## Bio screening of herbal and allopathic antianxiety drugs using various animal models

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## Abstract: In this study we have tried to study detailed about one of the central nervous system related panic disorders (anxiety) including various pharmacological parameters. We have tried here to explore anxiety as in detailed which shows that it is one of the manifestations related to both stress and lack of coping a close association with socio-cultural factors. Treatment like various allopathic drugs and herbal remedies find very effective usefulness in such disorders for examples lebbeck plant extracts, wort exrtract, benzodiazepines and barbiturates. Also, along with detailed study of pathogenesis and treatment schedules it has been focused on the various models for the evaluation of antianxiety herbal preparations.

## Key words: Wort, lebbeck, benzodiazepines, barbiturates

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## Introduction

Anxiety is arguably feeling that exist before the evolution of man. Its universality in humans, and its presence in a range of anxiety disorders, it’s an important clinical focus. Developments in nosology, epidemiology and psychobiology have led to significant advancement in our understanding of the anxiety disorders in recent years. Advances in pharmacotherapy and psychotherapy of these disorders have brought realistic hope for relief of symptoms and improvement in functioning to patients. Anxious disorders are basically related to stress, reaction to stress and individual tendency to anxiety. Interestingly, both stress and coping have a close association with socio-cultural factors. Culture can affect symptom presentation, explanation of the illness and help-seeking. Importance given to the symptoms and meaning assigned by the physician according to their cultural background also differs across culture. In this way culture can affect epidemiology, phenomenology as well as treatment outcome of psychiatric illness especially anxiety disorders. In this review an attempt has been made to discuss such differences, as well as to reflect the important areas in which Indian studies are lacking. An attempt has been made to include most Indian studies, especially those published in Indian Journal of Psychiatry (J. K. Trivedi and Pawan Kumar Gupta 2010)

Anxiety that results from fear caused by an acute illness or a stressful event, such as loss of a loved one, is usually self-limiting and can be of relatively short duration. The current options include various kinds of psychotherapy and pharmacotherapy such as benzodiazepines, a zapirones, and anti-depressants and others. (K. Latha et. al, 2015). The recognition of anxiolytic effects of no benzodiazepine azapirones agents, which acts as 5-HT1A partial agonists, such as buspirone, gepirone, and ipsapirone and their therapeutic role in clinical anxiety and mood disorders has further focused attention on the 5-HT1A receptor. However, the anxiolytic effects of azapirones follow a time course observed with antidepressants where therapeutic effects are delayedfor3–4 weeks, which is unlike the rapid effects observed with benzodiazepine anxiolytics. Thus, there is a need for robust anxiolytic compounds that have lesser side effects than benzodiazepines and more immediate onset of action than currently available 5-HT1A receptor acting drugs (K. Lathaet.al,2015).

Anxiety usually refers to the experience of fear, apprehensiveness, nervousness, panic, restlessness, tension, and agitation. Manifest symptoms include trembling, faint headaches

,and sweating, possibly elevated blood pressure, and changes in other psycho physiological in dices such as heart rate, muscle tone, and skin conductance. Neurotransmitters involved In anxiety generation include serotonin, dopamine, noradrenalin, GABA, Corticotrophin releasing factor (CRF), Melanocyte stimulating hormone (MSH) neuropeptides and neurosteroids benzodiazepines present a narrow safety margin between the anxiolytic

Effect and those causing unwanted side effects has prompted many researchers to evaluate new compounds in the hope that other anxiolytic drugs will have fewer undesirable effects. There cognition of anxiolytic effects of non-benzodiazepine azapirones agents, which act as5HT1A partial agonists and their therapeutic role in clinical anxiety and mood disorders has further focused attention on the 5-HT1A receptor. Although the azapirones display nanomolar affinity for 5HT1A receptor sites (J.P. Jhabarmal et.al,2013).

## Classification of anxiety disorders

Includes the following major categories of anxiety disorders:

Panic disorder (with or without agoraphobia), agoraphobia without panic, social phobia (social anxiety disorder), specific phobia, generalized anxiety disorder (GAD), acute stress disorder, posttraumatic stress disorder, obsessive compulsive disorder, and anxiety disorder not otherwise specified. DSM-IV also lists anxiety occurring as an adjustment disorder, or secondary to substance abuse or a general medical condition. Finally, anxiety not amounting to a psychiatric diagnosis could be situational in normal persons, or a symptom of another psychiatric disorder.([J. K. Trivedi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Trivedi%20JK%5BAuthor%5D&cauthor=true&cauthor_uid=21836680) and Pawan Kumar Gupta2010)

# Necessity of research on anxiety disorder in India

Neurotic disorders are basically related to stress, reaction to stress (usually maladaptive) and individual proneness to anxiety. Interestingly, both stress and coping have close association with socio-cultural factors. Culture can affect symptom presentation, explanation of the illness and help-seeking. Importance given to the symptoms and meaning assigned by the physician according to their cultural background also differ across culture. In this way culture can affect epidemiology, phenomenology as well as treatment outcome of psychiatric illness especially anxiety disorders. In this review an attempt has been made to highlight on any such difference if there, as well as this review will also reflect the important areas, in which Indian studies are lacking. This review will summarize most Indian studies pertaining to anxiety disorders published in Indian Journal of Psychiatry as well as found in other journals too (J. K.Trivedi and [Pawan Kumar Gupta](https://www.ncbi.nlm.nih.gov/pubmed/?term=Gupta%20PK%5BAuthor%5D&cauthor=true&cauthor_uid=21836680) 2010)

**Types of anxiety disorder**

Different Anxiety Disorders are

* Panic disorder
* Obsessive compulsive disorder
* Posttraumatic stress disorder
* Social phobia
* Specific phobias
* Generalized anxiety disorder

