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Review Article

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A Review on Receptor in the Brain Responsible for Anxiety and List of Higher Plants for Treatment Anxiety

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Abstract

Anxiety is defined as nervousness and an inability to relax. Some level of anxiety is normal in human beings; however, excessive anxiety can interfere with relationships, sleeping patterns, eating habits, work, school, and all areas of life. Anxiety can take several forms, including phobias, obsessive-compulsions, and panic attacks, and it is often associated with depression. Anxiety is often found in people with psychotic symptoms, especially those who are paranoid. There are lots of plants and receptors which are responsible for antianxiety activity. The review is revealed that to enlist the antianxiety plants and receptor which is responsible for anxiety.

Key words: Anxiety, Receptors and Higher Plants.

Contents

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1. Introduction

Anxiety is a Central Nervous System disorder [1-2]. Anxiety is a common emotional phenomenon in humans [3].Anxiety is an emotional state, unpleasant in nature and is associated with uneasiness, discomfort and concern or fear about some defined or undefined future threat [4].Anxiety is considered to be a normal reaction to stress and is characterized by heart palpitations, fatigue, nausea and shortness of breath. Anxiety is the most common mental illness affecting one eighth of the total population and has become a very important area of research in psychopharmacology in the current decade [5].Anxiety disorders are psychiatric disorders affecting nearly 25% of the adult population at some point in their life. The prevalence of anxiety disorders is 30.5% and 19.2% in women and men respectively. The prevalence of anxiety disorders is remarkably high in young people. Children aged 7 to 11 years reported a 15.4% prevalence rate of anxiety disorders. A survey has also stated that less than 14% of people with such psychiatric disorders receive treatment [6]. Anxiety can aggravate many physical and mental ailments and also impede recovery from any other problems. Classically, anxiety is distinguished into them 'state' and the 'trait' anxiety. "State anxiety" is anxiety a subject experiences at a particular moment and is increased by the presence of

an anxiogenic stimulus. In contrast, "trait anxiety" does not vary from moment to moment and is considered to be an "enduring" feature of an individual [7-9]

Physiology of Anxiety

The human brain is the centre of human nervous system and is a highly complex organ. The part of the brain that triggers a response to danger is the Locus ceruleus and the area of the brain responsible for the acquisition and expression of fear conditioning is the Amygdala [12]. Once the neurotransmitters pick up over activity/hyperactivity in the locus ceruleus, the amygdala senses danger and instructs us to run from danger. Hence, once the amygdala gets activated it sends an alarm to the heart to beat faster, breathing to become rapid and in turn activates all the biological components of fight/flight response.

The symptoms experienced during an anxiety attack include:

- Rapid heartbeat and rapid breathing
- Twitching or trembling
- Muscle tension
- Headaches
- Sweating
- Dry mouth and difficulty in Swallowing and Abdominal pain

Sometimes other symptoms accompany anxiety, such as:

- Blurred vision and Dizziness
- Diarrhoea or frequent need to urinate
- Irritability, including loss of temper
- Sleeping difficulties and nightmares
- Decreased concentration and
- Sexual problems.

All these physical symptoms are felt when one is anxious or having a panic attack and are part of a system that is designed to keep one safe and do not cause any harm. They cause a problem only when they occur in response to situations where one is not physically threatened.

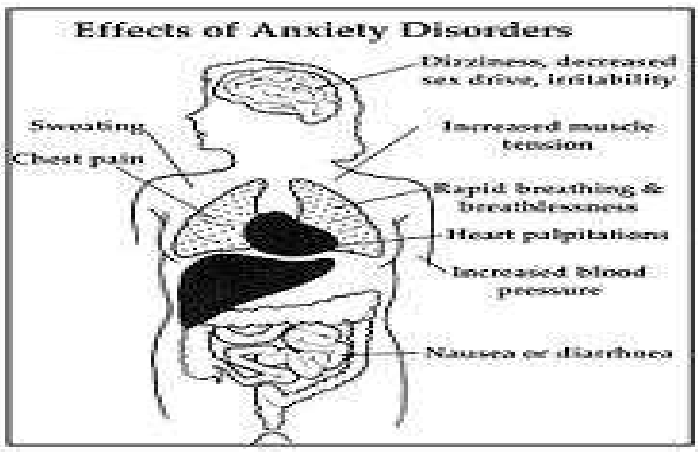

Figure 1: Symptoms of anxiety

Classification of antianxiety drugs [13]:

The anxiolytic-sedative drugs differ markedly from antipsychotics, and more closely resemble sedative-hypnotics. They

- Have no therapeutic effect to control thought disorder of schizophrenia.
- Do not produced extrapyramidal side effects.
- Have anti-convulsion property
- Produce physical dependence and carry abuse liability.
- Do not selective block conditioned avoid dance response in animals.

