



A systematic review on neuropharmacological activities of *Morinda citrifolia* Linn fruit

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Abstract

The scientific name of noni fruit is *Morinda citrifolia* which belongs to the family *Rubiaceae*. There are many pharmacological activities which are reported on *Morinda citrifolia* Linn fruit among these this review mainly focused on neuropharmacological actions of *Morinda citrifolia* Linn fruit. Anti-depression, Anti-anxiety, are the neuropharmacological activities reported on *Morinda citrifolia* Linn fruit by using *in vivo*, *invitro* models. Scopoletin, rutin, Eugenol, Hydroxy-chavicol, Quercetin, phenylpropanoid, are derivatives some of the Active principal compounds in which produce neuropharmacological actions and their quantification techniques mentioned in this review.

Keywords: *Morinda citrifolia* Linn fruit, anti-depression, anti-anxiety

Introduction

Herbal and natural products of medicine have been used for centuries in every culture throughout the universe. Scientists and medical professionals have shown increased interest in this field as they recognize the true health benefits of these remedies. India is a rich diversity of medicinal plants and since ancient times these plants have been utilized as therapeutic agents or a source of modern medicine. Today's research is mainly attentive on medicinal plants because the bioactive compounds from various parts of plants such as leaves, flowers, fruits, barks and roots are prototype drugs for novel drug discovery. *Morinda citrifolia* Linn. is a commonly used medicinal plant belonging to the family of Rubiaceae with a diverse therapeutic property. *Morinda citrifolia* fruit has a long history and variety of use as a food in tropical regions throughout the universe. Written documentation of the utilization of this fruit as a food source precedes the twentieth century. (Wang *et al.*, 2002) [13]

Morinda citrifolia is also known noni, Indianmulberry, hog apple and cheese fruit by different cultures. In fact, the fruits of this plant have benefited the Polynesians over 2000 years as an alternative medicine for antibacterial, antimalarial, antiviral and anticancer, immune enhancing properties. (Pandey *et al.*, 2014) [8]. The Noni plant, a small evergreen tree is found growing in open coastal regions at sea level and in forest areas grown up to about 1300 feet above sea level. The plant is often found growing along with lava flows. It has a straight trunk, large, bright green and elliptical leaves, white tubular flowers, and its distinctive, ovoid, "grenade-like" yellow fruit. The fruit can grow in size up to 12 cm or more and has a lumpy surface covered by polygonal-shaped sections as shown in Figure 1. The seeds, which are triangular shaped and reddish brown, have an air sac attached at one end, which makes the seeds buoyant. This would explain, in part, a wide distribution of the plant throughout the Polynesian islands. The mature

Noni fruit has a foul taste and odor and make it as unpalatable fruit.

The Polynesians used the whole Noni plant in various combinations as herbal remedies to treat many diseases. The fruit juice is in high demand in alternative medicine for treating different kinds of illnesses such as arthritis, diabetes, high blood pressure, muscle aches and pains, menstrual difficulties, headaches, heart disease, AIDS, cancers, gastric ulcers, sprains, mental depression, senility, poor digestion, atherosclerosis, blood vessel problem and importantly, neurological diseases. Till date, many reviews on phytochemical and pharmacological properties of Noni has been reported. (Pandey *et al.*, 2014) [8]. However, a detailed review on its neuropharmacological properties hitherto has not been reported in the literature. Therefore, the present systematic review is focused on compiling information about the neuropharmacological properties of Noni fruit and propose the possible therapeutic indications to treat various neurological diseases/conditions such as depression, anxiety, psychosis, Parkinson's disease, Alzheimer's disease, pain, emesis and substance abuse like opioid, methamphetamine and alcohol dependence.

