WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 17, 580-597. Review Article ISSN 2277– 7105

FROM MONOAMINES TO OXIDATIVE STRESS- TARGETS AND HERBAL APPROACH IN DEPRESSION

***Dharti M. Panchal and Dr. Kedar S. Prabhavalkar**

Department of Pharmacology, Dr Bhanuben Nanavati College of Pharmacy, Maharashtra, Mumbai, Vile Parle (W), 40005, India.

Article Received on
14 August 2018,

Revised on 05 Sept. 2018,
Accepted on 26 Sept. 2018,

DOI: 10.20959/wjpr201817-13422

***Corresponding Author**
Dharti M. Panchal
Department of Pharmacology, Dr Bhanuben Nanavati College of Pharmacy, Maharashtra, Mumbai, Vile Parle (W), 40005, India.

ABSTRACT

Depression is the major leading common mental disorder affecting people at a large. The treatment options are not limited but due to non-compliance, resistance and side effects of conventional therapies, the positive outcome is limited. Hence, there is a need for different options, which can overcome these limitations. Other treatment option can be of herbal origin. There are many research studies going on to find a safe and efficacious therapy with various mechanism that can be used in depression. Oxidative stress and inflammation apart from the basic hypothesis of monoamines (5-HT, DA and NA) are also the root cause that leads to depression. There are many studies on drugs that targets monoaminergic pathways and other mechanisms. This paper will give insights on the herbal options that can be useful in reducing depressive symptoms caused by stress, oxidative stress and inflammation. The role and source of omega 3 fatty acids and its mechanism in reducing depressive symptoms are discussed in this review.

KEYWORDS: Serotonin (5-HT), Dopamine(DA), Noradrenaline/Norepinephrine (NA/NE), ALA (Alpha linolenic acid), DHA (Docosahexaenoic acid), SOD (Superoxide dismutase), Omega 3 fatty acids, Flaxseeds.

INTRODUCTION

Depression is a common mental disorder and one of the main causes of disability worldwide. Globally, an estimated 300 million people are affected by depression. More women are affected than men (WHO 2017).

Depression is characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, tiredness, and poor concentration. It is also characterized by impairments in cognition, emotional regulation, memory, motoric function, motivation, and neurovegetative symptoms. Sufferers may also have multiple physical complaints with no apparent physical cause. Depression can be long-lasting or recurrent, substantially impairing people's ability to function at work or school and to cope with daily life. At its most severe, depression can lead to suicide. The World Health Organization estimated that by 2020 unipolar major depression will become the second largest cause of global disease problems in the world, only behind ischemic heart disease (Hu et al., 2010).

Symptoms of Depression

Nestler EJ et.al. 2002 study showed the following signs and symptoms of depression.

- Depressed mood
- Irritability
- Low self-esteem
- Feelings of hopelessness, worthlessness, and guilt.
- Decreased ability to concentrate and think
- Decreased or increased appetite
- Weight loss or weight gain
- Insomnia or hypersomnia
- Low energy, fatigue, or increased agitation
- Decreased interest in pleasurable stimuli (e.g., sex, food, social interactions)
- Recurrent thoughts of death and suicide.

A diagnosis of major depression is made when a certain number of symptoms that are mentioned above occurs for more than 2 week period time, and when these symptoms disrupt normal social and occupational functioning (DSMIV, 2000).

Types of depression:- There are different types of depression as

1. Melancholic depression
2. Reactive depression
3. Psychotic depression
4. Atypical depression
5. Dysthymia

The two types of depression are

Melancholic depression is similar to a syndrome classified as "endogenous depression", based on the speculation that it is caused by innate factors.

Where Reactive Depression is similar to a syndrome classified as "exogenous depression", based on the hypothesis that is caused by external factors

The mediating role of monoamines in depression

An association of specific features and symptoms of depression and a deficiency or dysfunction of certain neurotransmitters has been proposed. (Nutt DJ., 2008) has, a 5-HT deficiency is related to anxiety, obsessions, and compulsions; reduced NE neurotransmission is associated with decreased alertness, low energy, problems of inattention, concentration, and cognitive ability; while dysfunctional dopamine (DA) activity is implicated in problems of motivation, pleasure, and reward. Interestingly, the increased 5-HT activity can be associated with certain symptoms such as fatigue. (Marin H and Menza MA., 2005)

Most of the serotonergic, noradrenergic and dopaminergic neurons are located in midbrain and brainstem nuclei and project to large areas of the entire brain. This anatomy suggests that monoaminergic systems are involved in the regulation of a broad range of brain functions, including mood, and attention; reward processing, sleep, appetite, and cognition. Almost every compound that inhibits monoamine reuptake, leading to an increased concentration of monoamines in the synaptic cleft, has been proven to be a clinically effective antidepressant (Belmaker RH, et al., 2008) Inhibiting the enzyme monoamine oxidase, which induces an increased availability of monoamines in presynaptic neurons, also has antidepressant effects. These observations led to the pharmacologically most relevant theory of depression, referred to as the monoamine-deficiency hypothesis.

The monoamine-deficiency theory posits that the underlying pathophysiological basis of depression is a depletion of the neurotransmitters serotonin, norepinephrine or dopamine in the central nervous system. Many attempts have been made to prove the hypothesis of reduced monoamine availability by measurement of neurotransmitters and/or their metabolites in postmortem brain tissues and body fluids, such as cerebrospinal fluid (CSF), blood, and urine. (Potter WZ et.al., 1985).

