International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Consequences and Therapeutics of Reactive Oxygen Species (ROS) in Depression- A Systematic Review

Vanita Jamba[1], Bijay Pattnaik[2], Sandesh Chibber[3]

[1]PhD Scholar, Department of Science, Ganpat University
[2]Manager, Research and Development, Meril Life sciences India Pvt. Ltd.
[3]Assistant Professor, Department of Science, Ganpat University

Abstract
Depression, a prevalent psychiatric disorder, affects 15% of the population and up to one-sixth of the general population. Research suggests a relationship between stress and depressive episodes, with most severe events leading to depression within the first month. The monoamine hypothesis suggests depression is caused by decreased functioning in noradrenaline and/or serotonin, but this symmetry is incorrect due to differences in neural bases. Reactive oxygen species (ROS) are crucial in human physiological and pathological processes, causing irreversible functional changes or destruction. Treatments for ROS have been effective in treating conditions like Chronic Respiratory Syndrome, depression, and oxidative stress. Research shows that ROS can cause alterations in cellular metabolic activities and can be reduced in various ways. Further research is needed to understand ROS and its potential as a biomarker and treatment agent.

Keywords: Reactive Oxygen Species (ROS), Depression, Antidepressants, NADPH oxidase, Major Depressive Disorder (MDD), antioxidants, Oxidative stress

1. INTRODUCTION

Depression and Antidepressants

Depression, a prevalent psychiatric disorder, affects 15% of the population and up to one-sixth of the general population. Despite its high prevalence, the etiology remains unknown. Heritability estimates show a 50% genetic component, with environmental influences increasing susceptibility. Technological advances offer hope for identifying the genetic basis of mental illness [1].

Research indicates a relationship between stress and depressive episodes, primarily based on episodic stressors with negative content. Studies typically assess events within three to six months, with most severe events leading to depression within the first month [2].

The monoamine hypothesis suggests depression is caused by decreased functioning in noradrenaline and/or serotonin, which antidepressants restore to normal. However, this symmetry is incorrect as there are differences in the neural bases of depression and antidepressant action. Therefore, separate examination is needed for depression neurobiology and antidepressant action mechanisms [3].

Reactive Oxygen Species (ROS)

Reactive oxygen species (ROS) are crucial in human patho-physiological processes, causing irreversible

functional changes or destruction. Initially believed to be linked to diseases, they can be produced in various forms, including mitochondrial metabolism, and can cause premature electron exit, especially under pathological conditions [4].

ROS plays crucial role not only in oxidative stress but also in promoting inflammation [5]. Oxidative stress is related to various diseases like atherosclerosis, cardiovascular and neurodegenerative diseases [6].

ROS can be produced through various biochemical pathways, including, the NADPH oxidase (NOX) enzyme family, mitochondria, flavoenzyme, xanthine oxidase, cyclo-oxygenases, cytochrome p450 enzymes, lipoxygenases, flavin-dependent demethylase, oxidases for polyamines and amino acids, and nitric oxide synthases are key contributors. Biological sources of singlet oxygen include phagocyte enzyme myeloperoxidase and NOX [7].

It has been observed that the ROS also produced exogenous by ultraviolet light, ionizing radiation, and pollutants. They can amplify initial ionization events and can be generated by environmental agents, including non-DNA reactive carcinogens, leading to DNA damage and cell death [7].

H_2O_2 (hydrogen peroxide) and O_2^- (oxygen anion) are key oxidants in redox signalling, impacting gene transcription and cell homeostasis. Understanding their species and production rates is crucial for developing redox-based therapies. Accurate oxidant definitions and real-time imaging techniques are needed to modify mechanisms like antioxidant defences, mitochondrial biogenesis, cell quality control, and hypoxia adaptation [8].

2. Method

Inclusion criteria

PubMed is used as an electronic database for the screening of relevant studies from Jan 2000 to March 2025. Abstracts and full texts were reviewed properly for the information regarding eligibility criteria, excluding the texts not related to reactive oxygen species and also the ones having language other than English.