Phytochemical profile of *Morinda citrifolia* fruit

The medicinal power of any medicinal plants is mainly depending on the presence of phytochemical constituents that impart a great pharmacological significance. The phytochemicals are classified into two major groups namely primary constituents like amino acids, sugars, proteins and chlorophyll etc., and secondary constituents which include alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins and phenolic compounds etc. During last few decades, many bioactive compounds were identified and structurally elucidated from many plant species. The phytochemical profiling of *Morinda citrifolia* Linn fruit has been well established and reported. (Thomaz *et al.*, 2018) [11]

Table 1

Plant parts are used	Name of the compound present
Root	Phenols, coumarins, cardiac glycosides and steroids.
Fruit	Alkaloids, phenols, tannins, coumarins, cardiac glycosides and steroids.
Leaves	Alkaloids, saponins, phenols, tannins and coumarins.

The major phytochemicals such as scopoletin, octoanoic acid, potassium, vitamin C, terpenoids, alkaloids, anthraquinones (such as nordamnacanthal, morindone, rubiadin, and rubiadin-1-methyl ether, anthraquinone glycoside), β -sitosterol, carotene, vitamin A, flavone glycosides, linoleic acid, Alizarin, amino acids, acubin, L-asperuloside, caproic acid, caprylic acid, ursolic acid, rutin, and a putative proxeronine have been identified in the Noni plant. (Meng *et al.*, 2017) ^[6]

Neuropharmacological studies on *Morinda citrifolia* L. fruit

Antidepressant activity

Depression is a significant psychiatric illness manifested by a lack of interest in sports, anxiety, anorexia and constant sadness. A constant depressive mood, a sense of worthlessness, disability, cognitive, sleeplessness, exhaustion and even suicidal tendencies clinically describe depression. Numerous evidence has been shown that cell proliferation dysregulation, neuroplasticity modification, and abnormal inflammatory cytokine secretion are the signs of depression in pathophysiology. (Narasingham *et al.*, 2017) ^[7]

Based on many hypotheses, such as the monoamine hypothesis, depression has been clarified. This assumption notes that decreased levels of serotonin (5-HT) and norepinephrine (NE) remain responsible for depression in the brain; nevertheless, depression pathophysiology relies on multiple hormonal, biochemical and neuronal processes. This research examined the effect of *Morinda citrifolia* Linn methanolic extract (MMC) and its bioactive principles, rutin and scopoletin. In MMC, the bioactive compounds, scopoletin, and rutin were quantified as 18.95 and 1.66 μ g/mg, respectively. (Narasingham *et al.*, 2017) ^[7]

For the treatment of depression, classical antidepressants such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) or selective noradrenaline reuptake inhibitors (SNRIs) and inhibitors of monoamine oxidase (MAOIs) are quite efficient. *Morinda citrifolia* L. has been used by Polynesians. Customary fruit in the treatment of depressive disorders. The purpose of the current study is to improve established awareness of the antidepressant-like behaviors of *M. Citrifolia* fruit with elevated plus maze (EPM), light/dark test (LDT) and tail suspension test using other preclinical mouse models of anxiety and depression (TST). Importantly, the present research makes an early attempt to explore the potential mechanism of action of *M. Fruit* with *citrifolia* Using animal behavioural models with the antidepressant-like behavior. (Martins & Brijesh, 2018) ^[5]

Ex Vivo Studies

Quantification of Scopoletin and Rutin in MMC by LCMS/MS Analysis

Chromatography Conditions and Instrumentation. MMC prepared as above was subjected to 1100 HPLC instrument (Agilent Technologies, California, USA) equipped with auto sampler and collector. HPLC-purified MMC was further

subjected to LCMS analysis. Drugs and Chemicals. Dopamine hydrochloride, L-noradrenaline, prazosin hydrochloride, haloperidol, rutin hydrate, dimethyl sulfoxide (Sigma-Aldrich), and scopoletin (Friendemann Schmidt Chemicals) were used. Thus, the present results have demonstrated the biphasic effect of MMC on dopaminergic system with dopaminergic antagonistic effect at lower concentrations (<40mg/mL) and dopaminergic agonistic effect at higher concentration (>60mg/mL) it can be postulated that the anti-dopaminergic effects of MMC might be mediated by its active principles of scopoletin and rutin. (Cheng *et al.*, 2017) ^[1]

