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The Role of Oxidative Stress in Major Depression: Does The Multiple Pathways Lead to Same Destination?

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Abstract **Original Research Article**

Major depression can be defined as changes in concern, perception, neurovegetative functions for at least two weeks coupled with periods of normal behavior in between the episodes. It has higher lifetime risk among single/ widowed or divorced women. Family history, genetic factors as well as serotonin and norepinephrine play an important role in the etiology. The exact diagnosis of major depression could not be made using the available laboratory test so rating scales are used for (i) identifying the severity and (ii) evaluating the response to the treatment. Any disparity between levels of oxidants and antioxidants with the equilibrium shifting towards oxidants due to either increase in the levels of oxidants or a decrease in the levels of antioxidants or both is known as oxidative stress. Many hypotheses have been proposed signifying the role of oxidative stress in the development of major depression. In the current review, a total of 63 results were used; out of those, 6 were books, 54 were original articles, and 3 were review articles, and the rest were excluded. The current study suggested multiple pathways terminating in oxidative stress and manifesting as various symptoms. The roles of various markers of oxidative stress suggested an increase in the levels of oxidants and reduction in the levels of antioxidant (enzymatic or nonenzymatic) which was reversed following the treatment with anti-depressant drugs. Since the oxidative stress is not exclusively present in major depression, the changes in oxidative stress markers cannot be considered as diagnostic of major depression.

Keywords: Oxidative Stress, Major Depression, etiology.

1. INTRODUCTION

Depression, one of the constituents of the mood disorder spectrum, is characterized by disturbed mood regulation and behavioral activities, bipolar disorders, episodes of heightened emotions, hypomania, and mixed symptoms [1]. Major depression, one of the types of depressive disorders, can be defined as specific events of changes in concern, perception, and neurovegetative functions for at least two weeks coupled with periods of normal behavior in between the episodes [2].

A higher lifetime risk of major depression was reported by Hasin *et al.* among women, mainly belonging to 45 to 64-year age-groups and those who were staying alone, widowed, or divorced [3]. Family history, genetic factors as well as serotonin and norepinephrine play an important role in the etiology, progression of major depression, and treatment response [4]. Dugue *et al.* found an increased level of interleukin-6 (IL-6) and C-reactive protein in the patients encountering stressful conditions [5]. Similarly, elevated levels of interleukin1β (IL-1β) were detected among students by Dobbin *et al.* [6].

The definite diagnosis of major depression is indicated by the manifestation of any of the five symptoms of criterion 'A' as suggested by fifth edition of Diagnostic and Statistical Manual of mental disorders (DSM-V), consistently for two weeks and consisting of either (1) disheartened feeling or (2) loss of concern or delight in almost all deeds for atleast two weeks [2].

No single laboratory test could be developed which could suggest exact diagnosis of major depression despite the availability of literature describing the association of major depression with various neuroanatomical, neuroendocrinal and neurophysiological factors [2]. Hence, rating scales or assessment instruments were used for: (i) specifying the severity of depression, (ii) facilitating the interaction

between patients and the observers, and (iii) evaluation of treatment response [7].

'The monoamine hypothesis or the biogenic amine hypothesis' depicted very significant role of a complete or partial deficiency of catecholamines in the development of depression [8, 9]. The 'inflammatory response system (IRS) model' described major depression as an immuno-neuro-psychological disorder [10].

Multiple hypotheses have been proposed in the past, which indicated the role of oxidative stress in the development of major depression. Any disparity between levels of oxidants and antioxidants with the equilibrium shifting towards oxidants due to either increase in the levels of oxidants or a decrease in the levels of antioxidants or both is known as oxidative stress [11].

So the oxidative stress was characterized by the elevated levels of oxidative product such as reactive oxygen species (ROS) like superoxide, hydrogen peroxide and hydroxyl free radical; pro-oxidant enzymes like xanthine oxidase (XO), inducible NO synthetase (iNOS); reactive nitrogen species (RNS) like nitrogen oxide (NO), nitrogen dioxide and peroxynitrite; RNA damage product 8-oxo-7, 8-dihydroguanosine (8-oxoGuo) and DNA damage product 8-hydroxy-2-deoxyguanosine (8-OHdG), lipid peroxidation products, malondialdehyde (MDA), 8-iso-PGF2α and protein damage product such as protein carbonyl content (PCC), coupled with reduced levels of enzymatic antioxidants such as paraoxonase1, glutathione peroxidase, catalase, superoxide dismutase, glutathione reductase or nonenzymatic antioxidants like vitamins C and E, ceruloplasmin, albumin, selenium, uric acid, GSH, coenzyme Q10, zinc, high-density lipoprotein cholesterol (HDL-C) [12-18].

