Journal of Diabetes & Metabolic Disorders (2022) 21:1149–1169
https://doi.org/10.1007/s40200-022-01038-8

REVIEW ARTICLE

Prospective dietary radical scavengers: Boon in Pharmacokinetics, overcome insulin obstruction via signaling cascade for absorption during impediments in metabolic disorder like Diabetic Mellitus

Varuna Suresh[1] · **John Kunnath**[1] · **Amala Reddy**[1]

Received: 21 February 2022 / Accepted: 1 April 2022 / Published online: 21 April 2022

Abstract
Diabetes mellitus is a metabolic disorder which is characterized based on the blood glucose level. This can be due to the lack of efficiency of utilizing insulin or lack of production of insulin. There are numerous therapies and medications which are available for the treatment of this disease which can reduce the risk of diabetes. But there is no permanent cure found. Nutritional antioxidants show a foremost role in sustaining the homeostasis of the oxidative equilibrium. They have imparted their electron donor efficacy in preventing aging and in cancer. Vitamin C, E, β-carotene, carotenoids, polyphenols and selenium have been appraised as antioxidant constituents in the human diet nourishment. This paper emphasizes on the role of antioxidants which help in reducing or maintaining the level of glucose in the body. Antioxidants are substances that reduces the damages to the cells caused by free radicals. The available treatment and medications and how the supplementation of antioxidants is different from them is also discussed. Different type of antioxidants and their treatment in curing the disease is further focused in this paper.

Keywords Diabetes · Glucose level · Insulin · Treatment · Free radicals · Antioxidants

Introduction

Diabetes mellitus, a chronic metabolic disease designated by raise in the level of glucose in blood which is termed as hyperglycemia. This condition is due to impaired production of insulin or insulin resistance leading to micro and macro vascular complications [1]. The increased level of glucose results in long-term illness, dysfunction, and failure of different organs, mainly nerves, heart, kidney, eyes and blood vessels. There are some processes associated with the progress of diabetes which involves autoimmune destruction of β cells or impairment in insulin secretion. This leads to the deficiency of insulin and abnormalities which causes resistance in insulin action. Polydipsia, polyuria, weight loss and blurred vision. Chronic hyperglycemia can cause impairment of growth and makes susceptible to certain infections. Retinopathy, Nephropathy, Neuropathy are the long-term complications related to diabetes mellitus [2]. Hyperglycemia and its complication is related to the type and duration of the disease. The most accepted classification of diabetes and the one adopted by ADA (American diabetes association) is categorized into Type 1, Type 2, Gestational diabetes and other types. It is majorly divided into two categories; (Insulin dependent diabetes)-Type 1 diabetes mellitus: It's the destruction of β cells by immune cells of the body. This is because the immune cells recognize the β cells as foreign. (Non-insulin dependent diabetes)-Type 2 diabetes mellitus: the inability or insufficiency in the production of insulin or insulin resistance. The two major reason for Type 2 diabetes are obesity and lifestyle changes [3]

So, far there has been many drugs which is currently available in the market which is advised to be administrated to lower the blood glucose level or any other complications related to it. Several reports demonstrate the side effects of such drugs, thus there is a huge need for an alternative. Therefore, this review focus on antioxidants which can be described as compounds that prevent oxidation. The process of production of free radicals which leads to chain reaction causing damage to the DNA is known as oxidation

✉ Amala Reddy
amalar@srmist.edu.in

[1] Animal Cell Culture Laboratory, Department of Biotechnology, SRMIST, Kancheepuram district, Kattankulathur 603203, Tamilnadu, India

[4]. Antioxidants are substances that defend the body from harmful substances known as free radicals. Antioxidants can be obtained through diet or produced within the body. When there is an accumulation of free radical's oxidative stress occur [5].

There are many health benefits for anti-oxidants and this article pay attention on the benefits shown by antioxidants against oxidative stress, how it helps to reduce the formation of reactive species and thus in preventing or treating of diabetes and related complications that is the pharmacokinetics of antioxidants in treating diabetes. Pharmacokinetics can be explained as what body does to a drug. It explains what happens or what all are the events that takes place when a drug is administrated to the body until it gets eliminated from the body. The administration of antioxidants and the signaling cascades related to it are also explained.

Pathological state of diabetes and its impediments

Diabetes is a metabolic disorder which has high level of glucose in blood for a long period of time. As per the statistical survey the people affected by diabetes is increasing all over the world there were 108 million people effected by diabetes in the year 1980 followed by 422 million in 2014 with an increase of 5% mortality rate. The global diabetes prevalence in 2019 estimated a rise of 10.2% that is nearly 578 million population will be termed as diabetic in the year 2030 and 700 million by 2045. Thus, a detailed understanding on the cause and cure of this disease has turned in to a necessity [6].

When an individual takes food, the blood sugar level gets elevated. This stimulates the production of insulin by β cells, this insulin decreases the glucose level in the blood by biotransformation, transportation, storage in muscles and serves as an energy source [7]. When an individual is under fasting the glucose is provided by liver which is stored in the form of glycogen. In type 2 diabetes mellitus there is an inadequate amount of insulin production or insulin resistance this results in various complications such as oxidative stress, inflammation which leads to further complications such as cardio vascular disease, stroke, neuropathy, nephropathy, and diabetic foot ulcers etc.… [8].

Longer the period you have got diabetes and also, little your glucose is controlled, there is a higher risk of complications. Complications of diabetes can potentially be debilitating or perhaps life-threatening [9]. Cardiovascular disorder, the chance of different cardiovascular complications, which includes angina (artery disease with pain), attack, narrowing of arteries and stroke, are significantly increased by diabetes (atherosclerosis) [10]. Harm to nerves (neuropathy) occurs when there is excess sugar, the walls of the small blood vessels which nutrify our nerves specifically in our legs will be injured. It might cause tingling, burning or pain, numbness that typically starts and eventually escalates upward at the ideas of the toes or fingers [11]. Harm to kidneys (nephropathy) occurs when filtration of waste products from blood takes place through clusters of small blood vessels known as glomeruli. This intricate filtering system will be weakened by diabetes. The weakening of this system, results in serious injury to the kidney which needs dialysis or transplant of kidney, this leads to renal failure or permanent end-stage nephrosis [12]. Harm to the eye (retinopathy) can damage the retina (diabetic retinopathy) blood vessels, potentially resulting in blindness. The risk of other critical vision problems, like cataracts and glaucoma, is additionally escalated by diabetes [13]. Harm to foot, the risk of varied foot problems is elevated by damage to the nerves within the feet or insufficient supply of blood to the feet. If it is not treated properly, the cuts and blisters can result in serious infection with poor healing capacity [14]. These infections may result in amputation of the toe, foot or leg. Skin situations; Diabetes, including bacterial and fungal infections, can cause you to more prone to skin problems. Hearing disability, in individuals with diabetes, hearing problems are more common [15]. Diabetes Type 2 may escalate the danger of dementia, and Alzheimer's disease. The lower management of glucose, the greater the risk it poses to be. Even though there are various theories on the connectivity between these disorders, most of them remains to be not yet proven. In individuals with Type 1 and Type 2 diabetes symptoms of depression are commonly found. Depression can also affect diabetes management. There are many treatments and drug now available within the market which is supposed to treat diabetes and also the complications associated with it. As they're providing or working as a remedy for lowering glucose level there also are limitations or side effects which is observed on regular usage of the same [16].

Cascade of oxidative chain reaction and antogonist action of antioxidants

Antioxidants, compounds have the ability to neutralize the oxidants. It is steady enough to give an electron to free radical and balance it, this scavenging property prevents the damage to the organs and prevents its failure [17]. They associate with free radicals in a safe manner and cease the chain reaction in advance to escape from getting damaged. The antioxidants neutralize or remove the free radicals and prevents it harmful effect upto a threshold [18]. Oxidative stress arises when the free radicals overwhelm the effect of antioxidants so if this imbalance is corrected it can reduce the complications generated by oxidative stress [19]. The antioxidants may be endogenous

and exogenous which can be available through diet. The mechanism in which some antioxidants reacting with other antioxidants restoring their primary properties is known as "Antioxidant network" [20]. This substance prevents the cell from premature and abnormal ageing. In various diseases there is an elevated level of free radicals with the down regulation of antioxidant activity. The antioxidants may be categorized into enzymatic, non-enzymatic and chain breaking antioxidants [21].

Enzymatic anti-oxidants that hold back the deleterious effect of Reactive species are catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPX) (Fig. 1). Non- enzymatic antioxidants comprise vitamin E, Ascorbic acid, α-lipoic acid etc.… [22]. The chain breaking antioxidants breaks the chain reaction in which one oxidant react with other stable molecules producing more and more free radicals. The chain breaking anti-oxidants include α topocherol, carotenoids, flavonoids, ubiquinol [23].

Pharmacokinetics and its mechanism

Pharmacokinetics can be referred as an area of pharmacology that determine the outcome of a substance which is administered to living organism [24]. Pharmaceutical drugs, food additives, cosmetics, pesticides etc. can be termed as chemical xenobiotic which can be included as the substance of interest. Pharmacokinetics aims at the metabolism of a drug starting from its administration point, it monitors the time when drug is inside the body until it gets eliminated outside the body in simple words it can be defined as how an organism affects a drug [25].

Pharmacokinetics can explain the effects of a chemical or xenobiotic after it is been administrated through the mechanism of absorption and distribution, it can also make a note on the metabolic changes made in the body by that substance It can depend on the route of administration of the drug as well as the dose of the administrated drug [26].

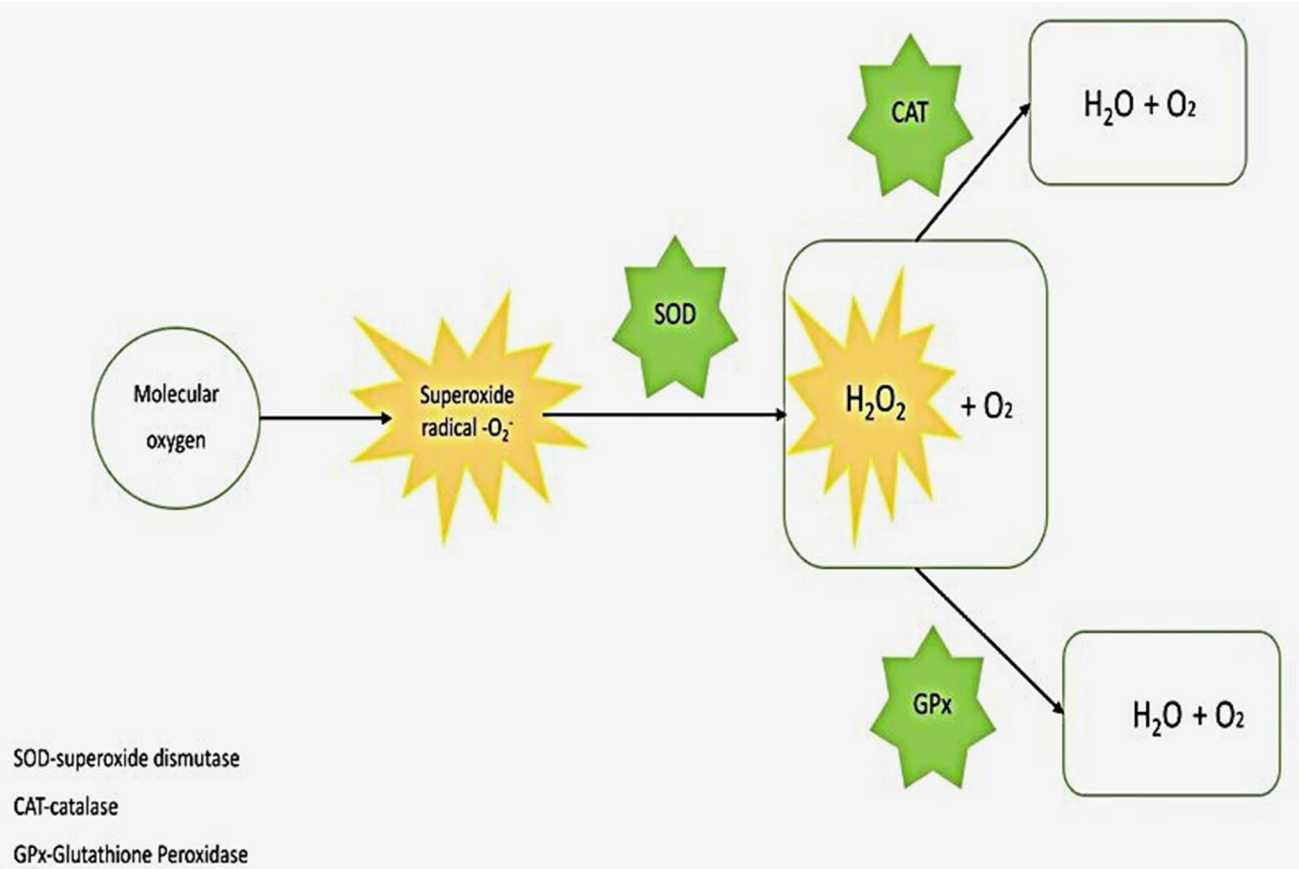

Fig. 1 Conversion of superoxide radical into water and molecular oxygen by antioxidant enzymes. Reactive oxygen species (ROS) formed from molecular oxygen. Singlet oxygen is a highly reactive form of di-oxygen (O 2) in which one of the un-paired electrons of ground-state di-oxygen is promoted to an orbital of higher energy. The superoxide radical ($O^{-}{}_2$), hydrogen peroxide (H_2O_2) and the highly reactive hydroxyl radical (OH) are formed by one-electron reductions of molecular di-oxygen. Cellular defences such as superoxide dismutase (SOD), catalase and peroxidase serve to scavenge O − 2 and hydrogen peroxide (H 2 O 2), thereby preventing their participation in the formation of hydroxyl radical (OH) via the iron catalysed Haber–Weiss reaction

The Fig. 2 depicts the topics or the steps which comes under pharmacokinetics and they include the the process by which the drug is released from the formulation which can be termed as liberation. The next process is the entrance of the substance in to blood circulation which is absorption and the spreading of substances through the tissue and fluid of the body which is distribution (Leopold 1986). Metabolism can be the recognition that a foreign substance has entered by the body and the non-reversible transformation of parent compounds into daughter metabolites. Next is the elimination of substance from the body which can be termed as excretion [27].

