Glutathione in Mental Disorders: Mechanisms and Therapies

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Abstract: In recent decades, topics related to mental diseases have gradually become important, and the treatments for mental diseases have also attracted attention from increasing number of researchers. Research directions have been focused on glutathione metabolism and oxidative stress. Appreciable number of reports have suggested that the content of reduced glutathione in patients with mental diseases, including Alzheimer's disease, depression, anxiety disorder, autism, bipolar disorder and schizophrenia, is lower than that in normal people, suggesting that the dysregulation of glutathione redox may be one of leading the pathogeneses of these mental diseases. Regulation of glutathione metabolism involves many enzymes, such as GPx1 and GST, which have been comprehensively analyzed in this paper. Additionally, the potential of targeting glutathione metabolism balance as a breakthrough point for the treatment of psychiatric disorders will be discussed, listing some reported that have proven therapeutic effects of N-Acetyl-L-cysteine (NAC), minocycline and dimethyl fumarate (DMF) on mental disorders as well as their further therapeutic potential. The general purpose of this paper aims to study the recent progress focusing on glutathione metabolism in mental disorders mechanism and treatment, highlighting that GSH redox problems for mental illness is indispensable and outlook the potential development of treatments for mental disorders that target glutathione metabolism.

1 INTRODUCTION

Glutathione (GSH), a kind of tripeptide composed of glutamic acid, cysteine and glycine, exists in practically every cell inside human bodies. Glutathione system acts as the most essential antioxidant defense that maintaining cellular viability and function. Normally, glutathione in healthy human body mainly exists in the reduced form, while Oxidized glutathione (GSSG) takes merely a tiny part as the inactive state (Tao, 2014). Meanwhile, the GSH:GSSG ratio in vivo should be within a reasonable range and defined as a reliable biomarker of cellular redox homeostasis (Geir Bjørklund, 2020). Serving as an antioxidant, glutathione has the function of eliminating free radicals in vivo. Free radicals are considered as unstable substances that can cause cell damage, especially when they accumulate at higher content than antioxidants. Oxidative stress will be caused when redox dysregulation of glutathione occurs, meanwhile reactive oxygen species (ROS) and reactive nitrogen species (RNS) become overproduced, leading to the inhibition of the activity of endogenous antioxidant system, in which the circumstance may engender over-loading free radicals damaging cell (Javier Toro-Pérez, 2021). Then a series of psychiatric disorders, such as bipolar disorder (Lagopoulos, 2013), depression (Kyle, 2014), autism (Xi, 2015), Alzheimer's disease (Tandra Ghosh, 2012), obsessive-compulsive disorder, post-traumatic stress disorder (PTSD), schizophrenia, etc. can be caused. To maintain the homeostasis of glutathione, impacts of peroxidase enzymes are indispensable, which will be discussed in this paper.

Increasing evidence and achievements about therapies on mental disorders targeting glutathione pathway are emerging. The function of glutathione that can influence and regulate DNA methylation and epigenetics is highlighted, which can cause the cell and organ perturbations, particularly in the brain (Geir Bjørklund, 2020). In response to the association between dysregulation in glutathione metabolism and bipolar disorder, Murrough et al. have found that Minocycline can effectively treat symptoms of bipolar disorder by modulating oxidative stress in patients with bipolar disorder (Murrough, 2018). Therefore, taking glutathione metabolism as the

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breakthrough point to study the pathogenesis and treatment of mental diseases has considerable value. This passage aiming to dig deeper into the value of glutathione, homeostasis of glutathione and oxidative, as well as biological enzymes which regulate glutathione metabolism, including GPx1 and GST. In addition, the pathogenesis and therapeutic potential of mental disorders focusing on the glutathione pathway will also be depicted in detail.

2 COMPOSITION OF GLUTATHIONE SYSTEM

2.1 Oxidative Stress and Homeostasis

Oxidative stress of glutathione has been implicated in the pathogenesis of several neuropsychiatric disorders, which is considered as a mechanism linking genetic, immune and external pathogenic factors in mental disorders (Xi, 2015). Under normal circumstances, intracellular ROS and antioxidant capacity are in a dynamic balance (Currenti, 2010). As an antioxidant produced by human cells, glutathione has a limited ability to remove active oxides. When the content of active oxides exceeds the reducing capacity of glutathione, imbalance between cellular oxidation and antioxidant effects will occur. This oxidative stress can hinder or disrupt cell signaling and affect cell proliferation as well as gene expression (Betancur, 2011). In addition to glutathione, glutathione peroxidase (GPX) also acts as antioxidant effects, which will be discussed in detail in the following parts.