Table 1. Classification of Antianxiety drugs

Benzodiazepines	
Diazepam	Quickly absorbed, Produces brief initial phase of strong action followed by prolonged milder effect due to a two phase plasma concentration decay curve. It is preferred in acute panic state and anxiety associated with organic disease.
Chlordiazepoxide	It was first BZD to be used clinically, oral absorption is slow, and produces smooth long lasting effect, preferred in chronic anxiety state, combined with other drugs in psychosomatic diseases. It has poor anticonvulsant action.
Oxazepam	It is slowly absorbed, being relatively polar. Its penetration in brain is also slow. It may preferred in the elderly and in those with liver disease because its hepatic metabolism is not significant and duration of action is short. It has been mainly used in short lasting anxiety state.
Lorazepam	Has slow oral absorption, being less lipid soluble than diazepam, its rate of entry in brain is slower. It is sedative and capable of producing marked amnesia when given i.v. It has been preferred for short-lived anxiety states, obsessive-compulsive neurosis and tension syndromes, as well as psychosomatic diseases.
Alprazolam	High potency anxiolytic BZD which in addition has some mood elevating action in mild depression. It is particularly useful in anxiety associated with depression.
Azapirones	
Buspirone	First azapirones, relieves mild to moderate generalized anxiety but ineffective in severe case such as those showing panic reaction and in OCD. Has weak dopamine D_2 blocking action but no antipsychotic or extrapyramidal effects.
Sedative Antihistaminics	
Hydroxyzine	H_1 antihistaminic with sedative, anti-emetic, anti-muscarinic and spasmodic properties. It is claimed to have selective anxiolytic action but accompanying sedative is quite marked, May be used in reactive anxiety or that associated with marked autonomic symptoms.
β-Blocker	
Propranolol	Many symptoms of anxiety (palpitation, rise in BP, shaking, tremor, gastrointestinal hurrying) are due to sympathetic over activity and these symptoms reinforce anxiety. They do not effect psychological symptoms like-worry, tension, fear, but are valuable in acutely stressful situation.

Mechanism of action of Anxiety:

Anxiety is recognised as one of the most important emotional processes with firm neurobiological roots. The neurochemistry of anxiety although not well understood has emerged to be a major area of research leading to new approaches in the treatment of anxiety. Anxiety is caused due to too many or too few neurotransmitters in the brain. Brain synthesizes several neurotransmitters such as acetylcholine, adrenaline, dopamine, endorphins, serotonin, gamma amino butyric acid, glutamate etc. Most information has come from studying the action of anxiety-reducing or anxiolytic drugs. The evidences suggest anxiety to be caused by dysfunction of one or more neurotransmitters and their receptors. The major thrusts of current work dealing with anxiety disorders have centered on the gamma amino butyric acid mechanisms, the serotonergic system, noradrenergic mechanisms and neuropeptides [10]. New evidences suggest a role for adenosine and cholecystokinin in the development of anxiety; drugs interactions with these neurotransmitters also may have anxiolytic effects.

2. Receptor in the Brain Responsible for Anxiety [14]

A. **Benzodiazepine Receptors:** BDZ-Rs; The specific antagonist of the BDZ-R, RO 15-1788, blocks the anxiolytic effects while the agonists or partial agonists potentiate the anxiolytic effects e.g.: Flavonoids.

B. **Drawback of benzodiazepines**:BDZs is often associated with tolerance development and withdrawal symptoms, which poses a risk of relapse upon discontinuation.

C. **Serotonin receptors (5-hydroxytriptamine):**5-hydroxytryptamine$_1$A (5-HT$_1$A); 5-HT$_1$Areceptors are located at the presynaptic and postsynaptic sites.The somato-dendritic autoreceptor, when activated by systemic stimulation, is believed to exert anxiolytic-like effects and to reduce 5- HT release both in the cell body and in the terminal regions of the serotonergic neurons. The other 5-HT$_1$A receptor is localized postsynaptic to the serotonergic neurons in the hippocampus, septum, amygdala, and cortex, where it increases signal transfer, which leads to an inhibition of the firing activity. Thus (5-HT$_1$A) receptor is viewed as a relevant target for the treatment of psychiatric disorders, notably anxiety and depression.

