IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Molecular Docking Analysis Of Bioactive Compounds From *Tridax Procumbens* As Potential Antipsychotic Agents.

Swapnil Prabhakar Garad

Research scholar Department of pharmacology,Rajgad Dnyanpeeth College of Pharmacy Bhor, Pune

Abstract.

Objective

The objective of this study was to investigate the bioactive compounds present in *Tridax procumbens* leaves and to evaluate their potential antipsychotic properties.

Significance

The study is noteworthy since it investigates a natural substitute for the administration of antipsychotics. There is considerable interest in discovering safer and more effective natural chemicals as traditional antips ychotics can have severe adverse effects.An accessible plant called *Tridax procumbens* may provide a new way to treat psychotic symptoms.

Methods

To acquire the bioactive components, the leaves of Tridax procumbens were extracted using suitable solvents, such as methanol. To identify and measure the different bioactive chemicals present in the extracts, chromatography techniques (e.g., HPLC, GC-MS) were employed in the analysis process. To identify their probable interactions and modes of action, the discovered compounds were docked with target proteins involved in psychotic symptoms (e.g., monoamine oxidase, NMDA receptor, serotonin receptor, 2 Dopamine receptor).

Result

The leaves of Tridax procumbens are rich in bioactive substances, such as akuammidine and kaempferol. By affecting the PI3K/Akt pathway, blocking monoamine oxidase, and interacting with NMDA and serotonin receptors, these substances may have antipsychotic effects.

Keywords: Antipsychotic, Tridax procumbens, akuammidine, kaempferol, epicatechin, ferulic acid, galgravin.

Introduction:- Tridax procumbens is a procumbent, hispid herb that grows widely and is typically encountered as a weed. T. procumbens is a perennial plant that bears fruit all year round. Based on the appearance of the bloom, T. procumbens is also known by the names "Jayantiveda" in Sanskrit, "Tikki-kasa/Ghamra" in Hindi, and "Wild daisy," "Mexican daisy," and "Coat buttons" in English. Tridax procumbens is the term given in science. The generic name, which means "summer eating" in Greek, suggests that the food was a summer vegetable.

T. procumbens is a member of the following groups: class: Magnoliopsida, subclass: Asteridae, order: Asterales, family: Asteraceae, genus: Tridax L., species: procumbens; kingdom: Plantae; subkingdom: Tracheobionta; division: Magnoliophyta–Dicotyledons.

Up to 2400 meters above sea level, T. procumbens is widely found throughout India. The plant's leaves are used by humans as food additives and as raw feed for cattle. The leaves are used medicinally to treat diarrhea, dysentery, and catarrh. Various leaf extracts are used as antiseptics for treating burns, cuts, and anemia. It also has the capacity to enhance hair growth.

The Tridax procumbens Linn is a member of the Asteraceae family. Indigenous medicine has utilized several extracts of Tridax procumbens to treat a range of illnesses and conditions in both humans and animals. It has been widely utilized in Indian traditional medicine for many years for a variety of purposes, including immunomodulatory, anticoagulant, fungal infection, diarrhea, and dysentery. In folk medicine, leaf extracts are used to treat infectious skin problems. Additionally, it is prescribed as "Bhringraj," a well-known ayurvedic treatment for liver conditions. Phenols or their oxygen-substituted derivatives, which are primarily secondary metabolites, are found in plants. 12,000 people at least have been left out. These compounds function as defensive mechanisms for plants against herbivores, insects, and bacteria [2,3].

INDIAN NAMES:

Hindi: Ghamra.

Sanskrit: Jayanti Veda.

Marathi: Dagadi Pala and Ghav Pala,

Telugu: Gaddi Chemanthi.

Tamil: Thatapoodu.

Malayalam: Chiravanak.

FIG: 1.0

CHEMICAL CONSTITUENTS:

The presence of flavonoids, carotenoids, alkaloids, tannins, and saponins was shown by the phytochemical analysis. As can be seen from the adjacent profile, the plant has high calcium, potassium, and sodium content. Tridax procumbens leaves are mostly composed of proteins, fiber, carbohydrates, and calcium oxide. However, reports of fumaric acid and tannin in the plant have also been made. When oleanolic acid was tested against a-glucosidase, it was discovered to be a possible antidiabetic drug and was obtained in good quantities from Tridax. Numerous chemical components, including fumaric acid, lauric acid, carotenoids, alkaloids, and tannins, have been identified in the plant. The existence of certain chemicals, known as secondary metabolites, which are responsible for producing various effects on the human body, is what gives plants their medicinal worth [3].

PATHOPHYSIOLOGY OF PSYCHOSIS

Although the dopamine and glutamate systems have different roles in neural signaling, both have been implicated in the pathophysiology of schizophrenia. The primary excitatory neurotransmitter in the central nervous system is glutamate. Numerous studies have linked the glutamate system to the pathophysiology of schizophrenia when it was discovered that antagonists of one particular glutamate receptor, the N-methyl-D-aspartate (NMDA) receptor, cause psychotic symptoms. It is thought that dopaminergic and glutamatergic dysfunction are fundamental to the pathogenesis of schizophrenia. For those with a high clinical or genetic risk of developing schizophrenia, it is unknown if problems occur before the condition manifests itself. We conducted a thorough review and meta-analysis of research using neuroimaging to study glutamate and dopamine function in those with a higher genetic or clinical risk of psychosis.

The dopaminergic and glutamatergic systems are the two main neurotransmitter systems that have been widely researched in the pathophysiology of psychosis, notably in diseases like schizophrenia, being central to the most widely accepted hypotheses. Here's an overview:

Dopaminergic Hypothesis: One of the most significant contributions to our understanding of psychosis, and specifically schizophrenia, has come from the dopaminergic hypothesis. It implies that one of the main contributing factors to the emergence of psychotic symptoms is irregularities in dopamine function.

Hyperdopaminergic: The most well-known version of the dopaminergic theory suggests that positive symptoms of psychosis, such as delusions and hallucinations, are caused by an overabundance of dopamine, especially in the mesolimbic pathway. It is believed that elevated dopamine production, release, or receptor sensitivity is the cause of this hyperdopaminergic condition.