Metabolism and excretion grouped together called as elimination (Fig. 3). To know more about these phases there should be knowledge on manipulation of basic concept to understand dynamics. To gain knowledge on kinetics of drug

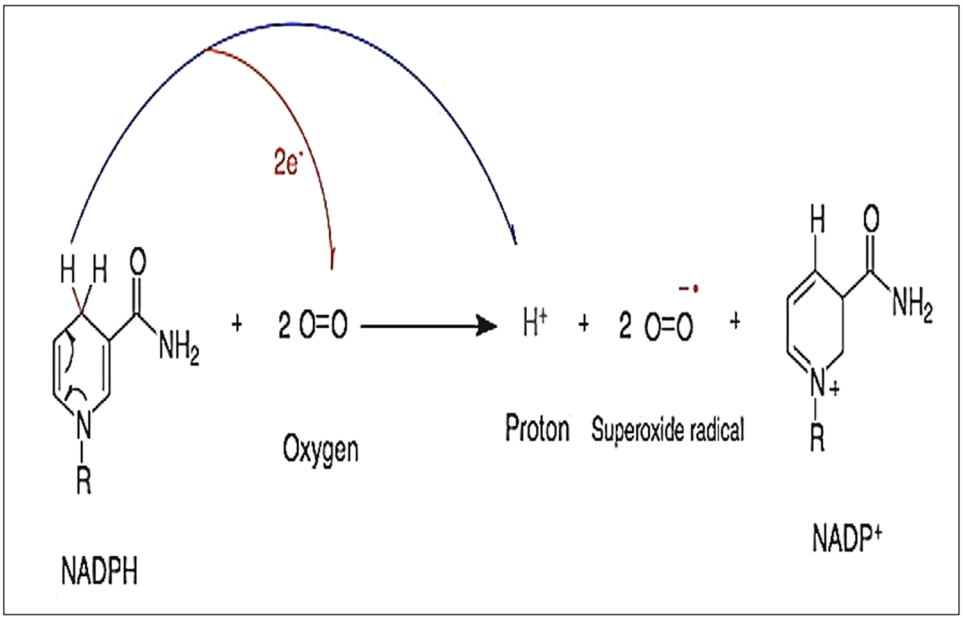

Fig. 2 Depicts the function of NADPH and its conversion to superoxide radical and $NADP^{+\cdot}$ From the above reaction NADPH is reduced to NADPH + giving out its one hydrogen from the top (reduction reaction) and donating one of its electrons to the O2 and transforming it into superoxide free radical which really is lethal on accumulating

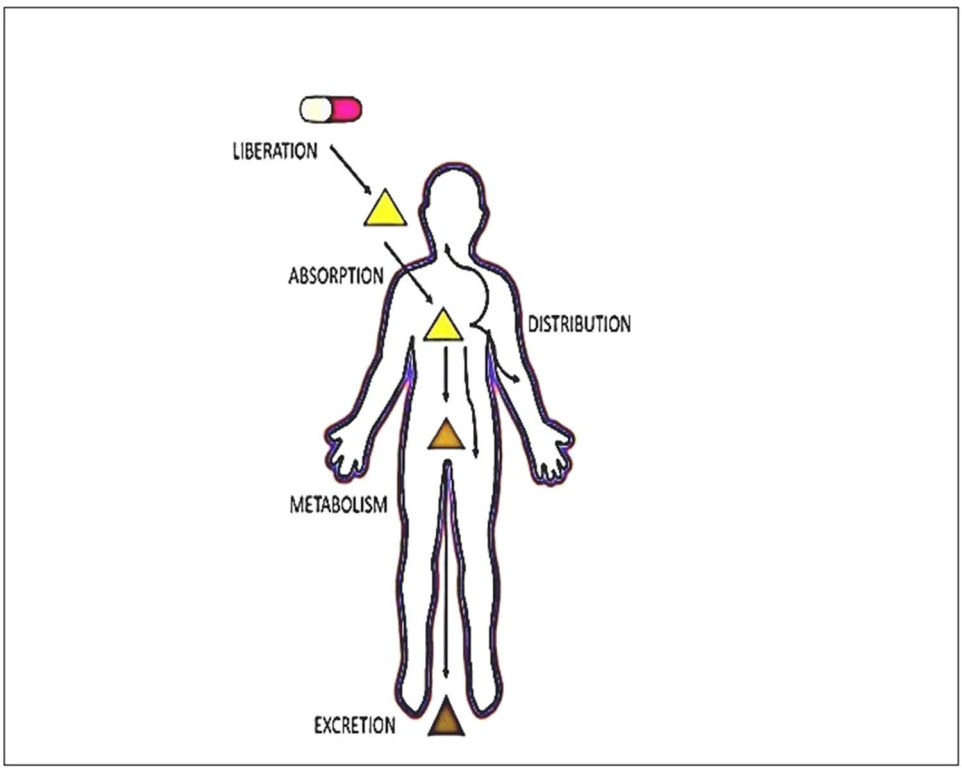

Fig. 3 Process of pharmacokinetics inside Human body. The complete mechanism of a drug when it enters the body from the liberation stage to excretion phase. pharmacokinetics as a drug's journey through the body, during which it passes through four different phases: absorption, distribution, metabolism, and excretion (ADME)

it is important to know properties of substances that act as excipients, the biological membrane, mechanisms of enzymatic reactions that inactivate the drug. There are different models that explains the characteristics of molecules and to understand how a drug will behave includes bioavailability, acid dissociation constant and solubility [28].

At a particular level a drugs availability is termed as the quantity of drug that out stretch to its active site. From the intravenous view point on dispensing of drug gives the possible bioavailability and this procedure is expected to relent a bioavailability of 1 or 100% [29]. The changes that are required to be made in the dosage is known once the drug availability is estimated so as to achieve the required blood plasma levels. Therefore, bioavailability can be termed as a mathematical factor for every single drug that influence the dosage that is administered [30].

β cells dysfunction

Inflammation induced by cytokine, insulin resistance, obesity and consumption of excess saturated fat and free fatty acids includes β cell dysfunction [31]. β cell demise is followed by a gradual decrease in β cell function that give rise to β cell exhaustion. For the development of both type 1 and 2 diabetes, decrease in β cell mass and function are the key factors [32].

An inflammatory response is caused by particular class of pro inflammatory cytokines. Where, Obesity is correlated with inflammation and these two are related to resistance of insulin [33]. Through the activation of mitochondrial stress, pro inflammatory cytokines induce β cell death. It is documented that cytokines produced by cells of immune system which have invaded the pancreas are essential mediators of the β cells impairment [34].

Chronic hyperglycemia exposure, induce oxidative stress and inflammation that can cause changes in gene expression regulation that merge on decreased secretion of insulin and elevated apoptosis [35]. Specifically in mitochondria, proteins, lipids and nucleic acids, oxidative stress leads to damage. Although these mechanisms are not fully established, It initiates and leads to both endoplasmic reticulum stress and autophagy. For type 2 diabetes, ER tension is correlated with apoptosis of β cells [36].

Reactive oxygen species and reactive nitrogen species are created by cytokine induced pro-inflammatory β-cell damage in type 1 diabetes as well as glucolipotoxicity-induced dysfunction of β cells in diabetes type 2. Increased production of ROS from over activation of mitochondria and RNS from overproduction of nitric oxide in β cells contributes to hampering of the electron transport chain, causing decreased production of energy, damage to DNA and the production of glycated end products [37].

The restricted extent of glycolytic uptake by β cells has the ability to create ROS and the following oxidative stress may dissociate glucose detecting from insulin secretion. These insulin secreting cells are profoundly subjected to ATP generation for Glucose stimulated insulin secretion (GSIS) and they are powerless against abundant ROS on account of their characteristically less articulation of enzymes which has antioxidant properties. The disparity or decreased accessibility of supplements to β cells, little rehashed increments in ROS creation, reduce synthesis of ATP and inefficient antioxidant equilibrium can incline to dysfunction of β cells [38].

β cell dysfunction and insulin obstruction by Saturated fat and free unsaturated fats

Higher Body Mass Index (BMI) can enhance the impact of hereditary variations on pathways of insulin obstruction, it's an impact that can be ascribed to tissue-explicit reactions to the environment which is obesogenic [39]. The impacts of Free fatty acid (FFA) on function of β cells are function of time. Limited subjection to Free fatty acid (FFA) builds Glucose stimulated insulin secretion (GSIS) which brings about elevated insulin discharge after a blended meal and facilitate piling of abundant quantity as fat which adds to tremendous weight gain and leads to obesity. Free fatty acid(FFA) represent the remunerative stimulation of function of β cells because of insulin obstruction [40]. On the other hand, long time subjection to Free fatty acid(FFA) smothers Glucose stimulated insulin secretion (GSIS) and has been proposed to include impeded metabolism of glucose, decreased biosynthesis of insulin and loss of β cells [41].

Obese conditions and high fat intake tend to imitate the impacts of extended period propagation of islets with Free fatty acid(FFA) on secretion of insulin and dissemination of Ca2 + -channel (Fig. 4). This in connection with elevated measure of fat inside the islets and the encompassing exocrine pancreas. There is additionally a reverse connection linking the measure of the quantity of fat in the pancreas of humans and Glucose stimulated insulin secretion (GSIS), with resilience to glucose and secretion of insulin improves in correspondence with a decrease in pancreatic fat [42]. Fat deposits which are intra pancreatic or intra islet can serve Free fatty acid(FFA) source over an extended period of time unfavorably which influences function of β cell. Obesity along with insulin obstruction expands the operational requirements of each β cell which can build the load and quicken dysfunction of β cells. β cell dysfunction related pathogenesis can to a limited degree, mirror hepatic steatosis: increased fat builds up in liver cause inflammation there by stimulating death of cells and improper functioning of cells [43]. Intra-islet, specifically the fat in the β cell internally could impede Glucose stimulated insulin

