

A comprehensive review on potential pharmacological activities of *Morinda citrifolia* Linn. for the treatment of central nervous system disorders

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Abstract

Back ground: In Brazil, the plant *Morinda citrifolia*, popularly known as noni, is widely utilized in traditional medicine. Many components of the noni tree, including the roots, leaves, and seeds, are used in these traditions. Because of its high antioxidant activity and established health advantages *Morinda citrifolia* (Noni) has been widely utilized as a complementary and alternative medicine in many countries. The noni plant has an ancient legacy of being used to cure a range of diseases including CNS abnormalities. It has historically been used as an antidepressant, anxiolytic, antiepileptic activity, antipsychotic, nootropic activity, anticraving activity against alcohol dependence, antiemetic activity, neuroprotective agent. **Objective:** Based on preclinical research published in the literature, the current study underlines noni therapeutic potential activities for the treatment of CNS disorders. The literature was collected from research gate, Wikipedia, Medline, scholarly articles, online databases and academic search. The present review targeted on mostly receptors, enzyme transporters and *in vivo*, *in vitro* and *in silico* methods for different CNS disorders. **Conclusion:** The monoamine oxidase (MAO) A and B bioassays were used to evaluate the antidepressant effects of *Morinda citrifolia* (noni) fruit extracts *in vitro*. Noni fruit has a synergistic impact because of its active components, involved in inhibiting MAOA and MAOB enzymes. The methanolic extract of noni shows antipsychotic activity by inhibiting dopaminergic receptors. Administration of benzodiazepine and MMC attenuated anxiolytic activity in mouse models. Noni inhibits acetylcholine esterase enzyme and exhibits nootropic activity. Noni exhibits anticraving activity against alcohol dependence by CPP test. Noni exhibits neuroprotective activity by decreasing the brain damage and dysfunction caused by reperfusion injury.

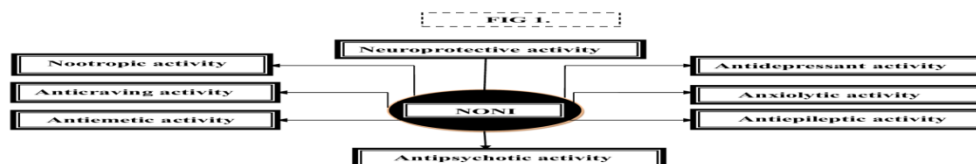
Key words: therapeutic potential, noni, CNS disorders, *in vivo*, *in vitro*, *in silico*

Introduction

Psychosis is a persistent chronic neuropsychiatric disease that affects people's quality of life and is a serious public health problem. At this moment the drug tolerability and drug efficacy is finite. Since day by day the psychiatric disorders are rising, for the treatment of neuropsychological problems, doctors are searching for herbal remedies and pharmacological treatments¹. In the present situation the patients affected with COVID-19 undergo an isolated hospital stay or are quarantined at home; this isolation has been shown to have a substantial effect on psychological well-being. Patients staying in isolation rooms for prolonged time with limited social interaction and loss of freedom, which may result in anger, fear, stress, insomnia, irritability, CNS disorders such as anxiety, depression, psychosis etc. Multiple corona virus variants have been shown to have neurotropism and neuro-invasive symptoms in the past, causing neuro and psychological effects in a group of COVID-19-affected people. A variety of neurological disorders have been reported as risk factors for suicide, neurologists should be aware of these conditions and have a general understanding of suicide risk and treatment options. Males are very well risk factor for suicide, due to alcohol addiction. One of the most single powerful sources of CNS disorders is depression². Conventional drugs such as antidepressants, anti-anxiety, antipsychotics shows minimal effect and have adverse effects such as extra pyramidal effects. In modern medicine, phytotherapy research is an integral part for the discovery and development of novel drugs³.

In the present review one of the medicinal plants has large and variety of medicinal properties. *Morinda Citrifolia* Linn., (family: Rubiaceae) noni, Indian mulberry, hog apple, and cheese fruit. Its fruit is ovoid in shape and when it grows up gives a nasty butyric acid odor and astringent taste. Every component of the plant is utilized as traditional medicine, from the roots to the seeds, and various medicinal properties have already been reported. To determine the therapeutic potential of *M. Citrifolia*, various *in vivo* and *in vitro* studies were performed. These all studies accentuate the pharmacological activities such as anti-anxiety, antidepressant, antipsychotic, antidopaminergic, antioxidant activity. Mainly the noni juice extracted from noni fruit has its pharmacological

