TARGETING YIN-YANG 1 INFLAMMATORY PATHWAY AS AN ALTERNATIVE TO MITIGATE THE SYMPTOMS OF MDD

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I Aditi Singh, Roll Number: 2K22/MSCBIO/03 hereby certify that the work which is being presented the thesis entitled- **"Targeting Yin-Yang 1 inflammatory pathway as an alternative to mitigate the symptoms of MDD."** in partial fulfilment of the requirements for the award of Master of Science, submitted in the Department of Biotechnology, Delhi Technological University is an authentic record of my own work carried out during the period from May 2023 to May 2024 under the supervision of Prof. Yasha Hasija.

The matter presented in the thesis has not been submitted by me for the award of any other degree of this or any other Institute.

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TARGETING YIN-YANG 1 INFLAMMATORY PATHWAY AS AN ALTERNATIVE TO MITIGATE THE SYMPTOMS OF MDD

ADITI SINGH

ABSTRACT

Major Depressive Disorder (MDD) poses a substantial burden on global health and calls for innovative therapeutic approaches. MDD is associated with disruptions in inflammatory pathways, making it a promising target for alternative treatments to antidepressants (I. Bin Kim et al., 2022). For decades the main goal of antidepressant therapy has traditionally been to increase levels of monoamine neurotransmitters in the synaptic cleft. However, this approach is not effective for all patients, as depressive symptoms can return after discontinuing antidepressants (Smit et al., 2023). Research has evaluated that 25% of patients with MDD experience neuroinflammation, which is associated with resistance to treatment and decreased quality of life(Smit et al., 2023). This in-silico study explores a novel approach to MDD treatment by targeting the YY1-NF-κB inflammatory pathway, which is involved in the pathophysiology of neuroinflammation linked MDD. The molecular docking study of fifteen candidate compounds with YIN-YANG 1((YY1) reveals a stable and favourable interaction with almost six of them, namely Turgorin , Flavylium , Kaempferol , Sitosterol , Luteolin and Sulindac suggesting , they may directly bind to the YY1 transcription factor in the inflammatory pathway in order to further control the casting of interleukin-1β (IL-1β) and interleukin-6 (IL-6), two important pro-inflammatory cytokines involved in inflammation-mediated depression, ADMET analysis further explored the potential of these compounds as way outs for treating depression wherein Flavylium, an anthocyanin ,emerges as a potential drug and presents a novel therapeutic approach over antidepressants for treating Major Depressive Disorder. This discussion marks the theoretical foundations, potential advantages over traditional antidepressants, and the need for further research to fully understand the therapeutic potential of targeting the YY1-NF-κB inflammatory pathway in MDD treatment.

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CONTENTS

List of Tables **ix**

List of Figures **x-xi**

List of Abbreviations **xii**

CHAPTER 1: INTRODUCTION **1-3**

1.1 : Background 1-2

1.2 : Objectives 3

CHAPTER 2: LITERATURE REVIEW **4-11**

2.1 : MDD and Inflammation 4-5

2.2 : Yin Yang 1 6

2.3 : Nuclear Factor kappa B 6-7

2.4 : Interleukin-1β (IL-1β) 7-8

2.5 : Pathway interaction 8-9

2.5.1 : Dual role of YY1 as a regulator of NF-κB

2.5.2: Experimental proofs

2.6 : Working of antidepressants 10-11

2.6.1 : Tricyclic Antidepressants (TCAs)

2.6.2 : Monoamine Oxidase Inhibitors (MAOIs)

2.6.3 : Selective Serotonin Reuptake Inhibitors (SSRIs)

2.6.4: Limitations of current antidepressants

CHAPTER 3: MATERIALS AND METHODOLOGY **12-18**

IN-SILICO STUDY

3.1 : Data collection 12

3.1.1 : Protein Data Bank

3.1.2: PubChem Database

3.2 : Molecular docking and visualization tools 13

3.2.1 : PyMOL

3.2.2 : PyRx
3.2.3 : PLIP
3.3 : Protein preparation for docking 13-15
3.3.1 : Structure retrieval of protein
3.3.2: Initial overview and problem
3.3.3: Refinement using BIOVIA discovery studio
3.3.4: Final prepared structure
3.4 : Ligands preparation for docking 15-16
3.4.1 : Ligands structure retrieval
3.4.2 : Initial inspection and optimization
3.4.3: Conformational analysis
3.4.4 : Energy minimization
3.4.5 : Validation and final preparation
3.4.6: Importing to docking software
3.5 : Ligand-Protein docking 17
3.6 : Protein-Ligand interaction structure analysis 17
3.7 : ADMET analysis 17-18
3.8 : Protein-Protein network analysis 18
CHAPTER 4: RESULTS 19-32
4.1 : Molecular docking 19-28
4.2 : ADMET analysis 28-31
4.2.1 : Blood-Brain barrier Permeability
4.2.2: Lipinski's Rule of Five
4.2.3: Bioavailability score
4.3 : Protein Network Analysis 31-33
DISCUSSION 34
CONCLUSION AND FUTURE PROSPECTS 35
REFERENCES 36-39
PUBLICATIONS PROOF 40
PLAGIARISM REPORT 41-42
CURRICULUM VITAE 43

LIST OF TABLES

S.no.	Name of Tables	Page no.
I.	Binding energies of all fifteen compounds docked with YY1.	27-28
II.	ADMET Analysis of fifteen drug candidates taken into consideration.	30
III.	ADMET Analysis of over-the-counter Antidepressants.	31
IV.	PPI Network statistics of YIN YANG 1.	33

LIST OF FIGURES

S.No	Name of Figures	Page No.
1.	Fig 2.1, NF-κB when inactivated, sequestered in cytoplasm by Iκb.	7
2.	Fig 2.2, Canonical and Non-canonical pathway followed by NF-κB.	7
3.	Fig 4.1, 2D image of Flavylium docked with YY1.	20
4.	Fig 4.2, 2D image of Linalool docked with YY1.	20
5.	Fig 4.3, 2D image of Sulindac docked with YY1.	21
6.	Fig 4.4, 2D docked image of Ricinoleic acid with YY1.	21
7.	Fig 4.5, 2D image of Luteolin docked with YY1.	22
8.	Fig 4.6, 2D image of Linoleic acid docked with YY1.	22
9.	Fig 4.7, 2D image of Kaempferol docked with YY1.	23
10.	Fig 4.8, 2D image of Vitexilactone docked with YY1.	23
11.	Fig 4.9, 2D image of Sitosterol docked with YY1.	24
12.	Fig 4.10, 2D image of Mimosine docked with YY1	24
13.	Fig 4.11, 2D image of Palmitoleic acid docked with YY1.	25
14.	Fig 4.12, 2D image of Arachidonic acid docked with YY1.	25
15.	Fig 4.13, 2D image of Lauric acid docked with YY1.	26

S.No.	Name of Figures	Page No.
16.	Fig 4.14, 2D image of Oleic acid docked with YY1.	26
17.	Fig 4.15, 2D image of Turgorin docked with YY1.	27
18.	Interaction network of YY1 with 20 other proteins including NF-κB.	32

LIST OF ABBREVIATIONS

MDD: Major Depressive Disorder.

YY1: YIN YANG 1

NF-κ B: Nuclear Factor Kappa B

TNF-α: Tumor Necrosis Factor Alpha

IL: Interleukin

LPS: Lipopolysaccharide

BBB: Blood-Brain Barrier

TLR: Toll-Like Receptor

TCA: Tricyclic Antidepressant

MAOI: Monoamine Oxidase Inhibitor

SSRI: Selective Serotonin Reuptake Inhibitor

RCSB: The Research Collaboratory for Structural Bioinformatics

PDB: Protein Data Bank

STRING: Search Tool for the Retrieval of Interacting Genes/Proteins

PPI: Protein-Protein Interaction

ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Major Depressive Disorder (MDD) is a widely recognized mental health disorder that has a substantial impact on global health. The most prevalent severe psychiatric illness is a mood disorder. Major depressive episodes can happen in both unipolar depression (where mood swings between euthymic and depression) and bipolar disorder (where mood swings between euthymic and depression as well as pathological "highs" called hypomania and mania). A constellation of symptoms and signs is used by the DSM-5 to define major depressive episodes(Carvalho et al., 2016) . Patients who experience major depression show changes in many important areas, such as sleep, appetite, psychomotor activity, cognition, and, of course, mood. Major depression is linked to a notable decrease in lifespan, partly as a result of suicide and partly as a result of a marked increase in susceptibility to major medical disorders, such as diabetes, cancer, autoimmune diseases, and cardiovascular disease. Major depression is the leading cause of disability globally due to its high morbidity and mortality rates, which also place a significant financial burden on society in the form of lost productivity. Depression risk factors include early childhood maltreatment and neglect, female sex, recent life stressors, and a family history of depression (hereditary depression accounts for about 35 percent of the risk). Depression is also more common in those with medical conditions, and its prevalence is highest in those with metabolic (e.g. g. autoimmune diseases, and cardiovascular disease. Depression is treated with antidepressants and other drugs that enhance their effects, evidence-based psychotherapies like cognitive-behavioural therapy (CBT) and interpersonal psychotherapy (IPT), and somatic, non-pharmacological treatments like vagus nerve stimulation (VNS), electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS) (Zou et al., 2019) .In about 50% of previously untreated depressed patients, monotherapy with either an antidepressant or evidence-based psychotherapy leads to the virtual absence of any depressive symptoms and a return to the premorbid state, termed remission. Increases in inflammatory markers in depressed patients may indicate a population that is relatively resistant to treatment. It's interesting to note that individuals with autoimmune disorders have in this regard.