The deficiency in serotonergic, Noradrenergic and dopaminergic pathways has always played a major role in depression and is one of the common pathways for targets. Apart from these, there are many other mechanical and chemical reactions that is taking place when exposed to stressful situations. Apart from these, many other targets have evolved and are under clinical trials. Inflammation and inflammatory response also have a clinical impact in depression. Many antioxidants have emerged in treating depression that reduces free radicals caused due to inflammation. Omega 3 fatty acids that act as antioxidants can reduce inflammation by reducing pro-inflammatory response and reduce depressive symptoms by a different mechanism.

Many novel targets like brain derived neurotropic factor (BDNF), Glutamatergic pathways, ketamine etc are developed, Let's see how oxidative stress play an important role in depression and what are different treatment options.

1. Overview of cellular respiration

Oxidative stress, being the main endogenous source of DNA damage, can destroy cellular vital components like DNA, proteins, and lipid by resulting in free radicals from oxygen metabolism as byproducts such as reactive oxygen species (ROS).

Conversion of nutrients into readily usable chemical energy such as adenosine triphosphate (ATP) is performed by cells in the form of respiration. During this respiration, metabolic reactions occur in the form of redox reactions, transferring electrons from a molecule that is oxidized by losing electrons to another molecule whose oxidation is reduced by gaining electrons. Respiration in human cells occurs by pathways. First, glycolysis, an anaerobic reaction, occurs in the cytosol of cells. Second, a series of aerobic reactions involving the tricarboxylic acid cycle, and then oxidative phosphorylation takes place in the mitochondria. Whereas the anaerobic reaction gives off two ATPs per 1 mol glucose, and aerobic reaction yields 34 ATPs per 1 mol glucose. This means, aerobic respiration is much more efficient in producing energy and accounts for 90-95% of the total amount of ATP produced (Acuna-Castroviejo et al., 2001).

Oxidative phosphorylation involves an electron transport chain in which electrons are moved from an electron donor that is produced in a tricarboxylic acid cycle – nicotinamide adenine dinucleotide H (NADH) or flavin adenine dinucleotide H2 (FADH2) -to a terminal electron acceptor (oxygen) via a series of redox reactions. In this process, a proton (H+) gradient is

created across the mitochondrial membrane. This, in turn, is utilized in creating ATPs. Normally, the reduced oxygen, which is chemically unstable, then reacts with H+ to form H2O. However, oxidative stress occurs when the Reactive Oxygen Species (ROS) react with other molecules. As a result, damage to the cellular components and alterations in neuronal functions follow.

2. The brain: prone to oxidative stress

The human brain requires a good amount of energy to function adequately i.e say 4×1021 ATP molecules per minute. This high energy demand results from the need for ATPs to maintain and restore the ion gradients that are dissipated in signaling processes such as action potentials (i.e., maintaining the negative membrane gradient of high intracellular K+ and low Na+), neurotransmitter releases via exocytosis (i.e., keeping very low intracellular Ca2+ to enable sensitive reactions following the Ca2+ influx induced by action potentials by sequestering Ca2+ in the endoplasmic reticulum and mitochondria; (Simpson and Russell, 1998), and the uptake and recycling of neurotransmitters (Alle et al., 2009; Attwell and Laughlin, 2001). The brain uses aerobic respiration to meet this high demand for energy. Although the brain accounts for only 2% of the total body weight, it consumes about 20% of the oxygen and 25% of the glucose (Belanger et al., 2011). Aerobic respiration allows the brain to produce the needed ATPs in an efficient manner. However, the brain's heavy reliance on oxygen acts as a double-edged sword. Although the oxidative processes meet the brain's high energy needs, they also render the brain vulnerable to oxidative/nitrosative stress. Both oxidative and nitrosative stresses have been reported to alter lipids, proteins, and genes (Yao and Keshavan, 2011). Lipids account for up to 50% of the brain's dry weight, and 50%-70% of the brain lipids are phospholipids, which are rich in free-radical-prone polyunsaturated fatty acids (Siegel et al., 1981). In addition to the phospholipid-rich composition of the brain, the lack of neuronal regeneration in all but certain stem-cell regions renders the brain susceptible to oxidative/ nitrosative stress. This means that the intracellular damage done by oxidative/nitrosative stress may accumulate during the entire lifespan of neurons (Yao and Keshavan, 2011).

3. Oxidative/nitrosative stress and its mechanism

Although ROS can be generated exogenously from ultraviolet light or ionizing radiation, they are usually generated endogenously. The primary endogenous source is the mitochondria, but ROS can also be generated from the electron transport chains contained in the endoplasmic

reticulum and nuclear membranes. Various enzymatic activities other than those involved in electron transport chains also generate intracellular ROS. These include xanthine oxidase, NADPH oxidase, cytochrome P450 monooxygenase, cyclooxygenase, and monoamine oxidase. There can be chances that that H2O2 is produced by the metabolism of dopamine or serotonin via monoamine oxidase (Maker et al., 1981). This then, underlies the neurotoxicity of dopamine in the exacerbation of psychosis or cocaine/methamphetamine abuse and the neurotoxicity of serotonin in 3, 4-methylenedioxy-N-methylamphetamine (MDMA). Nitric oxide (NO) is synthesized from L-arginine by a family consisting of NO synthase (NOS) isoenzymes i.e neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). nNOS and eNOS are constitutive enzymes which get activated when there is an increase in intracellular Ca2+. iNOS is expressed independently of calcium by inflammatory cells induced by endotoxic or pro-inflammatory cytokines (Zhou and Zhu, 2009). Therefore, inflammation or neuronal excitation that can lead to increased intracellular Ca2+ may enhance the production of NO. As illustrated by the schematic depiction of the flow characterizing radical generation (Fig. 1), RNS are produced by superoxide anion and NO. Superoxide dismutase (SOD) normally competes with NO for superoxide anion. When insufficient SOD is available or the production of NO is more, peroxynitrite, a very reactive radical, is formed. Nitrosylation of proteins may inhibit their critical functions or promote apoptosis (Eu et al., 2000).

