

DEPRESSION; COMPLEMENTARY THERAPY

FOR PARTIAL FULFILLMENT OF B.Sc. BIOTECHNOLOGY

REVIEW

BY

ANGEESTA ALEY

T.Y. B.Sc.



UNDER THE GUIDANCE OF

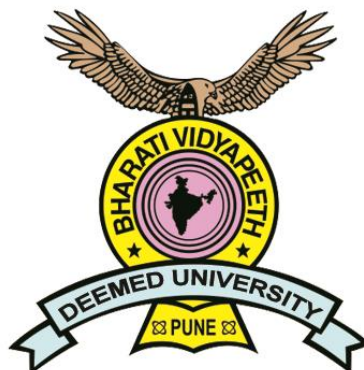
Mrs. NEELAMBIKA METI

BHARATI VIDYAPEETH DEEMED UNIVERSITY

RAJIV GANDHI INSTITUTE OF IT AND BIOTECHNOLOGY, KATRAJ,

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BHARATI VIDYAPEETH UNIVERSITY
RAJIV GANDHI INSTITUTE OF IT & BIOTECHNOLOGY, Katraj, Pune-46

CERTIFICATE

23/03/16

This is to certify that **Ms. Angeesta Aley** of **Third year, B.Sc Biotechnology** has satisfactorily completed the REVIEW REPORT for fulfillment of Bachelor Degree in Biotechnology as prescribed in the syllabus of **Rajiv Gandhi Institute of IT and Biotechnology, B.V.D.U, Pune,** in the academic year **2012-2013.**

Candidate

Mrs. Neelambika Meti

Dr. G.D. Sharma

Angeesta Aley

Review Guide

Principal

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Abstract

The condition of depression appears to have increased over the past three decades. There is an evidence that a range of lifestyle factors are involved in the pathogenesis of depression. “Lifestyle Medicine” provides a nexus between public health promotion and clinical treatments, involving the application of environmental, behavioral, and psychological principles to enhance physical and mental wellbeing. The major components of Lifestyle Medicine, consisting of the evidence-based adoption of physical activity or exercise, dietary modification, adequate relaxation/sleep and social interaction, use of mindfulness-based meditation techniques, and the reduction of recreational substances such as nicotine, drugs, and alcohol.

Over the past several decades, complementary and alternative medications have increasingly become a part of everyday treatment. With the rising cost of prescription medications and their production of unwanted side effects, patients are exploring herbal and other natural remedies for the management and treatment of psychological conditions. As a result, there has been increased interest in the use of complementary and alternative medicines (CAM) as a natural method for treating numerous types of anxiety.

Complementary and alternative medicine (CAM) has been used either alone or in combination with conventional therapies in patients with mood disorders. This review of the literature examines evidence based data on the use of CAM in mood disorders. Mood disorders are a major public health problem and are associated with considerable burden of disease, suicides, physical comorbidities, high economic costs, and poor quality of life. Ayurvedic and homeopathic therapies have the potential to improve symptoms of depression, although larger controlled trials are needed. Mind-body-spirit and integrative medicine approaches can be used effectively in mild to moderate depression and in treatment-resistant depression. People are using herbal medicines from centuries for safety, efficacy, cultural acceptability and lesser side effects. Plant and plant products have utilized with varying success to cure and prevent diseases throughout history. Written records about medicinal plants date back at least 5000 years to the Sumerians and ancient records are suggested earlier use of medicinal plants. Due to side effects of synthetic products, herbal products are gaining popularity in the world market.

1.0 Introduction

Depressive disorders are amongst the most severe and important illnesses globally. They affect a person's thoughts, feelings, body, and social relationships - their entire being in effect. In spite of its enormous importance, depression often goes undetected or is not suitably treated. This results in great suffering and a lower quality of life for those affected and their family members. It has become increasingly clear over recent years that depression is a chronic stress-induced disorder. Hence, it is also referred to as "stress depression". It is a risk factor in the development of other widespread serious illnesses, including heart attacks, strokes, osteoporosis and diabetes. If not treated properly, depression can reduce life expectancy.

Depression is a serious illness, but it can be cured. It is not normal sadness, nor a breakdown, nor a weakness of will. Advances over recent years have given us a new, more comprehensive picture of the ways in which depression can be treated.

Sustained and specialized psychotherapy and drug treatment of depression is important for complete recovery as 80% of patients with lingering symptoms will suffer a relapse. During maintenance treatment to prevent relapses, patients are monitored for at least six months after the symptoms of the disorder have regressed [3] While modernity has provided multiple technological and medical advances including increased life-expectancy, it has come at a cost, in that a range of lifestyle issues are now negatively affecting our mental health. In combination with sleep/wake cycle pressures, substance misuse, and psychosocial factors such as more competition and time pressure, social isolation and less intimate engagement with the family unit, may exert a cost on mental health. Further, combination of stress, fatigue, inactivity, and sleep deficiency in people who are "time-poor", may advance obesity, and this in turn may promote a sedentary life with potential for resultant depression. While medication and psychological interventions are first-line treatments for depression, lifestyle medicine offers a potentially safe and low-cost option for augmenting the management of the condition. Many patients with mood disorders who are dissatisfied with conventional treatment seek other interventions, in particular complementary and alternative medicine (CAM). In general, CAM is safe and cost-effective, has limited comparative efficacy to modern allopathic treatments, and is well tolerated by patients with physical and mental disorders.[5]

2.0 What is depression?

Depression is a syndrome, a cluster of emotional, physical, and behavioral symptoms characterized by sadness, low self-esteem, loss of pleasure, and, sometimes, difficulty functioning. If these problems persist for more than two weeks, cause real suffering, and interfere with the business and pleasure of daily life you may have a clinical depression [9].

