# THE REVIEW ON ROLE OF IMMUNOMODULATORS IN TREATMENT RESISTANT DEPRESSION

**Abstract**

**The whole conditions associated with the raise or lowering a person's mood such as depression. It is characterised by determined sadness and lack of interest or pleasure in previously satisfying or enjoyable activities. It can also disturb the sleep and appetite. Chemicals in our brain called neurotransmitter play an important part in the mood. The primary treatment for severe depression we used serotonin nor epinephrine reuptake inhibitor, fluoxetine, ketamine, cytokines, curcumin. The major depression can lead to a range of behavioural and physical syndrome. These may include changes in energy level, concentration or self-esteem. It is associated with thoughts of suicide.**

**Keywords: Depression, Treatment resistance, diseases, immune system, major depressive disorder, neurotransmission, cytokines, serotonin, central nervous system.**

## INTRODUTION

Depression is a disorder of major public health importance, in terms of its prevalence and the suffering, deficient, morbidity, and economic burden. Depression is more ordinary in women than men. The report on Global load of Disease estimates the point prevalence of unipolar depressive episodes to be 1.9% for men and 3.2% for females and the one-year prevalence has been estimated to be 5.8% for men and 9.5% for women. In view of the disease, depression as a disorder has always been a focus of attention of researchers in India. Various authors have tried to study its prevalence, oncological issues, psychosocial risk factors including life events, symptomatology in the cultural context, comorbidity, psych neurobiology, treatment, outcome, prevention, disability and burden. Some of the studies have also tried to address several issues in children and elderly.[1] Major depressive disorder is a maniac illness that presents as a deficit of serotonergic neurotransmission in the central nervous system. MDD patients also experience alterations in cortisol as well as cytokines levels. Treatment with selective serotonin reuptake inhibitors is the first-line antidepressant regime for MDD. The focus of this study was to determine the effect of a combination of SSRIs and an immunomodulator human dialyzable leukocyte extract (HDLE)on cortisol and cytokines levels. The proinflammatory cytokines IL-1β, IL-2, and IFN-γ; anti-inflammatory cytokines IL-13 and IL-10; and 24-hr urine cortisol were calculated at weeks (W) 0,5, 20, 36, and 52 of treatment. The reduce in cortisol levels in the SSRI-treated group was 30% until W52, in contrast, the combined treatment induced a 54% decrease at W36. The decrease in cortisol in patients who were treated with SSRI plus HDLE correlated with lowering of anti-inflammatory cytokines and is rising levels of proinflammatory cytokines at the study conclusion. These results suggest that the immune-stimulating activity of HDLE, in mixture with SSRIs, returned the pro- and anti-inflammatory cytokine balance and cortisol levels in depressed patients versus those who were given SSRIs alone. [2] Major depression is a longstanding mood disorder, which may be seen commonly and repetitively, disrupting the quality of life and social cohesion of patients, and may even have serious consequences, such as suicide.[3] Immunomodulators are those extrinsic or intrinsic substances which manage or alteration the scope, type, Duration or competency of the immune response. [4] Activation of the innate immune system is normally connected with depression. Immunomodulatory drugs may have potency for depressive symptoms that are comorbidly related with inflammatory disorders. [5]

### Depression Symptom

1] Feelings of sadness or unhappy
2] Irritability or frustration, even over matters
3] Loss of concentration or pleasure in normal activities
4] Insomnia or excessive sleeping
5] Changes in appetite depression often Causes decreased appetite and weight loss, but in some people, it causes increased cravings for food and weight gain
6] Slowed thinking, talking or body movements

Depression affects each person in different ways, so symptoms caused by depression vary from Person to person. Genetic traits, age, gender and Cultural background all play a role in how depression may affect you.[6]

### Pathophysiology of Depression

The depressive syndrome, in one or other of its various forms, must surely be one of the most mutual problems encountered in the repetition of medicine. During this period of rapidly advancing knowledge, the illumination of factors involved in depression has continued along three main lines of aim:

1. Intensive scrutiny of the psychodynamic mechanisms involved in the precipitation and continuance of depressive attacks.
2. Study of the organic factors which may initiate, underlie, or accompany the illness.
3. Development of effective measures of treatment.[7]