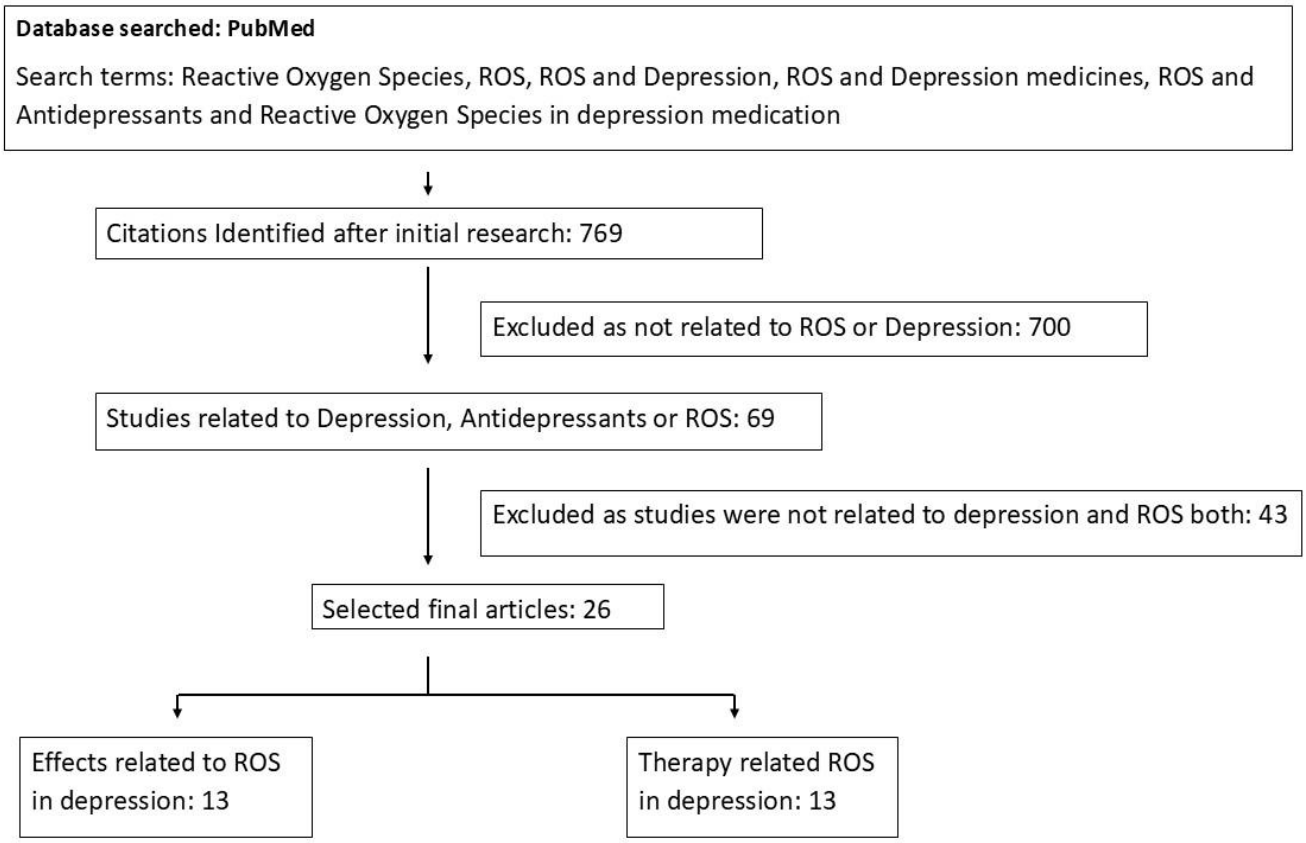
Search strategy

A systematic search of the PubMed database was performed to extract relevant studies using the following search terms: “Reactive Oxygen Species”, “ROS”, “ROS and Depression”,” ROS and Depression medicines”, “ROS and Antidepressants” and “Reactive Oxygen Species in depression medication.” Full text of the qualifying articles was retrieved and studied in detail.

3. Results

The initial search revealed total 769 studies, of which 700 studies were excluded as those were not related to reactive oxygen species and depression. Maximum articles were excluded just by screening their titles of the articles. Further, out of 69, 34 studies were excluded as there were was no specification about depression, ROS and oxidative stress. 35 studies were included as it showed the relevance with depression and ROS. Moreover, among these studies the effects of ROS and therapy related to ROS were included. The flow diagram of study screening and selection is shown in figure 1.

Fig 1- Methodology of a systematic review of the literature regarding role of ROS in depression medication.



Effects of ROS

Table 1, shows the studies which includes the effects of ROS in patients/ animal models/ cell cultures coming under depression. Cardiovascular health issues are seen, when T cell mitochondrial ROS increases in adults suffering from depression [9]. Patients falling under major depression category shows imbalances in neuroprotective factors, antioxidants, prooxidants, proinflammatory molecules and reactive species, which could result in damage of proteins, lipids, nucleic acids, thus triggering the autoimmune and inflammatory responses. This could be controlled by proper dietary intake [6]. Changes seen in neurocognitive dysfunctions could be early manifestation of dementia in elder people suffering from major depression. Recent studies have also revealed the changes in ROS, autoimmunity, apoptosis and neurogenesis [10].