activity, treatment of CNS disorders⁴. Several plants were used as traditional medicine, and they were considered to be the important sources of novel drugs, but *Morinda Citrifolia* Linn., for year's mankind utilised it as food and medicine. The noni plant has a long history of being used to cure a range of diseases, including CNS abnormalities⁵. The therapeutic action of some plants such as *Ginkgobiloba*, *Hypericum perforatum*, *Apocynum venetum*, *Valerian officianalis*, *Melissa officinalis* and *M.citrifolia* for treatment of depression and anxiety were reported in previous studies. Furthermore recent studies predicted *M.citrifolia* as an inhibitor of MAO-A and MAO-B enzyme⁶. The percentage of menopausal women is steadily growing in parallel with ageing society. Stroke risk increased during this time period. According to the previous studies it has been demonstrated that oxidative stress regulation disruption plays a critical role in the pathogenesis of stroke. Furthermore, the earlier researchers confirmed the antioxidant activity of *M.citrifolia* leaf. Because of the previously mentioned neurological properties of *M.citrifolia*, researchers speculated that extract of the leaves of *M.citrifolia*, would reduce the stroke⁷. Post stroke depression (PSD) is a kind of depression that occurs after a cerebrovascular event. PSD accounts for over one-third of all stroke survivors. MOOs, herbal extracts derived from the roots of the plant *Morinda officinalis* have an antidepressive action in PSD rat models. MOOs were certified as a prescription drug for light or moderate depression by the CFDA in 2012⁸. The previous study indicates GM-MS analysis of *Morinda citrifolia* fruit extract and insilico docking analysis of phytoconstituents found in *Morinda citrifolia* fruit extract against antipsychotic medication targets such as dopamine receptors (D2 and D3). The phytoconstituents of *Morinda citrifolia* were extracted from Pubchem chemical databases using GC-MS analysis⁹. The neuropharmacological activity of noni discussed in fig1.



**Figure1. flow chart determining about neuropharmacological activity of *Morinda citrifolia* Linn.,
Table 1. Neuropsychopharmacological activity of *Morinda citrifolia* Linn..**

Sl.No:	Plant parts/Plant extracts	Mechanism of Action	Neuropsychopharmacological activity
1.	Methanolic extract of <i>Morinda citrifolia</i> fruit	Benzodiazepine –GABAergic and serotonergic mechanism is involved, shows anxiolytic like activity ¹⁰ .	Anxiolytic and antidepressant activity.
2.	Methanolic extract of <i>Morinda citrifolia</i> Linn., unripe fruit	sco- poletin and rutin were reported for its interaction with dopamine D2 and D3 receptors in in silico molecular docking studies. It has been postulated that a selective dopamine D3 receptor antagonist could be used to alleviate drug-induced motivation and reward ¹¹ . MMC (3 and 5 g/ kg, p.o.) and BUPR (20 mg/kg, p.o.) could attenuate the expression of Meth-induced CPP in mice ¹¹ .	Learning and memory ehancement ¹¹ .
3.	Methanolic extract of unripe coarse fruit powder ¹² of <i>Morinda citrifolia</i>	MMC demonstrated biphasic action on dopaminergic system, that is, antidopaminergic effect at lower dose (40mg/mL) and dopaminergic agonistic effect at higher dose (>60mg/mL). Scopoletin (<200µg/mL) and	Antiadrenergic and antidopaminergic activity if scopoletin and rutin hydrate ¹² .

		rutin hydrate (<312.6µg/mL) have antidopaminergic and antiadrenergic actions ¹² .	
4.	acetate extract of freeze-dried noni fruit powder ¹³	inhibited MAO-A and B enzymes 78 % and 49%. Prior findings indicate that noni fruit is a natural MAO-A and MAO-B inhibitor, involving a synergistic effect from multiple active components ¹³ .	Antidepressant activity ¹³ .
5.	methanol crude extract of Noni fruit powder ¹⁴ .	Noni fruit may contain a competitive ligand or ligands that bind to the GABA _A receptor as an agonist and so elicit its anxiolytic and sedative properties ¹⁴	Antianxiety and sedative action ¹⁴ .
6.	Noni juice ¹⁵ .	Neurochemical research indicated substantial alterations in noradrenergic, dopaminergic, or serotonergic systems in the noni-treated group's amygdala, hippocampus, and substantia nigra ¹⁵ .	Antianxiety activity ¹⁵ .
7.	Methanolic crude extract of fruit powder ¹⁶ of <i>Morinda citrifolia</i>	The treatment of <i>M. citrifolia</i> fruit extract for 15 days improved the seizure threshold in MES-induced rats, and the putative causes include suppression of prostaglandin production and the monoamine oxidase enzyme ¹⁶ . PHE's antiepileptic action may be due to a reduction in calcium ion influx ¹⁶ .	Antiepileptic activity ¹⁶ .
8.	Methanolic extract of <i>Morinda citrifolia</i> Linn., ¹	Acute MMC (1, 3, 5, 10 g/kg, p.o.) therapy significantly reduced apomorphine-induced cage climbing behaviour and climbing duration in mice in a dose-dependent manner. The MMC also decreased methamphetamine-induced stereotypy behaviour and climbing time in mice in a dose-dependent manner. Apomorphine-induced climbing behaviour and climbing duration in mice were dramatically reduced after 7 and 21 days of treatment with TNJ in drinking water at 50 and 100 percent v/v ¹ .	Antipsychotic activity ¹ .
9.	Hydroalcoholic extract of fruit powder ¹⁷ of <i>Morinda citrifolia</i>	The neuroprotective action of MCFE was determined using both in vitro and ex vivo approaches, and it was shown that the phytoconstituents had the capacity to enhance learning and memory function by inhibiting acetylcholinesterase ¹⁷ .	Enhancing memory and learning ¹⁷ .
10.	Ethylacetate fraction of fruit powder ¹⁸ of <i>Morinda citrifolia</i>	EMC at a dose of 400 mg/kg exhibited a significant increase ($p < 0.01$) in the levels of serotonin and dopamine ¹⁸ .	Enhancing short term memory and long term memory ¹⁸ .
11.	Noni juice ¹⁹ .	NONI treatment to mice reverses retention deficit in a step-down latency inhibitory test. NONI protects against scopolamine-induced oxidative damage by sustaining the activities of SOD. Noni has a therapeutic action for prevention of Alzheimer's disease ¹⁹ .	Antialzheimer activity ¹⁹ .
12.	Boiled and dried noni fruit powder extract ²⁰ .	<i>Morinda citrifolia</i> Linn. exhibits antiemetic properties, and a 600 mg prophylactic noni extract (equal to 20g dried noni fruit or scopoletin 8.712µg) substantially lowers the risk of early postoperative nausea (0-6 hours) ²⁰ .	Prevents post operative nausea and vomiting ²⁰
13.	Leaves extract ⁷ of <i>Morinda citrifolia</i>	neuroprotective effect was assessed by giving <i>M. citrifolia</i> leaf extract at doses of 2, 10, and 50 mg/ kg BW to the bilateral ovariectomized (OVX) rats for 7 days. neuroprotective effect of the extract might occur partly via the improvement of oxidative stress status in the	Prevents cerebral ischemia ⁷ .

