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A comprehensive review on the therapeutic potential of *Piper betel* leaf for the treatment of neurological diseases

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Abstract
The scientific name of betel leaf is *Piper betel* which belongs to the family *Piperaceae.* There are many pharmacological activities which are reported on *Piper betel* leaf among these this review mainly focused on neuropharmacological actions of *Piper betel* leaf. Anti-depression, Anti-anxiety, learning Memory, Anti Alzheimer's are the neuropharmacological activities reported on *Piper betel* leaf by using *in vivo*, invitro models. Eugenol, Hydroxy-chavicol, Quercetin, phenylpropanoid, Apigenin, luteolin derivatives are some of the Active principal compounds in Piper betel leaf which produce neuropharmacological actions and their quantification techniques mentioned in this review.

Keywords: *Piper betel* leaf, anti-depression, anti-anxiety, alzheimer's

Introduction

Betel vine is scientifically called *Piper betel* L. which belongs to the *Piperaceae* family. The plant is most common in India, despite its alienation, then in any other country in the world since ancient times. This is proof of the numerous quotations, particularly in the Indian scriptures, mentioned in ancient literature. In the traditional Indian method of medicine, *piper betel* is said to be useful to improve learning and memory. Vernacular Names of *piper betel* is:

A. **Sanskrit:** Tamboolavalli, Tamboola, Tamboola vallika.
B. **English:** Betel leaf plant.
C. **Hindi:** Pan.
D. **Malayalam:** Vett, Vettila.
E. **Bengali:** Pan.
F. **Telugu:** Tamalapaakku.
G. **Tamil:** Vettrilai/ Vettilai.
H. **Kannada:** Veeleyadelae/ Eleballi[1]

Fig 1

Plant Profile

Scientific classification
Synonyms: Chavica Beta, Artanthe Hixagona
kingdom: Plantae
Order: Piperales
Family: *Piperaceae*
Genus: *Piper*
Species: *P. betle*
Taste: Pungent tasting and warming.
Division: Magnoliophyte [2]

India, Sri lanka, Malaysia, Indonesia, the Philippine Islands and East Africa, *Piper betle* is cultivated and has historically been used in India as' breath fresheners.' The betel plant is a small, fragrant creeper that roots at the nodes. At the nodes, the branches of this plant are swollen and the plant has alternate, heart-shaped, smooth, glossy and long stalked, pointed apex leaves.

From the review of literature, it appears that the neuro psychopharmacological effect of *Piper betle* has been less investigated. So, it was found of interest to evaluate these activities of betel leaves extract in experimental models.[3]

Pharmacological Actions of *Piper Betel* Leaf

1. **Antimicrobial Activity:** The aqueous and methanol extracts from the leaves of Terminalia catappa L., Manilkara zapota L. were studied (Nair and Chanda *et al* 2008). Against 10 Gram positive, 12 Gram negative bacteria and one of the fungal strains, Candida tropicalis, *Piper betel* L. has antibacterial activity. These three plants display varying degrees of activity against the investigated micro-organisms. between aqueous and methanolic extracts, methanolic extract was significantly more effective in inhibiting microbial strains than aqueous extract. *Piper betel* leaf is the most active antimicrobial herb. [4]
2. **Antihistaminic activity:** (Hajare *et al*., 2011), that the *Piper betel* Linn has been evaluated. Leaves have an antihistamine influence. The essential oil extract of P. betel Linn leaves. Has antihistamine activity in the preparation of the isolated guinea pig tracheal chain, and histamine's dose response curve (DRC) moved to the right side. The standard drug used was chlor-pheniramine maleate. The ethanolic extract and essential oil of *P. betel* Linn possess antihistaminic activity [4, 5].

3. **Anti-inflammatory effects:** The *Piper betel* leaf has been used in the oral cavity as a popular household remedy for inflammation. (Dohi *et al*., 1989), proved that in the complete adjuvant-induced arthritis model of Freund in rats, the ethanolic extract of betel leaf has anti-inflammatory activities at non-toxic concentrations. Eugenol was one of the key components of betel leaf, which also displays anti-inflammatory effects in different studies of animal models with different inflammogens [4].

