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Review

REVIEW

Ameliorating effects of antioxidative compounds from four plant extracts in experimental models of diabetes

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Abstract: Given that oxidative stress plays a major role in pancreatic *β*-cell dysfunction and ultimate destruction, as well as in different complications of diabetes, therapy with antioxidants has assumed an important place in the management of diabetes. The relatively limited effects of established antioxidant compounds have stimulated efforts to develop new therapeutic strategies, *e.g.* to increase the endogenous antioxidant defences through pharmacological modulation of key antioxidant enzymes. Plant extracts are gaining popularity in treating diabetes because many substances synthesized by higher plants and fungi possess antioxidant activities and can prevent or protect tissues against the damaging effects of free radicals. This review summarizes experimental models of diabetes and possible mechanisms that lie behind the antioxidative effects of *α*-lipoic acid (LA), a powerful antioxidant and compound that stimulates cellular glucose uptake, as well as of plant extracts from sweet chestnut (*Castanea sativa*), edible mushroom (*Lactarius deterrimus*) and natural products containing *β*-glucans in the treatment of diabetes. Their roles in preventing pancreatic *β*-cell death and in ameliorating the effects of severe diabetic complications are discussed.

Keywords: diabetes; oxidative stress; lipoic acid; plant antioxidants.

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1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disease with an aetiology linked to both genetic and environmental factors. Diabetes has become a global health problem due to its high incidence and latent harmful and lethal effects. According to the World Health Organization (WHO),[1] 347 million people worldwide have diabetes, which has greatly increased the cost of treating both the disease and its numerous devastating complications. According to the International Diabetes Federation (IDF), 4.6 million people die each year from the consequences of diabetes,[2] with more than 80 % of diabetes-related deaths occurring in low and middle income countries.[1] According to The Public Health Institute of Serbia "Dr Milan Jovanović Batut",[3] 630,000 people or 8.2 % of the Serbian population suffer from diabetes and about 3,000 diabetics die each year. Type 1 diabetes (T1D) is characterized by destruction of pancreatic *β*-cells and thereby loss of insulin secretion. Type 2 diabetes (T2D) is associated with progressive insulin resistance and *β*-cell dysfunction. Deficiency of insulin secretion or action in diabetes causes prolonged hyperglycaemia that in turn leads to severe diabetic complications, such as retinopathy, neuropathy, nephropathy, cardiovascular problems, liver disease and limb amputation. Diabetes treatment includes insulin injection in combination with application of hypoglycaemic drugs. However, current control of diabetes-associated complications and mortality is not satisfactory.

Limitations in diabetes treatment have stimulated efforts to develop new therapeutic strategies. Growing evidence in both experimental and clinical studies suggests that oxidative stress plays an important role in pancreatic *β*-cell destruction/dysfunction and subsequent complications of diabetes. Therefore, strategies for diabetes management include antioxidant protection. However, established antioxidant compounds, such as vitamins C and E, have yielded limited effects, indicating the necessity for examination of other antioxidant compounds. Given that antioxidant enzyme expression and function is deregulated in diabetes, pharmacological modulation of key enzymes that are responsible for reducing the oxygen radical load is a potentially more effective approach than the use of systemic antioxidants.[4,5] It is therefore imperative to continuously identify new products with antioxidant activities for use in "causal" therapy of diabetes.[6]

Plant extracts are gaining popularity in diabetes treatment because of their efficacy, low incidence of side effects, their accessibility and low cost. Identifying new agents from plants with hypoglycaemic and antioxidative activities is of great importance. In this review, a summary will be given of the ameliorating effects and potential mechanisms of the actions of the known antioxidant compound α-lipoic acid (LA), extracts of the sweet chestnut (*Castanea sativa*), edible mushroom (*Lactarius deterrimus*) and their combination (MIX Cs/Ld), and of a β-glucan-enriched extract in the treatment of diabetes, *i.e.*, in the prevention of pancreatic β-cell death and amelioration of the severe complications in diabetes. Experimental models of diabetes will also be discussed.