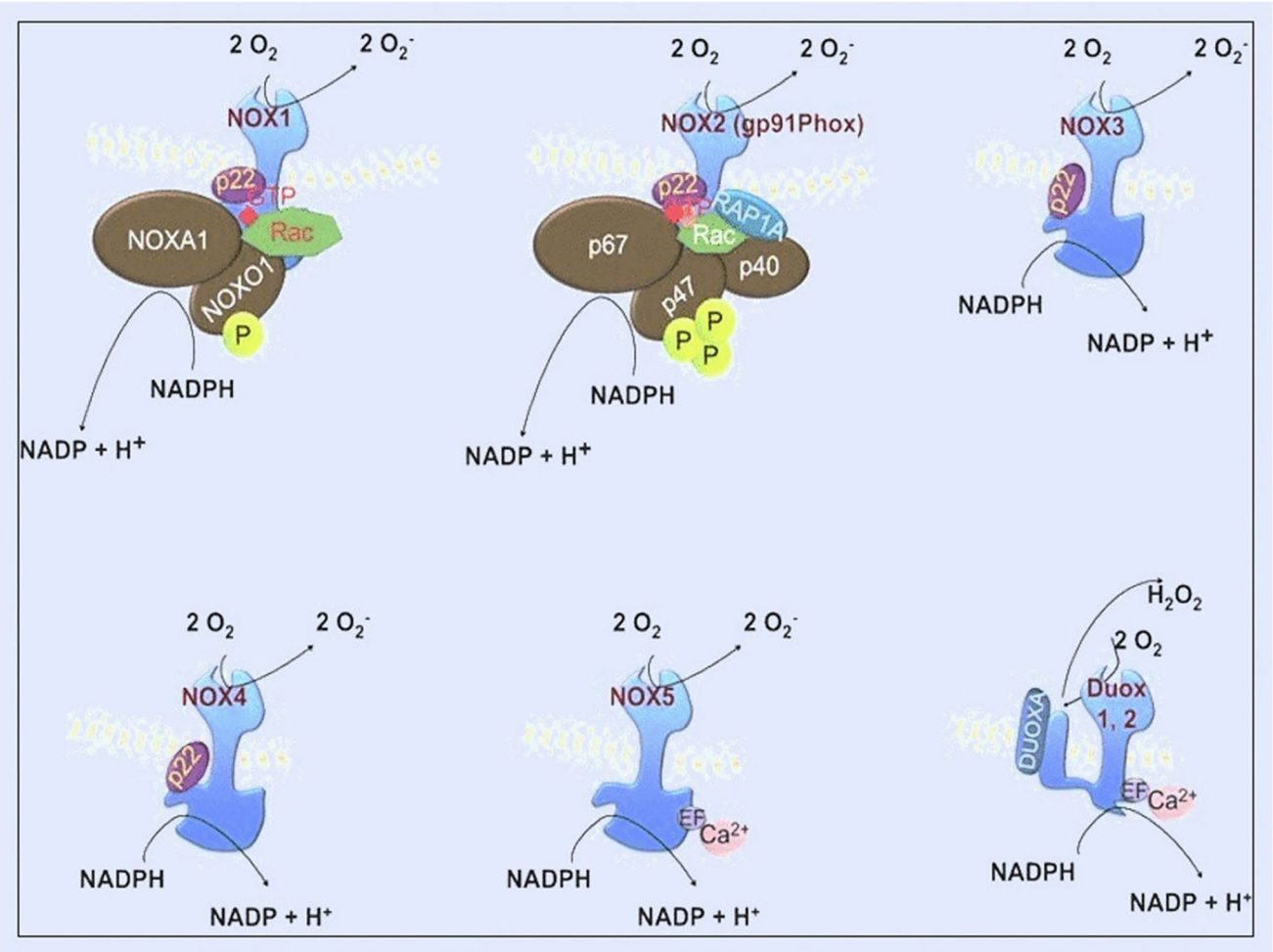

Fig. 4 Shows the assembly and activation of NOX enzymes. The above picture represents the activation of NOX. NOX1 is activated by the phosphorylation of NOXO1 (Here due to phosphorylation free radical of oxygen is released). Similarly, in NOX 2 which is activated by the phosphorylation of P47 (which is multi domain regulatory sub units) which form free radical of oxygen species. NOX 3 is a P22 PHOX dependent and doesn't bind with RAC (RAC is a low molecular weight guanine nucleotide binding proteins which helps in translocation with the membrane). NOX 4 activation involves P22 and Polydip2 (polymerase delta interacting protein 2 precursor which is considered as a Novel regulator of NOX 4). In contrast to NOX 5 and DUOX activation is Ca + dependent and DUOX proteins which are from thyroid glands contains peroxide like domain which generates the hydrogen peroxide which leads to rapid oxidation and reduction of superoxide

secretion (GSIS) and insulin signaling in islets. This probably addresses a system for dysfunction of β cell and decreased β cell remuneration which disables Glucose stimulated insulin secretion (GSIS) by sensing non glucose by β cells like weakened signaling of insulin and subsequently uptake of glucose into tissues which are glucose beneficiary, this stimulates the resistance of insulin [44].

Inflammation of islets in diabetes type 2 is ascribed to abundance of nutrients causes exhaustion in metabolism of β cells. This can cause the confined cytokine production, which results in immune cell enrollment to the generation site this will stimulate dysfunction of β cell and intensify the insulin. In inflammation induced by Free fatty acid(FFA) and apoptosis of β cells an enhancer in β cells known as nuclear factor of kappa light polypeptide gene enhancer (NF-κB) plays a main controlling part in inflammation induced by Free fatty acid(FFA) and apoptosis of β cells [45]. Palmitate, induces dysfunction of β cells in vivo by activation of inflammatory processes within islets of mouse. Treatment with palmitate escalated the important cytokine expression implicated in dysfunction of β cells, viz., interleukin (IL) 6, IL8 (CXCL1), IP10 (CXCL10), MCP1 (CCL2), and MIP1A (CCL3), this can affect the β cell in a autocrine manner. The sensitivity of insulin is hampered by Free fatty acid(FFA) which are saturated and enhanced by Free fatty acid(FFA) which are polyunsaturated. The FFA which are saturated has shown to elevate the palmitic acid build up intramuscularly in rats thus causing a resistance to insulin [46].

Antioxidant therapy in curing β CELLS AND T2DM

The subjection of humans to environmental oxidants plays a vital contributive issue to the origin of spread of the diseases, which includes atherosclerosis, neurodegeneration, cancer and polygenic disorder [47]. In order to prevent damage cause by oxidants and to prevent humans from life threatening diseases supplementation with dietary antioxidants has been arduously suggested [48].

Several studies demonstrate health advantages of supplementation with antioxidants particularly for antioxidants and phase II enzyme-inducing phytochemicals on interception of cancer. Yet, different studies show that the treatment with antioxidants isn't as effective for several disease endpoints [49]. Variety of clinical studies which are well controlled with immediate ROS-scavenging vitamins and a few with endogenous antioxidant-inducing phytochemical didn't exhibit unequivocal helpful outcomes. In some studies, there have been even raised occurrence of diabetes, varied cancers, and all-cause death related to uptake of antioxidants. These clinical information forged major questions on the quality of antioxidant supplementation and presumably on the elemental thought that improving inhibitor capability is in general helpful [50].

Whereas the shortage on results of antioxidant supplements is also attributed to several factors, like the design of trial, intake dose, frequency, and bioavailability, a lot of broad mechanistic research are required to judge the biological effects of antioxidants which are exogenous. Only if ROS communication is involved in Glucose stimulated insulin secretion (GSIS) in intracellular ROS and pancreatic β cells is weakened by antioxidants, we cannot tend to exclude the likelihood that the escalated occurrence of T2D over the decades may be due, a minimum of partly, to self-prescribed preventive supplementations of antioxidants. The antioxidant supplementation for patients with type 2 diabetes could exacerbate their situation by diminishing the signaling of ROS [51]. For interception of cancer, phase II catalyst inducers, which causes activation of Nrf2, are thought as new compounds for chemoprevention. However seemingly to be effective in prevention of cancer, such treatments might pre dispose patients to T2D due to antioxidant-impede β cell functioning. The long-run harmful outcomes of antioxidants which immediately scavenge ROS and endogenous antioxidant-inducing phytochemicals obviously want a lot of careful studies to ensure attaining the specified therapeutic outcomes and preventing harmful results. On the whole that ROS could play self-contradictory part in pancreatic β cell function which is related to the first and later phase of diabetes type 2, the side effects could be reduced with new generation antioxidants which are target specific [52].

Oxidative stress

ROS include free radicals together with superoxide ($\bullet O_2$-), radical (•OH), peroxyl ($\bullet RO_2$), hydroperoxyl ($\bullet HRO_2$-) additionally to non-reactive species which has oxide (H_2O_2) and hydrochlorous acid (HOCl). RNS comprises of free radicals like gas (•NO) and gas ($\bullet NO_2$-), additionally to non-radicals consisting of peroxynitrite (ONOO-), inhalation anesthetic (HNO_2) and chemical group peroxynitrates (RONOO) (Sato et al. 2013). NO is often generated through epithelial tissue gas synthase (eNOS) within side the vasculature from L-arginine [53]. Through its effect on guanylate cyclase in vascular simple muscle cells (VSMC), NO mediates endothelium-dependent vasorelaxation, initiating a cascade which ends in vasorelaxation. NO to boot reveals antiproliferative homes and stops vascular epithelial tissue adhesion to platelets and leukocytes. Therefore, NO is taken into thought as a vasculoprotective substance. Yet, NO interacts certainly with oxide radical, producing the notably reactive radical ONOO, and inflicting a series of damaging events. So, its surroundings like the existence of •O2-, decides whether or not nitroxyl radical makes use of its defensive or dangerous results [54].

Although ROS is created beneath physiological things and to some extent disturbed in signaling molecules and defense mechanisms as visible in vasorelaxation caused through activity, white blood cell feature, and shear-pressure, further era in aerophilous pressure has pathological results comprehensive of supermolecule, lipid, and DNA harm [55]. LDL oxidization is precipitated through ROS and ox-LDL, that is not regarded through the low-density lipoprotein receptor, is absorbed via manner of suggests that of scavenger receptors in macrophages, main to spume mobileular generation and arterial sclerosis plaque [56]. O_2 will reason several dangerous pathways in polygenic disorder, in conjunction with increased produce of superior glycation end product (AGE), polyol and hexosamine pathway and Protein kinase C activation, leads to increase in chance for micro- and macrovascular complications. O_2 and H_2O_2 activate strain-associated signaling pathways consisting of NF-kB, p38-MAPK and STAT-JAK, succeeding withinside the migration and proliferation of VSMC [57].

In epithelial tissue cells, H_2O_2 bring about necrobiosis and pathological ontogenesis. Additionally, superoxide reacts promptly with nitric oxide manufacturing cytotoxic $ONOO^-$ and their square measure some implications for this response itself. Firstly, $ONOO^-$ modifications the characteristic of biomolecules via manner of suggests that of nitrating proteins and causing lipid peroxidation. $ONOO^-$ reasons the breakage of single strand of DNA that in flip stimulates nuclear protein poly (ADP-ribose) enzyme. It alleviates NO bioavailability inflicting impede rest and inhibition of the

antiproliferative results of NO. Additionally, tetrahydrobiopterin (BH_4), associate with chemical compound for NOS, is to modify through ONOO- and reasons NOS uncoupling, that generates $\bullet O^2$- as opposition NO. ROS-brought regarding membrane lipid peroxidation changes organic membrane form and runniness, that within the finish impacts its feature. The pathologic process of vascular disorder leads to these sorts of pathological modifications [58].

NADPH Oxidase (C21H29N7O17P3)

Nicotinamide adenine dinucleotide phosphate in any other case referred to as NADPH, acts as a cofactor in anaerobic reactions like Calvin cycle, nucleic acid synthesis, etc,. In a few cycles they take location as decreasing agent. As a cofactor they donate electrons and hydrogen to react catalysed through a few enzymes. It is a membrane sure enzymatic complicated which faces extracellular space [59]. There are seven isoforms namely, NOX1, NOX2, NOX3, NOX4, NOX5, DUOX1 and DUOX2. The subunits which are involved in regulatory mechanism are p22PHOX, p47 PHOX, p40 PHOX, p67 PHOX and small G-proteins RAC1 or RAC 2. The oxidase translocation to the membrane and pals with CYT558 to turn out to be lively oxidase and next switch of electron from donor to substrate, molecular oxygen takes region [60].

The above response explains that the NADPH catalyze the manufacturing of super-oxide unfastened radical through the transformation of an electron to hydrogen. Reactive oxygen species (ROS), derived from molecular oxygen consist of oxygen free radicals, consisting of •O2- and •OH and non-reactive substances, which comprises of HOCL and ozone. These oxidants play duplex, opposite part subject to the context. The pressure mediated by the oxidants has been involved in diverse diseases and abnormal functioning, consisting of pathology of cardiovascular disease, immunodeficiency and pulmonary artery diseases [61]. Still, the launch of oxidants mediated by NADPH oxidase and NOX, additionally known as oxidative burst, which results in the removal of invaded microorganisms, acting as inflammatory mediators [62].

The NOX genes generate the transmembrane proteins chargeable for movement of electrons throughout organic membranes, that ends up in the conversion of molecular oxygen into superoxide radical. The not unusual place features of NOX proteins have been ascribed to the conserved structural homes of those enzymes such as the binding of NADPH on the C-terminus, the flavin adenine dinucleotide (FAD)-binding area placed next to the C-terminal transmembrane domain, six conserved trans membrane domains, and four conserved heme-binding histidines. eight NOX enzymes bring about numerous capabilities in several different organisms thru redox signaling [63]. The significance of oxidants in host has been actually decided via the invention of the disorder related to genetics, continual granulomatous disease (CGD), which displays fault in NOX2 (or related subunits). continual granulomatous disease is characterized through faulty killing of neutrophil because of extraordinarily reduced oxidative burst in those cells throughout phagocytes. Hypersensitivity to variety of bacterial and fungal infections are symptoms of patients with CGD, and the bacterial buildup in phagocytes results in the improvement of granulomas. The accumulation of this phagocyte displays the lack of ability of those phagocytes to eliminate pathogens that are ingested or go through cell death process, because of faulty NOX2 interest. The position of NOX has additionally been nicely hooked up beneath non-pathological conditions. Vascular NOX produce oxidants that are vital for retaining regular cardiovascular fitness by controlling blood pressure, that is important to fitness, as deviation from ordinary stages may cause death. The existence of oxidants decreases the bioavailability of the endothelial-derived antioxidants element, nitric oxide (NO), which maintain the blood pressure. In kidneys, oxidants are produced via NOX3, and those substances adjust renal characteristic by the management of Na + transport, tubule glomerular remarks and renal oxygenation [64].

In addition to that, the oxidants boom the absorption of NaCl withinside the loop of Henle and ensures the regulation of Na + /H + exchange. Pulmonary NOX2 are involved in remodeling of vascular system and airway. The p22phox structured NOX2 controls the proliferation and differentiation of easy muscle cells thru the stimulation of nuclear aspect kappa B (NF-B) and inducible nitric oxide syntheses (iNOS). ROS era thru DUOX and NOX1 withinside the colon mucosa assists in synthesis of serotonin, that's important in controlling the secretion and motility. NOX2 is concerned withinside the regular functioning of the CNS via angiotensin II signaling withinside the nucleus tractus solitarius and the hypothalamic cardiovascular regulator nuclei. Furthermore, microglial cells explicit NOX2 and p22PHOX, and each of those enzymes take part withinside the of microglial proliferation and when there is a reduction in nerve growth factor it causes apoptosis of neuronal cells [65].