Hypodopaminergic: On the other hand, decreased dopamine function in the mesocortical pathway, namely in the prefrontal cortex, is hypothesized to be connected to the negative symptoms (such as anhedonia, social withdrawal), as well as the cognitive deficiencies associated with psychosis. This indicates a low dopaminergic condition [4,5].

Glutamatergic Hypothesis

The glutamatergic theory has drawn interest as a substitute or additional theory to explain psychosis. It is centered on problems with glutamate, the brain's main excitatory neurotransmitter, and specifically addresses issues with NMDA (N-methyl-D-aspartate) receptors.

Hypofunction of NMDA Receptors: The fundamental tenet of the glutamatergic hypothesis is that a series of dysfunctions are caused by decreased NMDA receptor activity, especially on inhibitory interneurons. This hypofunction of the NMDA receptor may cause excitatory pathways to become disinhibited, which would then cause an excessive release of glutamate and excitotoxicity.

Links to Dopamine Dysfunction: There is a close interaction between the dopaminergic and glutamatergic systems. Positive psychotic symptoms may be partially attributed to NMDA receptor hypofunction, which can subsequently result in mesolimbic pathway hyperdopaminergic states. On the other hand, it might also result in less dopamine being released in the prefrontal cortex, which would then exacerbate negative symptoms and cognitive impairments.

Pharmacology's assistance: NMDA receptor dysfunction is further supported by the fact that drugs that block NMDA receptors, such as phencyclidine (PCP) and ketamine, can cause psychotic symptoms and cognitive deficits in healthy people [4,5].

Serotonin hypothesis

Early research on the interplay between the hallucinogenic drug LSD (d-lysergic acid diethylamide) and 5-HT in peripheral systems gave rise to the serotonin (5-HT) hypothesis of schizophrenia.

The serotonin hypothesis in psychosis postulates that anomalies in serotonin (5-HT) neurotransmission are important for the emergence and expression of psychotic symptoms, especially in relation to schizophrenia and other similar illnesses. The dopamine hypothesis, which mainly addressed dopamine's involvement in psychosis, especially in schizophrenia, gave rise to this theory.

Key Points of the Serotonin Hypothesis:

Serotonin and Hallucinogens: Researchers have studied the role of serotonin in naturally occurring psychosis because of the effects of hallucinogenic drugs, such as psilocybin and LSD (lysergic acid diethylamide), which are known to affect serotonin receptors, particularly the 5-HT2A receptor, and to induce hallucinogenic experiences that are similar to psychotic episodes.

5-HT2A Receptor: Research has specifically concentrated on the 5-HT2A receptor. It is believed that this receptor's overactivity plays a role in the positive symptoms of psychosis, like delusions and hallucinations. As a result, atypical antipsychotic medications—which specifically target the 5-HT2A receptor—that target serotonin and dopamine receptors have been developed. Compared to standard antipsychotics, which primarily target dopamine receptors, these medications, such as risperidone and clozapine, are frequently more effective at treating the positive symptoms of schizophrenia and have fewer adverse effects..

Serotonin-Dopamine Interactions: The brain's serotonin and dopamine systems interact with each other quite a bit. Dopamine release is modulated by serotonin, and anomalies in this modulation may be a factor in psychosis. For example, high serotonin levels may result in low dopamine levels in specific brain areas (such as the prefrontal cortex), which may exacerbate negative and cognitive symptoms of schizophrenia [6,7].

❖ **Mechanism of kaempferol in psychosis**

Flavonoid kaempferol is present in many plants, including fruits, vegetables, tea, and herbs. It has drawn interest because of its possible medical uses, including treating psychosis. Although there is still much to learn in this field, a number of processes have been put out to explain how it affects psychosis:

1) Antioxidant Activity: The strong antioxidant kaempferol aids in lowering the brain's oxidative stress. It is well recognized that oxidative stress plays a role in the pathophysiology of psychosis, especially in conditions like schizophrenia. Kaempferol may lessen the symptoms of psychosis by shielding neurons from oxidative damage through the scavenging of free radicals.
2) Anti-inflammatory Effects: Progression and onset of psychosis have been associated with chronic inflammation. By suppressing pro-inflammatory cytokines and enzymes such as lipoxygenase (LOX) and cyclooxygenase (COX), kaempferol has anti-inflammatory effects. This anti-inflammatory property may be able to lessen the neuroinflammation linked to psychosis.
3) Neurotransmitter System Modification: Psychosis is frequently linked to dopaminergic neurotransmitter imbalance. It has been demonstrated that kaempferol affects a number of neurotransmitter systems, including glutamate, serotonin, and dopamine, all of which are essential for the emergence of psychotic symptoms. Kaempferol may lessen symptoms associated with psychosis by restoring the balance of these neurotransmitters.
4) Effects on Neuroprotection: Kaempferol possesses neuroprotective qualities that may help avoid or lessen the neurodegeneration that is frequently observed in psychotic diseases. It has the ability to prevent and improve neuronal apoptosis, or cell death, which is essential for preserving normal brain function.
5) Brain-Derived Neurotrophic Factor (BDNF) Modulation: BDNF is a protein that promotes the development of new synapses and maintains the viability of existing neurons. Psychosis has been

related to BDNF dysregulation. It has been demonstrated that kaempferol increases BDNF levels, which may be one factor in its possible antipsychotic effects.

a. Kaempferol has been shown to inhibit monoamine oxidase (MAO), an enzyme that catabolizes neurotransmitters such as norepinephrine, dopamine, and serotonin. Increased levels of these neurotransmitters may result from MAO inhibition, which may lessen psychotic symptoms.

b. These mechanisms imply that kaempferol may be a good option for treating psychosis, but further study—especially clinical trials—is required to completely determine the drug's safety and effectiveness in this situation [8,9,10.]