		cortex ⁷ .	
14.	Fruit juice ²¹ of noni	3% or 10% juice in the drinking water for 7d, and compared to the control group. Neurological deficit scores (NDS) were decreased after the reperfusion in the juice-supplied mice. Noni juice have a preventive effect against cerebral ischemic stress ²¹ .	Prevents cerebral ischemia ²¹ .

Antidepressant activity

Invivo studies

A significant body of research indicates that *Morinda citrifolia* Linn., may well have pharmacological potential for the treatment of depression and anxiety¹⁰. The prospective role of serotonergic and / noradrenergic pathways in antidepressant activity of MMC was designed by its interaction with AMPT (adrenergic and dopaminergic depletory), or PCPA (Serotonergic depletor), or WAY 100635 (5HT1A receptor antagonist) in mice¹⁰. The potential activity of serotonergic system in antidepressant like activity of MMC (1g/kg, p.o.) in TST was examined. TST is a highly approved animal model in depression studies, in part due to its sensitivity and predictability of the outcomes. In the mouse model TST, MMC at dose of (0.5 and 0.75g/kg) dramatically decreased immobility time. MMC diminished immobility to a level similar to that reported after intraperitoneal dose of standard antidepressant desipramine (30mg/kg)¹⁶. Biogenic and dietary amines deteriorate by key isoenzymes such as MAO-A and MAO-B. MAO-A discriminatorily oxidizes serotonin (5-HT) and noradrenaline (NA), although MAO-B discriminatorily oxidizes phenyl ethylamine (PEA). Pair of isoenzymes can oxidize dopamine. A non selective and irreversible inhibitor of MAO-A and MAO-B, tranylcypromine is very efficacious in treatment of critical depression. MMC shows similar activity like tranylcypromine by inhibiting both MAO-A and MAO-B enzymes. MMC indicate antidepressant like activity in mice consequently raise the level of biogenic amines 5HT and NA. Previous studies illustrated that antidepressant like effect of noni fruit is arbitrated through its interaction with serotonergic and noradrenergic systems¹⁷. As per earlier procedure the inhibition of MAO A and MAO B enzyme, employing invitro studies was investigated by therapeutic potential antidepressant activity of noni fruit extract and its identified components¹³.

Antidepressant activity

Exvivo studies

Previous studies shown that noni fruit contains variety of chemical constituents such as rutin, scopoletin and coumarin derivatives. It has been described that rutin has pharmacological activities like antidepressant, antioxidant, neuroprotective and antianxiety activity. It has been exemplify that scopoletin and rutin sequentially showed antidepressant activity conciliate interaction with α_1 - and α_2 -adrenoreceptor¹².

Anxiolytic activity

Invivo studies

Considering animal behavior models, the recent research represents an early attempt to examine the therapeutic effect of potential mechanism of action of *M. citrifolia* for its anxiolytic and antidepressant like activity¹⁷. Drug interaction findings with the selective benzodiazepine receptor antagonist, flumazenil, or the GABA_A receptor antagonist, bicuculine, or the 5HT1A receptor antagonist, WAY 100635, were designed to examine the involvement of benzodiazepine – GABAergic and/or serotonergic systems associated with anxiolytic like effect of *M. citrifolia*¹⁷. The recent findings shows that MMC (1g/kg, p.o.) exhibited anxiolytic like activity in mice models of EPM and LDT, which was identical to a very well known anxiolytic standard drug diazepam (1mg/kg, i.p.)¹⁷. MMC at a dose of 1g/kg significantly improved the number of open arm entries and time spent in open arms of EPM. In accordance with a recent study that found that 15 days of noni juice administration showed anxiolytics – like effects in the rat EPM. Benzodiazepine-GABA_Aergic neurotransmission plays a vital role in control of anxiety. Previous in vitro research showed that the methanolic extract of *M. citrifolia* preferentially binds to GABA_A receptors. Benzodiazepine-GABAergic plays a vital role in control of anxiety. Previous invitro research showed that the methanolic extract of noni fruit preferentially binds to GABA_A receptors. Benzodiazepines decreases anxiety by selectively enhancing GABA_Aergic transmission in neurons with α_2 subunit in their GABA_A receptors, blocking neuronal circuits in the limbic portion of the brain. Benzodiazepine – GABA_A and serotonergic (5HT1A) receptor mechanism mediated by noni for the treatment of anxiety. Hence noni used for treatment of both acute and chronic GAD. When rats were administered noni juice orally for 15 days, they spent more time explore the uncomfortable opened arms, shown by increased time spent in these arms, in addition to a prolonged time per entry in these arms. Whereas the control rats avoided it and remained in safe closed arm. The rats motor activity, particularly indicated by the total number of entries into both arms, and rearing activity did not change between treatments. According to the previous studies the anxiety related behavior in rats in EPM was decreased by noni juice²¹. The noni juice had antianxiety activity similar to benzodiazepine a class of anxiolytic standard drug.