NOX inhibitors

Recent analysis has targeted on proteins additionally upstream to reduce aerobic strain the utilization of choking up enzymes that sell ROS producing. sadly, the presently accessible inhibitors of NOX lack specificity. As a result, the form of NOX2 enzymes has been interpreted and its suggest that the suitable NOX assembly is important for its function, the inhibition of meeting represents a singular healing technique [66]. For instance, the membrane affiliation of the GTPase RAC one, that's important for oxidant activation, is

avoided the usage of 5-hydroxy-3-methylglutaryl-coenzyme a enzyme inhibitors. Similarly, apocynin (4hydroxy-3-methoxyacetophenone) is associate degree orally spirited agent that also blocks Roman deity meeting. Originally remoted from the healthful plant *Picrorhiza Kurroa*, apocynin inhibits every entity or living thing ROS produces through the inhibition of the phagosomal affiliation of the cytosolic macromolecule p47PHOX. Still, a bother of apocynin is that this macromolecule needs oxidase for activation, and thus, apocynin interest isn't fast. The nitration and nitrosylation in addition cause the hampering of NOX. for instance, the NO donor, deta-nonoate, represses basal NOX-established superoxide producing. additionally, alkyl pyruvate performs a life-sized position in aerobic chemical change associate degreed is a powerful matter of antioxidant [67]. Moreover, there are inhibitors that perturb the sign transduction of NOX-associated pathways. Binary compound associate with pyruvate occupies an aldol-like condensation response to form 2-hydroxy-2methyl-4-ketoglutarate (Para pyruvate), an effective process of producing ROS through globulin receptor focused on for the recognition of LPS in glia cells. Membrane channel blockers in addition act as oxidant inhibitors. Hypertensin stimulates NOX-derived ROS producing in simple muscle cells via the activation of Ca channels. Felodipine and amlodipine typically used Ca channel blockers that significantly suppress the binding. Gomicin C, a polymer extract from *Schizandra chinensis*, decreases cytosolic Ca and portrays a restrictive motion towards NOX2. Compounds, which has 6-aminonicotinamide, dearth the supply of lepton donors, that embrace NADPH, and hampers the monosaccharose phosphate pathway, that precludes oxidant activation. moreover, oxidants activation is likewise regulated through Hypertensin, platelet-derived increase side and TGF, all of which may be blocked through valsartan [68].

Structure

NOX refers back to the primary characterized isoform NOX2, consisting of six exceptional subunits that engage in the formation of oxide radical. The dual NOX subunits, GP91PHOX and P22PHOX, are important proteins that together embody the massive heterodimeric unit flavocytochrome B558 (Cyt B558). Beneath unmodulated conditions, the multidomain restrictive subunits, p40PHOX, p47 PHOX and p67 PHOX, exist withinside the cytoplasm as a compound [69]. Upon modulation, p47 PHOX undergoes phosphorylation, and therefore the complete sophisticated eventually transported to the membrane and assists with Cyt b558 to form the active form of oxidase. The activated compound moves electrons from the substrate to element via a prosthetic cluster, flavin, and a pigment team, which incorporates electrons. The stimulation of the compound also needs low-molecular-weight purine nucleotide-binding proteins, RAC2 and RAP1A. RAC2 is localized withinside the cytoplasm in a very dimeric sophisticated with Rho-GDI (guanine ester dissociation inhibitor), as RAP1A may be a membrane macromolecule. Upon stimulation, RAC2 associates with nucleoside triphosphate (GTP) and transported to the membrane at the side of p40PHOX, p47 PHOX, and p67 PHOX (cytosolic complicated). The cell membrane is internalized and within the finish turns into the inside wall of the phagocytic cell vesicle in a process called phagocytosis [70]. later on, O_2 is embarked on the vesicle via the accelerator compound, and upon conversion of O_2 into its successor product, the internalized goal can become submerged in a very toxic combination of oxidants. RAP1A and Cyt b558 area unit delivered to the cell membrane via the fusion of humor vesicles, thereby facilitating the discharge of these proteins to the outside. ROS producing is not restricted to cells which are phagocytic, and therefore the invention of gp91PHOX homologs has significantly progressed our data of loose radical producing together said because the NOX family, those gp91PHOX homologs contains varied differentially expressed members: NOX1, NOX2 (previously said as gp91PHOX), NOX3, NOX4, NOX5, twin oxidase DUOX proteins (DUOX 1 and DUOX 2) (Fig. 5).

Signaling cascade

Nrf2-ARE signaling pathway

Nuclear issue blood corpuscle a pair of connected issue (Nrf2), associate degree inhibitor response part. Its cell signal pathway has a very important role in reducing the oxidative stress by dominant the organic phenomenon whose macromolecule merchandise square measure related to reducing the oxidative stress and increasing the cellular anti-oxidant activity [71]. Nrf-2 is a very important molecule regulation the inhibitor enzymes. It belongs to the taxonomic group of basic essential amino acid zipper (bZIP) transcription factors and has seven purposeful domains ((Nrf2 ECH Homology) Neh1 to NEH 7). NEH1 permits dimerization of Nrf2 with MAF proteins (Musculo facia fibrosarcoma) and alternative transcription factors that permits the formation of nuclear advanced with ubiquitin –conjugating catalyst (UbcM2). DLG and ETGE square measure the 2 motifs of NHE2, this square measure vital for the association between Nrf2 and its substance Keap1 [72].

Under traditional state, Nrf2 is in sure state with kelch-like ECH associated macromolecule one (Keap1). Keap1, a Cullin based mostly E3-ubiquitin ligase substrate adapter. underneath traditional condition, the transcriptional activity of Nrf-2 is reserved by Keap1 through ubiquitination and proteosomal degradation. Underneath the condition of oxidative stress Nrf-2 becomes activated, it moves to the nucleus of the cell wherever the formation of heterodimer

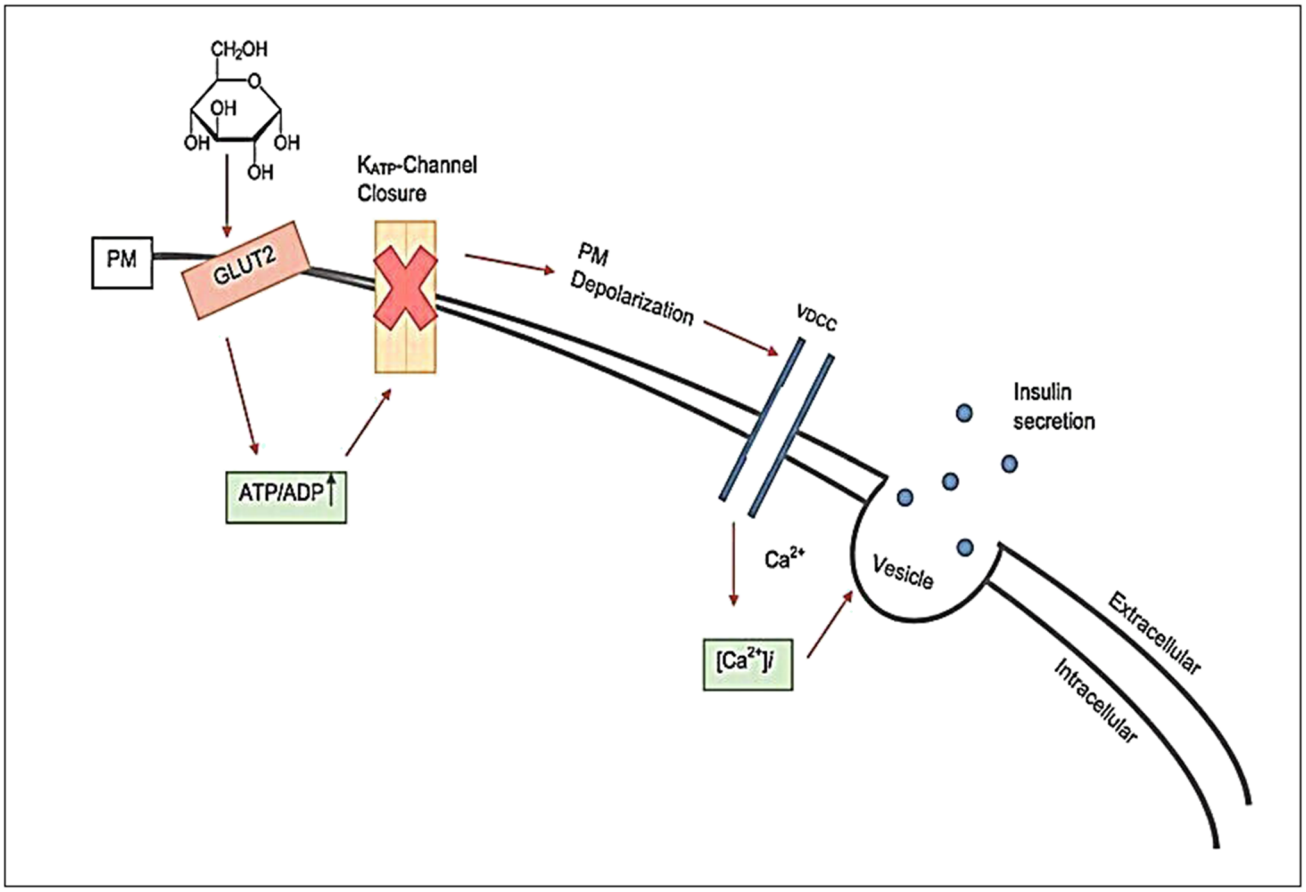

Fig. 5 Glucose-stimulated insulin secretion model. Classic model of glucose-stimulated insulin secretion. An increase in the glucose concentration in the extracellular space induces metabolic and energy production processes with subsequent ATP/ADP elevation, KATP channel. This glucose-induced initial event is called the first phase or triggering pathway if it is followed by persistent and enhanced insulin secretion that is known as the second phase or potentiating pathway

takes place and attaches to inhibitor response part (ARE) with transcription factors like c-Jun and tiny MAF proteins [73]. ARE, cis-acting part on the promoters of genes that encodes for two crucial detoxification enzymes NQO1 (NADPH: compound enzyme 1) and GSTA2 (glutathione S-transferase A2). The binding of Nrf2 with ARE modulates the expression of more than two hundred genes associated within the inhibitor and anti- inflammatory activity [74].

MAP Kinase pathway

Mitogen activated protein kinases (MAPK) belongs to the family of serine-threonine protein kinases that are concerned within the transmission of signals from plasma membrane to the nucleus. These kinases are divided into 3 subcategories.

Extracellular signal connected kinases (ERK)—ERK1 and ERK a pair of Isoform.

- c-Jun N-terminal kinases (JNK)
- JNK -1, JNK-2, JNK-3
- p38MAPKs: p38-α(alpha), p38-β(Beta), p38-γ(Gamma), and p38-δ (delta) Isoforms [75].

MAPKs are turned on through a series of resultant phosphorylation events. Firstly, MAP3K (MAP enzyme enzyme kinase) is activated that causes phosphorylation and activation of MAP2K. MAP2K activation triggers the activation and phosphorylation of MAPK. MAPK activation ends up in the phosphorylation of assorted substrate protein leading to regulation of cellular activities [76]. The harmful effects of activation of MAPK pathways embody the excessive proliferation of cells, uncontrolled necrobiosis and excessive regulation of MAPK genes. ROS has the potential to induce MAPK pathways at totally different cell sorts. Antioxidants and alternative inhibitors of reactive element species will inhibit the MAPK pathway [77]

The activation of ERK is majorly by growth factors (EGF and PGDF) and cytokines. ROS will cause the activation of EGF and PGDF while not its corresponding substance. When the protein or protein binds to the receptors it ends

up in the activation of Ras. once gross domestic product certain to the Ras is reborn to GTP. For activation, living substance Raf is recruited to the plasma membrane. The activated Raf (MAPKKK) phosphorylates (MAPKK) that successively phosphorylates MAPK and ends up in the activation of many transcription factors. what is more, once some cells are treated with peroxide it causes the activation of PLC-gamma (Phospholipase-c) [75]. This ends up in the assembly of IP3 and DAG. IP3 will cause elevated level of animate thing Ca from the animate thing stores. This causes the activation of ERK pathways and high level of Ca causes the stimulation of many macros molecule enzyme c resulting in the activation of RAS and RAF proteins. JNK pathway is activated by aerophilic stress and cytokines. It's the same as the ERK pathway. Once there's higher level of ROS it ends up in activation of JNK pathway and causes phosphatases inactivation and leads to prolonged activation of JNK [78].

Different anti-oxidants and their role in diabetes

Mechanism of drug action in medicine defines the biochemical interaction through that the substance delivers a medicine result. Mechanism of action embody a selected target wherever the drug ought to bind like associate degree catalyst or receptor. supported the chemical structure of the drug the receptor has specific affinities to that the drug binds [79].