2. OXIDATIVE STRESS IN THE DEVELOPMENT OF DIABETES AND ITS COMPLICATIONS

Oxidative stress is generally defined as a persistent imbalance between the concentrations of generated highly reactive free radical reactive oxygen species (ROS) and reactive nitrogen species (RNS) on the one hand and the antioxidant defence of the organism on the other. Hyperglycaemia promotes the formation of elevated levels of free radicals, especially ROS, *via* different routes of activation: glucose autoxidation,[7] non-enzymatic protein glycation,[8] increased metabolism of glucose through the hexosamine pathway,[9] excessive activation of the polyol pathway by unused glucose,[10] and by advanced glycation end-products (AGE) formed by the interaction of glucose with proteins.[11] One of the main sources of free radicals in diabetes is glucose autoxidation.[12] In a transition-metal dependent reaction, the enediol form of glucose is oxidized to an enediol radical anion that is converted into reactive ketoaldehydes and to superoxide anion radicals ($O_2^{\bullet-}$). The superoxide anion radicals undergo dismutation to hydrogen peroxide (H_2O_2), which, if not degraded by catalase (CAT) or glutathione peroxidase (GSH-Px), in the presence of transition metals can lead to the production of extremely reactive hydroxyl radicals (OH·).[13] Superoxide anion radicals can also react with nitric oxide (NO) to form reactive peroxynitrite. Peroxynitrite is chemically unstable under physiological conditions and reacts with all major classes of biomolecules, mediating cytotoxicity,[14] AGE signalling, through the receptor for AGE (RAGE), and inactivation of enzymes by altering their structure,[15] thereby supporting additional free radical accumulation.[16] Excess levels of free radicals damage cellular proteins, lipids and nucleic acids, leading to cell death in various tissues (the cardiovascular system, retina, kidneys, liver, peripheral nerves and skin), thus contributing to diabetes complications. The harmful effects of ROS and RNS are neutralized by the endogenously expressed antioxidant enzymes (superoxide dismutases (SODs), CAT, GSH-Px) and non-enzymatic antioxidants (endogenous reduced glutathione (GSH) and exogenous vitamins C and E).[7]

3. EXPERIMENTAL MODELS OF DIABETES MELLITUS

Experimental models play an important role in understanding diabetes, as well as in evaluating the pharmacological actions of different agents. Isolated rat, mouse and human pancreatic islets are used for investigating the mechanisms involved in *β*-cell dysfunction and destruction in diabetes.[17–19] The use of primary *β*-cells in research is limited because their purification and maintenance of native characteristics is technically demanding. To overcome these limitations, investigators have produced immortalized *β*-cell lines.[20] The most widely used insulin-secreting cell lines are rat insulinoma cells (RIN and INS-1), hamster pancreatic *β*-cells (HIT) and mouse insulinoma cells (MIN and *β*TC). Although the properties of the cell lines differ slightly from those of primary *β*-cells, they are extremely valuable tools for the study of molecular events underlying *β*-cell function, including the testing of the effects of potential drugs in diabetes management.

Several animal models have been developed for *in vivo* studies of diabetes and anti-diabetic agents. Genetic models of diabetes include the spontaneous development of diabetes in rats[21,22] and genetically engineered diabetic mice to either overexpress (transgenic) or underexpress (knockout) proteins thought to play a key role in glucose metabolism.[23,24] Surgical model of diabetes include the complete removal of the pancreas (pancreatectomy) or partial pancreatectomy (more than 80 % resection in rats). These models allow for the evaluation of the effect of natural products in an animal without the interference of side effects induced by chemical drugs used to induce experimental diabetes.[25,26] However, these models are rarely used because of the highly specialized technical skills required and the high percentage of animal mortalities.

