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Importance of traditional medicinal plants in the treatment of anxiety: A review

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Abstract
The pervasiveness of mental problems, for example, anxiety, is exceptionally normal and impacts numerous individuals all around the globe. Presently, may engineer pharmacological items/drugs are accessible in the market to fix the issue however connected with different unfavorable responses or results, which may make anxiety and here and there different problems the patients. In the previous years, the utilization of corresponding and elective medication has expanded. The investigation in the zone of natural psychopharmacology has gotten a lot of consideration as individuals are utilizing more home-grown treatment for advantage of their wellbeing. In this study, we included plants, plant extracts and isolated components (if any) along with models used to explore anxiolytic properties; in retrospect, there was still a lot of research to develop them clinically. Literature reports have suggested that several medicinal plants are effective in the management of anxiety. Based on the evidence available, medicinal plants tend to be an effective way to treat anxiety and anxiety-related disorders without the possibility of significant side effects. Medicinal plant exploration is helpful in identifying further potential compounds for the treatment of anxiety disorders.

Keywords: anxiety, ADRs of existing treatment, alternate therapy, medicinal plants in anxiety

Introduction

Anxiety is orchestrated by World Health Organization (WHO) as the sixth most prominent partner of in general feebleness. The aggregate overviewed number of people living with stress issues in the world is 264 million. Misgiving wrecks are more average among females than people. As demonstrated by WHO, 7.7% of the female additionally, 3.6% of male individuals is assessed to encounter the savvy impacts of anxiety issue. As demonstrated by NMHS of India during 2015-16, in ordinary weighted routineness for any psychological awfulness was 13.7% for lifetime and 10.6% for current mental ominousness. [1]. Mental issues are tended to extra in age group of 30–49 or more than 60 years. Anxiety and Depression Association of America (ADAA) saw that only 36.9% of anxiety patients gets treatment from 18.1% of U.S. individuals (40 million) which is experiencing anxiety and ladies are twice influenced than of men [2]. Apprehension or fear is an unavoidable event of routine life. It has been considered to affect the nature of human wellbeing. It is a cardinal indication of different mental issues and nearly unavoidable fragment of various clinical and cautious conditions [3, 4]. It is an inevitable human feeling, immovably associated with fear and much of the time filling psycho biologically versatile prerequisites. It isn't confined to any age, sex, innate factor, working condition or one's yield [5]. Fear or apprehension may happen due to over-advancement (progression) of adrenergic framework (adrenergic system) similarly as dysregulation of serotonergic framework [6, 7]. Anxiety might be 'pathological' or 'normal' and is hard to see yet can be disconnected by results which meddle with normal productive works out.

Anxiety is all around associated with different issues, for instance, melancholy, diabetes mellitus, male impotency, hypertension, peptic ulcers and awkward developing [8, 9].

Currently, pharmacological therapy is the most commonly used treatment for mood disorders. Although many drugs appear to play an important role in the treatment of the most severe mental illnesses, there are numerous complaints that the drugs are ineffective for all patients and cause a variety of adverse events, as well as tolerance [10]. Most synthetic antidepressants have significant faults, including a restricted antidepressant range, unpleasant responses, expensive medication pricing, and rapid recurrence. Many individuals are turning to herbal therapy in quest of multi-target antidepressants that are minimal in toxicity [11].

The increasing interest in phyto medicine among health practitioners and patients has been demonstrated by emerging clinical cases. The development of plant-derived anti-anxiety drugs employs a multidisciplinary approach that includes, but is not limited to, ethno pharmacological surveys, phytochemical, and pharmacological studies. Number of studies have shown that the use of complementary and alternative medicine in the treatment of psychiatric disorders, particularly depression and anxiety, is a common occurrence [12].

