REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org
Article Received: 28/08/2024 Revised: 09/11/2024 Accepted: 20/11/2024

The Potential Of *Artocarpus Lacucha Linn* In Alleviating Depressant & Anxiety Disorder Effects: A Review

Reeta Rai[1]*, Dr. Aaditya Singh[2], Dr. Rahul Sharma[3]

[1*,2,3]Aryakul college of pharmacy and research Lucknow

***Corresponding Author:** Reeta Rai
*Aryakul College of Pharmacy and Research Lucknow, India,

Abstract:
Artocarpus lacucha Linn is a traditional herbal medicine used for different diseases and they have a good anti-oxidant nature to help treat neuroinflammation and protect the potential of anti-depressants, anti-anxiety. Commonly known as Monkey Jack or Monkey Fruit, is a tropical fruit-bearing tree found in Southeast Asia. This review article aims to explore the potential mechanisms and evidence supporting the role of *Artocarpus lacucha* in combating antidepressant and antianxiety effects, and increase the GABA, $GABA_{A\&B}$ levels and improving mental health, shedding light on its pharmacological properties, and highlighting avenues for further research. The findings indicate that while mitochondrial protection was difficult to achieve, both of the substances studied *Artocarpus lacucha* Linn —improved cell survival, particularly in relation to ROS and lipid peroxidation. Because of the effectiveness of the redox-sensitive expression of antioxidant enzymes and its pharmacokinetic properties, oral *Artocarpus lacucha* Linn may offer useful protection against acute neurodegenerative diseases.

Keywords: Anti-depressants, Anti-anxiety, GABA, Antioxidant, Neurotransmitter Modulation, Anxiety

Introduction:
Over 700 million individuals worldwide are thought to be affected by mental health illnesses, making them one of the main sources of both health problems and financial losses. (1). Psychotropic medications like antidepressants and anxiolytics are useful and frequently suggested as first-line treatments for a range of mental health conditions. Antidepressant and anxiolytic drug use has increased over the past few decades worldwide, especially in highly industrialized nations. (2). The rising incidence of pertinent mental health conditions, broader prescription indications, and the release of generic substitutes into the market could all be contributing factors to this rise.(3).
From 2008 and 2019, there were significant differences in the use of psychotropic drugs between over 65 areas globally, with high- and middle-income countries having the highest use.(4).
Scandinavian nations used anxiolytics less frequently than other nations in 2020, yet they remain among the top 10 antidepressant users in Europe.(5). Despite having similar cultures, economies, and rates of prevalent mental health conditions like depression, current research indicates that over the last twenty years, there have been disparities in the use of antidepressants & anxiolytics across Scandinavia in terms of both total and age-specific usage.(6).
To place Blonanserin in a definitive relationship with other antipsychotic medications, further thorough research is needed. There was no definitive research on its demonstrated anxiolytic and depressive properties. Some meta-analyses have suggested a potential anxiolytic effect, but we were unable to locate any planned or completed studies with Blonanserin alone as a group.(7).

Figure 1 impact of health in human being

Mechanism of action anti-depressant & antianxiety:
Important modes of action for ketamine, TCA, & SSRI antidepressants. Because MAOIs disrupt the metabolism of nerve endings, they increase the amount of NE and 5-HT stored in vesicles, which raises brain amine levels(8). Stimulating

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org
Article Received: 28/08/2024 Revised: 09/11/2024 Accepted: 20/11/2024

nerve activity produces vesicles that increase neurotransmitter activity and hence increase amine levels. By obstructing the reuptake pathway that causes the brain's synaptic termination of NE and 5-HT, tricyclic antidepressants directly affect neurotransmitter activity at post-synaptic receptors. SSRIs have very specific acute effects on the serotonin transporter (SERT)(9). Through their binding to locations other than serotonin, SSRIs allosterically inhibit the transporter **(Figure 3).** They might not significantly inhibit the NE transporter or obstruct cholinergic and adrenergic receptors. SNRI binds to the NE and SERT transporters (NET), improving the actions of both neurotransmitters. In contrast to TCA, SNRI does not significantly inhibit peripheral receptors including muscarinic, adrenergic, or histamine H1 receptors(10).
Antianxiety drugs are those that reduce anxiety by preserving the body's and the brain's natural state of calm. By acting on the GABA receptor, anxiety-relieving drugs open a chloride channel or increase its penetration through it. The chloride channels are what give a cell its negative charge; over time, the presence of potassium ions causes negativity to balance, maintaining the body's physiological state through ongoing polarization and depolarization.(11). However, the polarization that is produced is much longer than typical polarization, which is why it is also known as hyperpolarization.(12). (**Figure. 2)**. The postsynaptic potential is moved away from the action threshold and is inhibited in the hyperpolarized situation because the depolarization stage is delayed. In Addition to their ability to reduce anxiety, benzodiazepines also exhibit additional properties that are related to their assessment. Additional actions include anterograde amnesia, drowsiness and hypnosis, anticonvulsant action, and muscle relaxant action.(13).

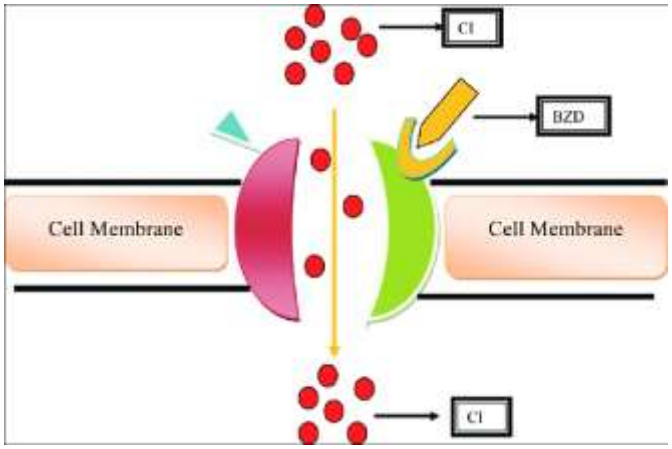

Figure 2 MOA of antianxiety (14)

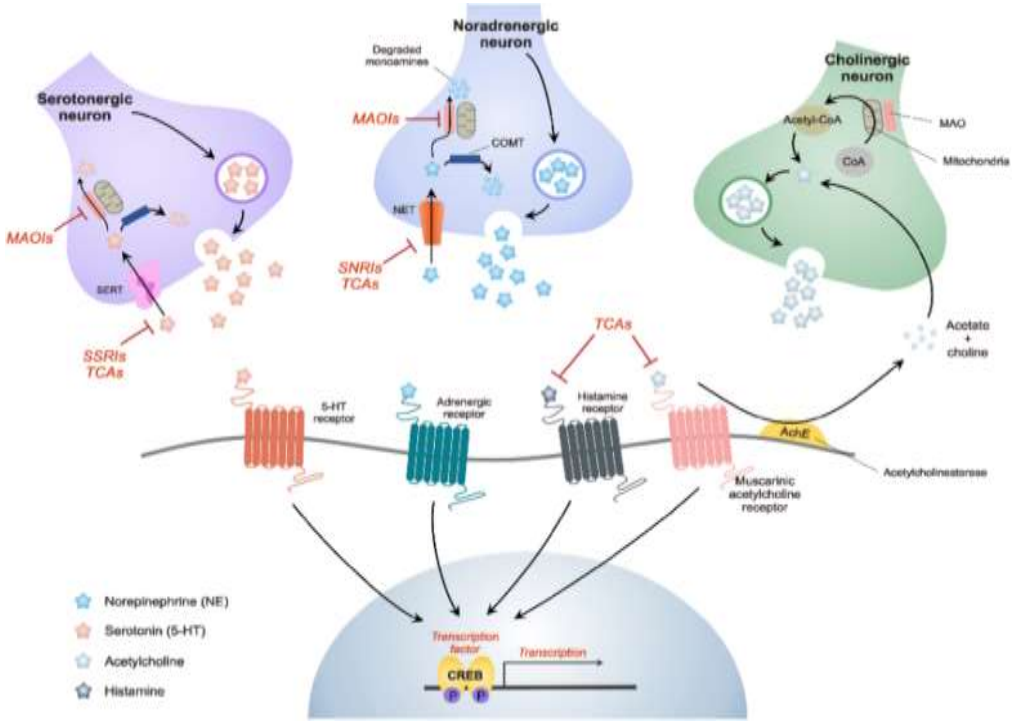

Figure 3 MOA of anti-depressant(8)

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org
Article Received: 28/08/2024 Revised: 09/11/2024 Accepted: 20/11/2024

Symptoms:
Depression:
Lack of interest or pleasure, sadness, guilt or low self-worth, restless nights or restless eating, exhaustion, and difficulty concentrating, are signs of depressive disorders, which can result in suicide. These can be further classified as dysthymia, major depression, or depressive phases. Depressive mood, diminished interest and enjoyment, and low energy are all signs of major depressive illness. Similar symptoms that are less severe but persist longer are seen in dysthymia.(15).

Anxiety:
Different symptoms of anxiety like fatigue, tiredness, difficulty of concentration, increased irritation, tension or acne, feeling of control, etc. The severity of the symptoms varies, but they are usually persistent.(16).