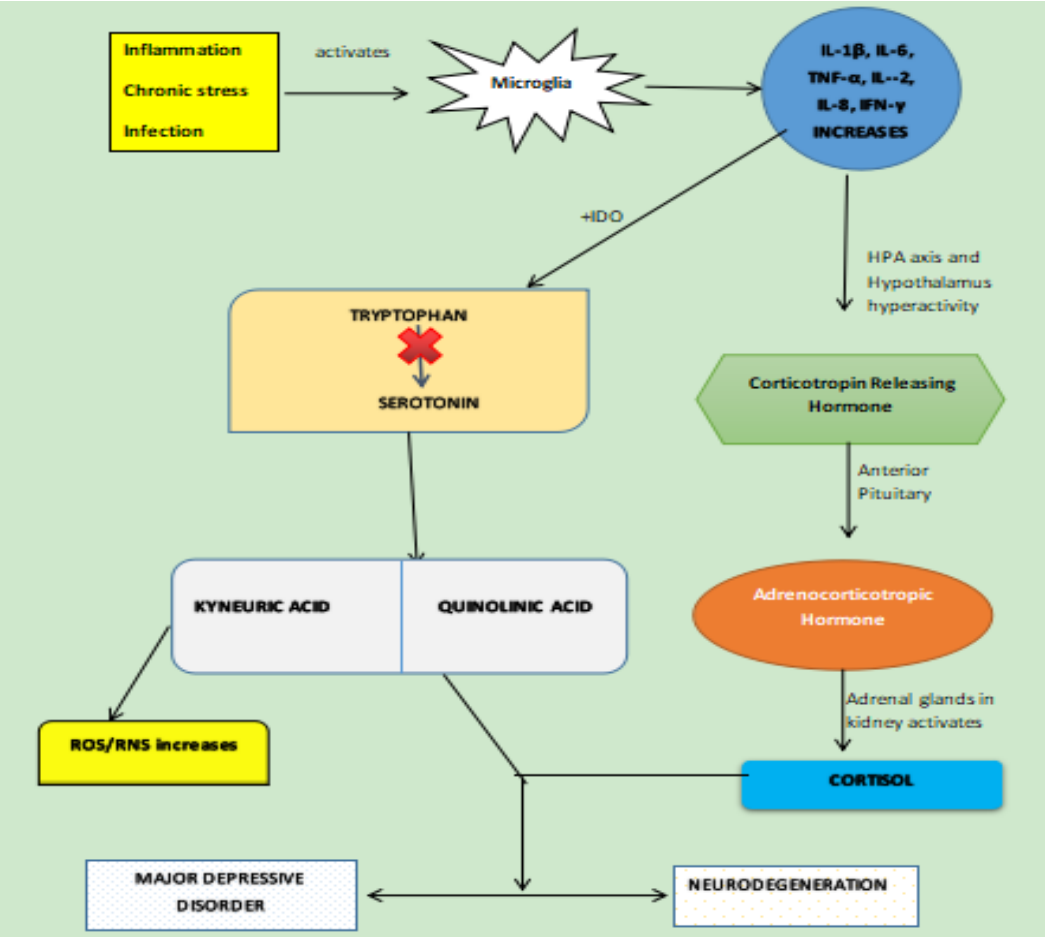

Fig. 1: The figure describes how chronic stress can lead to major depressive disorder. When the body is exposed to inflammation, chronic stress and infection lead to activation of Microglia which further activates pro-inflammatory cytokines. This then activates the HPA axis releasing Corticotropin-releasing hormone (CRH). This CRH activates Adrenocorticotropic hormone (ACTH) from the anterior pituitary. Activation of ACTH releases cortisol form adrenal glands in kidneys. Excess cortisol leads to depression and neurodegeneration. These pro-inflammatory cytokines in the presence of Indoleamine 2,3-dioxygenase enzyme catabolyses tryptophan further depleting serotonin. This promotes Kynurenic acid (KYNA) and Quinolinic acid (QUNA) and this further leads to major depressive disorder and neurodegeneration. Also, promotion of KYNA and QUNA produces Reactive Oxygen species (ROS) and reactive nitrogen species (RNS) which also further leads to Major depressive disorder.

Further to simplify this, oxidative/nitrosative stress occurs when the redox balance is breached, and pro-oxidative processes overwhelm the antioxidant defense system. Factors favoring oxidative processes may also have roots in genetic endowment (Galecki et al., 2011; Shelton et al., 2011), immune activation (Fujii et al., 2006), excitotoxicity,

neurogenesis/neuroplasticity, psychosocial stress, energy failure (e.g., stroke) and etc. Firstly, genetic vulnerability to oxidative/nitrosative stress would be reviewed.