A nationally representative study conducted in the United States found that 53.6 percent of people with self-reported depression and 4.5 percent of non-institutionalized adults with insomnia used complementary and Alternate medicine to treat their psychiatric disorders in the previous year [13].
Herbal medicine found a significant place among the complementary medicine used for treatment [14].
In recent years, comprehensive descriptions of herbs used to treat depression, anxiety, or insomnia have been documented. However, to the best of the author's knowledge, these reviews either concentrated on a single psychiatric disorder, a specific herbal medicine, or a single pattern. Given the limitations of previous research, we conducted a review to explore the herbalanxiolytic antidepressant activities, and the most widely used and effective single herbs and herbal formulas for treating anxiety. A general overview of the causes and associated factors related to anxiety are given in fig. 1.

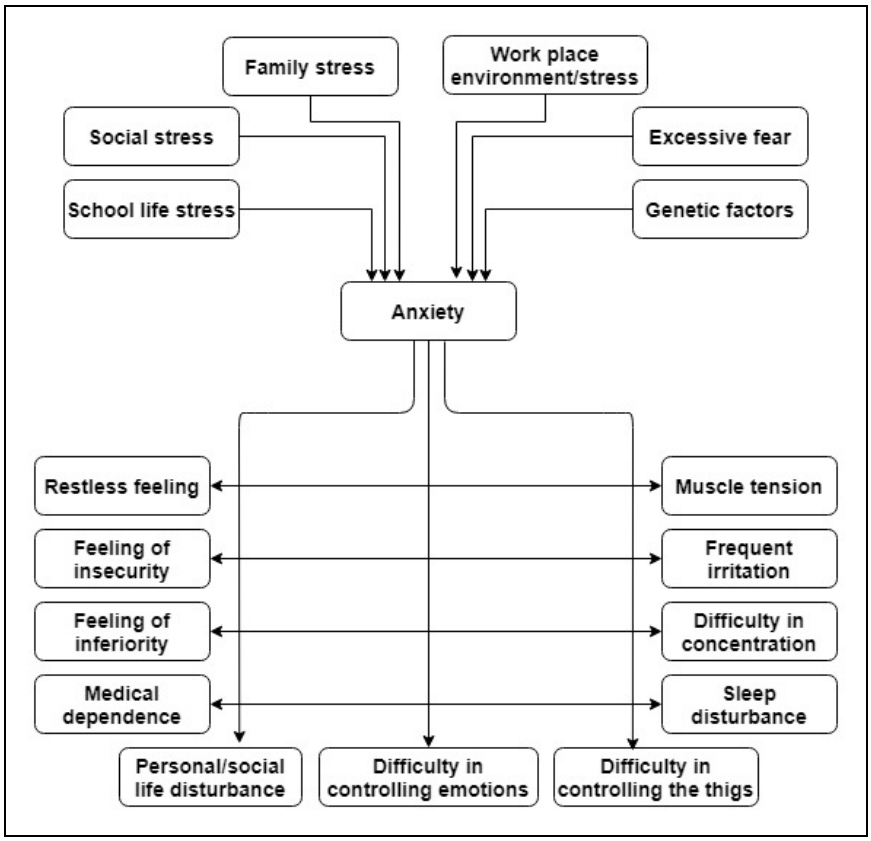

Fig.1: General overview of anxiety disorder

Types of anxiety disorders

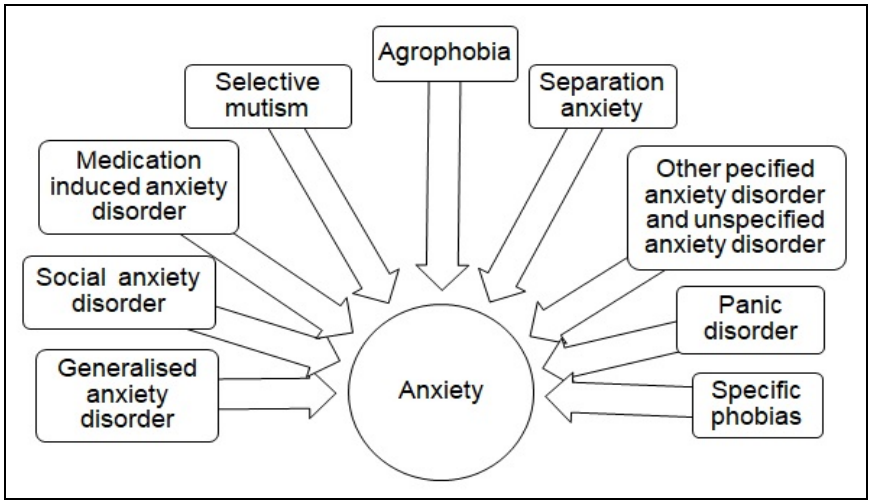

Fig 2: Types of anxiety disorder

Symptoms of anxiety
Symptoms of anxiety can be cateogorised under physical, emotional, pathological state and external. An overview of the symptoms of anxiety disorder are given in fig. 3.