Treatments for anxiety:
In medical care, drugs that have not been approved for a specific illness are often employed "off-label," despite these designations. Similar to the FDA, other European countries are given indications as to how SNRIs & SSRIs are to treat anxiety disorders.(16). A list of anxiety drugs that are both FDA-approved and off-label can be found in **Table 1**.

Table 1 Latest drugs used in anxiety.

Class	Use	Volume (mg/day)	Mechanism	Approval by FDA
Anti-psychotics				
Trifluoperazine	G.A.D, PD, S.A.D	2–6	D_2 antagonist (23)	NA
Olanzapine	Anxiety, G.A.D	5–15	D_2, 5-HT_2 H_1 antagonist (24)	Nervousness
Quetiapine	Anxiety, G.A.D	50–300	D_2, 5-HT_2 H_1 antagonist(24)	NA
Anti-histamines				
Hydroxyzine	G.A.D, PD, S.A.D	25–100	H_1 antagonist(26)	Anxiety
TCAs:				
Clomipramine	G.A.D, PD, S.A.D	100–250	NE and an inhibitor of 5-HT reuptake(17)	NA
Imipramine	G.A.D, PD, S.A.D	100–300		NA
Desipramine		100–200		NA
Nortriptyline		50–150		NA
Mixed anti- Depressants				
Mirtazapine	Anxiety, G.A.D, PD, S.A.D	15–45	5-HT_2, 5-HT_3, α_2, H_1 antagonist (20)	NA
β -blockers:				
Propranolol	Anxiety, PD, S.A.D	60–120	β-1, β-2 antagonist(25)	NA
GABAergic drugs:				
Pregabalin	S.A.D G.A.D, PD, S.A.D,	150–600	Unclear, may modulate Ca channels (21)	NA
Gabapentin	G.A.D	600–2,400		NA
SSRIs				
Citalopram	S.A.D, PD, S.A.D, G.A.D, PD	20–40	specific 5-HT reuptake inhibitor (17)	NA
Paroxetine ER	G.A.D	27-75		G.A.D
Paroxetine	S.A.D	20–60		PD, S.A.D,
Escitalopram		10-20		G.A.D
Fluvoxamine		100–300		PD, S.A.D
MAOIs				
Phenelzine	G.A.D, PD, S.A.D	30–90	MAO inhibitor (19)	NA
SNRIs:				
Duloxetine	PD, S.A.D	30–60	DA, 5-HT, and NE reuptake inhibitors(18)	G.A.D
Venlafaxine (XR)	PD, S.A.D	75–300		G.A.D
Desvenlafaxine	G.A.D, PD, S.A.D	50–100		NA

Novel Treatments for Anxiety:
Research on the use of pharmacological treatments for anxiety disorders has moved from the GABA, norepinephrine, & serotonin systems to additional neurotransmitters and pathways, such as glutamate and neuropeptides. A summary of current and ongoing research on drugs for PD, S.A.D, & G.A.D is given below.(28). **Table 2** presents an overview of the results.

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org
Article Received: 28/08/2024 Revised: 09/11/2024 Accepted: 20/11/2024

Table 2: Innovative drugs for anxiety disorders

Class	MOA	FDA approvals	Past RCTs in anxiety	In Trial
Glutamate:				
LY354740	mGluR2-3(46)	-	PD (46)	-
LY544344	mGluR2-3 (47)	-	G.A.D (47)	-
JNJ40411813	mGluR2 (+)(48)	-	Mental disorder (48)	-
$C_{13}H_{16}ClNO$	Antagonist of NMDA (49)	M.D.D	S.A.D (50)	-
$C_8H_5F_3N_2OS$	Stop glutamate release (51)	Amyotrophic lateral sclerosis	G.A.D (51)	-
$C_{15}H_{16}F_3N_5O_4S$ (BHV-4157)	Decrease glutamate (NCT03829241)	-	G.A.D (NCT03829241)	-
$C_3H_6N_2O_2$	NMDA partial agonist (52)	TB	PD, S.A.D and specific phobias (53)	-
$C_{12}H_{21}N$	Antagonist of NMDA (54)	dementia Alzheimer	G.A.D (54)	-
N_2O	Antagonist of NMDA (55)	Inhaled anesthetic	-	-
GABAergic				
AZD7325	Alpha-2-3 modulator of GABA-A (NCT00808249)	-	G.A.D (NCT00808249)	-
PF-06372865	GABA-A (+) allosteric modulator (56)	-	G.A.D (56)	-
BNC-210	Ach(-) allosteric modulator α7, GABA modulator (57)	-	G.A.D (57)	-
Neuro-peptides:				
Oxytocin	Unclear	Labor induction	SP (60) S.A.D (61)	Anxiety + depression (NCT03566069)
LY686017	Neurokinin-1 antagonist (62)	-	S.A.D(62)	-
L-759274	Neurokinin-1 antagonist (63)	-	G.A.D (63)	-
SSR-149415	antagonist (V1b) (66)	-	M.D.D + G.A.D (66)	-
SRX246	V1a antagonist(67)	-	-	Experimental anxiety (NCT02922166)
Pexacerfont (BMS-562086)	CRF-1 antagonist(68)	-	G.A.D (68)	-
Verucerfont (GSK561679)	CRF-1 antagonist (NCT00555139)	-	G.A.D (NCT00555139)	-
Emicerfont (GW876008)	CRF-1 antagonist (NCT00555139)	-	G.A.D (NCT00555139)	-
Cannabinoids:				
Delta-9-tetrahydrocannabinol	CB1, CB2 partial agonist(73)	-	-	-
Dronabinol	CB1 agonist (73)	Chemo-related nausea/vomiting	-	-
Nabilone	CB1, CB2 agonist(73)	Chemo-related nausea/vomiting	G.A.D, "Anxiety neuroses" (75)	-
Natural remedies:				
Kava	Activity of Na Indistinct, Ca channels or GABA-A receptor (76)	-	G.A.D (77)	-
Galphimine-B (G-B)	Inhibit DA neurons in (ventral tegmental area) (78)	-	G.A.D (78)	Anxiety (NCT03702803)
Chamomile	Unclear, modulates GABA receptors (79)	-	G.A.D (79)	-

Herbal drugs used in anxiety and depressants:

Many people who suffer from anxiety or depression turn to herbal medicines. Therefore, it's critical to determine whether they produce more benefits than drawbacks. The motivations for people's use of herbal remedies are varied. It has been

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org
Article Received: 28/08/2024 Revised: 09/11/2024 Accepted: 20/11/2024

shown that British customers anticipate self-help guidance, knowledge, a holistic approach, and symptom alleviation when speaking with alternative therapists. **Table no. 3** shows different herbal medicines are used in anti-anxiety & anti-depression symptoms of these disorders (82).

Table 3. Herbal drugs are used in anxiety & anti- depression with MOA

Herbal drug	Part Used	MOA
St. John's Wort	Flowering tops	Increases serotonin, dopamine, and norepinephrine levels, and modulates GABA receptors, alleviating symptoms of anxiety and dopaminergic activity (83)
Ashwagandha	Root	Regulates cortisol levels, enhances GAB-Aergic activity, and supports neurogenesis, promoting relief from depression (84)
Passionflower	Aerial parts (flowers)	Boosts GABA levels, reducing anxiety symptoms, and exhibits serotoninergic activity, alleviating depressive symptoms, Benzodiazepine receptor partial agonist(85)
Lavender	Flowering tops	GABA modulation (based on volatile constituents) and anxiolysis shown in animal models (elevated plus maze and open field tests)(86)
Valerian	Root	Enhances GAB-Aergic transmission, promoting relaxation and mitigating anxiety symptoms, aiding in depression relief(87)
Rhodiola	Root	Modulates serotonin, dopamine, and norepinephrine levels improving mood and reducing stress-related symptoms (88)
Chamomile	Flower	Binds to GABA receptors, exerting anxiolytic and antidepressant effects, promoting relaxation and sleep(89)
Lemon Balm	Leaf	Increases GABA levels, reducing anxiety symptoms, and enhancing mood, providing relief from mild depression(90)
Kava	Root	Enhances GABAergic activity, inducing relaxation and reducing anxiety symptoms, potentially easing depression(91)
Holy Basil (Tulsi)	Leaf	Modulates cortisol levels, exerting adaptogenic effects and enhancing neurotransmitter balance, relieving anxiety(92)
Artocarpus lacucha Linn	Leaf	Binds to GABA receptors, exerting anxiolytic and antidepressant effects, promoting relaxation and sleep(93)

Artocarpus lacucha: -
A growing variety of plant-based medications are utilized in Indonesia, a country home to several ethnic groups. Documenting the applications of Indonesia's unknown variety of medicinal plant species is crucial. Due to the economic downturn, which has decreased people's ability to afford expensive modern medications, as well as the growing popularity of a return to nature philosophy, the use of natural compounds as medications, has increased. Natural remedies rarely have side effects. Local knowledge enables rural societies to use plants as remedies.(94).

Plant-based remedies have been utilized for thousands of years. Medicinal plants are popular because they not only keep people fine but may be utilized as decorative plants, food seasonings, and nutritional supplements. Indonesia has a fantastic chance to create novel medication candidates using medicinal plants.(95).

