Review Article

Relationship of Oxidative Stress as a Link between Diabetes Mellitus and Major Depressive Disorder

Gislaine Z. Réus,1 Anelise S. Carlessi,1 Ritele H. Silva,1 Luciane B. Ceretta,2 and João Quevedo1,3,4,5

1Translational Psychiatry Laboratory, Graduate Program in Health Sciences, Health Sciences Unit, University of Southern Santa Catarina, Criciúma, SC, Brazil
2Programa de Pós-graduação em Saúde Coletiva, Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil
3Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, USA
4Translational Psychiatry Program, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, USA
5Neuroscience Graduate Program, Graduate School of Biomedical Sciences, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, USA

Correspondence should be addressed to Gislaine Z. Réus; gislainezilli@hotmail.com

Received 9 November 2018; Revised 21 January 2019; Accepted 14 February 2019; Published 3 March 2019

Guest Editor: Maria Luca

Both conditions, major depressive disorder (MDD) and diabetes mellitus (DM) are chronic and disabling diseases that affect a very significant percentage of the world’s population. Studies have been shown that patients with DM are more susceptible to develop depression, when compared to the general population. The opposite also happens; MDD could be a risk factor for DM development. Some mechanisms have been proposed to explain the pathophysiological mechanisms involved with these conditions, such as excess of glucocorticoids, hyperglycemia, insulin resistance, and inflammation. These processes can lead to an increase in damage to biomolecules and a decrease in antioxidant defense capacity, leading to oxidative stress.

1. Introduction

1.1. Diabetes Mellitus. Diabetes mellitus (DM) is characterized by hyperglycemia due to changes in the production or action of insulin; the chronicity of this condition is associated with damage, dysfunction, and insufficiency of target systems such as cardiovascular and central nervous systems [1]. The physiopathology of DM is related to changes in β-pancreatic cells that compromise the synthesis and secretion of insulin, together with resistance to the action of insulin in peripheral tissues. Insulin secretion is controlled by several factors, including nutrients, hormones, and neural factors [2]. One of the roles of insulin is to influence inflammatory reactions by it acting on oxidative stress and in the release of cytokines [3]. The inflammatory component in the physiopathology of DM is evidenced by the involvement of the factor nuclear kappa B (NF-κB), which is one of the transcription factors that control the production of proinflammatory cytokines. The NF-κB pathway binds the inflammatory and metabolic responses and represents a point of connection for a better understanding of metabolic diseases [4]. In addition, chronic conditions of low-grade inflammation appear to play an important role in the pathogenesis of renal failure, one of the consequences of DM [5]. Hyperglycemia, a frequent condition in DM, is related to cellular and tissue damage, due to changes in cell signaling, gene transcription, and protein and lipid changes [6].

1.2. Major Depressive Disorder. Major depressive disorder (MDD) has high morbidity, and nearly 350 million people are affected worldwide. The physiopathological mechanism is not widely understood, but is believed to have a
multifactorial origin, involving dysfunction in multiple brain areas such as the hippocampus, prefrontal cortex, nucleus accumbens, and amygdala [7]. Moreover, MDD pathophysiology is associated to an inflammatory process due to microglial activation, elevated cytokine release, and increased oxidative stress, with astrocyte atrophy and alteration in glutamatergic system regulation, which may lead to local damage [8]. These processes may also activate the enzyme indoleamine 2,3-dioxxygenase, diverting tryptophan to the kynurenine pathway, causing the production of active neurotoxic metabolites [9]. In fact, it is known that microglial cells regulate the activation and progression of several neuroimmune pathways that are mediated by macrophages, growth factors, cytokines, and others. In addition, they also initiate the formation of intracellular multiprotein complexes, the inflammasomes, which in turn cleave precursor forms of interleukin-1β (IL-1β) in its active form [10]. The inflammatory process, when exacerbated, can cause a significant increase in the production and expression of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-1β, as well as reactive species of oxygen (ROS) and nitric oxide, contributing to the neuroinflammatory and neurodegenerative processes associated with psychiatric disorders, including MDD [11]. In another recent study, it was identified that MDD, associated or not to posttraumatic stress disorder, presents changes in the cytokines and increased oxidative stress [12], thus demonstrating that the association of several factors contributes to the pathophysiology of MDD.