4. **Antioxidant effects:** It was reported (Azuine *et al*., 1991) and (Bhide *et al*., 1991) that the eugenol, hydroxychavicol and alpha-tocopherol of the betel leaf constituent increase GSH levels in the skin and liver of the mouse. All these findings clearly suggested that the extracts of betel leaves increase cellular antioxidants and at least partially facilitate the preventive effects of chemo [4, 6].
5. **Antimutagenic effects:** Several studies have shown that the betel leaf in the prokaryotic and eukaryotic system is devoid of mutagenic activities and that the betel leaf also has antimutagenic (Shirname *et al*., 1983) and anticlastogenic effects (Bhattacharya *et al*., 2005). *In vitro* cultured cell studies have shown that the betel leaves have not induced any morphological transformation of hamster embryo cells or induced sister chromatid exchanges in human lymphocytes stimulated by both virally transformed cells and PHA. In addition, it is also stated that the ethanolic extract of betel leaf has γ-ray mediated clastogenesis in plasmids [4, 6].
6. **Anti-haemolytic activity:** Anti-haemolytic activity was studied by Chakraborty *et al*., by using erythrocyte model piper betel leaf extracts (2011). Since they are rich in polyunsaturated fatty acids, the erythrocyte membranes are responsible for peroxidation. They contain haemoglobin that can catalyse oxidation and are constantly exposed to high oxygen concentrations. Erythrocyte oxidation is a good model for oxidative damage to biological membranes It has also been found that certain chemicals are capable of producing radicals that strike the erythrocyte membrane, which induces lipid and protein chain oxidation and ultimately causes haemolysis to destroy the membrane. Reducing haemolysis has been established when red blood cells are treated with betel leaf extract along with H2O2 [4].
7. **Antiulcer Activity:** Vyawahare *et al*., (2010), by using HCl-ethanol, acute stress and pylorus ligation models to cause gastric ulcers, found the antiulcer activity of hydroalcoholic extract of *Piper betel* (HEPB) leaves in rats. In all experimental models, pre-treated with *Piper betel* extract produced a mild ulcer protective effect along with a moderate increase in gastric pH and a reduction in gastric fluid volume. *Piper betel* leaves' hydroalcoholic extract has antiulcer activity that can be correlated with its assumed mechanism of action [4, 7].
8. **Antibacterial activity:** The four varieties of *Piper betel*, which are grown in India, are Desawari, Desi, Bangladeshi, and Jaleswar. (Agarwal *et al*., 2012) assessed that the cold aqueous, methanolic, ethanolic and ethyl acetate extracts of dried leaves of all four *Piper betel* varieties were screened against pathogenic microorganisms such as Pseudomonas aeruginosa, Staphylococcus aureus and Escherichia coli using the method of agar well diffusion at a final concentration of 500 mg/ml [4, 6].
9. **Antifungal activity:** Hydroxychavicol, extracted from the chloroform extraction of *Piper betel* L. aqueous leaf extract (Piperaceae), was investigated for its antifungal activity against 124 strains of selected fungi (Ali *et al*., 2010). Hydroxychavicol exhibits a clinically important inhibitory effect on fungal species, with MICs ranging from 15.62 to 500 μg/ml for yeasts, from 125 to 500 μg/ml for Aspergillus species, and from 7.81 to 62.5 μg/ml for dermatophytes, while MFCs are found to be equivalent to or double the MICs. There was a concentration-dependent killing of *Candida albicans* and *Candida glabrata* up to 8 × MIC. Hydroxychavicol also exhibits the extended post antifungal effect of 6.25 to 8.70 h at 4 × MIC for Candida species and diminished the emergence of mutants of the fungal species tested at 2 × to 8 × MIC concentration. It was concluded that the antifungal activity demonstrated by this compound can be used experimentally as an antifungal agent to treat topical infections as well as gargle mouthwash against oral infections with Candida [4, 6].
10. **Anti-diabetic activity:** The antidiabetic activity of *Piper betel* leaves tested in normoglycemic and streptozotocin (STZ)-induced diabetic rats with oral administration of hot water extract (HWE) and cold ethanol extract (CEE) was investigated (Arambewela *et al*., 2005). (CEE). Both HWE and CEE moderately reduced the blood glucose level in a dose-dependent manner in normoglycemic rats. Both extracts markedly reduced the external glucose load in the glucose tolerance test. HWE's antidiabetic activity is close to that of CEE. After chronic oral administration, both extracts were found to be non-toxic and also well tolerated (no overt signs of toxicity, hepatotoxicity or Reno toxicity). However, in treated populations, the weight of the spleen has increased, likely suggesting lympho-proliferative activity [4, 5].
11. **Palpebral skin antiseptic:** Antiseptic efficacy was assessed by counting the microbial colonies before and after antiseptic solutions were administered (Amalia *et al*., 2009). This study showed that after application of 20 percent of *Piper betel* leaf infusion, the mean colony counts showed a modest decrease of 27-100 percent relative to those before administration (p=0.001). After 10 percent povidone-iodine administration, mean colony counts showed a modest decrease of 88-100 percent relative to the mean solution counts applied before (p=0.000). A possible antiseptic activity is the 20 percent *Piper betel* infusion [4].
12. **As contraceptive:** The mitochondrial function of sperm was examined (Singh *et al*., (2011), after treating semen with distinct concentrations of *Piper betel*. Mitochondrial activity was also studied for various incubation time periods after the semen samples were treated. More than 75 percent of the motile normozoospermia semen sample was tested and it was found that as the concentration of extracts decreases the mitochondrial activity moderately ($p < 0.001$), similar findings were observed when the concentration of extracts increased constantly with increasing time intervals. Mitochondrial activity