**Panic Disorder** is a real illness that can be successfully treated. It is characterized by sudden attacks of terror, usually accompanied by a pounding heart, sweatiness, weakness, faintness, or dizziness. During these attacks, people with panic disorder may flusher feel chilled; their hands may tingle or feel numb; and they may experience nausea, chest pain sensations. Panic attacks usually produce a sense of unreality, a fear of impending doom, or a fear of losing control. A fear of one ‘sown unexplained physical symptoms is also symptom of panic disorder. People having panic attacks sometimes believe they are having heart attacks, (NIHPublicationet.al,2009) losing their minds, or on the verge of death. They can’t predict when or where an attack will occur, and between episodes many worry intensely and dread the next attack. Panic attacks can occur at any time, even during sleep. An attack usually peaks within 10 minutes, but some symptoms may last much longer. Panic disorder affects about 6 million American adults and is twice as common in women as men. Panic attacks often begin in late adolescence or early adulthood, but not everyone who experiences panic attacks will develop panic disorder. Many people have just one attack and never have another. The tendency to develop panic attacks appears to be inherited (NIHPublicationet.al,2009).

**Obsessive Compulsive Disorder (OCD)** has persistent, upsetting thoughts(obsessions) and use rituals (compulsions) to control the anxiety these thoughts produce. Most of the time, the rituals end up controlling them. For example, if people are obsessed with germs or dirt, they may develop compulsion to wash their hands over and over again. If they develop an obsession with in traders, they may lock and relock their doors many times before going to bed. Being afraid of social embarrassment may prompt people with OCD to comb their hair compulsively in from to mirror—sometimes they get―caught in the mirror and can ‘remove away from it. Performing such rituals is not pleasurable. At best, it produces temporary relief from the anxiety created by obsessive thoughts. Other common rituals are a need to repeatedly check things, touch things (especially in a particular sequence), or count things Some common obsessions include having frequent thoughts of violence and harming loved ones, persistently thinking about performing sexual acts the person dislikes, or having thoughts that are prohibited by religious beliefs. People with OCD may also be preoccupied with order and symmetry, have difficulty throwing things out (so they accumulate), or hoardun needed items (NIH Publication et. al, 2009).

## Post Traumatic Stress Disorder (PTSD)

It occurs as a result of a terrible encounter in which bodily harm or the potential of physical injury was present. The individual who develops PTSD may have been the one who was harmed, a loved one was damaged, or the person observed a damaging occurrence that occurred to loved ones or strangers. PTSD was promptly and effectively brought to the tent! public attention in relation to war veterans Mugging, rape, torture, being abducted or held captive, child abuse, vehicle accidents, train wrecks, plane crashes, bombings, or natural catastrophes such as floods or earthquakes are all examples of traumatic experiences. (NIHPublicationet.al,2009).

People with PTSD may start easily, become emotionally numb (especially in relation to people with whom they used to be close), lose interest in things they used to enjoy, have trouble feeling affectionate, be irritable, become more aggressive, or even become violent. They avoid situations that remind them of the original incident, and anniversaries of the incident are often very difficult. PTSD symptoms seem to be worse if the event that triggered them was deliberately initiated by flashback may lose touch with reality and believe that the traumatic incident is happening all over again (NIHPublicationet.al, 2009).

Not every traumatized person develops full-blow nor even minor PTSD. Symptoms usually begin within 3 months of the incident but occasionally emerge years afterward. They must last more than a month to be considered PTSD. The course of the illness varies. Some people recover within 6 months, while others have symptoms that last much longer. In some people, the condition becomes chronic (NIH Publicationet.al,2009).

Social Phobia (Social Anxiety Disorder) is diagnosed when people become over whelming anxious and excessively self-conscious in everyday social situations. People with social phobia have an intense, persistent, and chronic fear of being watched and judged by others and of doing things that will embarrass them. They can worry for days or weeks before a dreaded situation. This fear may become so severe that it interferes with work, school, and other ordinary activities, and can make it hard to make and keep friends. While many people with social phobia realize that their fears about being with people are excessive or unreasonable, they are unable too overcome them. Even if they manage to confront their fears and be around hers, they are usually very anxious beforehand, are intensely uncomfortable throughout then counter, and worry about how they we prejudged for hours afterward. Physical symptoms that often accompany social phobia include blushing, profuse sweating, trembling, nausea, and difficulty talking. When these symptoms occur, people with PTSD feel as though all eyes are focused on them (NIH Publicationet.al,2009).

**Generalized Anxiety Disorder (GAD)** People with generalized anxiety disorder (GAD) go through the day filled with exaggerated worry and tension, even though there is little or nothing to Provo kit. They anticipate disaster and are overly concerned about health issues, money, family problems, or difficulties at work. Sometimes just the thought of getting through the day produces anxiety. GAD is diagnosed when a person worries excessively about a variety of everyday problems for at least 6 months. 13 People with GAD can’t seem to get rid of their concerns, even though they usually realize that their anxiety is more intense than the situation warrants. They can‘t relax, startle easily, and have difficulty concentrating. Often, they have trouble falling asleep or staying a sleep. Physical symptoms that often accompany the anxiety include fatigue, headaches, muscle tension, muscle aches, difficulties swallowing, trembling, twitching, irritability, sweating, nausea, light headedness, having to go to the bathroom frequently, feeling out of breath, and hot flashes (NIHPublicationet.al,2009).