Chemical induction is the most popular procedure for inducing diabetes in experimental animals and has been proven repeatedly to be useful for the study of multiple aspects of the disease. Streptozotocin (STZ), a naturally occurring glucosamine–nitrosourea compound is the most frequently used drug for experimental diabetes induction in laboratory rats. As a glucose analogue, STZ selectively accumulates in *β*-cells *via* the glucose transporter (GLUT2). As an alkylating agent, STZ fragments DNA.[27] DNA damage induces activation of the DNA repair process that leads to enhanced ATP dephosphorylation, which supplies a substrate for xanthine oxidase, resulting in ROS formation. The diabetogenic effect of STZ also relies on its ability to liberate NO which participates in DNA damage. STZ is capable of inducing T1D either by direct *β*-cell destruction after administration of a single large dose of STZ (65–150 mg kg^{-1}),[28] or *via* an immune cell-mediated mechanism using multiple low doses of STZ (40 mg kg^{-1}).[29] A single high dose of STZ causes extensive non-physiological *β*-cell necrosis, whereas multiple low doses of STZ induce limited apoptosis, which elicits an autoimmune reaction that eliminates the remaining cells.[30] There is a general

consensus that the experimental model of multiple low-dose STZ-induced diabetes resembles more closely the *in vivo* state of insulinaemia, reflecting its autoimmune nature and resulting onset of diabetes.

4. NUMEROUS ANTIOXIDANT COMPOUNDS AND PLANT EXTRACTS IN DIABETES MANAGEMENT

A number of studies have demonstrated that treatment with antioxidants reduces oxidative stress and alleviates diabetic complications in diabetic subjects and animals.[31] Vitamins C and E, and LA are the most studied antioxidants. Vitamin C is the strongest physiological antioxidant. It regenerates vitamin E through redox cycling and increases intracellular GSH levels.[32] Small clinical trials showed that vitamin E, as well as a combination of vitamin E and C, exerted beneficial effects on the cardiovascular system in T1D patients[33,34] and improved renal function in T2D patients.[35] However, in large-scale clinical trials, *i.e.*, Heart Outcomes Prevention Evaluation (HOPE),[36] Secondary Prevention with Antioxidants of Cardiovascular Disease in End Stage Renal Disease (SPACE),[37] the Primary Prevention Project (PPP)[38] and the Study to Evaluate Carotid Ultrasound Changes in Patients Treated With Ramipril and Vitamin E (SECURE),[39] vitamin E treatment failed to provide any benefit in cardiovascular disorders or nephropathy. A multifactorial approach is more efficient than conventional therapy for the prevention of oxidative stress-induced vascular complications in diabetes.[40] Daily supplementation of vitamin C (250 mg), vitamin E (100 mg), folic acid (400 mg) and chromium picolinate (100 mg) in combination with multifactorial intensive therapy resulted in an almost 50 % decrease in cardiovascular incidents.

LA stimulates cellular glucose uptake and possesses direct radical-scavenging and metal-chelating properties, and has the ability to regenerate other antioxidants.[41] Naturally occurring LA is present in low amounts in vegetables and animal tissues where it functions as a coenzyme in pyruvate dehydrogenase and α-ketoglutarate dehydrogenase mitochondrial reactions. The most abundant plant sources of LA are spinach, followed by broccoli and tomatoes. Synthetic LA has a relatively long history of use as a nutritional supplement in European countries and the United States, and as a therapeutic agent in the treatment of diabetic neuropathy and retinopathy.[42] Studies with LA, *i.e.*, Alpha Lipoic Acid in Diabetic Neuropathy (ALADIN) I, II and III,[43–45] and Deutsche Kardiale Autonome Neuropathie (DEKAN),[46] investigated the effect of LA treatment on sensory symptoms of diabetic polyneuropathy as assessed by the Total Symptom Score (SYDNEY)[47] and meta-analysis[48] led to its approval for the treatment of diabetic neuropathy, and initial results are more promising than those obtained with vitamin E. Parallel with LA use, questions of its safety and effectiveness have been raised. A daily oral dose of 600 mg provides an optimum risk-to-benefit ratio in

human diabetics.[42] LA supplementation at higher doses causes a few serious side effects, such as gastrointestinal disorders and allergic reactions. Selection of the appropriate dose of LA for application in diabetes is critical.[49] As cholestatic hepatitis was probably caused by LA (600 mg day^{-1}) treatment of symptomatic diabetic neuropathy,[50] the authors suggest liver enzyme levels be monitored during LA treatment.