The importance of this topic lies in the need for novel therapeutic strategies for MDD, given the limitations of current antidepressant treatments. While current treatment modalities for MDD, including antidepressants and psychotherapy, have shown efficacy in some patients, a considerable percentage of individuals do not achieve remission with existing interventions. Chronic inflammation is linked to depressive symptoms, with inflammatory cytokines contributing to depressive states (Dantzer et al., 2008) .Previous studies found elevated plasma cytokine levels in patients with mood disorders, associated with increased inflammation(Park et al., 2017) (Na et al., 2014). Even after trying multiple classes of antidepressants, only about two-thirds of patients respond, underscoring the need for more effective treatments. The latency period of several weeks before the effects of existing antidepressants manifest, raising the likelihood of suicide and self-harm. The belated onset of action of traditional antidepressants represents a critical public health issue in psychiatric practice, necessitating the identification of novel antidepressants that act more quickly and effectively for a greater number of people with mood disorders**.** Personalized treatment approaches based on an individual's neurobiological profile have the potential to improve response rates for those with depression who are not improving with existing antidepressant therapies.

YY1 has an important function in influencing NF-κB activity (Mu et al., 2016; Musso et al., n.d.), influencing the expression of pro-inflammatory genes and inflammatory mediators. Through the maintenance of immune homeostasis and the balance between pro- and anti-inflammatory signals, all of these interactions aid in the fine-tuning of the immune response (Na et al., 2014). This interaction may be one that can induce inflammatory diseases because of deregulated interactions. Managing inflammatory conditions may benefit from therapeutic opportunities provided by comprehending and addressing this interaction. Immune regulation, being context-dependent, allows for tailored responses to different inflammatory stimuli through modulation of signaling pathways (Ting et al., 2020). The interaction of YY1/NF-κB controls the ratio of pro- to anti-inflammatory pathways. Proper YY1-NF-κB crosstalk is crucial for responses against pathogens and prevention of excessive inflammation (S. Chen et al., 2023). The deregulated interaction might be one that induces inflammatory diseases. Comprehending and targeting this interaction may give therapeutic opportunities in managing inflammatory conditions (Rius-Pérez et al., 2020). The YY1/NF-κB interaction's context-dependent nature enables customized reactions to various inflammatory stimuli. This crosstalk has the ability to modify particular signaling pathways, underscoring its significance in immune regulation.

OBJECTIVES

- To fill the comprehension gap by exploring the potential of targeting the YY1-NF-κB inflammatory pathway in MDD treatment as research investigating the YY1-NF-κB inflammatory pathway as a novel therapeutic approach for MDD is lacking, despite the potential benefits of targeting inflammatory pathways.
- To explore previous literature and identify the crosstalk between YY1, NF-κB, MDD and develop a structured review study.
- To highlight the ill-effects in general of over-the-counter drugs available for Major Depressive Disorder.
- To explore the consequences of relying on Antidepressant therapy for all MDD patients.
- To bring out personalized medicine strategies for treating inflammation induced MDD through computational approach.

CHAPTER 2

LITERATURE REVIEW

2.1 MDD and inflammation

Previous research has explored the link between major depressive disorder (MDD) and inflammation, finding that subjects with MDD often have elevated amounts of inflammatory markers compared to those without depression. Some experimentations put forward that not all individuals with depression exhibit the same levels of inflammation, potentially indicating subtypes of "inflammatory" depression (Y. Liu et al., 2012). The usefulness of anti-inflammatory therapies for depression is being studied in on-going research, which may shed light on the significance of inflammatory pathways in MDD (Bridge et al., n.d.-b). YY1 has an important function in influencing NF-κB activity, influencing the expression of pro-inflammatory genes and inflammatory mediators. The immune system keeps itself stable by balancing pro-inflammatory and anti-inflammatory chemical messengers as a result of these cellular interactions. The proper YY1/NF-κB crosstalk is of great importance for immune responses against pathogens and avoidance of too much inflammation. This interaction may be one that can induce inflammatory diseases because of deregulated interactions. Managing inflammatory conditions may benefit from therapeutic opportunities provided by comprehending and addressing this interaction. Immune regulation, being context-dependent, allows for tailored responses to different inflammatory stimuli through modulation of signaling pathways. The interaction of YY1/NF-κB controls the ratio of pro- to anti-inflammatory pathways (Mu et al., 2016). Proper YY1-NF-κB crosstalk is crucial for responses against pathogens and prevention of excessive inflammation (Mu et al., 2016). The deregulated interaction might be one that induces inflammatory diseases. Comprehending and targeting this interaction may give therapeutic opportunities in managing inflammatory conditions. Context dependency of the YY1/NF-κB interaction imparts specificity of signaling to the cell context. The data indicates that, although inflammation is linked to major depressive disorder (MDD), it is neither sufficient nor necessary to produce depression in all cases; additionally, the fact that some people exhibit elevated inflammation while others do not may point to the vulnerability patterns of larger systems. While there is a correlation between major depressive disorder (MDD) and increased inflammation, it is not always present in depressed individuals. Depressed individuals may exhibit varying levels of

inflammatory biomarkers, with some showing increased inflammation while others do not, suggesting that immune processes are not the only factor driving depression. Various studies in progress aim to determine the effectiveness of anti-inflammatory intermediations for depression, which could authenticate the role of inflammatory signaling trajectory in MDD (Fan et al., 2017).

Previous research has identified disruptions in inflammatory pathways as a potential target for MDD treatment (Duda et al., 2019). Emerging evidence suggests that dysregulation of inflammatory pathways, including the YY1 pathway, could be very important to the pathophysiology of MDD. An immune response and inflammatory transcription factor called YY1 has been linked to a number of neurological conditions, including MDD. Developing new therapeutic approaches for MDD becomes possible when the YY1 pathway is targeted. Yin Yang 1 (YY1) is a multifunctional nuclear protein that works as a transcriptional regulator with dual activities: repressor or activator. This highly conserved protein acts in the regulation of genes in a wide variety of tissues, such as the brain, heart, limb, and immune system. In the central nervous system, YY1 participates in regional gene expression patterning, thus affecting cell migration and differentiation. Its context-dependent function enables dynamism in adjustment to the changeable needs of the cell, modulating NF-κB activity finely in immune homeostasis and control of the degree of inflammatory responses.

The varied function of YY1 clearly demonstrates the importance of exact modulation of NF-κB activity depending on different cellular conditions and signaling inputs. Other than that, perusing the literature on YY1 reveals the complicated function it serves to NF-κB, acting either as an inhibitor or promoter for that particular gene, depending on the target gene it regulates (Musso et al., n.d.). In the neurons, the expression levels of YY1 are reported to be high, suggesting that it might be involved in the neurological process, and also implicated in neurodegenerative illnesses such as Alzheimer's. (Zhang et al., 2018). YY1 operates in the nervous system and performs its function in gene expression, cell proliferation, differentiation in a very complicated context, hence presenting a multifarious scope of cellular effects. Looking at the altered levels of cytokines in depressed patients may reveal how some cytokines such as TNF-α or IL-6 might be involved in the pathophysiology of depression. (Fan et al., 2017; Zou et al., 2019). Said results propose that dysregulated cytokine control could account for the severity and symptoms of depression making it explicit that the wider implications of cytokine imbalances in the brain are cognitive impairment, inflammation as well as regulating emotions. (Raison & Miller, 2011). This thus introduces the diverse functions and significance of YY1 in gene regulation, the context-dependent nature of its role in the nervous system, and how this cytokine dysregulation may impact depressive disorder (Na et al., 2014). Integrating these features however is an equivalent of getting into the nuts and bolts behind gene regulation, cellular processes as well as pathophysiology of neurological and psychiatric conditions.

2.2 YIN YANG 1

YY1 is a nuclear protein that has polyvalent properties and can serve as both an activator and inhibitor of transcription. It interacts with NF-κB in genes that enhance the activity of some while inhibiting that of others, to show its regulatory role specific to individual genes (Lu et al., n.d.). This flexibility in YY1 makes it possible for NF-κB activity to be precisely increased or reduced during immune homeostasis and inflammation mediated by different types of stimulus from the external environment. This is also because the gene plays important roles in many biological processes, which include but are not limited to the nervous system, heart, limb and immune system. In the nervous system specifically, it serves as a critical transcription factor involved in regional gene expression patterning, cell migration and differentiation.YY1 is an essential transcription regulator with a wide range of functions, but this introduction focuses on its complex and context-dependent roles, especially in the intricate processes of gene regulation and cellular homeostasis. The ubiquitous transcription factor Yin Yang 1 controls a wide range of biological processes.

The outcome of gene transcription being activated, enhanced, or inhibited depends on the specific binding site of the protein and seems to be mediated by either direct or indirect activation or repression of genes. Molecular elucidation shows detailed information, suggesting that YY1 is able to depress p53 activity, inhibit poly-ADP-ribose polymerase, trigger events of genes such as c-myc and nuclear factor-kappa B, modulate genes controlling the mechanism of cell death, and display differential binding activity in the presence of inflammatory molecules (He & Casaccia-Bonnefil, 2008). In addition, further studies highlight the role of this gene in the development of resistance to therapeutic procedures in tumor cells in the form of chemotherapy and immune-mediated cell death. Fundamentally, the sum of evidence supports the fact that apart from the traditional trans-activating and trans-inhibiting functions, YY1 might also be involved in the process of carcinogenic growth pattern formation and hence is becoming a biomarker of cancer prognosis and detection and, finally, a target for pharmacological intervention aimed at chemotherapy and immunotherapy (Dong & Kwan, 2020).