In the present study, various theories regarding etiopathogenesis of major depression have been discussed, and the role of various markers of oxidative stress in the diagnosis and the treatment has been highlighted.

2. MATERIALS and METHODS

Various articles were searched from October 2016 to July 2020 using various search engines such as PubMed, Scopus, EMBASE, CINAHL, Google Scholar etc. using the combinations of keywords "mood disorder," "mental disorder," "depressive disorder," "major depression," "screening for depression," "rating scales in psychiatry," "epidemiology of major depression," "prevalence of depression," "the inflammatory response in major depression," "anti-inflammatory agents in depression," "antioxidant enzyme activities in major depression," "DNA damage in major depression," "pathogenesis of major depression," "cytokines in major depression," "oxidative stress in major depression," "oxidative stress markers". Articles published in english language were alone selected.

The above search yielded 538 results. Removal of duplicate articles resulted in 497 articles. Among them the articles that dealt with mood disorders, major depressive disorder, rating scales for the screening of depression, epidemiology, prevalence and pathogenesis of depression, oxidative stress were selected. Overall, there were total of 63 results, which ultimately were included in the present study. Out of those, 6 were books, 54 were original articles, and 3 were review articles.

3. DISCUSSION

3.1. Major depression

The mood disorders are a broad spectrum of diseases characterized by extensive disturbances in mood regulation and behavioral activities. They include major depressive disorders or their symptomatically less severe varieties such as cyclothymia and dysthymia; and also bipolar disorders as well as episodes of heightened emotions, hypomania or mixed symptoms [1]. The term "Depression" includes different psychic and somatic symptoms and is diagnosed by meticulous clinical observation [19]. Depression is characterized by highly variable etiopathogenesis, inconsistent course, and differential treatment-response [20]. The global burden of disease (GBD) study was started in 1990, analyzed debilitating effects of various diseases and it had shown depression as a significant worldwide-prevalent cause of morbidity [21–23].

Major depression is a part of the depression disorder spectrum that includes mood disturbances disorder, persistent depressive disorder (dysthymia), premenstrual disturbed feeling, substance / medication-induced depression, depression caused by a medical condition or any other specified and nonspecified depressive disorder [2].

3.1.1. Diagnostic criteria of major depression

Major depression can be defined as distinct events of changes in concern, perception, neurovegetative functions for at least 2 weeks coupled with periods of normal behaviour in between the episodes [2]. Major depression is a disease characterized by the presence of symptoms categorized by criterion 'A-C' as suggested by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). The definite diagnosis of major depression is indicated by the manifestation of any of the five symptoms of criterion 'A' consistently for two weeks and consisting of either (1) disheartened feeling or (2) loss of concern or delight in almost all deeds for at least two weeks [2].

3.1.2 Screening tests for major depression

Rating scales or assessment instruments are psychiatric measuring tools consisting of informative

words and phrases which help in: (i) specifying the severity of depression, (ii) facilitating the interaction between patients and the observers, and (iii) evaluation of treatment response [7].

3.1.3. Lifetime risk and prevalence of major depression

Poongothai et al. in their study among the urban population in south India observed an inclusive prevalence of 15.1%, with a higher number of female patients, and noted that the depressed mood was the most constant presenting symptom [24]. The reason for higher morbidity and mortality among the major depressive patients was a higher incidence of attempted suicides [25].

3.1.4. Etiology of major depression

Apart from the family history and genetic factors, serotonin and norepinephrine play an essential role in the progression of major depression and response to the treatment [4]. Dugue *et al*. found increased levels of interleukin-6 (IL-6) and C-reactive protein among the patients encountering stressful conditions [5]. Elevated levels of interleukin1β (IL-1β) were detected among students by Dobbin *et al.* [6]. Thus, the stressful condition of any type can act as an external stressor in the pathogenesis of depression. Any medical illness with increased cytokine production (e.g., myocardial infarction, stroke, or post-partum) can act as an internal or intrinsic stressor leading to the development of major depression [10]. Shadrina *et al*. described the genetic basis of depressive disorders [26].