Considerable evidence has grown in the last two decades to support the theory that changes in serotonergic neuronal role in the central nervous system occur in patients with major depression. These findings the following:(a) decrease cerebrospinal fluid (CSF) attentions of depressed patients; (b) reduced Concentrations of 5-HT and 5-HIM in post-mortem brain tis sue of depressed and suicidal patients; (c) decreased plasma tryptophan concentrations in depressed patients and A profound relapse in remitted depressed patients who have responded to a serotonergic antidepressant when brain tryptophan availability is reduced; (d) in

general, all clinically efficacious antidepressants augment 5-HT neurotransmission following long-lasting treatment; clinically efficacious antidepressant action by all inhibitors of 5-HT uptake In our studies, this decrease in platelet 5-HT transporter binding is not due to prior antidepressant treatment or hypercortisolaemia and is not observed in mania, Alzheimer disease, schizophrenia, panic disorder, fibromyalgia, or atypical depression. In a pilot study, this deficit predicted treatment reply to an experimental antidepressant. These findings support the hypothesis that changes in 5-HT neurons play a part in the pathophysiology of depression. [8]

**Treatment Resistant Depression**

While experts don't always agree on how to define treatment resistant depression, most use this term to describe when a person has tried at least 2 traditional depression treatments (such as psychotherapy and antidepressants), but unsuccessful to achieve positive results after a reasonable amount of time. to be clear, this doesn't mean that depression isn't curable. It simply says that a person's symptoms don't recover with standard treatment methods. In cases such as these, electroconvulsive therapy (ECT) as well as transcranial magnetic stimulation (TMS) can both help. The problem is that they may not deliver relief for some weeks. This can be discouraging if you're the one with treatment-resistant depression, creation you wonder if your feelings will ever go away. It may also help clarify why people with treatment-resistant depression have increases risk of abusing alcohol and drugs, and an increased suicide risk. Ketamine is a medication-based choice for treatment-resistant depression that, unlike ECT and TMS, doesn't require the use of specialized devices. [9]

Cytokines also have an important role in immune responses, neurogenesis and neuroprotection which are mediated by macrophages and monocytes. Studies have shown that not only the rise of the immune cytokines can be a trigger to depression, but depression can stimulate the immune system and release cytokine and interleukins although depression reductions proliferation of B cell and T cells and decreases natural killer cell activity, it up-regulates serum levels of interleukins and increases the cellular response of the immune system On the other hand, inflammatory cytokine can lead to a major depressive episode in the physically ill patient. Cytokine and interleukins that are raised in infections and trauma induce ill symptoms, like malaise, weakness and loss of interest in the physical activity, but more significantly it can trigger depressive symptoms. Among the immunologic factors, interleukin 6 and the tumour necrosis factor α are increased more compared to other cytokines. The raise of these cytokines in a normal functioning body is irregular. [10] Ketamine is a well-known, commonly used anaesthetic and analgesic drug Its rapid anti depressive activity has been confirmed in numbers of studies. Newport's meta-analysis shows that a single intravenous infusion of ketamine at a dose of 0.5 mg/kg produces robust and rapid antidepressant response within 24 hours after administration that failed steadily, but remained statistically significant up to 2 weeks. However, the mechanism in which ketamine decreases depressive symptoms in treatment-resistant depression (TRD) patients is still not completely understood. [11] major depression (MD) has been as-associated with immune system disfunction. One example of this is the altered level of cytokines important inflammatory mediators in blood, and a proinflammatory immune state has been describe in some subgroups of patients. A knock to the immune system in early life might trigger a life-long improved immune reactivity, and infections and autoimmune disorders are now Known to be risk factors for development of MD. Pro-inflammatory and anti-inflammatory cytokines mediate indole amine 2,3-dioxygenase activity; this enzyme drives metabolism of tryptophan and kynurenines in the central nervous system and damages serotonin. Alterations of serotonergic, noradrenergic, and glutamatergic neurotransmission have been associated with low-level neuroinflammation, and anti-inflammatory compounds have a therapeutic advantage in MD as shown in metanalyses.[12]