❖ **Mechanism of Kaempferol Based on Docking**

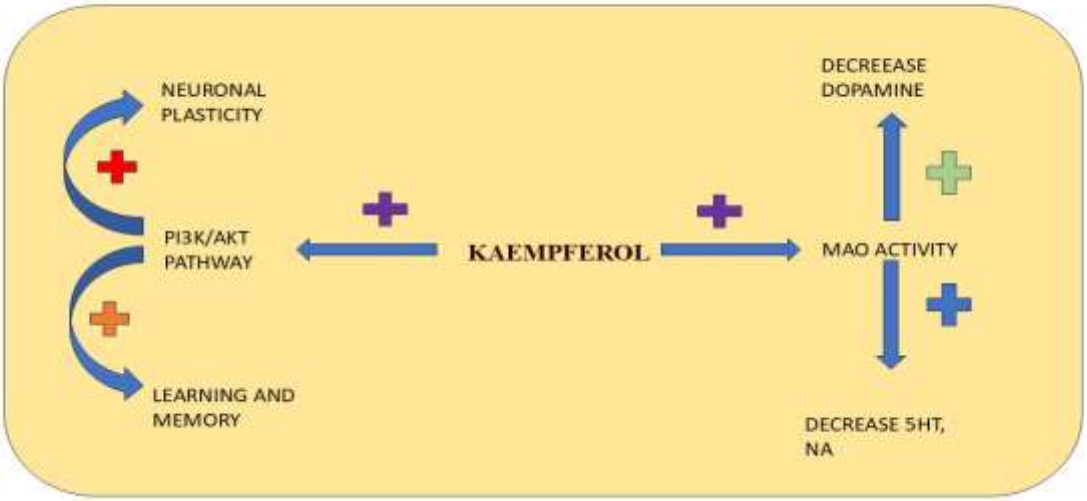

FIG: 1

❖ The 3D structures of active chemical constituents Kaempferol, were downloaded from PubChem which are present in *Tridax procumbens.* The RCSB PDB protein data repository provided the 3D structures of the Pi3k/Akt and MAO. Subsequently, co-crystallized ligand and crystallographic water were eliminated to produce the results. Argus Lab 4.0.1 was used to simulate molecular docking with the default settings and Discovery Studio was used for visualization

Using the Argus lab software the kaempferol a chemical constituent of tridax procumbens docked with pi3k/Akt and MAO, and the docking score of kaempferol with pi3k was -8.18385 kcal/mol, and kaempferol with Dopamine was -6.67014 kcal/mol

❖ **Mechanism of Akuammidine**

An indole alkaloid is akuammidine. Numerous pharmacological effects, such as analgesic, anti-inflammatory, and hypotensive qualities, have been investigated. Its precise function in psychosis, however, is still being studied and has limited evidence.

1) Relationship to Serotonin Receptors: Yohimbine, another indole alkaloid, shares structural similarities with akuammidine, which may have an effect on serotonin receptors, specifically the 5-HT1A and 5-HT2 receptors. A major factor in mood control is serotonin (5-HT), and abnormalities in serotonin receptor function or levels are linked to psychosis, especially in conditions like schizophrenia. The possible modification of serotonin receptors by akuammidine may have an impact on psychotic symptoms.

2) Modulation of the Dopaminergic System: The pathophysiology of psychosis mostly involves the dopaminergic system. Although it is not thoroughly established, there is some evidence to suggest that akuammidine may play a function in regulating dopamine receptors. Given that excessive dopaminergic activity is a major characteristic of schizophrenia and other psychotic diseases, if it has an impact on dopamine levels or receptor activity, this may be relevant to how it affects psychosis.

3) Antioxidant and Neuroprotective Effects: Antioxidant-containing substances may have therapeutic value because they have been linked to the development of psychosis. Given its mild antioxidant activity, akuammidine may have neuroprotective benefits as well as the ability to reduce psychotic symptoms [11,12].

❖ **MECHANISM OF AKUAMMIDINE BASED ON DOCKING**

The akuammidine influence NMDA or glutamate pathway used for psychosis and inhibits the serotonin receptor 2 which may cause psychotic symptoms and hallucinations.

The 3D structures of active chemical constituents Akuammidine, were downloaded from PubChem which are present in *Tridax procumbens.* The RCSB PDB protein data repository provided the 3D structures of the glutamate pathway and 5HT2A . Subsequently, co-crystallized ligand and crystallographic water were eliminated to produce the results. Argus Lab 4.0.1 was used to simulate molecular docking with the default settings and Discovery Studio was used for visualization

Using the Argus lab software the akummidine a chemical constituent of tridax procumbens docked with NMDA and 5HT2A, and the docking score of Akummidine with NMDA was -7.69455 kcal/mol and akummidine with 5HT2A was -6.7759 kcal/mol