Recently a study showed that although A/A-homozygous carriers of the gene that encodes iNOS showed a decreased risk of developing recurrent depression, the G/A single nucleotide polymorphism (SNP) was associated with an increased risk in this regard. Moreover, the presence of the CC-homozygous genotype for the gene encoding nNOS was associated with decreased risk of recurrent depression, whereas the T allele and T/T-homozygous genotype increased vulnerability in this regard (Galecki et al., 2011). Likewise, a number of genetic studies on the role of enzymes involved in oxidative stress suggested the importance of an SNP in the NOS genes in depression. Indeed, significant associations between depression and different SNPs of these genes have been found previously. A recent post-mortem study examined the prefrontal cortex samples from psychotropic-naive persons with a history of major depressive disorder to elucidate the involvement of inflammatory, apoptotic, and oxidative stress (Shelton et al., 2011). The incubation of endothelial progenitor cells with C-reactive protein (CRP) caused a dose-dependent increase in ROS formation and apoptosis. Treatment with either an antioxidant, N-acetylcysteine (NAC), or anti-CRP antibodies reduced toxicity (Fujii et al., 2006). Another antioxidant, superoxide dismutase (SOD), was reported to attenuate tumor necrosis factor-alpha (TNF-α)-induced superoxide anion production and adhesion molecule expression (Lin et al., 2005). Lin et al. suggested that the protective effect of SOD was mediated by decreased c-Jun N-terminal kinases (JNK) and p38 phosphorylation; and activatorprotein-1 and nuclear-factor kappaB (NF-kB) inactivation. In summary, inflammatory reactions may escalate pro-oxidative processes, whereas antioxidants may have a protective role.

Depression occurs by increased levels of IL-1, IL-6 and, TNF- α (Hannestad et al., 2011). When bacterial compounds or INF-Y stimulates a macrophage, It then polarizes to a pro-inflammatory (M1) macrophage. M1 macrophages, in turn, further potentiate inflammatory reaction via production of proinflammatory cytokines such as IL-1, IL-6, IL-12 and TNF-α; and releasing ROS and RNS as killing agents (Wolfs et al., 2011). This fact may lead to a possible role of M1 macrophage activation in depression. However, as natural killer cell activities were found to be decreased repeatedly in depression (Caldwell et al. 1991; Evans et al., 1992; Irwin et al., 1990, 1992), the overall role of cell-mediated immunity in depression remains to be elucidated. Next, an involvement of excitotoxicity in

oxidative/nitrosative stress would be inspected. Along with immune activation, excitotoxicity may also contribute to oxidative/nitrosative stress. Pro-inflammatory cytokines such as interleukin (IL)-1b, 2, interferon-gamma (INF- γ), or TNF- α have been reported to enhance indoleamine 2,3-dioxygenase (IDO) activity (Muller and Schwarz, 2007; Zunszain et al., 2012) under stress, promoting the kynurenine pathway instead of the 5-hydroxytryptamine (5-HT) pathway of tryptophan (Miura et al., 2008). As a result, 5-HT synthesis is reduced and quinolinic acid, known to have a neurotoxicity (Poeggeler et al., 2007), is increased.

Pro-inflammatory cytokines activate hypothalamic-pituitary-adrenal (HPA) axis and suppress sex and growth hormones release and the inhibiting HPA axis. (Haddad et al., 2002). These stimulating effects of cytokines and inhibition normal hippocampus impairment on the feedback activity in the HPA axis in total contribute to the altered HPA axis in depression.

Lets see Herbal drugs and their sources that can be beneficial in reducing oxidative stress with various mechanism.

1. Omega 3 fatty acids

Omega 3 polyunsaturated fatty acids (n-3 PUFA) are found in sea food, fishes, and olive oil in high concentrations.

Alpha linoleic (ALA) acid acids is found abundantly in flaxseeds, walnut and echium seed oils. (Kurowska et al., 2003; DeFilippis and Sperling, 2006).

Breivik, 2007 showed that flaxseed oil (linseed oil) contains upto 50% ALA when it is cold pressed. Kaul et al. 2008 showed dose of 2g/day of flaxseed was found to increase ALA in plasma. Simopoulos, 2002 showed walnut oil contained up to 10% ALA. Flaxseed doses of 2.4 and 3.6 g/day were found to significantly elevate erythrocyte ALA and eicosapentaenoic (EPA) levels by 0.23 and 0.42 (mol%), respectively ($p < 0.05$ for both), although no significant changes were noted in docosahexaenoic acid (DHA) levels (Katie L et al, 2014).

Echium plantagineum plant is the source for echium seed oil which contains 33% ALA. Algae oils have been recent area of interest in the food industry. They are produced in tightly controlled, closed fermentation facilities and are entirely vegetarian as they do not come in contact with oceanic contaminants (Breivik, 2007). they are capable of providing large amounts of DHA in the food chain. Also they are available for use in fortification of foods and dietary supplements with infant formulas. Fish oil is also a rich source of DHA and EPA.

When omega 3 and omega 6 PUFA when consumed from diet, they have a direct co-relation in influencing inflammation. Linoleic acid is the precursor of Arachidonic acid (AA) which is a n-6 PUFA are derived from sunflower, corn and safflower oils. The eicosanoids that are produced from AA increases the production of pro-inflammatory cytokines (Calder, 2005). In contrast, eicosanoids that are derived from eicosapentaenoic acid (EPA) which is a long chain n-3 PUFA and are found in fish oils, restricts the production of eicosanoids derived from AA (Calder, 2005). Therefore, higher levels of plasma n-3 PUFAs as well as lower levels of plasma n-6: n-3 PUFA ratios will restrict the production of pro-inflammatory cytokines.

Dietary omega-3 fatty acids compete with the omega-6 family of dietary polyunsaturated fatty acids for incorporation into all cell membranes (Calder PC, 2006; Healy DA et al, 2000). This is illustrated in figure below.

