Nature: Anxiolytics in the Lap of Nature

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Abstract

Background
A large number of populations depend on traditional practitioners, who in turn are dependent on medicinal plants, to meet their primary health care needs. Today "traditional medicine," characterized by the use of herbs and other natural products, still remains a regular component of health care in the world.

Aims
To explore the natural and traditional medicines in relation to anxiolytics

Method
Electronic literature searches were conducted using the following databases: AMED, Cinahl, Embase, Elsevier, Medline, PsychInfo, PubMed (all from inception to August 2004), Google scholar and many important text books. The terms used for the electronic searches were limited to important receptors and neurotransmitters present in brain which help to modulate anxiety, plants with neurological bioactivity and bioactive compounds with respective receptors and mechanism of action along with few chemical structures involved in the treatment of anxiety.

Results
Systematic review were located with the above search strategy

Discussion and conclusion
The review covered all aspects of traditional medicines and revealed that a detailed study is required to explore the plants and their uses to treat serious complication of central nervous system. Nature and tradition both is wonder agent of God for the treatment of diseases. The review will pave a way for new drug search.

Keywords: Anxiety, Anxiolytics, Traditional medicines, Neurotransmitters.

Introduction

There is a high prevalence of mental and neurological disorders worldwide; these account for 13% of total disability adjusted life years (DALYs) lost due to all diseases and injuries in the world. WHO estimates that 450 million persons suffer from mental illness. Anxiety is widespread, with lifetime prevalence rates ranging from 13.6 to 28.8% in Western countries. Individuals aged between 10 and 25 years are at highest risk for developing an anxiety condition. These conditions are among the most common mental diseases, and their prevalence and disease course are reasonably well documented. On the other hand, WHO launched its first-ever comprehensive traditional medicine strategy in 2002 with the objective of recognizing traditional medicine in the treatment of public health problems [1]. Anxiety is a feeling of uneasiness, uncertainty or fear, in response to a real or imagined danger. The body responds to anxiety by releasing a number of "stress" hormones, like adrenaline and cortisol, which have an effect on almost every organ in the body. Mild forms of anxiety caused by emotional conflict or life stress are common and unproblematic. Anxiety disorders are a group of conditions in which the feelings of anxiety are not associated with a real or appropriate threat, or are much more intense and long lasting than they should be. People feel frightened and distressed for no apparent reason. This condition can paralyze the individual into inactivity or withdrawal, and can dramatically reduce productivity and significantly diminish a person's quality of life. Anxiety disorders are common - nearly 25% of people will experience anxiety disorders at some time in their lives. Physical symptoms of anxiety disorders are due to released stress hormones. These may increase blood pressure, cause heart palpitations, chest pain, rapid breathing or breathlessness, sweating, increased muscle tension or irritability. Intestinal blood flow decreases, resulting in nausea or diarrhea. There is often a decreased sex drive. Children may also have a fear of being away from the family, a refusal to go to school, a fear of strangers, a fear of falling asleep or have recurrent nightmares. Specific anxiety disorders each have their own particular pattern of symptoms and additional behavioural characteristics Figure 1.

Depression and Anxiety

The simultaneous occurrence of depression and anxiety is very common. Figures show that between 60% and 90% of people with depression also have symptoms of anxiety. The combination is well recognized and can significantly increase the disability and disruption of normal function suffered by the patient. The anxiety associated with depression can take many forms including panic attacks, obsessive...
compulsive disorder, post-traumatic stress disorder, social anxiety disorder or a generalized anxiety disorder. Fortunately medication is available which can effectively relieve both depression and anxiety.

Anxiety is different type like Panic Disorder, Phobias, Post-Traumatic Stress Disorder (PTSD), Obsessive-Compulsive Disorder (OCD), Generalised Anxiety Disorder (GAD).

Anxiety disorders in a modern society have relatively high prevalence affecting between 10 and 30% of the general population with considerable financial resources. Excessive anxiety can debilitate and damage the quality of life. In the clinical treatment of anxiety benzodiazepines, GABA receptor agonist and buspirone, 5-HT1A receptor agonist, are mainly prescribed as first choice treatment. Chronic administration of benzodiazepines, however result in physical dependence such as sedation, myelo relaxation, ataxia, amnesia and pharmacological dependence. More over buspirone also results in dizziness, headache, nervousness, paresthesia, diarrhea, excitation and sweating as adverse. Therefore, research has been conducted to identify safer, more specific medications possessing anxiolytic effect without the complications. In past few years, several herbal medicines have been used for the management of anxiety in the world [2].