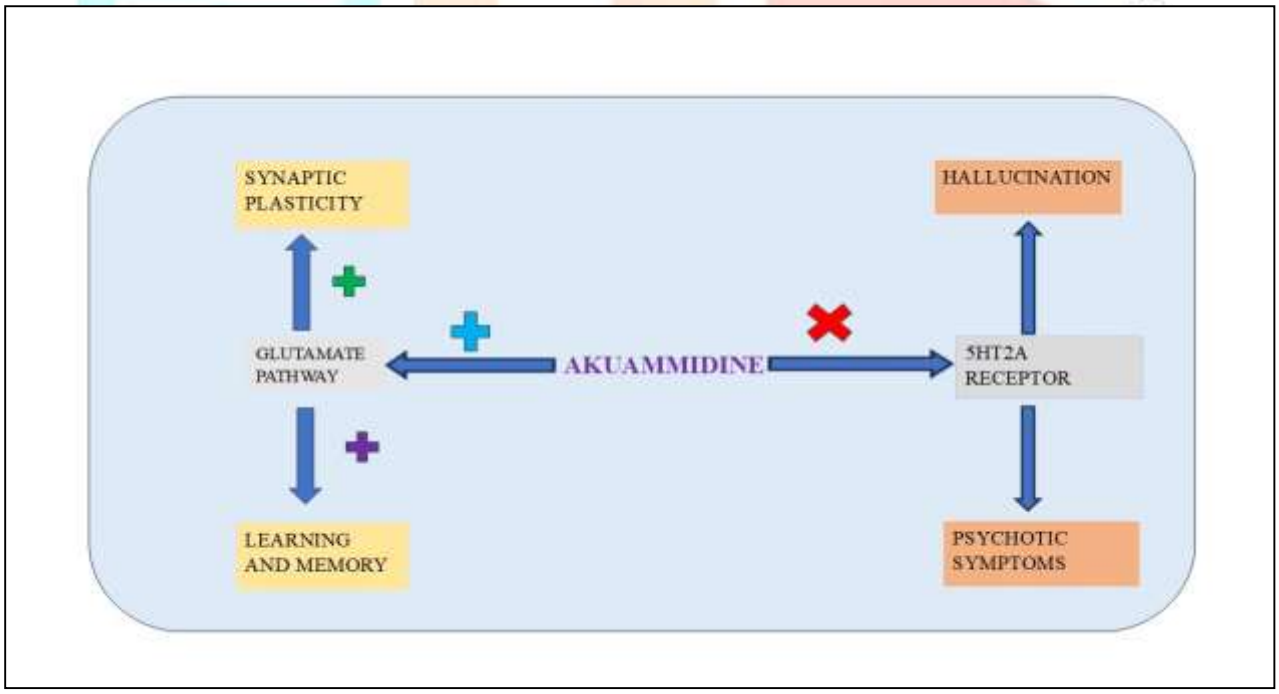

FIG 1.2

Mechanism of lutein

Lutein, a carotenoid primarily known for its role in eye health, has been studied for its potential effects on brain function, including its role in psychosis. While research is still emerging, some mechanisms by which lutein may influence psychosis include:

1. Antioxidant Properties: Oxidative Stress in Psychosis: Higher levels of oxidative stress in the brain are linked to psychotic diseases, such as schizophrenia, which can harm brain cells and worsen symptoms. The Function of Lutein: Due to its potent antioxidant qualities, lutein helps lessen oxidative stress and neutralize free radicals. In doing so, it might lessen some of the symptoms associated with psychosis and help shield neural cells from harm.

2. Effects on Inflammation:
Inflammation in Mental Illness: Another element connected to the pathophysiology of psychosis is chronic inflammation. Pro-inflammatory cytokine levels have been found to be higher in those with psychotic illnesses.
Lutein's Role: Due to its anti-inflammatory qualities, lutein may be able to improve psychotic symptoms by regulating the immune system and reducing inflammation in the brain.

3. Neuroprotective Effects: Neurodegeneration in Psychosis: A common feature of psychotic diseases is abnormalities in the structure and function of the brain.
The Function of Lutein: Research has demonstrated that lutein promotes neurogenesis and shields neurons from apoptosis, or programmed cell death. This neuroprotective impact may slow the advancement of the neurodegenerative elements of psychosis and assist preserve brain function.

4. Neurotransmitter Modulation:
An imbalance of neurotransmitters in psychosis One of the main characteristics of psychosis is the dysregulation of neurotransmitters like glutamate and dopamine.
The Function of Lutein: According to certain studies, lutein may affect neurotransmitter function, namely by modifying cholinergic pathways, which are connected to cognitive processes. Lutein may help manage the balance of neurotransmitters, which may help reduce the behavioural and cognitive symptoms of psychosis [13,14].

❖ **Mechanism of ferulic acid** [15,16]

- Neurotransmitter Modulation:

Mechanism: Dopamine, serotonin, and GABA are just a few of the neurotransmitter systems that ferulic acid may affect. Ferulic acid, for example, may be able to regulate serotonin and dopamine levels, which are linked to mood and mental illnesses.

Effect on Psychosis: Ferulic acid may help balance the chemical imbalances frequently seen in psychosis by perhaps normalizing neurotransmitter levels.

- Effects of Neuroprotection:

Mechanism: By increasing antioxidant enzyme activity and lowering neurotoxicity, ferulic acid may have neuroprotective effects. This involves enhancing neuronal health and preventing harm from excitotoxicity, or the overactivation of glutamate receptors.

Effect on Psychosis: Preserving neurons from harm may contribute to the preservation of normal brain activity and lessen the intensity of symptoms associated with psychotic illnesses.

- Antioxidant Activity:

Mechanism: Free radicals can be neutralized and oxidative stress can be decreased by the strong antioxidant ferulic acid. Psychosis and other mental health issues, as well as neurodegenerative diseases, are believed to be exacerbated by oxidative stress.

Impact on Psychosis: Ferulic acid may help shield the brain from the damaging effects of oxidative stress by lowering oxidative damage in neuronal cells, which may lessen the symptoms or course of psychotic diseases.

Mechanism of Regulation of Neuroplasticity**:** Ferulic acid may affect neuroplasticity by acting on brain-derived neurotrophic factor (BDNF) and other signaling pathways that are connected to the development and maintenance of neurons.

Effect on Psychosis: Improving neuroplasticity may aid in the restoration of brain functioning and enhance emotional and cognitive control in people suffering from psychotic disorders.

Methods

These actions were probably taken as part of the study:

1. Extraction: To acquire the bioactive components, the leaves of Tridax procumbens were extracted using the proper solvent, methanol.

2. Chemical Analysis: To identify and measure the different bioactive chemicals present, the extracts were subjected to chromatography techniques such as HPLC and GC-MS.

3. Molecular Docking: To predict possible interactions and modes of action, the selected compounds were docked with target proteins implicated in psychotic symptoms (e.g., monoamine oxidase, NMDA receptor, serotonin receptor 2).

Docking:- A molecular docking investigation was conducted under the assumption of a model in which the docking process treated the protein and ligand as flexible entities. estimated docking score presented in Tables.