2.3 NUCLEAR FACTOR KAPPA B

In mammalian cells, the five members of the NF-KB transcription factor family are typically divided into two groups according to their structural makeup. The longer precursor proteins that make up Class 1 are NFKB1 (p105/p50) and NFKB2 (p100/p52), which can be processed into shorter DNA-binding forms. RelA (p65), RelB, and c-Rel, which have distinct transcriptional activation domains and don't need to be processed, make up Class two (Chiba et al., 2013). NF-κB subunits, originally discovered as a RelA: p50 heterodimer, are essential for cell proliferation, innate and adaptive immunity, stress responses, and apoptosis. The subunits are usually inactive in the cytoplasm because of the ankyrin repeat proteins referred to as the inhibitors of NF-κB, or IκBs (Chiba et al., 2013). These inhibitors include IκBa, IκBb, IκBc, IκBNS, IκBe, and IκBf. Additionally, the p50 and p52 precursors contain

IκB-like repeats and can act as NF-κB inhibitors before processing (Tsui et al., 2015). In addition, there are other IκB-like proteins present in the nucleus that could regulate the transcriptional activity of the NF-κB subunit, which include B-cell lymphoma. When referring to the gene or studies that do not distinguish between the p105 and p50 isoforms, we use NFκB1 for the purposes of this review. Nonetheless, the terms p50 and p105 will be used to denote the distinct roles played by the proteins. Activation of NF-κB is mediated by several pathways (T. Liu et al., 2017). A thorough analysis of NF-κB's activation pathways has been conducted (Ahmad et al., 2021). In conclusion, cells respond to inflammatory cytokines like TNFα and IL-1 or are exposed to inflammatory signals like LPS from bacteria to initiate the classical route, also referred to as the canonical route. The IκB kinase (IκK) complex, which is made up of IκKa (IκK1), IκKb (IκK2), and NFκ-B essential modifier (NEMO, also referred to as Iκc), is activated by these stimuli (L. Chen et al., 2021). The phosphorylation-driven polyubiquitination and 26-second proteasomal degradation of IκBa that results from this process allow active NF-κB subunits to localize in the nucleus and regulate gene transcription, primarily of RelA: p50 and c-Rel: p50 heterodimers (Rius-Pérez et al., 2020). A distinct, though occasionally overlapping, set of classical pathway stimuli, such as CD40 ligand or lymphotoxin B, can activate IκKa in the non-canonical (alternative) pathway. After that, IκKa phosphorylates p100 several times, directing the 26s proteasome to convert it to p52 (T. Liu et al., 2017).

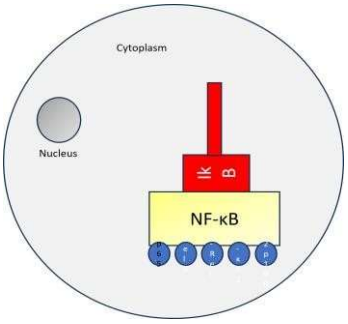

Fig 2.1 NF-κB when inactivated, sequestered in cytoplasm by Iκb.

2.4 INTERLEUKIN-1β (IL-1β)

The IL-1 group consists of at least three proteins: IL-1α, IL-1β, and IL-1ra, which are produced from different genes with significant similarities and are implicated in the development of numerous human diseases. IL-1β is a cytokine that plays a crucial role in regulating the immune system and can induce inflammation affecting various cell types. It is produced by macrophages, microglia, and monocytes following the activation of the inflammasome (Rius-Pérez et al., 2020). IL-1β can activate NF-κB by stimulating TLRs, leading to the activation of genes related to chemokines, cytokines, and other proinflammatory factors. It can also interact with the vascular endothelium, increasing leukocyte adhesion and promoting edema formation. When bound to its receptor (IL-1R), IL-1β can stimulate NF-κB pathways in an IL-1R-dependent manner. IL-6 generation requires the presence of IL-1 and TNF, as they

can activate fibroblasts, endothelial cells, and keratinocytes while also enhancing IL-6 expression (Na et al., 2014). IL-6 is a critical proinflammatory protein with various important roles. Cytokines such as IL-6 and TNF-α are key players in the body's inflammatory response (Ting et al., 2020).

The blood-brain barrier (BBB) is responsible for controlling the passage of substances into the central nervous system (CNS), only allowing essential molecules to cross(Maida et al., 2020) . It acts as a protective barrier between the bloodstream and the CNS. Alterations in the BBB's ability to regulate which substances can enter the CNS can lead to the development of various diseases (Na et al., 2014).

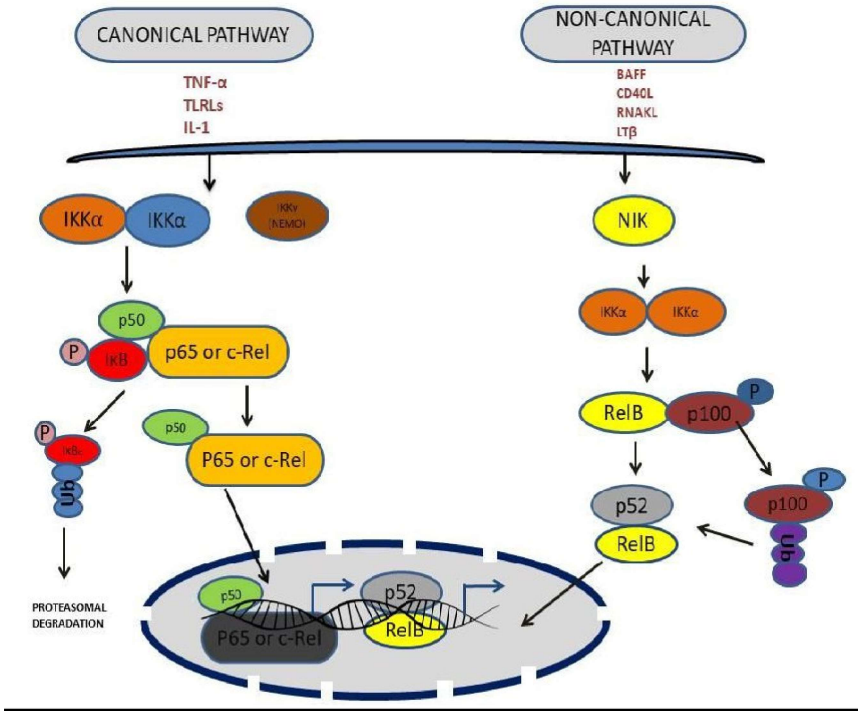

Fig. 2.2 Canonical and Non-canonical pathway followed by NF-κB

2.5 PATHWAY INTERACTION

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 signaling cascade.

2.5.1 Dual Role of YY1 as a Regulator of NF-κB

Research has indicated that YY1 may influence NF-κB activity either directly or indirectly.

- **Direct binding**: YY1 has the ability to bind directly to the IL-6 promoter or to other DNA regions, which may modify the accessibility of NF-κB binding sites. This has the ability to alter the IL-6 gene's transcriptional activity (He & Casaccia-Bonnefil, 2008).
- **Protein-Protein Interactions**: Through its interactions with NF-κB subunits like p65/RelA, YY1 can affect NF-κB's ability to bind to its target sequences on the IL-6 promoter. YY1 may either promote or prevent the transcriptional complex from forming, which is necessary for NF-κB to function properly (He & Casaccia-Bonnefil, 2008).
- **Histone-modifying enzymes and chromatin remodelling complexes** are known to be attracted by YY1. Through modifications to the chromatin state at the IL-6 promoter, YY1 can indirectly influence NF-κB binding by varying the accessibility of the promoter region (L. Chen et al., 2021). Collaborative Binding: Certain research indicates that NF-κB and YY1 may be able to bind to the IL-6 promoter together, which would increase transcriptional activation (Lu et al., n.d.). Contextual factors, such as the presence of other cofactors and the particular cellular environment, can affect this cooperation. Competitive Binding: In different situations, YY1 may recruit repressive complexes that block NF-κB function or compete with NF-κB for binding sites, which would reduce (He & Casaccia-Bonnefil, 2008; Lu et al., n.d.).

2.5.1 Experimental Proofs:

Promoter Assays: YY1-mediated transcriptional activity has been demonstrated to be altered by YY1 overexpression or knockdown through the use of luciferase reporter assays that employ constructs that carry the IL-6 promoter (He & Casaccia-Bonnefil, 2008).

Chromatin immunoprecipitation assay: YY1 and NF-κB are both capable of binding to the Interleukin-6 promoter, and the presence of YY1 can influence the level of NF-κB binding in response to various stimuli, as determined by chromatin (He & Casaccia-Bonnefil, 2008).

2.6 WORKING OF ANTIDEPRESSANTS

Over-the-counter (OTC) antidepressants mainly work by adjusting the amounts of important neurotransmitters in the brain, like dopamine (DA), norepinephrine (NE), and serotonin (5HT), via a variety of methods. The main targets in the treatment for

depression and other mood disorders are these neurotransmitters because of their critical roles in mood regulation.

2.6.1 Tricyclic Antidepressants (TCAs):

Tricyclic antidepressants are a type of medication that were among the first class of antidepressants developed. They work by blocking the reabsorption of serotonin and norepinephrine, two important neurotransmitters in the brain. The higher levels of tricyclic antidepressants in the space between neurons, known as the synaptic cleft, leads to impediment of reabsorption of these neurotransmitters increasing their concentration; consequently, alleviating symptoms of depression through prolongation of their effects. Regrettably, tricyclic antidepressants come with consequential side effects. These can comprise dry mouth, blurred vision, constipation, difficulty urinating, and probable damage to the heart (Bridge et al., n.d.-a; Carvalho et al., 2016). These ill-effects are majorly due to the path tricyclic antidepressants follow to bind to various receptors in the body, such as histaminergic, cholinergic, and adrenergic receptors, without discrimination.

2.6.2 Monoamine Oxidase Inhibitors (MAOIs):

Various monoamines, namely, Serotonin, dopamine, and norepinephrine are the are broken down by this enzyme. MAOIs raise these neurotransmitter levels in the brain by obstructing Monoamine Oxidase. MAOIs are useful, but they are typically only used for depression that is resistant to treatment because of their high risk of side effects and dietary restrictions (Carvalho et al., 2016). They are not recommended for general use because they have numerous drug-drug interactions and can result in hypertensive crises when consumed with foods high in tyramine (Bridge et al., n.d.-a).

2.6.3 Selective Serotonin Reuptake Inhibitors (SSRIs):

In contrast to TCAs and MAOIs, selective serotonin reuptake inhibitors are a relatively new class of antidepressants with superior safety records. Serotonin reuptake is specifically inhibited by SSRIs, which increases serotonin availability in the synaptic cleft. This focused approach, which has fewer side effects, aids in reducing depressive symptoms. Citalopram, sertraline, and fluoxetine are examples of common SSRIs. Despite their generally low risk of side effects, SSRIs have a number of drawbacks. They have side effects that include gastrointestinal issues, weight gain, and sexual dysfunction(Bridge et al., n.d.-b). Furthermore, among young adults between the ages of 18 and 24, SSRIs have been connected to a higher risk of suicidal thoughts and actions, especially during the first phase of treatment.