Phytochemicals, the bioactive non-nutrient plant compounds in fruit, vegetables, grains and other plant foods, have been linked to reductions in the risk of major chronic diseases. It is estimated that more than 5,000 phytochemicals have been identified, but that a large percentage remains unknown.[51] Phytochemicals with antioxidative effects include a variety of phytosterols, terpenes and especially polyphenols, such as flavonoids, tannins and phenylpropanoids. A direct correlation between the total phenolic content and antioxidant capacity was established and explained through a number of different mechanisms, such as free radical scavenging, metal ion chelation and hydrogen donation.[52–54]

There is a growing interest for the use of plant extracts because purified bioavailable phenolic compounds are difficult to obtain, and because extracts sometimes have better antioxidant activities than the pure molecules.[55] Taken alone, the individual antioxidants studied in clinical trials do not appear to have consistent diabetes-preventive effects. Studies of different fruit combinations showed greater total antioxidant activity because of their additive and synergistic relationships.[51] An isolated pure compound can lose its bioactivity or may not exhibit it in the same way as when present in whole foods. This partially explains why no single antioxidant can replace a combination of natural phytochemicals contained in plants in accomplishing health benefits. Although plants are rich in antioxidants, individual “antioxidant” molecules cannot just be extracted, packed in pills in high doses and expected to provide high levels of protection.[5] Pills or tablets cannot mimic the balanced natural combination of phytochemicals present in plants. Phytochemicals differ in molecular size, polarity, and solubility, and these differences may affect the bioavailability and distribution of each phytochemical in different macromolecules, sub-cellular organelles, cells, organs, and tissues. These observations have lead to the concept that antioxidants are better implemented through whole food consumption than as expensive dietary supplements. Further research on the health benefits of phytochemicals in whole foods is of essential interest.[56]

Many investigations have studied the effects of antioxidant components of plants on diabetes and its complications. Antioxidant and antihyperglycemic properties of *Allium cepa* L., *Anoectochilus formosanus*, *Lycium barbarum*, *Cassia fistula* L., *Aloe vera*, *Vitis aestivalis* and *Coffea arabica* in chemical models of diabetes have been demonstrated.[57–63] In addition, *Centaurium erythrea* and *Aegle marmelos* extracts and quercetin, a flavonoid antioxidant present in many

plants, alleviate STZ-induced cell damage and oxidative stress in rat pancreas.[65–66] Medicinal plants with proven antidiabetic and related beneficial effects in diabetes treatment also include: *Allium sativum*, *Eugenia jambolana*, *Momordica charantia*, *Ocimum sanctum*, *Phyllanthus amarus*, *Pterocarpus marsupium*, *Tinospora cordifolia*, *Trigonella foenum graecum* and *Withania somnifera*.[67]

5. NOVEL MECHANISM OF ANTIOXIDATIVE EFFECT OF LA IN DIABETES

Numerous studies indicate that LA exerts its antioxidant effect by increasing the endogenous defence response of cells through enhanced synthesis of endogenous low molecular weight antioxidants and antioxidant enzymes.[42] The levels of antioxidant enzymes are regulated by gene expression, as well as by post-translational modifications.[68] Emerging data indicates that the post-translational addition of *β*-*N*-acetylglucosamine (*O*-GlcNAc) to proteins has a role in the aetiology of diabetes.[69] *O*-linked glycosylation of certain proteins is increased in hyperglycaemia because of activation of the hexosamine pathway, which produces uridine-diphospho-*N*-acetylglucosamine (UDP-GlcNAc), a substrate for the glycosylation reaction. This modification is dynamic and may disturb the normal dynamic balance between *O*-GlcNAcylation and *O*-phosphorylation that controls enzyme activity, DNA binding, protein–protein interactions, the half-life of proteins and their sub-cellular localization. Elucidation of the specific roles of *O*-GlcNAc in transcription, cell signalling, glucose toxicity and insulin resistance should lead to new avenues for the diagnosis and treatment of diabetes.[69]