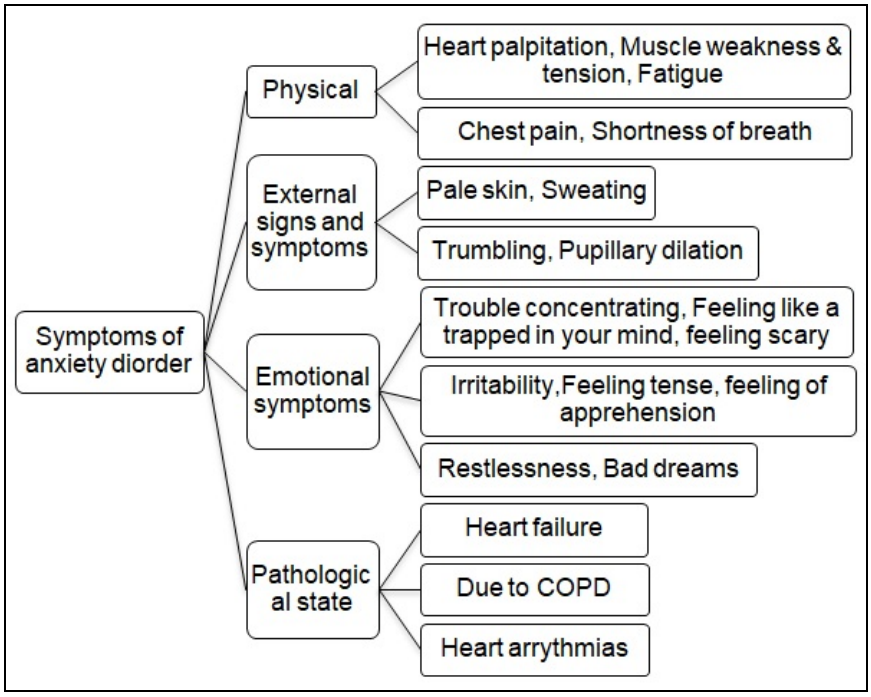

Fig 3: Symptoms of anxiety disorder [30].

Various mechanisms involved in the anxiety

Various neurotransmitters play totally different and necessary role in anxiety regulation, amongst them, serotonin/ 5-Hydroxy Tryptamine (5-HT), Gamma Amino Butyric Acid (GABA), benzodiazepines receptor, nor-epinephrine/ nor-adrenaline (NE/NA) and plenty of others like have additionally been joined to anxiety disorders [32]. It is estimated that genes contribute 30% to 50% s to the development of an anxiety disorder. Conversely, development of an anxiety disorder due to non-genetic factors is approximately 50% to 70%. Hence it is necessary to study the mechanism of action. Documented literatures were available for various models like GABA model, Benzodiazepine model, Nor adrenergic model and 5HT.

Management of anxiety

Management of anxiety depends on various factors such as the type of disorder and characteristics of the individual patient. The treatment strategies of the anxiety involve the application of the following, such as Medications, Psychological treatment, and Alternative therapies.

Medications for the treatment of anxiety

Treatment and management of anxiety can be possible with the personalized therapies selected based on the individual patient need using the available formulation in the market. The drugs used for the treatment of anxiety are elaborated below in Table 1.