1.3. Oxidative Stress. The term oxidative stress is used to characterize the imbalance between the production of ROS and antioxidant defenses. Elevated levels of ROS cause damage to lipids, proteins, and DNA [13], and it is associated with several diseases including cancer, DM, cardiovascular, neurodegenerative diseases, and MDD [14].

Under normal physiological conditions, there is formation of ROS and reactive nitrogen species (RNS) that act as messengers and also regulate intracellular signal transduction pathways involved with survival and cell death, being removed by several mechanisms of antioxidant defense, such as catalase and superoxide dismutase enzymes [15]. However, when in excess, they are harmful to the metabolism, mainly because of being able to inactivate important cellular molecules which are necessary for the regulation and homeostasis [16]. Antioxidants are a defense system for the body against these and all free radicals. They act by eliminating or by preventing their transformation into products that are less toxic to cells [17].

There is an important relationship between some diseases and oxidative stress, because they participate in vital processes, such as inflammation, glucose homeostasis, and cell survival [18]. In DM, hyperglycemia induces increased oxidative stress through several biochemical processes [19], including the glucose self-activation, increase of glycation and diacylglycerol, and the activation of protein kinase C and polyol pathways. Also, this process causes the progression and complications of DM due to increased free radicals and decreased antioxidant enzymes leading to an increase in lipid peroxidation [20]. A significant increase in oxidative stress in diabetic patients compared to controls was observed, but this change appears to be more evident during disease progression and complications [21, 22].

Oxidative stress also may be related to some psychiatric disorders. There is evidence that in the MDD patients, excess of ROS may be a relevant mechanism related to immune activation [23], increased oxidation of monoaminergic neurotransmitters [24], and lipid peroxidation [25]. Furthermore, in MDD there is also a decrease in important antioxidant substances as well as a lower activity of the antioxidant enzymes [26].

1.4. Diabetes Mellitus, Major Depressive Disorder, and Oxidative Stress. Studies have shown that patients with DM have a higher risk to develop MDD, when compared to the general population [27–30]. Patients with MDD, as well as the use of antidepressant drugs, could be risk factors for the development of DM [31–34]. In addition, depression in patients with DM is a major cause of poor self-care, which are very important for these patients to avoid future complications, for example, renal, ocular, and neurological damage [35].

It is believed that the glucose accumulation in the extracellular space due to DM can cross the blood brain barrier (BBB) and affect specific brain areas involved with memory and mood regulation [36, 37]. On the other hand, MDD may be correlated with insulin resistance due to higher levels of glucocorticoid and a decrease in insulin sensitivity [38, 39]. It was proposed by Watson [40] that DM and other diseases such as cancer and dementias are accelerated or caused by failure of the endoplasmic reticulum to generate sufficient oxidative redox potential for disulphide bonds to be formed. Indeed, genomics, epigenomics, and exposomics methods are suggested to characterize redox components and their functional organization in health and disease [41].

The pathophysiological mechanism involved when both DM and MDD are together is still not clear. One of these mechanisms could be related to the oxidative stress (Table 1). In fact, oxidative stress plays an important role in the development and progression of DM due to higher free radical production, damage to cell constituents, and impairment in the antioxidant defense enzymes, such as superoxide dismutase and catalase [42, 43]. MDD also is characterized by activated oxygen and nitrogen species pathways, leading to lipid, protein, and DNA damage [44–47].

Experimental studies have been shown that alloxan-diabetic rats displayed a depressive-like behavior in the forced swimming test [48, 49], while the treatment with the antidepressant imipramine [48] and with the antioxidant N-acetylcysteine (NAC) [49] was able to reverse the depressive-like behavior, thus showing that both antidepressant and antioxidant could improve depressive behavior induced by the animal model of diabetes. The treatment with clonazepam, a positive GABA<sub>α</sub> receptor modulator, alone or in combination with insulin also reversed the depressive-like behavior in diabetic rats [50–52]. Interestingly, the treatment with insulin and clonazepam was able to restore the antioxidant status in the brain of diabetic rats [52]. A study carried
out by Tang et al. [53] demonstrated that hydrogen sulfide (H2S), a signaling molecule in the brain, with antioxidant activity was able to reverse the depressive-like behavior in streptozotocin- (STZ-) induced diabetic rats. The authors suggested that this behavioral change was associated to a reduction in oxidative stress in the hippocampus. Recently, Shivavedi et al. [54] showed that a combination treatment with metformin and ascorbic acid reduced the depressive-like behavior, oxidative stress and inflammation, and elevated monoamine levels in STZ-induced diabetic rats. It was suggested that the antidepressant effects exerted by metformin and ascorbic acid in diabetic rats were associated with a reduction in blood glucose and oxidative stress and increased plasma insulin levels [54]. Ascorbic acid, a natural antioxidant, was proposed as a potential strategy against comorbid depression-like behavior in diabetic rats. It was revealed that ascorbic acid treatment reduced the depressive behavior in STZ-nicotinamide-induced diabetic rats [55]. Also, it was demonstrated that ascorbic acid reduced oxidative stress, hyperglycemia, and inflammation [55, 56]; on the other hand, positive results with Aloe vera treatment were found, which has antioxidant, neuroprotective, and anti-diabetic effects. The study revealed that Aloe vera displayed antidepressant effects in STZ-induced diabetic rats, and these effects were suggested to be related to hypoglycemic and antioxidant properties of Aloe vera in the hippocampus [56].