The term “depression” can be used to describe many types of emotional states. Most often it is used to describe a feeling or mood. Feeling depressed at times is a normal part of life. Depression can also be a symptom related to short term or long standing difficulties in dealing with aspects of life. A small percentage of the time, depression can be part of serious psychiatric syndromes.

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Moreover, depression often comes with symptoms of anxiety. These problems can become chronic or recurrent and lead to substantial impairments in an individual’s ability to take care of his or her everyday responsibilities [8]. At its worst, depression can lead to suicide. Almost 1 million lives are lost yearly due to suicide, which translates to 3000 suicide deaths every day. For every person who completes a suicide, 20 or more may attempt to end his or her life (WHO, 2012). There are multiple variations of depression that a person can suffer from, with the most general distinction being depression in people who have or do not have a history of manic episodes.

3.0 What are the different forms of depression?

There are several forms of depressive disorders.

3.1 Major depression - severe symptoms that interfere with your ability to work, sleep, study, eat, and enjoy life. An episode can occur only once in a person’s lifetime, but more often, a person has several episodes.

Depression is a common but serious illness. Most who experience depression need treatment to get better.

3.2 Persistent depressive disorder (Dysthymia) - Those living with chronic, low-grade depression have what is called dysthymia and it lasts for at least 2 years. A person diagnosed with persistent

depressive disorder may have episodes of major depression along with periods of less severe symptoms, but symptoms must last for 2 years.

When people experience both dysthymia and major depression, they are sometimes said to have double depression [1-2].

Some forms of depression are slightly different, or they may develop under unique circumstances. They include:

- **Psychotic depression**- which occurs when a person has severe depression plus some form of psychosis, such as having disturbing false beliefs or a break with reality (delusions), or hearing or seeing upsetting things that others cannot hear or see (hallucinations) [5].
- **Postpartum depression**- which is much more serious than the “baby blues” that many women experience after giving birth, when hormonal and physical changes and the new responsibility of caring for a newborn can be overwhelming. It is estimated that 10 to 15 percent of women experience postpartum depression after giving birth [6].
- **Seasonal affective disorder (SAD)** - which is characterized by the onset of depression during the winter months, when there is less natural sunlight. The depression generally lifts during spring and summer. SAD may be effectively treated with light therapy, but nearly half of those with SAD do not get better with light therapy alone. Antidepressant medication and psychotherapy can reduce SAD symptoms, either alone or in combination with light therapy [6].

Some cases of “seasonal depression” or “winter depression” can lead to a severe and even life-threatening disorder. The lower amount of light reaching us through our eyes at this time of year is the cause. In the case of people susceptible to this, it can cause a metabolic disorder in the brain and thus depression.

3.3 Unipolar Disorder- People who have recurrent episodes of major depression are sometimes said to have unipolar depression (or “clinical depression”), because they only experience periods of low, or depressed mood [3].

3.4 **Bipolar Disorder**- Bipolar disorder is another type of mood disorder, different from unipolar depression. People diagnosed with this illness have mood swings involving both lows (bipolar

depression) and highs (called mania if severe or hypomania if mild). It's estimated that 2 to five percent of American adults will suffer some form of bipolar disorder

The two most common types are bipolar I and bipolar II.

- **Bipolar I** disorder used to be called “manic depressive illness.” It's the “classic” form of the illness in which the individual experiences extreme highs (mania) and lows (bipolar depression) in mood.
- **Bipolar II** disorder don't have such extreme highs or manic symptoms. Instead, they experience just mild highs, or hypomania. The symptoms of hypomania are similar to those of mania, but less intense and severe. People who experience hypomania might not feel impaired at all. For example, people who are hypomanic might be more talkative than usual, but their speech makes sense and seems to follow a logical pattern. They don't experience hallucinations or delusions. Hypomania might make them appear more energetic or productive. But if their illness goes untreated, they can become severely depressed. Those with bipolar II disorder tend to have more depressive episodes than those with bipolar I [4].

In a severe case of bipolar disorder, people experience extreme highs known as mania.

4.0 What are the signs and symptoms of depression?

People with depressive illnesses do not all experience the same symptoms. The severity, frequency, and duration of symptoms vary depending on the individual and his or her particular illness.