Invitro studies

A methanolic extract of noni fruit manifest 75% binding suppression to GABA A receptor as an agonist in an in vitro assay, illustrating its anxiolytic activity. To examine the GABAergic activity of noni fruit, a competitive GABA_A receptor binding test was designed and performed. The initial findings showed that at a concentration of 100mg/ml, the methanol crude extract of noni inhibited the binding of the agonist radioligand [3H] muscimol to GABA_A receptors, approximately 75%¹⁴. Binding of ligand to GABA_A receptor leads to regulate level of an inhibitory neurotransmitter – GABA as agonist which produces anxiolytic and sedative effects²⁰. Neurochemical evaluation was also performed in the previous studies, researchers identified modifications in the monoaminergic system in noni treated rats compared to control rats. Noni juice may very well have anxiolytic effects resulting in a decrease in neurotransmitters such as NE in the amygdale and hippocampus, 5-HT in the amygdale, DOPAC in the hippocampus and substantia nigra, and HVA in the substantia nigra. Many analyses on the 5-HT hypothesis indicate that anxiety is related with increased endogenous 5-HT, whereas anxiolytics tend to lower endogenous 5-HT. The anxiolytic property can be determined by lower level of 5-HT in frontal lobe of nonigroup. In noni group the lower level of NE in amygdala and hippocampus was observed. In aspects of DA activity, earlier research has demonstrated that apathetic situations raise the levels of DA, DOPAC, and HVA in brain areas associated with anxiety (eg. Frontal cortex, amygdale etc.). The decreased level of anxiety in noni –treated rats is most likely due to reduced DA and its intermediates throughout the brain, with a notable effect in the hippocampus and substantia nigra region. Because the control of GABA on the monoaminergic system has been hypothesized through the collocation of the GABA receptor on noradrenergic neuron, dopaminergic neuron and serotonergic neuron the modulation of different neurotransmitters by noni may be regulated through GABAergic system. In the previous studies it was found that methanol crude extract of noni fruit exhibited GABA_A receptor binding affinity. Noni may regulate the activity of monoaminergic neurons in numerous areas of brain by acting on the GABA_A receptor. In previous studies when tested with using an elevated plus maze test, noni juice a natural compound of Morinda citrifolia Linn, had an anxiolytic effect in rats, which was mediated in part by alterations in monoaminergic neurotransmitter levels¹⁵. The results provided an invitro basis for noni's widespread utilization as both as natural antidepressant to relieve anxiety and promote well – being.

Antiepileptic activity

Invivo studies

In comparison with reference standard phenytoin 20mg/kg, p.o., the M. citrifolia fruit extract showed a dose related significant ($P < 0.01$ and $P < 0.001$) decrease in different phases of epileptic seizures¹⁶. MES induced seizures were reduced by using extract of Morinda citrifolia 200 and 400mg/kg, p.o for 15 days respectively.

Invitro studies

The Morinda citrifolia fruit extract at a dose of 200mg and 400mg/kg, p.o for 15 days raised the brain levels of serotonin, dopamine and noradrenaline that may be related to strong protection provided against MES- induced seizures. In many animal test systems, increased serotonergic transmission raises the threshold of pentylenetetrazole (PTZ) mediated seizures, therefore protecting against PTZ- induced convulsions. Suppression of prostaglandin synthesis has been shown to raise the dopamine and noradrenaline levels in the brain resulting in seizure inhibition. In MES induced rats, treatment of Morinda citrifolia Linn., fruit extract for 15 days enhanced the seizure threshold, it's because of suppression of prostaglandin synthesis and monoamino oxidase enzyme. PHE antiepileptic action is due to reduction in calcium ion influx¹⁶.