Table No 1.0 Interaction between kaempferol and dopamine receptor (PDB: https://doi.org/10.2210/pdb4XPF/pdb)

Drug	Docking score or binding energy	Van Der Waals	H bond	UNFAVORABLE BOND	Alkyl
kaempferol	-6.67014 kcal/mol	ASN A:340 TYR A:342 MET A:510 ILE A: 511 GLY A:512 SER L:607	ARG H:848	PHE A:513 TYR L:608 HIS A:338GLN H:849	--

DOCKING IMGAGE

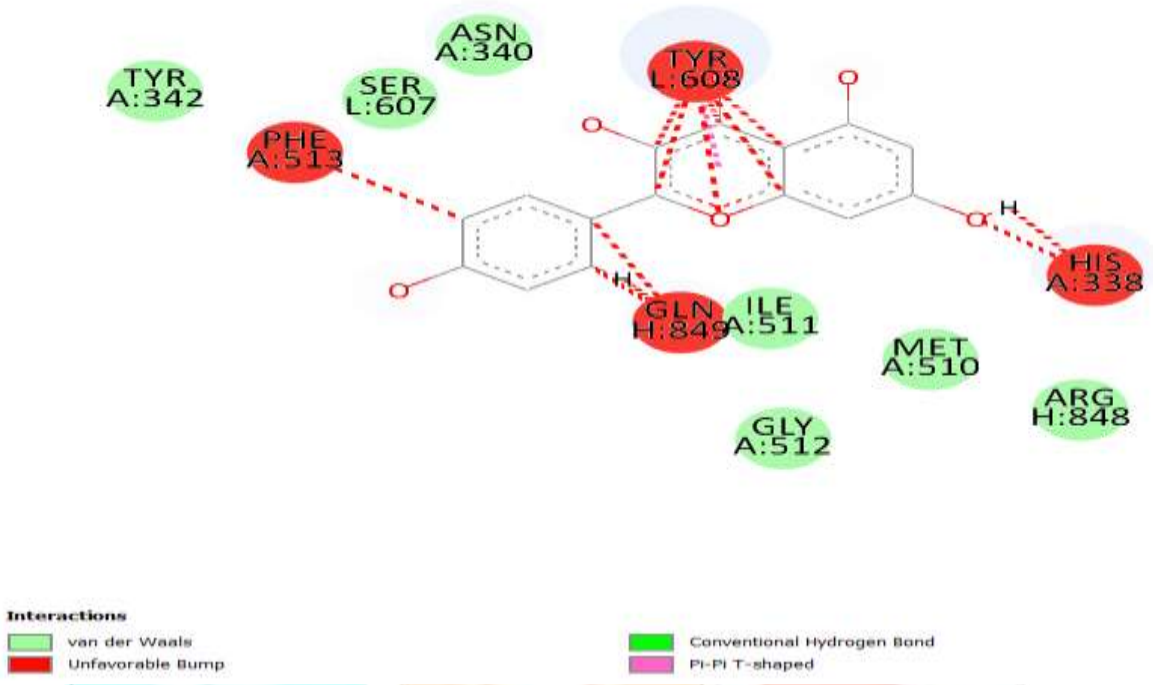

FIG 1,3

1.1 KAEMPFEROL AND PI3K RECEPTOR

Interaction between kaempferol and PI3K (PDB: https://doi.org/10.2210/pdb8V8H/pdb)

Drug	Docking score or binding energy	Van Der Waals	H bond	PI - ALKYL	PI - SULFUR
kaempferol	-8.18385 kcal/mol	VAL A :193	LYS A:206 MET A:282 ASN A:284 ARG D:2401	LYS A: 204 LEU A:792	--