The active compounds of herbal remedies possess are what give them their potency. Medicinal plants with the proper soil & climate are known to have these therapeutic chemicals. This natural medicine or substance has been used traditionally for many thousands of years and is still gone (96). It has been demonstrated that a number of extracts of herbs reduce the number of germs that cause oral cavities. *A. lacucha* family Moraceae **(Figure 4)** with a high content of phenolics, including flavonoids and phenolic acid. Phenolic derivatives, phenolic acids, & flavonoids are examples of phenolic substances anti-plasmodial, anti-atherosclerotic, anti-fungal, anti-diarrheal, anti-diabetic, wound healing, anti-inflammatory, and anticancer are among the biological characteristics of *A. lacucha* plants. This plant has so many other chemicals like flavonoids and phenols & alkaloids etc.

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org
Article Received: 28/08/2024 Revised: 09/11/2024 Accepted: 20/11/2024

Figure 4 Artocarpus lacucha Linn plant, leaf

Active chemical component:

The *A. lacucha* possesses anti-bacterial, and anthelmintic, qualities, according to the findings of the literature review **(Table.4).** People think it benefits the digestive system, blood, and liver. Overall, eating this fruit is a lot of fun and has a distinct sweet-and-sour taste. Eat the ripe *A. lacucha* fruit fresh for maximum health benefits. It's frequently used to produce sauces, pickles, chutneys, curries, and medications. Frequent tropical fruit-eating may lower the risk of developing non-communicable diseases such as diabetes, cancer, heart disease, and neurological conditions.(97). They are also rich in pharmacological components and phytochemicals. These isolates' capacity to inhibit herpes simplex virus types one & two were evaluated using the inactivation technique. An excellent origin of the Alzheimer's disease-related acetylcholinesterase, or AChE, agent is the chemical 2-Arylbenzofurans(98).

Table 4. Chemical constituent is actively present in *Artocarpus lacucha*

S. No.	Formula	Name	Activity	Reference
1.	$C_{30}H_{50}O$	Cycloartenone	Used in Hypolipidemic & Anti-hyperglycaemic	(99)
2.	$C_{32}H_{52}O_2$	α-amyrin acetate	Used in inflammation & anti-hyperlipidaemic	(100)
3.	$C_{32}H_{52}O_2$	β-amyrin acetate	It used as Anti-inflammatory radical scavenging	(100)
4.	$C_{14}H_{12}O_4$	Oxyresveratrol	Used as skin care Antiviral, cytotoxic, anti-HIV	(102)
5.	$C_{29}H_{34}O_4$ & $C_{26}H_{30}O_4$	Lakoochin A & B	It used Anti-mycobacterial, breast cancer, cytotoxic	(103)
6.	$C_{26}H_{28}O$	Artocarpin	For special used in lungs of Anti- cancer	(105)
7.	$C_{29}H_{32}O_4$	Artolakoochol	Herpes simplex virus (HSV-1 & 2)	(106)
8.	$C_{12}H_9NO$	4-hydroxyartolakoochol	Anti- acetylcholinesterase	(106)
9.	$C_{26}H_{26}O_6$	Cycloartocarpin	antiplasmodial & antitubercular anti- cancer	(107)
10.	$C_{12}H_{14}O_4$	Diethyl phthalate	Antioxidant	(108)
	$C_8H_8O_5$	3,4 Dihydroxymandelic acid	Antimicrobial & antioxidant	(108)

Artocarpus lacucha profile in pharmacological activity:

In vitro, cytotoxic agents are toxic to tumor cells & may also be harmful to quickly proliferating normal cells. These medications have anticancer properties if the harm spreads in cancer cells in vivo.(109). A. lacucha plant cytotoxicity is one of its biological activities (Figure.5). According to the previous studies we find the comparison between different dose volume variation & they show very effectful (10, 20, 40, 60, 80, and 160 µg/mL) was carried out & identify the activity of antioxidant LD50 value analyzed used the pericarp extract of methanol at doses of 10–1000 µg/ml. It was discovered that the way in which *A. lacucha* extract killed brine shrimp varied depending on the dosage. The extract may have contained cardiac glycosides, alkaloids, and saponins, which would account for the brine shrimp's death(110).

When A. lacucha leaf extract and methanol are combined, When the dosage is increased, the anti-inflammatory benefits become significant ($p < 0.05$). Domethacin was not as actual in reducing inflammation as A. lacucha, at 200 mg/kg (64.90%). The writhing response was decreased by A. lacucha leaf ME at a dosage of 28.71% and 58.25%, respectively ($p < 0.05$). **(Table 5).**(111)

One consequence of arachidonic acid breakdown is something that might induce inflammation. Fatty acids with 20 carbon atoms and no saturation are called arachidonic acid. (112).

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org
Article Received: 28/08/2024 Revised: 09/11/2024 Accepted: 20/11/2024

Medications known as analgesics, or pain blockers, reduce or eliminate pain without causing unconsciousness. Hydro-methanolic *A. lacucha* wood extract has been demonstrated to have a potent anti-pain effect at dosages ranging from 50–200 mg/Kg b.w. **(Table 4),** and it did not cause any damage to the test animals. The injured area of the body is healing, nociceptive pain goes away. Both acute and chronic pain can be effectively treated with opioid-containing painkillers. Drug properties are employed instead of opioid medicines to reduce the adverse effects of pain.(113)

The plant *A. lacucha* (leaf) (100 mg/kg) has a modest antidiarrheal effect. This is predicated on the gathered data. However, at 200 mg/kg, it was halted (68.11%), which is comparable to the efficacy of loperamide, the conventional medication, which is 71.1%). Thus, the extract in question prevented diarrhea by acting as an antisecretory mechanism(114). The fact that there were less moist stools in the experimental test group further demonstrated this. The objectives of treating diarrhea include correcting the diet, preventing excessive water and electrolyte loss, correcting acid-base imbalances, treating the symptoms, treating the underlying identifying the root causes of the diarrhoea and managing any underlying illnesses that make the GI illness worse(115).

Additionally, *A. lacucha* plants have other pharmacological actions that include liver and nerve cell protection(116). Even while the two medications under investigation—paughaad and oxyresveratrol—improve cell survival, particularly the neuroprotective effects of A. lacucha wood extract indicate that mitochondrial protection is difficult to detect due to ROS levels and lipid peroxidation.(116). Oxyresveratrol's impact on the pharmacokinetics & levels of redox-sensitive antioxidant enzymes indicates that taking puaghaad orally might be a fantastic approach to guard against neurodegenerative illnesses that come and go. Using the Thin layer chromatography densitometric approach & QNMR technique, various investigations have quantitatively evaluated the amounts of oxyresveratrol(117).

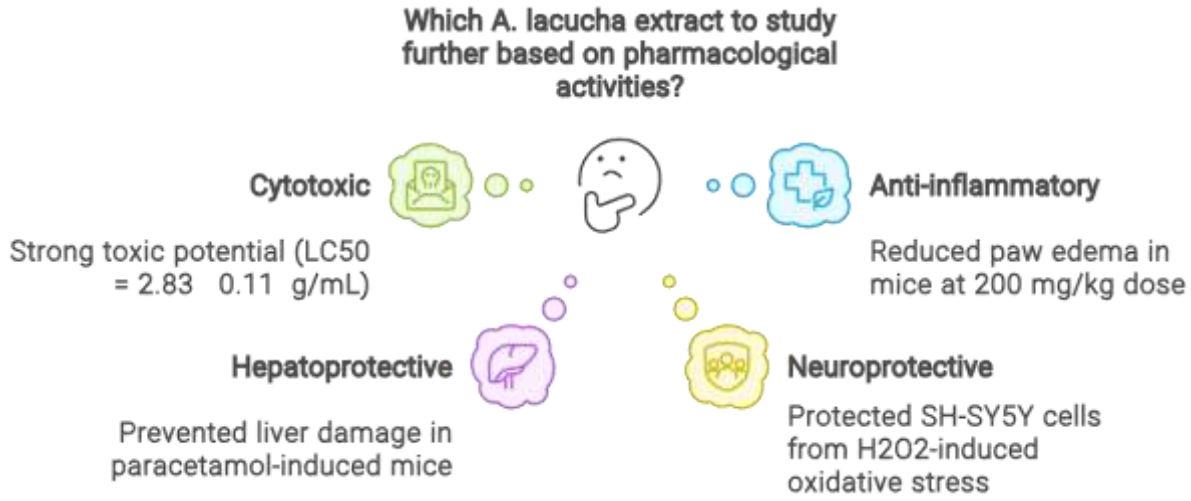

Figure 5 Pharmacology activity of A. Lacucha

Table 5: A. lacucha's pharmacological efficacy according to scientific evidence.