Table 1: Available marketed formulation for the treatment of anxiety

Sr. No.	Category	Drug Name	Brand Name
1.	GAB Amimetics Benzodiazepines (BZD)	Alprazolam	Xanax
		Chlordiazepoxide	Librel
		Diazepam	Valium
		Lorazepam	Lrpose
		Oxazepam	Serax
2.	Sedative antihistaminic	Hydroxizine	---
3.	β-blocker	Atenolol	Tenormin
		Propranolol	Indral
4.	Selective serotonin inhibitors (SSRIs)	Buspirone	BuSpar
		Citalopram	Cipramil
		Gepirone	Travivo
		Ispapirone	---
		Sertaline	Lustral
5.	SNRIs	Atomoxitine	Strattera
		Dulomoxetine	Cymbalta

The treatment of anxiety also includes the use of Selective Serotonin Reuptake Inhibitors (SSRIs) which can be the primary choice of treatment for the generalized social phobia. The medications such as fluoxetin, sertraline, paroxetine, citalopram etc., elevates the extent of neurotransmitter serotoninamong alternative effects.

Medicinal plants in the treatment of anxiety

Since ancient times, plants have been known to have enormous potential to treat illnesses. Ayurveda and Unani are inherited ancient health and longevity systems based on plant treatments. The 'World Health Organization' has approved that ancient health and folk medication systems have proved to be more practical in health problems worldwide [15]. Traditional medicine is utilized by about 60% of the world's population in rural regions in underdeveloped countries, and it is gaining popularity in wealthy countries where modern treatments are mostly used. Arguably, the most significant barrier to the unrestricted use of herbal medicines in the normal practice of prescription is a lack of comfortable scientific knowledge and a better understanding of the efficacy and safety of the herbal product [16]. A variety of plants are being studied for their anxiolytic properties. The plant species used in the treatment of anxiety disorders triggered by various types of mechanism are given in Table 2-5.

Table 2: Plants influencing GABAergic system (17-33)

Sr. No	Plant Name	Chemical constituents	Mechanism of action and effects	Animal used for study
1.	Pineapple. *Ananascosmosus* (Bromeliaceae)	Ascorbic acid, quercetin, flavones-3-ol, flavones, and ferulic acid	Inhibition of monoamine oxidase MAO-A and MAO-B activity, reduced malondialdehyde (MDA) levels	Mice
2.	Chinese angelica, *Angelica sinesis* (Umbellaceae)	Ligustilide and ferulic acid	Upregulation of the BDNF signalling pathway	Rat
3.	Soursop, *Annona muricata* (Annonaceae)	Annonaine asimilobine nornuciferine	Influence on the CNS via the 5HT1A receptor	In-vitro study
4.	Custard apple, *Annona squamosa* (Annonaceae)	Annonacin β-caryophyllene δ-cadinene, α-muurolene, α-cadinol and isoquinoline alkaloids	Increased brain GABA and Serotonin levels.	Mice
5.	Groundnut, *Arachis hypogaea*(Fabaceae)	Flavonoids, phenolic acids, phytosterols, alkaloids, and stilbenes	Stimulation of activity of GABA	Mice
6.	Begger's buttons, *Arctium lappa* (Asteraceae)	Volatile oils, lignans, sesquiterpene	Stimulation of activity of GABA	Mice
7.	Tarragon, *Artemisia dracunculus* (Artemisia)	Sabinene, isoelemicin, methyl eugenol, elemicin and beta-ocimene	Stimulation of activity of GABA	Mice
8.	Membranous milk vetch, *Astragalus membranaceus*	Astragalosides I-IV and trigonosides I-III), formononetin, ononin, calycosin, and its glycoside, saponins, several minor isoflavonoids, and other biogenic amines	Stimulation of activity of GABA	Rat
9.	Beetroot, *Beta vulgaris subsp* (Amaranthacae)	Betalains, betacyanins and betaxanthins, flavonoids, polyphenols, Saponins and inorganic Nitrate	Stimulation of activity of GABA	Rat
10.	Coconut, *Cocos nucifera* (Arecaceae)	Vitamin B, nicotinic acid, pantothenic acid (B5), biotin, riboflavin (B2), folic acid, vitamins B1, B6, and C, pyridoxine, thiamine, folic acid, amino acids, L-arginine	Mediation of the effect ofGABA neurotransmitter	Mice
11.	Acorn squash, *Cucurbita pepo* (Cucurbitaceae)	Alkaloids, flavonoids, and palmitic, oleic and linoleic acids	GABA receptor agonist	Rat
12.	Marginal fern, *Dryopteris marginalis* (Dryopteridaceae)		Stimulation of GABAreceptor	Rat