**Depression due to a general medical condition**

Several medical diseases have been informed to be accompanied by depression. These include acute and chronic infectious conditions e.g., gastroenteritis and Infections with cytomegalovirus or influenza virus; as well as non-infectious situations associated with chronic inflammation, such as rheumatoid arthritis (RA), cancer, Alzheimer's disease, MS, And other neurodegenerative diseases. Furthermore, depressive symptoms that are connected with immune responses can be diminished by pre-treatment with cytokine synthesis inhibitors and cytokine antagonists, or by cytokine gene manipulation. Moreover, LPS-induced immune activation in healthy humans, which was too mild to produce subjective symptoms of physical illness, has been found to be associated with depressed mood, anxiety and memory impairments the severity of these emotional and cognitive disturbances has been reported to be positively interrelated with the LPS induced release of proinflammatory cytokines, such as IL-1and TNF-a which again provides evidence in support of the clue that cytokines may be responsible for the pathogenesis of illness-associated depression. [13]

**Immunomodulatory Drug as Antidepressant Treatment**

An added argument that the treatment of depression may be really due to the alteration of the immune response, is the outcomes of investigates carried out with the use of non-steroidal anti-inflammatory drugs, cytokine inhibitors, polyunsaturated fatty acids or curcumin. For example, it has been shown that administration of NSAIDs can decrease the symptoms of depression. The cyclooxygenase-2 inhibitor Celecoxib turned out to be mostly effective. Intercept, a soluble TNF-α receptor, also was shown to diminish depressive symptoms. Patients suffering from depression treated with infliximab, an anti-TNF antibody, for longer period of time, also profited from the treatment in terms of improving their mental state. Curcumin, a nutrient present in plants of the ginger family, may also contribute to the reduction of depressive symptoms when supplemented with classic antidepressant treatment, most likely by inhibiting the manufacture of inflammatory mediators, such as prostaglandins, leukotrienes or nitric oxide and growing in the concentration of biogenic amines in the brain.[14]

**Fluoxetine**

Selective serotonin reuptake inhibitor (SSRI) antidepressant drug is a fluoxetine. Fluoxetine prevents the uptake of serotonin by a nerve cell and helps people with depression, panic, anxiety, or obsessive-compulsive symptoms. Fluoxetine is a prescription medicine used to cure major depressive disorder, bulimia nervosa (an eating disorder), obsessive-compulsive disorder, panic disorder, and premenstrual dysphoric disorder (PMDD).Fluoxetine is occasionally used together with extra medication called olanzapine (Zyprexa) to treat manic depression caused by bipolar disorder.[15]