3.1.5. Pathogenesis of major depression:

According to 'The monoamine hypothesis or the biogenic amine hypothesis', complete or partial deficiency of catecholamines, specifically norepinephrine and 5-HT (5-hydroxytryptamine; serotonin) play a very significant role in the development of depression [8, 9]. Elevated levels of macrophages, monokines like interleukin-1 (IL-1), interferon-alpha (INF-α), and tumour necrosis factor (TNF) are also involved in the pathogenesis of depression [27, 28].

The activated monocyte and T lymphocyte can cross the blood-brain barrier (BBB) and synthesize the cytokines; receptors for those cytokines were identified in the brain, mainly the area concerned with depression [29]. Major depression was illustrated as an immuno-neuro-psychological disorder as per the 'inflammatory response system (IRS) model of major depression' [10].

The role of stressors in IRS activation resulting changes in levels of various immunobiological markers and subsequent manifestation of symptoms of major depression has been depicted in Fig. 1, 2, 3.

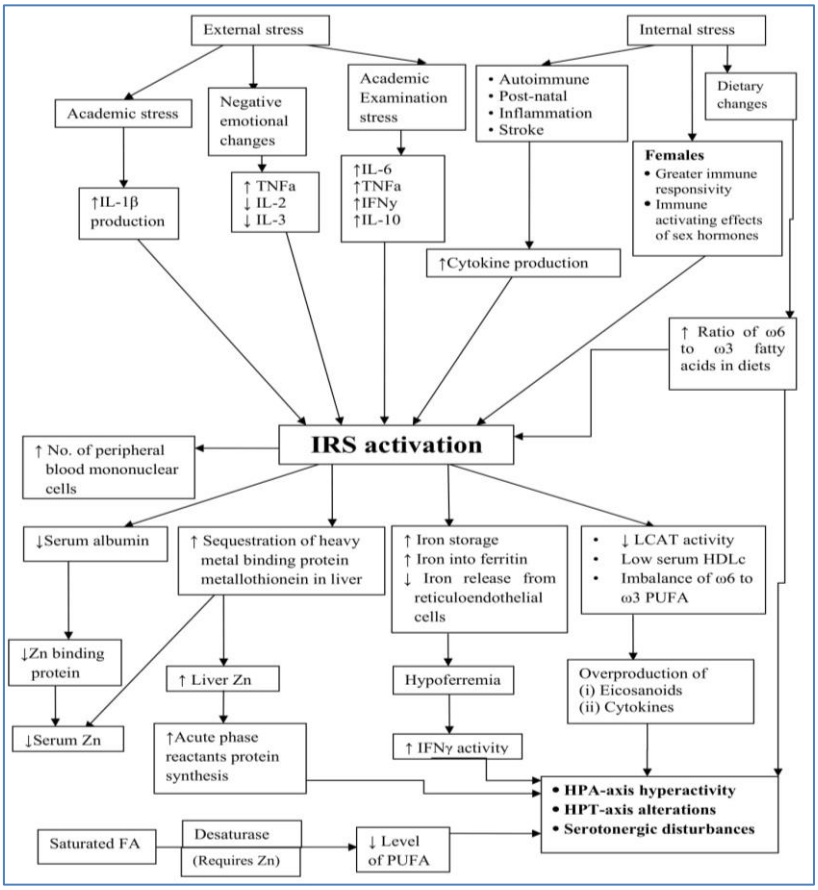

Fig-1: Role of stressors in activation of inflammatory response system (IRS), and the subsequent role of IRS activation in the etiopathogenesis of major depression