Microglial changes were seen in the major depressive disorder (MDD) patients, where ROS plays crucial role in eliminating the pathogenic threats in the brain, but the balance between ROS and antioxidant seen disrupted in MDD patients, that could lead to neuronal death. Finally, results in microglial activation and ROS production [11]. Depression and anxiety might be linked to alteration in oxidative stress, as in this population-based study it was found a strong association between depression and prooxidant-antioxidant balance (PAB) [12].

Hippocampus region of brain responsible for the learning and memory, could play an important role in onset of psychiatric illness. Moreover, mitochondrial dysfunction could lead to Post Traumatic Stress Disorder (PTSD) [13]. Decrease in succinate dehydrogenase activity in peripheral blood mononuclear

cells in depressed bipolar patients was noted that could result in oxidative damage that could lead to the damage of proteins and lipids, and altered levels of antioxidant enzymes in submitochondrial particles [14].

A prenatal exposure to titanium oxide nanoparticles decreases the brains antioxidant enzyme levels, that further leads to the oxidative damage, which reveals that stress during fetal life may contribute to adult issues [15]. Depression patients showed elevated level of mitochondrial DNA damage in their peripheral blood mononuclear cells. Thus, oxidative stress induced mitochondrial DNA damage [16]. Serum starvation in mammalian cell cultures resulted in decrease in NADH-ubiquinone oxidoreductase activity, which thus caused ROS production that leads to accumulation in mitochondria [17]. Due to impaired DNA repair pathways in depression patients, showed high levels of DNA breaks, alkali-labile sites and oxidative damage [18]. One of the studies reveals that central administration of H_2S in the Rostral Ventrolateral Medulla (RVLM) decreases NADPH oxidase phosphorylation, activity, and $O_2^{\cdot-}$ production, reducing Mean Arterial Blood Pressure (MAP) and heart rate in hypertensive rats, but not conclusive [19]. Neuromuscular junctions in frog revealed that hydroxyl radicals play a role in the synergistic interaction between Fe^{2+} and H_2O_2 in the reduction of synaptic transmission [20].

Table 1: Effects of ROS on cell cultures, animal models and humans

Sr. No.	Title	Effects of ROS	Reference
1	Augmented T cell mitochondrial reactive oxygen species in adults with major depressive disorder	Significant increases in T cell mitochondrial ROS in young healthy adults with metabolic syndrome and Major Depressive Disorder (MDD), indicating alterations in T cell mitochondrial health, suggests immune dysregulation, potentially causing cardiovascular health issues.	[9]
2	Markers of Oxidative Stress and Neuroprogression in Depression Disorder	Major depression, linked to imbalances in neuroprotective factors, antioxidants, prooxidants, proinflammatory molecules, and reactive species. That can lead to damage to proteins, lipids, and nucleic acids, triggering autoimmune and inflammatory responses.	[6]
3	Mechanisms Underlying Neurocognitive Dysfunctions in Recurrent Major Depression	Depression, linked to cognitive changes and neurodegenerative and neuroprogressive conditions, could be an early manifestation of dementia, in elderly. Recent studies reveal changes in tryptophan catabolites, ROS, autoimmunity, apoptosis, neurogenesis, and immuno-inflammatory processes, linked to neurodegenerative conditions.	[10]
4	Microglial-driven changes in synaptic plasticity: A	Balance between ROS and antioxidant production is disrupted in MDD. ROS can	[11]

	possible role in major depressive disorder	induce long term potentiation and impair neuronal functions, like neurogenesis and neuronal death. Chronic mild stress can disrupt this balance, shows increased microglial activation and ROS production.	
5	Depression and anxiety symptoms are associated with prooxidant-antioxidant balance: a population-based study	A study suggests that depression and anxiety symptoms may be linked to altered oxidative stress status, as indicated by higher prooxidant-antioxidant balance (PAB) values. Previous research, linked depression to increased markers of oxidative stress, with inconsistent results on the relationship between depression and antioxidant defence biomarkers. The study found a stronger association between depression and PAB values in men, possibly due to estrogen's antioxidant properties.	[12]
6	Physical exercise ameliorates psychiatric disorders and cognitive dysfunctions by hippocampal mitochondrial function and neuroplasticity in post-traumatic stress disorder	Hippocampus plays a crucial role in onset of psychiatric illness, and mitochondrial dysfunction can increase the risk of PTSD (Post Traumatic Stress Disorder).	[13]
7	Increased oxidative stress in the mitochondria isolated from lymphocytes of bipolar disorder patients during depressive episodes	Significant decrease in complex II (succinate dehydrogenase) activity in peripheral blood mononuclear cells from depressed bipolar patients compared to euthymic patients, which was accompanied by oxidative damage to lipids and proteins, and altered levels of antioxidant enzymes in submitochondrial particles. Pharmacotherapy may also interfere with mitochondrial function and oxidative stress, but no significant differences were observed.	[14]
8	Prenatal exposure to nanoparticulate titanium dioxide enhances depressive-like behaviors in adult rats	Prenatal exposure to TiO_2 (Titanium Oxide)nanoparticles decreases brain antioxidant enzyme levels and increases oxidative damage in newborn pups'	[15]