Signs and symptoms include:

- Persistent sad, anxious, or “empty” feelings
- Feelings of hopelessness
- Feelings of guilt, worthlessness, or helplessness
- Irritability, restlessness
- Loss of interest in activities or hobbies once pleasurable, including sex
- Fatigue and decreased energy

- Difficulty concentrating, remembering details, and making decisions
- Insomnia, early-morning wakefulness, or excessive sleeping
- Overeating, or appetite loss
- Thoughts of suicide, suicide attempts
- Aches or pains, headaches, cramps, or digestive problems that do not ease even with treatment [11]

Sign and symptoms of Major Depressive Episodes

- Prolonged sadness or unexplained crying spells
- Significant changes in appetite and sleep patterns
- Irritability, anger, worry, agitation, anxiety
- Loss of energy, persistent lethargy, fatigue
- Feelings of guilt, worthlessness or helplessness
- Inability to concentrate, difficulty making decisions
- Social withdrawal
- Inability to take pleasure in activities or hobbies once pleasurable
- Unexplained aches and pains, or aches and pains that don't ease with treatment
- Recurring thoughts of death or suicide [13]

Sign and symptoms of mania

- Restlessness, increased physical/mental activity and energy
- Heightened or “high” mood, exaggerated optimism and self-confidence
- Excessive and extreme irritability, aggressive behavior
- Decreased need for sleep without feeling tired
- Inflated sense of self-importance and abilities
- Racing speech, racing thoughts, flight of ideas
- Impulsiveness, poor judgment, distractibility, inability to concentrate
- Reckless behavior like spending sprees, drug use, sexual indiscretions
- A period of unusual or uncharacteristic behavior
- In the most severe cases, delusions and hallucinations [14]

5.0 What causes depression?

Most likely, depression is caused by a combination of genetic, biological, environmental, and psychological factors.

Research indicates that ongoing difficulties, such as long term unemployment, alcohol problems, chronic illness, or living in an abusive or uncaring relationship, are more likely to cause depression than recent stressful situations. These include:

5.1 Family

- A family or personal history of depression.
- Conflict or violence within your family.
- Bad things that happen when you were a child [15]

5.2 Events

- Death or loss of someone close.
- Breaking up with a partner.
- Falling out with someone you care about.
- Traumatic or life threatening events.
- Too much pressure and stress at work, school or university.
- Feeling you're being bullied or undermined.
- Losing your job or being unemployed for a long time.
- Having a head injury or other trauma, epilepsy, or a long term or serious illness.
- Some women experience depression during or after childbirth [16]

Lifestyle

- Drinking too much alcohol.
- Using a lot of recreational drugs such as cannabis.
- Social isolation.
- Lack of sleep.
- Poor diet and lack of exercise.

Depressive illnesses are disorders of the brain. Some types of depression tend to run in families. However, depression can occur in people without family histories of depression too.⁹ Scientists are studying certain genes that may make some people more prone to depression. Some genetics research indicates that risk for depression results from the influence of several genes acting together with environmental or other factors [17]. In addition, trauma, loss of a loved one, a difficult relationship, or any stressful situation may trigger a depressive episode. Longstanding theories about depression suggest that important neurotransmitters—chemicals that brain cells use to communicate—are out of balance in depression. Acute stresses such as the loss or death of an important person to whom we are close or chronic pressure situations can trigger a depressive disorder.

The brain's metabolism is disturbed during depression, with the neurotransmitters serotonin, noradrenalin and dopamine out of kilter with one another. The disturbed control system for stress hormones is the cause as persistent over activation of the stress hormone system can disturb nerve cell metabolism to such a degree that the production and degradation of the transmitters is derailed. They are either present in too low of a concentration or transmission is no longer working correctly. If transmission between the nerve cells is disturbed as a result, this also gradually lowers how we feel and our thoughts resulting in a lack of drive, loss of appetite, sleep disorders, difficulty concentrating and other symptoms of depression [18].

6.0 How is depression diagnosed and treated?

The first step to getting appropriate treatment is to visit a doctor or mental health specialist. When depression is suspected, doctors will usually ask a series of questions and even order medical and psychological tests. These test may include:

- **A physical exam**, including regular check-up measurements of height, weight, blood pressure, temperature, heart rate, as well as listening to your heart and lungs.
- **Laboratory tests**, which may include a complete blood count (CBC) or a test to make sure your thyroid is working properly.
- **A psychological evaluation**, to check for signs of depression. Usually involves talking about your thoughts, feelings, and behavior patterns, as well as any symptoms you may be having now, and similar episodes you may have had in the past. If the doctor can find no

medical condition that may be causing the depression, then the psychological evaluation is takes place.

The doctor may refer you to a mental health professional, who should discuss with you any family history of depression or other mental disorder, and get a complete history of your symptoms. You should discuss when your symptoms started, how long they have lasted, how severe they are, and whether they have occurred before and if so, how they were treated. The mental health professional may also ask if you are using alcohol or drugs, and if you are thinking about death or suicide. Once diagnosed, a person with depression can be treated in several way.

6.1 Physical treatment

The main physical treatments for depression comprise drug treatments and Electroconvulsive therapy (ECT).

Medications

Antidepressants primarily work on brain chemicals called neurotransmitters, especially serotonin and norepinephrine. Other antidepressants work on the neurotransmitter dopamine. Scientists have found that these particular chemicals are involved in regulating mood, but they are unsure of the exact ways that they work [18].

There are three groups of drugs most likely to be used for depression.