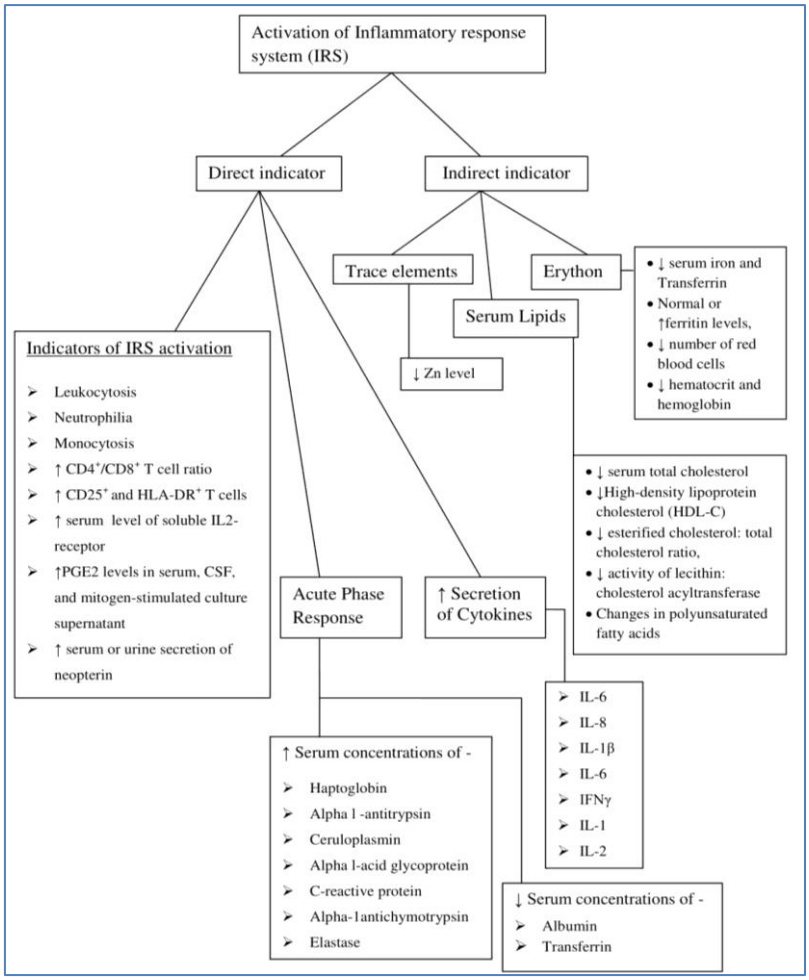

Fig-2: Changes in levels of various immunobiological markers on inflammatory response system (IRS) activation

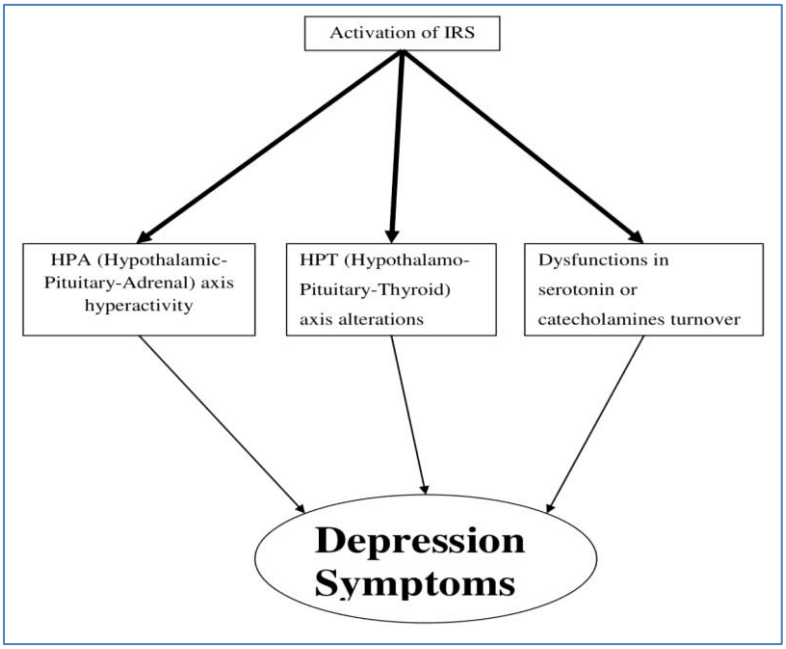

Fig-3: Role of inflammatory response system (IRS) activation in manifestation symptoms of major depression

Activation of Hypothalamic-Pituitary-Adrenal (HPA) axis results in transmission of impulses from particular areas of brain to the hypothalamus, leading to increased secretion of corticotrophin-releasing hormone (CRH), which in-turn cause increase in the levels of adrenocorticotropic hormone (ACTH) and subsequently

culminating in the augmented secretion of glucocorticoids and mineralocorticoids. In normal scenarios, CRH release is kept in check because of the negative feedback control over hypothalamus, higher centres of brain and pituitary gland. But in major depression, CRH receptors are reduced along with disruption of feedback inhibition of CRH release leading to elevated levels of CRH in cerebrospinal fluid (CSF) [30]. Stress-induced hypersecretion of cortisol as well as alterations in serotonergic, noradrenergic and dopaminergic play significant role in the pathogenesis of major depression [31].