Some studies have reported a potential therapeutic for ebselen, a glutathione peroxidase mimetic and which can contribute to regulation of cell function [57, 58]. Experimental studies revealed that treatment with ebselen reduced diabetes-associated atherosclerosis in apolipoprotein E/GPx1 double-knockout mouse [59], prevented islet apoptosis, and preserved the β-cell mass and function in Zucker diabetic fatty (ZDF) rats [60]. Also, ebselen treatment in human erythrocytes from patients with uncontrolled diabetes exerted glycation-inhibiting properties [61]. Contrarily, a randomized, crossover trial with DM patients did not show improvement in the oxidative stress profile and it did not affect the endothelium-dependent vasodilation [62]. There are no studies evaluating the effects of ebselen in depression; however, a study demonstrated that ebselen due to its capacity to inhibit the inositol monophosphatase could be an alternative treatment for bipolar disorder, comparable to lithium [58]. Future studies evaluating the efficacy of ebselen in depression and DM comorbidity could be interesting.

A human study with MDD and bipolar disorder patients revealed no association with mood disorder symptoms and insulin resistance or increased glucose toxicity [63]. However, the same study demonstrated effects for severity of mood disorders on glucose levels and in the number of mood episodes on glucose toxicity. In addition, β-cell function and insulin resistance were associated with immune-inflammatory, ROS, and RNS pathways, which in turn induced glucose toxicity [63]. Contrarily, a recent cohort study revealed that higher levels of systemic oxidative stress, marked by DNA/RNA damage from oxidation (8-oxodG/8-oxoGuo) in patients with DM, were not associated with higher risk for psychiatric diseases, such as unipolar depression, anxiety, bipolar disorder, and schizophrenia [64]. Discrepancies in these studies may be related to the type of marker studied, study time, and psychiatric disorder conditions analyzed.

2. Conclusion

The imbalance between ROS formation and the antioxidant system can result in several pathological alterations that are related to both psychiatric and metabolic diseases, and these changes are evident mainly in progressive and chronic pathologies such as DM and MDD. Although few studies have evaluated the relationship of oxidative stress when MDD and DM are present in the same patient, oxidative stress oxidative redox potential may be the key factor in triggering comorbidities such as MDD associated with DM and vice versa; nevertheless, many other factors such as inflammation, hyperglycemia, and insulin

| Species/model | Damage | Antioxidant effect | Reference |
|---------------|--------|------------------|-----------|
| Alloxan-diabetic rats | Depressive behavior | N-Acetylcysteine and imipramine displayed antidepressant effects | [48, 49] |
| Diabetic rats | Depressive behavior and oxidative stress | Clonazepam and insulin reversed the depressive behavior and restored the antioxidant status | [50, 52] |
| STZ-diabetic rats | Depressive behavior | Hydrogen sulfide induced antidepressant effects | [53] |
| STZ-diabetic rats | Depressive behavior, oxidative stress, and inflammation | Metformin plus ascorbic acid reduced the depressive behavior and had antioxidant and anti-inflammatory effects | [54] |
| STZ-nicotinamide-diabetic rats | Depressive behavior | Ascorbic acid had antidepressant effects, reduced oxidative stress, and inflammation | [55, 56] |
| STZ-diabetic rats | Depressive behavior | Aloe vera displayed antidepressant, antioxidant, and anti-diabetic effects | [56] |
| MDD and bipolar disorder patients | Severity of symptoms was associated to glucose levels and the number of episodes to glucose toxicity | — | [63] |
resistance are also involved, although all these conditions increase the levels of oxidative stress.