Methods

Electronic literature searches were conducted using the following databases: AMED, Cinahl, Embase, Elsevier, Medline, PsychInfo, PubMed (all from inception to August 2004), Google scholar and many important text books. The terms used for the electronic searches were limited to important receptors and neurotransmitters present in brain which help to modulate anxiety, plants with neurological bioactivity and bioactive compounds with respective receptors and mechanism of action along with few chemical structures involved in the treatment of anxiety.

Results

Systematic review was located with the above search strategy. Nature and tradition in relation to anxieolitics

4.1 Neurotransmitter involve in the CNS disorder especially in anxiety

There are approximately 50 neurotransmitters identified. There are billions of nerve cells located in the brain, which do not directly touch each other. Nerve cells communicate messages by secreting neurotransmitters. Neurotransmitters can excite or inhibit neurons (nerve cells). Some common neurotransmitters are acetylcholine, norepinephrine, dopamine, serotonin and gamma aminobutyric acid (GABA). Acetylcholine and norepinephrine are excitatory neurotransmitters while dopamine, serotonin, and GABA are inhibitory. Each neurotransmitter can directly or indirectly influence neurons in a specific portion of the brain, thereby affecting behaviour. Cholecystokinin (CCK) is a neurotransmitter in the brain closely related to anxiety.

4.2 Mechanism of impulse transmission

Neurotransmitters are chemicals that transmit messages from one nerve cell (neuron) to another. The nerve impulse travels from the first nerve cell through the axon—a single smooth body arising from the nerve cell—to the axon terminal and the synaptic knobs. Each synaptic knob communicates with a dendrite or cell body of another neuron, and the synaptic knobs contain neurovesicles that store and release neurotransmitters. The synapse lies between the synaptic knob and the next cell. For the impulse to continue traveling across the synapse to reach the next cell, the synaptic knobs release the neurotransmitter into that space, and the next nerve cell is stimulated to pick up the impulse and continue it. Any changes in its normal function may cause CNS disorders Figure 2.

The mechanism of action and localization of neurotransmitters in the brain has provided valuable information concerning the cause of many mental disorders, including clinical depression and chemical dependency, and in researching medications that allow normal flow and movement of neurotransmitter molecules.

4.3 Noradrenaline; Dysregulation of norepinephrine in depression and adaptation with treatment:

Noradrenaline is one of the neurotransmitter in the brain and its proper regulation helps to normalize the brain. Any change in regulation leads to psychological disorders Figure 2.

4.4 Role of Norepinephrine in Mood Disorders:

Norepinephrine is highly involved in mood disorders Figure 3 and 4.
4.4.1 Receptor in the brain responsible for anxiety/antianxiety

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.

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

Serotonin receptors (5-hydroxytryptamine):
- 5-hydroxytryptamine1A (5-HT1A); 5-HT1A receptors are located at the presynaptic and postsynaptic sites. The somatodendritic 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-HT1A receptor is localized postsynaptically 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-HT1A) receptor is viewed as a relevant target for the treatment of psychiatric disorders, notably anxiety and depression.

5-HT3 receptor:
5-HT3 receptor antagonism contributes the anxiolytic effect. Selective 5-HT reuptake inhibitors (SSRIs); γ-aminobutyric acid receptor (GABA): GABA receptor; GABA is a major inhibitory transmitter in the central nervous system. The γ-aminobutyric acid type A (GABAA) 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. GABAA receptors possess binding sites for several drugs, such as anxiolytics, anticonvulsants, general anesthetics, barbiturates, ethanol, and neurosteroids, which are known to elicit at least some of their pharmacological effects via the GABAA receptors.

GABAA-benzodiazepine receptorHistamine receptor (H-receptor):
Histamine receptor plays an important role in anxiety and other CNS disorder With reference to H1, H2, H3 receptors.

