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# Computational Approach Targetting YIN YAGN 1 Inflammatory Pathway as an Alternative to Alleviate the Symptoms of Major Depressive

Aditi Singh[1] and Yasha Hasija[2]
[1-2]Department of Biotechnology, Delhi technological university, Delhi, India
Email: aditi.rsvs@gmail.com, yashahasija06@gmail.com

***Abstract*—Major Depressive Disorder (MDD) poses a significant global health burden, necessitating ingenious therapeutic approaches. MDD is associated with dysregulation in inflammatory pathways, making it a promising target for novel treatments alternatives to antidepressants . For years, the primary focus of antidepressant therapy has been to pump up the levels of monoamine neurotransmitters in the synaptic cleft.[1] Even so this selective target on monoaminergic transmission is not effective for all patients. Depressive symptoms have also shown to reoccur in patients post to discontinuing antidepressants.[7] Previous researches have evaluated that 1 out of 4 patients with MDD are affected with neuroinflammation which is linked with treatment resistance, and reduced health-related quality of life.[1]This review explores a novel avenue in MDD treatment by targeting the YY1-NF-κB inflammatory pathway which is involved in the pathophysiology of MDD.[2] The molecular docking study of Yin-Yang 1 or YY1(1UBD) with Ricinoleic Acid (RA) reveals a favorable and stable interaction. The findings demonstrate that Ricinoleic acid may inhibits YY1-mediated transcriptional activity by directly binding to the YY1 transcription factor in the inflammatory pathway so it may fail to further regulate the expression of interleukin-6 (IL-6), and interleukin-1β (IL-1β) which are major Pro-inflammatory cytokines, which play crucial role in inflammation. Blocking the activity of YY1 with Ricinoleic acid presents a novel therapeutic approach for MDD. ADME/T analysis further explored the potential of Ricinoleic acid as a novel therapeutic agent for treatment of MDD .We discuss the theoretical foundations, potential advantages over traditional antidepressants, and the need for further exploration through experimental validation and clinical studies.***

***Index Terms*— Major depressive disorder (MDD), Antidepressants ,YY1, NF-κB, IL-1β, Ricinoleic acid, Neuroinflammation.**

## I. INTRODUCTION

Major depressive disorder (MDD) is a proven mental health condition that negatively impacts behaviour and is marked by persistent low mood, melancholia, changes in appetite, feeling of worthlessness, sleep disturbance, anxiety etc. commanding immediate need for innovative therapeutic approaches. Standard antidepressant medications, the cornerstone of treatment, essential focus on correcting neurotransmitter imbalances in the brain. However, the effectiveness of these medications is often overstated, with approximately 40% of patients showing inadequate response to marketed drugs.[4] This in variation has fuelled the exploration of alternative

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therapeutic approaches and has raised concerns. An emerging avenue of research has unveiled the intricate relationship between MDD and inflammation. Chronic inflammation has been known to disrupts neurotransmitters such as serotonin and dopamine, thereby being important for mood modulation.[4] Blocking YY1 activity with Ricinoleic acid provides a new avenue for the therapeutics of MDD and it could have the potential to alleviate depressive symptoms by reviving neuroinflammatory homeostasis. [2] Also, the inflammatory patterns are known to significantly impact the functioning of neural circuit that mediates mood change and regulation, and this suggests potential role of anti-inflammatory agents in the treatment of MDD. Comprehending the inflammatory pathway in MDD has led to the identification of key players like Yin Yang 1, Nuclear Factor κB, and Interleukin-1β. In other words, this cascade proposes that YY1 regulates NF-κB, which further modulates IL-1β expression. [3] This pathway suggests inference for both mood disorders, including MDD, and alterations in glucose metabolism in the brain. Dysregulation of inflammatory cytokines and the activation of cascades such as Yin Yang 1 contribute to the development of clinical depression and has made it a probable target for novel approaches.

## II. LITERATURE

### *A.MDD andIinflammation*

It has been previously reported that there is a complex and bidirectional relationship between MDD and inflammation. Three major components , namely Yin-Yang 1 (YY1), NF-κB, and interleukin-1β (IL-1β), constitute the YY1–NF-κB–IL-1β signalling cascade .