D. **5-HT_3 receptor:** 5-HT_3 receptor antagonism contributes the anxiolytic effect.Selective 5-HT reuptake inhibitors (SSRIs).y-amino butyric acid receptor (GABA): $GABA_A$receptor; GABA is a major inhibitory transmitter in the central nervous system. The g-amino butyric acid type A ($GABA_A$) receptor, the chloride ion channel complex and the central benzodiazepine receptors located on the neuronal membranes within this complex have been suggested to play an important role in the regulation of the stress and anxiety states. $GABA_A$receptors possess binding sites for several drugs, such as anxiolytics, anticonvulsants, general anaesthetics, barbiturates, ethanol, and neurosteroids, which are known to elicit at least some of their pharmacological effects via the $GABA_A$ receptors.

E. **(H-receptor):** Histamine receptor plays an important role in anxiety and other CNS disorder With reference to H_1, H_2, H_3receptors.

F. **Opioid receptors:**Endogenous opioid peptides such as enkephalins, dynorphins and endo-morphins, and their receptors have been found in the peripheral and central nervous systems. Various bioactive peptides are known to be derived from enzymatic digests of food proteins. Among them, several bioactive peptides derived from food proteins such as bovine casein and wheat gluten show analgesic activities through opioid receptors.Three kinds of opioid receptors are known: μ, delta and k receptors. In general, opioids were reported to impair learning and memory and they are also play role in anxiety and antianxiety.

G. **Adenosine A_1 receptors:**Adenosine functions as a neuromodulator in the central nervous system (CNS), acting through cell-surface receptors. Adenosine receptors were recognised on the basis of the ability of caffeine to act as an antagonist at A_1 and A_2 receptors. At the moment, four adenosine receptor subtypes (A_1, A_2A, A_2B and A_3) have been cloned and characterised from several mammalian species, including humans and mice, and they all belong to the G-protein coupled receptor (GPCR) family. In addition, many studies using selective adenosine receptor agonists and antagonists have demonstrated that adenosine A_1receptors, localised in brain areas essential for motor control such as the striatum, the cerebellum and the motor cortex, are the primary site where adenosine modulates the incoordination induced by ethanol. Adenosine A_1 receptor agonist shows an anxiolytic-like profile or receptors modulate anxiolytic-like actions of ethanol.

H. **Dopaminergic Receptor:** (D_2) receptors; they have played role in psychological diseases and may have the role in anxiety.

I. **Somodendritic autoreceptors:**GAC treatment on behavioural perturbations in anxiety models may involve the somodendriticautoreceptorsof raphae nuclei, leading to decreased central serotonergic and augmented catecholaminergicfunction. Our fndings reflect the positive attributes ofginkgolic acid conjugates in the actions of Ginkgo biloba [20].

J. **Adrenergic receptors:**These receptors also play a key role in the nervous system. They might be a co receptor for the anxiety. CCK receptor: Cholecystokinin (CCK) was first identified (initially characterized as a 33-amino-acid long peptide) in the gastrointestinal tract and later it was found to be one of the most widely distributed peptides in the brain where it acts as a neurotransmitter.

K. **H_1, H_2, H_3 receptors:**Brain histamine localizes in both histamine neurons and non-neuronal mast cells, with the mast cells storing approximately 50% of whole brain histamine levels. Histaminergic neurons project to almost all regions of the mammalian brain from the tuberomammillary nucleus of the posterior hypothalamic region. Clinically effective anxiolytic drugs, diazepam, benzodiazepines and buspirone,serotonin (5-HT_1A) agonists have been found to decrease turnover rate of brain histamine in mice and rats. These findings suggest that histaminergic system in the brain plays an important role in the regulation of anxiety. Furthermore, Imaizumi and Onodera have demonstrated that anxiety-like behavioral activity is induced or enhanced by the combined administration of thioperamide, a neuronal histamine releaser having inhibitory effect of histamine H_3autoreceptors, with zolanitidine, a histamine H_2 receptor antagonist. In addition it has also demonstrated that anxiety like behavioral activity is also induced by co-injection of non-neuronal selective mast cell histamine releaser, Compound 48/80, with a histamine H_2 receptor antagonist, cimetidine. These neuronal and non-neuronal histaminergics induced experimental anxiety models in mice are useful for assessing the effect of any drug on brain histaminergic system in a state of anxiety.