Opioid receptors:
Endogenous opioid peptides such as enkephalins, dynorphins and endomorphins, 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, δ, and κ receptors. In general, opioids were reported to impair learning and memory and they are also play role in anxiety and antianxiety.

Adenosine A1 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 A1 and A2 receptors. At the moment, four adenosine receptor subtypes (A1, A2A, A2B and A3) 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 A1 receptors, 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 A1 receptor agonist shows an anxiolytic-like profile or receptors modulate anxiolytic-like actions of ethanol.

Dopaminergic Receptor: (D2) receptors; They have played role in psychological diseases and may have the role in anxiety.

Somatodendritic autoreceptors:
GAC treatment on behavioural perturbations in anxiety models may involve the somatodendritic autoreceptors of raphae nuclei, leading to decreased central serotonergic and augmented catecholaminergic function. Our findings reflect the positive attributes of ginkgolic acid conjugates in the actions of Ginkgo biloba [20].

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.

H1, H2, H3 receptors:
Brain histamine localizes in both histamine neurons and non-neuronal mast cells, with the mast cells storing approxi-mately 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-HT1A) 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 H3autoreceptors, with zolantidine, a histamine H2 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 H2receptor 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.

Role of histaminergic system in anxiety: Role of histaminergic system in anxiety showed in Table 1.

**CCK receptor subtypes:**

CCK1 and CCK2: High densities of CCK-binding sites in several areas including the cerebral cortex, striatum, olfactory bulb and tubercle, and certain amygadaloid nuclei. Moderate levels were observed in the hippocampus, claustrum, substantia nigra, superior colliculus, periaqueductal gray matter, and pontine nuclei. 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 CCK1 and CCK2/gastrin receptors within the CNS are overlapping and yet distinct. CCK2 receptors are the predominant subtype in the CNS, with CCK1 receptors restricted to some discrete nuclei. The widespread distribution of CCK2 receptors in the CNS is consistent with the diverse functions attributed to neural CCK, including the regulation of feeding (satiety), the control of learning and memory, behavioral expression of anxiety, 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.

4.5 Tradition and nature helps to treat diseases

During the last decade, there has been a growing interest in traditional and alternative systems of medicine in many developed countries. Medicinal plants are the oldest known health-care products. Their importance is still growing although it varies depending on the ethnomedical, medical and historical background of each country. Herbal medicines are assuming greater importance in the primary health care of individuals and communities in many developed as well as developing countries and there has been an increase in international trade in herbal medicines. India has 45000 diverse plant species spread over 16 different agro-climatic zones, 10 vegetation zones, 25 biotic provinces and 426 habitats of specific spieces. Besides, India has up to 18,000 flowering plants, 2500 algae, 23,000 fungi, 1600 types of lichen and 1,800 varieties of bryophytes. Of this vast quantum around 15,000 to 20,000 are of medicinal value, but out of this only, 7,000 to 7,500 plants are used by traditional medicine systems in India.The use of natural products with therapeutic properties is as ancient as human civilization and, for a long time, mineral, plant and animal products were the main sources of drugs. The Industrial Revolution and the development of organic chemistry resulted in a preference for synthetic products for pharmacological treatment. The reasons for this were that pure compounds were easily obtained, structural modifications to produce potentially more active and safer drugs could be easily performed and the economic power of the pharmaceutical companies was increasing. Furthermore, throughout the development of human culture, the use of natural products has had magical-religious significance and different points of view regarding the concepts of health and disease existed within each culture. Obviously, this approach was against the new modus Vivendi of the industrialized western societies, in which drugs from natural resources were considered either an option for poorly educated or low income people or simply as religious superstition of no pharmacological value. However, even if we only consider the impact of the discovery of the penicillin, obtained from micro-organisms, on the development of anti-infection therapy, the importance of natural products is clearly enormous. About 25% of the drugs prescribed worldwide come from plants, 121 such active compounds being in current use. Of the 252 drugs considered as basic and essential by the World Health Organization (WHO), 11% are exclusively of plant origin and a significant number are synthetic drugs obtained from natural precursors. Examples of important drugs obtained from plants are digoxin from Digitalis spp., quinine and quinidine from Cinchona spp., vincristine and vinblastine from Catharanthus roseus, atropine from Atropa belladonna and morphine and codeine from Papaver somniferum. It is estimated that 60% of anti-tumour and anti-infectious drugs already on the market or under clinical trial are of natural origin. The vast majority of these cannot yet be
synthesized economically and are still obtained from wild or cultivated plants. Natural compounds can be lead compounds, allowing the design and rational planning of new drugs, biomimetic synthesis development and the discovery of new therapeutic properties not yet attributed to known compounds [24].