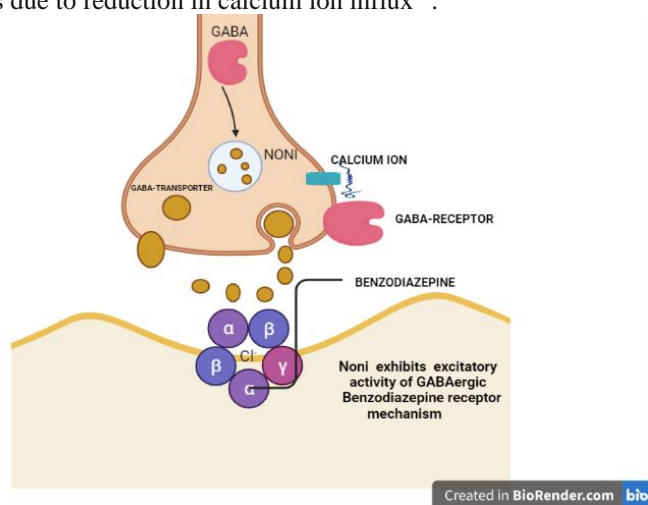


Fig2. Mechanism of action of antianxiety drugs

Antipsychotic activity

Invivo studies

In previous studies the cognitive effects observed in animals following the administration of dopamine agonist apomorphine are due to D1 and D2 receptor activation. Antipsychotic drugs evaluation is based on the neurochemical hypothesis of schizophrenia which predominantly affects the neurotransmitters dopamine and glutamate. Apomorphine, a direct agonist, or amphetamine, a medication that enhances the release of this neurotransmitter while blocking its reuptake, are commonly used in dopamine based models. In previous investigation acute MMC pre-treatment (1-10g/kg, p.o.) in mice resulted in a considerable dose dependent decline in climbing behavior and climbing duration caused by apomorphine. Similarly, 7 and 21 days of pre-treatment with TNJ (30, 50, and 100% v/v in daily drinking water) drastically decreased apomorphine – induced climbing behavior and time in mice. Different doses of noni juice (5, 10 and 100mg/kg, i.p) corresponding to dried juice powder doses (450, 900 and 1800mg/kg, i.p.) preferentially decreased stereotype induced by amphetamine (3mg/kg, s.c) in a dose dependent manner. From the previous findings MMC and TNJ has dopamine D1 and/or D2 receptor antagonistic activity. The methamphetamine – induced stereotype and cage climbing time in a dose dependent manner was substantially decreased by MMC (1, 3 and 5g/kg, p.o.). Previous studies confirm the antidopaminergic effect of MMC of noni unripe fruits. According to previous studies MMC inhibited the stereotyped behavior caused by apomorphine and methamphetamine in Swiss albino mice in a dose – dependent manner²².

Invitro studies

The impact of previous studies examined that methanolic extract of *Morinda citrifolia* Linn., MMC and its bioactive components, scopoletin and rutin, on dopamine – and noradrenaline evoked contractility in isolated rat vas deferens. MMC (1-40mg/ml), scopoletin (1-200µg/ml) and rutin hydrate (0.6-312.6µg/ml) reduced contractility in isolated rat vas deferens in dose dependent manner¹². In the previous study interaction with dopaminergic and noradrenergic systems was studied using scopoletin and rutin. MMC (<40mg/ml), scopoletin (100, 200µg/ml), and rutin hydrate (156.3, 312.6µg/ml) all exhibited a considerable concentration-dependent suppression of contraction induced by dopamine in isolated rat vas deferens preparations, suggesting MMC antidopaminergic activity. MMC (<40mg/ml) antagonistic effect on dopaminergic and noradrenergic pathways might be irreversible. MMC has a biphasic effect on the dopaminergic system, with an antagonistic effect at low doses (40mg/ml) and an agonistic effect at high concentrations (>60mg/ml). As a result both α_{1A} and $\alpha_{2A/D}$ adrenoreceptors may be involved in the antiadrenergic impact of MMC (30mg/ml) and its bioactive components scopoletin and rutin. It's possible that the contractility response to a large dose of MMC is not really mediated by an adrenergic mechanism. The biphasic activity of MMC in previous study using rat vas deferens preparation could be observed in dopaminergic system¹².

Insilico studies

The GC-MS chromatogram of *Morinda citrifolia* standardized extract revealed 16 main peaks. Suggesting the existence of 16 phytochemical components. The 16 phytochemicals were discovered and described by comparing the mass spectra of the components with the NIST library. According to the previous studies the molecular interaction of standard typical antipsychotic drugs (chlorpromazine, haloperidol) and atypical antipsychotic drugs (amisulpride, aripiprazole, clozapine, risperidone, paliperidone and pimozide), were compared with phytoconstituents of *Morinda citrifolia* with D2 and D3 receptors. The docking model using the D2 Dopamine receptor, PDB ID: 5AER, demonstrated that all interactions for both phytoconstituents and standard drugs included the A chain. Rutin had the lowest MolDock score, followed by pimozide and aripiprazole, with values of -120.52, -116.13, and -115.04, respectively. The phytoconstituents ascorbic acid, rutin, morindin and alizarin had the highest hydrogen bond interaction with values of -8.39, -7.56, -5.04 and -4.59 respectively followed by standard drugs paliperidone and haloperidol with interactions of -4.52 and -3.23. The docking model using the D3 Dopamine receptor with PDB ID: 3PBL found that all interactions involved both the A and B chains, except for the phytoconstituents morindone, alizarin, and scopoletin, which involved interactions with just the A chain amino acid residues. Rutin simulates the lowest MolDock score with a MolDock score of -143.02, followed by risperidone with a MolDock score of -131.53. Morindone's MolDock score and hydrogen bond energy were discovered to be -66.81 and -10.36, respectively, whereas paliperidone's were -121.16 and -10.10. Pimozide (-116.13) was ranked first on the docking analysis of standard drugs based on their MolDock score on the target D2 dopamine receptor, followed by aripiprazole (-115.04), paliperidone (-114.21), amisulpride (-101.66), risperidone (-96.34), haloperidol (-91.33), chlorpromazine (-83.47), and clozapine (-63.74). The ranking of standard drugs based on their MolDock score on the target D3 dopamine receptor was risperidone (-131.53), paliperidone (-121.16), amisulpride (-118.18), haloperidol (-109.10), pimozide (-103.77), clozapine (-102.58), aripiprazole (-97.04), and chlorpromazine (-97.04). (-83.27). The phytochemical constituents from *Morinda citrifolia* had the highest affinity to the target receptor compared to typical medicines⁹.