A novel mechanism of the antioxidant effect of LA in diabetes progression through decreased *O*-GlcNAcylation of the key proteins that are involved in redox signalling pathways was hypothesized.[70,71] In these experiments, LA was applied at a dose of 10 mg kg^{-1} i.p., which corresponds to 600 mg LA day^{-1} in humans for 4 weeks, starting from the last day of STZ administration (40 mg kg^{-1} i.p. for 5 consecutive days). These studies focused on the antioxidant defence system of red blood cells (RBC) and kidneys. RBC are exposed to some of the highest levels of oxidative stress in the body because they continuously transport oxygen and are the first cellular structures to respond to increased ROS presence. RBC damage is a reflection of the general state of oxidative stress in the whole organism.[72] In the hyperglycaemic environment, RBCs are subjected to compositional changes and are affected at the functional level.[73] In agreement with other reports, enzymatic silencing of CuZnSOD and CAT in RBC under diabetic conditions were observed,[74,75] which was associated with increased levels of *O*-GlcNAc-modification of CuZnSOD and CAT, and of the heat shock proteins HSP70 and HSP90.[70] *In vitro* studies showed that glycosylation causes a 40 % lowering of CuZnSOD activity in RBC.[76] It was shown that LA administration to diabetic rats preserved the structural and functional integrity of RBC by adjusting the redox disturbance and by decreasing the *O*-GlcNAcylation of SOD and CAT.

It was hypothesized that the induction of HSP90 and the lowering of the levels of *O*-GlcNAc-modification of HSP70 and HSP90 as a result of the LA treatment is an important defence mechanism in RBC, since HSPs monitor, protect and maintain the structure and stability of erythrocyte proteins. These results are valuable because functional and healthy RBC could delay or inhibit further diabetic complications, especially neuropathy.

The renal-protective effect of LA is associated with a reduction of oxidative stress.[77] Recently performed work revealed that LA administration activates a coordinated cytoprotective response against diabetes-induced oxidative injury in kidneys through an *O*-GlcNAc-dependent mechanism, which influences the expression and activities of CuZnSOD and CAT. The observed upregulation of the antioxidant enzyme genes during LA treatment in diabetic kidney was accompanied by nuclear translocation of the nuclear factor-erythroid-2-related factor (Nrf2), enhanced expression of HSPs and by a reduction of *O*-GlcNAcylation of HSP90 and HSP70, and of the extra-cellular regulated kinase (ERK) and p38. Under unstressed conditions, Nrf2 resides in the cytoplasm as an inactive complex bound to a repressor molecule known as Keap1 (Kelch-like ECH-associated protein 1) that facilitates its ubiquitination.[78] Upon activation, Nrf2 translocates to the nucleus where it heterodimerizes with specific cofactors and coordinates the upregulation of cytoprotective genes through the initiation of transcription at an antioxidant response element (ARE).[79] In addition, it was reported that HSP90 interaction with Keap1 can mediate Nrf2 activation.[80] LA can oxidize critical thiols on the Keap1 dimer to halt Nrf2 degradation and to prevent Keap1 from binding newly synthesized Nrf2. LA also activates the protein kinase signalling pathways that lead to the phosphorylation of Ser40 on Nrf2, allowing it to dissociate from Keap1 and to translocate to the nucleus.[42] Inhibition of nitrogen-activated kinases (MAPKs), ERK and p38 prevents the accumulation of Nrf2 in the nucleus independently of its phosphorylation.[81] It was suggested that MAPK-mediated phosphorylation of molecular chaperones or some other type of accessory protein is required for Nrf2 nuclear translocation.[82] Based on our obtained results and existing literature data, a model that illustrates the potential mechanisms by which LA ameliorates kidney damage in diabetes by inducing SOD and CAT expression is presented in Fig. 1.