In addition, compounds such as muscarine, physostigmine, cannabinoids, yohimbine, forskolin, colchicines and phorbol esters, all obtained from plants, are important tools used in pharmacological, physiological and biochemical studies.

Plants have been used by human beings since immemorial times to cure diseases and to promote relief from ailments. There were times when they were the most important sources of medicines for people. However, beginning in the late 1940s, this old form of therapeutics began to lose its importance, being more and more replaced by synthetic remedies. The lessons from millennia were forgotten and were considered "unscientific." Many species of plants possessing activity on the central nervous system (CNS) in fact, they cover the whole spectrum of central activity such as psychoanaleptic, psycholeptic and psychodyleptic effects, and several of these plants are currently used in therapeutics to treat human ailments. Mind-altering drugs, especially plants, have always fascinated human beings. Surrounded by mystic superstitions, magic thoughts and religious rituals, they have always occupied man's attention. Among the plants used by humans, those able to alter the conscience and the sensorium have drawn special consideration. In fact, due to their astonishing effects, the psychodyleptic drugs (hallucinogenic drugs) have occupied much of the researchers' time, directed most of their thoughts and efforts towards attempts to understand their mechanism of action and hence, to understand human behavior, thoughts, humor, sensations etc.

4.6 Traditional medicines previously evaluated for their claims as anxiolytics:

Plants have been evaluated for the treatment of anxiety showed in Table 2 along with their parts used, traditional claims related to anxiety, constituents isolated from respective plants.

4.7 Plant drugs and isolated compounds as anxiolytics:

Plant drugs as extract and their single molecules/compounds help to reduce anxiety has been showed in Table 3 along with their capacity for receptor site and mechanism of action [2, 6, 16, 17, 20, 28–32, 61-63].

4.8 Chemical structure of natural isolates responsible for treatment of anxiety:

The structure of natural isolatesshowed in Figure 5,6 and 7 which have the potential to treat anxiety and showed anxiolytic effects.

Discussion and Conclusion

During the past decade, the indigenous or traditional system of medicine has gained importance in the field of medicine. In most of the developing countries, a large number of populations depend on traditional practitioners, who in turn are dependent on medicinal plants, to meet their primary health care needs. Although modern medicines are available, herbal medicines have retained their image for historical and cultural reasons. As the usage of these herbal medicines has increased, issues and the motto regarding their quality, safety, and efficacy in industrialized and developing countries have cropped up [64].

The search for new molecules that act on the central nervous system (CNS) and that can be used for therapeutic purposes started with several studies in the 19th century. In fact, the first drugs used to treat pathologic conditions of the CNS were based on natural resources, specifically on plants. 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, it appears that plants with molecules that produce this kind of activity are increasingly attractive targets for the development of new drugs [20]. Flavonoids have recently increased in importance because they have been identified as a new type of ligand with in vivo anxiolytic properties. Different plant species utilized in traditional medicine have been submitted to neuropharmacological evaluation (among others, the EPM) in which sedative effects have been demonstrated [65]. The flavones chrysins and apigenin, obtained from medicinal plants, have shown an anxiolytic effect in rodents exposed to behavioral tests. Apparently, these compounds modulate the gama-aminobutyric acid (GABA)ergic system to produce the biological effect [66-67]. Many studies have examined the use of native plants for more specific, lower cost treatments with fewer harmful effects. The review covered all aspects of traditional medicines and revealed that a detailed study is required to explore the plants and their uses to treat serious complication of central nervous system. Medicines are hiding in the lap of nature and tradition always helps to shine the medicines for the treatment of human illness. Nature and tradition both is really a wonder agent of God for the treatment of diseases. This review helps to understand the anxiety or central nervous system disorders along with treatment by natural medicines. This review also stimulates the
young researchers and students to search out the novel drug from the lap of nature and tradition.