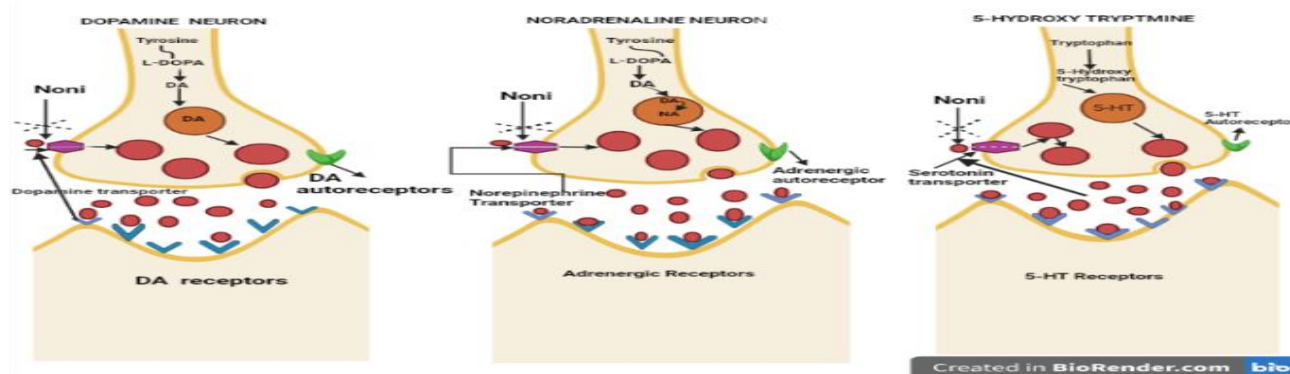


Fig3. Mechanism of action of antipsychotic agents

Nootropic activity

In vivo studies

In previous studies the percentage inhibition of acetylcholine enzyme by using standard drug neostigmine was observed as 62.1±2.5. The MCFE exhibited a dose dependent percentage inhibition of acetylcholinesterase activity with percentage inhibition of 37.8±46.8± at doses of 100 and 200mg/kg, correspondingly exhibiting a dose dependent percentage inhibition of acetylcholinesterase activity. Statistical analysis was performed for relevance of the P value. The control group was compared with standard group and MCFE treated group, when compared to control group, all three treated groups demonstrated a significant value of $P < 0.05$. This implies that activity of acetylcholinesterase enzyme was considerably reduced, following treatment with standard drug and MCFE. The previous study investigated the neuroprotective activity of MCFE phytochemical constituents have the ability to improve learning memory function by inhibiting acetylcholinesterase enzyme¹⁷.

In vitro studies

The neuroprotective action of ethylacetate fruit extract of *Morinda citrifolia* (Rubiaceae) Linn at doses of 200 and 400mg/kg, po in scopolamine induced dementia was examined¹⁷. Acetylcholine iodide was used as substrate, while 5,5-Dithiobis(2-nitrobenzoic acid) as a chromogen for assay of acetylcholine activity. According to previous studies in vitro inhibition of acetylcholine enzyme was determined by the percentage inhibition levels of MCFE were reported to be dose-dependent manner. At a dose of 800µg/ml, the highest percentage was attained resulting in a maximal inhibitory level of 76.77±1.10. The in vitro acetylcholinesterase inhibition experiment was carried out, and the IC₅₀ value of MCFE and neostigmine was found to be 31.84µg/ml and 19.71µg/ml correspondingly²⁴. In the previous studies when compared to control group, injection of Aβ peptide (25-35) drastically ($P < 0.01$) enhanced acetylcholine activity. In the extract treated group, enzyme levels were significantly decreased ($P < 0.05$). In extract treated groups there was a significant ($P < 0.05$) decline in enzyme levels in both 200mg/kg and 400mg/kg EMC treated mice¹⁸. Noni suppressed acetylcholine esterase activity in a dose dependent manner, with an IC₅₀ value of 152.90±1.90µg/ml¹⁹. Indian noni inhibited 49.5% of acetylcholinesterase.

In silico studies

According to previous studies computation of bioactivities for plant phytoconstituents, *M. citrifolia* plant compounds using the CAST-p tool, which predicts the pocket binding location of the chosen protein Viz. It was proposed that active sites of protein contains findings such as 1B41 has the following amino acids: Ser-203, Thr-83, Thr-238, Glu-313, Gly-234, Arg-296, Tyr-337, Ser-125, Glu-202, Tyr-503, Gln-413, Asn-533, His-405, Trp-532, and in the protein 1N5R. Ser-203, Gln-202, Tyr-133, Gly-120, Trp-86, Tyr-337 were the results. His-381, Asp-74, Tyr-124, Glu-202, Tyr-341, Tyr-133, Glu-71, and Ser125. According to prior research, the drug molecules would interact with the active areas of these two proteins, inhibiting the activity of AChE levels in AD. The findings obtained from previous studies demonstrates that The in silico molecular docking investigations on selected phytoconstituents of the plant, *Morinda citrifolia* Linn., revealed the best binding interactions with both proteins of the neurotransmitter AChE. According to prior report it is possible to emerge AChE inhibitors that are effective in the treatment of Alzheimer's disease²³.