decreases moderately ($p<0.001$) over an incubation period of 5 minutes to 20 minutes. They concluded that the *Piper betel leaf* has properties in human sperm to decrease mitochondrial activity and the ability to serve as a contraceptive [4].

13. **Role of betel leaf extract on thyroid function:** The effects of betel leaf extract (0.10, 0.40, 0.80 and 2.0 g kg−1day−1 for 15 days) on changes in thyroid hormone concentrations, lipid peroxidation (LPO) and superoxide dismutase (SOD) and catalase (CAT) activities were tested in male Swiss mice (Panda and Kar *et al*.1998). Depending on the different doses, betel leaf extract administration showed a dual role. Thyroxine (T4) and serum triiodothyronine (T3) concentrations decreased at the lowest dose, and reverse effects at two higher doses were reported. With a concerted decline in SOD and CAT movements, higher doses have also increased LPO. However, most of those effects were reversed at the lowest dose. This study shows that betel leaves, particularly for T3 generation and lipid peroxidation in male mice, can be both stimulatory and inhibitory to thyroid function, depending on the amount consumed [4, 8].
14. **Anti-malaria activity:** In contrast to known mosquito repellent citronella oil, essential oils of Piper betle show stronger protection from biting of Anopheles Stephens and Culex fatigues mosquitoes. When applied at a rate of 20 µl / cm2, *Piper betle* oil provided more than 4 hours protection against Anopheles stephensi and Culex fatigues, while other side citronella oil provided just 2.2- and 2.6-hours protection, respectively. Mosquito repellent behaviour of the pan has therefore been demonstrated [4, 8].
15. **Anti-filarial activity:** The anti-filarial activity of *Piper betle* has been investigated (Singh *et al*., 2009). The study identified the n-hexane and chloroform fractions of *Piper betle* L. In BALB/c mice, different arms of immune responses are activated and anti-filarial activity against human lymphatic filarid Brugia malayi is exhibited [4, 6].
16. **Wound healing activity:** Nilugal *et al*., 2014, researched the assessment of wound healing efficacy of *Piper betle* leaves and stem extract in experimental wistar rats. Wound healing had a very complex, multiple event factor that involved many cellular and biochemical procedures the findings showed wound healing and repair, encouraged by the application of the ointment formulation of Piper betle leaves and stem extract, which was highlighted by the maximum thickness of the wound region's epidermis coverage. The male albino rats treated with an ointment formulation containing 10 percent *Piper betle* leaves and stem, showed substantial results compared with the diseased population and control group [4, 6].

Along this based on some of the literature review *Piper betel* Leaf has some of the neuropharmacological actions (Krishna U *et al*. Int J Basic Clin Pharmacolgy. 2019 Jan; 8(1):143-146), (Mishra *et al* Mintage journal of Pharmaceutical & Medical Sciences.)

Neuro pharmacological effects of Piper Betel Leaf Are

1. Anti-depressant Activity.
2. Anti-nociceptive Activity.
3. Anti-Anxiety Activity.
4. Learning Memory and Alzheimer's Disorder.