- Antidepressants: There are a large number of antidepressants – they have a role in many types of depression and vary in their effectiveness across the more biological depressive conditions. Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclics (TCAs) and Irreversible Monoamine Oxidase Inhibitors (MAOIs) are three common classes of antidepressants, with the latter two having ‘broader’ actions (i.e. influencing more neurotransmitter pathways).
- Popular newer antidepressants: Some of the newest and most popular antidepressants are called selective serotonin reuptake inhibitors (SSRIs). Fluoxetine (Prozac), sertraline (Zoloft), escitalopram (Lexapro), paroxetine (Paxil), and citalopram (Celexa) are some of the most commonly prescribed SSRIs for depression [19]. Most are available in generic versions. Serotonin and norepinephrine reuptake inhibitors (SNRIs) are similar to SSRIs

and include venlafaxine (Effexor) and duloxetine (Cymbalta). SSRIs and SNRIs tend to have fewer side effects than older antidepressants, but they sometimes produce headaches, nausea, jitters, or insomnia when people first start to take them. These symptoms tend to fade with time. Some people also experience sexual problems with SSRIs or SNRIs, which may be helped by adjusting the dosage or switching to another medication. One popular antidepressant that works on dopamine is bupropion (Wellbutrin). Bupropion tends to have similar side effects as SSRIs and SNRIs, but it is less likely to cause sexual side effects. However, it can increase a person's risk for seizures.

- **Tricyclics:** Tricyclics are older antidepressants. Tricyclics are powerful, but they are not used as much today because their potential side effects are more serious. They may affect the heart in people with heart conditions. They sometimes cause dizziness, especially in older adults. They also may cause drowsiness, dry mouth, and weight gain. These side effects can usually be corrected by changing the dosage or switching to another medication. However, tricyclics may be especially dangerous if taken in overdose [20].
- **MAOIs:** Monoamine oxidase inhibitors (MAOIs) are the oldest class of antidepressant medications. They can be especially effective in cases of “atypical” depression, such as when a person experiences increased appetite and the need for more sleep rather than decreased appetite and sleep. They also may help with anxious feelings or panic and other specific symptoms. However, people who take MAOIs must avoid certain foods and beverages (including cheese and red wine) that contain a substance called tyramine. Certain medications, including some types of birth control pills, prescription pain relievers, cold and allergy medications, and herbal supplements, also should be avoided while taking an MAOI [21]. These substances can interact with MAOIs to cause dangerous increases in blood pressure. The development of a new MAOI skin patch may help reduce these risks. If you are taking an MAOI, your doctor should give you a complete list of foods, medicines, and substances to avoid. MAOIs can also react with SSRIs to produce a serious condition called “serotonin syndrome,” which can cause confusion, hallucinations, increased sweating, muscle stiffness, seizures, changes in blood pressure or heart rhythm, and other potentially life-threatening conditions. MAOIs should not be taken with SSRIs.

Tranquillizers: These medications are divided into ‘minor’ and ‘major’ tranquillizers. Minor tranquillizers (typically benzodiazepines) are usually not used in treating depression as they are

addictive. Major tranquilizers are used to treat psychotic or melancholic depression to control psychotic symptoms [22].

Mood stabilizers: These drugs are of great importance in bipolar disorder. Their use in treating mania makes them ‘anti-manic’, while their ability to reduce the severity and frequency of mood swings makes them ‘mood stabilizers’. Lithium carbonate, sodium valproate and carbamazepine are the most commonly used mood stabilizers. It is important to remember that people sometimes need to continue taking medication for some time after they are better to reduce the chance of a future relapse [23].

- **Electroconvulsive Therapy (ECT):** Also known as shock therapy, electroconvulsive therapy has been around for years, and misunderstood for almost all that time. For cases in which medication and/or psychotherapy does not help relieve a person’s treatment-resistant depression, electroconvulsive therapy (ECT) may be useful. ECT, formerly known as “shock therapy,” once had a bad reputation. But in recent years, it has greatly improved and can provide relief for people with severe depression who have not been able to feel better with other treatments. Before ECT begins, a patient is put under brief anesthesia and given a muscle relaxant. He or she sleeps through the treatment and does not consciously feel the electrical impulses. Within 1 hour after the treatment session, which takes only a few minutes, the patient is awake and alert [24].

A person typically will undergo ECT several times a week, and often will need to take an antidepressant or other medication along with the ECT treatments. Although some people will need only a few courses of ECT, others may need maintenance ECT—usually once a week at first, then gradually decreasing to monthly treatments [25].

ECT may cause some side effects, including confusion, disorientation, and memory loss. Usually these side effects are short-term, but sometimes they can linger. Newer methods of administering the treatment have reduced the memory loss and other cognitive difficulties associated with ECT. Clinicians at the Institute firmly believe that ECT has a small but important role in treatment, particularly in cases of:

- Psychotic depression

- Severe melancholic depression where there is a high risk of suicide or the patient is too ill to eat, drink or take medications
- Life-threatening mania
- Severe post-natal depression

Psychological treatments

Psychotherapy is a term used to describe treatment that involves talking through issues with a psychotherapist. This form of therapy is meant to relieve distress by allowing patients to talk about and express feelings, by helping to change attitudes, behavior and habits that may be contributing to depression, and by exploring more helpful or adaptive ways of coping. It is often used along with medication in the treatment of depression [26].

Two main types of psychotherapies—cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT)—are effective in treating depression. CBT helps people with depression restructure negative thought patterns. Doing so helps people interpret their environment and interactions with others in a positive and realistic way. It may also help to recognize things that may be contributing to the depression and will help to change behaviors that may be making the depression worse. IPT helps people understand and work through troubled relationships that may cause their depression or make it worse. For mild to moderate depression, psychotherapy may be the best option.