Plant part	Activity	pathway	Results	Ref.
Methanol extract (leaf)	Analgesic	Through acetic acid	Positive	(118)
	Anti- diarrhoeal	Through castor oil	Positive	
	Cytotoxic	Bioassay of brine shrimp	They are high toxic	
	Anti-inflammatory	Induced through the carrageenan paw edema in mice.	Positive	
Methanol extract (Fruit)	Liver protection	Induced with paracetamol (In-vivo method)	Positive.	(119)
Aqueous extract (heart wood)	Neuro-protective	Oxidative stress in SH-SY5Y cells.	Positive	(110)
Methanol extract (heart pericarp)	Cyto-toxic	bioassay of Brine shrimp	Hight Toxic (negative)	(120)
Aqueous extract (Crude)	Schistosomicidal	Schistosoma mansoni infection in vivo in rodents	Positive	(121)
Hydro-methanolic extract (bark)	Anti-nociceptive	Induced through the carrageenan paw edema	Positive.	(122)
Methanol extract (leaf)	Anti-cholesterol	In-vivo, hyperlipidaemia	Positive	(123)
Aqueous extract (heart wood)	Anti-glycation	Bovine Serum Albumin (BSA)	Positive	(124)
Ethanol extract (leaf)	Pro-liberative & Wound healing	Assay of MTT and in vivo, mouse NIH-3T3 cell	Positive	(124)

Moreover, *A. lacucha* plants have the ability to heal wounds, control cholesterol, eradicate schistosomes, and reduce discomfort. They can even prevent diabetes. The overall blood cholesterol, triglyceride, and low-density lipoprotein

(LDL) levels declined in the healthy group while the levels of serum high-density lipoprotein (HDL) rose(125). An excessively high blood fat level is known as hyperlipidemia, also known as hypercholesterolemia. As more individuals consume meals high in saturated fat, which is frequently present in fast food, the prevalence of cholesterol-related disorders is rising(126). In addition to diet, other factors that might raise blood cholesterol include inactivity and depression. In vivo schistosomicidal activity tests were conducted on mice, while mature were cultured containing different volume 250, 500, & 750 mg/ml. Results indicated that 250 mg/mL of *A. lacucha* water extract might have an impact on Schistosoma mansoni. One of the parasite illnesses that has the greatest impact on public health is schistosomiasis. This illness causes financial losses and health issues for many underdeveloped nations. (127).
Several active chemicals found in *A. lacucha* plants have been covered in this article. The anti-aging properties of oxyresveratrol, which has a high phenol content and acts as a free radical scavenger and antiglycation agent, are among them. Compounds containing oxyresveratrol may function as antioxidants and prevent B16 melanoma cells from producing melanin.(128).

Traditional uses of Artocarpus:
Several species from the species Artocarpus is are further used in South-East Asian traditional folk medicine to relieve inflammation, malaria, ulcers, abscesses, and diarrhea. Jackfruit pulp and seeds are used as a cooling tonic and pectorial; roots are used to treat fever and diarrhea; leaves are used to activate milk in women and animals; leaf ash is applied to wounds that have ulcers; or heated leaves, when pasted on wounds, have healing properties(129). The latex combined with vinegar helps to treat swellings in the glands, bites, and abscesses. The stem barks and leaves have been used as an expectorant and to cure anaemia, dermatitis, asthma, diarrhea, and coughing. The wood's pith is claimed to trigger abortions, as it has a calming effect on convulsions(129). The root is used as a treatment for skin conditions, asthma, & diarrhea and fever (ICUC, 2003). Its extract is also used for those reasons. Monks in rural northeastern Thailand's Forest Tradition monasteries dye their garments using the heartwood of Artocarpus heterophyllus. Actually, monks adhering to this custom never wash their garments(130). The robes are re-boiled in jackfruit dye and allowed to dry in the sun once a week. When maintained this way, robes never smell unpleasant and offer protection against fungi and skin conditions(131).
Parker's Artocarpus altilis. The small Fosberg tree is widely grown in the tropics as a staple crop, building material, & animal feed. Its leaves have long been used to cure liver cirrhosis, hypertension, and diabetes. Fresh lakocha fruits are typically consumed. The pulpy fruit may be eaten, and it's said to have liver-tonic properties. Chutneys and pickles are made from the uncooked fruits and the tannic and acidic spikes of the male flowers. In Thailand, this type of drug has been used as a traditional antibiotic drug to treat tapeworm infections(132).

Effects of Artocarpus lacucha as Anti-depressant:
Neurotransmitter Modulation:
It's probable that changes in neurotransmitter systems connected to the etiology of mood disorders is an aspect of Artocarpus lacucha's effects on depression. Studies on Artocarpus lacucha extracts, for example, have revealed that they may have an impact on the brain's levels of serotonin, dopamine, and norepinephrine, all of which are critical for mood regulation(133).

Neurogenesis and Neuro-plasticity:
By encouraging neurogenesis and neuroplasticity in brain areas linked in mood regulation, such the hippocampus, *Artocarpus lacucha* may have antidepressant benefits. Results from animal studies using extracts from *Artocarpus lacucha* have shown enhanced neurogenesis and synaptic plasticity, pointing to possible processes behind the plant's antidepressant effects(134).

Antioxidant effect:
Using the DPPH free radical test, the antioxidant activity for different doses of a methanolic extract of the pericarp of Artocarpus lacoocha fruit and ascorbic acid was assessed. By scavenging the free radical DPPH and converting it into DPPHH, the extract demonstrated strong antioxidant activity. It was discovered that the activity was dosage dependant. Ascorbic activity had a higher scavenging activity than methanolic extract. Ascorbic acid and extracts were found to have IC_{50} values of 06.09 µg/ml and 49.42 µg/ml, respectively(135).

Interaction with neurotransmitter systems:
Dopaminergic system and potential sites where depressive symptoms may arise:
Since the creation and popularity of SSRIs, there has been a great deal of study on the function of serotonin in M.D.D. But many SSRI users for depression do not fully recover, and this may be due in part to a greater loss of happy affect than an increase in negative affect. Therefore, medications that operate on the dopamine and noradrenergic receptors may be beneficial to them. Even though research on nor-adrenergic activity began in the 1960s when TCAs were introduced, only recently has the connection between dopamine and reduced happy emotion been studied(136). One method to assist doctors in prescribing symptom-specific antidepressants for patients is to connect the neuroanatomy of the brain's

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org
Article Received: 28/08/2024 Revised: 09/11/2024 Accepted: 20/11/2024

dopaminergic systems with certain depressive symptoms. The striatum, the nucleus accumbens (ventral striatum), and the prefrontal cortex are the three primary projection regions of the mid-brain dopamine system(137). While projections from the substantia nigra provide the majority of the dopamine in the striatum, projections from the ventral tegmental region are responsible for the dopamine found in the nucleus accumbens and the prefrontal cortex. A loss of dopamine in the striatum is a typical pathologic finding of Parkinson's disease, which is well documented to cause damage to the substantia nigra. The energy depletion and slowness that those with Parkinson's experience—symptoms of sadness—are thought to be signs linked to a kind of dopamine problems in the striatum.(138). The ventral tegmental region innervates the nucleus accumbens, which is linked to pleasant reward sensations. Thus, a faulty reaction to usual benefits may be linked to a malfunctioning dopamine system. Decreased dopamine activity in the nucleus accumbens may contribute to depression by reducing the worth of certain tasks that are not normally gratifying. This might lead to a lack of interest or pleasure(139).
In the frontal cortex, dopamine plays a special role for influencing behavior and focus. Though there isn't much data to support it, it's thought that a relative dopamine malfunction in the prefrontal cortex plays a role in the weariness, lack of motivation, and mental apathy that are frequently associated with depression. Disfunction of the brain's reward system, located in the nucleus accumbens, and motivational system, located in the prefrontal cortex, is likely to be a contributing factor to the loss of interest experienced by depression sufferers(140).

Model of Two Dimensions for Neurotransmitter Functions in Depression:
An increase in negative affect and a decrease in positive affect are the two components of depression, according to a well-known psychological notion. Perceiving the world as unfriendly, unpleasant, unsettling, and menacing is known as negative affect. Being unable to reap the benefits of regular pursuits like hobbies, family, or employment is known as loss of positive affect. There is some overlap between these two aspects when it comes to depressed and melancholy emotions(141). Psychological research indicates that these two components are present in many types of depression. Thus, might be applied to characterize the type of depression. For instance, certain individuals may have particularly resistant depression with a greater loss of positive affect, whereas other individuals may undergo depression with a greater rise in negative affect, such as anxiety symptoms(142). return to normal functioning(143). A medication with a dopaminergic and/or nor-adrenergic component can help patients with symptoms of loss of benefit return to normal functioning. This medication treats loss of motivation, interest, and enjoyment(144).

Antianxiety Effects of Artocarpus lacucha:
However, based on its pharmacological profile and traditional use, there is potential for *Artocarpus lacucha* to exhibit antianxiety effects(144).

Neurotransmitter Modulation:
When concern develops, an array of neurotransmitter-based neural pathways combine & are affected through proximal & distant synaptic inputs. Long believed to be important in the regulation of stress is the neurotransmitter that inhibits GABA. Treatments for anxiety disorders that target this neurotransmitter system include benzodiazepines and related drugs. (145). However, it should be mentioned that the amygdala is also involved in the regulation of anxiety reactions in response to a number of other neurotransmitters, including serotonin, opioid peptides, endocannabinoids, neuropeptide Y, oxytocin, and corticotropin-releasing hormone. These important neurotransmitter pathways are too complex for us to discuss in-depth in this review.(146).