Vitamins A, C and E; glutathione; α-lipoic acid; carotenoids; trace parts like copper, metal and selenium; molecule Q10 (CoQ10); and cofactors like acid, Folic acid, albumin, and vitamins B1, B2, B6 and B12 square measure a number of the non-enzymatic antioxidants [80]. As an instantaneous scavenger furthermore as a co-substrate for GSH oxidase, glutathione (GSH) works. it's a giant reaction tampon device that's intracellular. Fat-soluble {vitamin|antioxidant} may be a vitamin that's fat-soluble and twiddling my thumbs the peroxidation of lipids. It happens in eight distinct forms, of that the foremost operational kind in humans is α-tocopherol. group responds to antioxidant, by the formation of stabilized synthetic resin radical that's reduced by ascorbate and NAD(P)H primarily based enzyme enzymes back to the phenol [81].

Throughout mitochondrial lepton transport chain, molecule Q10 that is associate degree endogenously synthesized lipoid soluble inhibitor acts as a carrier of lepton within the advanced II. Once in higher concentrations, it reduces the epithelial tissue disfunction caused in polygenic disease by scavenging the superoxide radical. By stabilization of NOS chemical compound BH4 water-soluble vitamin elevates the assembly of NO within the epithelial tissue cells. α-Lipoic acid may be a hydrophilic inhibitor and might so exert useful effects in each binary compound and lipoid environments. Dihydrolipoate, reduced type of α-lipoic acid has the capability to revive alternative antioxidants such a antioxidant, reduced glutathione and vitamin C through the method of reaction athletics [82].

Vitamin E

Vitamin E, a fat-soluble antioxidant in a way that the body is able to store this and use whenever needed and α-tocopherol is the most functional type of vitamin E. Vitamin E is available in different food sources among which vegetable oil, green leafy vegetables and nuts are the prominent sources [83]. The main antioxidant property of Vitamin E is that it can stop the production of ROS which is formed when fat undergo oxidation, which are responsible for any adverse effects which include damage to DNA, RNA, and proteins, and it can also cause cell death. Vitamin E can protect the cell from damages. The anti-oxidant property of one molecule of α-tocopherol is lost when it neutralizes free radicle, which can then be restored using other antioxidants [84].

Vitamin E triggers the diacylglycerol activating kinase and holds back phosphatidate phosphohydrolase. This will reduce diacylglycerol activity and activates PKC which will eliminate the adverse effect of free fatty acid which can reduce the sensitivity of insulin by skeletal muscle. There are studies which provided proof that Vitamin E can reduce cardiovascular risk when they are administrated to patients on a daily basis [85]. Studies proved there is a decline in both the lipid the lipid peroxidation and free radical production by circulating monocytes when patients suffering from diabetes mellitus Type 2 were supplemented with tocopherol [86]. In another study, when patients who had diabetes mellitus Type 1 treated with tocopherol for four months it elevated the retinal blood flow and prevented renal dysfunction with no changes in the glycated haemoglobin levels (Bursell et al. 1999). Thus, these studies proved that the treatment of DM patients with vitamin E supress the progression of late complications like retinopathy, cardiovascular complications and foot ulcers after a period of 24 months. This suggests that the long-term antioxidant therapy can be beneficial, as it delays the development of diabetes complications [87].

It should also be noted that high dose of vitamin E can be toxic to the body. There are reports available which talks about the High-Dosage of Vitamin E and their effects on Insulin Resistance and other parameters related to it. studies shows that in the group which received vitamin E at 3 months the plasma peroxidases level lowered by 27% and at 6 months by 29% and the correlation was done positively by plasma vitamin E at 6 months' time point. The fasting glucose and the amount of insulin significantly decreased and there was an increase in homeostasis model assessment at a period of three months. These changes were not evident

at 6 months. Throughout the study period the plasma ALT concentrations declined significantly [88].

Vitamin C

Vitamin C also known a ascorbic acid a significant vitamin which is soluble in water with high antioxidant characteristics that can also restore the activity of other antioxidants. However, it can be a prooxidant and can glycate proteins in certain in vitro conditions. There has seen a decline in the level of vitamin C and high level of lipid peroxide in patients suffering from high glucose level and other metabolic diseases [89]. A significant inverse relation between vitamin C level and diabetes was recorded in a latest study among the adults of European origin. advancement in insulin activity, glycaemic regulation and function of endothelium on treatment with vitamin C are also reported. However, despite these studies, high-dose vitamin C administration in diabetes type 2 patients do not fully restore vitamin C plasma or endothelial control or insulin resistance levels. The rate of cardiovascular complications will actually increase with increased concentration of vitamin C. Vitamin C compensate for low blood levels of insulin, which regularly attempts to assist cells with retaining the nutrient [90]. Appropriate measures of vitamin C may assist the body with keeping a decent cholesterol level and monitor glucose levels [91].

Coenzyme Q10

Coenzyme Q10 also known as coenzyme Q, CoQ, Vitamin Q10, a benzoquine found in many oxygens in taking organisms going from microscopic to vertebrates. It is almost present in all the cells of the human body. This molecule can be an electron carrier in respiratory chain for generation of Adenosine triphosphate (ATP) in mitochondria. In 1957, Q10 was first isolated from mitochondria of cow's heart [92]. In coenzyme Q10, 10 stands for the number of isoprene repeats. The Coenzyme Q10 in its reduced form protects biological membrane against oxidation, inhibits peroxidation of lipids thus acting as antioxidants. It is a lipid-soluble antioxidant. Its lipophilic nature prevents the peroxidation of lipids present in circulation. The synthesis takes place through the mevalonate pathway and some of them may be made available through diet. Meat is the major source of CoQ10. The CQ10 occurs in the body both in oxidized (ubiquinone, CoQ10) and reduced (ubiquinol, $CoQ10H_2$) [93]. CoQ10 is the most crucial cofactor involved in mitochondrial phosphorylation and necessary in production of ATP. Flavoenzymes which includes NADH dehydrogenase and mitochondrial succinate dehydrogenase are involved in the conversion of oxidized (CoQ10) to reduced ($CoQ10H_2$). In mitochondria, CoQ10 acts as an electron transporter to cytochrome bc1 complex (complex III) from NADH Coenzyme Q reductase (complex I) or from succinate dehydrogenase (complex II) to cytochrome bc1 complex (complex III) [94].

Mitochondrial dysfunction and oxidative stress have an important role in diabetic complications. Coenzyme Q10 has gained interest due to its antioxidant activity that it can be used as a supplement to treat type 2 diabetes mellitus. The deficiency of CoQ10 mainly ubiquinol was observed in Type 2 diabetes patients. When 15 patients suffering from diabetes was treated using 60 mg of CoQ10 for 12 weeks there was a significant increase in synthesis and secretion of Insulin [95]. Glycemic control was also enhanced but this study does not contain a placebo control group. Some studies suggest that CoQ10 could possibly reduce the oxidative stress, restore mitochondrial function and enhance glycemic control [96].

Ruboxistaurin

In diabetes mellitus, chronic hyperglycemia leads to microvascular complications which include diabetic neuropathy, nephropathy, retinopathy and cardio vascular diseases [97]. PKC protein kinase C are family of calcium or lipid serine –threonine kinase enzymes involved in intracellular signalling. Under chronic hyperglycemic conditions, there is an elevated level of DAG Diacylglycerol which activates various isoforms of PKC. Of these PKC β and PKC delta are over activated. PKC –β show prominent characteristics in Oxidative stress, endothelial dysfunction with diabetic microvascular complications [98]. Ruboxistaurin (RBX) is a potent and specific inhibitor of β isoform of PKC. It inhibits the phosphorylation of substrates by interfering with adenosine triphosphate binding through its binding with PKC-β active site. RBX gets metabolized to its equally potent metabolite N-desmethyl RBX by CYP3A4. RBX half-life is 24 h and its primary route of excretion in human is through faecal and renal excretion playing a small role [99].

When streptozotocin treated diabetes rats were treated with PKC-β inhibitor RBX. the superoxide radical production was decreased along with the inhibition of PKC-β activation. It also prevented NADPH oxidase subunit Phox67 translocation and Phox22 overexpression. It can prevent the hyperglycemia induced oxidative stress [100]

PKC-β, a transduction mediator which can induce several processes that can result in kidney injury. This diabetic nephropathy can be prevented by selective inhibitor of PKC-β, Ruboxistaurin [101]. When diabetes type 2 patients and nephropathy were treated with RBX it showed reduced albuminuria and estimated glomerular filtrate rate over a period of 1 year [102]. In addition to this the treatment with oral Ruboxistaurin decreased loss of vision, reduced requirement for laser treatment and reduced progression of macular edema. It also increased the visual improvement of patients with non-proliferative retinopathy [103]. From this is evident

Table 1 Advantage and disadvantage of available medication that has been supplemented to patients suffering from diabetes

S.No	Drug name	Mechanism	Advantage	Disadvantage	Reference
1	Metformin	It decreases hepatic glucose production, intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization	glucose-lowering ability, weight-neutral effects, and low risk of hypoglycaemia	Nausea, vomiting, stomach upset, diarrhoea, weakness, or a metallic taste in the mouth may occur. Metformin usually does not cause hypoglycaemia; however, low blood sugar may occur if this drug is used with other anti-diabetic drugs	Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60:1577–85
2	Sulphonylureas	They close ATP-sensitive K-channels in the beta-cell plasma membrane, and so initiate a chain of events which results in insulin release	multiple formulations, low costs, minimal side effects, and demonstrated efficacy in controlling hyperglycaemia	The major disadvantage of sulfonylurea is secondary failure, which may occur with all oral agents as part of the progression of NIDDM	Ashcroft FM. Mechanisms of the glycaemia effects of sulfonylurea. Hormone and Metabolic Research. 1996 Sep;28(09):456–63 Zimmerman BR. Sulfonylureas. Endocrinology and metabolism clinics of North America. 1997 Sep 1;26(3):511–22
3	Thiazolidinediones	TZDs exert their anti diabetic effects through a mechanism that involves activation of the gamma isoform of the peroxisome proliferators-activated receptor (PPAR gamma), a nuclear receptor. TZDs reduce insulin resistance in adipose tissue, muscle and the liver	Decreased blood glucose levels and preservation of the pancreas's ability to produce sufficient levels of insulin. It also help lower blood pressure and improve lipid metabolism by increasing levels of HDL cholesterol and reducing levels of triglycerides – a type of fat in the bloodstream and fat tissue	Water retention, weight gain, eye sight problems, reduced sense of touch, chest pain, and infection, allergic skin reactions	Rizos CV, Elisaf M, Mikhailidis DP, Liberopoulos EN. How safe is the use of thiazolidinediones in clinical practice?. Expert opinion on drug safety. 2009 Jan 1;8(1):15–32
4	Empagliflozin	Empagliflozin works by inhibiting the sodium-glucose co-transporter-2 (SGLT-2) found in the proximal tubules in the kidneys. Through SGLT2 inhibition, empagliflozin reduces renal reabsorption of glucose and increases urinary excretion of glucose	Reduce sodium and volume load, weight loss, reduction in blood pressure without increased in hear rate	Urinary tract infections, with symptoms such as burning while urinating, urinating more often, and cloudy urine. Vaginal yeast infections, with symptoms such as itching, soreness, and pain while urinating. Some serious side effects are hypotension, kidney damage, increased density lipoprotein	Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papatheodorou K, Bekiari E, Tsapas A. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2014 Oct;16(10):984–93
5	Dapagliflozin	By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion	Lower blood glucose levels by helping the body to filter more excess glucose out of the blood. Lowering blood glucose levels, by passing glucose out of the body, the accompanying calories in the excreted glucose is also passed out	Hypoglycaemia, thrush, urinary tract infection, changes in blood fat, increased blood sugar	Plosker GL. Dapagliflozin. Drugs. 2012 Dec 1;72(17):2289–312 Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JF, McMurray JJ, Lindberg M, Rossing P, Sjöström CD. Dapagliflozin in patients with chronic kidney disease. New England Journal of Medicine. 2020 Oct 8;383(15):1436–46

Table 1 (continued)