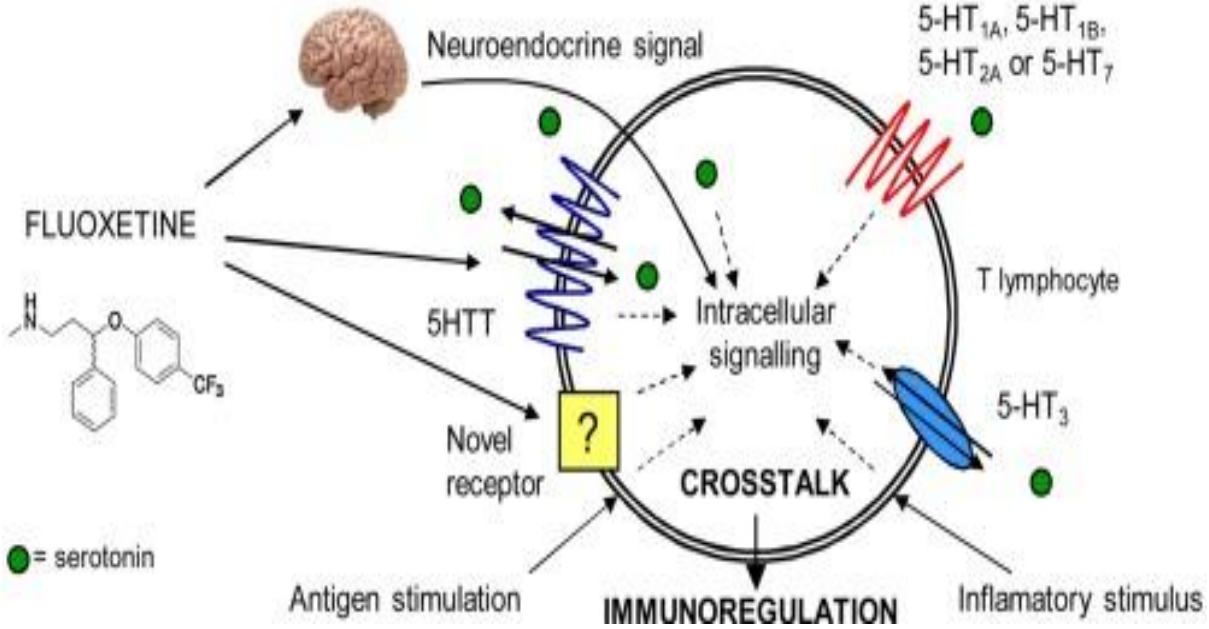
**Mechanism of Action:**

Serotonin and norepinephrine, together biological amines, have been shown to play a role in depression. Small concentrations of serotonin look in the cerebrospinal fluid of patients with depression. Moreover, lower numbers of serotonin uptake sites are situated on the platelets of patients with depression. Presynaptic serotonin (5HT1A) receptors are in the dorsal raphe nucleus and plan to the prefrontal cortex. Fluoxetine applies its effects by blocking the reuptake of serotonin into presynaptic serotonin neurons by blocking the reuptake transporter protein set in the presynaptic terminal. Fluoxetine has minor activity at the 5HT2A and 5HT2C receptors. Fluoxetine has nominal activity on noradrenergic reuptake. Due to its reuptake of serotonin, fluoxetine produces an activating effect, and due to its extended half-life, the initial antidepressant effect develops within 2 to 4 weeks. Fluoxetine's active metabolite is nor fluoxetine, which gets formed when the cytochrome P450 enzyme (CYP2D6) acts on it. [16]

**Fluoxetine Action on Immune System**

Experimental findings advise that antidepressants can moderate the proliferation of immune cells. However, there is differing evidence about the action of fluoxetine on the immune system. In addition, the sub chronic administration of fluoxetine in depressed patients regularized the initially improved plasma concentrations of pro-inflammatory cytokines IL-6and IL-1β. Frequent treatment with fluoxetine and tricyclic antidepressants (TCAs) might suppress the acute phase response in major depression. On the contrary, we described that after four weeks treatment with fluoxetine in typical mice, an augmentation of T cell mediated immunity occurs. Thus, a rise of T cell proliferation with no changes on CD4+/CD8+ ratio as well as an enhanced IFN-γ and TNF-α cytokines production was observe.[17]

**Graphical Representation of Fluoxetine**




**(Fig 1): graphical representation of Fluoxetine**

**Ketamine**

**Work Of Ketamine:**

It's totally unknown how ketamine works. Since it exerts an antidepressant effect through a new mechanism, ketamine may be able to help people effectively manage depression when other treatments have not worked. One expected target for ketamine is NMDA receptors in the brain. By binding to these receptors, ketamine looks to growth the amount of a neurotransmitter called glutamate in the places between neurons.[18]

**Ketamine help treatment resistant depression**

Ketamine is a dissociative anaesthetic, denotation that it can make you feel disconnected from your environment while also facilitation pain. ketamine is an N-methyl-D-aspartate receptor antagonist and, in this role, offers "rapid antidepressant effects" in people with treatment-resistant depression.[19]

**Immunomodulatory Effect of Ketamine:**

Regulation of immune system activity and chronic inflammation appears to play an important role in the pathogenesis of depression. Also, the increase in the level of pro-inflammatory cytokines is accompanied by an improved plasma concentrations of granulocyte macrophage colony-stimulating factor (GM-CSF) and monocyte chemoattractant protein. [11]