Role of GABA & GABA receptor:
The principal inhibitory neurotransmitter in the central nervous system (CNS), while at least one-third of CNS neurons are thought to use GABA as their primary neurotransmitter. The balance between neuronal excitation and inhibition, precise temporal and geographical regulation of transsynaptic transmission, temporal modulation of neuronal excitability, and the maintenance of rhythmic "pacemaker" activity in various brain areas are all dependent on GABAergic inhibition(147). While certain main projection routes, particularly those emerging in the thalamus and cortex, are GABAergic, the majority of GABA-containing neurons are interneurons, which control the excitability of local circuits within a particular brain area(148).
GABA inhibits neurons through two different kinds of GABA receptors. Metabotropic $GABA_B$ receptors are indirectly connected via G-proteins to either calcium or potassium channels, resulting in sluggish and sustained inhibitory responses. Ionotropic $GABA_A$ receptors, on the various hand, are fast-acting ligand-gated chloride channels that are responsible for rapid inhibition. Although the exact nature of their role in neurological & mental health is still unknown, baclofen, a chemical that mimics GABA's activity at these $GABA_B$ receptors, has strong myorelaxant effects and has been suggested as a potential therapy for alcohol dependency(149).

Conclusion:
In conclusion, mental health issues are a significant worldwide health concern that have resulted in a rise in the usage of psychotropic drugs including anxiolytics and antidepressants. The fact that these drugs are used differently in different

parts of the world emphasizes how crucial it is to comprehend cultural and economic influences on mental health care. Plant-based medicines hold great promise for natural and affordable therapies, especially when they come from medicinal plants like *Artocarpus lacucha* Linn in Indonesia. It contains strong medicinal substances such artocarpin, oxyresveratrol, phenols, and flavonoids. A. lacucha, exhibit a variety of possible pharmacological uses, such as anti-inflammatory, antinociceptive, anti-anxiety, and antidiarrheal qualities. Recent advancement showed *A. lacucha* is a good candidate for the creation of new antidepressant drugs due to its distinct modes of action, which include boosting neurogenesis and neuroplasticity, demonstrating antioxidant properties, and regulating neurotransmitter systems. Targeting different neurotransmitter like GABA Anergic, Metabotropic GABA, these developments provide a wider range of more potent therapeutic alternatives, which eventually enhance patients' quality of life and treatment outcomes. In general, investigating the potential of medicinal plants such as *A. lacucha* is a significant chance to create novel, all-natural, and culturally appropriate remedies for mental health issues.

The antioxidant nature of *Artocarpus lacucha* extracts of leaves is a useful for mental health disorders. Finally, we may state that more research is need to perform *in-vivo* antioxidant activity. Also, identify more novel moieties in extract of *Artocarpus lacucha* leaves' primary to increase its potential therapeutics profile for mental health disorders .

Abbreviation:

5-HT	5-hydroxytryptamine
AGP	Agoraphobia
BSA	Bovine Serum Albumin
DA	Dopamine
DPPH	2,2-Diphenyl-1-picrylhydrazyl
ER, XR	Extended Release
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
G.A.D	Generalized anxiety disorder
HDL	High-density lipoprotein
IC50	Half-maximal inhibitory concentration
ICUC	International Centre for Underutilised Crops
kg	Kilogram
LC	Lethal Concentration
LUC	Lacucha
LD50	Lethal Dose
MAO	Monoamine Oxidase
MAOIs	monoamine oxidase inhibitors
M.D.D	major depressive disorder
mg	Milligram
mL	milliliter
NE	norepinephrine
NET	norepinephrine transporter
PD	Panic Disorder
QNMR	Quantitative Nuclear Magnetic Resonance
ROS	reactive oxygen species
SAD	Social Anxiety Disorder
SERT	Specific acute effects on the serotonin transporter
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRIs	selective serotonin reuptake inhibitors
TCA	tricyclic antidepressants
TLC	Thin-layer chromatography
µg	microgram

Reference:

1. Marbin D, Gutwinski S, Schreiter S, Heinz A. Perspectives in poverty and mental health. Front Public Heal. 2022;10:975482.
2. Brauer R, Alfageh B, Blais JE, Chan EW, Chui CSL, Hayes JF, et al. Psychotropic medicine consumption in 65 countries and regions, 2008–19: a longitudinal study. The Lancet Psychiatry. 2021;8(12):1071–82.
3. Meghrajani VR, Marathe M, Sharma R, Potdukhe A, Wanjari MB, Taksande AB, et al. A Comprehensive Analysis of Mental Health Problems in India and the Role of Mental Asylums. Cureus. 2023;15(7).
4. Zhang X, Hu X, Zhao Y, Lu CY, Nie X, Shi L. Trends in the utilization of psychotropic medications in China from 2018 to 2021. Front Pharmacol. 2022;13:967826.
5. Tiger M, Wesselhoeft R, Karlsson P, Handal M, Bliddal M, Cesta CE, et al. Utilization of antidepressants,

anxiolytics, and hypnotics during the COVID-19 pandemic in Scandinavia. J Affect Disord. 2023;323:292–8.
6. Estrela M, Herdeiro MT, Ferreira PL, Roque F. The use of antidepressants, anxiolytics, sedatives and hypnotics in Europe: focusing on mental health care in Portugal and prescribing in older patients. Int J Environ Res Public Health. 2020;17(22):8612.
7. Woo YS, Park JE, Kim DH, Sohn I, Hwang TY, Park YM, et al. Blonanserin augmentation of atypical antipsychotics in patients with schizophrenia-who benefits from blonanserin augmentation?: an open-label, prospective, multicenter study. Psychiatry Investig. 2016;13(4):458.
8. Kim J, Kim TE, Lee SH, Koo JW. The Role of Glutamate Underlying Treatment-resistant Depression. Clin Psychopharmacol Neurosci. 2023;21(3):429.
9. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. Exp Clin Psychopharmacol. 2015;23(1):1.
10. Sanchez C, Reines EH, Montgomery SA. A comparative review of escitalopram, paroxetine, and sertraline: Are they all alike? Int Clin Psychopharmacol. 2014;29(4):185–96.
11. Balter MB, Levine J, Manheimer DI. Cross-national study of the extent of anti-anxiety/sedative drug use. N Engl J Med. 1974;290(14):769–74.
12. Horih SI. Basic neurochemistry: molecular, cellular, and medical aspects. Neurology. 1989;39(3):460.
13. Purves D, Augustine G, Fitzpatrick D, Katz L, LaMantia A, McNamara J, et al. Neuroscience 2nd edition. sunderland (ma) sinauer associates. Types Eye Movements Their Funct. 2001;
14. Chandel SS. Pharmacological models to appraisement of antianxiety activity in experimental animals. Int J Green Pharm. 2018;12(03).
15. Beck AT, Alford BA. Depression: Causes and treatment. University of Pennsylvania Press; 2009.
16. Goodwin GM. The overlap between anxiety, depression, and obsessive-compulsive disorder. Dialogues Clin Neurosci. 2015;17(3):249–60.
17. Bakker A, Van Balkom A, Spinhoven P. SSRIs vs. TCAs in the treatment of panic disorder: a meta-analysis. Acta Psychiatr Scand. 2002;106(3):163–7.
18. He H, Xiang Y, Gao F, Bai L, Gao F, Fan Y, et al. Comparative efficacy and acceptability of first-line drugs for the acute treatment of generalized anxiety disorder in adults: a network meta-analysis. J Psychiatr Res. 2019;118:21–30.
19. Curtiss J, Andrews L, Davis M, Smits J, Hofmann SG. A meta-analysis of pharmacotherapy for social anxiety disorder: an examination of efficacy, moderators, and mediators. Expert Opin Pharmacother. 2017;18(3):243–51.
20. Croom KF, Perry CM, Plosker GL. Mirtazapine: a review of its use in major depression and other psychiatric disorders. CNS Drugs. 2009;23:427–52.
21. Mula M, Pini S, Cassano GB. The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. J Clin Psychopharmacol. 2007;27(3):263–72.
22. Balon R, Starcevic V. Role of benzodiazepines in anxiety disorders. Anxiety Disord Rethink Underst Recent Discov. 2020;367–88.
23. Maher AR, Maglione M, Bagley S, Suttorp M, Hu JH, Ewing B, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. Jama. 2011;306(12):1359–69.
24. Depping AM, Komossa K, Kissling W, Leucht S. Second-generation antipsychotics for anxiety disorders. Cochrane Database Syst Rev. 2010;(12).
25. Steenen SA, Van Wijk AJ, Van Der Heijden GJMG, van Westrhenen R, de Lange J, de Jongh A. Propranolol for the treatment of anxiety disorders: Systematic review and meta-analysis. J Psychopharmacol. 2016;30(2):128–39.
26. Guaiana G, Barbui C, Cipriani A. Hydroxyzine for generalised anxiety disorder. Cochrane Database Syst Rev. 2010;(12).
27. Chessick CA, Allen MH, Thase ME, Batista Miralha da Cunha AABC, Kapczinski F, Silva de Lima M, et al. Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev. 1996;2015(6).
28. Griebel G, Holmes A. 50 years of hurdles and hope in anxiolytic drug discovery. Nat Rev Drug Discov. 2013;12(9):667–87.
29. Zareifopoulos N, Dylja I. Efficacy and tolerability of vilazodone for the acute treatment of generalized anxiety disorder: a meta-analysis. Asian J Psychiatr. 2017;26:115–22.
30. Schneier FR, Moskow DM, Choo T, Galfalvy H, Campeas R, Sanchez-Lacay A. A randomized controlled pilot trial of vilazodone for adult separation anxiety disorder. Depress Anxiety. 2017;34(12):1085–95.
31. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019;393(10173):768–77.
32. Yee A, Ng CG, Seng LH. Vortioxetine treatment for anxiety disorder: a meta-analysis study. Curr Drug Targets. 2018;19(12):1412–23.
33. Shah A, Northcutt J. An open-label, flexible dose adaptive study evaluating the efficacy of vortioxetine in subjects with panic disorder. Ann Gen Psychiatry. 2018;17:1–7.
34. Bansal Y, Bhandari R, Kaur S, Kaur J, Singh R, Kuhad A. Gepirone hydrochloride: a novel antidepressant with 5-