Anxiety disorders are common affecting approximately 13% of the population at any one time. Benzodiazepines are often a ﬁrst-line treatment for anxiety but chronic administration may result in physiological dependence, and when treatment is terminated, a severe withdrawal syndrome can occur. Animal models can be used for the study of the withdrawal syndrome, as compare is ones can be a med without con founding pre-existing anxiety. These of animal models has result edit the identiﬁcation of dosages, frequencies, and durations of treatment required for inducing withdrawal symptoms. They also allow examination of possible treatment regimes that may alleviate the withdrawal symptoms. Two common behavior models used to evaluate the potential anxiolytic activity of compounds are the elevated plus and social interaction test. In the elevated plus maze, it has been demonstrated that animals treated with anxiolytic drugs spends significantly less time in the perceived safety of the dark arms an adventure more often in to the open arm

(DenovanP.Begget.al,2005).

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## Cause of anxiety Disorder

* **Genetics**: Anxiety disorders can path in families. (Ranna Parekh, 2017)
* **Brain chemistry**: Anxiety disorders may be linked to faulty circuits in the brain that control fear and emotions. (Ranna Parekh, 2017)
* **Environmental stress**: In this refers to stressful actions you have seen or lived through. Life events often linked to anxiety disorders include childhood abuse and neglect, a death of a loved one, or being attacked or seeing violence. (Ranna Parekh, 2017)
* **Drug withdrawal or misuse**: Certain drugs may be used to hide or decrease certain anxiety symptoms. Anxiety disorder often goes hand in hand with alcohol and substance use. (Ranna Parekh, 2017)
* **Medical conditions**: Some heart, lung, and thyroid conditions can cause symptoms like anxiety disorders or make anxiety symptoms worse. It is important to get a full physical exam to rule out other medical conditions when talking to your doctor about anxiety. (Ranna Parekh, 2017)
* **Risk factor of anxiety disorder:**

Some things also make you more probable to develop an anxiety disorder. These are called risk factors. Some risk factors you cannot change, but others you can. Risk factors for anxiety disorders include.

* **History of mental health disorder**: Having additional mental health disorder, like depression, raises your risk for anxiety disorder. (Ranna Parekh,2017)
* **Childhood sexual abuse:** If there is **e**motional, physical, and sexual abuse or neglect during childhood is linked to anxiety disorders later in life (Ranna Parekh,2017).
* **Trauma**: Existing traumatic event increases the risk of posttraumatic stress disorder (PTSD), which can cause panic attacks (Ranna Parekh,2017).
* **Negative life events**: Stressful or negative life events, like losing a parent in early childhood, increase your risk for anxiety disorder. (Ranna Parekh,2017)
* **Severe illness or chronic health condition**: Constant worry about your health or the health of a loved one, or caring for someone who is sick, can cause you to feel overwhelmed and anxious. (Ranna Parekh,2017)
* **Substance abuse**: The use of alcohol and illegal drugs makes you more likely to get an anxiety disorder. Some people also use these substances to hide or ease anxiety symptoms. (Ranna Parekh,2017)
* **Being shy as a child**: Shyness and withdrawal from unfamiliar people and places during childhood is linked to social anxiety in teens and adults. (Ranna Parekh,2017)
* **Low self-esteem**: Negative perceptions about yourself may lead to social anxiety disorder. (Ranna Parekh,2017)

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## Medical procedure

* **Medication**[.](https://www.webmd.com/drugs/index-drugs.aspx) Several types of drugs are used to treat anxiety disorders. Talk to your doctor or psychiatrist about the pros and cons of each medicine to decide which one is best for you. (Alexander Bystritsky, et,al, 2013)
* [**Antidepressants**.](https://www.webmd.com/depression/guide/depression-medications-antidepressants) Modern antidepressants are typically the first drugs prescribed to someone with an anxiety disorder. Examples of SSRIs are [escitalopram](https://www.webmd.com/drugs/drug-63989-escitalopram%2Boral.aspx) ([Lexapro](https://www.webmd.com/drugs/drug-63990-lexapro%2Boral.aspx)) and fluoxetine ([Prozac](https://www.webmd.com/drugs/drug-6997-prozac%2Boral.aspx)). SNRIs include duloxetine (Cymbalta) and venlafaxine (Effexor). ([Alexander](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) Bystritsky, et,al, 2013)
* **Bupropion.** This is another type of antidepressant commonly used to treat chronic anxiety. It works differently than SSRIs and SNRIs. (Alexander Bystritsky[,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) et,al, 2013)
* **Other antidepressants**. These include tricyclics and monoamine oxidase inhibitors (MAOIs). They are less commonly used because side effects, like drops in blood pressure, dry mouth, blurry vision, and urinary retention, can be unpleasant or unsafe for some people. ([Alexander](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) [Bystritsky,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) et,al, 2013)
* **Benzodiazepines**. If you are having persistent panicky feelings or anxiety. They help lower anxiety. Examples are [alprazolam](https://www.webmd.com/drugs/2/drug-8171-7244/alprazolam-oral/alprazolam-oral/details) ([Xanax](https://www.webmd.com/drugs/drug-9824-xanax%2Boral.aspx)) and [clonazepam](https://www.webmd.com/drugs/2/drug-14403-6006/clonazepam-oral/clonazepam-oral/details) ([Klonopin](https://www.webmd.com/drugs/2/drug-920-6006/klonopin-oral/clonazepam-oral/details)). They work quickly, but you can become dependent on them. Usually, they are meant to be an add-on to your anxiety disorder treatment, and you shouldn’t take them for a long time. ([Alexander Bystritsky,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) et,al, 2013)
* **Beta-blockers.** This type of high blood pressure drug can help you feel better if you are having physical symptoms of anxiety, such as a racing heart, trembling, or shaking. A beta-blocker may help you relax during an acute anxiety attack. ([Alexander Bystritsky,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) et,al, 2013)
* **Anticonvulsants**. Used to prevent seizures in people with epilepsy, these drugs also can relieve certain anxiety disorder symptoms. ([Alexander Bystritsky,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) et,al, 2013)
* **Antipsychotics**. Low doses of these drugs can be added to help make other treatments work better. ([Alexander Bystritsky,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) et,al, 2013)
* **Buspirone (BuSpar).** This anti-anxiety drug is sometimes used to treat chronic anxiety. You’ll need to take it for a few weeks before seeing full symptom relief. ([Alexander Bystritsky,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) et,al, 2013)
* **Psychotherapy:** This is a type of [counseling](https://www.webmd.com/balance/video/farrell-therapy-counseling) that helps you learn how your emotions affect your behaviors. It’s sometimes called talk therapy. A trained mental health specialist listens and talks to you about your thoughts and feelings and suggests ways to understand and manage them and your anxiety disorder. ([Alexander Bystritsky,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) et,al, 2013)
* **Cognitive behavioral** [**therapy**](https://www.webmd.com/mental-health/mental-health-psychotherapy) (CBT): This common type of psychotherapy teaches you how to turn negative, or panic-causing, thoughts, and behaviors into positive ones. You will learn ways to careful approach and manage fearful or worrisome situations without anxiety. Some places offer family CBT sessions. (Alexander Bystritsky[,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bystritsky%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599668) et, al, 2013)