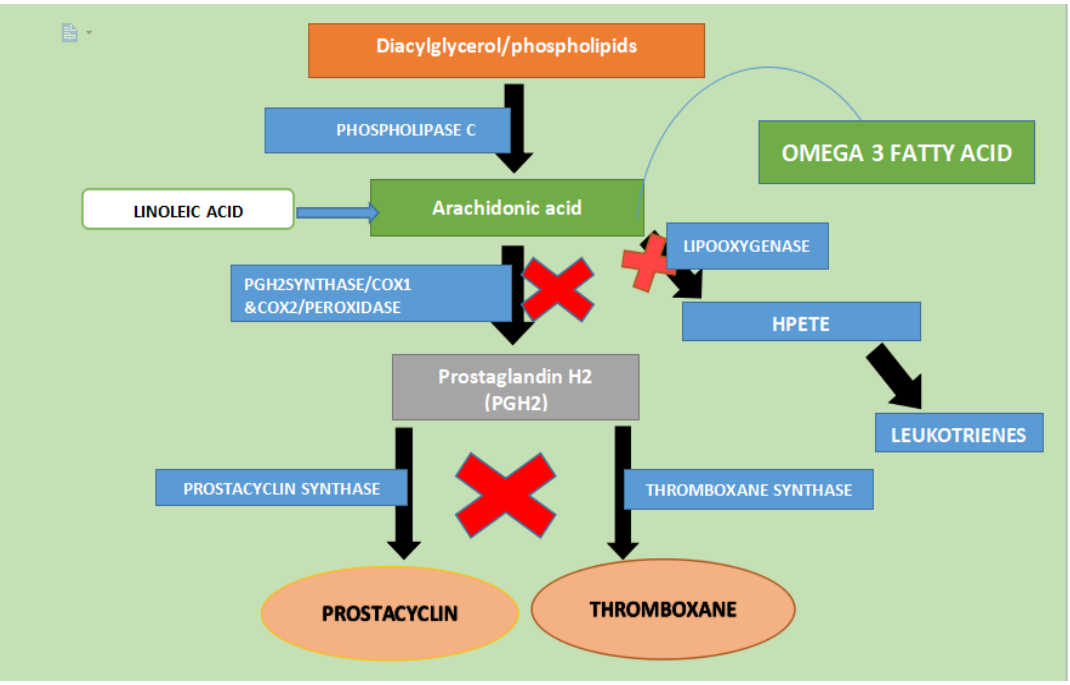

Fig. 2: Linoleic acid is the precursor of Arachidonic acid. Arachidonic acid which is PUFA is present in phospholipids of membranes of the body's cells and is abundant in brain, muscles and liver. When cell is exposed to inflammation/stress, the Diacylglycerol (DAG)/Phospholipids on the membranes in the presence of phoshoplipase are converted to Arachidonic acid (AA). This activation of AA produces Prostaglandins i.e PGH2 by PGH2 Synthase enzyme/COX1 &COX 2/ Peroxidase. This PGH2 releases Prostacyclin and Thromboxane under Prostacyclin synthase and Thromboxane synthase respectively. Also 5-hydroperoxyeicosatetraenoic acid (HPETE) is activated under lipooxygenase enzyme releasing Leukotrienes. This figure describes how n-3 Fatty acid competes with

Arachidonic acid and blocks further release of inflammatory response, hence reducing oxidation and inflammation. Changes in n-3 PUFA concentration in the brain which is induced by chronic deficiency in deficiency in dietary omega-3 PUFA can lead to an increase in serotonin 2 (5-HT2) and decrease in dopamine 2 (D2) receptor density in the frontal cortex (Delion S et al, 1994; Chalon S et al, 2001; Berg KA et al, 1996; Farooqui AA et al, 1992; Chalon S et al, 1998; Delion S et al, 1996).

Omega-3 fatty acids are considered an essential component of CNS membrane phospholipid-acyl chains and, as such, are critical to the dynamic structure of neuronal membranes (Bourre JM et la, 1991). DHA is continuously secreted by astrocytes, bathing the neuron in omega-3 fatty acid (Williard DE et al, 2001). When serotonin binds to the astroglial 5HT2A receptor, this mobilizes DHA to supply the neuron. (Garcia MC et al, 1997). Alterations in membrane lipids can alter function by changing fluidity. Proteins are embedded in the lipid bi-layer and the conformation or quaternary structure of these proteins appears to be sensitive to the lipid micro-environment. The proteins in the bi-layer have critical cellular functions, acting as receptors, enzymes, and transporters Brenner RR et al, 1984; Spector AA et al, 1985; Yehuda S et al, 1998; Bourre JM et al, 1995; Fernstrom JD, 1993).

In addition, EFAs can act as sources for second messengers within and between neurons (Ryback R, 2001). An optimal fluidity is required for neurotransmitter binding and the signaling within the cell (Heron DS et al, 1980). Omega-3 fatty acids can alter neuronal fluidity by displacing cholesterol from the membrane. (Yehuda S et al, 1998).

Other herbal drugs that are used as antioxidant and anti-inflammatory antidepressants are: Glycyrrhiza glabra, Valeriana wallichii V, Santalum album.

Glycyrrhiza glabra (Liquorice): one of the research study by Dhingra D et al, 2006 showed and proved that 150 mg/kg of liquorice extract showed antidepressant properties by hypothesizing that were increase in brain monoamines specifically dopamine and norepinephrine and not serotonin.

Santalum album (sandalwood): Setzer WN showed that essential oils are currently used to relieve anxiety, stress and depression as aromatherapy agents. Some of the anxiolytic oils of sandalwood (Santalum album), lavender (Lavandula angustifolia), rose (Rosa damascena),

orange (Citrus sinensis), bergamot (Citrus aurantium), lemon (Citrus limon), clary sage (Salvia sclarea), Roman chamomile (Anthemis nobilis), and rose-scented geranium (Pelargonium spp.).