HT1A agonistic properties. Drugs of Today (Barcelona, Spain: 1998). 2019;55(7):423–37.
35. Garakani A, Murrough JW, Freire RC, Thom RP, Larkin K, Buono FD, et al. Pharmacotherapy of anxiety disorders: current and emerging treatment options. Front psychiatry. 2020;11:595584.
36. Nishitsuji K, To H, Murakami Y, Kodama K, Kobayashi D, Yamada T, et al. Tandospirone in the treatment of generalised anxiety disorder and mixed anxiety-depression: results of a comparatively high dosage trial. Clin Drug Investig. 2004;24:121–6.
37. Rickels K, Mathew S, Banov MD, Zimbroff DL, Oshana S, Parsons Jr EC, et al. Effects of PRX-00023, a novel, selective serotonin 1A receptor agonist on measures of anxiety and depression in generalized anxiety disorder: results of a double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2008;28(2):235–9.
38. Staroń J, Bugno R, Hogendorf AS, Bojarski AJ. 5-HT1A receptor ligands and their therapeutic applications: review of new patents. Expert Opin Ther Pat. 2018;28(9):679–89.
39. Wesolowska A, Nikiforuk A, Stachowicz K. Anxiolytic-like and antidepressant-like effects produced by the selective 5-HT6 receptor antagonist SB-258585 after intrahippocampal administration to rats. Behav Pharmacol. 2007;18(5–6):439–46.
40. Ivachtchenko A V, Lavrovsky Y, Okun I. AVN-101: a multi-target drug candidate for the treatment of CNS disorders. J Alzheimer's Dis. 2016;53(2):583–620.
41. Freeman AM, Westphal JR, Norris Gt, Roggero BA, Webb PB, Freeman KL, et al. Efficacy of ondansetron in the treatment of generalized anxiety disorder. Depress Anxiety. 1997;5(3).
42. Schneier FR, Garfinkel R, Kennedy B, Campeas R, Fallon B, Marshall R, et al. Ondansetron in the treatment of panic disorder. Anxiety. 1996;2(4):199–202.
43. MacIsaac SE, Carvalho AF, Cha DS, Mansur RB, McIntyre RS. The mechanism, efficacy, and tolerability profile of agomelatine. Expert Opin Pharmacother. 2014;15(2):259–74.
44. Weston NM, Gibbs D, Bird CI V, Daniel A, Jelen LA, Knight G, et al. Historic psychedelic drug trials and the treatment of anxiety disorders. Depress Anxiety. 2020;37(12):1261–79.
45. Fuentes JJ, Fonseca F, Elices M, Farré M, Torrens M. Therapeutic use of LSD in psychiatry: a systematic review of randomized-controlled clinical trials. Front psychiatry. 2020;10:494327.
46. Bergink V, Westenberg HGM. Metabotropic glutamate II receptor agonists in panic disorder: a double blind clinical trial with LY354740. Int Clin Psychopharmacol. 2005;20(6):291–3.
47. Dunayevich E, Erickson J, Levine L, Landbloom R, Schoepp DD, Tollefson GD. Efficacy and tolerability of an mGlu2/3 agonist in the treatment of generalized anxiety disorder. Neuropsychopharmacology. 2008;33(7):1603–10.
48. Kent JM, Daly E, Kezic I, Lane R, Lim P, De Smedt H, et al. Efficacy and safety of an adjunctive mGlu2 receptor positive allosteric modulator to a SSRI/SNRI in anxious depression. Prog Neuro-Psychopharmacology Biol Psychiatry. 2016;67:66–73.
49. Wan LB, Levitch CF, Perez AM, Brallier JW, Iosifescu D V, Chang LC, et al. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. J Clin Psychiatry. 2014;76(3):10121.
50. Taylor JH, Landeros-Weisenberger A, Coughlin C, Mulqueen J, Johnson JA, Gabriel D, et al. Ketamine for social anxiety disorder: a randomized, placebo-controlled crossover trial. Neuropsychopharmacology. 2018;43(2):325–33.
51. Mathew SJ, Amiel JM, Coplan JD, Fitterling HA, Sackeim HA, Gorman JM. Open-label trial of riluzole in generalized anxiety disorder. Am J Psychiatry. 2005;162(12):2379–81.
52. Davis M, Ressler K, Rothbaum BO, Richardson R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. Biol Psychiatry. 2006;60(4):369–75.
53. Ori R, Amos T, Bergman H, Soares-Weiser K, Ipser JC, Stein DJ. Augmentation of cognitive and behavioural therapies (CBT) with d-cycloserine for anxiety and related disorders. Cochrane Database Syst Rev. 2015;(5).
54. Feusner JD, Kerwin L, Saxena S, Bystritsky A. Differential efficacy of memantine for obsessive-compulsive disorder vs. generalized anxiety disorder: an open-label trial. Psychopharmacol Bull. 2009;42(1):81–93.
55. Jevtović-Todorović V, Todorovć SM, Mennerick S, Powell S, Dikranian K, Benshoff N, et al. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med. 1998;4(4):460–3.
56. Simen A, Whitlock M, Qiu R, Miceli J, Zumpano L, Du Metz M, et al. An 8-week, randomized, phase 2, double-blind, sequential parallel-group comparison study of two dose levels of the GABAA positive allosteric modulator PF-06372865 compared with placebo as an adjunctive treatment in outpatients with inadequate response to standard of care for generalized anxiety disorder. J Clin Psychopharmacol. 2019;39(1):20–7.
57. Wise T, Patrick F, Meyer N, Mazibuko N, Oates AE, van der Bijl AHM, et al. Cholinergic modulation of disorder-relevant neural circuits in generalized anxiety disorder. Biol Psychiatry. 2020;87(10):908–15.
58. Hoffmann E, Nomikos GG, Kaul I, Raines S, Wald J, Bullock A, et al. SAGE-217, a novel GABA A receptor positive allosteric modulator: Clinical pharmacology and tolerability in randomized phase I dose-finding studies. Clin Pharmacokinet. 2020;59:111–20.
59. Hecking J, Davoudian PA, Wilkinson ST. Emerging therapeutics based on the amino acid neurotransmitter system: an update on the pharmaceutical pipeline for mood disorders. Chronic Stress. 2021;5:24705470211020450.
60. Acheson DT, Feifel D, Kamenski M, Mckinney R, Risbrough VB. Intranasal oxytocin administration prior to exposure therapy for arachnophobia impedes treatment response. Depress Anxiety. 2015;32(6):400–7.