## Animal Models of Anxiety What is a model?

In biomedical research, a model is usually described as an experimental setup or protocol (sometimes also called “a paradigm”) developed in a nonhuman species with the aim of replicating humans physiological, path physiological, or behavioural features. In other scientific disciplines (e.g, mathematics or physics), the term “model” usually refers to a theoretical construct from which specific hypotheses can be deduced and tested experimentally. Animal models of psychiatric disorders can belong to both categories. The most simple models, notably those aimed at testing psychotropic drugs or other treatments “empirical validity models” often have a limited if any theoretical background. This is also the case for those developed to simulate a specific sign or symptom (“Behavioural similarity models”). However, “theory-driven” and “mechanistic” models (according to McKinney's terminology), in particular those developed to study etiological aspects and/or the neurochemical and genetic mechanisms underlying anxiety disorders, often have an elaborate theoretical background. (Andre Ramoset.al,2008).

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## How do we measure anxiety in animals?

The only variables that can be observed and measured in animals are the behavioral and physiological responses elicited when they are exposed to more or less naturalistic, potentially anxiogenic situations under controlled laboratory conditions. Setup and protocols used to record these experimental data are usually called “tests,” and constitute instruments (or tools) to measure anxiety-related parameters. It should be mentioned that, in the animal research literature, particularly as regards the so-called preclinical (pharmacological) studies, the term “model” is often used abusively to characterize a test, ie, a particular experimental setup (eg, “The elevated plus-maze as a model of anxiety in rodents”!). This usage should be avoided, because it is misleading: a model in the true sense has a more elaborate theoretical background and may include several tests. In the following section, we will mention a few examples of (mainly ethological) anxiety tests for rodents, which are by far the most common species used as animals models nowadays. There are over 30 different procedures (and many variations) described in the literature, with two main categories: unconditioned response tests (which require no training and usually have a high eco/ethological validity) and conditioned response tests (which often require extensive training and may show interference with mnemonic and motivational processes).

More information regarding practical aspects of testing can be found in the literature and in the references. Although measurements can be done using a single test, it is better to use a battery of these tests (for instance, the open field, the EPM, and a dark/light transition test) to assess each individual's behavioral phenotype, since these tests measure anxiety under different conditions.

(Andre Ramoset.al,2008).

Data obtained from different tests can be combined to create derived variables which offer a more complete description of the individual behavioural profiles. Other elaborate forms of data analysis can (and should) be used: factorial analysis, structural analysis, or multivariate (principal component) analysis. Some of these tests are time-consuming, and therefore not always appropriate for large screening studies, but the throughput of behavioural assessment has been markedly improved in recent years by the use of automated monitoring, computer data processing, and the development of dedicated software for behavioural analysis. (Andre Ramoset.al,2008).

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## Animal models of anxiety:

Controlled experimental setups in which the behavioral repertoire of an animal is used to gain insight into human anxiety. Ideally, the animal model should resemble human anxiety in terms of its symptoms, behavioral signs, under lying biological mechanisms and effectiveness of pharmacological treatments (Andre Ramoset.al,2008).

## Elevated Plus Maze (EPM):

Currently the most popular test of anxiety; it consists of aplus-shaped maze, elevated from the floor with two open and two closed arms opposite to each other inter-connected by a central platform. Time spent in the unprotected open arms and percentage of entries in the open arms in relation to the total number of arm entries are used as experimental in dices of anxiety, whereas the entries in the closed (Andre Ramoset.al,2008).

## Factor Analysis:

A statistical technique used to replace a large number of variables with a smaller set of new indices that are linear combinations of the original variables. Because these indices are orthogonal and, thus, uncorrelated with each other, they are thought to represent different dimensions of the data (AndreRamoset.al,2008).

## Light–Dark box (LDB):

Also called black–white box, consists of two arm as connected to each other through a small opening. One area is smaller, black and non-illuminated, and the other is larger, white and brightly lit. Rodents tend to avoid the white compartment, thus, the measures of exploration in this area (time, locomotion and entrances) are used as experimental indices of anxiety (Andre Ramoset.al,2008).