- **Cognitive Behavioral Therapy:** All of us develop behavioral patterns, mindsets and emotional responses typical to us over our lifetime through personal experience and limitation. In respect of the development of depression, there are a range of typical thought and behavioral patterns which can lead to illness when combined with high pressure situations and chronic stress. Problematic behaviors, thought patterns and mindsets are specifically tackled and examined during treatment. “Cognitive behavioral therapy” focuses on both negative thought patterns and on the behavioral level. Changing a person’s behavior, such as by getting them to take up pleasant occupations and social activities again, slowly leads to positive emotions and new experiences [27]. This in turn fosters a changed mindset and vice versa. Amongst other things, the aim of cognitive behavioral therapy is to impart skills for successfully and satisfactorily constructing social relationships and dealing with one’s feelings. Another goal may be encouraging the patient

to work through stressful experiences from the past, current crises and difficult life situations.

- **Interpersonal Psychotherapy:** Interpersonal psychotherapy is specifically tailored to the treatment of depression. It assumes that interpersonal relationships can significantly contribute to the development of depression. It is thought that a patient's earlier interpersonal and mental experiences also manifest themselves in current behavior. For example, stressful events (such as the death of a loved one or separation from a partner) and difficult life circumstances (such as bullying in the workplace, losing a job and retirement or permanent disputes with family members) can cause depressive symptoms to appear. For other patients, working through moments of loss (mourning) or managing transitions between particular social roles (such as when children leave home or a person enters retirement) can be important [28]. The goal of interpersonal psychotherapy is to reduce depressive symptoms and improve interpersonal relationships in the private and/or professional spheres.
- **Counselling:** Counselling encompasses a broad set of approaches and goals that are essentially aimed at helping an individual to solve long standing problems within their family situation, at work or to resolve sudden major problems.

7.0 Lifestyle medicine for depression

7.1 Diet

Major dietary changes have occurred across the globe in the past century [15]. Specifically, there has been a shift in the common dietary patterns of Western societies to typically include high levels of energy, saturated fats and refined sugar. In fact, nutrient-insufficient and energy dense foods now contribute approximately 30% to the daily dietary intakes of American adults. Over recent years, evidence has emerged to suggest that poor diet may be a risk factor for the onset of depression. Diet modulates several key biological processes that underscore mood disorders, including brain plasticity and function, the stress response system, mitochondria, inflammation, and oxidative processes [29]. A Western dietary pattern is associated with increased markers of

systemic inflammation. A Western dietary pattern is associated with increased markers of systemic inflammation. Among people suffering from depression, systemic immune activation, characterised by increased levels of pro-inflammatory cytokines and alterations in the acute phase protein response, have been observed. Another aspect of consideration, is that a wholefood diet provides protein and essential fatty acids, in addition to a range of micronutrients that are critical in neurochemical function, including B vitamins, zinc, magnesium, vitamin C, and a range of plant compounds such as flavonoids that are potent antioxidants and anti-inflammatories. Altering dietary patterns may affect a variety of factors influencing the development and trajectory of depression. Other studies comprising depressed populations have demonstrated the benefits of dietary modification using supplements such as omega 3 polyunsaturated fatty acid (PUFAs) on mood outcomes.

7.2. Physical activity and exercise

Modernity has similarly reduced the amount of work- and leisure-time physical activity (PA) and formalized exercise undertaken by the average person. Epidemiological studies have shown that adequate PA (based on clinical guidelines) is associated with fewer depressive symptoms, while insufficient PA may be a risk factor for the development of depressive symptoms. Exercise is also a relatively cheap and safe intervention that has been shown to provide a range of additional health benefits. Aside from exercise providing marked beneficial effects on neuroendocrine systems, it also increases self-efficacy and self-esteem (via activity scheduling and attainment of goals) which are important psychological issues among people who are depressed. Exercise has been shown to moderate a range of biological pathways including: inflammatory cytokines, oxidative stress, neurotrophins and neurogenesis. Another form of exercise that combines a “mindfulness” element is the practice of yoga. Aside from the physiological benefits from yoga, the mindfulness component may also provide a benefits to our health.

7.3. Management of recreational substances (alcohol, cigarettes, caffeine)

Epidemiological studies and community surveys indicate that alcohol abuse and dependence commonly co-occur with affective disorders. While acute alcohol use reduces neuronal glutamate release, during alcohol withdrawal (colloquially known as the “hangover” stage) a greater amount of rebound glutamate is released from the synapses and in combination with dysregulated monoamine and neuroendocrine pathways, may provoke anxiety and dysphoria. A meta-analysis of four large-scale epidemiological studies found a two- to three fold increased lifetime risk for both depressive and anxiety disorders in those with alcohol dependence or abuse. There is also data from prospective community studies that shows heavy use of alcohol in adolescence and young adulthood predicts later onset of major depressive disorder. Smoking cigarettes increases the risk for the genesis of affective and anxiety disorders and appears to be a potential risk factor for the development of de-novo depression. Cigarette smoking in adolescence may also increase the risk of the later development of clinically significant depressive symptoms. Depression can be seen as having an inflammatory component, and smoking also aggravates inflammation and provokes marked oxidative stress. Caffeine is in many cultures the most commonly used psychoactive substance. It acutely increases attention, alertness, cognition and mood, with some individuals with dysphoric mood being predisposed to use caffeine more heavily, due to its mood-elevating potential (via activation of noradrenergic and dopaminergic pathways) [105]. Caffeine modulates the adenosine system, and the anxiogenic potential of caffeine is influenced by polymorphisms of the A2A receptor. While evidence supports the avoidance of caffeine in anxiety disorder, data suggests that caffeine use from coffee consumption may be protective against depression. While evidence supports the avoidance of caffeine in anxiety disorders, data suggests that caffeine use from coffee consumption may be protective against depression. Interestingly, decaffeinated coffee was not associated with depression risk. Regardless, there is the potential for people with high caffeine use affecting insomnia, and this in turn may increase risk or aggravation of depressed mood [29].