**Mechanism of Action Ketamine**

Ketamine affects multiple neurotransmitter systems, with the dopaminergic, monoaminergic, glutamatergic, and muscarinic systems. the precise mechanism of ketamine's antidepressant activity leftovers elusive, and other receptor systems may also be involved. The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, metabotropic glutamate receptor, and dopaminergic signalling pathways have all been concerned in ketamine's antidepressant properties. In count, a growing literature has implicated the role of inflammation in MDD, and ketamine's anti-inflammatory properties have thus gained increased attention as another mechanism potentially underlying its antidepressant effects. AMPA receptor activation in particular has been shown to modulate downstream factors, such as enhancing brain-derived neurotrophic factor (BDNF) release, which activates the tropomyosin receptor kinase B receptor and, after, mammalian target of rapamycin complex 1 (mTORC1). Present evidence suggests that a convergence of multiple pathways may best explain ketamine's exclusive therapeutic effects. The variable action of ketamine's enantiomers and respective metabolites on NMDA and AMPA receptors adds to the task of explicating ketamine's particular antidepressant effects, and additional downstream molecular and cellular pathways have been studied to better understand ketamine's rapid-acting antidepressant properties and its effects on promoting neuroplasticity. In preclinical animal model studies, the ketamine metabolites (2S,6S;2R,6R)-hydroxynorketamine (HNK) were found to be essential for its quick antidepressant effects. In addition, the antidepressant effects of the (2R,6R)-HNK enantiomer were independent of the NMDA receptor, supporting the role of AMPA receptor activity in the potentiation of excitatory synapses in mood-relevant brain regions. [20]