Further studies evaluating medications with antidepressant and antioxidant effects that can reduce oxidative stress may be clinically important to prevent comorbid MDD in DM condition.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The Translational Psychiatry Program (USA) is funded by the Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth). Translational Psychiatry Laboratory (Brazil) is one of the members of the Center of Excellence in Applied Neurosciences of Santa Catarina (NENASC). Its research is supported by grants from CNPq (JQ and GZR), FAPESC (JQ and GZR), Instituto Cérebro e Mente (JQ and GZR), and UNESC (JQ and GZR). JQ is a 1A CNPq Research Fellow.

References

[1] A. Uazman, O. Asghar, A. Chazli, and A. M. Rayaz, “Aspectos gerais do diabetes mellitus,” Manual de Neurologia Clinica, vol. 126, no. 15, pp. 211–222, 2014.

[2] D. S. Carvalho, A. A. de Almeida, A. F. Borges, and D. Vannucci Campos, “Treatments for diabetes mellitus type II: new perspectives regarding the possible role of calcium and cAMP interaction,” European Journal of Pharmacology, vol. 830, pp. 9–16, 2018.

[3] Q. Y. Qiu, B. L. Zhang, M. Z. Zhang et al., “Combined influence of insulin resistance and inflammatory biomarkers on type 2 diabetes: a population-based prospective cohort study of inner Mongolians in China,” Biomedical and Environmental Sciences, vol. 31, no. 4, pp. 300–305, 2018.

[4] Y. Lin, S. Ye, Y. He, S. Li, Y. Chen, and Z. Zhai, “Short-term insulin intensive therapy decreases MCP-1 and NF-kB expression of peripheral blood monocyte and the serum MCP-1 concentration in newlydiagnosed type 2 diabetics,” Archives of Endocrinology and Metabolism, vol. 62, pp. 212–220, 2018.

[5] Q. Zhang, W. Fang, L. Ma, Z. D. Wang, Y. M. Yang, and Y. Q. Lu, "VEGF levels in plasma in relation to metabolic control, inflammation, and microvascular complications in type-2 diabetes: a cohort study," Medicine, vol. 97, no. 15, article e0415, p. 15, 2018.

[6] J. H. P. Barbosa, S. L. d. Oliveira, and L. T. e. Seara, "Produtos da glicação avançada dietéticos e as complicações crônicas do diabetes," Revista de Nutrição, vol. 22, no. 1, pp. 113–124, 2009.

[7] F. N. Kaufmann, A. P. Costa, G. Ghisleni et al., "NLRP3 inflammasome-driven pathways in depression: clinical and preclinical findings," Brain, Behavior, and Immunology, vol. 64, pp. 367–383, 2017.

[8] A. Halasir and B. E. Leonard, "Modern trends in pharmacopsychiatry," Neuroproggression in Psychiatric Disorders Basel, Karger, vol. 31, pp. 27–36, 2017.

[9] G. Z. Réus, R. H. Silva, A. B. de Moura et al., “Early maternal deprivation induces microglial activation, alters glial fibrillary acidic protein immunoreactivity and indoleamine 2,3-dioxygenase during the development of offspring rats,” Molecular Neurobiology, vol. 5, no. 10, pp. 018–1161, 2018.

[10] G. Singhal, E. J. Jaehne, F. Corrigan, C. Toben, and B. T. Baune, “Inflammasomes in neuroinflammation and changes in brain function: a focused review,” Frontiers in Neuroscience, vol. 8, p. 315, 2014.

[11] G. Singhal and B. T. Baune, “Microglia: an Interface between the loss of neuroplasticity and depression,” Frontiers in Cellular Neuroscience, vol. 11, p. 270, 2017.

[12] E. A. Oglodek and M. J. Just, “The association between inflammatory markers (iNOS, HO-1, IL-33, MIP-1β) and depression with and without posttraumatic stress disorder,” Pharmacological Reports, vol. 70, no. 6, pp. 1065–1072, 2018.

[13] H. Sies, Oxidative Stress: Introductory Remarks, Academic Press Inc., 1985.

[14] T. Finkel and N. J. Holbrook, “Oxidants, oxidative stress and the biology of ageing,” Nature, vol. 408, no. 6809, pp. 239–247, 2000.