Yirmiya *et al*. described the role of cytokines such as IL-2, IFN-α, and TNF-α in the pathogenesis of major depression [32]. Cytokines are messenger molecules responsible for controlling the immune response and based on their role they can be pro-inflammatory or anti-inflammatory [33]. Cytokines cannot cross the BBB directly. However, they can enter the brain via (i) BBB deficient sites, (ii) sites damaged by any pathological process or chronic inflammatory condition, (iii) cytokines induced-injury site (iv) active transport involving carrier protein [34-37]. Nitric oxide (NO) and prostaglandins stimulate the central nervous system (CNS) via their second messenger function [34]. The cytokines can be produced inside the brain by astrocytes, microglia, or even by the neuron in certain conditions [34]. The levels of different monoamines is influenced by cytokines acting in different areas of the brain in different proportions; thus, the monoamines-stimulated neurotransmission is eventually affected by levels of cytokines [38, 39].

The role of inflammatory, oxidative and nitrosative (IO and NS) pathways, was suggested by Maes *et al*. in 'The cytokine hypothesis of depression' which discerned that the increased levels of cytokines and neurotoxic metabolite TRYCATs (tryptophan catabolites along with the indoleamine oxidase) resulted in behavioral changes and immunoglobulin M (IgM)-mediated autoimmunological reaction against the lipid membrane components [40].

Maes *et al*. formulated 'the inflammatory and neurodegenerative (I and ND) hypothesis of depression'. They described the role of various inflammatory processes in causing different neurodegenerative changes, which subsequently resulted in the manifestation of symptoms of major depression [41]. According to 'The new 5-HT hypothesis of depression' by Maes *et al*., IRS activation mediated indoleamine 2, 3-dioxygenase (IDO) induction leads to the augmented synthesis of TRYCATS and decreased plasma levels of tryptophan ultimately manifesting as depressive symptoms [42].

The inflammatory and neurodegenerative changes occurring in significant major depression are shown in figure 4.

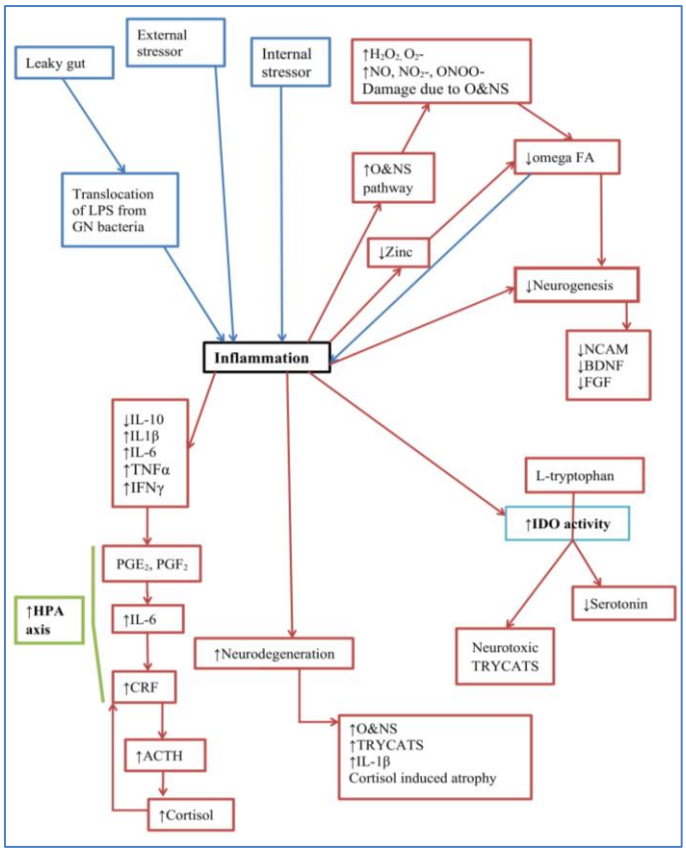

Fig-4: Inflammatory and Neurodegenerative (I and ND) pathways in depression

The summary of different theories and models regarding etiopathogenesis of major depression has been compiled in Table 1.