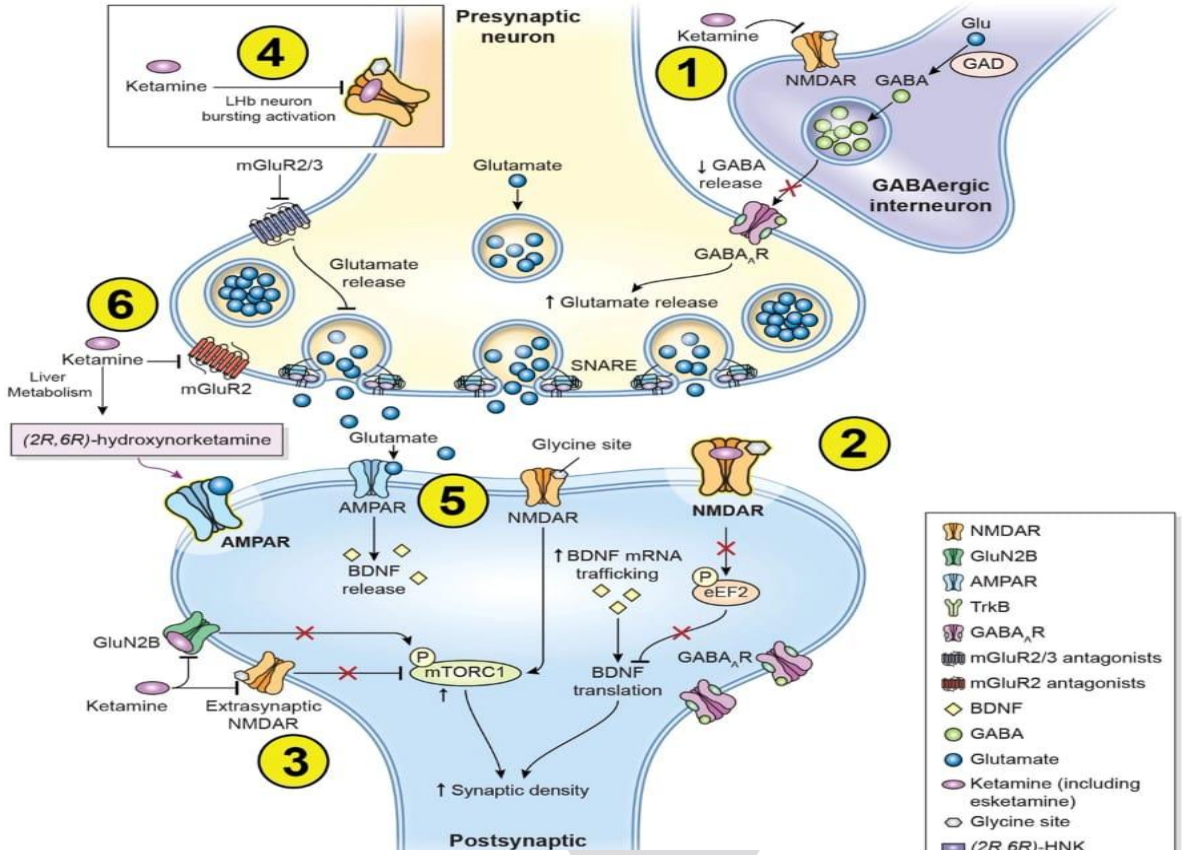



**Fig (2): ketamine treatment for Depression**

**Cytokines**

In adding, lymphatic cells, Inflammatory cells, and hematopoietic cells form an Effective immune response. The complex interactions among these cells depend on a group of proteins called Cytokines that act as mediators amongst these cells.[21] In the first 1980s cytokines were categorized as communication molecules between immune cells and endothelial cells. On the basis of their primary biological activities, cytokines are frequently grouped as lymphocyte growth factors, mesenchymal growth factors, interferons, chemokines, and colony-stimulating factors.[23] Several antidepressant actions may affect cytokine production and action both in the peripheral immune system and in the CNS. In one study, a significant decrease inIL-1-beta, IL-2 and IL-3-like activity in peripheral blood mononuclear cells was observed in untreated depressed patients when compared to controls. Synthesis of IL-1-beta and IL-3-like activity was significantly enlarged after clomipramine action. [22]

**Cytokines in depression:**
Immune responses in injuries, infections or other worrying conditions are controlled by Cytokines and chemokines Cytokines as pleiotropic molecules, play a significant role in inflammatory responses. They are measured as an important factor for brain development. Furthermore, cytokines can support neuronal integrity, neurogenesis and synaptic re-Modelling. However, chronic contact to inflammatory cytokines with High concentration may lead to neuropsychiatric dysfunction with depression being a Common one. Associated to the general population, patients with medical illnesses with Elevated level of inflammatory cytokines were more prone to depression. In depression, the neuro-inflammation is optional as a factor making imbalance between oxidative stress and anti-oxidative processes.[4]

**BIOLOGICAL PROPERTIES OF CYTOKINES**
Previously we examine the relationship among anti-Depressants and cytokines in more detail, we essential to Review the biological properties of cytokines in the CNS. Cytokines are a group of signalling molecules, primarily protein peptides or glycoproteins, used Widely in immune modulation. They are unseen by a wide variety of cells in the immune system. Conventionally they can be classed as lymphokines, Interleukins, and chemokines, depending on their Presumed function, target, or cells of origin. The term Interleukins initially indicated that these targeted leukocytes; however, this is out-Dated, since it is clear that the vast popular is produced by T-Helper cells. [23]

**Curcumin**
Curcumin, or diferuloylmethane, is the primary curcuminoid present in turmeric (Curcuma longa), a rhizomatous Plant belonging to the ginger family Zingiberaceae. [24] Turmeric has at least 6000 years of known history of its use as medicine and in various socio-religious practices. Turmeric is possibly a native of South East Asia, where many connected species of curcuma occur enthusiastically, though turmeric itself is not known to occur in the wild. India is the major producer, customer and exporter of turmeric. Rhizome of Curcuma aromatic is also used in medicines as a stomachic, carminative emmenagogue for skin diseases and recently as a health food in Japan [25] Curcumin's antioxidant, hepato- and nephroprotection, antimicrobial anti-inflammatory and potential anti-depressant properties are well recognized. It has also been optional that curcumin may diminish the incidence of Parkinson's disease (PD), as some studies have shown a nonappearance of age-related changes in nigral dopaminergic neurons in Indian populations that eat large amounts of curcumin. [26] The influence of curcumin oral administration on depression has been assessed through some clinical trials in these studies, curcumin was given orally at doses ranging from 500-1000 mg daily, alone with biopterin or in mixture with standard anti-depressive agents' escitalopram, venlafaxine or fluoxetine. [27]