1.Yin Yang 1 (YY1):

Nuclear protein Yin Yang 1 (YY1) is a multifunctional protein that regulates gene expression in a context-dependent manner and exhibits dual transcriptional activity as an activator and repressor. Because of its gene-specific regulatory function, its interactions with NF-κB can vary, enhancing activity for some genes while inhibiting it for others. Because of YY1's flexibility in responding to shifting cellular demands, NF-κB activity can be precisely modulated in response to a variety of stimuli and environmental cues, effectively preserving immune homeostasis and controlling inflammatory responses. Furthermore, the widespread expression of YY1 in a variety of tissues, such as the immune system, heart, brain, and limb, highlights the importance of this protein in a number of biological processes, especially in the nervous system where it is essential for cell migration, differentiation, and regional gene expression patterning.YY1, a transcription factor, has emerged as a major player in the inflammatory pathway strongly linked to peripheral and central inflammation by regulating NF-κB activity. Given that it controls gene expression, regulatory interventions aimed at regulating the inflammatory machinery of MDD may be directed towards it.

### *B. Nuclear Factor Kb*

NF-κB, is a transcription factor that plays a crucial role in regulating genes related to inflammation and intermodulation. It is composed of five subunits: NF-kB1, p52/p100, RelA, RelB, c-Rel, and p65 (RelA). Regulatory proteins (IkB) hold it in the cytoplasm and, once activated, it translocates to the nucleus. NF-KB subunits are widely expressed and play a crucial role in controlling apoptosis, stress responses, innate and adaptive immunity, and cell proliferation. The modulation of lower lineage inflammatory factors like IL-1β is associated with the NF-κB pathway, which has been linked to the inflammatory mechanism of MDD. [6].

### *C. Interleukin-1β (IL-1β)*

IL-1β is a pro-inflammatory cytokine that is crucial for the immune response and regulation of inflammation. IL-1β is one of the core mediators in the proposed YY1–NF-κB–IL-1β pathway and takes part in the inflammatory mechanisms associated with clinical depression.

### *D. Working of antidepressants*

All available antidepressants increase levels of serotonin (5HT), norepinephrine (NE) or dopamine (DA) or both with different remedial mechanisms. Tricyclic antidepressants mainly targets the reuptake inhibition of both serotonin and norepinephrine and it comes under first generation antidepressants. TCAs block the reuptake pumps for serotonin and norepinephrine, which leads to increased levels of both neurotransmitters in the synaptic cleft. Monoamine oxidase inhibitors (MAOIs), bags the inhibition of monoamine oxidase (MAO), an enzyme responsible for breaking down serotonin, dopamine and norepinephrine. However they generally possess unwanted side-effects, restricting their application. Selective serotonin reuptake inhibitors which are Newer-generation antidepressants, are more specific while they serve better safety , they basically target the

reuptake inhibition of serotonin (5-HT) neurotransmitter. SSRIs elevates the amount of serotonin available for signalling between neurons. This increase in serotonin levels help lower the symptoms of MDD and other mood disorders.[4] However SSRIs are linked to suicidal tendencies among MDD patients aged between eighteen to twenty four years of age. Antidepressants come with slow therapeutic onset, narrowed efficacy with scope of relapse. They generally work by increasing the monoamine levels, even if patients do not have lower levels of these neurotransmitters. Radically present day medications might be striking the false or indirect target, hampering their efficiency.[4]

### *E. Pathway Interaction*

The interaction between YY1 and NF-κB is considered crucial in understanding the inflammatory mechanisms correlated with depression.[3] Recent studies have uncovered its involvement in inflammation regulation, showing that YY1 is up regulated in Lipopolysaccharide induced BV2 microglia, a reaction reliant on nuclear factor kappa B's (NF-κB) transactivation function. In a recent study, interleukin 6 (IL-6) expression in microglia decreased and LPS-induced activation of the NF-κB signaling pathway was inhibited in YY1 knockout mice.YY1 was found to enhance the binding of NF-κB to the IL-6 promoter, reducing the H3K27ac modification of the IL-6 promoter and ultimately increasing IL-6 transcription.[8] Increased IL-6 activity is implicated in causing depression, potentially via the activation of the HPA , hypothalamic-pituitary-adrenal axis or influencing neurotransmitter metabolism.

### *F. Computational approach to target inflammatory pathway*

Chronic stress and low-grade inflammation have been linked to depressive symptoms,[5] indicating a potential role for anti-inflammatory agents in the treatment of MDD. In this paper ,Ricinoleic acid, a monounsaturated fatty acid found in castor oil, has been identified as a potential treatment for MDD by targeting the YY1 which further fails to influence gene expression and hence the expression of NF-kappa B and downstream factors like IL-1 beta which plays central role inflammation regulation in this inflammatory pathway. This suggests that ricinoleic acid may be a promising treatment option for MDD, as a convention to traditional Antidepressant treatment. Additionally, ricinoleic acid is derived from Cyperus rotundus, an ancient herb broadly dispersed in tropical and subtropical regions across the globe. Studies have shown that this herb possesses antioxidant, cytotoxic, antibacterial, and antifungal activity, further highlighting its potential as a treatment option for MDD.