In order to illustrate glutathione homeostasis systematically, normal state of glutathione redox and glutathione metabolism under oxidative stress are shown in Fig 1 and Fig 2 respectively. Under normal circumstance, methionine cycling, and sulfur transfer are the main factors regulating methylation and redox buffering activities (Xi, 2015). When oxidative stress occurs, a variety of regulatory mechanisms are activated to reduce methionine synthase and cysteine plus dioxygenase activity, as well as to increase cystathionine synthase activity to attain the purpose of changing sulfur flux in response to glutathione synthesis. Low methionine synthase can reduce methylation, including methylation of dopamine receptor phospholipids.

In recent decades, increasing number of studies on neurological diseases have focused on the glutathione pathway, from which the fact that glutathione and oxygen can affect the activities of enzymes controlling genetics and transcription has been generally accepted (Geir Bjørklund, 2020). The maintenance of redox homeostasis is of great significance for the central nervous system (CNS). Once homeostasis is disrupted, the nervous system can be harmed. Dysfunction of mitochondrial can be one of the reasons that elevated levels of oxidative stress, which was a phenomenon observed in autism spectrum disorders (ASD) individuals (Xi, 2015). A study carried out by ZHANG in 2018 had proved that GSH can restrain the cell damage by oxidative stress (Zhang, 2018). In this research, MPP+ was applied to MES 23.5 dopamine neuron cells, which results in increasing levels of ROS and MDA while CAT activity declines in cell MES 23.5, inducing abnormal mitochondrial function as well as oxidative stress to create models of oxidative damage cells.

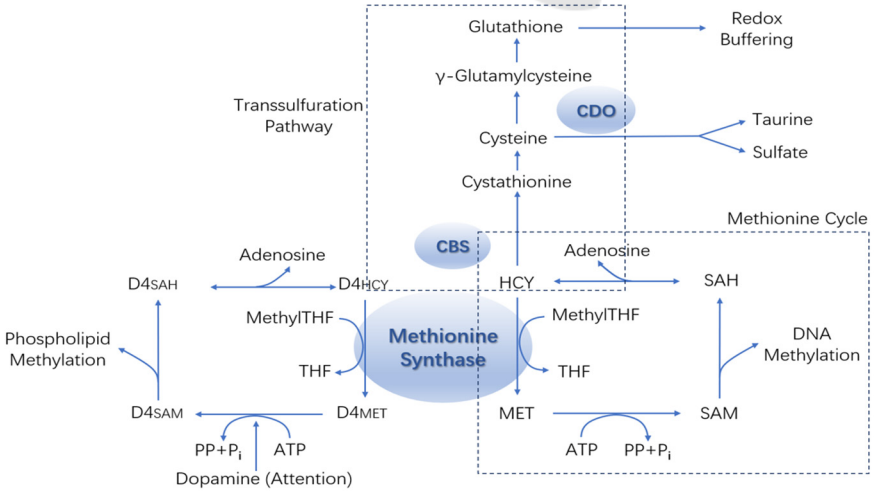

Figure 1: Normal redox status of glutathione. Adapted from (Xi, 2015).