DOCKING IMAGE

1.1 KAEMPFEROL AND PI3K RECEPTOR

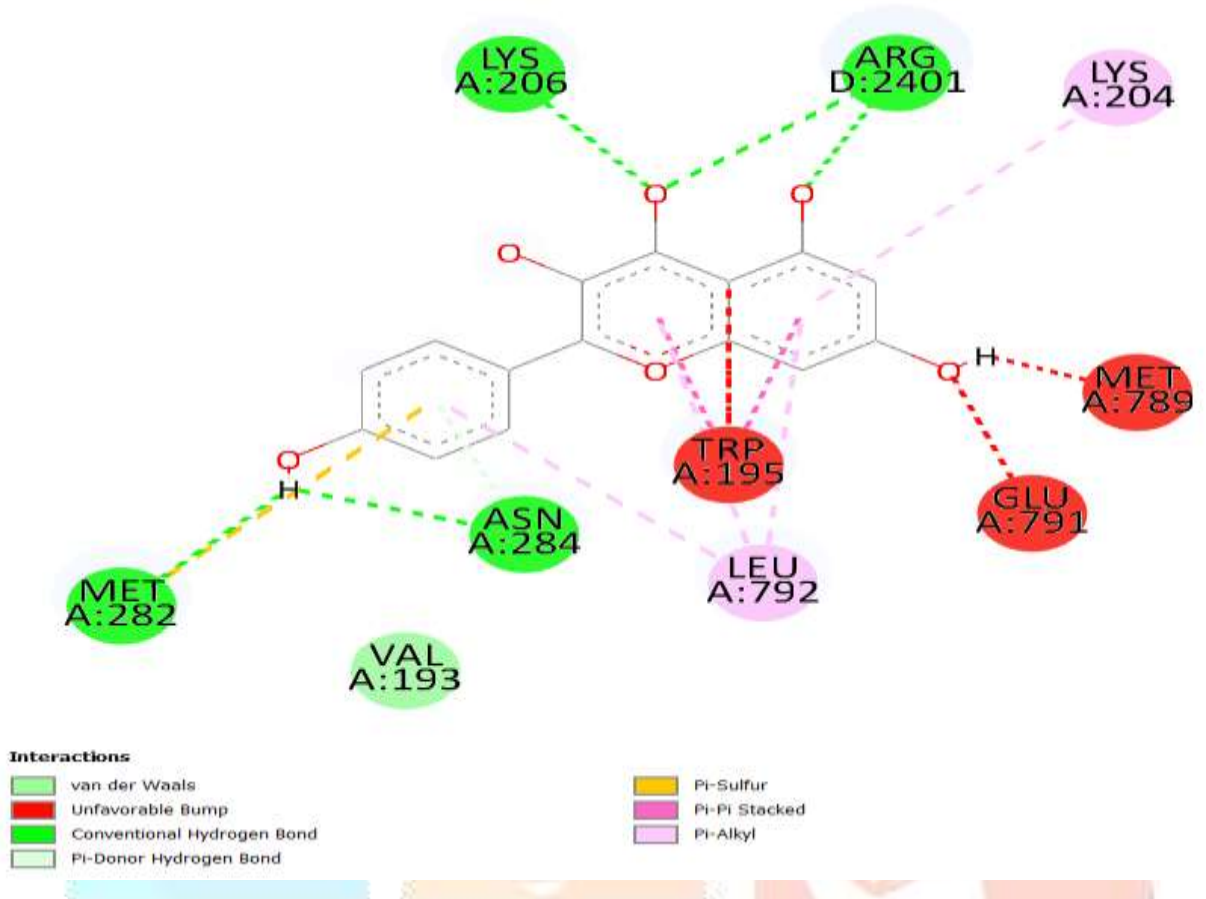

FIG 1,4

TABLE NO 1.2

Interaction between Akuammidine and NMDA (PDB: https://doi.org/10.2210/pdb7YFF/pdb)

Drug	Docking score or binding energy	Van Der Waals	H bond	PI - ALKYL	PI - ANION
Akuammidine	-7.69455 kcal/mol	GLN D:2968 GLU D:2974 ASP D:2972 THR D:2677 HIS D:2676 LEU D:2978 ARG D:2972	ASP D:2973	PHE D:2969 MET D:2977	--

DOCKING IMAGE

1.1 AKUAMMIDINE AND NMDA RECEPTOR

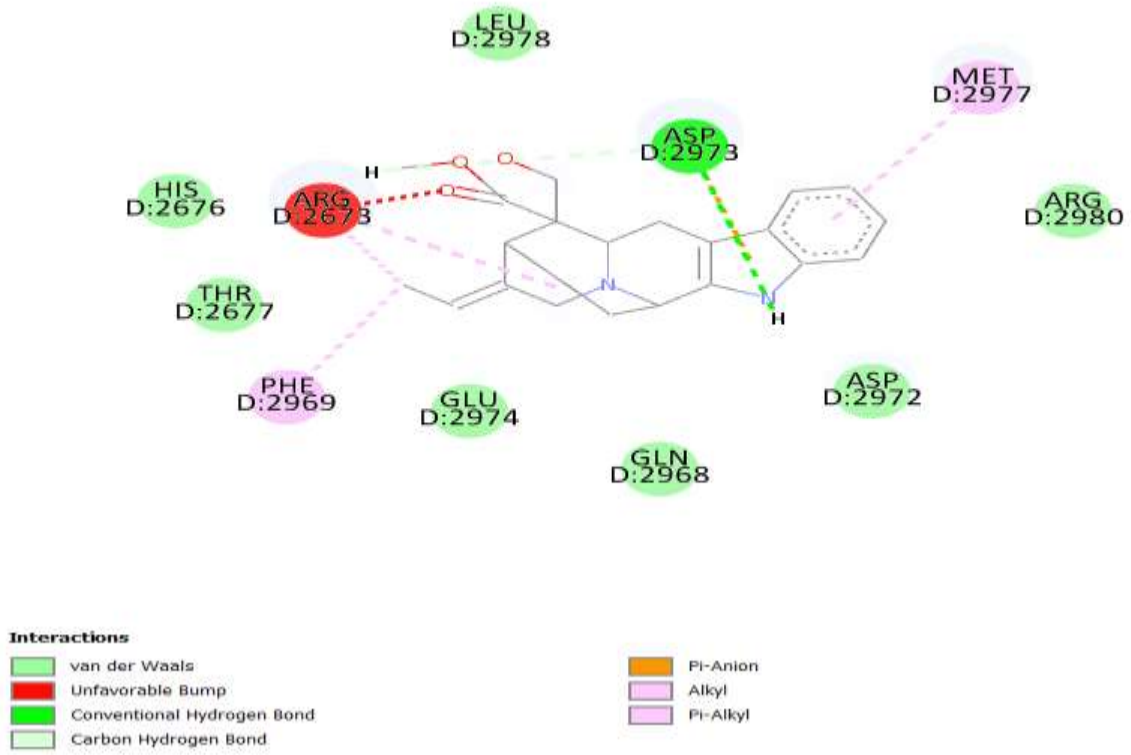

FIG 1,5

TABLE NO 1.3

Interaction between Akuammidine and 5HT2A (PDB: https://doi.org/10.2210/pdb6WGT/pdb)

Drug	Docking score or binding energy	Van Der Waals	H bond	AMIDE-PI-STACKED	PI - ALKYL
Akuammidine	-6.7759 kcal/mol	MET B:1132 ASN B:1127 ILE B:1224 TRP B:1228 ALA B:1152	SER B:1150 MET B:1149	ILE B:1131	ILE B:1128 MET B:1156 ILE B:1153 PHE B:1221