7.4 Sleep

A good night’s sleep is critical for mental and physical health. Sleep disturbance is a frequent symptom of depression, and a strong causal link exists between insomnia and depression. Further, residual sleep difficulties may be predictive of subsequent depression relapse. It is likely that this

is bidirectional; that is, insomnia can increase depression risk and vice versa. Research has shown that people with chronic insomnia have an increased risk of a major depressive disorder. People with a current depressive or anxiety disorder, or remittent depression had a significant association with sleep disturbance. Current treatment strategies are mainly based on sleep hygiene techniques and cognitive behavioral techniques; and via the use of hypnotic or antidepressant medications. the use of lifestyle modification programs may improve sleep by addressing factors associated poor sleep e.g. sedentary life, poor diet, caffeine and alcohol use [15].

7.5 Social Interaction

Another key lifestyle influence affecting mental health concerns a person's social environment. Positive, supportive, intimate relationships, be it via family, friends or a relationship, have been established to have a beneficial effect on general health, and in particular for maintaining psychological health. Data from the English Longitudinal Study of Aging, observed whether baseline positive and negative exchanges with partners, family and friends were linked to two-year changes in depression. Results showed that after adjusting for confounding factors, negative, but not positive, exchanges with family and friends were associated with greater occurrence of depression [27].

7.6 Recreational and Relaxation

Recreational activities provide an opportunity to experience pleasure, to direct the mind away from rumination and worry, and may provide a setting for increased social interaction. The benefits of participation in organised physical recreation have been investigated as one strategy for enhancing mental health and wellbeing. As Street, James and Cutt comment, evaluations by government departments in Australia and the US have found that people who participate in organised recreational activity enjoy better mental health, are more resilient against the stresses of modern living, with a reduction of depressed mood also evident; however the direction of the association remains speculative. One common form of inexpensive recreation involves listening to music. Aside from recreational activities that may provide psychological relaxation, formalized relaxation

techniques may also be incorporated into people's lifestyle. It should also be noted a meta-analysis of nine trials revealed that relaxation produced less effect than psychological interventions on self-reported depression [14].

7.7 Animal and pet therapy

Humans commonly have close relationships with animals, particularly pets, and such relationships may have a theoretical benefit for alleviating depressed mood. Having a pet can provide physical affection and a feeling of unconditional love, assist in the maintenance of a routine, and also provide responsibility and an additional sense of life purpose. Formalized animal-assisted therapy may involve horses (equine therapy), dogs, or even interactions with mammals such as dolphins. Time spent with farm animals by people with psychiatric disorders may reduce depression and state anxiety, and increase a sense of self-efficacy with a small and methodologically limited study suggesting beneficial effects of pet therapy on mood and perceived quality of life in 21 elderly inpatients affected by dementia, depression and psychosis [27].

8.0 Complementary therapies of depression

Complementary A group of diagnostic and therapeutic disciplines that are used together with conventional medicine. There are several complementary therapy having potential benefit in the treatment of anxiety, including interventions such as acupuncture, massage, and homeopathy. There are a large number of mind-body-spirit practices that have been used effectively in major depression. It is widely accepted that most conventional antidepressant drugs increase levels of the relevant neurotransmitters, such as serotonin, norepinephrine, and dopamine, in the synapse. Mind-body spirit approaches are also likely to operate through the same mechanism as antidepressants, and do so in a manner similar to that of psychotherapy. Evidently, psychotherapy-induced neurotransmitter changes are similar to those caused by antidepressants. Common approaches such as yoga, meditation, exercise, and acupuncture are mentioned below.

Regulation of these practices and their practitioners vary depending on jurisdiction, and if clinicians are referring patients for these treatments, several considerations should be recognised,

including evidence for the modality, cost of the treatment, and the training and qualification of the therapist.

8.1 Homeopathy

Homeopathy is a traditional medical system that uses a holistic approach. Homeopathy means treating diseases with minute doses of substances which are capable of producing symptoms similar to the disease when taken by healthy people. In homeopathy, the natural law of healing is known as *Similia Similibus Curantur*, meaning “likes are cured by likes”. Homeopathy is practiced in many places around the world. An audit of UK homeopathic clinics revealed that more than 84% of consultees reported improvement in mental health problems, including depression, and improvement in well-being. Homeopathic medicines have been shown to be safe in high dilutions. According to one study, the most commonly treated conditions in the practice of homeopathy were depression and anxiety disorders [30].