2.6.4 Limitations of Current Antidepressants:

Present-day antidepressants have various drawbacks despite their potential for effectiveness. A primary concern is the gradual commencement of treatment outcomes, which frequently require multiple weeks to yield notable symptom amelioration. Furthermore, their effectiveness may be restricted, as numerous patients report only mild or no relief at all. Even in cases where treatment is effective, there is a significant chance of relapse (Carvalho et al., 2016). These restrictions imply that the existing drugs might be focusing on the incorrect or indirect mechanisms because their main goal is to raise monoamine levels, even in individuals who might not be deficient in these neurotransmitters.

In research conducted to study how immune-inflammatory and kynurenine pathways interact in rats which had shown resistance to treatment or management of depression in order to find a cure for the same. Antidepressant imipramine (IMI) was administered to the rats with chronic mild stress (CMS) (Duda et al., 2019; Y. Liu et al., 2012)Although there was a substantial decline in anhedonia in majority of the animals following administration of IMI, some of these rats were resistant to this drug by at least 20%.The researcher monitored cytokine levels at the same time as part of the research to get an understanding of immuno-inflammatory response during depression and the treatment with antidepressants setup. Changes in IFN-γ, IL-6 or IL-10 levels(Y. Liu et al., 2012) , leading to increase in inflammatory cytokines pointed towards modifications occurring at an organism's immune levels which would ultimately affect medication ease depression. These findings proposed that understanding antidepressant resistance to IMI treatment in rats subjected to chronic stress may involve a cross play between the kynurenine pathway and immune-inflammatory markers. It also provides insights into the primary mechanisms associated with resistance to antidepressant treatment and potential targets for therapeutic approaches.(Duda et al., 2019).

CHAPTER 3

MATERIALS AND METHODOLOGY

3.1 DATA COLLECTION

Several bioinformatics tools and databases were used during the data collection process in this study to obtain the relevant protein and ligand structures. Effective molecular docking and simulation studies depend on comprehensive and accurate data, which is ensured by this multifaceted approach.

3.1.1 Protein Data Bank:

It provides the three-dimensional structure about proteins and nucleic acids. It carries full atomic coordinates for macromolecules, which are essential to understand their interactions and functioning. In the current work, the three-dimensional structure of the protein Yin Yang 1 was downloaded from the PDB, more precisely, the structure of YY1(1UBD). This precise tailoring and simulation depend upon high-quality, censored data, which is found in the PDB (Berman et al., 2000).

3.1.2 PubChem Database:

The National Center for Biotechnology Information is responsible for maintaining the widely used chemical database PubChem. Regarding the composition, structures, and biological roles of small molecules, it is a valuable resource. The necessary fifteen compounds' three-dimensional structures were obtained in SDF format from the PubChem database for this project (S. Kim et al., 2023). One important tool that helps researchers find standardized, trustworthy data sets for a wide range of chemical compounds is PubChem. SwissADME is an online tool that can be used to predict chemical compound ADMET properties. The pharmacokinetic characteristics and drug-likeness of compounds taken into consideration were examined in the current investigation using SwissADME. Taking into account the fatty acid's gastrointestinal absorption, blood-brain barrier permeability, and bioavailability score, it was discovered to have significant potential as a therapeutic agent.

3.2 MOLECULAR DOCKING AND VISUALIZATION TOOLS

3.2.1 PyMOL:

PyMOL is a molecular visualization program that offers the capability of close, three-dimensional study of the protein-ligand interaction. The results of docking from PyRx were imported into PyMOL for three-dimensional visualization of binding interactions to understand the underlying dynamics at the molecular level(Sethi et al., n.d.).

3.2.2 PyRx:

PyRx is an open-source virtual screening tool facilitating molecular docking. It gave very useful information on the interaction stability and binding affinity when used for modelling the interaction of all fifteen drug-candidates with YY1 protein (Agarwal & Mehrotra, 2016).

3.2.3 PLIP:

The Protein-Ligand Interaction Profiler is an online application that provides deep information on binding interactions between ligands and proteins. PLIP provides detailed insight into the molecular interactions of interaction patterns, such as hydrogen bonds, hydrophobic contacts, and salt bridges, through the submission of the 3D coordinates of the protein-ligand complex.

Therefore, by integrating the aforementioned tools and databases, the method's comprehensiveness and accuracy guarantee that the potential interactions and therapeutic efficacy of all the compounds considered on the YY1-NF-κB inflammatory pathway are analysed. Such an all-encompassing approach ought to become crucial in expanding our understanding of state-of-the-art MDD treatment options (Sethi et al., n.d.).

3.3 PROTEIN PREPARATION FOR DOCKING

Preparation of the Yin Yang 1 protein for molecular docking is a very important step to the process that guarantees accuracy and reliability of the interaction studies with the potential ligands. This procedure involves a series of meticulous steps, starting with obtaining the protein’s 3D structure and ending with distilling it for docking simulation.

3.3.2 Structure retrieval of protein:

In order to guarantee an accurate and reliable study on how potential ligands interact with Yin Yang 1 protein, preparation of this molecule is one of the most essential steps during molecular docking study. There are numerous painstaking steps involved in this process, as shown by retrieving YY1's 3D structure then optimizing it for future docking simulations. RCSB PDB (https://www.rcsb.org/) gave out information about the spatial arrangement of YY1 proteins in three dimensions. The YY1 complex with the Adeno-associated virus P5 initiator element, designated as 1UBD, is the structure that was used in this analysis. Accuracy, peer-review, and standardization of data acquired from the RCSB PDB are guaranteed; this is crucial for the ensuing computational analysis(Sethi et al., n.d.).

3.3.3 Initial Overview and Problems:

The protein YY1 is complexed with other molecules in structure 1UBD, particularly with the Adenovirus-Associated P5 Initiator Element. While a bound molecule can present certain challenges in molecular docking studies, it can also reveal details about the protein's functional context. Extraneous molecules and atoms can interfere with the precise binding of a ligand to a protein.

3.3.4 Refinement Using BIOVIA Discovery Studio:

Now that the 1UBD structure was imported, it was simple to overcome the aforementioned challenges using the feature-rich software suite BIOVIA Discovery Studio, designed for molecular modelling and simulation (Shaker et al., 2020). This is because it has advanced edit and refine capabilities for macromolecular structures, which are very useful during protein preparation. The following was carried out in BIOVIA Discovery Studio:

A. Deletion of Unwanted Molecules: In order to get rid of all unnecessary molecules, it is necessary to remove all superfluous molecules or ions and also the P5 initiator element of the Adeno-associated virus (AAV) in the protein YY1 structure. This is very important because they can interfere with the docking simulations accuracy.
B. Protein structure optimization wherein extraneous atoms and residues need to be eliminated so as not to disrupt how the ligand attaches itself onto the protein. There are also crystallography artefacts, such as ions and water molecules that are not part of the actual protein sequence.
C. Energy minimization is used to maintain the native conformation of proteins while obtaining a more realistic and stable docking model.
D. Verification of active site integrity involves removing irrelevant molecules before examining whether the ligand pocket of YY1 protein is in its correct conformation such that it remains accessible yet intact. It all begins with the prediction of the protein structure so that it could be used in drug discovery.

3.3.5 Final Prepared Structures

The refined 3D structure of the protein YY1 was stored in a format suitable for the docking simulations by following the steps mentioned above. This prepared structure is provided as a reliable model for studying the interplay of YY1 with ligands since it is free of unnecessary components and is suitable for the research involving binding interactions. The protein structure had been optimized in order to allow precise prediction of binding affinity and interaction patterns when doing molecular docking studies in future. These predictions help us understand how targeting the YY1-NFκB inflammatory pathway might be useful in major depressive disorder and related conditions. If we pay attention to this comprehensive preparatory work, molecular docking simulations are greatly improved in accuracy and reliability, which gives a great future for computational and experimental research.

3.4 LIGAND PREPARATION FOR DOCKING:

Preparing all fifteen ligands for molecular docking involves many crucial stages, culminating in ligand formation from them. During these processes, it is ensured that the formats and conformations of the ligands are suitable to make them interact accurately with certain target proteins like Yin Yang 1. The optimization process for the ligand needed during the docking simulation begins with retrieving the 3-dimensional structures of the ligand and proceeds with various refinements as well as validations.

3.4.1 Ligand structure retrieval

PubChem (https://pubchem.ncbi.nlm.nih.gov/) is one of the best chemical databases which is developed by NCBI (The National Center for Biotechnology Information). It is from here that the 3D structures of all the fifteen compounds were downloaded. PubChem hosts a lot of information relating to compounds such as their chemical structures as well as biological activities. Retrieval of structures was made essentially in Structure Data File (SDF) format, which is used to store data about chemical structures (S. Kim et al., 2023). SDF format is commonly used for conducting precise molecular docking studies owing to its ability of specifying the three-dimensional coordinates of the molecule exactly. In order for the ligand's structure to be represented accurately during computational simulations, the SDF format contains detailed information on the atoms, bonds and their spatial organization.

3.4.2 Initial Inspection and Optimization:

After highlighting the structures of all the fifteen compounds, the 3D structures were given a primary screening to cross-check their authenticity. This is done to check for

the chemical correctness and availability of missing atoms or any misplaced bond orders that could have been introduced during structure downloading.

3.4.3 Conformational Analysis:

After the first examination, a conformance review was finished that helped identify which conformations among others were most relevant, thereby enabling us to carry out precise docking. This stage assists in establishing the probable mode by which ligand binds unto target proteins.

3.4.4 Energy minimization:

The ligand structure was further refined by energy minimization. To minimize energy, atomic position must be changed to reduce steric collisions and optimize molecular geometry. Energy minimization makes the molecule in its minimum energy state which is closer to its natural conformation in the biological environment. This step had to be completed in order to obtain accurate and reliable docking results.