**Human Trials Examining the Antidepressant Effects of Curcumin**
Studies were recognized using the Medline, Cochrane Library, Scopus, Web of Science, and CINAHL Databases, and by investigative reference lists of related Papers to locate added studies that were not known by the database searches. An orderly search of human trials using the terms curcumin and action was finished. Specific insertion criteria for the human trials included the resulting: (1) published in English; (2) adult human interventional trial (randomised Controlled, non-randomised, and open-label) evaluating the Effects of curcumin or turmeric on depression or emotional Symptoms; (3) completed pre- and post-intervention out-Come procedures; and (4) used curcumin or turmeric as a Separate or adjunct involvement. [28]. Curcumin possesses some motivating properties that validate its use in major depression [29] Some antioxidant therapeutics, like N-acetyl-cysteine, seem to show some effect in depression action have shown that, on recurrently stressed mice, curcumin administration could right depressive behaviours and advance memory functions as well as improve oxidative stress as measured by the peroxidation of lipid and the antioxidant enzyme actions. Administrated curcumin in a model of oxidative stress induced by beta amyloid infusion in mice and observed an antidepressant-like result as well as a reduction of the Aβ-generated oxidative stress in the pre-frontal cortex, as demonstrated by the responsive species levels and the superoxide dismutase and catalase activities.[30]

**Curcumin is an inhibitor of monoamine oxidase (MAO) enzyme**
The MAO enzyme is stated on the outer membrane of mitochondria in most of the body's cells. It is known to occur in 2 isoforms, MAO-A and MAO-B. MAO-B is the major form of the enzyme in the human brain and oxidizes Dopamine, while norepinephrine in addition serotonin are the preferred substrates for MAO-A. Remarkably, curcumin has both MAO-A– and MAO-B–inhibiting properties [31].

**Role of immune system in depression**
Various studies have shown a relation between a Cooperated immune system and mental problems, particularly depression. Psychoneuroimmunology offers an understanding of the relationship between immune dysfunction and mental illness. The brain and the immune system interconnect bidirectional, the hypothalamus-pituitary-adrenal (HPA) axis presence the link among them. To continue homeostasis, the body will carry out an adaptive Response called allostasis, and the HPA axis will be involved in this process. [32] Approximately 3 decades ago, indication accumulated that main depression was attended by signs of mild immunosuppression, mostly in the form of lower proliferative responses of lymphocytes and reduced activity of natural killer (NK) cells. However, when knowledge on guideline of immune functioning enlarged, it became clear that depressed patients had improved levels of inflammatory mediators and activated immune cells. [33] Dominant cytokines may contribute to the pathophysiology of depression by their effects on neuroendocrine purposes. Depression may parallel to one of these situations where inhibitory feedback loops are altered and both neuroendocrine and immune systems become determinedly activated.[34] The antidepressant drugs decrease the serum levels of proinflammatory cytokines. Excepting from cytokines, there are other factors of immune system which play critical role in the pathogenesis of depression. [35] In addition to the effects of

antidepressants on the immune, endocrine and neurotransmitter systems, it is also possible that these drugs, by inhibiting the activity of cyclooxygenase in the brain and periphery, decrease the concentration of the inflammatory mediator PGE2. The concentration of PGE2 has been exposed to be elevated in the plasma and cerebrospinal fluid of depressed patients. [36]

**Conclusion**

The depression is a main disorder shown in both men's and women. The mechanism action of antidepressant is faraway more complex is assume by the monoamine theory of depression. The treatment resistance depression is basically saying that a person's symptoms don't improve with standard treatment methods. Occasionally depression occur due to medical condition. The immunomodulatory drug used in are antidepressant treatment like fluoxetine, ketamine, celecoxib, curcumin. Fluoxetine applies its effects by blocking the reuptake of serotonin into presynaptic serotonin neurons by blocking the reuptake transporter protein set in the presynaptic terminal. Ketamine is a fast-acting general anaesthetic & NMDA receptors antagonist used for the treatment of depression. Celecoxib with anti-depressants existing better efficacy than a placebo joint with anti-depressants. Curcumin affects serotonin & dopamine, brain chemical that control mood & behaviour. The above review needed to illuminate that exact mechanism of immunomodulatory drug in a treatment resistance depression.

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