61. Fang A, Treadway MT, Hofmann SG. Working hard for oneself or others: Effects of oxytocin on reward motivation in social anxiety disorder. Biol Psychol. 2017;127:157–62.
62. Tauscher J, Kielbasa W, Iyengar S, Vandenhende F, Peng X, Mozley D, et al. Development of the 2nd generation neurokinin-1 receptor antagonist LY686017 for social anxiety disorder. Eur Neuropsychopharmacol. 2010;20(2):80–7.
63. Michelson D, Hargreaves R, Alexander R, Ceesay P, Hietala J, Lines C, et al. Lack of efficacy of L-759274, a novel neurokinin 1 (substance P) receptor antagonist, for the treatment of generalized anxiety disorder. Int J Neuropsychopharmacol. 2013;16(1):1–11.
64. Reichmann F, Holzer P. Neuropeptide Y: A stressful review. Neuropeptides. 2016;55:99–109.
65. Sayed S, Van Dam NT, Horn SR, Kautz MM, Parides M, Costi S, et al. A randomized dose-ranging study of neuropeptide Y in patients with posttraumatic stress disorder. Int J Neuropsychopharmacol. 2018;21(1):3–11.
66. Fabio KM, Guillon CD, Lu SF, Heindel ND, Brownstein MJ, Lacey CJ, et al. Pharmacokinetics and metabolism of SRX246: a potent and selective vasopressin 1a antagonist. J Pharm Sci. 2013;102(6):2033–43.
67. Griebel G, Beeské S, Stahl SM. The Vasopressin V1b Receptor Antagonist SSR149415 in the Treatment of Major Depressive and Generalized Anxiety Disorders: Results From 4 Randomized, Double-Blind, Placebo-Controlled Studiese. J Clin Psychiatry. 2012;73(11):1403.
68. Coric V, Feldman HH, Oren DA, Shekhar A, Pultz J, Dockens RC, et al. Multicenter, randomized, double-blind, active comparator and placebo-controlled trial of a corticotropin-releasing factor receptor-1 antagonist in generalized anxiety disorder. Depress Anxiety. 2010;27(5):417–25.
69. Han Y, Yuan K, Zheng Y, Lu L. Orexin receptor antagonists as emerging treatments for psychiatric disorders. Neurosci Bull. 2020;36(4):432–48.
70. Lenze EJ, Hershey T, Newcomer JW, Karp JF, Blumberger D, Anger J, et al. Antiglucocorticoid therapy for older adults with anxiety and co-occurring cognitive dysfunction: results from a pilot study with mifepristone. Int J Geriatr Psychiatry. 2014;29(9):962–9.
71. Liebowitz MR, Salman E, Nicolini H, Rosenthal N, Hanover R, Monti L. Effect of an acute intranasal aerosol dose of PH94B on social and performance anxiety in women with social anxiety disorder. Am J Psychiatry. 2014;171(6):675–82.
72. Liebowitz MR, Hanover R, Draine A, Lemming R, Careri J, Monti L. Effect of as-needed use of intranasal PH94B on social and performance anxiety in individuals with social anxiety disorder. Depress Anxiety. 2016;33(12):1081–9.
73. Turna J, Patterson B, Van Ameringen M. Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? Depress Anxiety. 2017;34(11):1006–17.
74. Masataka N. Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. Front Psychol. 2019;10:476036.
75. GLASS RM, Uhlenhuth EH, HARTEL FW, SCHUSTER CR, FISCHMAN MW. Single-dose study of nabilone in anxious volunteers. J Clin Pharmacol. 1981;21(S1):383S-396S.
76. Singh YN, Singh NN. Therapeutic potential of kava in the treatment of anxiety disorders. CNS Drugs. 2002;16:731–43.
77. Ooi SL, Henderson P, Pak SC. Kava for generalized anxiety disorder: a review of current evidence. J Altern Complement Med. 2018;24(8):770–80.
78. Romero-Cerecero O, Islas-Garduño AL, Zamilpa A, Herrera-Arellano A, Jiménez-Ferrer E, Tortoriello J. Galphimine-B standardized extract versus alprazolam in patients with generalized anxiety disorder: a ten-week, double-blind, randomized clinical trial. Biomed Res Int. 2019;2019.
79. Hieu TH, Dibas M, Surya Dila KA, Sherif NA, Hashmi MU, Mahmoud M, et al. Therapeutic efficacy and safety of chamomile for state anxiety, generalized anxiety disorder, insomnia, and sleep quality: A systematic review and meta-analysis of randomized trials and quasi-randomized trials. Phyther Res. 2019;33(6):1604–15.
80. Sarris J, McIntyre E. Herbal anxiolytics with sedative actions. Evidence-based Herb Nutr Treat anxiety Psychiatr Disord. 2017;11–31.
81. Marx W, Lane M, Rocks T, Ruusunen A, Loughman A, Lopresti A, et al. Effect of saffron supplementation on symptoms of depression and anxiety: a systematic review and meta-analysis. Nutr Rev. 2019;77(8):557–71.
82. Liu L, Liu C, Wang Y, Wang P, Li Y, Li B. Herbal medicine for anxiety, depression and insomnia. Curr Neuropharmacol. 2015;13(4):481–93.
83. Klemow KM, Bilbow E, Grasso D, Jones K, McDermott J, Pape E. Medical attributes of St. John's wort (Hypericum perforatum). OXIDATIVE Stress Dis. 2004;14:757–80.
84. Lopresti AL, Smith SJ, Malvi H, Kodgule R. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (Withania somnifera) extract: A randomized, double-blind, placebo-controlled study. Medicine (Baltimore). 2019;98(37):e17186.
85. Janda K, Wojtkowska K, Jakubczyk K, Antoniewicz J, Skonieczna-Żydecka K. Passiflora incarnata in neuropsychiatric disorders—A systematic review. Nutrients. 2020;12(12):3894.
86. Koulivand PH, Khaleghi Ghadiri M, Gorji A. Lavender and the nervous system. Evidence-based Complement Altern

Med. 2013;2013.
87. Tammadon MR, Nobahar M, Hydarinia-Naieni Z, Ebrahimian A, Ghorbani R, Vafaei AA. The effects of valerian on sleep quality, depression, and state anxiety in hemodialysis patients: a randomized, double-blind, crossover clinical trial. Oman Med J. 2021;36(2):e255.
88. Ivanova Stojcheva E, Quintela JC. The effectiveness of Rhodiola rosea L. preparations in alleviating various aspects of life-stress symptoms and stress-induced conditions—encouraging clinical evidence. Molecules. 2022;27(12):3902.
89. Srivastava JK, Shankar E, Gupta S. Chamomile: A herbal medicine of the past with a bright future. Mol Med Rep. 2010;3(6):895–901.
90. Scholey A, Gibbs A, Neale C, Perry N, Ossoukhova A, Bilog V, et al. Anti-stress effects of lemon balm-containing foods. Nutrients. 2014;6(11):4805–21.
91. Bian T, Corral P, Wang Y, Botello J, Kingston R, Daniels T, et al. Kava as a clinical nutrient: promises and challenges. Nutrients. 2020;12(10):3044.
92. Cohen MM. Tulsi-Ocimum sanctum: A herb for all reasons. J Ayurveda Integr Med. 2014;5(4):251.
93. Khan I, Karim N, Ahmad W, Abdelhalim A, Chebib M. GABA-A receptor modulation and anticonvulsant, anxiolytic, and antidepressant activities of constituents from Artemisia indica Linn. Evidence-Based Complement Altern Med. 2016;2016.
94. Arozal W, Louisa M, Soetikno V. Selected Indonesian medicinal plants for the management of metabolic syndrome: Molecular basis and recent studies. Front Cardiovasc Med. 2020;7:82.
95. Petrovska BB. Historical review of medicinal plants' usage. Pharmacogn Rev. 2012;6(11):1.
96. Chaachouay N, Zidane L. Plant-Derived Natural Products: A Source for Drug Discovery and Development. Drugs Drug Candidates. 2024;3(1):184–207.
97. Hossain MF, Islam MA, Akhtar S, Numan SM. Nutritional value and medicinal uses of Monkey Jack fruit (Artocarpus lakoocha). Int Res J Biol Sci. 2016;5(1):60–3.
98. Sritularak B, Tantrakarnsakul K, Lipipun V, Likhitwitayawuid K. Flavonoids with anti-HSV activity from the root bark of Artocarpus lakoocha. Nat Prod Commun. 2013;8(8):1934578X1300800811.
99. Kumar MBS, Kumar MCR, Bharath AC, Kumar HRV, Kekuda TRP, Nandini KC, et al. Screening of selected biological activities of Artocarpus lakoocha Roxb (Moraceae) fruit pericarp. J basic Clin Pharm. 2010;1(4):239.
100. Krishnan K, Mathew LE, Vijayalakshmi NR, Helen A. Anti-inflammatory potential of β-amyrin, a triterpenoid isolated from Costus igneus. Inflammopharmacology. 2014;22:373–85.
101. Han N, Bakovic M. Biologically active triterpenoids and their cardioprotective and anti-inflammatory effects. J Bioanal Biomed S. 2015;12(005):1945–8.
102. Chuanasa T, Phromjai J, Lipipun V, Likhitwitayawuid K, Suzuki M, Pramyothin P, et al. Anti-herpes simplex virus (HSV-1) activity of oxyresveratrol derived from Thai medicinal plant: mechanism of action and therapeutic efficacy on cutaneous HSV-1 infection in mice. Antiviral Res. 2008;80(1):62–70.
103. Puntumchai A, Kittakoop P, Rajviroongit S, Vimuttipong S, Likhitwitayawuid K, Thebtaranonth Y. Lakoochins A and B, New Antimycobacterial Stilbene Derivatives from Artocarpus l akoocha. J Nat Prod. 2004;67(3):485–6.
104. Ko HH, Tsai YT, Yen MH, Lin CC, Liang CJ, Yang TH, et al. Norartocarpetin from a folk medicine Artocarpus communis plays a melanogenesis inhibitor without cytotoxicity in B16F10 cell and skin irritation in mice. BMC Complement Altern Med. 2013;13:1–12.
105. Tsai MH, Liu JF, Chiang YC, Hu SCS, Hsu LF, Lin YC, et al. Artocarpin, an isoprenyl flavonoid, induces p53-dependent or independent apoptosis via ROS-mediated MAPKs and Akt activation in non-small cell lung cancer cells. Oncotarget. 2017;8(17):28342.
106. Sritularak B, Tantrakarnsakul K, Likhitwitayawuid K, Lipipun V. New 2-arylbenzofurans from the root bark of Artocarpus lakoocha. Molecules. 2010;15(9):6548–58.
107. Sikarwar MS, Hui BJ, Subramaniam K, Valeisamy BD, Yean LK, Balaji K. A review on Artocarpus altilis (Parkinson) Fosberg (breadfruit). J Appl Pharm Sci. 2014;4(8):91–7.
108. Bhattacharya E, Dutta R, Chakraborty S, Biswas SM. Phytochemical profiling of Artocarpus lakoocha Roxb. leaf methanol extract and its antioxidant, antimicrobial and antioxidative activities. Asian Pac J Trop Biomed. 2019;9(11):484–92.
109. Li W, Zhou J, Xu Y. Study of the in vitro cytotoxicity testing of medical devices. Biomed reports. 2015;3(5):617–20.
110. Sitorus P, Keliat JM, Asfianti V, Muhammad M, Satria D. A literature review of Artocarpus lacucha focusing on the phytochemical constituents and pharmacological properties of the plant. Molecules. 2022;27(20):6940.
111. Alkhudhayri DA, Osman MA, Alshammari GM, Al Maiman SA, Yahya MA. Moringa peregrina leaf extracts produce anti-obesity, hypoglycemic, anti-hyperlipidemic, and hepatoprotective effects on high-fat diet fed rats. Saudi J Biol Sci. 2021;28(6):3333–42.
112. Tallima H, El Ridi R. Arachidonic acid: physiological roles and potential health benefits–a review. J Adv Res. 2018;11:33–41.
113. Milani DAQ, Davis DD. Pain management medications. In: StatPearls [Internet]. StatPearls Publishing; 2023.