Anti-depressant activity

In animal models of depression, the antidepressant capacity 0f *Piper betle* leaves extract tested in earlier studies showed a notable antidepressant effect in the most widely used behaviour samples. It has antidepressant efficacy and operates by blocking the dopamine, noradrenaline, and serotonin uptake pathways via their respective transporters. However, to analyse its mechanism of action in depth, further studies are required [3, 4, 3, 11, 14, 24, 25].

Anti nociceptive activity

Arambewela *et al*. (2005) reported that the antinociceptive behaviour of *P. betel* leaves using rats and animal models of nociception with hot water extract (HWE) and cold ethanol extract (CEE) are: tail flick, hot plate methods and formalin studies. Different HWE (125, 200, 300, 500mg/kg) and CEE (125, 200, 300, 500mg/kg) concentrations were produced and administered orally to rats, and reaction times were measured. The findings showed that, when tested in the hot plate and formalin tests, but not in the tail-flick test, the extracts exhibit antinociceptive behavior. The antinociceptive effect of CEE was higher than that of HWE [22, 27, 28, 29].

Anti-anxiety activity: The anxiolytic activity of *Piper betel* leaves extracts was evaluated in mice and one of the most commonly validated tests for the determination of sedative and anxiolytic substances will be considered to be this animal model, especially with a mouse. The anxiolytic effect of *Piper betel* leaf was achieved by triggering the role of Gulhane and co-workers in GABA (gamma amino butyric acid) (2015) [3, 13].

Learning memory and alzheimer's disorders:

Piper betel leaf inhibit the antic-cholinesterase enzyme and butyl- cholinesterase enzyme, to treat Alzheimer's disorder and improve the learning memory (Upadhyay *et al*.2019) Piper betel leaf also inhibits the Acetyl cholinesterase enzyme and butyl cholinesterase enzyme to treat memory impairment [23, 26].

Note: There is a lack of review on Neuropharmacological actions of *Piper betel* leaf, so, there is a need for review on pharmacological activities of *Piper betel* leaf.

Data Collection

This review article was done, based on the sources or literature in the form of primary data or official book forms and national and international journals in the last 20 years (2000-2020) as well as in making this review, traditional use, and pharmacology.

The primary references which were used in this review article were searched through official and genuine website such as Science Direct, Research Gate, Google Scholar, NCBI, and PubMed. The period of collection of this literature review is about for November (2020) to January (2021).

Key Words

Piper betel leaf, Antidepression, Antianxiety,

Phytochemicals of *Piper Betle* leaf Extracts

Table 1: phytoconstituents present in piper betel leaf on different extracts of *Piper betel* leaf

S. No.	Phyto Chemical	Results *(Shaik S*almasultana *et al.* 2018) [11] (Mishra *et al.*2020) [3], (Rahul Shivaji Patil *et al.2015)* [12]				
		Aqueous Extract	**Ethanolic Extract**	**Methanolic Extract**	**Butanolic Extract**	**Acetone Extract**
1	Steroids	+++	+	++	+++	+
2	Diterpenes: copper acetate test	++	+	+	+++	+
3	Phlobatannins	-	-	-	-	-
4	Tannins					
	Lead Acetate	+++	+	++	-	++
	Fecl3	-	+	++	+	++
5	Cardiac Glycosides Keller-Killani Test	+	-	-	-	-
6	Flavonoids					
	Alkaline Reagent Test	++	+	-	+	++
	NH4OH	++	+	-	+	-
	MgTurning Test	-	-	-	-	-
	Zn Dust test	+	-	-	-	-
7	Anthocyanin	-	-	-	-	-
8	Phytosterol: Salkowski's Test	-	-	-	-	-
9	Alkaloids					
	Wagner's reagent	++	-	-	++	-
	Hager's reagent	++	-	-	+++	-
10	Phenols: Fecl3 test	+	-	-	-	-
11	Emodin's	-	-	-	+	-
12	Coumarin	+++	+	+	-	+++
13	Leuco anthocyanin	-	-	-	-	-
14	Saponin: Foam test	+++	+	+	-	+

Key: (+) Positive Test, (-) Negative Test, (+) Low, (++) Moderate, (+++) High

Note: Few chemists were isolated important essential oils and other compounds from the leaves of betel, some of them are: chavibetol, chavicol, and hydroxychavicol derivatives are Phytochemicals present in *Piper betle Leaf* which are responsible for Anti-Depressant and Anti-Anxiety Activities. (Sualiha Lutfullha *et al*.2018) [13], *(Krishna U et al.2019)* [14].