3.4.5 Validation and Final Preparation:

When the final structures of all compounds were already set, it was confirmed that they complied with all molecular docking specifications. This also involves verifying whether the ligands are well formatted for the docking software, ensuring normal bond lengths and angles and addressing any possible structural problems.

3.4.6 Importing to Docking Software

After this setup and structural confirmation, the loaded structures were imported using docking software PyRx which also facilitated simulation for this study(Shaker et al., 2020). It makes a virtual screening program that imitates protein-ligand interactions and is open-source and freely distributed. After the SDF file is loaded into PyRx, the drugs are prepared to dock correctly and positioned with respect to the focal protein, YY1. Therefore, the ligands were made carefully as depicted in the stages below that enhanced the precision as well as reliability of the docking simulations. This intricate preparation procedure ensures that these compounds can be explored for their potential interaction with transcription factor YY1, thus giving significant insights to the conceivable therapeutic value of Major Depressive Disorder.

3.5 LIGAND-PROTEIN DOCKING

A molecular visualization tool named PyMOL (https://pymol.org/) was employed to import output files from PyRx. This software also allowed for further three-dimensional analyses concerning docking results. PyMOL was eventually useful in pulling out some of the specifics regarding the protein-ligand complex that enabled us to manipulate its 3D model through rotation, zooming out as well as changing viewpoints. It showcased key docking sites and ligand spatial dispositions in the corresponding protein's binding site, which connoted a holistic appreciation of how they (ligand vs. protein) interact during binding processes. Exhaustiveness was set to eight by default which offered sensible compromise between getting precise findings and managing computational means. Center of grid box was updated to have X , Y and Z coordinates as 5.8254 , 51.4793 and 15.2075 respectively with dimensions of each coordinate set to 56.4928 Å , 52.1314 Å and 25.0000 Å separately . This large grid box was set as the entire surface of YY1 was considered to evaluate the possible ligand bindings. Consequently, by being combined, PyRx and PyMOL provided a platform for appreciating all fifteen compounds against YY1 molecular interactions that is vital to increasing knowledge on ligand-protein interactions as well as help in drug development endeavours

3.6 PROTEIN-LIGAND INTERACTION STRUCTURE ANALYSIS

Understanding how proteins and ligands interact structurally is critical for understanding what influences their ability to stick together tightly versus loosely. We used an online tool called Protein-Ligand Interaction Profiler (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index) to study this particular protein and ligand complex. The final result of this study, a molecular model of the complex, was saved in a PDB format after performing its docking simulation PDB is likely the most widely used file format for storing 3D structural data as text files involving nucleic acids and proteins. All of the complex's atoms' 3D coordinates are available in the PDB file for the protein-ligand complex, which facilitates structural analysis. The intricate PDB file was uploaded to the web-based PLIP tool in order to comprehend the molecular interaction and binding pattern. A useful tool called PLIP automatically recognizes and displays the following types of protein-ligand interactions: salt bridges, hydrophobic, metal coordination, hydrogen bonding, and π-stacking. To perform the following significant analyses, the protein-ligand complex's 3D coordinates are imported into PLIP.

3.7 ADMET ANALYSIS

The ADMET analysis was made in order to analysed all fifteen different drug candidates for MDD, comparing them with conventional antidepressants. So far,

conventional antidepressants—like serotonin-norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors—have been vastly used in treating MDD. These drugs generally have a couple of drawbacks, including the delayed onset of action, side effects, and variability in efficacy depending upon the patients. The tool SwissADME (http://www.swissadme.ch/) was utilized for the same wherein SMILES conception of each compound taken into consideration was fed in for analysis. Results were displayed in organized manner and could be downloaded as excel sheet. In forecasting a compound's reactions inside the body of a human being , ADMET serves as a very important element of pharmacokinetics and pharmacodynamics in drug development to estimate the future conduct of potential drugs in terms of absorption, distribution, metabolism, and excretion .

3.8 PROTEIN - PROTEIN NETWORK ANALYSIS

The Search Tool for the Retrieval of Interacting Genes/Proteins, or STRING, (https://string-db.org/) is a one-stop shop for finding and studying interactions between proteins. It compiles information from multiple sources to provide comprehensive details on protein interactions, which are crucial for comprehending signal pathways, cellular functions, and the molecular causes of illnesses. The integration of various data sources, network visualization, functional annotations, and interaction scores are some of the STRING database's key features (Szklarczyk et al., 2021).

CHAPTER 4

RESULTS

4.1 MOLECULAR DOCKING:

Molecular docking is a computational biology method used for predicting the best conformation of one molecule (this is normally referred to as a ligand) when it is bound to another, usually a protein, referred to as the target, in order to form a stable complex. This approach is crucial for drug development as it aids in forecasting the binding strength and communication between potential drug options and their respective targets. In this specific scenario, the molecular docking study showed that the binding affinity of all compounds taken into consideration range between -4.0 Kcal/mol to -6.7 Kcal/mol. The strength of the interaction between the ligand and the protein (YY1) is analysed by the binding energy. A negative value denotes an exergonic binding process, which releases energy and is therefore thermodynamically advantageous. Binding energy six compounds among fifteen taken into consideration came out to be < 5.6 kcal/mol, with binding energy of Luteolin being the highest amongst others, i.e. -6.7 kcal/mol. This indicates a reasonably strong and stable interaction of these six compounds with YY1 highlighting the fact that they can be considered as candidates for blocking YY1 modulations on NF-κB and hence can be used as an alternative for MDD.