Valeriana wallichii V: V. wallichii has showed antidepressant effect. It is also used to treat anxiety and neurosis. Fazal S proved that 250 mg/kg showed antidepressant activity by reducing immobility period in FST. Where, in TST 50-200 mg/kg reduced immobility period.

Chrysin (2): Chrysin (2), which is a natural flavonoid found in bee propolis, honey, and several plants, possesses multiple biological activities such as anti-inflammatory, antineoplastic, hypolipidemic, and antioxidant (H. Cho et al, 2004; T. Lapidot et al, 2002; M. S. Zarzecki et al, 2014).The authors suggested an association existing between the antidepressant-like action of chrysin and the proinflammatory cytokines synthesis, 5-hydroxytryptamine metabolism, kynurenine pathway, and caspases activities (Hritcu L et al, 2017).

Korean ginseng (Panax ginseng): This herb has anti-inflammatory and antioxidant effects. The mechanism lies in HPA- axis modulation alomg with monoamine modulation (dopamine and serotonin). other mechanism includes nitirc oxide synthase inhibition (Bhattacharya and Mitra, 1991; Chen, 1996; Dang et al., 2009; Joo et al., 2005; Kim et al., 2003; Park et al., 2005).

Chia seeds: Also known as *Salvia hispanica* is a good source of dietary fiber and phenolic compounds having antioxidant activity (Eyes-Caudillo; Tecante; Valdivia-Lopez, 2008). It contains nearly 25-38% of oil and has the highest % of ALA i.e approx 60%.

DISCUSSION

Many people opt for safer therapeutic options when it comes to health and benefit. We all know that there are many side effects of conventional drugs used in any disease. The old hypothesis of monoamines depletion in depression is a very common pathway for target and many novel drugs have emerged. There are other mechanisms apart from monoamines that can lead to depression. Secondary to monoaminergic pathways, there is oxidative/nitrosative stress that plays a role in depression. Novel drugs that target the free radicals generated due to stress are needed. Herbal drugs are safe and efficacious and can be used in long run. This paper discusses the role of oxidative stress and nitrosative stress that elevates depressive

related mechanistic pathways and that herbal drugs used in targeting them. The main focus of this paper was the omega 3 fatty acids that have gained interest in targeting the free radicals generated due to oxidation. Also, other herbs that can be useful in depression due too oxidative stress are mentioned here. The main focus of how flaxseeds and its oil can be useful in the daily basis for depression from various studies are discussed in this paper.

CONCLUSION

Hence, there are many sources and treatment options that can be safe to use which help in reducing depression. Herbal drugs can be used as an alternative to conventional antidepressants to avoid the major side effects. Where there is a growing evidence of use of omega 3 fatty acids and its sources in the treatment of oxidative stress induced depression.

REFERENCES

1. Acuna-Castroviejo, D.; Martin, M.; Macias, M.; Escames, G.; Leon, J.; Khaldy, H.; Reiter, R.J. Melatonin, mitochondria, and cellular bioenergetics. J. Pineal Res., 2001; 30(2): 65-74.
2. Alle H, Roth A, Geiger JR. Energy-efficient action potentials in hippocampal mossy fibers. Science, 2009; 325: 1405-8.
3. Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. J Cereb Blood Flow Metab, 2001; 21: 1133-45.
4. Belanger M, Allaman I, Magistretti PJ. Brain energy metabolism: focus on astrocyte neuron metabolic cooperation. Cell Metab, 2011; 14: 724-38.
5. Belmaker RH, Agam G. Major depressive disorder. New England Journal of Medicine, 2008 Jan 3; 358(1): 55-68.
6. Berg KA, Maayani S, Clarke WP. 5-hydroxytryptamine2C receptor activation inhibits 5-hydroxytryptamine1B-like receptor function via arachidonic acid metabolism. Mol Pharmacol, 1996; 50: 1017-23.
7. Bhattacharya, S.K., Mitra, S.K., Anxiolytic activity of Panax ginseng roots: an experimental study. J. Ethnopharmacol, 1991; 34: 87-92.
8. Bourre JM, Bonneil M, Clement M, et al. Function of dietary polyunsaturated fatty acids in the nervous system. Prostaglandins Leukot Essent Fatty Acids, 1993; 48: 5-15.
9. Bourre JM, Dumont O, Piciotti M, et al. Essentiality of omega 3 fatty acids for brain structure and function. World Rev Nutr Diet., 1991; 66: 103-117.
10. Breivik, H., Ed. Long-Chain Omega-3 Speciality Oils. The Oily Press, Bridgwater, 2007.