114. Tadesse WT, Hailu AE, Gurmu AE, Mechesso AF. Experimental assessment of antidiarrheal and antisecretory activity of 80% methanolic leaf extract of Zehneria scabra in mice. BMC Complement Altern Med. 2014;14:1–8.
115. Nemeth V, Pfleghaar N. Diarrhea.[Updated 2021 Nov 29]. StatPearls [Internet] Treasure Isl StatPearls Publ. 2022;
116. Mahamud N, Songvut P, Muangnoi C, Rodsiri R, Dahlan W, Tansawat R. Untargeted metabolomics reveal pathways associated with neuroprotective effect of oxyresveratrol in SH-SY5Y cells. Sci Rep. 2023;13(1):20385.
117. Ashok A, Andrabi SS, Mansoor S, Kuang Y, Kwon BK, Labhasetwar V. Antioxidant therapy in oxidative stress-induced neurodegenerative diseases: Role of nanoparticle-based drug delivery systems in clinical translation. Antioxidants. 2022;11(2):408.
118. Nesa ML, Munira S, Bristy AS, Islam MM, Chayan H. Cytotoxic, anti-inflammatory, analgesic, CNS depressant, antidiarrhoeal activities of the methanolic extract of the Artocarpus Lakoocha leaves. World J Pharm Sci. 2015;167–74.
119. Saleem M, Asif A, Akhtar MF, Saleem A. Hepatoprotective potential and chemical characterization of Artocarpus lakoocha fruit extract. ||| Bangladesh J Pharmacol. 2018;13(1):90–7.
120. Raghavendra H, Mallikarjun N, Venugopal T, Anil Kumar HS. Elemental composition, anticariogenic, pancreatic lipase inhibitory and cytotoxic activity of Artocarpus lakoocha Roxb pericarp. Int J Drug Dev Res. 2012;4(1):330–6.
121. Preyavichyapugdee N, Sangfuang M, Chaiyapum S, Sriburin S, Pootaeng-on Y, Chusongsang P, et al. Schistosomicidal activity of the crude extract of Artocarpus lakoocha. Southeast Asian J Trop Med Public Heal. 2016;47:1–15.
122. Islam S, Shajib MS, Rashid R Bin, Khan MF, Al-Mansur MA, Datta BK, et al. Antinociceptive activities of Artocarpus lacucha Buch-ham (Moraceae) and its isolated phenolic compound, catechin, in mice. BMC Complement Altern Med. 2019;19:1–13.
123. Seiki S, Frishman WH. Pharmacologic inhibition of squalene synthase and other downstream enzymes of the cholesterol synthesis pathway: a new therapeutic approach to treatment of hypercholesterolemia. Cardiol Rev. 2009;17(2):70–6.
124. Pandey S, Poonia A. Monkey Jackfruit (Artocarpus lakoocha Roxb.): The Lesser-Known Fruit. Indian Food Ind. 2021;6:38–45.
125. Duarte Galhardo de Albuquerque RD, Mahomoodally MF, Lobine D, Suroowan S, Rengasamy KRR. Botanical products in the treatment and control of schistosomiasis: Recent studies and distribution of active plant resources according to affected regions. Biology (Basel). 2020;9(8):223.
126. Shohan FM, Baroi JA, Bhowmik P, Rupak MAHB, Ullah MR, Siddiq MAB, et al. An Evaluation of Anti-Hyperlipidemic Activity of Rubus idaeus on High Fat Induced Rat Model with Safety Profile Analysis. Asian J Res Cardiovasc Dis. 2023;5(1):163–70.
127. Crichton GE, Alkerwi A. Physical activity, sedentary behavior time and lipid levels in the Observation of Cardiovascular Risk Factors in Luxembourg study. Lipids Health Dis. 2015;14:1–9.
128. Wongon M, Limpeanchob N. Inhibitory effect of Artocarpus lakoocha Roxb and oxyresveratrol on α-glucosidase and sugar digestion in Caco-2 cells. Heliyon. 2020;6(3).
129. Tripathi K, Kumar P, Kumar R, Saxena R, Kumar A, Badoni H, et al. Efficacy of jackfruit components in prevention and control of human disease: A scoping review. J Educ Health Promot. 2023;12(1):361.
130. Oli B Sen, Rauniyar A, Chad D. A review on the significance of the medicinal plant Acorus calamus. Asian J Pharmacogn. 2021;5(3):30–8.
131. Nansereko S, Muyonga J, Byaruhanga YB. Influence of drying methods on jackfruit drying behavior and dried products physical characteristics. Int J Food Sci. 2022;2022.
132. Sairam S, Urooj A. Safety evaluation of Artocarpus altilis as pharmaceutical agent in wistar rats. J Toxicol. 2014;2014.
133. Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World psychiatry. 2010;9(3):155.
134. Wainwright SR, Galea LAM. The neural plasticity theory of depression: assessing the roles of adult neurogenesis and PSA-NCAM within the hippocampus. Neural Plast. 2013;2013.
135. Baliyan S, Mukherjee R, Priyadarshini A, Vibhuti A, Gupta A, Pandey RP, et al. Determination of antioxidants by DPPH radical scavenging activity and quantitative phytochemical analysis of Ficus religiosa. Molecules. 2022;27(4):1326.
136. Young SN. How to increase serotonin in the human brain without drugs. J psychiatry Neurosci JPN. 2007;32(6):394.
137. Shirayama Y, Chaki S. Neurochemistry of the nucleus accumbens and its relevance to depression and antidepressant action in rodents. Curr Neuropharmacol. 2006;4(4):277–91.
138. Juárez Olguín H, Calderón Guzmán D, Hernández García E, Barragán Mejía G. The role of dopamine and its dysfunction as a consequence of oxidative stress. Oxid Med Cell Longev. 2016;2016.
139. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology. 2010;35(1):4–26.
140. Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and

alerting. Neuron. 2010;68(5):815–34.
141. Danhauer SC, Legault C, Bandos H, Kidwell K, Costantino J, Vaughan L, et al. Positive and negative affect, depression, and cognitive processes in the Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) Trial. Aging, Neuropsychol Cogn. 2013;20(5):532–52.
142. Remes O, Mendes JF, Templeton P. Biological, psychological, and social determinants of depression: a review of recent literature. Brain Sci. 2021;11(12):1633.
143. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence. 2012;369–88.
144. Frank D, Gruenbaum BF, Zlotnik A, Semyonov M, Frenkel A, Boyko M. Pathophysiology and current drug treatments for post-stroke depression: a review. Int J Mol Sci. 2022;23(23):15114.
145. Steimer T. The biology of fear-and anxiety-related behaviors. Dialogues Clin Neurosci. 2002;4(3):231–49.
146. Yeo XY, Cunliffe G, Ho RC, Lee SS, Jung S. Potentials of neuropeptides as therapeutic agents for neurological diseases. Biomedicines. 2022;10(2):343.
147. Jewett BE, Sharma S. Physiology, GABA. 2018;
148. Tremblay R, Lee S, Rudy B. GABAergic interneurons in the neocortex: from cellular properties to circuits. Neuron. 2016;91(2):260–92.
149. Shaye H, Stauch B, Gati C, Cherezov V. Molecular mechanisms of metabotropic GABAB receptor function. Sci Adv. 2021;7(22):eabg3362.
150. Bryson A, Reid C, Petrou S. Fundamental neurochemistry review: GABAA receptor neurotransmission and epilepsy: principles, disease mechanisms and pharmacotherapy. J Neurochem. 2023;165(1):6–28.