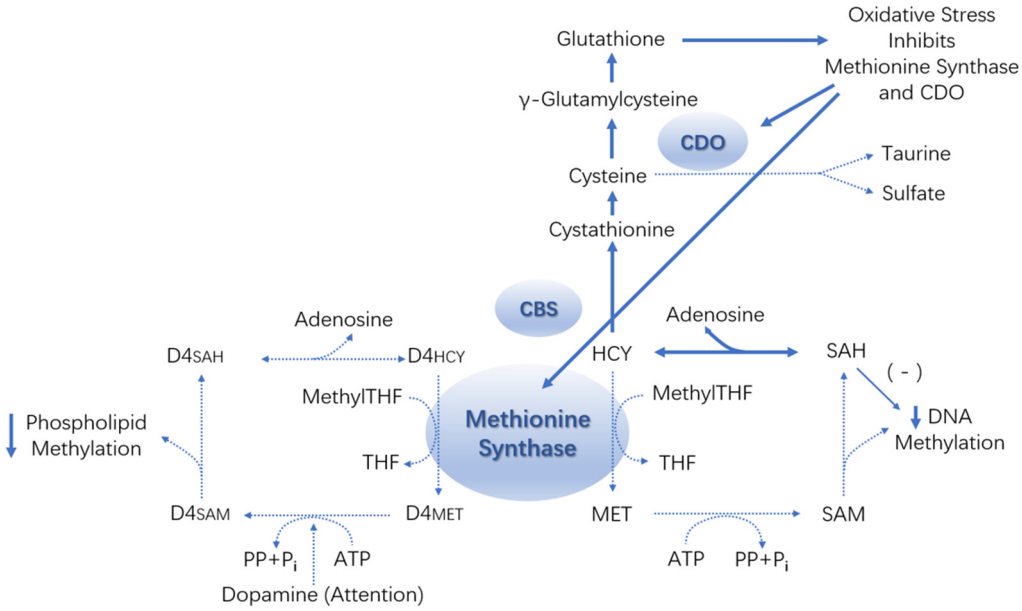

Figure 2: Glutathione metabolism under oxidative stress. Adapted from (Xi, 2015).

GSH was then applied to cells model, so the activity of MES 23.5 recovered considerably, indicating that GSH has the function of antioxidant protection. So, what contributes in keeping the glutathione homeostasis? Answer should be enzymes related to the metabolism of glutathione such as glutathione peroxidase and glutathione S-transferase.

2.2 GPx1

Glutathione peroxidase (GPx) can be divided into four major categories, including cytosolic GPx, plasma GPx, phospholipid hydroperoxide GPx and gastrointestinal specific GPx. It was recognized that the first vertebrate protein depends on selenium was GPx (Little C, 1968). Glutathione peroxidase family belongs to the antioxidant enzymes, of which GPx1 is one of the family.

1) Role of GPx1 in mental disorder. Until 1968, scientists claimed that GPx can lessen various kinds of organic peroxides, nucleic acids and hydroperoxides produced by unsaturated fatty acids (Little C, 1968). Existing as an important antioxidant enzyme, GPx1 can be found in both mitochondria and cytoplasm of mammalian cells (Leopold Flohé, 2022). The main function of GPx1 is to oxidate cellular GSH along with the reduction of hydrogen peroxide, which can control the thiol redox state while keeping necessary and harmful states of oxidants in balance (Diane E. Handy, 2022). One study by Zorov et al. showed that if dysfunction and damage occur in mitochondrial membranes or proteins, production of ATP and uncoupling of electron transport may happened, which can stimulate the mitochondria releasing ROS (Zorov D.B, 2014). In addition, GPx1 also has the potential ability to regulate the forming of these kinds of extra ROS. GPx1 is able to protect neurocyte against ROS-related neurotoxicity (Crack P.J., 2006). When gene expression of GPx1 dysregulates, the oxidative stress caused by this case can be related to neurodegeneration which is a considerable factor of chronic neurodegenerative diseases like Alzheimer's disease (Diane E. Handy, 2022).

Indeed, GPx1 helps to keep glutathione redox stable and provides neuroprotection. If expression of GPx1 increases, however, cellular dysfunction and other diseases can also be stimulated because some essential reactive oxygen species are removed in this case (Diane E. Handy, 2022). Superfluous oxidant like GPx1 can damage cellular DNA, proteins and lipid. Study by Martini et al. had found that upregulating GPx1 can mitigate suppression of ERK1/2 and memory impairment (Martini F, 2019). The process is illustrated in Figure 3. Interestingly, the activation of ERK1/2 can also be inhibited when GPx1 overexpressing, which may possibly be promoted by ROS production (Diane E. Handy, 2022). These results provide reasonable evidence to see the connection between GPx1 expression and psychiatric disorders, but also highlight the complexities of regulating antioxidant for therapies.