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References

actions of the hexane extract from leaves of Annona cherimolia in two anxiety paradigms: Possible involvement of the GABA/benzodiazepine receptor complex. Life Sciences, 78: 730 – 737.


Illustrations

Illustration 1

Figure 4: Dysregulation of norepinephrine in depression and adaptation with treatment.

Illustration 2

Figure 2: Mechanism of impulse transmission
Illustration 3

Figure 1: Symptoms of anxiety

Illustration 4

Figure 3. Regulation and function of the norepinephrine modulatory system.
Illustration 5

Figure 5: Structure of chrysin, apigenin, Sinapic acid, Sanjoinine A

Illustration 6

Figure 6: Flavonols, Flavanones, Flavanoid glycoside (1-12) showed anxiolytic activity
Illustration 7

Figure 7: Structure of Trideca-7, 9, 11-trienoic acid and Cardiospermin

Illustration 8

Table 1: Histaminergic system in anxiety

<table>
<thead>
<tr>
<th>Anxiety induction</th>
<th>Histamine in Brain</th>
<th>Mechanism of action</th>
<th>Intention antagonised</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1 receptor antagonist (triphenside) and with H1 antagonist (Compound 4020)</td>
<td>Histamine localized in both hypothalamic and histamine release via histamine neurones and different mechanisms. Degradation from nonnornephrine and noradrenaline stores in the case of Compound 4020.</td>
<td>Histamine release in the case of triphenylmethanes.</td>
<td>This inhibition antagonised by H1 antagonist, diphenhydramine.</td>
</tr>
<tr>
<td>Co-injection of H1 blocker and histamine releaser.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Illustration 9

Table 2: Traditional medicines as anxiolytics

<table>
<thead>
<tr>
<th>Biological source</th>
<th>Part used</th>
<th>Traditional uses related to anxiety</th>
<th>Compounds having anxiolytic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ficus religiosa Linn. (Moraceae)</td>
<td>Roots, stem, barks</td>
<td>Nervous disorders, nerve tonic, epilepsy, unconsciousness, and drug addiction (bhang and opium)</td>
<td></td>
</tr>
<tr>
<td>Uncaria rhynchophylla (Rubiaceae)</td>
<td>Stem</td>
<td>Anti-hypertensive, anti-epileptic, and neuroprotective activities</td>
<td>Quercetin, kaempferol, flavonoids</td>
</tr>
<tr>
<td>Tilia americana var. Mexicana (Tiliaceae)</td>
<td></td>
<td>Anxiolytic-like effect</td>
<td></td>
</tr>
<tr>
<td>Rubus brasiliensis Martius (Rosaceae)</td>
<td>Leaf</td>
<td>Nervous breakdown treatment</td>
<td>Sanjoinine A</td>
</tr>
<tr>
<td>Zizyphi Spinosi Semen (ZSS), the dried seed of Zizyphus jujuba Mill var. spinosa (Rhamnaceae), Magnolia obovata</td>
<td>Seed</td>
<td>Analgesic, tranquilizer and anticonvulsant anxiolytic like effect</td>
<td>Honokiol, obovatol, magnolol</td>
</tr>
<tr>
<td>Valeriana Officinalis L.</td>
<td>Roots</td>
<td>Tranquilizer insomnia, anxiety and sleep inducer</td>
<td></td>
</tr>
</tbody>
</table>
**Asteraceae**

*Turnera aphrodisiaca* Ward (Turneraceae)

Anxiety neurosis, and as an aphrodisiac

*Apigenin*

**Spondias mombin** L. leaves

Psychiatric disorders

*(Anacardiaceae)*

**Casimiroa pringlei** (S. Watson) Engl. (Rutaceae)

Leaves

**Casimiroa edulis** Llave and Lex.

Bark, leaves

Induce sleep and as an anxiolytic

**Matricaria recutita** L

Sedative and anticonvulsant properties

**Passiflora incarnata** L.

Flower

Anxiolytic and sedative properties

**Piper methysticum** Forst

Anxiolytic and sedative properties

**Valeriana officinalis** L.

Anxiolytic and sedative properties, insomnia

**Euphorbia hirta** L.

Whole herb

Anxiolytic and sedative properties

*(Euphorbiaceae)*

**Lavandula angustifolia**

Linalyl acetate and linalool are considered to have sedative and local anesthetic effects