		hippocampus, leading to depressive-like behaviors in adulthood.	
9	Mitochondrial DNA copy number, damage, repair and degradation in depressive disorder	The study confirms previous reports of elevated Mitochondrial DNA (mtDNA) damage in peripheral blood mononuclear cells from depressed patients. Although not significant, changes in copy number were more rapid in controls. Oxidative stress induction affected mtDNA damage only in patients' cells. Further research is needed to understand this phenomenon in naïve and severe patients.	[16]
10	Regulation by the cAMP Cascade of Oxygen Free Radical Balance in Mammalian Cells	Serum starvation in mammalian cell cultures leads to a decrease in forward NADH-ubiquinone oxidoreductase activity and the appearance of H_2O_2 around mitochondria. This can be due to increased production of reactive oxygen species (ROS), depression of scavenger systems, or both.	[17]
11	Elevated Level of DNA Damage and Impaired Repair of Oxidative DNA Damage in Patients with Recurrent Depressive Disorder	The study revealed that depression patients experience high levels of DNA breaks, alkali-labile sites, and oxidative damage, possibly due to impaired DNA repair pathways. Further research is needed to understand the role of nuclear and mitochondrial DNA damage and repair in depression.	[18]
12	Superoxide Mediates Depressive Effects Induced by Hydrogen Sulfide in Rostral Ventrolateral Medulla of Spontaneously Hypertensive Rats	H_2S metabolic system is present in the RVLM (rostral ventrolateral medulla), and central administration of H_2S decreases phosphorylation of NADPH oxidase, NADPH oxidase activity, and $O_2^{\cdot-}$ production, reducing MAP (mean arterial blood pressure) and heart rate in hypertensive rats. However, decreasing H_2S by microinjection of a CBS (cystathionine-β-synthase) antagonist increased MAP.	[19]
13	Dual action of hydrogen peroxide on synaptic transmission at the frog neuromuscular junction	Study has demonstrated that hydroxyl radicals play a role in the synergistic interaction between Fe^{2+} and H_2O_2 in the reduction of synaptic transmission in this way.	[20]

Therapies for ROS

Table 2, shows the various studies that were analysed on the basis of various treatments for the ROS. Intestinal ROS scavenger, siSMAPo TN, protects intestine from oxidative damage, also alleviates inflammation and behavioural depression symptoms caused by Chronic Respiratory Syndrome (CRS) [5]. A paper outlines the process for creating CeO2@BSA nano clusters, which demonstrate encouraging outcomes in reducing pathogenic alterations and depressive-like behaviours, establishing oxidative stress as a potential therapeutic target [21]. According to previous researches, symptoms and treatment problems may result from decreased antioxidant capacity in neuropsychiatric diseases. Antioxidant supplements are one of the new therapeutic approaches that may lessen symptoms and minimize the duration of Tardive dyskinesia [22]. Major antioxidants have shown promising results in treating depression, as they are also known as low-risk drugs [23]. Grape seed proanthocyanidins, responsible in decreasing excessive ROS generation and also activating NLRP3-Caspase-1, that could be used in adolescent depression treatment [24]. Some previous results suggested that blueberry extract treatment protects against the metabolic changes and depression-like symptoms caused by NPS [25]. Moreover, some previous studies suggests that tea alcohol dramatically decreased the liver's oxidative stress, lipogenic enzyme expression and lipid content, indicating that caffeine and catechin may provide a protective measure against alcoholic liver damage [26].

Few studies investigate the biological effects of ODG on PC12 cells and demonstrate that pretreatment increases the expression of HO-1 gene and protects cells from ROS. ODG extract however, does not lessen intracellular ROS levels or ameliorate the oxidative stress [28]. Some studies enhance the antioxidant state in brain tissue and validate the antidepressant-like effects of petroleum ether extract from maca in the CUMS model of depression in mice, which are probably mediated by noradrenergic and dopaminergic systems [29]. Allicin is a promising treatment for obesity-comorbid depression because it inhibits the generation of ROS, attenuates oxidative stress, mitochondrial damage, autophagy and insulin resistance and lowers depressive like behaviours in obese situations [30].