Bio Active Constituents of *Piper betel* leaf responsible for Neuro pharmacological Actions

Table 2: Bio active compounds responsible for neuro pharmacological effects of *Piper betel* leaf.

S. No	Name of Bio Active Compound	Neuro Pharmacological Action	Mechanism of Action	Quantification Technique	References
1.	Eugenol	Anti-Depression Effect, Treat Parkinson's Disorder and Treat Alzheimer's Disorder.	Monoamine oxidase inhibitor (MAOI). Acetyl cholinesterase Inhibitor and α-Glucosidase inhibitor.	HPTLC (High Performance Thin Layer Chromatography) technique (A. Syahidah *et al*. 2017)[15], (K.S. Chitnis *et al*.2017) [16] (Lam Thi Truc Nguyen *et al*. 2020) [17]	(Guy P. Kamatou *et al*.2012) [18], (S. Karak *et al*.2018), (Yoshifumi Irie *et al*. 2006) [19]
2.	Chavicol	Anti- Anxiety Effect	Increases levels of norepinephrine, serotonin and dopamine levels.	HPLC (High Performance Liquid Chromatography) Technique. A. Syahidah *et al*. 2017) [15]	*(Krishna U et al.2019)* [14]
3.	Hydroxy Chavicol	Anti-Depression Effect	Efficacy against acetyl- and butyrylcholinesterase enzymes.	HPLC (High Performance Liquid Chromatography) Technique (Nguyen *et al*. 2020) [17]	*(Bahare Salehi et al. 2019* [20]
4.	Apigenin, luteolin derivatives	Anti- Depression Effect	Inhibits Cholinesterase enzyme	HPLC coupled with diode array detector and combined with mass spectroscopy (Federico etal.2012) [10]	*(Andrei. p et al. 2014)* [10]
5.	Quercetin, phenyl-propanoid	Analgesic Effect	Prostaglandin-synthesis inhibition.	HPLC Method (Purba *et al*.2019) [21]	Badrul alam *et al.2013)* [22]
6.	Hydroxyl Chavicol, Caryophyllene, Quercetin	Cognitive Effect	Inhibits both αandβ secretase enzymes and also inhibits acetyl- and butyrylcholinesterase enzymes.	HPLC (High Performance Liquid Chromatography) Technique (Nguyen *et al*. 2020)20 and HPLC Method (Purba *et al*.2019) [21]	(Upadhyay *et al*.2019) [23]

Note: Based on some of the review and research articles of *Piper betel* leaf bio active constituents responsible for Anti -depressant activity, Analgesic activity, treatment for Parkinson's disease, treatment for Alzheimer's disorder, improve cognitive functions were reported, but, bio active compound responsible for Anti-anxiety activity was not reported.

The Therapeutic potential of *Piper betle* leaf for the Treatment of Neurological Diseases

***In vivo* models for Neurological disorders on *piper betel* leaf**

Some of the *in vivo* methods which are screened for Neurological Disorders on *Piper betel* leaf, by using different solvent extracts and different doses of extracts *of Piper betel* leaf. Here *In vivo* models used are:

For Anti-Depressant Activity
1. (TST) Tail Suspension Test.
2. (FST) Forced Suspension Test.

For Anti-Anxiety Activity
1. Elevated Plus Maze.
2. Light /Dark Exploration Test.

For Analgesic Activity
1. Hot Plate Method.
2. Formalin Test.
3. Tail Flick Method.
4. Acetic Acid Induced Writhing Method.
5. Heat Conduction Method.

For Alzheimer's and Memory Learning Activities
1. Passive Avoidance Test.
2. Morris Water Maze.
3. Y- Maze Test.

***In vivo* models on *Piper betel* leaf on neurological disorders**

There are many *in vivo* animal models to screen anti-depressant and anti-anxiety activities, anti-nociception, Alzheimer's disorder, memory learning and amnesia but, based on the literature review only few models were used to screen the neuro pharmacological activities using *Piper betel* leaf extract which are mentioned above in the table.