* **Open Field (OF):** A large arena (much larger than the home cage) originally conceived to measure emotionality in rats. It is usually brightly illuminated and a naive animal is observed for a variable amount of time. Rodents tend to avoid the central un protected area and concentrate their ambulation near the walls. Measures of central exploration are often regarded as anxiety-related indices (Andre Ramos et.al,2008)

Anxiety is a aversive emotional state, in which the feeling of fear is disproportionate to the nature of the threat. In response to threatening situations, the feeling of the emotion that constitutes the subjective feature of anxiety is accompanied by emotional stress, which involves behavioral, expressive and physiological features, such as an avoidance of the source of the danger, assuming defensive postures and an increase in blood pressure, respectively. Anxiety is a normal emotional response to at heat or potential threat. When this emotion is inappropriate, extreme and persistent, it is classified as pathological. Anxiety is implicated in a number of psychiatric Disorders, such as depression, panic attacks, phobias, generalized anxiety disorder, obsessive compulsive disorder rand post-traumatic stress disorder. Anxiety disorder safest approximately 28.8% of the US population, imposing both an individual and a social burden that amounts to a total cost of $42.3billion in the U Sin 1990.5Anxietydisorders are the most common class of psychiatric disorders in the US4andmanyother countries. According to an ESEMeD study including six European countries, the12-month prevalence of in appropriate anxiety was 6.4%. In the most recent systematic review of studies conducted in16 European countries, however, this value was estimated to be 12%. In an obese population in the UK, 56% of patients met the minimum criteria for an anxiety disorder. It is estimated that one-eighth of the total population worldwide suffers from in appropriate anxiety. (JaouadBouayedet.al,2009).

Population-based studies have shown that anxiety disorders frequently go untreated. Predominantly, the research that has been performed on anxiety has focused on the regulatory systems, including gamma amino butyric acid ergic (GABAergic) and serotoninergic systems among others. Demonstrating that other systems, such as oxidative metabolism, can affect their anxiety. These findings, which establish a link between oxidative stress and pathological anxiety, inspired a number of other recent studies focus in on the link between oxidative status and normal anxiety and also on a possible causal relationship between cellular oxidative stress and emotional stress .It is well known that low/moderate concentrations of reactive oxygen species (ROS) affect a great number of physiological functions. However, when ROS concentration exceeds the ant oxidative capacity of an organism, animal cells enter a state termed oxidative stress, in which the excess ROS induces oxidative damage on cellular components. As a result, oxidative stress has been implicated in a large range of diseases, including cancer, diabetes, male infertility, autoimmune diseases, atherosclerosis and cardiovascular disorders. (Jaouad Bouayed et.al, 2009).

The brains highly vulnerable to oxidative stress due to its high O2 consumption, its modest antioxidant defenses and its lipid-rich constitution. Human brain utilizes 20% of oxygen consumed by the body even though this organ constitutes only about 2% of the bodyweight. When the production of oxygen-derived metabolites prevails over the brain defense systems, however, oxidative damage to nucleic acids, proteins and neuronal membrane lipids, which are rich in highly polyunsaturated fatty acids, can occur. In presence of oxidative stress, the lipid-rich constitution of brain favors lipid per oxidation that results in decrease in membrane fluidity and damage in membrane proteins inactivating receptors, enzymes and ion channels. As a result, oxidative stress can alter neurotransmission, neuronal function and overall brain activity. (Jaouad Bouayed et. al,2009).

Oxidative stress has been associated with several diseases which are specific for nervous system impairment including neurodegenerative diseases and neuropsychiatric diseases, such as schizophrenia and major depressive disorder. The intrinsic oxidative vulnerability of the brain has led some authors to suggest that oxidative damage may be a possible pathogenic factor for certain neurological diseases including neuropsychiatric disorders. In this review, we m discuss the relationship between oxidative stress and normal anxiety by presenting the recent advances in the field and the different views that exist. We also review the methodological approach for determining the causal relationship between oxidative stress and emotional stress (JaouadBouayedet.al,2009).

**Link Between Oxidative Stress Metabolic Pathways and Anxiety –Related Phenotypes**

In 2005, Hovatta identified a close relationship between anti oxidative defense mechanisms and anxiety-related phenotypes in six inbred mouse strains. They found that, in the brain, the expression of glutathione reductase1 and glyoxalase1, which are genes involved in anti-oxidative metabolism, is highly correlated with anxiety-related phenotypes. Furthermore, they also found that the activity of these enzymes is highest in the most anxious mice and lowest in the least anxious strains. These authors were the first to demonstrate a link between oxidative stress metabolic pathways and normal anxiety. A link between oxidative stress and emotional stress is not surprising, since it is well accepted that oxidative damage in the brain causes an impairment of the nervous system. In living organisms, an imbalance between (JaouadBouayedet.al,2009). Oxidant production and antioxidant protection that favors oxidants causes a state termed oxidative stress. In this state, there can be differences gene expression protein on formation and cellular signaling. This state may also alter neurotransmission, neuronal function and overall brain activity, as well as disrupting membrane integrity; even neuronal cell death may result. Most studies have shown that anxiety is controlled by the nervous system and that GABA nergic and serotoninergic systems play important roles in the regulation of anxiety. Abnormalities in these regulatory systems in rodents, which are used as translational models for human anxiety, can resulting anxious behavior. Altering the function the hypothalamic-pituitary- adrenal (HPA) axis,which is implicated in stress responses and anxiety disorders, could also impact the emotional response.

Neverthless, Hovatta obtained surprising results in a genetic manipulation in antivirus-mediate gene transfer: local over expression of glutathione reducates 1 and glyoxalase 1 in the cingulated cortex of the marine brain results in an increase of anxiety-like behavior, while inhibition of glyoxalase1expression produces low-anxiety mice. Thus, Hovatta were able to make a causal link between the anti-oxidative status of the brain and anxiety-related behavior and hypothesize that glyoxalase 1 and glutathione reductase 1 regulate anxiety in mice. It is worth mentioning that in vivo, antioxidant genes are over expressed in response to an uncontrolled production of ROS. Indeed, in vivo, excessive ROS accumulation induces the over expression of the glutathione redox system, including glutathione reeducates, and a general over expression of endogenous antioxidants. In the antivirus experiments of Hovatta, however, the over expression of the transgenic (glyoxalase1and glutathione reductase1) was induced in vivo with antiviral vector and not an excessive production of toxic oxygen metabolites. Clearly, the mechanism by which these enzymes regulate anxiety is of great interest. During the same period in which the Hovatta study was being conducted, other studies were performed on two Swiss CD1mouselines with contrasting anxiety-like behavioral phenotypes. (JaouadBouayedet.al,2009).