11. Brenner RR. Effect of unsaturated acids on membrane structure and enzyme kinetics. Prog Lipid Res., 1984; 23: 69-96.
12. Calder PC. n-3 polyunsaturated fatty acids, inflammation and inflammatory diseases. Am J Clin Nutr, 2006; 83: 1505S-19S.
13. Calder PC. Polyunsaturated fatty acids and inflammation. Biochem Soc Trans, 2005; 33: 423-427.
14. Caldwell CL, Irwin M, Lohr J. Reduced natural killer cell cytotoxicity in depression but not in schizophrenia. Biol Psychiatry, 1991; 30: 1131-8.
15. Chalon S, Delion-Vancassel S, Belzung C, et al. Dietary fish oil affects monoaminergic neurotransmission and behavior in rats. J Nutr., 1998; 128: 2512-19.
16. Chalon S, Vancassel S, Zimmer L, et al. Polyunsaturated fatty acids and cerebral function: focus on monoaminergic neurotransmission. Lipids, 2001; 36: 937-44.
17. Chen, X., Cardiovascular protection by ginsenosides and their nitric oxide releasing action. Clin. Exp. Pharmacol. Physiol, 1996; 23: 728-732.
18. Dang, H., Chen, Y., Liu, X., Wang, Q., Wang, L., Jia, W., Wang, Y., Antidepressant effects of ginseng total saponins in the forced swimming test and chronic mild stress models of depression. Prog Neuropsychopharmacol Biol Psychiatry, 2009; 33: 1417-1424.
19. DeFilippis, N. P. and Sperling, S. Understanding Omega-3's. Am. Heart J., 2006; 151: 7.
20. Delion S, Chalon S, Guilloteau D, et al. alpha-Linolenic acid dietary deficiency alters age-related changes of dopaminergic and serotoninergic neurotransmission in the rat frontal cortex. J Neurochem, 1996; 66: 1582-91.
21. Delion S, Chalon S, Herault J, et al. Chronic dietary alpha-linolenic acid deficiency alters dopaminergic and serotonergic neurotransmission in rats. J Nutr, 1994; 124: 2466-75.
22. Dhingra D, Sharma A. Antidepressant-like activity of Glycyrrhiza glabra L. in mouse models of immobility tests. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2006 May 1; 30(3): 449-54.
23. Eu JP, Liu L, Zeng M, Stamler JS. An apoptotic model for nitrosative stress. Biochemistry, 2000; 39: 1040-7.
24. Evans DL, Folds JD, Petitto JM, Golden RN, Pedersen CA, Corrigan M, et al. Circulating natural killer cell phenotypes in men and women with major depression. Relation to cytotoxic activity and severity of depression. Arch Gen Psychiatry, 1992; 49: 388-95.
25. Farooqui AA, Hirashima Y, Horrocks LA. Brain phospholipases and their role in signal transduction. Adv Exp Med Biol., 1992; 318: 11-25.

26. Fernstrom JD. Effects of dietary polyunsaturated fatty acids on neuronal function. Lipids, 1999; 34: 161-169.
27. Fujii H, Li SH, Szmitko PE, Fedak PW, Verma S. C-reactive protein alters antioxidant defenses and promotes apoptosis in endothelial progenitor cells. Arterioscler Thromb Vasc Biol., 2006; 26: 2476-82.
28. Galecki P, Maes M, Flor kowski A, Lewinski A, Galecka E, Bienkiewicz M, et al. Association between inducible and neuronal nitric oxide synthase polymorphisms and recurrent depressive disorder. J Affect Disord, 2011; 129: 175-82.
29. Garcia MC, Kim HY. Mobilization of arachidonate and decosahexaenoate by stimulation of the 5-HT2A receptor in rat C6 glioma cells. Brain Res, 1997; 768: 43-48.
30. H. Cho, C. W. Yun, W. K. Park et al., "Modulation of the activity of pro-inflammatory enzymes, COX-2 and iNOS, by chrysin derivatives," Pharmacological Research, 2004; 49(1): 37-43.
31. Haddad JJ, Saade NE, Safi eh-Garabedian B. Cytokines and neuro-immune-endocrine interactions: a role for the hypothalamic- pituitary- adrenal revolving axis. J Neuroimmunol, 2002; 133: 1-1 9.
32. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of infl ammatory cytokines: a meta-analysis. Neuropsychopharmacology, 2011; 36: 2452- 9.
33. Healy DA, Wallace FA, Miles EA, et al. Effect of low-to-moderate amounts of dietary fish oil on neutrophil lipid composition and function. Lipids, 2000; 35: 763-8.
34. Heron DS, Shinitzky M, Hershkowitz M, Samuel D. Lipid fluidity markedly modulates the binding of serotonin to mouse brain membranes. Proc Natl Acad Sci U S A, 1980; 77: 7463-7467.
35. Hritcu L, Ionita R, Postu PA, Gupta GK, Turkez H, Lima TC, Carvalho CU, de Sousa DP. Antidepressant Flavonoids and Their Relationship with Oxidative Stress. Oxidative medicine and cellular longevity, 2017; 2017.
36. Hu Y, Liu P, Guo DH, Rahman K, Wang DX, Xie TT. Antidepressant effects of the extract YZ-50 from Polygala tenuifolia in chronic mild stress treated rats and its possible mechanisms. Pharmaceutical biology, 2010 Jul 1; 48(7): 794-800.
37. Irwin M, Caldwelll C, Smith TL, Brown S, Schuckit MA, Gillin JC. Major depressive disorder, alcohlism, and reduced natural killer cell cytotoxicity. Role of severity of depressive symptoms and alcohol consumption. Arch Gen Psychiatry, 1990; 47: 713-9.