For protecting mitochondrial malfunction, oxidative stress and neuroinflammation, the neuroprotective drug sericin was discovered to be able to reverse stress-induced anxiety and depressed behaviours in mice [31]. One of the studies found that, by lowering the mechanisms that lead to oxidative stress, acetylsalicylic acid can lessen antioxidative stress in depression. Following combined therapy, the data indicated enhanced total antioxidant stress, decreased MDA levels, and limited antioxidative enzyme activity [27]. In order to better understand the physio pathological mechanisms behind sepsis and the function of mitochondrial respiration and ROS production, this study suggests an in vitro model to directly evaluate the impact of sepsis on human fibroblast cell cultures. Antioxidant substances may be used to promote mitochondrial complex I activity as a result of the findings [32].

Table 2: Therapies for ROS using various alternatives as the antioxidants

Sr. No.	Title	Therapies related to ROS	Reference
1	Direct evidence for the involvement of intestinal reactive oxygen species in the progress of depression via the gut-brain axis	Targeting intestinal ROS, potential antidepressant candidate for depression treatment. The proposed intestinal ROS scavenger, siSMAPo^{TN} (polymer-based antioxidant), protects the intestine from oxidative damage, also alleviates	[5]

		inflammation and behavioural depression symptoms caused by Chronic Respiratory Syndrome (CRS).	
2	ROS-Targeted Depression Therapy via BSA-Incubated Ceria Nanoclusters	Study shows method to synthesize CeO_2@BSA nano clusters, which overcome shortcomings of current anti-ROS natural enzymes and small molecule drugs. The nanoclusters showed results in ameliorating depression-like behaviors and pathological changes, such as neuroinflammation and neuroprotection impairment, proving oxidative stress as a therapeutic target for depression.	[21]
3	Oxidative stress and therapeutic implications in psychiatric disorders	New therapeutic strategies, including antioxidant supplementation, may reduce symptoms and shorten TD (Tardive dyskinesia) duration, emphasizing early and preventive intervention for high-risk populations.	[22]
4	Antioxidants as potential therapeutics for neuropsychiatric disorders	Oxidative stress is linked to neuropsychiatric disorders, affecting free radicals and antioxidant defence mechanisms. Antioxidants have shown promising results as supplements for treating these disorders.	[23]
5	Grape seed proanthocyanidins (GSps) improves depression-like behavior by alleviating oxidative stress and NLRP3 activation in the hippocampus of prenatally-stressed female offspring rats	GSPs can counteract neuron loss and depression in juvenile rats, suppressing excessive ROS generation and activating NLRP3-Caspase-1, providing a new theoretical foundation for adolescent depression treatment.	[24]
6	Effect of blueberry (Vaccinium virgatum) extract on depressive- like behaviour and metabolic serum alterations in lipopolysaccharide-challenged mic	In conclusion, our findings imply that blueberry extract therapy guards against the metabolic alterations and depressive-like behaviour brought on by LPS. Consequently, these data could help the creation of novel pharmaceutical and prophylactic measures for MDD patients.	[25]
7	Depression by a Green Tea Extract of Alcohol-Induced Oxidative Stress and Lipogenesis in Rat Liver	Triglyceride content, lipogenic enzyme (SERBP-1c and FAS) expression, ALT level in the liver, CYP2E1 and NADPH oxidase p47phox protein expression, 4-	[26]

		HNE and ED-1 expression, and alcohol-induced elevation of liver and bile ROS were all considerably reduced by tea alcohol.	
8	Oxidative stress parameters after combined fluoxetine and acetylsalicylic acid therapy in depressive patients	Acetylsalicylic acid can reduce antioxidative stress in depression by reducing mechanisms contributing to oxidative stress. The results showed limited antioxidative enzyme activity, lower methyl aldehyde concentration, and increased Total Antioxidant Stress after combined therapy.	[27]
9	Ondamtanggamibang protects neurons from oxidative stress with induction of heme oxygenase-1	Biological effects of ODG on PC12 cells, showing that pretreatment shields cells against ROS and induces HO-1 gene expression. However, ODG extract doesn't mitigate oxidative stress and reduces intracellular ROS increase.	[28]
10	Antidepressant-Like Behavioural, Anatomical, and Biochemical Effects of Petroleum Ether Extract from Maca (Lepidium meyenii) in Mice Exposed to Chronic Unpredictable Mild Stress	The study confirms the antidepressant-like effects of petroleum ether extract from maca in the CUMS model of depression in mice, likely mediated by noradrenergic and dopaminergic systems, and improves antioxidant status in brain tissue.	[29]
11	Induction of mitochondrial dysfunction and oxidative stress in human fibroblast cultures exposed to serum from septic patients	This study proposes an in vitro model to study sepsis effects on human fibroblast cell cultures, aiming to understand physio pathological mechanisms and the role of mitochondrial respiration and ROS production, potentially utilizing anti-oxidant compounds.	[32]
12	Allicin ameliorates obesity comorbid depressive like behaviours: involvement of the oxidative stress, mitochondrial function, autophagy, insulin resistance and NOX/Nrf2 imbalance in mice	Allicin reduces depressive-like behaviours in obesity contexts by inhibiting ROS production, attenuating oxidative stress, mitochondrial damage, autophagy, and insulin resistance, making it a potential therapy for obesity-comorbid depression.	[30]
13	Sericin alleviates restraint stress induced depressive- and anxiety-like behaviours via	The study found that sericin, a neuroprotective agent, can counteract stress-induced anxiety and depressive	[31]