13.	Black henbane, *Hyoscymus niger* (Solanaceae)	Chlorogenic acid, quercetin-3O-glucoside-rhamnoside-rhamnoside (QGRR) and rutin, tropane alkaloids, hyoscyamine and scopolamine	Lowering BP throughCa++antagonist and antianxiety activity	Mice
14.	Chinese boxthorn, *Lycium barbarum* (Solanaceae)	Arabinose, rhamnose, xylose, mannose, galactose, glucose, galacturonic acid and eighteen amino acids, Polysaccharides	Stimulation of GABAreceptor	Rat
15.	Mango, *Mangifera indica* (Anacardiaceae)	Mangiferone, mangiferin, myricetin, myricitrin, rutin, and quercetin	Production of anxiolytic-like effect through its affinity for 5-HT2 and benzodiazepine receptors	Rat
16.	Currybush, *Murraya koenigii* (Rutaceae)	Carbazole alkaloids, coumarin galactoside, Carbazole carboxylic acid, glycolipids, Phospholipids	Increased GABA level	Rat
17.	Tobacco, *Nicotiana tabacum*(Solanaceae)	Toxic alkaloid, nicotine	Increased GABA release by binding to excitatory presynaptic nACh receptors located on GABA neurons	Rat

Table 3: Plants influencing the serotonergic system (34-45)

Sr. No.	Plant Name	Chemical constituents	Mechanism of action and effects	Animal used for study
1.	Turmeric, *Curcuma longa* (Zingiberaceae)	Curcuminoids (mixture of curcumin, dimethoxycurcumin and bisdemethoxycurcumin)	Increased levels neurotransmitterserotonin	Mice
2.	Peony, *Paeonia* (Paeoniaceae)	Gallic acid,methyl gallate,ethyl gallate,1,2,3,6-tetragalloyl-beta-D-glucopyranoside, 1,2,3,4,6-pentagalloyl-beta-D-glucopyranoside, quercetin-3-O-glucoside-6-gallate, kaempferol-3-O-glucoside-6-gallate, 1-O-galloyl-beta-D-glucose	Increased levels of serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid	Mice
3.	Rosemary, *Rosmarinus officinalis* (Lamiaceae)	Osmarinic acid, camphor, caffeic acid, ursolic acid, betulinic acid, carnosic acid and carnosol	Upregulation of tyrosine hydroxylase and pyruvate carboxylase	Mice
4.	Ironwort,*Sideritis syriaca*	Flavonoids, tannins, monoterpenes (iridoids), sesquiterpenes, phenylpropanoid glycosides, hydrocarbons (sterols, fatty acids)	Effects on triple monoamine reuptake inhibitor	Rat
5.	Akebia fruit, *Fructus akebiae* (Lardizabalaceae)	Triterpenoid saponins with hederagenin as their sapogenin	Increase in the extracellular HT-5	Rat
6.	Thorow-Wax, *Bupleurum falcatum* (Apiaceae)	Quinic derivatives (1-3), saikosaponin A (12), saikosaponin D (13), and saikosaponin C (14)	Antidepressant properties through affecting the serotonergic system.	Mice
7.	Daylily,*Hemerocallis citrina* (Asphodelaceae)	Chrysophanol(I), 2-methoxy-obtusifolin (II), obtusifolin (III), rhein (IV), aloe-emodin (V), hemerocallone	Effect on monoamine neurotransmitters serotonin	Mice
8.	Scotch heather, *Calluna vulgaris* (Ericaceae)	Flavonoids, tannins, proanthocyanidins, caffeic acid derivatives, phenols, triterpenes, steroids and hydroquinone glycosides (arbutin)	Increased serotonin levels through MAO-A	In-vitro study
9.	Mexican mint, *Borago officinalis* (Boraginaceae)	Mucilage, tannin, saponins, essential oil, alkaloid (pyrrolizidine), vitamin C, calcium and potassium, essential fatty acids, linoleic acid and gamma-linolenic acid	Increased serotonin levels through affecting serotonin transporter	Rat
10.	Areca nut palm, *Areca catechu nut* (Arecaceae)	Arecoline, arecaidine, guvacine, and guvacoline	Increased serotonin levels	Rat