[15] F. Locatelli, B. Canaud, K.-U. Eckardt, P. Stenvinkel, C. Wanner, and C. Zoccali, “Oxidative stress in end-stage renal disease: an emerging threat to patient outcome,” Nephrology, Dialysis, Transplantation, vol. 18, no. 7, pp. 1272–1280, 2003.

[16] H. Sies, Oxidative Stress: Oxidants and Antioxidants, Academic Press Inc., 1991.

[17] H. Sies, “Strategies of antioxidant defense,” European Journal of Biochemistry, vol. 215, no. 2, pp. 213–219, 1993.

[18] G. S. Dave and K. Kalia, “Hyperglycemia induced oxidative stress in type-1 and type-2 diabetic patients with and without nephropathy,” Cellular and Molecular Biology, vol. 53, no. 5, pp. 68–78, 2007.

[19] R. Rajendran, R. Garva, M. Krstic-Demonacos, and C. Demonacos, “Sirtuins: molecular traffic lights in the cross-road of oxidative stress, chromatin remodeling, and transcription,” Journal of Biomedicine and Biotechnology, vol. 2011, 17 pages, 2011.

[20] T. Nishikawa, D. Edelstein, X. L. du et al., “Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage,” Nature, vol. 404, no. 6779, pp. 787–790, 2000.

[21] A. Malik, R. K. Morya, S. K. Bhadada, and S. Rana, “Type 1 diabetes mellitus: complex interplay of oxidative stress, cytokines, gastrointestinal motility and small intestinal bacterial overgrowth,” European Journal of Clinical Investigation, vol. 48, no. 11, article e13021, 2018.

[22] W. T. Hsu, L. Y. Tsai, S. K. Lin, J. K. Hsiao, and B. H. Chen, “Effects of diabetes duration and glycemic control on free radicals in children with type 1 diabetes mellitus,” Annals of Clinical and Laboratory Science, vol. 36, no. 2, pp. 174–178, 2006.

[23] P. Palta, L. J. Samuel, E. R. Miller III, and S. L. Sontan, “Depression and oxidative stress: results from a meta-analysis of observational studies,” Psychosomatic Medicine, vol. 76, no. 1, pp. 12–19, 2014.

[24] J. M. Gutteridge, “Lipid peroxidation and antioxidants as biomarkers of tissue damage,” Clinical Chemistry, vol. 41, 12, Part 2, pp. 1819–1828, 1995.

[25] A. Sarandol, E. Sarandol, S. S. Eker et al., “Oxidation of apolipoprotein B-containing lipoproteins and serum...
paraoxonase/arylesterase activities in major depressive disorder,” *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 30, no. 6, pp. 1103–1108, 2006.

[26] M. Maes, N. de Vos, R. Pioli et al., “Lower serum vitamin E concentrations in major depression. Another marker of lowered antioxidant defenses in that illness,” *Journal of Affective Disorders*, vol. 58, no. 3, pp. 241–246, 2000.

[27] G. Z. Réus, M. A. B. dos Santos, A. P. Strassi, H. M. Abelaira, L. B. Ceretta, and J. Quevedo, “Pathophysiological mechanisms involved in the relationship between diabetes and major depressive disorder,” *Life Sciences*, vol. 183, pp. 78–82, 2017.

[28] H. S. Dhavale, V. Panikkar, B. S. Jadhav, M. Ghulghule, and A. D. Agari, “Depression and diabetes: impact of antidepressant medications on glycaemic control,” *Journal of the Association of Physicians of India*, vol. 61, no. 12, pp. 896–899, 2013.

[29] E. H. B. Lin, C. M. Rutter, W. Katon et al., “Depression and advanced complications of diabetes: a prospective cohort study,” *Diabetes Care*, vol. 33, no. 2, pp. 264–269, 2010.

[30] S. Ali, M. A. Stone, J. L. Peters, M. J. Davies, and K. Khunti, “The prevalence of co-morbid depression in adults with type 2 diabetes: a systematic review and meta-analysis,” *Diabetic Medicine*, vol. 23, no. 11, pp. 1165–1173, 2006.

[31] R. R. Rubin, Y. Ma, D. G. Marrero et al., “Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program,” *Diabetes Care*, vol. 31, no. 3, pp. 420–426, 2008.

[32] A. Pan, M. Lucas, Q. Sun et al., “Bidirectional association between depression and type 2 diabetes mellitus in women,” *Archives of Internal Medicine*, vol. 170, no. 21, pp. 1884–1891, 2010.