Table-1: Different theories and models regarding etiopathogenesis of major depression

Sr. No.	Hypothesis or model name	Mechanism involved
1.	The catecholamine hypothesis of affective disorders [8]	Depression disorder arises due to an absolute or relative decrease in catecholamines, especially norepinephrine, at central adrenergic receptor sites
2.	The monoamine hypothesis or the biogenic amine hypothesis [9]	Complete or partial deficiency of catecholamines, specifically norepinephrine or 5-HT (5-hydroxytryptamine; serotonin) significant in the development of depression
3.	The macrophage theory of depression [27]	Excessive secretion of macrophage can be the cause of depression
4.	The monocyte-T-lymphocyte hypothesis of major depression [29]	The role of activated monocyte and T lymphocyte in the synthesis of cytokines, and their receptors in the brain
5.	Inflammatory response system (IRS) model [10]	Major depression was considered as an immuno-neuro-psychological disorder as per the 'inflammatory response system (IRS) model
6.	Prototypical G*E (gene * environment) interaction model	Stress-induced hypersecretion of cortisol causing alterations in serotonergic, noradrenergic, and dopaminergic systems, present as symptoms of major depression
7.	The role of cytokines such as IL-2, IFN-α, and TNF-α [32]	Immune activation, via the release of peripheral and brain cytokines, may be involved in the etiology and symptomatology of "depression due to a general medical condition."
8.	'The cytokine hypothesis of depression [42]	Increased levels of cytokines and neurotoxic metabolite TRYCATs (tryptophan catabolites along with the indoleamine oxidase) result in behavioral changes and immunoglobulin M (IgM)-mediated autoimmunological reaction against the lipid membrane components
9.	The inflammatory and neurodegenerative (I and ND) hypothesis of depression [41]	Various inflammatory processes causing different neurodegenerative changes result in the manifestation of symptoms of major depression
10.	The new 5-HT hypothesis of depression [42]	Depressive symptoms result due to decreased plasma levels of tryptophan and augmented synthesis of TRYCATS caused by indoleamine 2, 3-dioxygenase (IDO) induction; due to IRS activation.

3.2. OXIDATIVE STRESS

3.2.1. Definition

ROS and RNS, such as superoxide, hydrogen peroxide, NO., have a highly reactive oxidizing property because of a reactive atom of oxygen or nitrogen in their molecular structure, known as oxidants, and are produced as a result of oxidative and nitrosative stress (O and NS) pathways. ROS/RNS are kept under check by a group of defence pathways under normal physiological conditions, known as antioxidants [43]. Oxidative stress can be stated as the disparity between levels of oxidants and antioxidants with the equilibrium shifting towards oxidants due to either increase in the levels of oxidants or a decrease in the levels of antioxidants or both [11].

3.2.2. Different markers

Oxidative products include ROS like superoxide, hydrogen peroxide, and hydroxyl free radical; pro-oxidant enzymes like xanthine oxidase (XO), inducible NO synthetase (iNOS); RNS like NO, nitrogen dioxide, and peroxynitrite; RNA damage product 8-oxo-7, 8-dihydro guanosine (8-oxoGuo) and DNA damage product 8-hydroxy-2-deoxyguanosine (8-OHdG), lipid peroxidation products, malondialdehyde (MDA), 8-iso-PGF2α and protein damage product such as protein carbonyl content (PCC) [12-18].

Antioxidant defence system comprises of different antioxidants, which are either enzymatic or nonenzymatic [12, 13]. Paraoxonase1, glutathione peroxidase, catalase, superoxide dismutase, glutathione reductase are few examples of enzymatic antioxidants, and vitamins C and E, ceruloplasmin, albumin, selenium, uric acid, GSH, coenzyme Q10, zinc, high-density lipoprotein cholesterol (HDL-C) are few of the examples of nonenzymatic antioxidants [13].

3.2.3. (A). Oxidative products

ROS/RNS radicals are essential for cell signalling, physiologic immunological response, and mitosis. However, because of having an unpaired electron, they are highly reactive molecules having a remarkable oxidative capacity to damage carbohydrates,

lipids, proteins, and nucleic acids [44]. Hypoxanthine is oxidized to xanthine and further to uric acid due to the action of XO along with the reduction of O_2 into superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) [45]. According to Aranda *et al*., XO activity increases with age resulting in augmented oxidative stress in old age [46]. In the post-mortem analysis of the brain tissue of the patients who were recurrently suffering from a depressive disorder, there were increased levels of XO in the cortico-limbic-thalamic-striatal tract [47]. NO is produced from L-arginine in the presence of NADPH by the action of nitric oxide synthetase (NOS) enzyme, which exists in two forms constitutive (cNOS) and inducible (iNOS) [48]. The significance of NO in the pathogenesis of depression by analyzing levels of nitrites and nitrates present in serum in end-stage renal disease patient and studying their association with the symptoms was proposed by Papageorgiou *et al*. [49]. The levels of nitric oxide metabolites (NOx) were significantly elevated in the depressed patient who recently tried to end their lives [50].