S.No	Drug name	Mechanism	Advantage	Disadvantage	Reference
6	Linaglipton	Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretion hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP)	Linagliptin is a multitasking agent that improves insulin secretion, reduces glucagon production, slows gastric emptying, promotes satiety and reduces appetite. Lack of severe hypoglycaemia, weight neutrality and good overall tolerability inflammation of the pancreas,	Fever and headache with a severe blistering, peeling, and red skin rash	Scott LJ. Linagliptin. Drugs. 2011 Mar 1;71(5):611–24 Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with Type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study 1. Diabetic Medicine. 2011 Nov;28(11):1352–61
7	Glyciphage	The free-flowing glucose in the blood enters the cell with the help of insulin. In type 2 diabetes, the insulin produced by the body is not utilized properly, or the body fails to make sufficient insulin, due to which glucose cannot enter the cells. Glyciphage reduces glucose absorption from the intestine, and therefore, is used for lowering the sugar levels created in the liver and acts by facilitating glucose into the cells	It works by lowering glucose production in the liver, delaying the absorption of sugar (glucose) from the intestines, and increasing the body's sensitivity to insulin. Lowering blood glucose levels is an essential part of managing diabetes	Lactic acidosis	VERY A. Glyciphage. The Journal of the Association of Physicians of India. 1987;35(3–11):250
8	Glimepiride	The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extra pancreatic effects may also play a role in the activity of sulfonylurea such as glimepiride	glimepiride was generally associated with lower risk of hypoglycaemia and less weight gain compared to other sulfonylureas. Glimepiride use may be safer in patients with cardiovascular disease because of its lack of detrimental effects on ischemic preconditioning	Low blood sugar,headache, nausea,dizziness, weakness	Langtry HD, Balfour JA. Glimepiride. Drugs. 1998 Apr 1;55(4):563–84 Basit A, Riaz M, Fawwad A. Glimepiride: evidence-based facts, trends, and observations. Vascular health and risk management. 2012;8:463
9	Sitagliptin	Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes mellitus by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones	Sitagliptin significantly reduces hemoglobin A1c in patients with Type 2 diabetes, enabling significantly more patients to achieve a hemoglobin level of lower than 7%. Sitagliptin significantly reduces fasting plasma glucose and 2-h postprandial glucose. Sitagliptin improves insulin secretion and ß-cell function	Sitagliptin may increase your risk of pancreatitis (inflammation of the pancreas). This can be severe and sometimes fatal	Dhillon S. Sitagliptin. Drugs. 2010 Mar 1;70(4):489–512 Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P, Study S. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clinical therapeutics. 2006 Oct 1;28(10):1556–68

Table 1 (continued)

S.No	Drug name	Mechanism	Advantage	Disadvantage	Reference
10	Gliclazide	Gliclazide stimulates insulin secretion through the beta cell sulphonylurea receptor, and possibly through a direct effect on intracellular calcium transport. It specifically improves the abnormal first phase insulin release in type 2 diabetes, and also has an effect on the second phase	gliclazide reduces platelet reactivity and stimulates endothelial prostacyclin synthesis; it also increases fibrinolysis by its effects on tissue plasminogen activator. These effects, seen both in vitro and in vivo, are independent of glycemic control and are not seen with other sulfonylureas	Stomach ache or indigestion feeling sick (nausea) Being sick (vomiting) or diarrhoea Constipation	Palmer KJ, Brogden RN. Gliclazide. Drugs. 1993 Jul 1;46(1):92–125 Campbell DB, Lavielle R, Nathan C. The mode of action and clinical pharmacology of gliclazide: a review. Diabetes research and clinical practice. 1991 Jan 1;14:S21-36
11	Pioglitazone	Pioglitazone works by making cells more sensitive to insulin, which is used to regulate the level of glucose in the body. Improving insulin sensitivity (or reducing insulin resistance) makes it easier for sugar (glucose) in the blood to get into the cells	Pioglitazone is known to improve insulin sensitivity, glycemic control, dyslipidemia, hypertension, and microalbuminuria in patients with T2DM. Pioglitazone decreases fasting and postprandial plasma glucose levels by improving the sensitivity of hepatic and peripheral (muscle) tissue to insulin	Have been associated with edema and increased risk of congestive heart failure, and should not be used in patients with heart failure. Additionally, pioglitazone use has been associated with worsened osteoporosis and increased risk of fractures	Gillies PS, Dunn CJ. Pioglitazone. Drugs. 2000 Aug 1;60(2):333–43 Smith U. Pioglitazone: mechanism of action. International journal of clinical practice. Supplement. 2001 Sep(121):13–8
12	Alogliptin	Alogliptin is a selective dipeptidyl peptidase IV inhibitor. The mechanism of action is to inhibit the inactivation of incretion hormones glucagon-like peptide-1 and glucose-dependent insulin tropic peptide, which are involved in blood glucose regulation	Alogliptin is an oral selective inhibitor of dipeptidyl peptidase-4 (DPP-4). These medicines are thought to work by enhancing the levels of active incretin hormones, which enhance insulin and reduce glucagon secretions, thereby reducing blood glucose levels	Alogliptin may cause hypoglycemia (low blood sugar). This is more common when alogliptin is taken together with certain medicines. Low blood sugar must be treated before it causes you to pass out (unconsciousness). People feel different symptoms of low blood sugar	Scott LJ. Alogliptin. Drugs. 2010 Oct 1;70(15):2051–72 White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl j Med. 2013 Oct 3;369:1327–35
13	Vidagliptin	Vildagliptin binds covalently to the catalytic site of DPP-4, eliciting prolonged enzyme inhibition. This raises intact GLP-1 levels, both after meal ingestion and in the fasting state. Vildagliptin has been shown to stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner	Vildagliptin is a potent DPP-4 inhibitor. When used alone or added to other OADs, it effectively improves glycemic control, preserves both the α- and β-cell function, and reduces lipotoxicity and insulin resistance. This drug is well tolerated and is weight-neutral	Nasopharyngitis: 9% Headache: 7% Dizziness: 6% Back pain: 6% Diarrhoea: 6%	Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes care. 2007 Apr 1;30(4):890–5 Keating GM. Vildagliptin. Drugs. 2010 Nov 1;70(16):2089–112 Croxtall JD, Keam SJ. Vildagliptin. Drugs. 2008 Nov 1;68(16):2387–409

Table 1 (continued)

S.No	Drug name	Mechanism	Advantage	Disadvantage	Reference
14	Glipizide	Glipizide involve a partial block of the potassium channels in the beta cells of the pancreatic islets. This potassium channel blockade results in cell depolarization, which opens up the voltage-gated calcium channels, causing insulin secretion from the pancreatic beta cells	Glipizide is used with a proper diet and exercise program to control high blood sugar in people with type 2 diabetes. It may also be used with other diabetes medications. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems	hypoglycemia, jaundice, liver damage, fever, bleeding or bruising, skin changes, SIADH, and porphyria	Correa R, Rodriguez Q, Nappe TM. Glipizide Basit A, Riaz M, Fawwad A. Glimepiride: evidence-based facts, trends, and observations. Vascular health and risk management. 2012;8:463
15	Liraglutide	Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia	Mild degrees of weight loss and hyperglycemia	The frequent occurrence of gastrointestinal adverse effects, the requirement of subcutaneous injection once daily, and the lack of long-term efficacy and safety data	Jackson SH, Martin TS, Jones JD, Seal D, Emanuel F. Liraglutide (victoza): the first once-daily incretin mimetic injection for type-2 diabetes. Pharmacy and Therapeutics. 2010 Sep;35(9):498

that RBX can be a promising treatment to treat complications related with diabetes Type 2.

Carnitine and its derivative and insulin resistance

Diabetes has now become a common illness which can be a result of insufficient insulin. Stimulating the glucose uptake is the role played by insulin. The glucose which is taken is stored as glycogen for the generation of tryglycerols in the adipose tissue. It has the ability to inhibit glucose efflux from liver [104]. In patient suffering from T2DM, insulin resistance is experienced, many theories are proposed for studying the action of insulin and how it works in lipid and glucose metabolism. Some theories studied that the lipid contributes to improving insulin resistance [105]. Many research works showed the over action of lipid on insulin resistance, it was studied that the oversupply of nutritional fat can show insulin resistance. It was found that fatty acyl CoA derivatives hampers insulin signalling and oxidation of glucose. Though the exact mechanism is not yet understood studies focus on the signalling of fatty acid which is meant to trigger insulin resistance. Lipid over accumulation can result in production of bioactive lipid metabolites [106].

Insulin receptor substrate phosphorylation. Some theory suggests that, the long-chain Acyl-CoAs are precursors of ceramide, and as such, resistance to insulin is improved through inhibition of ceramide synthesis [107–110]. Some researches recommend that oversupply of lipid ended in aggregation of incompletely metabolized fatty acids within-inside the mitochondria causing 'mitochondrial pressure', main to insulin resistance [111–114]. To provide an explanation for lipid-brought about repression of muscle glucose disposal, Randle and co-workers put forward the glucose fatty acid cycle. With reference this speculation acetyl-CoA molecules derived from glucose and lipid substrates compete for access into the TCA cycle. The precise process of the effect of lipid oversupply on insulin resistance is still not clear. Since the essential organic characteristic of carnitine is its ester-forming functionality with natural acids of each exogenous and endogenous origin, it could lessen the gathered acetyl CoA derivatives and/or their metabolites through transporting the outside the mitochondria.so, carnitine may be a capacity adjuvant with inside the remedy or prevention of insulin resistance and T2D [115].

Several human and animal research verified wherein L-carnitine supply has useful impact. On complete frame using glucose increase numerous lipid factors or oxidative pressure. Low amount of L-carnitine is associated to problems related to diabetes [116]. Medical studies showed that by managing the derivatives of carnitine with PLC and ALS can improve parameters associated to neurophysiology and decreases the symptoms shown by diabetic people, thus acting as a remedy for treating diabetes [117].

Table 2 Dietary anti-oxidants and their available food sources

S.No	Antioxidants	Food source	Quantity of Antioxidants	Advantages
1	β carotene	Green leafy vegetables, orange and yellow fruits	Spinach, raw 5.6 mg/100 mg Carrots, raw 18.3 mg/100 mg Sweet potato, cooked 9.5/100 mg	It Is a major chain breaking antioxidant. it prevents lipid peroxidation [1, 2]
2	Lycopene	Tomato, pink grapefruit, Watermelon	Processed tomatoes—9.9–13.44 mg lycopene/100 g, fresh tomatoes—0.88–7.74 mg lycopene/100 g	It's Anti-oxidant and anti-inflammatory properties prevents cardio vascular diseases and it regulates oxidative stress and pro-inflammatory stress. [2–4]
3	Lutein	Lettuce, green pepper, Egg yolk	Lettuce – 10.0–47.8 µg/g Green pepper-8.8 µg/g Egg yolk- 3.84–13.2 µg/g	It has the ability to scavenge superoxide and hydroxide radicals and also inhibited the lipid peroxidation [2, 5, 6]
4	catechin	Strawberry, cider,beans, Green tea, algae	Strawberry- 2-50 mg/100 g Cider-4 mg/100 g Beans-35-55 mg/100 g Green tea-10-80 mg/100 g	It scavenges ROS, induce Antioxidant enzymes, inhibits pro-oxidant enzymes such as xanthine oxidase, NADPH-oxidase [7, 8]
5	zinc	Oysters, tomatoes, flax seeds, pumpkin seeds, sunflower seeds, sesame seeds, beef	Oysters (raw)—47.9 mg/100 mg Pumpkin seeds- 7.5 mg/100 mg Sun dried tomatoes- 13.6 mg/100 mg Sesame seeds-5.5 mg/100 mg	Zinc inhibits the enzyme NADPH oxidases. It acts a cofactor for important antioxidant enzymes and induces the synthesis of metallothioneins which helps in attenuating the effects of free radicals[9, 10]
6	Selenium	Fish, vegetables Meat and poultry, Egg,	Fish- (0.152–0.788 µg/g) Meat and poultry. (0.043–0.324 µg/g) Egg- (0.267 µg/g)	Selenium in the form of selenoenzymes and selenoproteins reduces the lipid peroxidation and prevents heart diseases[11, 12]

However, current studies improve the chance wherein L-carnitine-associated metabolites exert accelerated cardio-metabolic complications [118].

Conclusion

A disease characterized with increased level of glucose is diabetes mellitus. Chronic hyperglycemia lead to many complications such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cardiovascular diseases and stroke [108]. The hyperglycemic state also leads stress associated with progression of diabetic complications. The high concentration of free radicals leads to vascular dysfunction and peroxidation of lipid. Hyperglycemic condition can be lowered by many drugs such as Sulphonylureas, Thiazolidinediones, Metformin but it comes with certain side effects on regular usage of them (Table 1). In this we have seen that though oxidants at certain level are involved in defense mechanisms but when the oxidants accumulate or overwhelm the antioxidants it leads to oxidative stress. The oxidants cause the advanced glycation products production, PKC-DAG activation and endothelial dysfunction. NADPH oxidases the enzyme involved in electron transfer from the cytosolic NADPH to molecular oxygen. Some reports suggests that β cells on exposure to glucose causes the generation of PHOX 47, a subunit of NADPH oxidases which causes the tremendous free radicals' generation. In addition, the oxidative stress triggers various cell signalling pathways such as MAPK and NFkβ. This activation leads to the apoptosis and pathological effects so it's important to lower the oxidative stress to prevent further progression of complications related to diabetes mellitus. Here comes use of antioxidants this substance can naturally neutralize the free radicals there by lowering oxidative stress. These antioxidants can be enzymatic or non-enzymatic. Some evidences shows that the substances such as β carotene, lycopene, lutein, catechin, zinc and selenium serves as dietary source of antioxidants as it is present in green vegetables, egg yolks, fruits etc.…(Table 2). These above-mentioned substances are important chain breaking antioxidants, scavenges the reactive oxygen species, induce antioxidant enzymes. It also has the ability to inhibit NADPH oxidases and prevent lipid peroxidation. Several other antioxidants include vitamin E, Vitamin C, Lipoic acid, coenzyme 10 and RBX. Here we see that vitamin E has radical scavenging characteristics and reduce the action of DAG. In addition to this some studies suggest that it reduced the risk of cardiovascular diseases, lowered the level of free radicals and reduced lipid peroxidation. Vitamin C helps in maintaining proper blood sugar level and cholesterol. Also, α-lipoic acid reduces the oxidative stress and helps restoring the function of antioxidant enzymes.