## III. PROPOSED METHODOLOGY

### *A. Data Collection*

Bioinformatics tool and databases were made into use to retrieve protein and ligand structure . Protein Data Bank (PDB) , PubChem databases were used along with ADMET analysis software SWISS ADME besides web tools PyRx, Pymol and PLIP

### *B. Protein Preparation for Docking*

YING YANG 1 protein 3D structure was extracted from RCSB Protein Data Bank(https://www.rcsb.org/) YY1 (1UBD) was found bound with Adeno-associated virus P5 initiator element so it was moved to BIOVIA DISCOVERY STUDIO. BIOVIA is a potent toolkit that facilitates a broad spectrum of scientific research.Advanced docking algorithms are available in Discovery Studio to forecast how proteins will interact with possible therapeutic candidates. This aids in the identification of compounds that show promise for additional research. Here YY1 was made acceptable for docking by removing unwanted molecules and atoms which can otherwise interfere with ligand- protein binding and make the interaction less stable.

### *C. Ligand Preparation for Docking*

Ricinoleic acid three dimensional configuration was downloaded from PubChem ( https://pubchem.ncbi.nlm.nih.gov/ ) in Structure Data File (SDF) format. The main source of ricinoleic acid, a monounsaturated fatty acid, is castor oil, obtained from the seeds of the Ricinus communis plant. Due to its distinct chemical characteristics, anti-inflammatory properties and numerous possible uses in industrial, cosmetic, and pharmaceutical products, it has attracted attention..The two-dimensional structures, toxicity profiles, chemical nature, biochemistry, physical characteristics, molecular formulas, and literature citations of a sizable number of compounds are also included in this database.

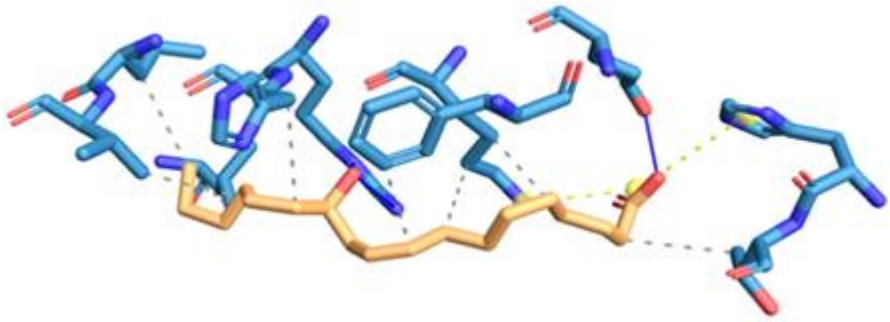

Fig.1. RA docked YY1 protein

*D. Ligand – Protein Docking*

Ligand–protein docking was done using PyRx software wherein all parameters of this computational method were set in the first place like protein in PDB format and Ligand in SDF format. Docking simulation was performed by censoring the interaction between RA and YY1 and a two dimensional configuration of this binding interaction was generated. Resultant file was imported to Pymol to analyze protein-ligand in three dimensional area.

*E. Structure Analysis of Protein-Ligand Interaction*

PDB format of this complex was stored and analysis was done using PLIP web tool (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index ) to understand the binding pattern and interaction at molecular level by inputting the protein-ligand complex 3D coordinates.

*F. ADMET Analysis*

This analysis was performed using SwissADME ( http://www.swissadme.ch/ ) web too to predict ADMET parameters of Ricinoelic acid. Absorption, Distribution, Metabolism, Excretion, and Toxicity are the acronyms for ADMET. In drug development, it is an essential component of pharmacokinetics and pharmacodynamics that aids in forecasting a compound's actions within the human body. SMILE format of RA along with SMILE formats of other major antidepressants drugs like Vortioxetine, Imipramine, Clomipramine, Reboxetine, Duloxetine and Venlafaxine was introduced into this web tool to obtain a comparative analysis of drug – likeness of them all .

## IV. RESULTS

**Molecular docking** results show strong binding between RA and YY1 and a stable interaction between them and a binding energy of -4.8 Kcal/mol. The interacting amino acids contributing to this interaction are THR 319, HIS 318, GLU 336 , VAL 346 , PHE 334, HIS 343, LYS 339, ARG 342, LEU 345 , LEU 366, SER 365 and VAL 335.