6. POSITIVE EFFECTS OF *L. deterrimus* (Ld) AND *C. sativa* (Cs) EXTRACTS AND THEIR COMBINATION (MIX Ld/Cs) ON *β*-CELL SURVIVAL

Examination of compounds and factors that can regulate *β*-cell survival, growth and functioning is of great interest in the context of the prevention of diabetes development and its progress. The antioxidant properties and beneficial effects of extracts obtained from the edible mushroom *Lactarius deterrimus* (Ld), the sweet chestnut *Castanea sativa* (Cs) and their combination (MIX Ld/Cs) on STZ-induced rat pancreatic *β*-cell (Rin-5F cells) death have been described.[83,84]

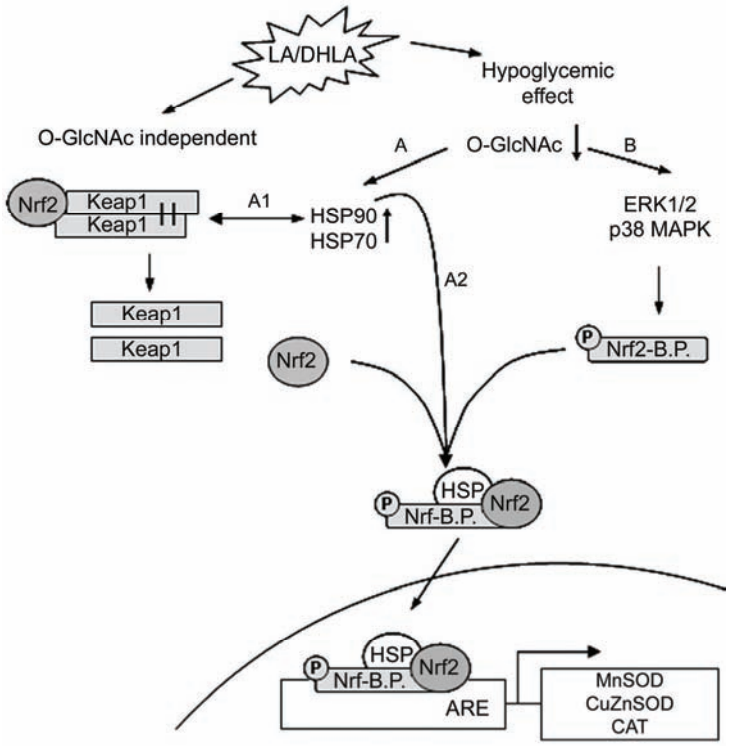

Fig. 1. Potential mechanisms of LA-regulated SOD and CAT gene expression in kidneys of diabetic rats. Pathway **A** illustrates LA-induced protein expression of HSPs and their decreased *O*-GlcNAc modifications that could influence their interaction with Keap1, causing a subsequent release of Nrf2 (**A1**) and/or formation of HSP-Nrf2 heterocomplex that translocates to the nucleus and binds ARE (**A2**), promoting the transcription of genes for MnSOD, CuZnSOD and CAT. In a LA-orchestrated *O*-GlcNAc-dependent mechanism (pathway **B**), reduced *O*-GlcNAc modification of ERK and p38 could enhance their activity. Activated ERK and p38 could phosphorylate a certain Nrf2-binding protein (Nrf2-B.P.) that could assist the nuclear translocation of Nrf2 released from Keap1.

The Cs extract exhibited a remarkably high level of antioxidant activity *in vitro*, while the Ld extract displayed good H_2O_2 and NO scavenging activities. MIX Ld/Cs demonstrated strong antioxidant effects *in vitro*, and astonishingly, a very effective Fe^{2+} chelating effect, despite the very low individual chelating activities of the Ld and Cs extracts. This is in correlation with the concept that no single antioxidant can replace the health benefits of a combination of natural phytochemicals because of their additive and synergistic effects.[51] Each extract and especially their combination increased Rin-5F cell viability after the STZ treatment as a result of a significant reduction in DNA damage and improved redox status. It is suggested that different mechanisms underlie the antioxidant effects of Cs, Ld and MIX Ld/Cs (Fig. 2). The antioxidant property of the Cs extract probably re-