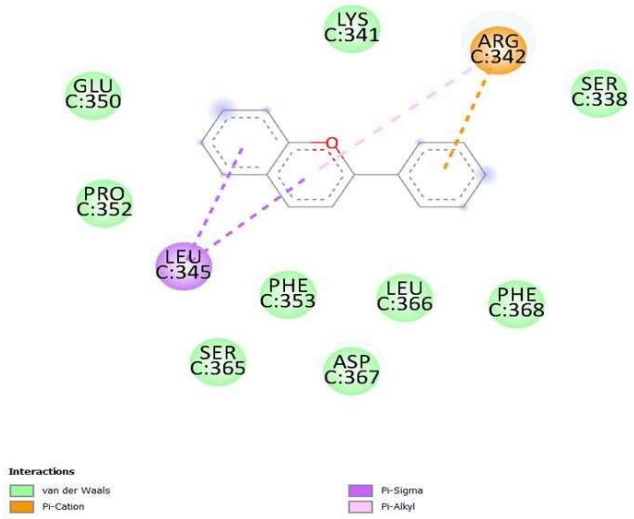

Fig. 4.1 2D image of Flavylium docked with YY1

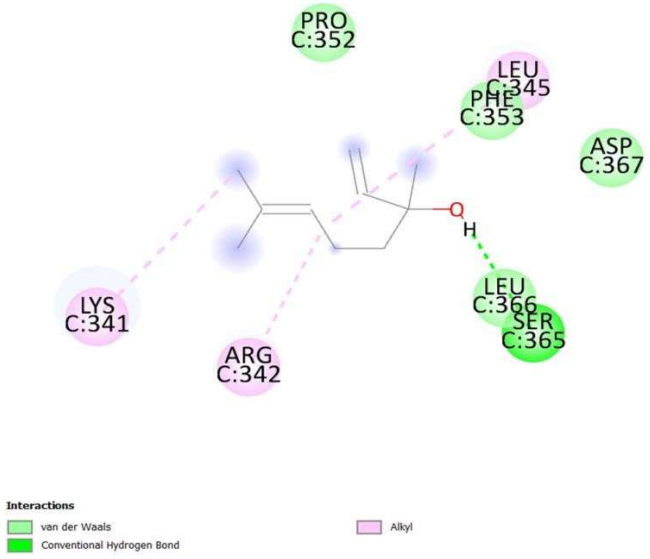

Fig 4.2 2D image of Linalool docked with YY1

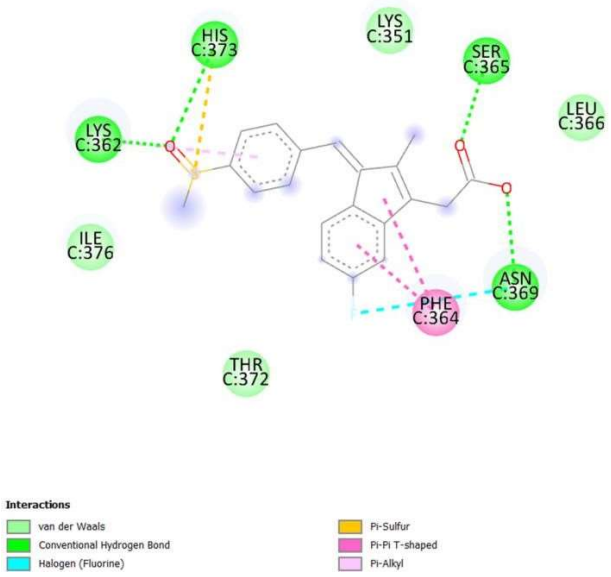

Fig 4.3 2D image of Sulindac docked with YY1

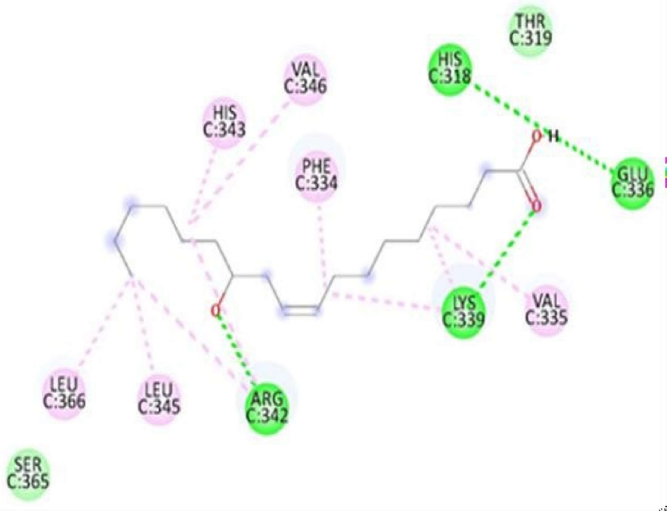

Fig 4.4 2D image of Ricinoleic acid docked with YY1

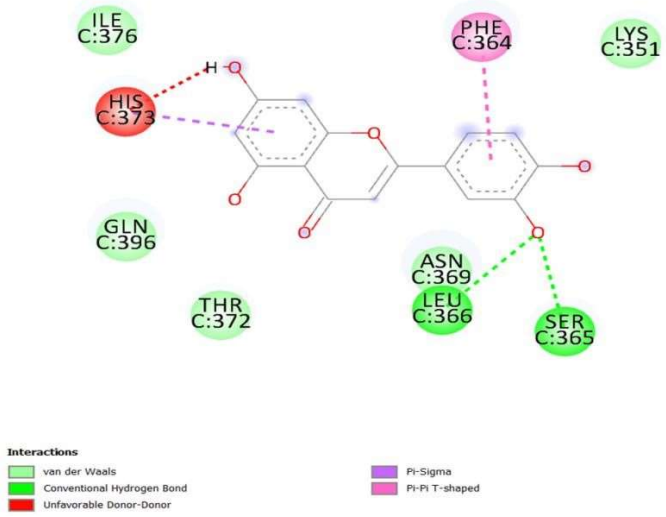

Fig 4.5 2D image of Luteolin acid docked with YY1

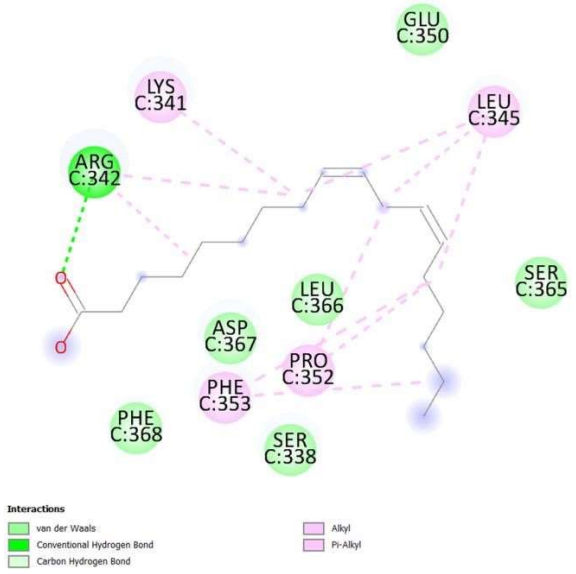

Fig 4.6 2D image of Linoleic acid docked with YY1

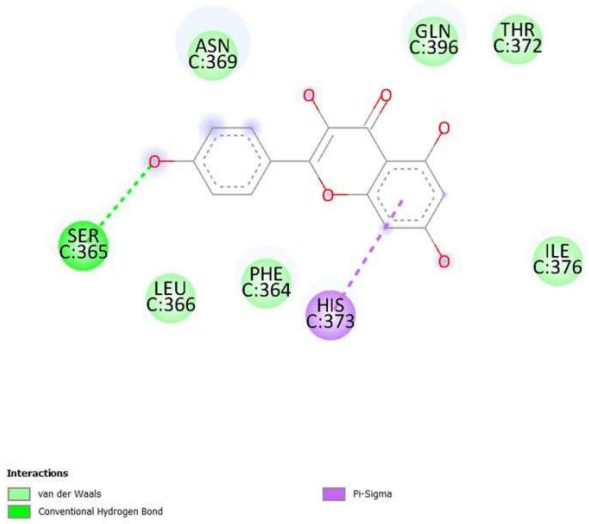

Fig 4.7 2D image of Kaempferol docked with YY1

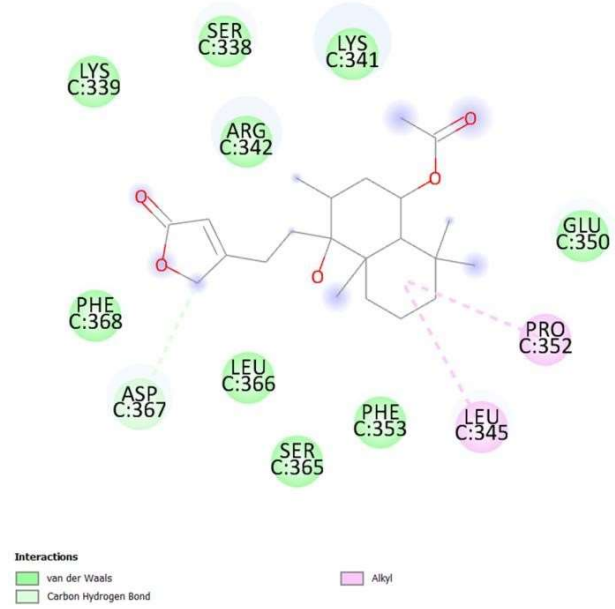

Fig 4.8 2D image of Vitexilactone docked with YY1

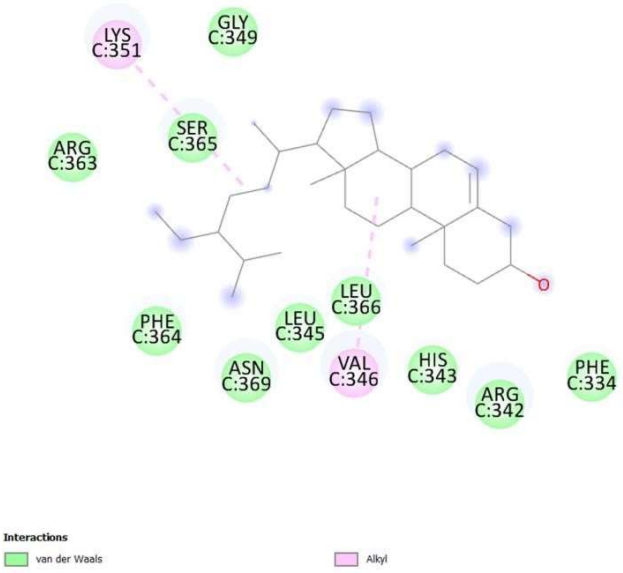

Fig 4.9 2D image of Sitosterol docked with YY1

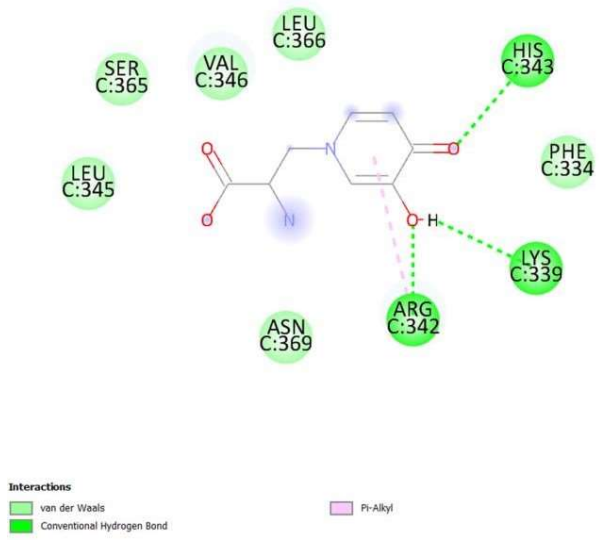

Fig 4.10 2D image of Mimosine docked with YY1

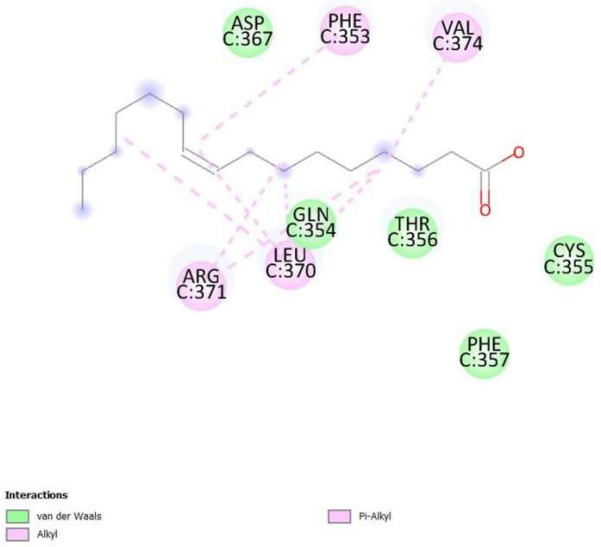

Fig 4.11 2D image of Palmitoleic acid docked with YY1

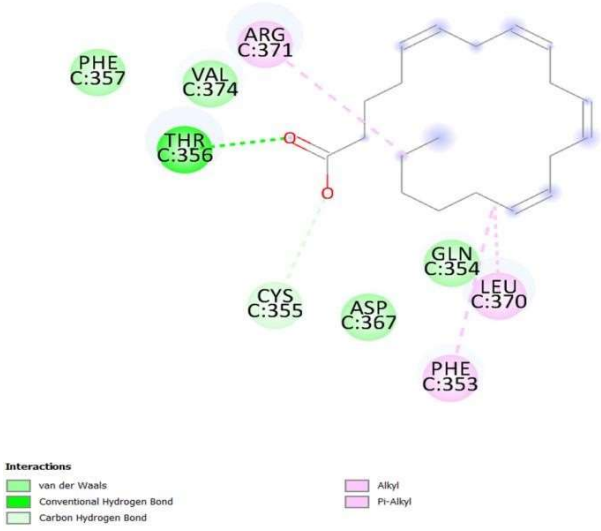

Fig 4.12 2D image of Arachidonic acid docked with YY1

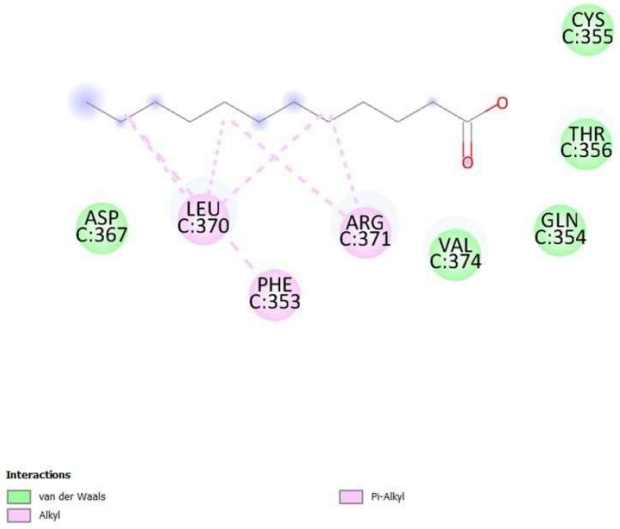

Fig 4.13 2D image of Lauric acid docked with YY1

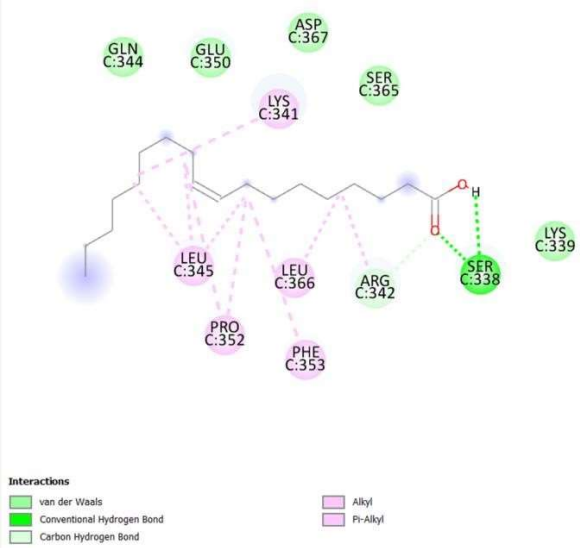

Fig 4.14 2D image of Oleic acid docked with YY1

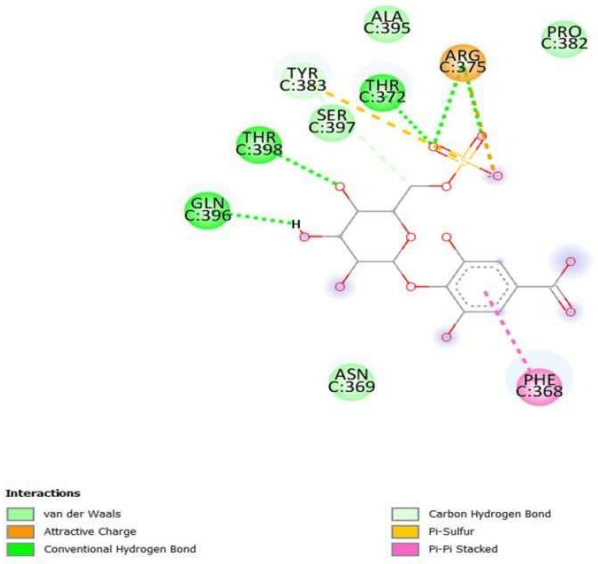

Fig 4.15 2D image of Turgorin docked with YY1

The molecular docking results, in summary, demonstrate a robust and stable interaction between YY1 and compounds namely, **Turgorin, Flavylium, Kaempferol, Sitosterol, Luteolin (highest), Sulindac.** Sulindac has also been studied as a drug for blocking NF kappa B itself. Further biochemical and pharmacological research that aims to use this interaction for therapeutic purposes will require this information.

Table I. Binding energies of fifteen compounds docked with YY1

S.NO.	LIGAND	BINDING ENERGY(Kcal/mol)
1.	TURGORIN	-5.7
2.	**FLAVYLIUM**	**-6.1**
3.	MIMOSINE	-4.5
4.	KAEMPFEROL	-5.9
5.	VITEXILACTONE	-5.9
6.	LINALOOL	-4.0

S.NO.	LIGAND	BINDING ENERGY(Kcal/mol)
7.	**SITOSTEROL**	**-6.6**
8.	ARACHIDONIC ACID	-4.3
9.	**LUTEOLIN**	**-6.7**
10.	**SULINDAC**	**-6.4**
11.	LAURIC ACID	-4.0
12.	LINOLEIC ACID	-4.2
13.	PALMITOLEIC ACID	-4.4
14.	OLEIC ACID	-4.0
15.	RICINOLEIC ACID	-4.08

4.2 ADMET ANALYSIS

The drug-likeness of listed compounds in relation to conventional antidepressants was evaluated using the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis. Understanding a potential drug's behaviour in the body and suitability for therapeutic use depends on this analysis. Various significant parameters were assessed during ADMET analysis presenting insights into pharmacokinetic attributes of all fifteen compounds.

4.2.1 Blood-Brain Barrier (BBB) Permeability

One of the notable results of the ADMET analysis was the high value of BBB permeability for all compounds came out to be more than equal to 0.55 except Turgorin which reflected a permeability of 0.11. The blood-brain barrier is a semipermeable barrier that separates the brain from the circulatory system, thereby protecting it from harmful substances in the blood while still allowing for essential

nutrients to pass through it. For neurological disorder treatment, a compound must be able to enter the CNS (Banks, 2005). For CNS disorders such as major depressive disorder, all compounds except Turgorin are a promising treatment option due to their high blood-brain barrier permeability, which makes it possible for them to penetrate and reach their targets within the brain effectively. Drugs that can pass through the blood-brain barrier are important in the management of brain-related conditions, since it is then that the drug will be able to reach its actual site of action within the brain.

4.2.2 Lipinski's Rule of Five