Table 3: *In vivo* animal models for neurological disorders on *Piper betel* leaf

S.No	Type of Extract Used	Name of the Animal Used and sex	Dose and Route of Administration and no of days Drug given	Active constituents	Method used	Mechanism of Action	Study Observed	Name of the disease to treat	References
1.	Hydro Alcoholic Extract	Swiss albino mice (both sex)	100mg/kg,200mg/kg,400 mg/kg (p.o), for 7 days	Essential and volatile oils	1) Tail Suspension Test (TST) and Forced Swim Test (FST) for Anti-Depression Activity. 2) Light /Dark Exploration Test and Elevated Plus Maze Test for Anti-Anxiety Activity.	1) It has Antidepressant activity by the mechanism of blocking the uptake of dopamine 1, noradrenaline and serotonin with their respective transporters. 2) It enhances the action of inhibitory neurotransmitter activity i.e., GABA (Gamma Amino Butyric Acid)	1) Three doses were found to have significant antidepressant activity. 2) Three doses showed significant anxiolytic activity.	Depression and Anxiety.	(Mishra *et al*.2015) [3]
2.	Methyl Alcoholic Extract	NMR Mice (Both sex)	15mg/kg, 30mg/kg,60mg/kg, (p.o) for 1 day	Phenolic compounds (chavicols)	1) Light /Dark Exploration Test and Elevated Plus Maze Test for Anti-Anxiety Activity.	1) It enhances the action of inhibitory neurotransmitter activity i.e., GABA (Gamma Amino Butyric Acid).	1) This study explained that treatment of these doses, 15mg/kg, 30mg/kg and 60mg/kg showed antianxiety effects.	Anxiety.	(Sualiha Lutfullha *et al*.2018) [13]
3.	Ethanolic Extract	Albino Rats (Male)	10mg/kg, 20mg/kg (i.p) once for 5 days.	Chavibetol, chavicol, hydroxy chavico, eugenol.	1) Forced Swim Test (FST) for Anti-Depression Activity.	1) It has Antidepressant activity by the mechanism of blocking the uptake of dopamine, noradrenaline and serotonin with their respective transporters.	1)They concluded that the combination of both *Piper betel* and clove was having more antidepressant activity when compared to use as an individual dosage form.	Depression.	(Shaik Salmasultana *et al*. 2018) [11]
4.	Aqueous Extract	Swiss Albino Mice (Either	100mg/kg, 200mg/kg, (p.o) for one day.	Cocaine	1) Tail Suspension	1) It increases the levels of	1)Aqueous extract of	Depression.	(Krishna U *et al*.2019) [14]

		sex)			Test (TST) and Forced Swim Test (FST) for Anti-Depression Activity.	monoamines like norepinephrine, serotonin and dopamine levels thus causing antidepressant like activity.	*Piper betle* 100mg/kg body weight has showed significant antidepressant activity		
5.	Ethanolic Extract	Swiss Albino Mice (Either sex)	100mg/kg, 200mg/kg, (p.o) for 10 days.	chavicol, chavibetol,	1) Tail Suspension Test (TST) and Forced Swim Test (FST) for Anti-Depression Activity.	1) Inhibiting the re uptake of nor epinephrine and 5HT and increasing their synaptic levels.	1) Two doses were found to have significant activity.	Depression.	(Vinayak meti *et al*. 2012) [24]
6.	Ethanolic Extract or Methanolic extract.	Wister rats and Swiss albino mice (either sex).	100mg/kg, 200mg/kg,400mg/kg (i.p) for 7 days.	chavibetol acetate and eugenol.	1) Tail Suspension Test (TST), Forced Swim Test (FST) and Open field Test for Anti-Depression Activity.	1) (M.A.O. INHIBITOR), Monoamine oxidase Inhibitor.	1) Three doses were found to have significant activity.	Depression.	(Dakshina Gupta *et al*. 2016) [26]
7.	Hydroethanolic extract	Swiss albino mice (either sex)	100mg/kg, 200mg/kg,400mg/kg (p.o) for 14 days.	Cocaine, chavicol	1) Tail Suspension Test (TST) and Forced Swim Test (FST) for Anti Depression Activity. 2) Light /Dark Exploration Test and Elevated Plus Maze Test for Anti-Anxiety Activity.	1) It increases the levels of monoamines like norepinephrine, serotonin and dopamine levels thus causing antidepressant like activity. 2) It enhances the action of inhibitory neurotransmitter activity i.e., GABA (Gamma Amino Butyric Acid).	1) In this study, the *Piper betle* leaves extract at doses of 100 mg/kg, 200 mg/kg and 400 mg per kg and showed significant activity. 2) On the other hand, when compared with the control, *Piper betle* leaves extract used in the anxiolytic model showed substantial anxiolytic activity.	Depression and Anxiety.	(DR. HITESH GULHANE *et al*. 2015) [3]
8.	Aqueous Extract	Wistar rats (Male)	200mg/kg and 400mg/kg, (p.o)	allyl pyrocatechol, Chavibetol, Eugenol and Hydroxy chavicol.	Y- Maze Test	Acetyl cholinesterase Inhibitor.	Aqueous extract (200 mg and 400 mg/kg body weight) moderately improved memory. Among these doses 400 mg/kg body dose showed a major reversal effect on scopolamine-induced amnesia.	Amnesia.	(Vara Prasad Saka *et al*. 2017) [26]
9.	Aqueous Extract	Wistar rats (Male)	400mg/kg and 500mg/kg (p.o) for 21 days.	hydroxy chavicol, caryophyllene,	1) Passive Avoidance Test. 2) Morris	Increases Acetyl cholinesterase Inhibitor	The research shows that in an animal model of	Alzheimer's.	(Upadhyay *et al*.2019) [23]