**Cecropia glazioui** Sneth leaves

Antihypertensive, cardiotonic, and antiasthmatic

*(Moraceae)*

**Butea frondosa** leaves

Rejuvenato and stress treatment

*(Leguminosae)*
<table>
<thead>
<tr>
<th><strong>Bacopa monniera</strong></th>
<th>Whole herb</th>
<th>Cognitive functions of the brain</th>
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</thead>
<tbody>
<tr>
<td><strong>Azadirachta indica</strong></td>
<td>Leaves</td>
<td>Cognitive functions of the brain</td>
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<tr>
<td><strong>Withania somnifera</strong></td>
<td>Roots and Whole plant</td>
<td>Cognitive functions of the brain</td>
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<tr>
<td><strong>Ocimum sanctum</strong></td>
<td>Whole plant</td>
<td>Cognitive functions of the brain</td>
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<td><strong>Annona muricata</strong> (Annonaceae)</td>
<td>Leaves</td>
<td>Anticonvulsant activity, tranquilizing and sedative properties</td>
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<td><strong>Annona Cherimolia</strong> (Annonaceae)</td>
<td></td>
<td>Tranquilizing and sedative properties</td>
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<td><strong>A. glabra</strong> (Annonaceae)</td>
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<td>tranquilizing and sedative properties</td>
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<td><strong>A. Montana</strong> (Annonaceae)</td>
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<td>tranquilizing and sedative properties</td>
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<td><strong>Salvia reuterana</strong> Boiss. (Labiatae)</td>
<td>Arial part of the plant</td>
<td>Anti-anxiety herbal drugs</td>
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<td><strong>Portulaca oleracea</strong> L. (Portulacaceae)</td>
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<td>Anxiolytic agent</td>
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<td><strong>Kaempferia parviflora</strong> Zingiberaceae</td>
<td>Rhizomes</td>
<td>Impotent symptoms and promote longevity</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Part(s)</td>
<td>Effect(s)</td>
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<td><em>Elaeocarpus sphaericus</em></td>
<td>Fruits</td>
<td>Sedative, hypnotic, tranquillizing, antiepileptic, and antihypotensive properties</td>
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<td>Mood enhancer, anxiety</td>
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<td><em>Citrus nobilis</em></td>
<td>Fruits</td>
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<td><em>Citrus aurantium</em></td>
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<td><em>Passiflora incarnata</em></td>
<td>Whole plants</td>
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<td>Flower</td>
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<td>Aerial parts</td>
<td>Relieve sleeplessness, headache, and nervous excitement</td>
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<td>Leaves</td>
<td>Mental illnesses</td>
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<tr>
<td><em>Ginkgo biloba</em></td>
<td>Leaves</td>
<td>Cerebrovascular insufficiency, cardiovascular malfunction and bronchitis</td>
</tr>
<tr>
<td><em>Clerodendrum philippinum</em></td>
<td>Flower</td>
<td>Treatment of neuropsychological diseases</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Part</td>
<td>Activity</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Angelica sinensis</td>
<td>Whole plant</td>
<td>Sedative and antianxiety activities</td>
</tr>
<tr>
<td>Aniba riparia (Nees) Mez</td>
<td>Fruit</td>
<td>Sedative and antianxiety activities</td>
</tr>
<tr>
<td>Aethusa cynapium L.</td>
<td>Aerial parts</td>
<td>Convulsions, mental tension, sleep disorders,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>delirium</td>
</tr>
<tr>
<td>Cardiospermum halicacabum</td>
<td>Roots</td>
<td>Curing diseases related to the nervous system</td>
</tr>
<tr>
<td>Nardostachys jatamansi</td>
<td>Roots</td>
<td>Nervous system</td>
</tr>
<tr>
<td>Bacopa monnieri L.</td>
<td></td>
<td>Anxiety, poor cognition and a lack of concentration</td>
</tr>
<tr>
<td>Centella asiatica (Apiaceae)</td>
<td></td>
<td>Nervine tonic in various brain diseases, In parts of India it is given with milk to improve memory against dementia and aging.</td>
</tr>
</tbody>
</table>
Illustration 10