Based on the chemical structure and physical characteristics of a compound, Lipinski's Rule of Five provides predictions about how drug-like the compound will be. This rule states that if a compound satisfies the following requirements, it has a higher chance of being an oral active drug in humans:

1. Molecular Weight (MW) less than 500 Daltons.

2. Log P (octanol-water partition coefficient) less than 5.

3. No more than 5 hydrogen bond donors (HBD).

4. No more than 10 hydrogen bond acceptors (HBA).

Based on the ADMET analysis, Flavylium, Mimosine, Kaempferol, Vitexilactone, Linalool, Luteolin, Sulindac, Lauric acid, Palmitoleic acid and Ricinoleic acid satisfied every requirement and does not violate any of Lipinski's Rule of Five. This shows that they all may be an option for better oral MDD treatment due to their advantageous physicochemical characteristics for oral bioavailability.

4.2.3 Bioavailability Score

The amount of a drug that can be absorbed by the body and exert an active effect is referred to as its bioavailability. All compounds considered here except Turgorin flexed bioavailability scores more than or equal to 0.55, which is regarded as good and ideal. When a medication has a high bioavailability score, it means that a considerable amount of it enters the bloodstream and is available at the site of action. This is especially crucial to guarantee the medication's effectiveness because, in order for the medication to have a therapeutic effect, it must be effectively absorbed and distributed throughout the body.

The above-described qualities are essential for a successful CNS treatment plan because they modulate the YY1–NF-κB–IL-1β inflammatory pathway. Adherence to Lipinski's Rule of Five and an elevated bioavailability index bolster its appropriateness for oral administration. Turgorin showed low GI ABSORPTION VALUE and a low BIOAVAILABILITY SCORE OF 0.11 while all others showcased high GI absorption value and a good BIOAVAILABILITY SCORE more than or equal to 0.55.

Table II. ADMET analysis of all fifteen drug candidates taken into consideration

S.NO.	NAME	GI absorption	BBB permeability	Lipinski violations	Bioavailability Score
1.	**TURGORIN**	Low	No	2	**0.11**
2.	**FLAVYLIUM**	High	Yes	0	**0.55**
3.	**MIMOSINE**	High	No	0	**0.55**
4.	**KAEMPFEROL**	High	No	0	**0.55**
5.	**VITEXILACTONE**	High	Yes	0	**0.55**
6.	**LINALOOL**	High	Yes	0	**0.55**
7.	**SITOSTEROL**	Low	No	1	**0.55**
8.	**ARACHIDONIC**	High	No	1	**0.85**
9.	**LUTEOLIN**	High	No	0	**0.55**
10.	**SULINDAC**	High	No	0	**0.85**
11.	**LAURIC ACID**	High	Yes	0	**0.85**
12.	**LINOLEIC ACID**	High	Yes	1	**0.85**
13.	**PALMITOLEIC ACID**	High	Yes	0	**0.85**
14.	**OLEIC ACID**	High	No	1	**0.85**
15.	**RICINOLEIC ACID**	High	Yes	0	**0.85**

Table III. ADMET Analysis of over-the-counter Antidepressants

Drugs	BBB permeability	Lipinski violations	Bioavailability Score	GI absorption
Fluoxetine *(SSRI)*	**Yes**	**0**	**0.55**	**High**
Sertralin *(SSRI)*	**Yes**	**1**	**0.55**	**High**
Venlafaxine *(SNRI)*	**Yes**	**0**	**0.55**	**High**
Desvenlafaxine (SNRI)	**Yes**	**0**	**0.55**	**High**
Bupropion *(NDRI)*	**Yes**	**0**	**0.55**	**High**
Amitriptyline (TCA)	**Yes**	**1**	**0.55**	**High**
Imipramine *(TCA)*	**Yes**	**0**	**0.55**	**High**
Mirtazapine *(NaSSA)*	**Yes**	**0**	**0.55**	**High**

4.3 Protein - Protein Network Analysis

Protein-Protein Interaction (PPI) Network Analysis is done using the STRING database. The number of nodes represents the total proteins involved in the network. In this case, 21 proteins form the basis of the interaction network. Each node corresponds to a protein, and these nodes are interconnected by edges that represent the interactions between them. Here, 85 edges suggest a densely connected network where many proteins interact with each other.