	modulation of oxidative stress, neuroinflammation and apoptosis in the prefrontal cortex and hippocampus	behaviours in mice by reversing mitochondrial dysfunction, oxidative stress, and neuroinflammation.	

4. DISCUSSION

Through this collectable research evidences, ROS could be reason for the alterations in the cellular metabolic activities. There are also many different ways in which ROS production could be reduced. According to the results, there were 13 studies which showed that increase in ROS could be marker seen in depression patients who are or are not taking any medications. Moreover, another 13 studies were also included in this review, which shows the various ways for the treatment of ROS.

According to the results of effects related to ROS, it promotes macrophage killing bacteria through oxidative damage and apoptosis and can also function as signalling molecules in multiple cellular pathways. Moreover, it shows negative effects like inflammation and cytotoxicity. ROS thrive in energy-demanding conditions like cancer cell proliferation and immune system function, but clinically modulating ROS in vivo and its multiple metabolic functions may limit their potential [33]. The NOX family of enzymes has opened new avenues for research and targeted therapy. Loss of NOX enzyme function is rare but can cause severe diseases like chronic granulomatous disease and hypothyroidism. Increased NOX function is common in cardiovascular and neurodegenerative diseases [34]. ROS, such as H2O2, superoxide, anion and hydroxyl radicals, are considered a “redox biology” that regulates physiological functions. More reliable oxidative biomarkers and epigenetic mechanisms have emerged as potential tools to design therapeutic approaches aimed at modulating in vivo enhanced oxidative stress [35].

Therapeutic strategies for neuroprotection and brain function have shown promise in preclinical models, but clinical trial have been negative. Oxidative stress contributes to neurodegeneration, and antioxidant therapy could improve cognitive functions [36].

Oxidative regulation refers to the actions of ROS, which can be physiological or pathological. Redox regulators, active mediators and cellular organelles are interconnected, affecting health, metabolism and lifespan [37]. Although ROS-responsive theranostic prodrugs are mainly utilized to treat cancer, research into other ROS-related disorders has great promise. They also diagnose and treat diseases while examining disease causes [38].

Elevated ROS levels can reverse chemotherapy resistance in cancerous cells, causing cytotoxicity and oxidative stress. While antioxidant agents may cure ROS-derived cancers, chemotherapy and radiotherapy primary action is primarily increased ROS generation, which can effectively kill cancer cells []. ROS boosting or scavenging therapy, elevate ROS scavenging by consuming antioxidants or target tumor cells with pro-oxidant agents. This could help modulate drug selectivity and reduce chemotherapeutic resistance [39].

In conclusion, there are many diseases among which alterations in ROS could lead to various diseases. Moreover, there are many diseases among which ROS could be used as a therapeutic agent like in cancer treatment. Further, research is needed for the ROS, how it could be used as a particular biomarker in certain diseases and also how we can reduce the ROS in certain diseases, so that it does not alters the metabolic functions of cell.