Anticraving activity against alcohol dependence

In vivo studies

In previous studies research was done on mouse conditioned place preference test to evaluate the impact of a standardized methanolic extract of *Morinda citrifolia* Linn., unripe fruit on compulsive ethanol-seeking behavior. According to the Bonferroni test results revealed that conditioning score of the vehicle treated group on the post conditioning day was considerably ($P < 0.05$) higher than the preconditioning day. MMC (3 and 5g/kg P.O.) and ACAM (300mg/kg P.O.) in treated groups had no effect on conditioning score on the postconditioning day. When compared to the vehicle control group the conditioning score ($P < 0.001$) was decreased by MMC (3 and 5g/kg p.o.) and ACAM (300mg/kg p.o.) which indicates that MMC and ACAM had an anticraving effect. Treatment with acamprosate (300mg/kg, p.o.) resulted in a substantial reduction in

conditioning score during the extinction phase. Throughout the extinction phase, MMC at a dose of (1g/kg) had no effect on predilection for the ethanol-paired habitat. The Bonferroni tests showed that the conditioning score of the vehicle treated group was considerably ($P < 0.05$) elevated on the reinstatement day following a prime low dose of ethanol (0.4g/kg, i.p.) as compared to pre-reinstatement. According to the Bonferroni methods include MMC (1,3,5g/kg p.o.) and ACAM (300mg/kg, p.o.) had no considerable influence on the reinstatement caused by ethanol priming injection. Our new findings show that MMC has an antidopaminergic activity in both *in vivo* and *in vivo* investigations. Therefore we postulate that MMC influences the expression and facilitation of extinction of ethanol induced CPPs are due to its antidopaminergic activity. Due to presence of scopoletin and rutin as phytochemical constituents in noni, responsible for many pharmacological activities and antidopaminergic activity. The foregoing study concludes that MMC attenuated expression and accelerated the extinction of ethanol – induced CPP in mice³.

Antiemetic activity

In vivo studies

Certain plants, such as *Morinda citrifolia* Linn., are recommended in traditional medicine for the treatment and prevention of nausea and vomiting. Hot water extract of dried ripe noni fruit has an antiemetic activity, according to traditional Thai Pharmacopoeias, and regular sips of the extract can ease nausea and vomiting. Dried powdered noni fruit is widely accessible in global markets and is marketed as having a variety of applications, including antiemetic properties. In previous studies. The primary goal of such an exploratory investigation was to assess the ability of noni fruit extract to prevent nausea and vomiting in surgical patients who were at risk. The secondary outcomes of previous investigation discover the appropriate dose of the extract for PONV treatment, as well as to identify additional possible advantages and adverse side effects of its use for PONV prophylaxis. According to foregoing study it was observed that 600mg dose of noni extract, extracted from 20mg of dried noni fruit corresponding to exactly 8.712mcg of noni phytochemical constituent such as scopoletin can reduce the nausea in early postoperative phase. The antiemetic activity appears to be moderate and lasts no longer than six hours. In previous studies compared with placebo group (48 percent for the 600mg noni group and 80 percent for the placebo group, p -value = 0.04), patients who received the 600mg of noni extract reported significantly determined decreased level of nausea within first 6 hours. In other time periods the occurrence of PONV was not significantly different for all 3 noni doses versus placebo²⁰. There were no adverse effects mentioned in any of the groups [27].

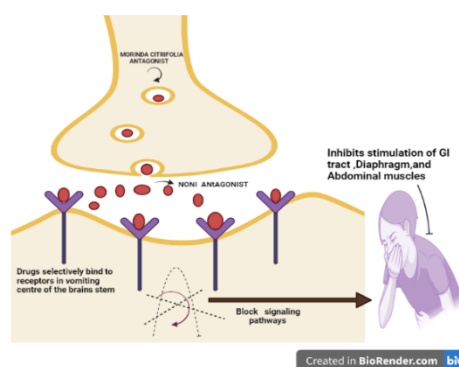


Fig4. Mechanism of action of antiemetic drugs

Neuroprotective activity

In vivo studies

In previous study the researchers demonstrated that neuroprotective activity of *M. citrifolia* leaf extract in ovariectomized rats, an animal model of menopausal condition. The recent findings demonstrated that *M. citrifolia* leaves extract resulted in an increase in neurocognitive score and extent of infraction in the cerebral cortex of OVX rats with MCAO. *M. citrifolia* at a dose of 2 and 50mg/kg BW improves oxidative stress. OVX rats were subjected to ischemic reperfusion damage through temporary closure of the middle cerebral artery exhibited an increase in MDA levels, as an indicator of oxidative stress status in the cortex region. All the above changes were observed by *M. citrifolia* at a dose of 50mg/kg BW. The neuroprotective effect of *M. citrifolia* leaf extract was determined by administering it to bilateral ovariectomized (OVX) rats at dosages of 2, 10, and 50 mg/kg BW for 7 days. In the cortex of OVX rats, *M. citrifolia* enhanced neurological score, brain infraction, and brain oxidative stress state as well as the MCAO. There were no alterations in the ERK1/2 signal pathway or NOS expression in this region. Previous findings reported that the extracts neuroprotective may be mediated in part by an improvement in oxidative stress in the brain. According to the dose ranges of *M. citrifolia* employed in the previous studies the decrease in the cerebral infraction in the cortex region was observed OVX rats

subjected to MCAO. Ischemia-reperfusion damage to the right middle cerebral artery in OVX rats increased peroxy radicals, and all dosages of *M. citrifolia* utilised in this study reduced this alteration. High doses of *M. citrifolia* extract reduced brain infarction level, and decreased MDA levels in the cortex. In OVX rats, *M. citrifolia* decreased brain damage and dysfunctions caused by reperfusion injury. According to previous studies the possible mechanisms might occur by development of oxidative stress⁷.