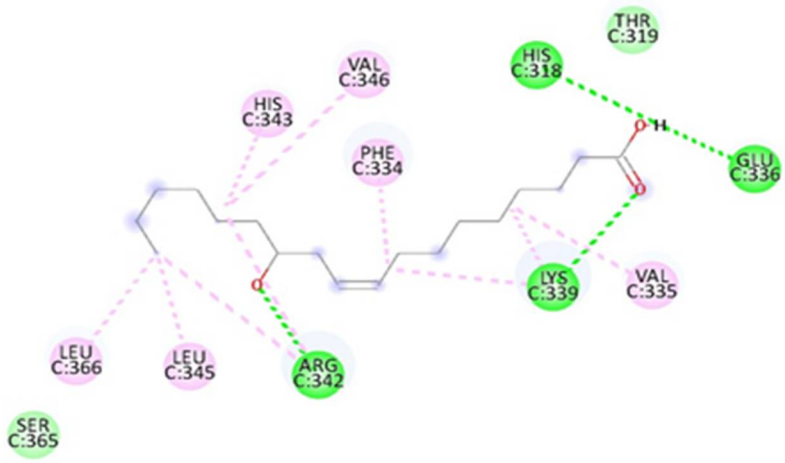


Fig.2.2- D Structural Interaction of Ricinoleic Acid with YY1 Amino Acids

**ADMET analysis** is performed to compare the drug-likeness of RA with traditional antidepressants. It predicted high value of BBB permeant which refers to a substance or drug that can effectively cross this Blood brain barrier and penetrate into the brain tissue. Drugs with BBB permeability are crucial for treating neurological disorders and zero violations of Lipinski rule of five where in molecular Weight (MW) should be less than 500 Daltons, Lipophilicity (LogP) and Hydrogen Bond Donors (HBD) should be less than 5 , Hydrogen Bond Acceptors (HBA) should be less than 10, and a good bioavailability score of 0.85, indicating that it has the capacity to enter the bloodstream, travel , and reach the targeted tissues or organs to exert an active effect. It is frequently stated as a fraction or as a percentage of the dose administered.

TABLE I. SWISSADME COMPARATIVE ANALYSIS OF VARIOUS ANTI-DEPRESSANT WITH RICINOLEIC ACID

| Drugs | GI absorption | BBB permeant | Lipinski | Bioavailability |
|---|---|---|---|---|
| Vortioxetine | High | Yes | 0 | 0.55 |
| Imipramine | High | Yes | 0 | 0.55 |
| Clomipramine | High | Yes | 1 | 0.55 |
| Reboxetine | High | Yes | 0 | 0.55 |
| Duloxetine | High | Yes | 0 | 0.55 |
| Venlafaxine | High | Yes | 0 | 0.55 |
| RA | High | yes | 0 | 0.85 |

## V. DISCUSSIONS AND FUTURE PROSPECTS

The binding energy of -4.8 Kcal/mol for the interaction between ricinoleic acid and YY1 indicates a robust and stable interaction. A number of essential amino acids, including THR 319, HIS 318, and GLU 336, are involved in the binding of ricinoleic acid to YY1. Additionally, the ADMET analysis supports the drug-likeness, oral bioavailability, and overall potential of our drug candidate, ricinoleic acid, as an effective treatment option for Major Depressive Disorder by targeting the YY1-NF-κB inflammatory pathway. It also demonstrates an excellent bioavailability score of 0.85, which is close to 1 (or 100 percent), indicating that nearly all of the administered drug reaches the systemic circulation. These findings are consistent with the Lipinski rule of five. Based on these interactions, it appears that ricinoleic acid may be able to suppress YY1-mediated transcriptional activity and lower the production of cytokines that promote inflammation. This mechanism is consistent with the discoveries that neuroinflammation contributes significantly to MDD and that reducing this inflammation may have therapeutic advantages. Although the ADMET analysis and computational studies show promise, experimental validation is essential. In order to validate the inhibitory effects of Ricinoleic acid on YY1 and its consequent influence on inflammatory cytokines, future research should concentrate on both in vitro and in vivo experiments.

## VI. CONCLUSION

In conclusion, by focusing on inflammatory pathways, the literature and computational techniques employed here demonstrate a paradigm shift in the understanding and treatment of MDD. While the bioinformatic and computational analyses provide a solid foundation, more empirical research is necessary to confirm these findings and fully realize the therapeutic potential of targeting this pathway. To ascertain the safety and effectiveness of ricinoleic acid in treating MDD in human subjects, clinical trials will also be required. Furthermore, it is crucial to comprehend the long-term consequences of modifying the YY1-NF-κB pathway. It is important to evaluate chronic inhibition of this pathway for any potential side effects or compensatory mechanisms that may develop with continued therapy. Should this strategy prove successful, it could greatly increase the number of treatments available for major depressive disorder (MDD), providing hope to those who do not respond to existing antidepressant treatments.

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