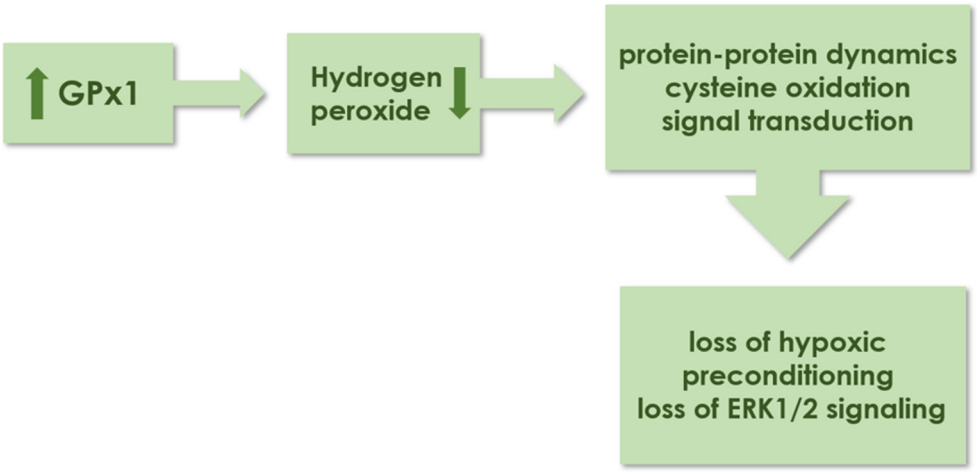

Figure 3: Process illustrating how the increase of GPx1 lead to inhibition of ERK1/2. Adapted from (Diane E. Handy, 2022).

2) Regulation of GPx1 expression. It was claimed that not all the glutathione peroxidases are selenoproteins but GPx1 is, which includes the amino acid selenocysteine at the active site (Floh´e L., 1973). Selenium deficiency may not result in a defective GSH regeneration but cause the utilized impairment (Leopold Flohé, 2022). Another research by Smesny et al. revealed how omega-3 PUFA affects the glutathione antioxidant defense system (AODS) in individuals with ultra-high risk of psychosis (Stefan Smesny, 2015). Result of this study had shown the mechanisms underlying clinical effectiveness, of which the effects were not specific. Contrarily, it is certain that omega-3 PUFA can influence the antioxidative effects in AODS, decreasing the demand of glutathione. However, there is no absolute association between omega-3 PUFA and GPx1.Therefore, it is reasonable to give an opinion that GSH levels in vivo can be indirectly influenced by selenium, also further study about substances that can affect the production of GPx1 is needed.

2.3 GST

1)Role of GST in mental disorder. Comparing with GPx1, GST has different chemical properties and biological effects. Details are listed in Table 1. With detoxification, GST mainly helps to promote the electrophilic groups from endogenous substances or xenobiotics coupling to the sulfhydryl group of reduced glutathione, increasing the hydrophobicity of the combination to cross the cell membrane, decompose and then be excreted (Sen Ma, 2008). In this way, GST can remove peroxide as well as detoxify xenobiotics. However, mechanism of GST may be affected by GPx. When the activity of GPx decreases, GST can only eliminate the lipid peroxides (LPO), losing the ability of detoxification.

As one of the members of family of phase-II isoenzymes, GST protect human cells from electrophiles and substances produced by oxidative stress, playing a critical role in pathogenesis of Alzheimer's disease. In 2012, Ghosh et al. digged into the relationship between GST and Alzheimer's disease, indicating that gene deletion of GSTM1(Mu) and GSTT1(theta) which are belong to GST family, can decline the expression of related enzymes (Tandra Ghosh, 2012). Result shown that deletion of GSTT1 was dramatically related to Alzheimer's disease. Probability of people getting Alzheimer's disease with gene deletion of GSTT1 was 2.47 times higher than that of people with positive GSTT1. Also, study by Spalletta et al. found that patients with schizophrenia who carry the GSTA1*B allele were facing to higher risk of damage by oxidative stress than non-B carriers, displaying severer symptoms of illusion (Gianfranco Spalletta, 2012).

2) Factors influence metabolism of GST. Several factors can affect the metabolism of GST. Activity, inner concentration, issue localization of GST varies in different people. Gene expression of GST reveals polymorphism in people who are not living in the same geographical area (Buratti F.M, 2021). GST exists in practically all parts of human body, with highest levels in the cytoplasm of liver, kidney and blood, in which the elimination of peroxide and detoxification of xenobiotics mainly take place. Certain product of metabolism can also influence GST expression. In 2021, Crawford et al. found that 3,4-dihydroxyphenylacetaldehyde (DOPAL), an aldehyde metabolite of dopamine can inhibit the

Table 1: Comparison between GPx1 and GST.

GPx1	GST
can catalyze the reduction of H_2O_2 and organic hydrogen peroxide compounds	cannot decompose H_2O_2
removing peroxide only	removing peroxide and detoxifying
poor thermal stability	better thermal stability

activity and function of GST, but 1 mM carnosine can completely protect GST from DOPAL (Crawford R.A., 2021).