DOCKING IMAGE

1.1 AKUAMMIDINE AND 5HT2A RECEPTOR

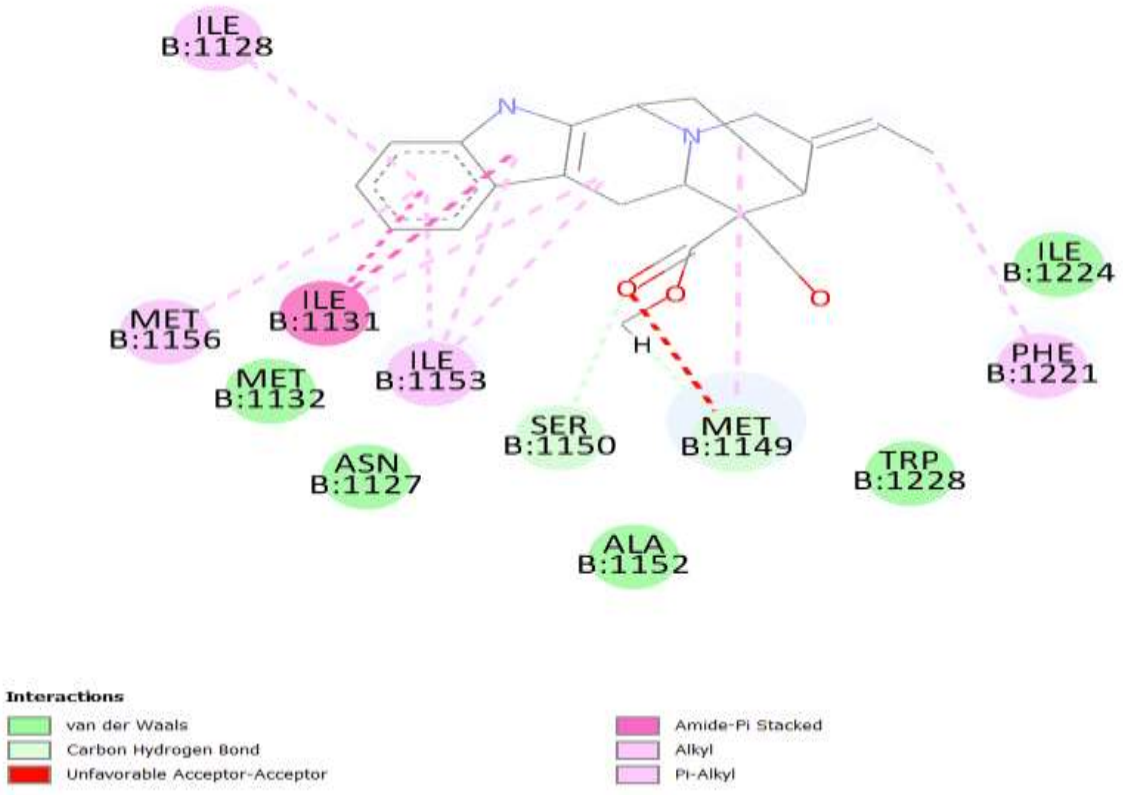

FIG 1,6

TABLE NO 1.4

Interaction between ferulic acid and serotonin (PDB: https://doi.org/10.2210/pdb6WGT/pdb)

Drug	Docking score or binding energy	Van Der Waals	H bond	PI - ALKYL	PI-SULFUR
Ferulic acid	-6.11529 kcal/mol	SER B:1150 PHE B: 1221 ILE B:1224 TRP B:1228 SER B:1135 TYR B:1146	--	ILE B:1131 ILE B:1153	--

DOCKING IMAGE

FERULIC ACID AND SEROTONIN

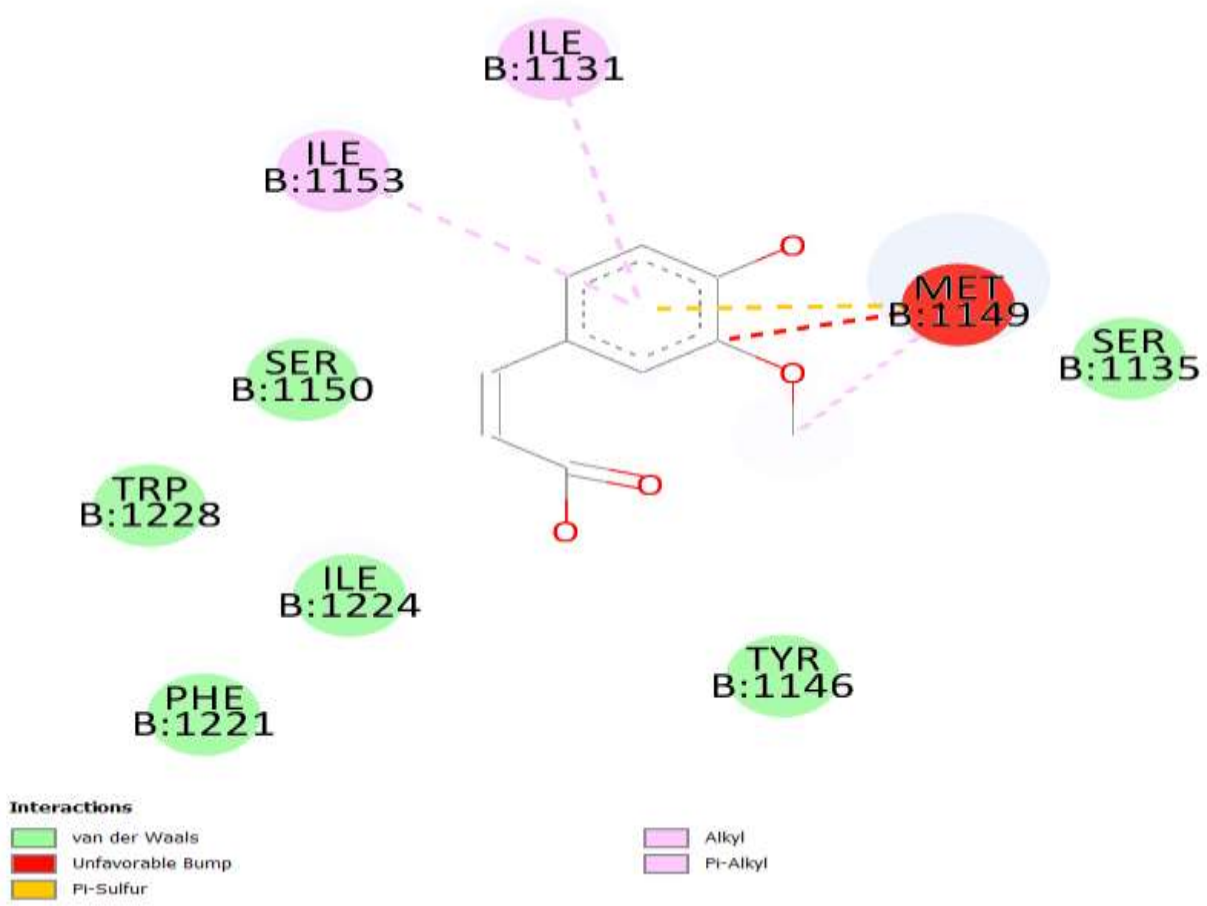

FIG 1,7

Results:

According to the study, Tridax procumbens leaves contain a wide range of bioactive substances, such as tannins, phytosterols, hydroxycinnamates, flavonoids, and alkaloids. Among these, there were notable concentrations of flavonoids (kaempferol) and alkaloids (akuammidine, in particular). According to molecular docking studies, these substances may have antipsychotic effects via a variety of mechanisms:

• Kaempferol: Said to affect the PI3K/Akt pathway, improving cognitive and neural plasticity. It is also thought to inhibit monoamine oxidase, which raises serotonin and dopamine levels.