Table 4: Nor-adrenergic or nor-epinephrine model (45-46)

Sr. No	Plant Name	Chemical constituents	Mechanism of action and effects	Animal used for study
1	Yellow banana, *Musa acuminata* (Musaceae)	Noradrenaline, apigenin glycosides, myricetin-3-O-rutinoside, kaempferol-3-O-rutinoside, dopamine, and serotonin	Effects on noradrenaline and brain activity	Male mice
2	Red banana,*Musa sapientum var baracoa* (Musaceae)	Dopamine, Norepinephrine, Pantothenic acid (B5),Pyridoxine (B6),Choline, Vitamin C	Effects on noradrenaline and brain activity	Male mice
3	Plantain, *Plantago major* (Plantaginaceae)	Dopamine, Norepinephrine, flavonoids, alkaloids, terpenoids, phenolic compounds (caffeic acid derivatives), iridoid glycosides, fatty acids, polysaccharides and vitamins	Increased release of norepinephrine in brain (locus coeruleus, hypothalamus, hippocampus and amygdala)	Rat
4	Fuerte avocado, *Persea americana* (Lauraceae)	Norepinephrine, Dopamine, Peptone, b-galactoside, glycosylated abscisic acid, alkaloids, cellulose, polygalacto urease, polyuronoids, cytochrome P-450, and volatile oils	Effects on the release of norepinephrine and brain activity	Mice
5	Banana,*Cavendish banana* (Musaceae)	Gallic acid, catechin, epicatechin, Norepinephrine, tannins, anthocyanin, serotonin, Dopamine, Catecholamines, β-Sitosterol, Campesterol, and stigmasterol	Effects on noradrenaline and brain activity	Albino Wistar mice
6	Cocoa, *Theobroma cacao* (Malvaceae)	Pro- cyanidin B2, Norepinephrine, catechin, theobromine and caffeine	Effects on the release of norepinephrine and brain activity	Male swiss mice
7	Broccoli, *Brassica olereacea var italica* (Brassicaceae)	Sulforaphane, Norepinephrine, Dopamine, glucoiberin, glucoraphanin, carotenoids, myrosinase and vitamins	Effects on noradrenaline and brain activity	Rat
8	Brousel sprouts, *Brassica olereacea Vargemmifera* (Cruciferae)	Polyphenols, phenolic acids, flavonoids, norepinephrine, dopamine, carotenoids (zeaxanthin, lutein, β-carotene), alkaloids, tannins, saponins, anthocyanins, phytosterols chlorophyll, glucosinolates, phytosteroids, terpenoids, glycosides, vitamin-C	Effects on the release of norepinephrine and brain activity	Mice and rats
9	Oranges, *Citrus sinensis* (Rutaceae)	Flavonoids, hydroxyamides, norepinephrine, dopamine, steroids, alkanes and fatty acids, coumarins, carbohydrates, peptides, carbamates and alkylamines, carotenoids, volatile compounds, and minerals	Effects on noradrenaline and brain activity	Rat
10	Tomato,*Lycopersicon esculentum* (Solanaceae)	Lycopene, vitamins C and E, lutein, epinephrine, norepinephrine, dopamine, quercetin, myricetin, β-carotene, and flavanones	Effects on the release of norepinephrine and brain activity	Rat
11	Potato, *Solanum tuberosum var. Desiree-leaves* (Solanaceace)	Carbohydrates, proteins, lipids, carotenoids, epinephrine, norepinephrine, dopamine, anthocyanins, conjugated phenolic acids, and minerals	Effects on noradrenaline and brain activity	Swiss albino mice

Table 5: 5-HT (serotonin) model (47-50)