These mice were generated from wild type mice after >15 generations of selection. Results from these studies have led researchers to propose that glyoxalase 1 might be a biological marker for trait anxiety these results are discordant with those of Hovatta however, and complicate the understanding of the relationship between oxidative stress and trait anxiety. Krömer and Ditzenexamined the expression of glyoxalase 1 in several areas of the brain areas and in red blood cells and found that this protein is expressed more in a line with a low-anxiety-related behavioral phenotype than in a line with a high-anxiety-related behavioral phenotype. It is worth noting that Hovatta suggested the there is a link between glyoxalase 1 and oxidative stress but that this link is indirect. Indeed, glyoxalase 1 is an enzyme of the glyoxalase system, which protects against carbonyl stress; glutathione is a determinant cofactor for the enzymatic reaction that is catalyzed by glyoxalase 1(JaouadBouayedet.al,2009).

Anxiety may be regarded as a particular form of behavioral inhibition that occurs in response to environmental events that are novel. Anxiety affects one-eighth of the total population worldwide and has become a very important area of research interest in psychopharmacology during this decade. There are various ways of explaining themechanisms of action of anti-anxiety agents because of the involvement of many CNS chemical mediators. The effect of most of the anxiolytic agents is to enhance the response to GABA, by facilitating the opening of GABA activated chloride channels. GABAA receptors were involved in anxiety and their direct activation would have ananxiolytic effect. Anti-anxiety drugs have also been shown to act on limbic system, hypothalamus, and the brain stem reticular system. Benzodiazepines are still the most frequently used drugs for the treatment of generalized anxiety disorder despite their undesirable side effects such as muscle relaxation, sedation, physical dependence, memory disturbance, and interaction with other drugs. However, the realization that benzodiazepines present a narrow safety margin between the anxiolytic effect and those causing unwanted side effects has prompted many researchers to evaluate new compounds in the hope that to the anxiolytic drugs will have less undesirable effects. (JaouadBouayedet.al,2009).

In recent years, the development of new anxiolytics has been an area of interest. It has been established that there are lot of secondary plant metabolites being employed in the treatment of psychotic disorders specially for anxiety in traditional medicine practice, most of which directly or indirectly affect the central nervous system such as nor adrenaline, serotonin, gamma-amino butyric acid (GABA), and benzodiazepine (BDZ) neurotransmitters activities. (Jaouad Bouayed et. al, 2009).

Various types of herbal medicines have been used as anxiolytic agents in different parts of the world. Drugs derived from traditional herbs may have possible therapeutic relevance in the treatment of anxiety. Research has been conducted to investigate natural anxiolytic agents in the search for an alternative, more specific, and perhaps cost-free therapy. Various types of herbal medicines have been used as anxiolytics in different parts of the world. The root of the kava plant from the tropical Pacific region, St. John’s wort extract from Europe, and the saponin-containing fraction of the leaves of A. lebbeck from India are known to have anxiolytic effects. (Jaouad Bouayed et. al,2009).

The elevated plus-maze is a well-established animal model for testing anxiolytic drugs. Diazepam, a standard anxiolytic used clinically, is also employed in behavioral pharmacology as a reference compound for inducing anxiolytic-like effects, even when the compound being screened does not act via benzodiazepine receptors. In the present study, we found that the various plants extract increased the percentage of open arm entries and time spent in open arms and thus showed anxiolytic effects in this model. The anxiolytic effects of drugs such as benzodiazepines are accompanied by decreased locomotor activity and sedation. However, the various plants extract inhibited locomotor activity to a lesser extent than diazepam, and thus has a better profile for an anxiolytic agent. There is considerable interest in the development of new anxiolytics that do not induce sedative effects and do not inhibit locomotion. The effect of most of the anxiolytic agents is to enhance the response to GABA, by facilitating the opening of GABA-activated chloride channels. GABAA receptors were involved in anxiety and their direct activation would have an anxiolytic effect. It is well documented that pentylenetetrazole-induced convulsions are produced due to diminution of GABA level in brain (K. Lathaet.al,2015).

About 40 % of people with Parkinson‘s disease (PD) and depression also have an anxiety

disorder. The link between PD, depression and anxiety is complex. Its neuropathology includes the degeneration of dopaminergic nigrostriatal pathway, which is accumulative effect to glutathione depletion, iron deposition, increased lipid per oxidation, oxidative DNA damage, mitochondrial dysfunction, excite toxicity and alterations in antioxidant enzymes activities. Previous studies indicated the role of the a amygdale in regulating anxiety, depression responses and fear memory in both humans and animals. Furthermore, the dopamine neurotransmitter system is involved in a large number of higher brain functions, and regulates the activity of the amygdale. The most widely used animal models of PD involve intracranial infusion of the neurotoxin 6-OHDA directly into the ascending dopaminergic forebrain bundle, thereby inducing severe dopaminergic neuronal degeneration associated with profound deficits in feeding, drinking, sensory motor and learning functions (AlainDongmoet.al,2015).