L. **CCK receptor subtypes:**CCK_1 and CCK_2: High densities of CCK-binding sites in several areas including the cerebral cortex, striatum, olfactory bulb and tubercle, and certain amygdaloidnuclei. Moderate levels were observed in the hippocampus, claustrum, substantianigra, superior colliculus, periaqueductal gray matter, and pontinenuclei. Low densities were reported in several thalamic and hypothalamic nuclei and in the spinal cord. With the advent of specific radioligands that could differentiate between the two types of CCK receptors, it has become apparent that the distributions of $CCK_1$and CCK_2/gastrin receptors within the CNS are overlapping and yet distinct. CCK_2 receptors are the predominant subtype in the CNS, with CCK1 receptors restricted to some discrete nuclei. The widespread distribution of CCK_2 receptors in the CNS is consistent with the diverse functions attributed to neural CCK, including the regulation of feeding (satiety),

the controlof learning and memory, behavioral expression ofanxiety, mediation of pain, cardiovascular regulation, neuroendocrine control, osmotic stress, neuropsychiatric disorders (such as panic attacks) and modulation of dependence and withdrawal processes as well as functions controlled by the dopaminergic, serotonergic, and opioid systems.

3. Higher Plants for Anxiety

From the ancient times immemorial plants have been used by mankind for their relieving and therapeutic abilities and still we rely on their healing properties. Plants having active constituent have a direct pharmacological action on our body including various organs. One such major organ is brain, so complex that still only few drugs are approved by drug authorities for ailments like neuronal disorders[15]. Ayurvedic had developed certain dietary and therapeutic measures to delay ageing and rejuvenating whole functional dynamics of the body organs. This revitalization and rejuvenation is known as the 'Rasayanachikitsa' (rejuvenation therapy) [16]. There are lots of herbal plants who have anti-anxiety activity which are shown below

Table 2. Herbal remedies and their active constituents which are useful for anti-anxiety activity

S.no	Plant name	Family	Plant Part used	Active constituents
1	*AbiespindrowRoyle*	Pinaceae	fresh leaves	Yield 0.25% oil which contains α pinene, (14.7%),llimonene (10.6%),T3carene(11.8%),dipentene(8.4%),lbornyl acetate (15.7%) and l-codinene (9.9%).
2	*Achilleamillefoliu m.*	Asteraceae	The herb	The herb contains an alkaloid achilleine, isovaleric acid, salicylic acid, asparagines, sterols, flavonoids, tannins, choline and trigonelline and Coumarins. Flowers yield an essential oil azulene. Presence of choline has been shown to impart hypotensive effect.
3	*Angelica sinensis*	Apiaceae	fresh leaves	The essential oil contains lingustilide.
4	*Albizzialebbeck.*	Fabaceae	fresh leaves	The leaves have been shown to contain caffeic acid, alkaloids, kaempferol and quercetin.[44]
5	*Albizzia julibrissinDurazz*	Fabaceae	fresh leaves	Two flavonol glycosides quercitrin and isoquercitrin
6	*Apocynumvenetum .*	Apocynaceae	leaves and flowers	The chemical constituents of the leaves and flowers include ionone glucosides named apocynoside I and II, several compounds have been isolated and include kaempferol, kaempferol 3-0-beta-D-glucoside, vanillic acid, baimaside, daucosterol.
7	*Azadirachtaindica.*	Meliaceae	seeds	The chemical compounds isolated from Neem oil include nimbin, nimbinin, and nimbidin. The seeds contain a complex secondary metabolite azadirachtin
8	*Bacopamonnieri*	Scrophulariaceae	Leaves	Major chemical constituents found in B.monnieri are saponins, triterpenes&dammoranes such as bacosides A, B & C, bacosaponines D, E & F.
9	*Cannabis sativa*	Cannabaceae	Leaves	Cannabidiol an cannabinoid exerts anti-anxiety effects
10	*Centellaasiatica*	Apiaceae	Whole plant	The essential oil includes triterpeniodsaponins such as asiaticoside (got from fresh leaves, a glucoside), brahmoside and thankuniside, alkaloids (hydrocotyline, isolated from the dried plant) an some bitter principles
11	*Citrus sinensis*	Rutaceae	Leaves	The chemical constituents include monoterpenes, sesquiterpenes,flavonoids, caretenoids, alkaloids, coumarins and vitamin c.