8.2 Yoga and Tai chi

Yoga and Tai chi are mind-body practices that both have a long standing history of use. Yoga is generally defined as a practice which consists of three components: gentle stretching, exercises for breath control, and meditation as a mind-body intervention [144]. Tai chi is practiced in China as both a form of exercise and as a martial art and involves moving from a standing position through a series of postures like a choreographed dance. Sequences of postures are known as “forms”, which require considerable time and concentration to master [31]. Positive results were reported for the effects of yoga treatments of durations up to three months, although many of the studies suffered from methodological limitations such as inadequate randomisation and high dropout rates. In another study, 113 psychiatric inpatients who attended Hatha yoga classes experienced a significant reduction in symptoms of depression. Improvements also occurred in anxiety, depression, hostility, fatigue, and confusion

8.3 Massage therapy

Therapeutic massage is one of the most popular CAM treatments for anxiety, but has had few rigorous evaluations for diagnosed anxiety disorders. AM proved the more acceptable therapy based on sessions attended, and both treatments were significantly effective based on the Profile of Mood States (in respect to total mood, depression, and anxiety scores) [31].

8.4 Acupuncture

Acupuncture is a traditional Chinese method used widely for treating a variety of physical and mental health problems. Acupuncture is a very popular CAM intervention that, unlike the previously mentioned interventions, has a more substantive body of clinical trial evidence regarding its efficacy and safety in the treatment of anxiety and depression. Acupuncture appears effective in short-term use for anxiety symptoms, but we cannot yet make clear recommendations for specific clinical anxiety disorders. Acupuncture has been documented to interact with opioid pathways, and interventions which modify these pathways have been shown to have potential mood modulatory activity. Other potential mechanisms of action that may induce anxiolysis include increased release of serotonin and norepinephrine, and cortisol modulation [32].

8.5 Meditation

Meditation is a highly introspective practice that is used worldwide by people with and without health problems. The concept of meditation is varied, with a key attribute of the practice involving “mindfulness,” commonly defined as the awareness which arises through “paying attention in a particular way: on purpose, in the present moment, non-judgmentally”. Over the past 60 years, ever since the advent of Buddhism in the West, there has been growing interest in the relationship between mindfulness, meditation, and mental health. The use of meditation as a Western behavioral intervention was pioneered by Kabat-Zinn who originally investigated structured mindfulness training for the treatment of chronic pain. The training program has become known as Mindfulness-Based Stress Reduction (MBSR). MBSR is an 8–10 week structured program which involves (i) training in mindfulness meditation practice, (ii) mindful awareness, for example, during yoga postures, and (iii) mindfulness during stressful everyday situations and

social interaction. There is also evidence to suggest that amongst the general population, the MBSR technique may bring about a reduction in trait and state anxiety and symptoms.

8.6 Mudra

Mudra literally means 'gesture'. Mudra expresses and channelizes cosmic energy within the mind and body. Mudras are the expression of our inner feeling. Mudras that are part of yogic gestures are called yogic mudra. Mudras done using hands are called Hasta mudra.

When the tip of the thumb joins the tip of the other fingers, respective tatvas get balanced in the body. When the tip of the thumb joins the base of the other fingers, respective tatvas get increased in the body. When the tip of the fingers brought to the base of the thumb, respective tatvas get reduced in the body. Hasta mudras can be done by anyone. As far as possible, the hands should face upwards while doing the mudras. Doing the mudras on both hands is more beneficial. When mudra is done with right hand, it affects the left part of the body and vice versa. Mudras can be done for few seconds, 10 minutes, half an hour or 50 minutes. If done for 50 minutes, desired results will come. While doing the mudras, only the tip of the fingers are used. Pressing the tip of fingers is not needed. Other fingers should be straight. There is no side effect in this. This can be done while one is on medication also. Mudras not only improves the physical health but also improves the mental health by reducing the anger, increasing the peace and releasing one from the addictions [32].

8.7 Exercise

Exercise

Regular exercise is important for maintaining good physical and mental health. Engaging in exercise for 45 minutes on five days a week is associated with improvement in patients with moderate depression. This effect is irrespective of age, gender, severity of depression, and type of exercise. The positive impact of exercise on depression is mainly attributed to an increase in serotonin, norepinephrine, and endorphins in the brain [33]. Numerous other studies support the benefits of moderate aerobic exercise on depression in various populations. Exercise has been used

as an adjunct and also as augmentation therapy with psychotherapy in depressive symptoms, and in patients with mild-to-moderate depression and anxiety with good outcomes. In addition, dance therapy has been shown to decrease depression to a greater extent than either music therapy or a movement-only control.

9.0 Complementary and alternative medicine for depression

Complementary and alternative medicine, or CAM, is a category of medicine that includes a variety of treatment approaches that fall outside the realm of conventional medicine. Complementary medicine refers to healing practices and products that work in conjunction with traditional medicine. Complementary and alternative medicine is the most practiced but least researched form of treatment because of the complexities inherent in assessment of its effectiveness in major depression and other mood disorders.

9.1 Dietary supplements as CAM therapies

Public health and governmental agencies support a balanced diet low in processed foods and rich in fruits, vegetables, whole grains, legumes, fish and lean meats as part of a healthy lifestyle. Such a diet reduces the risk of developing numerous medical disorders including cardiovascular disease and some cancers. There is now emerging evidence that diet also affects our mental health, although the relationship appears to be complex and bidirectional. Many would recognise that changes in stress levels influence our dietary choices. In a study of self reported eating behavior, Oliver and Wardle noted that although people differentially increase or decrease their food intake when anxious and stressed, the choice of food appears to consistently move away from normal meal-type foods toward high fat, high palatable snacks. Recent evidence has demonstrated that intake of highly palatable foods is associated with increased production of reactive oxygen species (ROS). Increased ROS production and subsequent oxidative stress are postulated to contribute to the development of anxiety disorders [34]. The emerging body of evidence encourages the recommendation for bettering general mental health by adopting a diet rich in lean protein, complex carbohydrates, fruit and vegetables, with adequate omega and low in refined carbohydrates, saturated fats and processed food.