Anxious reaction is an adaptive reaction of an individual when confronted with danger or threat. Behavioral and physiological responses accompanying anxiety prepare an individual to react appropriately to such situation. One of the most widely used animal models for screening putative anxiolytic is the elevated plus-maze. The EPM is considered to be an etiologically valid animal model of anxiety because it uses natural stimuli, such as a fear of a new, brightly-lit open space and the fear of balancing on relatively narrow raised platform, moreover it is known that anxiolytic agent increases the frequency of entries and time spent in open arm of the EPM. In agreement with previously published reports, diazepam increased the percentage time spent on open arms and the number of entries on open arms . Total number of open arm entries and number of closed arm entries are usually employed as measures of general activity. In the present study its noted that administration of AEPA prolonged the time spent in the open arms and the number of entries into open arms. The light/dark box is also widely used model for screening anxiolytic or antigenic drugs, based on the innate aversion of rodents to brightly illuminated areas and on the spontaneous exploratory behavior of rodents in response to mild stressors, that is, a novel environment and light .It has been reported that simply the measurement of the time spent in the light area, but not the number of transfers, is the most consistent and useful parameter for assessing ananxiolytic action. The present study showed that AEPA could increase the time in the light area, suggesting again that AEPA possesses anxiolytic properties. The hole- board test provides a simple method for measuring the response of an animal to an unfamiliar environment and is widely used to assess emotionality, anxiety and/or responses to stress in animals. It has been shown that head-dipping behavior was sensitive to changes in the emotional state of the animal, and suggested that the expression of an anxiolytic state in animals may be reflected by an increase in head dipping behavior. In the person study AEPA increased head-dip counts and head-dip duration without changing locomotion.

These results indicate that AEPA has a significant anxiolytic effect in this paradigm (J.P.Jhabarmalet.al,2013). Anxiety and mood disorders account for the vast majority of individuals suffering from mental health problems. Given this, it is important to gain a better understanding of the shared and unique vulnerabilities to these forms of psychopathology so that more effective prevention and early intervention efforts can be developed. One potentially important risk factor is childhood temperament, which can be understood as one‘s natural disposition toward his or her physical and interpersonal world. A chill ‘temperament is believed to have a notable impact on the way in which the child adapts to his or her world. The temperament style of behavioral inhibition (BI) is characterized by reticence to interact with novel people and situations, and may represent a shared vulnerability for internalizing disorders such as anxiety and depression. In considering the role of BI in the subsequent development of psychopathology, previous research has largely focused on the role of BI in the development of pathological anxiety, and more speciﬁcally, social anxiety. More recently, there has been evidence to suggest that BI may be a more general risk factor for internalizing disorders. For example, studies have suggested that childhood BI may also be related to internalizing disorders such as panic anxiety, obsessive– compulsive anxiety, and depression. Thus, there is evidence to suggest that BI may represent a general vulnerability factor for internalizing disorders rather than a septic predisposition to social phobia. The relation between BI and depression, it is important to note that individuals suffering from anxiety disorders are at an increased risk for developing depression in comparison to non-anxious individuals, and evidence suggests that in many instances the presence of an anxiety disorder precedes the development to from or depression. Given such temporal relationship between anxiety and depression, it is important to consider that associations between BI and depression may be largely contingent upon the presence of anxiety. In fact, one study found that social anxiety fully mediated the relation between I and depression, supporting the hypothesis that the link between childhood BI and later depression was not direct, but rather mediated by the presence of social anxiety symptoms(Casey.A.Schofieldet.al,2009).

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## Importance of Medicinal Herbs:-

Plant is an important source of medicine and plays a key role in world health. Medicinal herbs or plants have been known to be an important potential source of therapeutics or curative aids. The use of medicinal plants has attained a commanding role in health system all over the world. This involves the use of medicinal plants not only for the treatment of diseases but also as potential material for maintaining good health and conditions. Many countries in the world, that is, two-third of the world’s population depends on herbal medicine for primary health care. The reasons for this is because of their better cultural acceptability, better compatibility and adaptability with the human body and pose lesser side effects. From records, most of the used drugs contain plant extracts. Some contain active ingredients (bio active components or substances) obtained from plants. Through recent researches, plant-derived drugs were discovered from the study of curative, therapeutic, traditional cures and most especially the folk knowledge of indigenous people and some of these claims and believe of people are irreplaceable despite the recent advancement in science and technology. Some of the drugs believed to be obtained from plants are aspirin, atropine, art immersing in, colchicine, digoxin, ephedrine, morphine, physostigmine, pilocarpine, quinine, quinidine, reserpine, taxol, tubocurarine, vincristine and vinblastine. (OlodejiO.et.al,2016)

Medicinal plants may be defined as those plants that are commonly used in treating and preventing specific ailments and diseases and that are generally considered to be harmful to humans. These plants are either―wild plants pieces‖ those growing spontaneously in self maintaining populations in natural or semi-natural ecosystems and could exist independently of direct human actions or the contrasting ―Domesticated plants species those that have arisen through human actions such as selection or breeding and depend on management for their existence. Herbal medicines proved to be the major remedy in traditional system of medicine. They have been used extensively in medical practices since ancient times. This prompts the development in the practices of medicinal plants. The reasons are because of their biomedical benefits as well as place in cultural beliefs in many parts of world in the development of potent therapeutic agents. During 1950-1970, approximately 100 plants based new drugs were introduced in the USA drug market including deserpidine, reseinnamine and vincristine which are derived from higher plants. Medicinal plants have provided mankind a large variety of potent drugs to all eviateor eradicate infections and suffering from diseases in spite of advancement in synthetic drugs, some of the plant-derived drugs still retained their importance and relevance. The use of plant-based drugs all over world is increasing. (OlodejiO.et.al,2016)