[33] F. Andersohn, R. Schade, S. Suisse, and E. Garbe, “Long-term use of antidepressants for depressive disorders and the risk of diabetes mellitus,” *The American Journal of Psychiatry*, vol. 166, no. 5, pp. 591–598, 2009.

[34] C. Carney, “Diabetes mellitus and major depressive disorder: an overview of prevalence, complications, and treatment,” *Depression and Anxiety*, vol. 7, no. 4, pp. 149–157, 1998.

[35] E. H. B. Lin, W. Katon, M. von Korff et al., “Relationship of depression and diabetes self-care, medication adherence, and preventive care,” *Diabetes Care*, vol. 27, no. 9, pp. 2154–2160, 2004.

[36] M. W. Schwartz, D. P. Figlewicz, D. G. Baskin, S. C. Woods, and D. Porte Jr., “Insulin in the brain: a hormonal regulator of energy balance,” *Endocrine Reviews*, vol. 13, no. 3, pp. 387–414, 1992.

[37] M. Barber, B. S. Kasturi, M. E. Austin, K. P. Patel, S. M. J. MohanKumar, and P. S. MohanKumar, “Diabetes-induced neuroendocrine changes in rats: role of brain monoamines, insulin and leptin,” *Brain Research*, vol. 964, no. 1, pp. 128–135, 2003.

[38] C. Tsigos and G. P. Chrousos, “Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress,” *Journal of Psychosomatic Research*, vol. 53, no. 4, pp. 865–871, 2002.

[39] N. Vogelzangs, K. Suthers, L. Ferrucci et al., “Hypercortisolismic depression is associated with the metabolic syndrome in late-life,” *Psychoneuroendocrinology*, vol. 32, no. 2, pp. 151–159, 2007.

[40] J. D. Watson, “Type 2 diabetes as a redox disease,” *Lancet*, vol. 383, no. 9919, pp. 841–843, 2014.

[41] H. Sies, C. Berndt, and D. P. Jones, “Oxidative stress,” *Annual Review of Biochemistry*, vol. 86, no. 1, pp. 715–748, 2017.

[42] A. Ceriello, “New insights on oxidative stress and diabetic complications may lead to a “causal” antioxidant therapy,” *Diabetes Care*, vol. 26, no. 5, pp. 1589–1596, 2003.

[43] L. B. Ceretta, G. Z. Réus, H. M. Abelaira et al., “Increased oxidative stress and imbalance in antioxidant enzymes in the brains of alloxan-induced diabetic rats,” *Experimental Diabetes Research*, vol. 2012, Article ID 302682, 8 pages, 2012.

[44] S. Moylan, M. Berk, O. M. Dean et al., “Oxidative & nitrosative stress in depression: why so much stress?,” *Neuroscience & Biobehavioral Reviews*, vol. 45, pp. 46–62, 2014.

[45] M. Maes, P. Galecki, Y. S. Chang, and M. Berk, “A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness,” *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 35, no. 3, pp. 676–692, 2011.

[46] Z. M. Ignácio, G. Z. Réus, H. M. Abelaira et al., “Acute and chronic treatment with quetiapine induces antidepressant-like behavior and exerts antidepressant effects in the rat brain,” *Metabolic Brain Disease*, vol. 32, no. 4, pp. 1195–1208, 2017.

[47] G. Z. Réus, A. L. Maciel, H. M. Abelaira et al., “o-3 and folic acid act against depressive-like behavior and oxidative damage in the brain of rats subjected to early- or late-life stress,” *Nutrition*, vol. 53, pp. 120–133, 2018.

[48] L. B. Ceretta, G. Z. Réus, R. B. Stringari et al., “Imipramine treatment reverses depressive-like behavior in alloxan-diabetic rats,” *Diabetes/Metabolism Research and Reviews*, vol. 28, no. 2, pp. 139–144, 2012.

[49] G. Z. Réus, M. A. B. dos Santos, H. M. Abelaira et al., “Antioxidant treatment ameliorates experimental diabetes-induced depressive-like behaviour and reduces oxidative stress in brain and pancreas,” *Diabetes/Metabolism Research and Reviews*, vol. 32, no. 3, pp. 278–288, 2016.