lies on its ROS scavenging activity.[55,83,85,86] It directly correlates with the extremely high content of phenolic compounds, especially of hydrolysable tannins (ellagic and gallic acids and their derivatives). The beneficial biological effects of these compounds *in vivo* are related to the high free radical-scavenging activity they exhibit *in vitro*.[87] The antioxidant properties of the Ld can be explained by a strong NO scavenging activity. The low phenolic content of the Ls extract suggests that some other non-phenolic compounds or secondary metabolites[88] were responsible for its beneficial effect, such as the essential trace elements Se and Zn. Se functions as a cofactor of some antioxidant enzymes,[89] while Zn protects enzyme sulfhydryls from oxidation and reduces the formation of the hydroxyl radical from H_2O_2 by competing with redox-active transition metals.[90] It is suggested that the MIX Ld/Cs displayed the most beneficial effect on cell survival through the additive and synergistic effects of the different antioxidant activities contained in Cs and Ld extracts.[56] These results provide compelling evidence that mixtures of extracts acquire new qualities with respect to the individual extracts and individual components. This feature explains the improved antioxidant and beneficial effects that were exerted on *β*-cells.

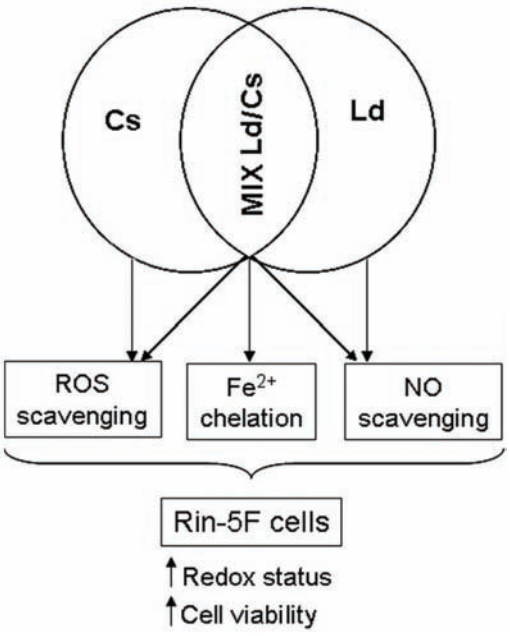

Fig. 2. Potential mechanism of Cs, Ld and MIX Ld/Cs action on the improvement of Rin-5F cell redox status and survival.

The antioxidant properties of the mushroom and chestnut extracts need to be confirmed *in vivo* on a rat model of STZ-induced diabetes (work in progress).

Duly aware of the limitations of the *in vitro* model system, it is proposed that the MIX Ld/Cs can reduce oxidative stress in β-cells and that it could thereby potentially attenuate the process that underlies the development and progression of diabetes.

7. EFFECTS OF β-GLUCANS ON DIABETES AND THE ASSOCIATED COMPLICATIONS

Natural products containing β-glucans as active components have been proposed to improve general health.[91–93] β-Glucans belong to a group of polysaccharides that are characterized by their location in the cell wall. Some microorganisms, mushrooms and cereals, such as barley and oats, are rich in β-glucans.[94] The macromolecular structure of β-glucans depends on both the source and method of isolation. The biological activities of β-glucans are determined by their primary structure, solubility, degree of branching, molecular weight, the charge on their polymers and structure in aqueous media.[95] On reviewing the literature, it became obvious that the observed effects of β-glucans and glucan-containing products are controversial.[96] While there are reports that emphasize the immune stimulatory[97,98] and pro-inflammatory effects of β-glucans,[99] as well as increased generation of ROS,[100] other studies described their free radical scavenging activities,[101] and anti-inflammatory[102] and antioxidative effects.[103] Among several mechanisms proposed for the protective effects of β-glucan, a major one is related to its antioxidant activity.[104]