References

1. Lanni, C., Govoni, S., Lucchelli, A., & Boselli, C. (2009). Depression and antidepressants: molecular and cellular aspects. Cellular and molecular life sciences, 66, 2985-3008.
2. Hammen, C. (2005). Stress and depression. Annu. Rev. Clin. Psychol., 1(1), 293-319.
3. Willner, P., Scheel-Krüger, J., & Belzung, C. (2013). The neurobiology of depression and antidepressant action. Neuroscience & biobehavioral reviews, 37(10), 2331-2371.
4. Brieger, K., Schiavone, S., Miller Jr, F. J., & Krause, K. H. (2012). Reactive oxygen species: from health to disease. Swiss medical weekly, 142(3334), w13659-w13659.
5. Ikeda, Y., Saigo, N., & Nagasaki, Y. (2023). Direct evidence for the involvement of intestinal reactive oxygen species in the progress of depression via the gut-brain axis. Biomaterials, 295, 122053.
6. Vaváková, M., Ďuračková, Z., & Trebatická, J. Markers of oxidative stress and neuroprogression in depression disorder. Oxid Med Cell Longev. 2015; 2015: 898393. Přejít k původnímu zdroji... Přejít na PubMed.
7. Krumova, K., & Cosa, G. (2016). Overview of reactive oxygen species.
8. Sies, H., Belousov, V. V., Chandel, N. S., Davies, M. J., Jones, D. P., Mann, G. E., ... & Winterbourn, C. (2022). Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. Nature reviews Molecular cell biology, 23(7), 499-515.
9. Grotle, A. K., Darling, A. M., Saunders, E. F., Fadel, P. J., Trott, D. W., & Greaney, J. L. (2022). Augmented T-cell mitochondrial reactive oxygen species in adults with major depressive disorder. American Journal of Physiology-Heart and Circulatory Physiology, 322(4), H568-H574.
10. Gałecki, P., Talarowska, M., Anderson, G., Berk, M., & Maes, M. (2015). Mechanisms underlying neurocognitive dysfunctions in recurrent major depression. Medical science monitor: international medical journal of experimental and clinical research, 21, 1535.
11. Innes, S., Pariante, C. M., & Borsini, A. (2019). Microglial-driven changes in synaptic plasticity: a possible role in major depressive disorder. Psychoneuroendocrinology, 102, 236-247.
12. Shafiee, M., Ahmadnezhad, M., Tayefi, M., Arekhi, S., Vatanparast, H., Esmaeili, H., ... & Ghayour-Mobarhan, M. (2018). Depression and anxiety symptoms are associated with prooxidant-antioxidant balance: A population-based study. Journal of affective disorders, 238, 491-498.
13. Seo, J. H., Park, H. S., Park, S. S., Kim, C. J., Kim, D. H., & Kim, T. W. (2019). Physical exercise ameliorates psychiatric disorders and cognitive dysfunctions by hippocampal mitochondrial function and neuroplasticity in post-traumatic stress disorder. Experimental neurology, 322, 113043.
14. Valvassori, S. S., Bavaresco, D. V., Feier, G., Cechinel-Recco, K., Steckert, A. V., Varela, R. B., ... & Quevedo, J. (2018). Increased oxidative stress in the mitochondria isolated from lymphocytes of bipolar disorder patients during depressive episodes. Psychiatry research, 264, 192-201.
15. Cui, Y., Chen, X., Zhou, Z., Lei, Y., Ma, M., Cao, R., ... & Che, Y. (2014). Prenatal exposure to nanoparticulate titanium dioxide enhances depressive-like behaviors in adult rats. Chemosphere, 96, 99-104.
16. Czarny, P., Wigner, P., Strycharz, J., Swiderska, E., Synowiec, E., Szatkowska, M., ... & Galecki, P. (2020). Mitochondrial DNA copy number, damage, repair and degradation in depressive disorder. The World Journal of Biological Psychiatry, 21(2), 91-101.
17. Bellomo, F., Piccoli, C., Cocco, T., Scacco, S., Papa, F., Gaballo, A., ... & Papa, S. (2006). Regulation by the cAMP cascade of oxygen free radical balance in mammalian cells. Antioxidants & redox signaling, 8(3-4), 495-502.