[50] C. A. Y. Wayhs, V. Manfredini, A. Sitta et al., “Protein and lipid oxidative damage in streptozotocin-induced diabetic rats submitted to forced swimming test: the insulin and clonazepam effect,” *Metabolic Brain Disease*, vol. 25, no. 3, pp. 297–304, 2010.

[51] C. A. Y. Wayhs, C. P. Mescka, C. S. Vanzin et al., “Brain effect of insulin and clonazepam in diabetic rats under depressive-like behavior,” *Metabolic Brain Disease*, vol. 28, no. 4, pp. 563–570, 2013.

[52] C. A. Y. Wayhs, C. P. Mescka, G. Guerreiro et al., “Diabetic encephalopathy-related depression: experimental evidence that insulin and clonazepam restore antioxidant status in rat brain,” *Cell Biochemistry and Function*, vol. 32, no. 8, pp. 711–719, 2014.

[53] Z. J. Tang, W. Zou, J. Yuan et al., “Antidepressant-like and anxiolytic-like effects of hydrogen sulfide in streptozotocin-induced diabetic rats through inhibition of hippocampal oxidative stress,” *Behavioural Pharmacology*, vol. 26, no. 5, pp. 427–435, 2015.

[54] N. Shivavedi, M. Kumar, G. N. V. C. Tej, and P. K. Nayak, “Metformin and ascorbic acid combination therapy ameliorates type 2 diabetes mellitus and comorbid depression in rats,” *Brain Research*, vol. 1674, no. 1674, pp. 1–9, 2017.

[55] N. Shivavedi, G. N. V. Charan Tej, K. Neogi, and P. K. Nayak, “Ascorbic acid therapy: a potential strategy against comorbid depression-like behavior in streptozotocin-nicotinamide-induced diabetic rats,” *Biomedicine & Pharmacotherapy*, vol. 109, pp. 351–359, 2019.
[56] S. R. F. Tabatabaei, S. Ghaderi, M. Bahrami-Tapehebur, Y. Farbood, and M. Rashno, “Aloe vera gel improves behavioral deficits and oxidative status in streptozotocin-induced diabetic rats,” Biomedicine & Pharmacotherapy, vol. 96, pp. 279–290, 2017.

[57] N. Noguchi, “Ebselen, a useful tool for understanding cellular redox biology and a promising drug candidate for use in human diseases,” Archives of Biochemistry and Biophysics, vol. 595, pp. 109–112, 2016.

[58] N. Singh, A. C. Halliday, J. M. Thomas et al., “A safe lithium mimetic for bipolar disorder,” Nature Communications, vol. 4, no. 1, p. 1332, 2013.

[59] P. Chew, D. Y. C. Yuen, N. Stefanovic et al., “Antiatherosclerotic and renoprotective effects of ebselen in the diabetic apolipoprotein E/GPx1-double knockout mouse,” Diabetes, vol. 59, no. 12, pp. 3198–3207, 2010.

[60] J. Mahadevan, S. Parazzoli, E. Oseid et al., “Ebselen treatment prevents islet apoptosis, maintains intranuclear Pdx-1 and MafA levels, and preserves β-cell mass and function in ZDF rats,” Diabetes, vol. 62, no. 10, pp. 3582–3588, 2013.

[61] J. C. M. Soares, V. Folmer, J. B. T. da Rocha, and C. W. Nogueira, “Ebselen exhibits glycation-inhibiting properties and protects against osmotic fragility of human erythrocytes in vitro,” Cell Biology International, vol. 38, no. 5, pp. 625–630, 2014.

[62] J. A. Beckman, A. B. Goldfine, J. A. Leopold, and M. A. Creager, “Ebselen does not improve oxidative stress and vascular function in patients with diabetes: a randomized, crossover trial,” American Journal of Physiology. Heart and Circulatory Physiology, vol. 311, no. 6, pp. H1431–H1436, 2016.

[63] K. Landucci Bonifácio, D. Sabbatini Barbosa, E. Gastaldello Moreira et al., “Indices of insulin resistance and glucotoxicity are not associated with bipolar disorder or major depressive disorder, but are differently associated with inflammatory, oxidative and nitrosative biomarkers,” Journal of Affective Disorders, vol. 222, pp. 185–194, 2017.

[64] A. Jorgensen, V. Siersma, A. S. Davidsen et al., “Markers of DNA/RNA damage from oxidation as predictors of a registry-based diagnosis of psychiatric illness in type 2 diabetic patients,” Psychiatry Research, vol. 259, pp. 370–376, 2018.