β-Glucans have shown great potential in the treatment of diabetes.[92] They are effective in lowering blood glucose concentrations and decreasing hyperlipidaemia and hypertension. In addition, β-glucans also promote wound healing and alleviate ischemic heart injury. Foods containing β-glucans have been used in clinical trials in the treatment of diabetes.[105,106] Our preliminary results are based on observations obtained after treating STZ-induced diabetic rats with a comercially available β-glucan-enriched extract (80 mg kg^{-1} for four weeks, starting from the last day of STZ treatment). Treating diabetic rats with β-glucan promoted a systemic improvement that could be expected to increase the resistance of the organism to the onset of diabetic complications. The beneficial effect of the β-glucan-enriched extract against diabetes-associated liver and kidney injury was mediated through its hyperglycaemia lowering, anti-inflammatory and antioxidant actions. It was speculated that the observed properties of the applied commercial β-glucan-enriched extract could be attributed to the effects of β-glucan and other components of the preparation. Mechanisms underlying its effect on diabetes and associated complications need to be investigated using pure β-glucan.

8. CONCLUSIONS

Despite numerous strategies designed to improve different diabetes-related symptoms, the current control of diabetes-associated complications and mortality

is not satisfactory. Targeting of oxidative stress in the management of diabetes using synthetic antioxidants, such as vitamins A, C and E, yielded limited results and the presence of side effects. This has renewed interest in the therapeutic potential of bioavailable compounds, extracts and complex mixtures. Due to the relatively lower number of side effects and lower cost, naturally derived substances provide a useful source of potential novel anti-diabetogenic pharmaceutical entities and dietary supplements to existing therapies. Considering that phytochemicals can reduce the major risk factors in diabetes, such as hyperglycaemia, hyperlipidaemia and oxidative stress, the use of medicinal plants represents a promising approach for treating diabetes. It is therefore imperative to continuously identify naturally occurring products with antioxidant activities for use in the "causal" therapy of diabetes.

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И З В О Д

ПОЗИТИВНО ДЕЈСТВО АНТИОКСИДАТИВНИХ ЈЕДИЊЕЊА ИЗ БИЉНИХ ЕКСТРАКАТА У ЕКСПЕРИМЕНТАЛНОМ МОДЕЛУ ДИЈАБЕТЕСА

СВЕТЛАНА ДИНИЋ, АЛЕКСАНДРА УСКОКОВИЋ, МИРЈАНА МИХАИЛОВИЋ, НЕВЕНА ГРДОВИЋ, ЈЕЛЕНА АРАМБАШИЋ, ЈЕЛЕНА МАРКОВИЋ, ГОРАН ПОЗНАНОВИЋ И МЕЛИТА ВИДАКОВИЋ

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Терапија антиоксидансима заузима значајно место у лечењу дијабетеса с обзиром да оксидативни стрес у великој мери доприноси нарушавању функције и структуре *β*-ћелија панкреаса као и развоју компликација у дијабетесу. Због ограниченог дејства постојећих антиоксидативних једињења трага се за новим терапијским решењима у третману дијабетеса, као што је повећање ендогене антиоксидативне заштите организма путем фармаколошке модулације кључних антиоксидативних ензима. Примена биљних екстраката у лечењу дијабетеса постаје све популарнија. Многе супстанце које се налазе у саставу виших биљака и гљива поседују антиоксидативна својства која могу да заштите ткива од штетних утицаја слободних радикала. У овом ревијалном раду описани су експериментални модели дијабетеса као и могући механизми који леже у основи антиоксидативног дејства α-липонске киселине (LA), снажног антиоксиданса и једињења које стимулише ћелијску апсорпцију глукозе, као и биљних екстраката изолованих из слатког кестена (*Castanea sativa*), јестивих печурака (*Lactarius deterrimus*) и природних производа који садрже *β*-глукан у лечењу дијабетеса. Описани су њихова улога у спречавању смрти *β*-ћелија панкреаса као и благотворно дејство на компликације у дијабетесу.

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