Table 3: Plant drugs and isolated compounds as anxiolytics

<table>
<thead>
<tr>
<th>Plant extracts/drugs</th>
<th>Natural isolates or compounds</th>
<th>Binding Receptor/ compete/ Mimick Action receptor</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chrysin</td>
<td>[5,7-dihydroxyflavone]</td>
<td>BDZ-Rs</td>
<td>Partial agonists</td>
</tr>
<tr>
<td>Apigenen</td>
<td>[5,7,4\textsuperscript{1}trihydroxyflavone]</td>
<td>BDZ-Rs</td>
<td>Partial agonists</td>
</tr>
</tbody>
</table>

\textbf{50\% EtOH extract of Cinnamomum cassia (stem barks)}

Somatodendritic autoreceptors (5-HT\textsubscript{1A})

WAY100635, a somatodendritic 5-HT\textsubscript{1A} antagonist, enhances serotonergic system activity via complete blockade of the somatodendritic autoreceptors and possesses anxiogenic activity. The anxiolytic-like effect of C. cassia was significantly blocked by WAY100635 at 0.3 and 1.0 mg/kg and the above mentioned that the action of extract is due to 5-HT\textsubscript{1A} receptor.

\textbf{50\% EtOH extract of Cinnamomum cassia (stem barks)}

GABA\textsubscript{A} receptors

GABA\textsubscript{A} receptors are potentially inhibited by picrotoxin bicuculline and SR95531 (competitive antagonist) and the anxiolytic-like effect of C. cassia is significantly blocked by WAY100635.
Cinnamic acid of phenylpropa

p-Coumaric acid, caffeic acid, and ferulic acid of cinnamic acid derivatives

**Uncaria rhynchophylla**

5-HT$_1$A receptor activation.

Quercetin and kaempferol cinnamic acid, p-coumaric acid, caffeic acid and ferulic acid

GABA$_A$ receptor, Agonist of GABA$_A$ receptor

Magnolol and Honokiol Histaminergic system

Sanjoinine A GABA receptor

Sanjoinine A may exert its anxiolytic effect by increasing GABA synthesis via GAD65/67 activation and increasing receptors for benzodiazepine or GABA.
<table>
<thead>
<tr>
<th>Hexanic fraction of</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Rubus brasiliensis</em></td>
</tr>
<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;-benzodiazepine receptor complex</td>
</tr>
<tr>
<td>By acting as an agonist on GABA&lt;sub&gt;A&lt;/sub&gt;-benzodiazepine receptor complex.</td>
</tr>
<tr>
<td>Obovatol</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;/benzodiazepine receptor complex</td>
</tr>
<tr>
<td>Anxiolytic effect mediated by GABA-benzodiazepine receptors-activated Cl-channel opening.</td>
</tr>
<tr>
<td>Trideca-7,9,11-trienoic acid</td>
</tr>
<tr>
<td>Cardiospermin</td>
</tr>
<tr>
<td>Valerenic acid</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;-minergic system</td>
</tr>
<tr>
<td>Valerenic acid interacts with the GABA&lt;sub&gt;A&lt;/sub&gt;-ergic system, a mechanism of action similar to benzodiazepine drugs.</td>
</tr>
<tr>
<td>Ginkgolic acid conjugates (GAC) (6-alkylsalicylates, namely n-tridecyl-, n-pentadecyl-, n-heptadecyl-, n-pentadecenyl- and n-heptadecenylsalicylates)</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1&lt;/sub&gt;, receptor, dopamine D&lt;sub&gt;2&lt;/sub&gt; receptor</td>
</tr>
<tr>
<td>Indian Ginkgo biloba extracts (unpurified) containing GAC have been found to decrease the serotonin 5-HT&lt;sub&gt;1&lt;/sub&gt;, receptor binding activity in the frontal cortex and dopamine D&lt;sub&gt;2&lt;/sub&gt; receptor binding activity in corpus striatum.</td>
</tr>
</tbody>
</table>
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