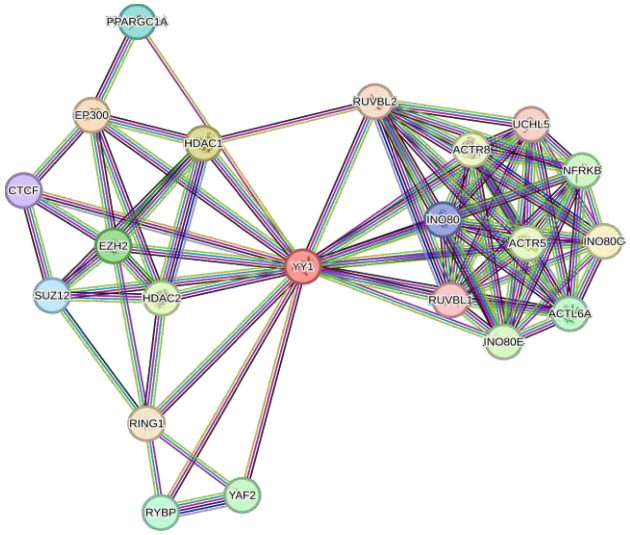

Fig. 4.16 Interaction Network of YY1 with 20 other proteins including NF-κB

An average node degree of 8.1 implies that, on average, each protein interacts with approximately 8 other proteins, indicating a highly interactive network. A coefficient of 0.863 is quite high, suggesting that the proteins in this network tend to form tightly knit groups, where a protein's neighbours are also likely to interact with each other.

A p-value of less than 1.0e-16 points towards an exceptionally notable enhancement of interactions, suggesting that the network is biologically meaningful and the interactions are not due to random chance.

Such a dense and enriched network likely engages in specific cellular processes or pathways. Understanding these networks can dispense understanding of the functional organization of proteins and help identify key regulatory elements or potential therapeutic targets within the network. The use of the STRING database facilitates this detailed analysis, providing a comprehensive view of protein interactions and their significance.

Table IV. PPI network statistics of YIN YANG 1

NUMBER OF NODES	**21**
NUMBER OF EDGES	**85**
LOCAL CLUSTERING COEFFICIENT, AVERAGE	**0.863**
NODE DEGREE, AVERAGE	**8.1**
PPI ENRICHMENT p- VALUE	**< 1.0e-16**

DISCUSSIONS

A large number of individuals do not respond to treatment with general medications for managing MDD, which may lead to refractory major depressive disorder (MDD). This study suggests a new direction for treating MDD by focusing on the inflammatory pathways associated with neuroinflammation in MDD through YY1/NF-κB. This could be another way of treating this disease when current practices fail. We examined the Protein-Protein Interaction (PPI) network using the STRING database and showed that the network involves 21 proteins connected through 85 edges which suggests that it is a densely linked network with numerous protein interactions. The p-value < 0.001 suggests a biologically meaningful network that these interactions are non-random but likely play a significant part in certain cellular processes or pathways. This network's comprehension can offer hints about proteins' functional structure, pinpoint vital regulatory features as well as expose novel therapeutic targets situated in it thereby underscoring the necessity for exploring how proteins interact under various conditions including Major Depressive Disorder (MDD).

This study employed molecular docking to assess how fifteen candidate compounds could interact with YY1, a transcriptase in an inflammatory pathway that has been linked to major depressive disorder (MDD). In order to keep the original state of proteins and obtain an accurate and steady model for ligand-protein interactions, energy minimization technique was used. The analysis indicates that compounds namely Turgorin, Flavylium, Kaempferol, Sitosterol, Luteolin, and Sulindac, bind to YY1 protein and thereby inhibit the inflammatory process. We utilized several bioinformatics tools and databases for the purpose of gathering relevant protein and ligand structures, which ensured comprehensive and accurate data that could be used for following molecular docking and simulation studies. Molecular Docking shows highest binding energy, -6.7kcal/mol with the interaction YY1(protein) and Luteolin(ligand) followed by binding energy of -6.6kcal/mol and -6.1kcal/mol with interaction of YY1 with Sitosterol and Flavylium respectively, suggesting them to be potentially strong inhibitor of YY1 compared to other drug candidates. However, the ADMET study pointed out the inability of Luteolin and Sitosterol to cross the blood brain barrier making them inferior to other candidates. After closely investigating the binding energies and ADMET analysis results of all fifteen drugs, Flavylium though with comparatively less binding energy than Luteolin and Sitosterol stands out as a superior drug candidate because of its ability to cross BBB, also it follows Lipinski rule of five. With a bioavailability score of 0.55, as well as structural properties, flavylium is thought to be a potential drug for treating MDD. Therefore, further studies and evaluations are needed to confirm the safety and efficacy of this agent in depression treatment. Such computational predictions should be tested experimentally for biological accuracy.

CONCLUSION AND FUTURE PROSPECTS

Current antidepressant treatments have many limitations, so developing new therapeutic strategies is important. The complex neurobiology of depression, such as alterations in neuroplasticity, inflammation, and genetic components, may lead to the identification of new targets for the development of new drugs. Other novel approaches, such as ketamine, which modulates glutamate signaling, and the development of personalized medicine based on genetic and biomarker profiles, are promising ways for more effective treatment options in the future. In a nutshell, although the current generation of over-the-counter antidepressants actually controls the levels of neurotransmitters to quell depression, their effectiveness is frequently marred by side effects, a slow onset of action, and the risk of relapse. Our increasing understanding of the basic mechanisms underlying depression will be crucial in the creation of new treatments. Chronic stress and low-grade inflammation have been linked with the symptoms of depression and may indicate that anti-inflammatory drugs could also be used as treatment for MDD. In such a context, patients who do not respond to the current regimens of antidepressant therapy may be helped with individualized treatment strategies, based on their different neurobiological profiles.

In conclusion, the literature and computational methods used herein showcase a paradigm shift in understanding and treating MDD by targeting inflammatory pathways. The YY1–NF-κB–IL-1β cascade comes out as a focal point. Additionally, investigating the interactions between the YY1 pathway and other biological pathways involved in depression could provide a more comprehensive understanding of the disorder. Longitudinal studies to assess the impact of YY1 modulation over time would also be valuable.

Flavylium is found in Callistephus chinensis and Tradescantia pallida, it is a type of phytochemical belonging to the class of compounds known as anthocyanin. These pigments, which are soluble in water, give a variety of fruits, vegetables, and flowers their hues of purple, blue, and red. Numerous anthocyanins have the flavylium cation, or basic flavylium structure, as their central structural component (Pina et al., 2015). Herein it 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 a key role in inflammation modulation in this pathway as a convention to traditional antidepressant treatment. However, further research is mandatory to authenticate these findings and flag a way for innovative and effectual treatments for MDD. Future research should be centralized on experimental validation of uncovered inhibitors of YY1 like Flavylium in preclinical and clinical environments exploring its effectiveness in real-world situations to cater to the unmet needs of individuals with Major Depressive Disorder (MDD).

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APPENDIX: LIST OF PUBLICATIONS AND THEIR PROOF

- "**Computational approach Targetting Yin Yang 1 inflammatory pathway as an alternative to alleviate the symptoms of Major Depressive Disorder**". International Conference on Emerging Technologies in Science and Engineering **(ICETSE)-2024** organised by the Akshaya Institute of Technology and technically co-sponsored by Hinweis Research.

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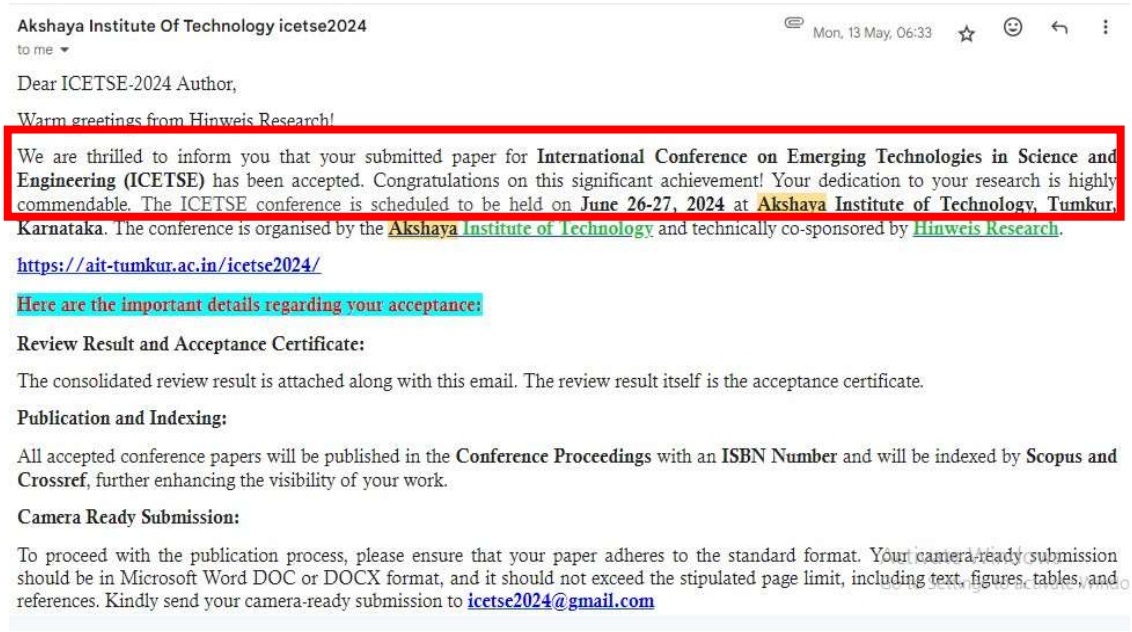

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to me

Dear ICETSE-2024 Author,

Warm greetings from Hinweis Research!

We are thrilled to inform you that your submitted paper for **International Conference on Emerging Technologies in Science and Engineering (ICETSE)** has been accepted. Congratulations on this significant achievement! Your dedication to your research is highly commendable. The ICETSE conference is scheduled to be held on **June 26-27, 2024** at **Akshaya Institute of Technology, Tumkur, Karnataka**. The conference is organised by the Akshaya Institute of Technology and technically co-sponsored by Hinweis Research.

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Summary

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Comprehensively Address Mental Health (CAMH) issues during COVID-19 Pandemic.