Sr. No.	Plant Name	Chemical constituents	Mechanism of action and effects	Animal used for study
1	Plum, *Prunus domestica* (Rosaceae)	Chlorogenic acids, Serotonin, noradrenaline, anthocyanins, flavanols, flavonols, and coumarins	Action on the binding of serotonergic receptor(5-HT), cell hyperpolarization and action on anxiety	Wistar and Wistar-Kyoto rats
2	Yellow banana, *Musa acuminata* (Musaceae)	Serotonin, noradrenaline, apigenin glycosides, myricetin-3-O-rutinoside, kaempferol-3-O-rutinoside, dopamine, and serotonin	Increases serotonin level in the brain	Male mice

3	Kiwi,*Actinidia deliciosa* (Actinidiaceae)	Serotonin, epicatechin, quercitrin, rutin, catechin, chlorogenic acid, ferulic acid, and vanillic acid.	Action on the binding of serotonergic receptor(5-HT), cell hyperpolarization and action on anxiety	Wistar and Wistar-Kyoto rats
4	Hickory, *Carya illinoinensis* (Juglandaceae)	Serotonin, thiamine, pantothenic acid, vitamin B-6, and riboflavin	Increase in serotonin level decrease anxiety	Mice
5	Pineapples, *Ananas comosus* (Bromeliaceae)	Serotonin, Proteolytic enzymes (bromelain or bromelain). Citric and malic acids. Vitamins A, B and C. Sugars: glucose, sucrose.	Increase in serotonin level decrease anxiety	Mice
6	Walnuts, *Juglans regia* (Juglandaceae)	Serotonin, juglone, niacin, pantothenic acid, pyridoxine, riboflavin, thiamin, vitamin A, vitamin C, vitamin E and vitamin K	Action on the binding of serotonergic receptor(5-HT), cell hyperpolarization and action on anxiety	Rats
7	Tomato, *Lycopersicon esculentum* (Solanaceae)	lycopene, vitamins C and E, lutein, epinephrine, serotonin norepinephrine, dopamine, quercetin, myricetin, β-carotene, and flavanones	Action on the binding of serotonergic receptor(5-HT), cell hyperpolarization and action on anxiety	Rats
8	Salmon	arsenic, mercury, PCBs, DDT, dioxins, lead, serotonin norepinephrine, dopamine, selenium, arginine, histidine, isoleucine, leucine, lysine, methionine	Increase in serotonin level decrease anxiety	Mice
9	Nuts, *Prunus amygdalus* (Fagaceae)	arecaidine, arecoline, arecolidine, epinephrine, serotonin norepinephrine, omega-3 fatty acids, dopamine, guvacoline, guvacine, arecatannin A1, arecatannin A2, isoguvacine, homoarecoline, nicotine, and dichroine	Action on the binding of serotonergic receptor(5-HT), cell hyperpolarization and action on anxiety	Rats
10	Spinach, *Spinacia oleracea* (amaranth)	Flavonoids, serotonin norepinephrine, dopamine, palmitic, palmitoleic, hexadecatrienoic, stearic, oleic, linoleic, linolenic and erucic acid	Increase in serotonin level decrease anxiety	Mouse, rat, and rabbit

Conclusions

It is impossible to imagine life without natural products owing to its enormous benefits provided to mankind. Herbal products have a significant public health impact, particularly in the case of traditional medicines and nature-based modern drugs. Despite their limitations, traditional medicines are meeting the health needs of millions of people around the world. Herbs have been prized since ancient times for their pain-relieving and healing properties, and we still rely heavily on the curative properties of plants today. A statistic from World Health Organization, mention medicinal herbs are used as the primary healthcare system by 80% rural dwellers.

The natural herbs/herbal mixtures that work synergistically claim to provide an effective anxiety treatment. However, only a handful of them have been shown to be effective anxiolytes in human studies. Because manufactured medications and pharmaceuticals have severe side effects, these plants with high therapeutic relevance promise to alleviate anxiety while having low side effects. The review examined all elements of traditional medicines and found that a comprehensive experimental and standardized research is needed to investigate the plants and their applications to treat significant complications such as anxiety. The use of natural products/medicinal plants in a more efficient and effective manner is aimed to enhance the drug development process.

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