Anxiolytic activity

Conventional anxiolytics pose a risk of multiple adverse effects, responsibility for violence, and potential for dependency. As a World Health Organization (WHO) estimate shows that about 70-80 percent of the population has used some form of alternative or complementary medicine, including ayurvedic, homeopathic, naturopathic, conventional oriental, and traditional oriental medicine, there is a growing trend towards using herbal remedies globally and native American Indian medicine. (Narasingham *et al.*, 2017) ^[7]

Numerous herbal agents have been enlisted to have anxiolytic effects and *Morinda citrifolia* is one of them. Any big adverse effects are also absent. In the berries, various alkaloids, polysaccharides, scopoletin, have been identified. Noni's comprehensive conventional therapeutic uses harness its *in vivo* sedative, antidepressant, and anxiolytic impact (Younas *et al.*, 1990; Kalandakanond *et al.*, 2004) ^[14]. In a clinical pilot study of TAHITIAN NONI Juice, changes in mental health scores have also been reported in (Langford *et al.*, 2004). In this survey, Gamma-aminobutyric acid (GABA) is the key inhibitory neurotransmitter in the central nervous system and is an *in vitro* biological mechanism for these results (CNS). It works by binding both pre- and post-synaptic neurons to particular receptors in the plasma membrane. The GABA receptor is one of the most promising targets for a wide range of CNS-related diseases including anxiety, GABA has been identified as an important neurohormonal system mediating various anxiety disorders from clinical experience and well evaluated experiments. (Deng *et al.*, 2007) ^[2] Additionally, norepinephrine and serotonin neurotransmitters have. In these cases, it was seen to be changed. Therefore, for the treatment of anxiety disorders, medications that either stimulate the GABAergic or serotonergic system or that attenuate adrenergic activity are currently used. A recent research in rats showed a major decrease in amygdala and hippocampus norepinephrine.

Antipsychotic activity

Psychosis has become a significant public health problem and is a persistent recurrent neuropsychiatric condition that alters the quality of life of the sufferers. Poor efficacy and tolerability limit existing drug therapies. As psychological conditions are growing, physicians are searching for natural

therapies and herbal medicines to treat neurobehavioral disorders.(Deng *et al.*, 2007) ^[2]. in tropical regions from Indonesia to the Hawaiian Islands, Noni fruit is widely consumed. The present research was aimed at testing the antipsychotic effect of noni fruits (*Morinda citrifolia* Linn.) using mouse models of climbing activity induced by apomorphine and stereotypy induced by methamphetamine (licking, biting, gnawing and sniffing). The antidopaminergic effect of *Morinda citrifolia* Linn has been shown in the current study findings.in mice, this means that noni has antipsychotic-like activity that can be used to treat mental conditions.

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Haloperidol (Manace InjectionW, Duo pharma (M) SDN BHD, Malaysia) and methamphetamine hydrochloride (MOSTI, Malaysia) is used for apomorphine hydrochloride and sodium metabisulphite (Sigma-Aldrich, USA). The behavioral responses observed in animals after administration of apomorphine, a dopamine agonist, are due to activation of the receptors D1 and D2. In mediating locomotor function and stereotyped behaviour, mesolimbic and nigrostriatal dopaminergic pathways play key roles Animal models used for the screening of antipsychotic drugs are focused on the neurochemical schizophrenia theory, which primarily involves dopamine and glutamate neurotransmitters. Dopamine D2 receptor antagonism may be a popular feature of the most clinically successful antipsychotic drugs. Those who are particularly active against hallucinations and delusions. (Marshall and Lockwood, 2003) ^[4] The models based on dopamine normally use apomorphine, a direct agonist, or amphetamine, a drug that enhances the release of this neurotransmitter and blocks its reuptake. Dose-dependent Noni juice at various doses (5, 10 and 100 ml/kg, i.p) equal to dried juice powder doses (450, 900 and 1800 mg/kg, i.p) greatly decreased amphetamine-induced myths (3 mg/kg, s.c) Swiss mice. The extract was given orally with apomorphine and methamphetamine for 21 days, implying that the noni extract has antipsychotic activity. The same extract also prevents the compensatory effect of heroin (Narasingham *et al.*, 2016) ^[8]