				quercetin.	Water Maze.	enzyme activity.	Alzheimer's disease, the learning and memory enhancing activity of *Piper betel* leaves. In the human population, it can be beneficial and can be a promising field for future study.		
10.	Methanolic Extract.	Swiss albino mice and Wister Rats (either sex)	100mg/kg, 200 mg/kg (p.o)	chavibetol and chavic0l, cadinene, and hydroxy chavicol.	1) Hot Plate Method. 2) Acetic Acid Induced Writhing Test. 3) Formalin Test	cyclooxygenase-2 inhibitors	The oral administration of both doses of MPBL significantly ($p<0.05$) inhibited writhing response induced by acetic acid in a dose-dependent manner.	Nociception.	(Badrul Alam *et al.2013)* [22]
11.	Hot water extract (HWE) and Cold ethanol extract (CEE).	Swiss albino Mice (Male)	125mg/kg, 200mg/kg, 300mg/kg,500 mg/kg (p.o)	flavonoids, tannins, and phenols	1) Hot Plate Method. 2) Formalin Test.	cyclooxygenase-2 inhibitors.	The highest antinociceptive activity was evident with 200 mg=kg dose of both HWE and CEE.	Nociception.	*(L.S.R Arambewel et al.*2008) [27]
12.	Hydro Alcoholic	Swiss albino mice and Wister Rats (either sex).	50mg/kg, 100mg/kg, 200mg/kg (p.o)	flavonoids, tannins, phenols and glycosides.	1) Tail Flick Method. 2) Acetic Acid Induced Writhing Method.	Cox inhibitor.	Both 50mg/kg and 100mg/kg show significant Analgesic activity.	Nociception.	(Reddy PS *et al.*2016) [28]
13.	Aqueous Extract	Albino Rats (either sex)	100mg/kg, 200mg/kg (p.o)	NA	1)Hot Plate Method 2)Heat Conduction Me	NA	The aqueous extract of *piper betel* leaf has showing a significant analgesic activity aqueous extract (200 mg and 400 mg/kg body weight) moderately improved memory.	Nociception.	(Kambham Venkateswarlu *et al.*2014) [29]

Note: Based on the literature it was proven that *Piper betel* leaf have ability to treat depression, anxiety, Alzheimer's and amnesia and other neuronal disorders through *in vivo* animal studies which are mentioned above in the table.

In vitro **models for neurological diseases of piper betel leaf**

The *in vitro* studies for depression and anxiety in *Piper betel Leaf* were not reported but some of the *in vitro* studies for other neurological disorders in *Piper betel* leaf which are mentioned below.