18. Czarny, P., Kwiatkowski, D., Kacperska, D., Kawczyńska, D., Talarowska, M., Orzechowska, A., ... & Śliwiński, T. (2015). Elevated level of DNA damage and impaired repair of oxidative DNA damage in patients with recurrent depressive disorder. Medical science monitor: international medical journal of experimental and clinical research, 21, 412.
19. Yu, H., Xu, H., Liu, X., Zhang, N., He, A., Yu, J., & Lu, N. (2015). Superoxide mediates depressive effects induced by hydrogen sulfide in rostral ventrolateral medulla of spontaneously hypertensive rats. Oxidative Medicine and Cellular Longevity, 2015(1), 927686.
20. Giniatullin, A. R., & Giniatullin, R. A. (2003). Dual action of hydrogen peroxide on synaptic transmission at the frog neuromuscular junction. The Journal of physiology, 552(1), 283-293.
21. Fu, S., Chen, H., Yang, W., Xia, X., Zhao, S., Xu, X., ... & Zheng, J. C. (2022). ROS-targeted depression therapy via BSA-incubated ceria nanoclusters. Nano Letters, 22(11), 4519-4527.
22. Zhang, X. Y., & Yao, J. K. (2013). Oxidative stress and therapeutic implications in psychiatric disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 46, 197-199.
23. Pandya, C. D., Howell, K. R., & Pillai, A. (2013). Antioxidants as potential therapeutics for neuropsychiatric disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 46, 214-223.
24. Sun, Q., Jia, N., Ren, F., & Li, X. (2021). Grape seed proanthocyanidins improves depression-like behavior by alleviating oxidative stress and NLRP3 activation in the hippocampus of prenatally-stressed female offspring rats. Journal of histotechnology, 44(2), 90-98.
25. Vega Custódio, S., Spohr, L., Pontes Bona, N., de Souza, A. A., de Moraes Meine, B., Keske, S., ... & Sandrielly Pereira Soares, M. (2021). Effect of blueberry (Vaccinium virgatum) extract on depressive-like behavior and metabolic serum alterations in lipopolysaccharide-challenged mice. Journal of Food Biochemistry, 45(10), e13920.
26. Chen, K. H., Li, P. C., Lin, W. H., Chien, C. T., & Low, B. H. (2011). Depression by a green tea extract of alcohol-induced oxidative stress and lipogenesis in rat liver. Bioscience, biotechnology, and biochemistry, 75(9), 1668-1676.
27. Gałecki, P., Szemraj, J., Bieńkiewicz, M., Zboralski, K., & Gałecka, E. (2009). Oxidative stress parameters after combined fluoxetine and acetylsalicylic acid therapy in depressive patients. Human Psychopharmacology: Clinical and Experimental, 24(4), 277-286.
28. Lee, M. S., Lee, J., Kwon, D. Y., & Kim, M. S. (2006). Ondamtanggamibang protects neurons from oxidative stress with induction of heme oxygenase-1. Journal of ethnopharmacology, 108(2), 294-298.
29. Ai, Z., Cheng, A. F., Yu, Y. T., Yu, L. J., & Jin, W. (2014). Antidepressant-like behavioral, anatomical, and biochemical effects of petroleum ether extract from maca (Lepidium meyenii) in mice exposed to chronic unpredictable mild stress. Journal of medicinal food, 17(5), 535-542.
30. Gao, W., Wang, W., Zhang, J., Deng, P., Hu, J., Yang, J., & Deng, Z. (2019). Allicin ameliorates obesity comorbid depressive-like behaviors: involvement of the oxidative stress, mitochondrial function, autophagy, insulin resistance and NOX/Nrf2 imbalance in mice. Metabolic brain disease, 34, 1267-1280.
31. Mohammadi, A. B., Torbati, M., Farajdokht, F., Sadigh-Eteghad, S., Fazljou, S. M. B., Vatandoust, S. M., ... & Mahmoudi, J. (2019). Sericin alleviates restraint stress induced depressive-and anxiety-like behaviors via modulation of oxidative stress, neuroinflammation and apoptosis in the prefrontal cortex and hippocampus. Brain research, 1715, 47-56.
32. Raffaella, T., Fiore, F., Fabrizia, M., Francesco, P., Arcangela, I., Salvatore, S., ... & Nicola, B. (2012).

Induction of mitochondrial dysfunction and oxidative stress in human fibroblast cultures exposed to serum from septic patients. Life sciences, 91(7-8), 237-243.

33. Yang, S., & Lian, G. (2020). ROS and diseases: Role in metabolism and energy supply. Molecular and cellular biochemistry, 467, 1-12.
34. Brieger, K., Schiavone, S., Miller Jr, F. J., & Krause, K. H. (2012). Reactive oxygen species: from health to disease. Swiss medical weekly, 142(3334), w13659-w13659.
35. Davalli, P., Mitic, T., Caporali, A., Lauriola, A., & D'Arca, D. (2016). ROS, cell senescence, and novel molecular mechanisms in aging and age-related diseases. Oxidative medicine and cellular longevity, 2016(1), 3565127.
36. Popa-Wagner, A., Mitran, S., Sivanesan, S., Chang, E., & Buga, A. M. (2013). ROS and brain diseases: the good, the bad, and the ugly. Oxidative medicine and cellular longevity, 2013(1), 963520.
37. Alfadda, A. A., & Sallam, R. M. (2012). Reactive oxygen species in health and disease. BioMed research international, 2012(1), 936486.
38. Wang, P., Gong, Q., Hu, J., Li, X., & Zhang, X. (2020). Reactive oxygen species (ROS)-responsive prodrugs, probes, and theranostic prodrugs: applications in the ROS-related diseases. Journal of medicinal chemistry, 64(1), 298-325.
39. Raza, M. H., Siraj, S., Arshad, A., Waheed, U., Aldakheel, F., Alduraywish, S., & Arshad, M. (2017). ROS-modulated therapeutic approaches in cancer treatment. Journal of cancer research and clinical oncology, 143, 1789-1809.