its action against AR.

6. Conclusion

RSV exhibits strong mechanistic rationale and preclinical evidence as a potential adjunctive therapy for T2DM. However, its clinical application as an antiplatelet treatment for patients with AR is still in the early stages. To fully understand the protective effects of RSV, it is important to consider its inhibitory action on both mitochondrial and extra-mitochondrial ATP synthase in platelets, as well as the ectopic ATP synthase found in the plasma membrane of endothelial cells. Modulating these components, along with the ETC associated with them, can lead to a reduction in AR, endothelial activation, and ultimately inflammation. Future randomized controlled trials involving T2DM patients with confirmed AR may help clarify optimal dosages and treatment duration. There are some limitations to the clinical implementation of RSV for AR. These include its poor bioavailability due to rapid metabolism, the lack of sufficient data regarding AR in T2DM patients, uncertainties surrounding dose–response relationships, and the potential for interactions with antiplatelet or anticoagulant therapies that could increase the risk of bleeding.

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The following abbreviations are used in this manuscript:

CVD	Cardiovascular Disease
DM	Diabetes mellitus
ETC	Electron Trasport Chain
RSV	Resveratrol
AR	Aspirin Resistance
T2DM	Type 2 Diabetes mellitus
TXA_2	Thromboxane A_2

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