3 ROLE OF GLUTATHIONE IN MENTAL DISORDER

3.1 Pathogenesis

At present, a fair amount of research has been done to probe how glutathione metabolism associates with psychiatric disorders. However, there is still no clear evidence to confirm that metabolic disorders of glutathione can always cause psychiatric problems, but it is considerable to take glutathione as a biological indicator to analyze certain disease. Lack of glutathione and oxidative stress can be considered as primary symbols of some mental problems, but the precise and specific pathogenesis concerning glutathione remains uncertain.

Redox dysregulation act as a non-negligible factor in autism spectrum disorder (ASD). By affecting redox environment and redox-independent mechanisms, glutathione metabolism impacts multiple pathogenesis of ASD (Geir Bjørklund, 2020). N-methyl-Daspartate receptor, a glutamate receptor regulated by glutathione may contribute to glutamate excitotoxicity, in which case that synergistic and antagonistic interactions of glutathione and glutamate will lead to neuronal dysfunction (Geir Bjørklund, 2021). These kinds of synergistic and antagonistic interactions are likely to involve transcription factors in immune pathway, changing neuroinflammatory mechanisms and then neuronal damage emerges.

Pathogenesis of depression implicates oxidative stress as an essential mechanism. Lapidus et al. used proton magnetic resonance spectroscopy (1H MRS) to obtain the glutathione in vivo level of occipital cortex of patients with major depressive disorder and came to a conclusion that anhedonia severity shown negative relation to occipital glutathione level, which indicated glutathione and oxidative stress have similar pathogenesis in anhedonia and major depressive disorder (Kyle A.B. Lapidus, 2014). This may increase a support to the importance of oxidative stress of glutathione in pathogenesis of depression, which means low level of glutathione becoming potential symbols in the early state of major depressive disorder. Also, in vivo level of GST is one of the biomarkers to show the possibility of suffering from depression. Savushkina et al. found that people with depression have less platelet GST and erythrocyte glutathione reductase than normal people (Olga Savushkina, 2022). Interestingly, research by Lagopoulos et al. argued that no decline was found in baseline GSH concentration of the young with bipolar disorder, while no prominent result to support glutathione oxidative stress involved in mania (Lagopoulos J., 2013). Therefore, further study may be requested, but existing research has provided human-oriented information that may contribute to prospective clinical study and therapies.

3.2 Protective Effects

Disturbances in glutathione in the hippocampus can lead to some of the mental diseases. A mass of glutathione is needed in hippocampal neurons in order to protect and maintain dendrite integrity and cognitive function. In 2022, Ho et al. emphasized the interactions of glutathione and copper on physiology and Alzheimer's disease (Talia Ho, 2022). It was indicated that effects of glutathione and copper on Alzheimer's disease have been studied separately in previous researches, of which the fact that these two substances are actually more effective and regulate each other when interacting. To give details of mechanism of the interaction of glutathione and copper, a simplified illustration by Ho is shown in Figure 4. It can be observed from the figure that copper is imported into the cell by copper transporter 1 (Ctr1). Then glutathione chelates the copper almost immediately. Copper can be stored and passed by glutathione to different chaperones and metallothionein that functions as a storage molecule.