12	*Crocus sativus L. (Saffron/kesar)*	Iridaceae	Whole plant	Saffron contains more than 150 volatile and aroma yielding Compounds. Among the non-volatile active compounds include carotenoids like zeaxanthine, lycopene and various α and β-carotenes. α-crocin (a digentiobiose ester of carotenoid crocetin) imparts the Golden yellow-orange colour. Safranal and picrocrocin give saffron much of its distinctive aroma.
13	*Erythrinavariegata*	Fabaceae	Leaves, stems, seeds.	The chemical constituents include alkaloids, flavonoids and terpenes.The leaves and stems contain the alkaloid erythrinaline. The seeds yield the alkaloid hypaphorineansaponin-migarrhin
14	*Euphorbia neriifolia*	Euphorbia ceae	Whole Plant	The phytochemical constituents include a variety of triterpenes like nerifolione, euphol, euphorbol and others from latex, bark, root, whole plant and leaf. Anthocyanins like delphin and tulipanin and diterpenes were isolated from the bark and roots.[92] The phytochemical study showed the presence of steroidal saponins, reducing sugar, tannins, and flavonoids in the crude leaf extract.
15	*Ginkgo biloba*	Ginkgoace ae	Leaves	The phytoconstituents include flavonoids, glycosides and terpenoids(ginkgolides, bilobalides)
16	*Matricariachamo milla*	Asteraceae	flowers	The flowers possess 1-2% volatile oils containing alpha-bisabolol, alpha-bisabolol oxides A & B, and matricin (usually converted to chamazulene). Other active constituents include the bioflavonoids apigenin, luteolin, and quercetin. These active constituents contribute to the myriad health benefits of the plant.
17	*Melissa officinalis*	Lamiaceae		It contains rosmarinic acid, phenolic acids, triterpenes, monoterpene glycosides, flavonoids and the essential oil contains citronellal, citral,germacrene and caryophyllene
18	*Nepetacataria*	Lamiaceae	Whole plant	The principal constituents of the oil are nepetalactone and nepetalic Acid, nepetalic anhydride, β-caryophyllene and an ether and ester.
19	*Rauvolfiaserpentin a*	Apocynac eae.	Root, stems, leaves	It contains a variety of bioactive compounds including reserpine (the most important alkaloid present in the root, stem & leaves of the plant),ajmaline,deserpidine, rescinnamine,reserpinine, sarpagine,serpentinine.
20	*Santalum album*	Santalacea e	Leaves	The phytoconstituents include sesquiterpenes like santalene, farnesene and alcohols like santalol.
21	*Salvia officinalis*	Lamiaceae	Leaves	The active constituents are present in the essential oil, which contains cineole, borneol, and thujone
22	*Sesbaniagrandiflor a*	Fabaceae	Leaves	Triterpenes show anti-anxiety effects
23	*Tilia Americana*	Malvaceae	Leaves	The active constituents include flavonoids, volatile oils, mucilaginous constituents and tannins.
24	*Valerianaofficinali s*	Valerianac eae	Leaves	The chemical constituents include alkaloids, lignans, glycosides, volatile & non-volatile

				constituents, aminoacids, caffeic acid, chlorogenic acid, beta-sitosterol, methyl 2-pyrrolketone, choline, tannins, gum and a resin.
25	*Withaniasomnifera*	Solanacea e.	Herb, roots	The main constituents are alkaloids and steroidal lactones. Among the various alkaloids withanine is the main constituent. The steroidal lactones are commonly called withanolides and are the most important bio-active components present in roots that account for the multiple medicinal properties of the herb. Two acyl sterylglucoside namely sitoindoside VII and sitoindoside VIII have been isolated from root. The glycowithanolides exhibited significant anxiolytic activity.

4. Conclusion

Thus, higher plants/herbal mixtures that act synergistically promise to provide aneffective remedy for anxiety. However, studies targeting plants with this type of bioactivity represent only a very small percentage of those investigations. In a review of the existing literature, itappears that plants with molecules that produce thiskind of activity are increasingly attractive targets forthe development of new drugs. The review covered all aspects of receptors which is responsible for anxiety and also traditional medicines and revealed that a detailed study isrequired to explore the plants and their uses to treatserious complication of central nervous system.

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