In vivo studies

The previous work was done on focal ischemic mice model, which demonstrates cerebroprotective effect of noni juice on ischemic neuronal injury. Infarction caused by localized ischemia was detected not only in the cortex and striatum, which are engaged in MCAO territory, but also in the hippocampal area, which is not involved in MCAO territory. Following anoxic depolarization or breakdown of ion homeostasis-induced cell death in the core area, is due to development of infarction in the hippocampus might be attributed to secondary deleterious occurrences such as spreading depolarization or increasing post-ischemic inflammation. ONJ in a dose dependent manner inhibited the development of infarction. The raise of NDS after MCAO substantially reduced by daily intake of ONJ 3% or 10% in drinking water for 7 days prior to MCAO²¹. Significantly ONJ totally inhibited the development of ischemic infarction in all brain regions including penumbra region and ischemic core. It is probable that ONJ provides susceptibility to ischemic stress in general, such as the formation of free radicals, the depletion of ATP or the increase of intercellular calcium concentration. In the previous studies the components of noni juice that have an antioxidant action has been determined. Pre intake of ONJ may have an antioxidant impact and therefore able to reduce isochemic neuronal damage. Recent studies demonstrated that when ONJ administered in drinking water prior to ischemic stress ONJ greatly reduces the development of ischemic neuronal damage in a dose dependent manner²¹.

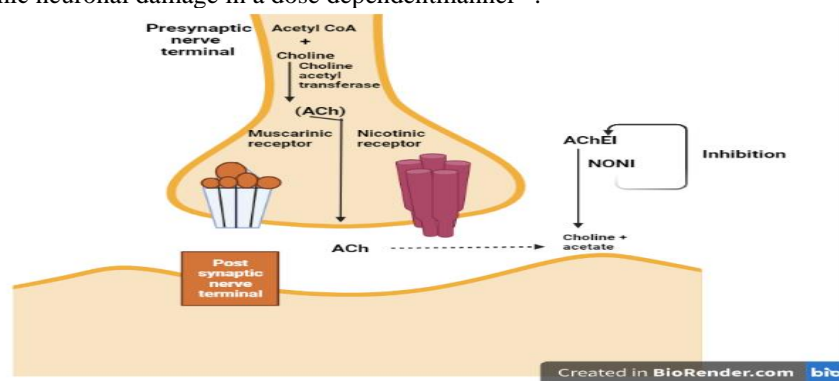


Fig5. Mechanism of action of neuroprotective agents

Neuroprotective activity

In vivo studies

Oral administration of MOOs to depressed rodent rats has been shown to enhance monoamine and brain derived neurotrophic factor (BDNF) levels, indicating that depression can be alleviated. According to previous studies MOOs have the potential to improve depressive – like behavior. Earlier researcher demonstrated that oral administration of MOOs can enhance monoamine and BDNF levels in a mouse depression model, indicating that it can help with depression. MOOs were shown to alleviate depressive like behaviors in PSD rats, which give evidence for therapeutic treatment of PSD patients. In rats, the blood brain barrier is disrupted with high permeability following cerebral ischemic injury, even up to one month after stroke. As a result, MOOs administered orally can finally reach the brain and conduct functions. Hippocampal inflammation has been widely investigated in depression. Reducing of hippocampal inflammation relieves LPS induced depressive behaviors in mice. Earlier research demonstrates that MOOs antidepressant activity and pharmacological mechanism were identified NLRP3, inflammation was proposed as a potential therapeutic target for PSD. MOOs reduce depressive like behavior in PSD rats via the IB/NF –Bp65/NLRP3 inflammation signaling pathway, which may also give insights for PSD therapy⁸.



Fig6. Mechanism of action of neuroprotective agents

Conclusion

The findings of this review given an *in vivo*, *in vitro* and *in silico* justification for noni fruit traditional usage as a natural cure for antidepressant, anti-anxiety, antiepileptic, antipsychotic, anti-craving, anti-emetic, nootropic and neuroprotective activity as well as a better sense of well-being based on a bunch of literature studies. The previous studies indicate that noni fruit is a natural MAO-A and MAO-B inhibitor with several active components interacting collectively to provide a synergistic effect. Noni acts on many neurotransmitters such as MAO-A and MAO-B, serotonergic, adrenergic, dopaminergic, acetylcholine esterases etc. Therefore noni could be used in clinical trials for its therapeutic potential to prevent and treat CNS disorders.

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Conflicts of interest

The authors declare no conflicts of interest.

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Author's contribution

V.P conceived, designed and co-drafted the manuscript. A.B collected literature and drafted the manuscript. Both authors reviewed and approved the final version of the manuscript.

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