There was a decrease in the MDA levels in the major depression patients on completion of three-month treatment with fluoxetine [51]. 8-OHdG and 8-oxoGuo were produced because of oxidative-stress induced damage of DNA and ribonucleic acid (RNA), respectively [18]. Forlenza *et al*. compared the levels of 8-OHdG in serum among the patients suffering from depression and the healthy individuals and among different subgroups of depressive disorder depending upon the presenting symptoms and found participants with major depression had significantly higher levels of 8-OHdG than controls and marginally higher levels than those with minor depression [17].

Isoprostanes (isoPs) produced due to lipid peroxidation of cell membrane phospholipids [52]. Various isomers are produced from different lipids, such as F2- isoPs from arachidonic acid, F3-isoPs from eicosapentaenoic acid, and F4-isoPs from docosahexaenoic acid [53]. F2-isoPs are studied in detail and further divided into four groups of regioisomers, which can be classified as 5-, 8-, 12- and 15- iso-$PGF_{2\alpha}$ according to Tabre et al. nomenclature [54].

3.2.3. (B). Antioxidants

3.2.3. (B). 1. Antioxidant enzymes

Dismutation of free radical superoxide into oxygen and less toxic H_2O_2 is done by a family of enzymes known as SODs, which requires copper and zinc as co-factor [44]. Selek *et al.* and Herken *et al*. found a decreased activity of SOD among primary depressive disorder patients than healthy control [55, 56]. GPX (Glutathione Peroxidase) catalyze the reduction of H_2O_2 using selenium which provides free electron and gives rise to a reduced form of selenocysteine [57]. Decreased activity of GPX1 was reported by Kodydková *et al*. in women suffering from a depressive disorder [58]. Catalase is an antioxidant enzyme that causes the reduction of hydrogen peroxide to water and oxygen [59]. Galecki *et al*. assessed the catalase levels before starting and after the three-month fluoxetine course in one group and fluoxetine and acetylsalicylic acid in the other group. They found a significant fall in catalase levels after three-month of antidepressant therapy [51].

3.2.3. (B).2. Nonenzymatic antioxidants

Levels of serum zinc (Zn) were significantly lower in the depression patients who were treatment-resistant than in the healthy individuals in the past studies [60]. Plasma vitamin E levels were notably lower in major depression patients than in the healthy controls, indicating the inverse relation between plasma vitamin E and peroxidation of lipids and resultant oxidative damage [61]. Glutathione is an antioxidant, active in the reduced state (GSH) by (i) providing protection against cell damage and recycling of vitamin C and E, (ii) acting as an energy source for white blood cells, and (iii) acting as a purifying agent in the liver [62]. Kodydková *et al.* reported a noteworthy fall in GSH levels in major depressive patients [58]. After three-month of fluoxetine therapy, there was an increase in total antioxidant status (TAS) demonstrated by Galecki *et al*. It was concluded that decreased oxidative stress and increased nonenzymatic antioxidant protection were the results of fluoxetine treatment [51]. Maes et al. did a study among healthy controls and major depression patients with suicidal tendencies and found significantly decreased levels of HDL-C in the patients and a significant association between HDL-C with the other markers of immunoinflammatory reactions [63].

Different markers of oxidative stress, either an oxidant or non-oxidant (enzymatic or nonenzymatic), have been summarized in Table 2.