Furthermore, Coenzyme Q10, helps in maintaining the blood sugar by increasing insulin secretion and restoring mitochondrial function there by reducing oxidative stress. Some studies shows that Ruboxistaurin, a PKC-β inhibitor treatment for diabetes decreased the superoxide radical production and prevented the overexpression of NADPH oxidases. In addition to this it prevented the progression of diabetic nephropathy and neuropathy. This suggest that antioxidants can be a boon to treat diabetes. Antioxidants, can be used to treat various diseases the above evidence suggest that it will be a potential add on to treat diabetes and its associated complications.

Declarations

Conflict of interest There is no potential Conflict of Interest.

References

1. Kharroubi AT, Darwish HM. Diabetes mellitus: the epidemic of the century. World J Diabetes. 2015. https://doi.org/10.4239/wjd.v6.i6.850.
2. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev. 2013;93(1):137–88. https://doi.org/10.1152/physrev.00045.2011.
3. Punthakee Z, Goldenberg R, Katz P. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can J Diabetes. 2018. https://doi.org/10.1016/j.jcjd.2017.10.003.
4. Sies H, Berndt C, Jones DP. Oxidative stress. Annu Rev Biochem. 2017. https://doi.org/10.1146/annurev-biochem-061516-045037.
5. Reische DW, Lillard DA, Eitenmiller RR. Antioxidants. Food lipids: chemistry, nutrition, and biotechnology. 2002. https://doi.org/10.1201/9780203908815.ch15.
6. Galtier F. Definition, epidemiology, risk factors. Diabetes Metab. 2010. https://doi.org/10.1016/j.diabet.2010.11.014.
7. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020. https://doi.org/10.3390/ijms21176275.
8. Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159(8):543–51. https://doi.org/10.7326/0003-4819-159-8-201310150-00007.
9. Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of diabetes. 2017. https://doi.org/10.1155/2018/3086167.
10. Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The diabetes mellitus–atherosclerosis connection: The role of lipid and glucose metabolism and chronic inflammation. Int J Mol Sci. 2020. https://doi.org/10.3390/ijms21051835.
11. Said G. Diabetic neuropathy—a review. Nat Clin Pract Neurol. 2007. https://doi.org/10.1038/ncpneuro0504.
12. Dronavalli S, Duka I, Bakris GL. The pathogenesis of diabetic nephropathy. Nat Clin Pract Endocrinol Metab. 2008. https://doi.org/10.1038/ncpendmet0894.
13. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL, Klein R. Retinopathy in diabetes. Diabetes Car. 2004. https://doi.org/10.2337/diacare.27.2007.s84.
14. Frykberg RG. Diabetic foot ulcers: pathogenesis and management. Am Fam Physician. 2002. https://pubmed.ncbi.nlm.nih.gov/?term=Frykberg+RG&cauthor_id=12449264.
15. Tay HL, Ray N, Ohri R, Frootko NJ. Diabetes mellitus and hearing loss. Clin Otolaryngol Allied Sci. 1995. https://doi.org/10.1111/j.1365-2273.1995.tb00029.x.
16. Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. Am J Epidemiol. 2001. https://doi.org/10.1093/aje/154.7.635.
17. Sies H. Oxidative stress: oxidants and antioxidants. Exp Physiol. 1997;82(2):291–5. https://doi.org/10.1113/expphysiol.1997.sp004024.
18. Beckman KB, Ames BN. The free radical theory of aging matures. Physiol Rev. 1998. https://doi.org/10.1152/physrev.1998.78.2.547.
19 Gilgun-Sherki Y, Melamed E, Offen D. Oxidative stress induced-neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier. Neuropharmacology. 2001;40(8):959–75. https://doi.org/10.2174/1570159097876028 23.
20 Vertuani S, Angusti A, Manfredini S. The antioxidants and pro-antioxidants network: an overview. Curr Pharm Des. 2004;10(14):1677–94. https://doi.org/10.2174/1381612043384655.
21. Halliwell B, Aeschbach R, Löliger J, Aruoma OI. The characterization of antioxidants. Food Chem Toxicol. 1995;33(7):601–17.
22. Kabel AM. Free radicals and antioxidants: role of enzymes and nutrition. World J Nutr Health. 2014;2(3):35–8. https://doi.org/10.12691/jnh-2-3-2.
23 Mirończuk-Chodakowska I, Witkowska AM, Zujko ME. Endogenous non-enzymatic antioxidants in the human body. Adv Med Sci. 2018;63(1):68–78.
24. Gibaldi M, Perrier D. Pharmacokinetics. 1982. https://doi.org/10.1002/bdd.2510040213.
25. Doogue MP, Polasek TM, Lowe RN, Marrs JC, Saseen JJ, Loke YK, Singh S, Grzeskowiak LE, Gilbert AL, Morrison JL. Therapeutic Advances in Drug Safety. 2012. https://doi.org/10.1177/2042098612469917.
26. Doogue MP, Polasek TM. The ABCD of clinical pharmacokinetics. 2013. https://doi.org/10.1177/2042098612469335.
27. Raghavan N, Frost CE, Yu Z, He K, Zhang H, Humphreys WG, Pinto D, Chen S, Bonacorsi S, Wong PC, Zhang D. Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab Dispos. 2009;37(1):74–81. https://doi.org/10.1111/bcp.12393.
28. Swinney DC. Biochemical mechanisms of drug action: what does it take for success? Nat Rev Drug Discovery. 2004;3(9):801–8.
29. Koch-Weser JAN. Bioavailability of drugs. N Engl J Med. 1974;291(5):233–7.
30. Melander A. Influence of food on the bioavailability of drugs. Clin Pharmacokinet. 1978;3(5):337–51. https://doi.org/10.2165/00003088-197803050-00001.
31 Cerf ME. β cell dysfunction and insulin resistance. Front Endocrinol. 2013;4:37. https://doi.org/10.3389/fendo.2013.00037.
32. Ashcroft FM, Rorsman P. Diabetes mellitus and the β cell: the last ten years. Cell. 2012;148(6):1160–71. https://doi.org/10.1016/j.cell.2012.02.010.
33. Kahn SE. The relative contributions of insulin resistance and β-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia. 2003;46(1):3–19.

34. Weir GC, Bonner-Weir S. Five stages of evolving β-cell dysfunction during progression to diabetes. Diabetes. 2004;53(suppl 3):S16–21. https://doi.org/10.2337/diabetes.53.suppl_3.s16.
35. Drews G, Krippeit-Drews P, Düfer M. Oxidative stress and β-cell dysfunction. Pflügers Archiv-Eur J Physiol. 2010;460(4):703–18. https://doi.org/10.1007/s00424-010-0862-9.
36 Victor VM, Rocha M, Herance R, Hernandez-Mijares A. Oxidative stress and mitochondrial dysfunction in type 2 diabetes. Curr Pharm Des. 2011;17(36):3947–58. https://doi.org/10.1155/2020/8878172.
37. Keane KN, Cruzat VF, Carlessi R, de Bittencourt PIH, Newsholme P. Molecular events linking oxidative stress and inflammation to insulin resistance and β-cell dysfunction. Oxid Med Cell Longev. 2015; 2015. https://doi.org/10.1155/2015/181643.
38. Kajimoto Y, Kaneto H. Role of oxidative stress in pancreatic β-cell dysfunction. In Mitochondrial Pathogenesis. Berlin: Springer; 2004, 168–176.
39. Russo GT, Giorda CB, Cercone S, Nicolucci A, Cucinotta D, β Decline Study Group. Factors associated with β-cell dysfunction in type 2 diabetes: the β DECLINE study. PLoS One. 2014;9(10):e109702. https://doi.org/10.1371/journal.pone.0109702.
40. Lee Y, Hirose H, Ohneda M, Johnson JH, McGarry JD, Unger RH. β-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-β-cell relationships. Proc Natl Acad Sci. 1994;91(23):10878–82.
41. Eguchi K, Manabe I, Oishi-Tanaka Y, Ohsugi M, Kono N, Ogata F, Yagi N, Ohto U, Kimoto M, Miyake K, Tobe K. Saturated fatty acid and TLR signaling link β cell dysfunction and islet inflammation. Cell Metab. 2012;15(4):518–33. https://doi.org/10.1016/j.cmet.2012.01.023.
42. DeFronzo RA. Dysfunctional fat cells, lipotoxicity and type 2 diabetes. Int J Clin Pract. 2004;58:9–21. https://doi.org/10.1111/j.1368-504X.2004.00389.x.
43 Sivitz WI. Lipotoxicity and glucotoxicity in type 2 diabetes: effects on development and progression. Postgrad Med. 2001;109(4):55–64.
44. Del Prato S. Role of glucotoxicity and lipotoxicity in the pathophysiology of Type 2 diabetes mellitus and emerging treatment strategies. Diabet Med. 2009;26(12):1185–92.
45. Boden G. Fatty acid—induced inflammation and insulin resistance in skeletal muscle and liver. Curr DiabRep. 2006;6(3):177–81.
46. Igoillo-Esteve M, Marselli L, Cunha DA, Ladrière L, Ortis F, Grieco FA, Dotta F, Weir GC, Marchetti P, Eizirik DL, Cnop M. Palmitate induces a pro-inflammatory response in human pancreatic islets that mimics CCL2 expression by β cells in type 2 diabetes. Diabetologia. 2010;53(7):1395–405. https://doi.org/10.1007/s00125-010-1707-y.
47. Zatalia SR, Sanusi H. The role of antioxidants in the pathophysiology, complications, and management of diabetes mellitus. Acta Med Indones. 2013;45(2):141–7.
48. Maxwell SR. Prospects for the use of antioxidant therapies. Drugs. 1995;49(3):345–61.
49. Sindhu RK, Koo JR, Roberts CK, Vaziri ND. Dysregulation of hepatic superoxide dismutase, catalase and glutathione peroxidase in diabetes: response to insulin and antioxidant therapies. Clin Exp Hypertens. 2004;26(1):43–53.
50. Vega-López S, Devaraj S, Jialal I. Oxidative stress and antioxidant supplementation in the management of diabetic cardiovascular disease. J Investig Med. 2004;52(1):24–32. https://doi.org/10.2310/6650.2004.11932.
51. Anderson JW, Gowri MS, Turner J, Nichols L, Diwadkar VA, Chow CK, Oeltjen PR. Antioxidant supplementation effects on low-density lipoprotein oxidation for individuals with type 2 diabetes mellitus. J Am Coll Nutr. 1999;18(5):451–61. https://doi.org/10.1080/07315724.1999.10718883.
52. Ceriello A. New insights on oxidative stress and diabetic complications may lead to a "causal" antioxidant therapy. Diabetes Care. 2003;26(5):1589–96. https://doi.org/10.2337/diacare.26.5.1589.
53. Korhonen R, Lahti A, Kankaanranta H, Moilanen E. Nitric oxide production and signaling in inflammation. Curr Drug Targets Inflamm Allergy. 2005;4(4):471–9. https://doi.org/10.2174/1568010054526359.
54. Neri S, Signorelli S, Pulvirenti D, Mauceri B, Cilio D, Bordonaro F, Abate G, Interlandi D, Misseri M, Ignaccolo L, Savastano M. Oxidative stress, nitric oxide, endothelial dysfunction and tinnitus. Free Radical Res. 2006;40(6):615–8. https://doi.org/10.1080/10715760600623825.
55. Indo HP, Davidson M, Yen HC, Suenaga S, Tomita K, Nishii T, Higuchi M, Koga Y, Ozawa T, Majima HJ. Evidence of ROS generation by mitochondria in cells with impaired electron transport chain and mitochondrial DNA damage. Mitochondrion. 2007;7(1–2):106–18. https://doi.org/10.1016/j.mito.2006.11.026.
56. Davì G, Falco A, Patrono C. Lipid peroxidation in diabetes mellitus. Antioxid Redox Signal. 2005;7(1–2):256–68. https://doi.org/10.1089/ars.2005.7.256.
57. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocr Rev. 2002;23(5):599–622. https://doi.org/10.1210/er.2001-0039.
58 Gunnett CA, Lund DD, McDowell AK, Faraci FM, Heistad DD. Mechanisms of inducible nitric oxide synthase–mediated vascular dysfunction. Arterioscler Thromb Vasc Biol. 2005;25(8):1617–22. https://doi.org/10.1161/01.ATV.0000172626.00296.ba.
59 Babior BM. NADPH oxidase. Curr Opin Immunol. 2004;16(1):42–7. https://doi.org/10.1016/j.coi.2003.12.001.
60 Groemping Y, Rittinger K. Activation and assembly of the NADPH oxidase: a structural perspective. Biochem J. 2005;386(3):401–16. https://doi.org/10.1042/BJ20041835.
61. Kayama Y, Raaz U, Jagger A, Adam M, Schellinger IN, Sakamoto M, Suzuki H, Toyama K, Spin JM, Tsao PS. Diabetic cardiovascular disease induced by oxidative stress. Int J Mol Sci. 2015;16(10):25234–63. https://doi.org/10.3390/ijms161025234.
62 Sumimoto H. Structure, regulation and evolution of Nox-family NADPH oxidases that produce reactive oxygen species. FEBS J. 2008;275(13):3249–77. https://doi.org/10.1111/j.1742-4658.2008.06488.x.
63. Selemidis S, Sobey CG, Wingler K, Schmidt HH, Drummond GR. NADPH oxidases in the vasculature: molecular features, roles in disease and pharmacological inhibition. Pharmacol Ther. 2008;120(3):254–91.
64. Kuroda J, Ago T, Matsushima S, Zhai P, Schneider MD, Sadoshima J. NADPH oxidase 4 (Nox4) is a major source of oxidative stress in the failing heart. Proc Natl Acad Sci. 2010;107(35):15565–70. https://doi.org/10.1073/pnas.1002178107.
65. Brandes RP, Weissmann N, Schröder K. Nox family NADPH oxidases: molecular mechanisms of activation. Free Radical Biol Med. 2014;76:208–26. https://doi.org/10.1016/j.freeradbiomed.2014.07.046.
66. Stielow C, Catar RA, Muller G, Wingler K, Scheurer P, Schmidt HH, Morawietz H. Novel Nox inhibitor of oxLDL-induced reactive oxygen species formation in human endothelial cells. Biochem Biophys Res Commun. 2006;344(1):200–5.
67 Jaquet V, Scapozza L, Clark RA, Krause KH, Lambeth JD. Small-molecule NOX inhibitors: ROS-generating NADPH oxidases as therapeutic targets. Antioxid Redox Signal. 2009;11(10):2535–52. https://doi.org/10.1089/ars.2009.2585.