Treatment of Parkinson's disease

Parkinson's disease is a progressive neurodegenerative movement disorder that leads to irregular movements and loss of activity, which in turn causes muscle damage. Parkinson's pharmaceutical drugs either improve or replicate dopamine levels This research therefore assesses the influence of SNpc lesions caused by rotenone on skeletal muscle apoptosis and the effectiveness of *Morinda citrifolia* ethyl acetate extract in safeguarding myocytes In the current research, biochemical assays along with apoptotic markers studied by immunoblot and reverse transcription-polymerase chain reaction showed that *Morinda citrifolia* supplementation significantly reversed changes in both biochemical and histological in rotenoneinfused PD rats. High-performance liquid chromatography quantitated scopoletin, quercetin, and rutin in MCE were quantitated by high performance liquid chromatography using a C-18 column. Skeletal muscle marker (serum/tissue) enzymes Skeletal muscle marker (serum/tissue) enzymes such as

creatine kinase (CK), lactate dehydrogenase (LDH) and aspartate transaminase (AST) have been analyzed in serum using Spinreact commercial kits in a semi-auto analyzer (Rx Monza, Randox, UK). As mentioned previously, the skeletal muscle enzyme assays were performed using standard protocols.(Torres *et al.*, 2017) ^[12]

Analgesic activity

Analgesic operation Joseph Betz claimed that Noni fruits have analgesic and relaxing activities the analgesic and sedative effects of *Morinda citrifolia* extracts have been tested by a French research team led by Younos. The extract did "show a significant, dose-related, central analgesic activity in the treated mice they reported that "these results validate this plant's traditional analgesic properties." The Noni extract's analgesic potency is 75% as high as morphine, but non-addictive and side effect free.

Hypotensive operation Vietnam's Dang Van Ho showed that a complete extract of the Noni roots has a hypotensive effect Moorthy and colleagues found that in an anesthetized dog Young ken's research team determined that a hot water extract of Noni roots reduced the blood pressure of an anesthetized dog by using an ethanol extract of the Noni roots. The diuretic effect of Noni fruit juice was confirmed by a Hawaiian doctor to be *Morinda citrifolia* is an inducer of sedatives. Since the sedative impact of M is known to be that opioids reduce behavioral parameters. Its key analgesic effect could be inked with citrifolia (Younos *et al.*, 1990) ^[14]

Antiemetic activity

Morinda citrifolia fruit extract has been reported to have delayed apomorphine (a potent agonist dopamine D2 receptor) in mice and apomorphine-induced emesis in dogs, respectively, due to antiemetic and prokinetic activity in intestinal transit. The antidopaminergic effect of the noni fruit extract is assigned to these acts.

Linn's *Morinda citrifolia*. Prophylactic noni extract at 600 mg (equivalent to 20g of dried noni fruit or scopoletin 8,712 microg) has an antiemetic property and effectively decreases the occurrence of early postoperative nausea (0-6 hours). The efficacy of noni in the prevention of nausea and vomiting has been shown in patients at high risk of developing these symptoms.) After various surgery styles. Noni extract had prophylactic antiemetic activity at a concentration of 600 mg, decreasing the occurrence of nausea in the immediate postoperative period (Prapaitrakool and Itharat, 2010).

Treatment of Substance abuse

Alcohol dependence

Alcoholism or dependency on alcohol is characterized as "a primary, ongoing, recurrent brain disease with prolonged periods of frequent, heavy use and even after long abstinence periods of severe relapse" (Weiss, 2005). It occurs in a series consisting of: acute alcohol reinforcement effects, transition from sporadic use of alcohol to compulsive use of alcohol, and end-stage alcohol abuse (Cami and Farre, 2003). Psychotherapy (e.g., counseling) and pharmacotherapy are the standard treatment methods for chronic alcoholism embraced worldwide (i.e., using detoxifying drugs such as disulfiram, naltrexone, and acamprosate; Miller and Gold, 1998). Due to its various phytoconstituents, such as scopoletin, rutin, quercetin, and kaempferol, Noni fruit has been believed to have

multifaceted therapeutic benefits (Chan-Blanco *et al.*, 2006). The major phytoconstituents of MMC have been described and quantified as scopoletin (18.95 µg/mg) and rutin (1.66 µg/mg) (Pandy *et al.*, 2014) ^[8] in our recent study.