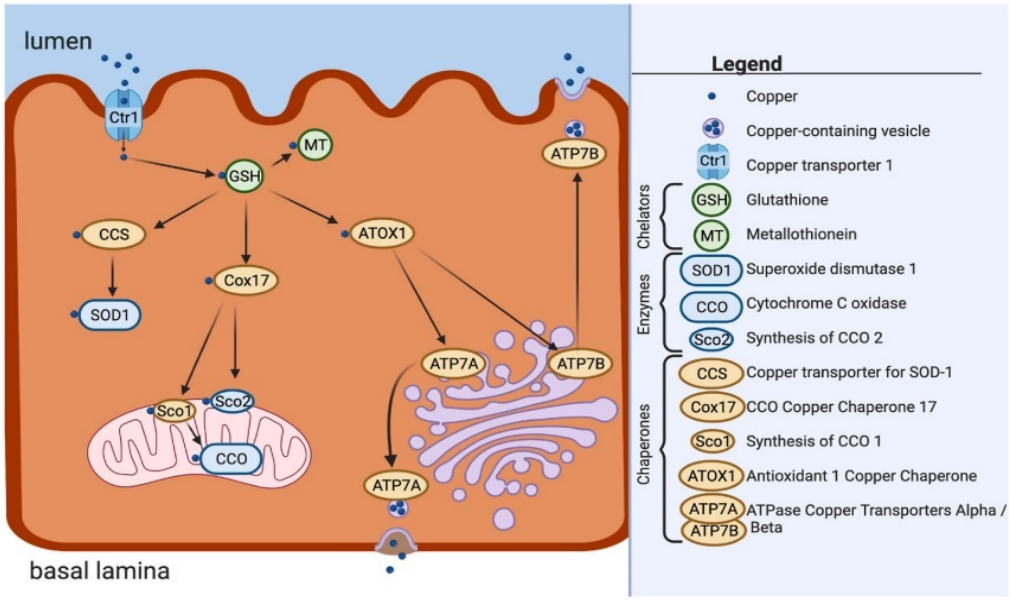

Figure 4: A simplified illustration for the overview of copper importation, utilization, and exportation within the cell. Referring to (Talia Ho, 2022).

4 THERAPEUTIC POTENTIAL

Although the aforementioned associations of glutathione homeostasis and oxidative stress with psychiatric disorders are preliminary results, targeting glutathione pathway for the treatment of mental disorders still possess prospective development. Appling N-Acetyl-L-cysteine (NAC) as a drug with pharmacological targeting of glutathione system can be a significant example. Yang et al. executed clinical studies with schizophrenics and found that after 8 weeks of treatment with NAC, prefrontal cortical levels of glutathione in schizophrenics have been raised (Yang, 2022). As a glutathione precursor, NAC has already shown adjunctive value in therapies of schizophrenia, of which the curative effect has been proved to be apparent (Schiavone S., 2016). In fact, NAC can also be effective in alleviating depressive symptoms or anxiety symptoms, but the condition under which NAC can work is limited. Porcu et al. conducted a 12-week clinical experiment in 2018, in which patients were assigned to receive the same daily dose of placebo or 1.8g NAC (Porcu M., 2018). It has been proved that only when high sensitivity C-reactive protein levels exceed 3 mg/L, can the therapeutic effect of NAC be observed.

Most of the reports about targeting glutathione pathway to treat psychiatric disorders are by applying NAC to schizophrenics. There is one sample study that rarely mentioned, which focused on minocycline for the treatment of bipolar depression. In 2018, Murrough et al. treated 20 people with bipolar disorder with minocycline at a daily dose of 256 mg (SD: 71 mg) and measuring the cortical glutathione within a voxel prescribed in the precuneus by proton magnetic resonance spectroscopy (1H MRS) (Murrough J.W., 2018). Results by this study proved that applying minocycline to patients with bipolar disorder, especially those with high baseline glutathione levels, is considered as a significant adjuvant treatment.

In addition, targeting the regulation of glutathione expression is also a potential therapeutic approach. Nrf2 can control the expression of various antioxidant enzymes, including those involved in GSH synthesis, such as GST and GPx1. As early in 2004, Chen et al. proposed to enhance the antioxidant capacity of GSH in response to oxidative stress by increasing Nrf2 activity (Chen, 2004). Dimethyl fumarate (DMF), a fumarate ester, was thought to have an ability to activate the action of Nrf2 (Linker, 2011). The principle for this is that DMF can modify the cysteine residues on Keapl, so that Nrf2 can be stabilized and transferred to the nucleus to activate ARE targets, thus reducing oxidative stress. In 2018, El-Fattah conducted experiments on mice in which DMF was administered orally at a dose of 25mg/kg 1 h before each exposure to stress and found that depressive symptoms due to oxidative stress in mice were

reduced (Abd El-Fattah, 2018). Although the results were collected from animal model, this study also provides us with considerable evidence and potential that DMF may be beneficial for the treatment of depression in humans.

Consequently, further study is required to discover and evaluate novel drug targeting glutathione pathway as therapy or adjuvant treatment to various sorts of mental disorders.

5 CONCLUSION

It is undoubted that oxidative stress caused by glutathione redox dysregulation is involved in the pathogenesis of a variety of psychiatric diseases. Studying the metabolic pathway of glutathione and factors influencing glutathione homeostasis is quite significant. Targeting the pharmacology of the redox regulatory system as a therapeutic modality is believed to be a promising approach for the treatment of psychiatric disorders. The treatment of mental disorders centered on glutathione metabolism is not yet fully developed, but the development of such topic may show great potential.

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