68 Bedard K, Krause KH. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol Rev. 2007;87(1):245–313. https://doi.org/10.1152/physrev.00044.2005.

69 Ma MW, Wang J, Dhandapani KM, Wang R, Brann DW. NADPH oxidases in traumatic brain injury–Promising therapeutic targets? Redox biology. 2018;16:285–93. https://doi.org/10.1016/j.redox.2018.03.005.

70. Panday A, Sahoo MK, Osorio D, Batra S. NADPH oxidases: an overview from structure to innate immunity-associated pathologies. Cell Mol Immunol. 2015;12(1):5–23.

71. Petri S, Körner S, Kiaei M. Nrf2/ARE signaling pathway: key mediator in oxidative stress and potential therapeutic target in ALS. Neurol Res Int. 2012. https://doi.org/10.1155/2012/878030.

72 Ma Q. Role of nrf2 in oxidative stress and toxicity. Ann Rev Pharmacol Toxicol. 2013;53:401–26. https://doi.org/10.1146/annurev-pharmtox-011112-140320.

73. Ahmed SMU, Luo L, Namani A, Wang XJ, Tang X. Nrf2 signaling pathway: Pivotal roles in inflammation. Biochim Biophys Acta Mol Basis Dis. 2017;1863(2):585–97. https://doi.org/10.1016/j.bbadis.2016.11.005.

74 Nguyen T, Nioi P, Pickett CB. The Nrf2-antioxidant response element signaling pathway and its activation by oxidative stress. J Biol Chem. 2009;284(20):13291–5. https://doi.org/10.1074/jbc.r900010200.

75. Son Y, Cheong YK, Kim NH, Chung HT, Kang DG, Pae HO. Mitogen-activated protein kinases and reactive oxygen species: how can ROS activate MAPK pathways? J Signal Transduction. 2011. https://doi.org/10.1155/2011/792639.

76. Zhang J, Wang X, Vikash V, Ye Q, Wu D, Liu Y, Dong W. ROS and ROS-mediated cellular signaling. Oxid Med Cell Longev. 2016. https://doi.org/10.1155/2016/4350965.

77 Boutros T, Chevet E, Metrakos P. Mitogen-activated protein (MAP) kinase/MAP kinase phosphatase regulation: roles in cell growth, death, and cancer. Pharmacol Rev. 2008;60(3):261–310. https://doi.org/10.1124/pr.107.00106.

78. Kyriakis JM, Avruch J. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiol Rev. 2001;81(2):807–69. https://doi.org/10.1152/physrev.2001.81.2.807.

79. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: impact on human health. Pharmacogn Rev. 2010;4(8):118. https://doi.org/10.4103/0973-7847.70902.

80. Moussa Z, Judeh ZM, Ahmed SA. Nonenzymatic exogenous and endogenous antioxidants. In Free Radical Medicine and Biology. IntechOpen; 2019.

81. Is Y, Woodside JV. Antioxidant in health and disease. J Clin Pathol. 2001;54(3):176–86. https://doi.org/10.1136/jcp.54.3.176.

82. Oldham KM, Bowen PE. Oxidative stress in critical care: is antioxidant supplementation beneficial? J Am Diet Assoc. 1998;98(9):1001–8. https://doi.org/10.1016/j.jff.2019.103508.

83. Chow CK. Vitamin E and oxidative stress. Free Radical Biol Med. 1991;11(2):215–32. https://doi.org/10.1016/0891-5849(91)90174-2.

84 Pazdro R, Burgess JR. The role of vitamin E and oxidative stress in diabetes complications. Mech Ageing Dev. 2010;131(4):276–86.

85. Singh U, Devaraj S, Jialal I. Vitamin E, oxidative stress, and inflammation. Annu Rev Nutr. 2005;25:151–74. https://doi.org/10.1146/annurev.nutr.24.012003.132446.

86. Feillet-Coudray C, Rock E, Coudray C, Grzelkowska K, Azais-Braesco V, Dardevet D, Mazur A. Lipid peroxidation and antioxidant status in experimental diabetes. Clin Chim Acta. 1999;284(1):31–43. https://doi.org/10.1016/s0009-8981(99)00046-7.

87. Jain AB, Jain VA. Vitamin E, its beneficial role in diabetes mellitus (DM) and its complications. J Clin Diagnostic Res. 2012;6(10):1624. https://doi.org/10.7860/jcdr/2012/4791.2625.

88 Scott DL, Kelleher J, Losowsky MS. The influence of dietary selenium and vitamin E on glutathione peroxidase and glutathione in the rat. Biochim Biophys Acta Gen Subjects. 1977;497(1):218–24. https://doi.org/10.1016/0304-4165(77)90154-4.

89. Wagh SP, Bhagat SP, Bankar N, Jain K. Role of Vitamin-C Supplementation in Type II Diabetes Mellitus. Int J Cur Res Rev. 2020. https://doi.org/10.31782/IJCRR.2020.121311.

90. Dakhale GN, Chaudhari HV, Shrivastava M. Supplementation of vitamin C reduces blood glucose and improves glycosylated hemoglobin in type 2 diabetes mellitus: a randomized, double-blind study. Adv Pharmacol Sci. 2011. https://doi.org/10.1155/2011/195271.

91 Chambial S, Dwivedi S, Shukla KK, John PJ, Sharma P. Vitamin C in disease prevention and cure: an overview. Indian J Clin Biochem. 2013;28(4):314–28. https://doi.org/10.1007/s12291-013-0375-3.

92. Casagrande D, Waib PH, Júnior AAJ. Mechanisms of action and effects of the administration of Coenzyme Q10 on metabolic syndrome. J Nutr Intermediary Metab. 2018;13:26–32.

93. Saini R. Coenzyme Q10: the essential nutrient. J Pharm Bioallied Sci. 2011;3(3):466–7.

94. Molyneux SL, Young JM, Florkowski CM, Lever M, George PM. Coenzyme Q10: is there a clinical role and a case for measurement? Clin Biochem Rev. 2008;29(2):71.

95 Shen Q, Pierce JD. Supplementation of coenzyme Q10 among patients with type 2 diabetes mellitus. Healthcare. 2015;3(2):296–309. https://doi.org/10.3390/healthcare3020296 (**Multidisciplinary Digital Publishing Institute**).

96. Shimura Y, Hogimoto S. Significance of coenzyme Q10 on the treatment of diabetes mellitus. Jpn J Clin Exp Med. 1981;58:1349–52.

97 Bansal D, Badhan Y, Gudala K, Schifano F. Ruboxistaurin for the treatment of diabetic peripheral neuropathy: a systematic review of randomized clinical trials. Diabetes Metab J. 2013;37(5):375. https://doi.org/10.4093/dmj.2013.37.5.375.

98. Liu Y, Lei S, Gao X, Mao X, Wang T, Wong GT, Vanhoutte PM, Irwin MG, Xia Z. PKCβ inhibition with ruboxistaurin reduces oxidative stress and attenuates left ventricular hypertrophy and dysfuntion in rats with streptozotocin-induced diabetes. Clin Sci. 2012;122(4):161–73. https://doi.org/10.1042/cs20110176.

99 Javey G, Schwartz SG, Flynn HW Jr, Aiello LP, Sheetz MJ. Ruboxistaurin: review of safety and efficacy in the treatment of diabetic retinopathy. Clin Med Insights Ther. 2010;2:CMT-S5046. https://doi.org/10.4137/CMT.S5046.

100. Budhiraja S, Singh J. Protein kinase C β inhibitors: a new therapeutic target for diabetic nephropathy and vascular complications. Fundam Clin Pharmacol. 2008;22(3):231–40.

101 Geraldes P, King GL. Activation of protein kinase C isoforms and its impact on diabetic complications. Circ Res. 2010;106(8):1319–31. https://doi.org/10.1161/CIRCRESAHA.110.217117.

102 Tuttle KR, Bakris GL, Toto RD, McGill JB, Hu K, Anderson PW. The effect of ruboxistaurin on nephropathy in type 2 diabetes. Diabetes Care. 2005;28(11):2686–90. https://doi.org/10.2337/diacare.28.11.2686.

103. Group, P.D. Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy. Ophthalmology. 2006;113(12):2221–30.

104. Ribas GS, Vargas CR, Wajner M. L-carnitine supplementation as a potential antioxidant therapy for inherited neurometabolic disorders. Gene. 2014;533(2):469–76. https://doi.org/10.1016/j.gene.2013.10.017.

105 Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet. 2010;375(9733):2267–77. https://doi.org/10.1016/S0140-6736(10)60408-4.
106. Itani SI, Ruderman NB, Schmieder F, Boden G. Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IκB-α. Diabetes. 2002;51(7):2005–11.
107 Arsenian MA. Carnitine and its derivatives in cardiovascular disease. Progress Cardiovasc Dis. 1997;40(3):265–86.
108 Bahtiyar G, Gutterman D, Lebovitz H. Heart failure: a major cardiovascular complication of diabetes mellitus. Curr Diabetes Rep. 2016;16(11):1–14.
109. Bursell SE, Clermont AC, Aiello LP, Aiello LM, Schlossman DK, Feener EP, Laffel LORL, King GL. High-dose vitamin E supplementation normalizes retinal blood flow and creatinine clearance in patients with type 1 diabetes. Diabetes Care. 1999;22(8):1245–51. https://doi.org/10.2337/diacare.22.8.1245.
110. Lahiri S, Park H, Laviad EL, Lu X, Bittman R, Futerman AH. Ceramide synthesis is modulated by the sphingosine analog FTY720 via a mixture of uncompetitive and noncompetitive inhibition in an Acyl-CoA chain length-de pend ent manner. J Biol Chem. 2009;284(24):16090–8.
111. Lambeth JD. NOX enzymes and the biology of reactive oxygen. Nat Rev Immunol. 2004;4(3):181–9. https://doi.org/10.1038/nri1312.
112 Leopold G. Balanced pharmacokinetics and metabolism of bisoprolol. J Cardiovasc Pharmacol. 1986;8:S16-20. https://doi.org/10.1097/00005344-198511001-00003.
113. Mingrone G. Carnitine in type 2 diabetes. Ann N Y Acad Sci. 2004;1033(1):99–107. https://doi.org/10.1196/annals.1320.009.
114. Power RA, Hulver MW, Zhang JY, Dubois J, Marchand RM, Ilkayeva O, Muoio DM, Mynatt RL. Carnitine revisited: potential use as adjunctive treatment in diabetes. Diabetologia. 2007;50(4):824–32.
115. Sato H, Shibata M, Shimizu T, Shibata S, Toriumi H, Ebine T, Kuroi T, Iwashita T, Funakubo M, Kayama Y, Akazawa C. Differential cellular localization of antioxidant enzymes in the trigeminal ganglion. Neuroscience. 2013;248:345–58. https://doi.org/10.1016/j.neuroscience.2013.06.010.
116 Son Y, Kim S, Chung HT, Pae HO. Reactive oxygen species in the activation of MAP kinases. Methods Enzymol. 2013;528:27–48.
117. Vidal-Casariego A, Burgos-Peláez R, Martínez-Faedo C, Calvo-Gracia F, Valero-Zanuy MÁ, Luengo-Pérez LM, Cuerda-Compés C. Metabolic effects of L-carnitine on type 2 diabetes mellitus: systematic review and meta-analysis. Exp Clin Endocrinol Diabetes. 2013;121(04):234–8. https://doi.org/10.1055/s-0033-1333688.
118. Zhang L, Jaswal JS, Ussher JR, Sankaralingam S, Wagg C, Zaugg M, Lopaschuk GD. Cardiac insulin-resistance and decreased mitochondrial energy production precede the development of systolic heart failure after pressure-overload hypertrophy. Circ Heart Fail. 2013;6(5):1039–48. https://doi.org/10.1161/circheartfailure.112.000228.