Table-2: Different markers of oxidative stress in major depression

Sr. No.	Name of the marker	Role	Action	Changes in levels	Study was done by
1.	Xanthine oxidase (XO)	Oxidant	Oxidizes hypoxanthine to xanthine then to uric acid along with the reduction of O_2 into superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2)	Increased XO activity in old age	Aranda *et al*. [46]
				Increased levels of XO found during post-mortem analysis in a cortico-limbic-thalamic-striatal tract of recurrent depressive disorder patients	Michel *et al*. [47]
2.	Nitric oxide (NO) metabolites	Oxidants	Produced from L-arginine in the presence of NADPH by the action of nitric oxide synthetase (NOs) enzyme	Increased levels of nitrites and nitrates in serum in end-stage renal disease and in depression	Papageorgiou *et al*. [49]
				Nitric oxide metabolites (NOx) were significantly elevated in the depressed patient who recently attempted suicides	Kim *et al*. [50]
3.	Malondialdehyde (MDA)	Oxidants	An end-product of oxidative stress-induced lipid peroxidation	The decrease in the MDA levels in major depression patients on completion of three-month treatment with fluoxetine	Gałecki *et al*. [51]
4.	8-hydroxy-2-deoxyguanosine (8-OHdG)	Oxidants	End-product of oxidative stress-induced RNA damage	Urinary excretion of 8-oxodG and 8-oxoGuo were higher with increasing severity of depression (controls, moderately depressed and severely depressed)	Jorgensen *et al*. [18]
5.	8-oxo-7, 8-dihydro guanosine (8-oxoGuo)		End-product of oxidative stress-induced DNA damage	The levels of 8-OHdG were higher in the serum of patients suffering from depression than healthy individuals	Forlenza *et al*. [17]
6.	Isoprostanes (isoPs)	Product of oxidative stress	Product of oxidative stress-induced lipid peroxidation of cell membrane phospholipids	The levels are increased in condition with increased oxidative stress	Morrow *et al*. [52]
7.	Super oxide dismutase (SOD)	Antioxidant	Dismutation of free radical superoxide into oxygen and less toxic in the presence of copper and zinc as co-factor	Decreased the activity of SOD among major depressive disorder patients than healthy control	Selek *et al*. and Herken *et al*. [55, 56]
8.	Glutathione Peroxidase (GPX)	Antioxidant	Reduction of H_2O_2 using selenium, provide free electron and gives rise to a reduced form of selenocysteine	Decreased activity of GPX1 in women suffering from a depressive disorder	Kodydková *et al*. [58]
9.	Catalase	Antioxidant	Reduction of hydrogen peroxide to water and oxygen	Significant fall in catalase levels after three-month of antidepressant therapy	Galecki *et al*. [51]
10.	Serum zinc (Zn)	Antioxidant	Co-factor for various antioxidant enzymes	Significantly reduced levels in the treatment-resistant depression patients than the healthy	Maes *et al*. [60]
11.	Vitamin E	Antioxidant	An inverse relation between plasma vitamin E levels and peroxidation of lipids and resultant oxidative damage.[77]	Reduced plasma levels in major depression patients than in the healthy controls	Maes *et al*. [61]
12.	Glutathione (GSH)	Antioxidant	(i) Protect against cell damage and recycling of vitamin C and E (ii) Act as an energy source for white blood cells (iii) Act as a purifying agent in liver.[78]	A decrease in levels of GSH major depressive patients	Kodydková *et al*. [58]
13.	Total antioxidant status (TAS)	Antioxidant		Increase in total antioxidant status (TAS) after three-month of fluoxetine therapy	Galecki *et al*. [51]
14.	High-density lipoprotein C (HDL-C)	Antioxidant	Association with another marker of immuno-inflammatory reaction	Decreased levels of HDL-C in the major depression patients with suicidal tendencies than the healthy controls	Maes *et al*. [63]

4. CONCLUSION

The current study suggests multiple pathways culminating in oxidative stress and manifesting as various symptoms of major depression. Majority of the theories regarding etiopathogenesis and progression of major depression indicate that the oxidative stress as a common factor. The role of various markers of oxidative stress suggests an increase in the levels of oxidants in major depression compared to healthy controls and reduction in the levels of antioxidant (enzymatic or nonenzymatic). Also, following the treatment with anti-depressant, reduction in the levels of oxidants and increased levels of antioxidants indicate antioxidant effects of anti-depressant drugs.

5. LIMITATIONS

The current study describes various theories and models regarding the role of oxidative stress in the etiopathogenesis of major depression. The oxidative stress is encountered in major depression and in other metabolic disorders, cancers, genetic disorders, and old age. Hence, the changes in oxidative stress markers alone cannot be considered as diagnostic of major depression but they can be adjunct indicators of propensity to major depression.

AUTHOR CONTRIBUTIONS

Rajeev Panwar (RP) conceptualized the idea, acquired the relevant data, did data analysis and drafted the manuscript. Rajasekhar S.S.S.N (RS) helped in conceptualization of idea, interpretation of data and critical revision of the manuscript. Both the author did the final proofreading and approved the final version of the manuscript.

Conflict of interests

No conflict of interest was reported.

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