Morinda citrifolia fruit with fruit extract substantially reversed the memory damage caused by scopolamine in mice. Similarly, the noni fruit ethyl acetate extract prevented beta-amyloid-induced cognitive dysfunction in mice in another study (Muralidharan *et al.*, 2010). It is also doubtful that the latest attenuation of ethanol-induced CPPs by the MMC is due to a drug-induced CPP. Impairment in memory process

The current study shows that MMC prevented the expression of and promoted the extinction of CPP caused by ethanol in mice. These findings indicate that MMC could function to attenuate ethanol's rewarding effects and could therefore be used to treat alcohol dependency. (Khan and Pandy, 2016) ^[3] The discovery of an efficient pharmacotherapy that tackles all aspects of alcohol dependency.

Heroin dependence

The most abused opioid medication is considered to be heroin, and studies have shown a steady rise in the number of users over the years to this product.

Opioid misuse and dependency are persistent and lasting phenomena that have been experienced worldwide. Many plants that have been used as conventional medicines have recently turned out to be significant sources of new drugs in health care systems. Several animal studies have established the basic effectiveness of plant-based medicinal products in the treatment of morphine, alcohol, nicotine and cocaine, as well as *Morinda citrifolia* L. (family: Rubiaceae) has been used for centuries by humans as food and medicine. It is commonly referred to as noni, a small tropical evergreen tree that grows widely in many tropical regions of the region.

From this viewpoint, the main aim of the present study was to establish the impact of a standardized *Morinda citrifolia* Linn methanolic extract. Fruit (MMC) on a heroin conditioned position preference (CPP) rat experiment, a model that examines the reinforcing impact of narcotics with responsibility for dependency. Furthermore, an attempt was made to investigate the potential impact of MMC on naloxone. precipitated withdrawal jumping behavior in mice. (Publication, 2015) ^[10]

Methamphetamine dependence

Methamphetamine (Meth), a psychostimulant with high abuse potential similar to heroin and nicotine, is currently a major global health concern. In several nations, including Malaysia, meth is commonly abused, resulting in serious medical, psychiatric, and legal consequences. Meth addiction has severe and grave consequences for a person. Meth initially boosts alertness, physical activity, and respiration while also lowering fatigue and body weight. Long-term violence, on the other hand, may result in psychosis, aggressive behaviour, mood disturbances, memory loss, and brain dysfunctions. Meth abuse causes dopaminergic and serotonergic neurons in the central nervous system to die. Chemical and molecular modifications in the brain are linked to changes in the function of the dopaminergic system, which are linked to decreased motor abilities, impaired learning, and an

increased risk of Parkinson's disease. Methamphetamine hydrochloride (Sigma-Aldrich, St. Louis, MO, USA) MMC and bupropion (LKT Laboratories, St. Paul, MN) are used. (Pandy *et al.*, 2018) ^[9].

In order to induce an effective conditioned place preference (CPP) in mice, the present study was to determine the optimal dose of methamphetamine (Meth). The next goal was to investigate the effect of a M methanolic extract. Against Meth-induced CPP in mice, *citrifolia* unripe fruit (MMC). In responding to the first goal.

Conclusion and future perspectives

Review sites of *Morinda citrifolia* Linn fruit based on neuro pharmacological profile and neurological disorders were deficient, so there is scope for more research into the neuropharmacological profile of *Morinda citrifolia* Linn fruit and related disorders. There is also opportunity for more research into anti-anxiety and anti-depression models on *Morinda citrifolia* Linn fruit.

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