• Akuammidine: Suggested to block serotonin receptor 2 and interact with the NMDA receptor, both of which are connected to psychotic symptoms.

CONCLUSION:

Tridax procumbens leaves offer a promising source of bioactive compounds with potential antipsychotic properties. The study's findings suggest that compounds like akuammidine, ferulic acid, and kaempferol play a significant role in mitigating psychotic symptoms. Mechanism-based on docking :

- Akuammidine: Inhibits serotonin receptors, leading to a reduction in hallucinations and psychotic symptoms. Additionally, it influences the glutamate pathway (NMDA receptors), promoting neuronal plasticity.
- Ferulic acid: Similar to akuammidine, ferulic acid appears to exert antipsychotic effects through its influence on the glutamate pathway.

- Kaempferol: Activates the PI3K pathway, which is crucial for neuronal signalling. It also inhibits dopamine receptors, contributing to a decrease in psychotic symptoms.

ACKNOWLEDGMENT:

The authors express thanks to the staff members of the pharmacology department of Rajgad Dnyanpeeth College of Pharmacy Bhor, Pune for their valuable advice and help**.**

REFERENCES:

1) Ikewuchi CC, Ikewuchi JC, Ifeanacho MO. Phytochemical composition of Tridax procumbens Linn leaves: potential as a functional food. Food and Nutrition Sciences. 2015;6(11):992.
2) Gubbiveeranna V, Nagaraju S. Ethnomedicinal, phytochemical constituents and pharmacological activities of Tridax procumbens: a review. Int J Pharm Pharm Sci. 2016;8(2):1-7
3) Chaudhari RD, Girase PR, Suryawanshi HP, Pawar SP. A review on Tridax procumbens Linn. Asian Journal of Pharmacy and Technology. 2018;8(3):158-60.
4) McCutcheon RA, Krystal JH, Howes OD. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. World Psychiatry. 2020 Feb;19(1):15-33.
5) Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. Journal of psychopharmacology. 2015 Feb;29(2):97-115.
6) Aghajanian GK, Marek GJ. Serotonin model of schizophrenia: emerging role of glutamate mechanisms. Brain research reviews. 2000 Mar 1;31(2-3):302-12.
7) Ciranna Á. Serotonin as a modulator of glutamate-and GABA-mediated neurotransmission: implications in physiological functions and in pathology. Current neuropharmacology. 2006 Apr 1;4(2):101-14.
8) Silva dos Santos J, Goncalves Cirino JP, de Oliveira Carvalho P, Ortega MM. The pharmacological action of kaempferol in central nervous system diseases: a review. Frontiers in Pharmacology. 2021 Jan 13;11:565700.
9) Jin S, Zhang L, Wang L. Kaempferol, a potential neuroprotective agent in neurodegenerative diseases: From chemistry to medicine. Biomedicine & Pharmacotherapy. 2023 Sep 1;165:115215.
10) Lim HJ, Prajapati R, Seong SH, Jung HA, Choi JS. Antioxidant and antineuroinflammatory mechanisms of kaempferol-3-O-β-D-glucuronate on lipopolysaccharide-stimulated BV2 microglial cells through the Nrf2/HO-1 signaling cascade and MAPK/NF-κB pathway. ACS omega. 2023 Feb 10;8(7):6538-49.
11) Hennessy MR, Gutridge AM, French AR, Rhoda ES, Meqbil YJ, Gill M, Kashyap Y, Appourchaux K, Paul B, Wang ZJ, van Rijn RM. Modified Akuamma Alkaloids with Increased Potency at the Mu-opioid Receptor. Journal of medicinal chemistry. 2023 Feb 24;66(5):3312-26.
12) Erharuyi O, Falodun A, Langer P. Medicinal uses, phytochemistry and pharmacology of Picralima nitida (Apocynaceae) in tropical diseases: A review. Asian Pacific journal of tropical medicine. 2014 Jan 1;7(1):1-8.
13) Nazari L, Komaki S, Salehi I, Raoufi S, Golipoor Z, Kourosh-Arami M, Komaki A. Investigation of the protective effects of lutein on memory and learning using behavioral methods in a male rat model of Alzheimer's disease. Journal of Functional Foods. 2022 Dec 1;99:105319.
14) Hammond Jr BR, Miller LS, Bello MO, Lindbergh CA, Mewborn C, Renzi-Hammond LM. Effects of lutein/zeaxanthin supplementation on the cognitive function of community dwelling older adults: a randomized, double-masked, placebo-controlled trial. Frontiers in aging neuroscience. 2017 Aug 3;9:254.
15) Di Giacomo S, Percaccio E, Gullì M, Romano A, Vitalone A, Mazzanti G, Gaetani S, Di Sotto A. Recent advances in the neuroprotective properties of ferulic acid in Alzheimer's disease: A narrative review. Nutrients. 2022 Sep 8;14(18):3709.

16) Hassanzadeh P, Arbabi E, Atyabi F, Dinarvand R. Ferulic acid, a phenolic compound with therapeutic effects in neuropsychiatric disorders, stimulates the production of nerve growth factor and endocannabinoids in rat brain. Physiology and Pharmacology. 2017 Dec 10;21(4):279-94.