Table 4: *In vitro* animal models of neurological disorders on *Piper betel* leaf

S. No.	Name of Extract	*In vitro* model	Study Observed	Name of the Disease	References
1.	Aqueous and Ethanolic Extract	HPLC-DAD/ESI/MSN analysis of phenolic compounds. 2) In-vitro cholinesterase inhibitory activity.	Due to presence of hydroxychavicol *Piper betel* leaf have ability to inhibit the antic-cholinesterase enzyme, Aqueous extract shows better action when compared to Ethanolic extract against choline- esterase enzyme.	Alzheimer's Disease	(F. Ferrers *et al*.2014) [10]
2.	Alcoholic Extract	Luciferase reporter gene assay.	*Piper betel* moderately decreases the relative luminescence activity as compared to the vehicle and control, which indicates that *Piper betel* extract exhibited a strong agonist activity towards Melatonin receptor so, it is used in treatment of stress induced sleep disorders.	Stress induced sleep disorders.	(Yatinesh Kumari *et al*. 2019) [22]
3.	Aqueous Extract	1) Analysis of cholinesterase inhibitory activity by micro plate method. 2) Analysis of cholinesterase activity B.M.k. Dalai *et al*.2013)34y bioautography method.	The results in these studies indicate that the constituents of *P. betel* have capable to inhibit of both AChE and BChE.	Alzheimer's Disease.	M.k. Dalai *et al*.2013) [6]
4.	Aqueous Extract	Cervical Dislocation Method.	*P. betle* exerts protective action on the brain of chronic ethanol-treated rat models.	Neuro Degenerative Disorders.	(Saravanan *et al*.2003) [30]
5.	Methanolic Extract	Anti-Cholinesterase Inhibition Assay.	Due to presence of caryophyllene and asaricin *Piper betel* leaf have ability to inhibit the antic-cholinesterase enzyme, and shows better action against choline- esterase enzyme.	Alzheimer's Disease and Neuro-Degenerative Disorders	(Cai-Peng Xiang *et al*.2017) [31]
6.	Propylene-glycol Extract	*In vitro* Evaluation for Effect of *Piper betle leaf* on Arachidonic Acid Induced Reactive Oxygen Species.	This research shows that there is a promising antinociceptive activity of Piper betle. There is a need for more study to delineate the mechanisms of *in vivo* PBE anti-nociceptive action by Estimating PGE2 Levels COX word, generation of Peroxynitrite and other markers that are pro-inflammatory in the Exudate of the peritoneum.	Analgesic Activity.	(De, *et al*.2013) [32]

Note: Based on literature search there is lack on *in vitro* models of *Piper betel* leaf on depression and anxiety

In silico models on *Piper Betel* leaf on neuro disorders

Based on my literature search In silico evidences of *Piper betel* leaf on Neurological D but there are some of the computers modelling methods done on *Piper betel* leaf (P. Tamil Sankar *et al*. 2015), (Amar Kumar Dey *et al*. 2016) [7], (Kalpana ray guru *et al*. 2009).

Conclusion

The above review concludes that *Piper betel* leaf has ability to treat neurological disorders like Depression, Anxiety, Alzheimer's disorder, Amnesia (improves learning memory), through some of the mechanism of actions like: for depression - Monoamine oxidase inhibition (MAOI). Acetyl cholinesterase Inhibition and α-Glucosidase inhibition mechanisms. For anxiety: Increases levels of norepinephrine, serotonin and dopamine levels. For Alzheimer's: inhibit the antic-cholinesterase enzyme and butyl- cholinesterase enzyme. For nociception: prostaglandin inhibition mechanism by using both in-vivo and in-vitro models. *Piper betel* leaf have some of the important bio active or principal constituents which are Eugenol, Hydroxy- chavicol, Quercetin, phenyl-propanoid, Apigenin, luteolin derivatives which produce pharmacological actions to treat those neurological disorders. *Piper betel* leaf shows significant anti-depressant, anti-anxiety, anti-Alzheimer's, improves memory actions.

Future Preferences

Reviews of *Piper betel* leaf based on neuro pharmacological profile and neurological disorder were insufficient so there is scope to do review on neuropharmacological profile of *piper betel* leaf and related disorders, there is also scope on study of anti-anxiety models on *Piper betel* leaf because there are no clear evidences on anti-anxiety activity of *Piper betel* leaf. Here there is scope to conduct invitro and Insilico studies of *Piper betel* leaf on neuro pharmacological profile and related disorders.

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