There have been records of advances made in the modern (synthetic) medicine there are still a large number of ailments or infection (diseases) for which suitable drugs are yet to be found. This have brought an urgent need to develop safer drugs (both for man and his environment) for the treatment of inflammatory disorders diabetes, liver diseases, and gastrointestinal disorder. Through recent researches on herbal plants or medicine, there have been great developments in the pharmacological evaluation of various plants used in traditional systems of medicine. Consequently, plants can be described as a major source of medicines, not only as isolated active principles to be dispensed in standardized dosage form but also as crude drugs for the population. Modern medicines and herbal medicines are complimentarily being used in areas for health care program in several developing countries such as countries in Africa, Asia and some part of Europe. Due to different outcomes on herbal plants, plant products surfaces all over the world due to the belief that many herbal medicines are known to be free from health and environmental effects. The fear of the masses in the utility of synthetic drug or modern drugs is always accompanied with its single or multiple adverse or health effects. Important properties of photochemical The use of plants for treating diseases is as old as the human species. Popular observations on these and efficacy of medicinal plants significantly contribute to the disclosure of their therapeutic properties, so that they are frequently prescribed, even if their chemical constituents are not always completely known. For example, Samna is used traditionally in Nigeria to treat bacterial and fungal infections. They also showed varying degrees of antibacterial and antifungal activities against pathogens. (OlodejiO.et.al,2016).

Flavonoids have been found to exhibit a greater antifungal and antibacterial activity against some human pathogenic fungi and bacteria. The therapeutic potency of medicinal plant is due to the presence of some bioactive components. These bioactive components are ascertained using photochemical screening such as photochemical tests and thin layer chromatography. Medicinal plants contain a wide variety of Secondary metabolites or compounds such as tannins terpenoids, alkaloids, flavonoids; that indicates the therapeutic potency of the plants most especially the antimicrobial activities. Similar photochemical constituents such as flavonoids and tannins were also revealed to be active against pathogenic bacteria such as Bacillus cereus, Staphylococcus aurous amongst others (OlodejiO.et.al,2016).

The tannins present in medicinal plants make it useful in production of anti-septic soap which hare commonly used in bathing or cleansing of skin surfaces. It was documented in literature that photochemical can be toxic to filamentous fungi, yeast sand bacteria, and also, inhibitory to viral reverse transcriptase . Saponins were reported as a major component acting as antifungal secondary metabolite. A wide range of physiological activity of saponins, steroids, phenols and tannins are found to be more predominant and therefore may be responsible for the antimicrobial action (OlodejiO.et.al,2016).

Tannins have astringent properties which hasten the healing of wounds and inflamed mucous membrane due to their physiological activities such as anti-oxidant, antimicrobial and anti-inflammatory properties. The healing properties of medicinal plants could be due to the presence of tannins. They are known to posses‗ astringent, anti-inflammatory, antidiarrheal, anti-oxidant and antimicrobial properties. Saponins have been traditionally used in detergents, pesticides and molluscides in addition to their industrial applications such as foaming and surface active agents. They help in controlling cardiovascular diseases and in controlling cholesterol in humans (Olodeji O. et. al,2016).

## Benefits of Herbal Medicine:

Herbal remedies have been used for huge number of years like conventional medicine. Infect, herbal medicine is the establishment of modern medicine. This medicine also has very less side effects. Tragically, herbal medicine usually takes a backseat when compared with conventional drug therapy, which is a shame since herbal remedies offer lots of health benefits .In today’s world, Herbal medicine most of the parts of the plants are used to treat intense and constant sicknesses (OlodejiO.et.al,2016).

* More affordable than conventional medicine.
* Easier to obtain than prescription medicine.
* Stabilizes hormones and metabolism.
* Natural healing.
* Strength in immune system.
* Fewer side effects.
* Cost effective.

**Role Of Medicinal Plants In Various Diseases:-** Frequently used traditional drugs in different ailments are:-

* **Cough & Cold:-**

Leaves of Angelica, Garlic, Tulsi, Eucalyptuses. Dried stigma of Saffron, Ginger (MohinuddinA.K.et.al,2019).

## GID is orders:-

Ispaghula husk, Senna leaves, honey (constipation), barkof Cascara, Cardamom, Cinnamon, Chirata (stomachic) (MohinuddinA.K.et.al,2019).

## Urinary disorders:-

Kalmegh, Picrorhiza, Jar-amla (Cholagogue disorders) ;Arjuna,Punarnava(Diureticailments) (MohinuddinA.K.et.al,2019).

## ArthritisandRheumatoiddisorders:-

Rasna (Rheumatism), Gugul resin (anti-arthritic) (Mohinuddin A.K. et.al,2019).

## Insomnia or other sleep disorders:-

Ashwagandha, Belladonna, Datura, Cannabis, Hyoscyamus, Wild Cherrybark (Mildsedative) (MohinuddinA.K.et.al,2019).

## Cardiac:-

Sarpagandha (hypotensive), Strophanthus (Cardiotonic) (Mohinuddin A.K. et.al,2019).

## Others:-

Chenopodiumoil (Anthelmintic), Vasaka (Anti-asthmatic), Turmeric, Punarnava, Ashwagandha (Anti-inflammatory) (Mohinuddin A.K. et. al, 2019).

**Frequently used traditional plants with specified pharmacological action :**-

**Anti-amoebic**:-Ipecuc root,Kurchibark.

**Anti-Asthmatic**:-Ephedra,Vasaka,Tylophora..

**Anti-spasmodic**:-Belladonna,Datura,Hyoscyamus.Analgesic:-Opium,Cannabis. **Carminative:**-Cinnamonbark, Cardamomseed, Nutmegfruit, Clove, Saffron.

**Purgative** :-Cascara bark,Sennaleaf,Rhubarb.

**Bitter Tonic:**-Nux-vomica, Gentian, Picorhiza, Chirata, Kalmegh.

**Cardiotonic**:-Digitalis, Squill, Strophanthus.

**Tranquilizers** :-Rauwolfia Roots.

**Expectorant**:-Benzoin, ToluBalsam, Vasaka.

**CNS action:**- Ergot, Belladonna, Stramonium, Ephedra, Physostigma (MohinuddinA.K.et.al,20

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