38. Irwin M, Lacher U, Caldwell C. Depression and reduced natural killer cytotoxicity: a longitudinal study of depressed patients and control subjects. Psychol Med, 1992; 22: 1045-50
39. Joo, S.S., Won, T.J., Lee, D.I., Reciprocal activity of ginsenosides in the production of proinflammatory repertoire, and their potential roles in neuroprotection in vivo. Planta Med, 2005; 71: 476-481.
40. Kaul, N., Kreml, R., Alejandro, J., Richard, M. N., Edel, A. L., Dibrov, E., Hirono, S., Zettler, M. E. and Pierce, G. N. A comparison of fish oil, flaxseed oil and hempseed oil supplementation on selected parameters of cardiovascular health in healthy volunteers. J. Am. Coll. Nutr, 2008; 27(1): 7.
41. Kim, D.H., Moon, Y.S., Jung, J.S., Min, S.K., Son, B.K., Suh, H.W., Song, D.K., Effects of ginseng saponin administered intraperitoneally on the hypothalamo-pituitary-adrenal axis in mice. Neurosci. Lett, 2003; 343: 62-66.
42. Kurowska, E. M., Dresser, G. K., Deutsch, L., Vachon, D. and Khalil, W. Bioavailability of Omega-3 essential fatty acids from perilla seed oil. Prostaglandins Leuokot. Essent. Fatty Acids, 2003; 68: 5.
43. Lin SJ, Shyue SK, Hung YY, Chen YH, Ku HH, Chen JW, et al. Superoxide dismutase inhibits the expression of vascular cell adhesion molecule-1 and intracellular cell adhesion molecule-1 induced by tumor necrosis factor-alpha in human endothelial cells through the JNK/p38 pathways. Arterioscler Thromb Vasc Biol., 2005; 25: 334-40.
44. M. S. Zarzecki, S. M. Araujo, V. C. Bortolotto, M. T. de Paula, C. R. Jesse, and M. Prigol, "Hypolipidemic action of chrysin on triton WR-1339-induced hyperlipidemia in female C57BL/6 mice," Toxicology Reports, 2014; 1: 200-208.
45. Maker HS, Weiss C, Silides DJ, Cohen G. Coupling of dopamine oxidation (monoamine oxidase activity) to glutathione oxidation via the generation of hydrogen peroxide in rat brain homogenates. J Neurochem, 1981; 36: 589-93.
46. Marin H, Menza MA. The management of fatigue in depressed patients. Essential Psychopharmacology, 2005; 6(4): 185-92.
47. Miura H, Ozaki N, Sawada M, Isobe K, Ohta T, Nagatsu T. A link between stress and depression: shifts in the balance between the kynurenine and serotonin pathways of tryptophan metabolism and the etiology and pathophysiology of depression. Stress, 2008; 11: 198-209.
48. Muller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integr ated view of depression. Mol Psychiatry, 2007; 12: 988-1000.

49. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron, 2002 Mar 28; 34(1): 13-25.
50. Nutt DJ. Relationship of neurotransmitters to the symptoms of major depressive disorder. The Journal of clinical psychiatry, 2008; 69: 4-7.
51. Park, J.H., Cha, H.Y., Seo, J.J., Hong, J.T., Han, K., Oh, K.W., Anxiolytic-like effects of ginseng in the elevated plus-maze model: comparison of red ginseng and sun ginseng. Prog Neuropsychopharmacol Biol Psychiatry, 2005; 29: 895-900.
52. Poeggeler B, Rassoulpour A, Wu HQ, Guidetti P, Roberts RC, Schwarcz R. Dopamine receptor activation reveals a novel, kynurenate-sensitive component of striatal N-methyl-D-aspartate neurotoxicity. Neuroscience, 2007; 148: 188-97.
53. Potter WZ., Scheinin M., Golden RN., et al. Selective antidepressants and cerebrospinal fluid. Lack of specificity on norepinephrine and serotonin metabolites. Arch Gen Psychiatry, 1985; 42: 1171-1177.
54. Ryback R. Bioelectrical modulators and the cell membrane in psychiatric medicine. Psychopharmacol Bull, 2001; 35: 5-44.
55. Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, Reddy R, Aschner M, Lewis DA, et al. Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. Mol Psychiatry, 2011; 16: 751-62.
56. Siegel GJ, AR, Agranoff BW, Katzman R, editors. Chemistry and metabolism of brain lipids. Basic neurochemistry, 3rd edition. Boston, MA: Little, Brown & Co, 1981.
57. Simopoulos, A. P. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed. Pharmacother, 2002; 56(8): 365-379.
58. Simpson PB, Russell JT. Role of mitochondrial Ca2+ regulation in neuronal and glial cell signalling. Brain Res Brain Res Rev., 1998; 26: 72-81.
59. Spector AA, Yorek MA. Membrane lipid composition and cellular function. J Lipid Res., 1985; 26: 1015-1035.
60. T. Lapidot, M. D. Walker, and J. Kanner, "Antioxidant and prooxidant effects of phenolics on pancreatic β-cells in vitro," Journal of Agricultural and Food Chemistry, 2002; 50(25): 7220-7225.
61. Williard DE, Harmon SD, Kaduce TL, et al. Docosahexaenoic acid synthesis from n-3 polyunsaturated fatty acids in differentiated rat brain astrocytes. J Lipid Res., 2001; 42: 1368- 1376.

62. Wolfs IM, Donners MM, de Winther MP. Differentiation factors and cytokines in the atherosclerotic plaque micro-environment as a trigger for macrophage polarisation. Thromb Haemost, 2011; 106: 763-71.
63. Yao JK, Keshavan MS. Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view. Antioxid Redox Signal, 2011; 15: 2011-35.
64. Yehuda S, Rabinovitz S, Carasso RL, Mostofsky DI. Fatty acids and brain peptides. Peptides, 1998; 19: 407-419.
65. Yehuda S, Rabinovitz S, Mostofsky DI. Modulation of learning and neuronal membrane composition in the rat by essential fatty acid preparation: time-course analysis. Neurochem Res, 1998; 23: 627-634.
66. Zhou L, Zhu DY. Neuronal nitric oxide synthase: structure, subcellular localization, regulation, and clinical implications. Nitric Oxide, 2009; 20: 223-30.
67. Zunszain PA, Anacker C, Cattaneo A, Choudhury S, Musaelyan K, Myint AM, et al. Interleukin-1beta: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. Neuropsychopharmacology, 2012; 37: 939-49.