- Nutraceuticals (Herbal and nutritional medicine)

Over-the-counter dietary supplements (nutraceuticals) are used extensively by patients with depression, and are categorized as nutrients, herbal and dietary supplements, traditional and nontraditional methods. Nutraceuticals have also been used to promote mental and physical health, to prevent illness, and to treat diseases, with substantial benefits. Over the past 25 years, there has been increasing interest in the use of nutraceuticals (herbal or nutritional medicines) for the treatment of anxiety disorders, with numerous human clinical trials emerging in the area. The most researched herbal medicine in the treatment of anxiety is *Piper methysticum* (Kava); a perennial plant native to various Regions of the South Pacific. The roots of the Kava plant are traditionally prepared as water-based beverage for its medicinal properties and psychotropic effects. Nutraceuticals, in particular S-adenosylmethionine, have benefited patients with major depression and other mood disorders. This compound provides methyl and sulfate groups used in the synthesis of deoxyribonucleic acid, proteins, phospholipids, neurotransmitters, and the antioxidant, glutathione, that are disturbed in people with mood disorders. Several researchers have appraised the clinical and pharmacological benefits of S-adenosylmethionine in depression and as an adjunct in treatment-resistant depression. S-adenosylmethionine alone or combined with other supplements has been shown to alleviate depression associated with musculoskeletal disease, liver disease, Parkinson's disease, and human immunodeficiency virus/acquired immune deficiency syndrome. S-adenosylmethionine acts similarly to noradrenergic antidepressants, but with fewer side effects [34]. S-adenosylmethionine is safe to use during pregnancy and breast-feeding. A secondary analysis of clinical trial data for S-adenosylmethionine administered to patients with major depression found a positive impact on symptoms of depression and related cognitive dysfunction.

- Vitamins in mood disorders

Vitamins B and D, folate, and trace elements are essential for the functioning of neurons, and have been shown to afford protection against certain types of mental disorders, particularly depression. These nutrients become depleted in the body for many reasons, including poor nutrition, chronic disease, old age, stress, and polymorphism. Low vitamin B12, vitamin D, and folate levels are also associated with poor memory and cognitive dysfunction. Folic acid and folate from the diet are converted into L-methylfolate in the

body clinical trials of vitamin B and folate have yielded equivocal results in patients with major depression. Although methylfolate and vitamin B have favorable safety profiles, allergic reactions may occur using these substances. Folate and vitamin B reduce homocysteine levels, so may be cardioprotective. Folate is required for the synthesis of dopamine, norepinephrine, and serotonin. It is also a key component of the methylation cycle, and deficiency of one or more components of this cycle leads to accumulation of homocysteine, which is associated with dementia, Parkinson disease, and cerebrovascular disease. People with folate deficiency are more likely to suffer from depression are more likely to have more severe and longer lasting relapses.

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- Omega-3 fatty acids in mood disorders

Fish-derived omega-3 fatty acids provide eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which help to maintain fluidity of the cell membrane, reduce inflammatory eicosanoids, and prevent the release of pro inflammatory cytokines. Alpha linoleic acid also converts differentially into omega-3 fatty acids, EPA, and DHA. Alpha-linolenic acid, an omega-3 precursor found in flax, soy, canola, and walnuts, is poorly

converted in most humans and thus is not an important source of omega-3 fats. Neurons contain high levels of omega-3 fatty acids, where they influence phospholipid membrane fluidity, receptors, ion channels, and neuroendocrine regulation and inflammation. Depression is less prevalent in societies with high fish consumption, and depressed patients have significantly lower red blood cell omega-3 levels. However, omega-6 fatty from domesticated animals and cultivated vegetables is consumed in much larger quantities than omega-3 fatty acids. Therefore, cell membranes acquire increasing proportions of omega-6 fatty acids that adversely affect membrane fluidity and flexibility. In contrast, supplementation of omega-3 fatty acids from fish oil in liquid or capsule form maintains cell membrane fluidity. Substitution of omega-6 fatty acids for omega-3 fatty acids in the cell membrane has been associated with unipolar and bipolar depression, which is thought to be due to loss of membrane fluidity and flexibility. The later results in disturbance of membrane proteins such as enzymes, receptors and ion channels, and neurotransmitters, which in turn increases levels of inflammatory eicosanoids and pro inflammatory cytokine. An increased risk of suicide, commonly associated with depression, has been linked with omega-3 fatty acid deficiency. Omega-3 fatty acids are both safe during infant development and effective for the treatment of major depression in pregnant women. Notably, low fish consumption and omega-3 fatty acids have been linked with depression more in women than in men [36].

Omega-3 fatty acids also have a preventive role. Interestingly, a lower lifetime prevalence of bipolar II disorder has been associated with greater consumption of seafood. A recent meta-analysis of five pooled databases related to use of omega-3 fatty acids in bipolar patients found a significant reduction in symptoms of depression, although scores for mania were unaffected, thus supporting the adjunctive role of omega-3 fatty acids in the treatment of symptoms of depression in bipolar patients. Pregnant women often have depleted omega-3 fatty acid stores and are at higher risk for postpartum depression and bipolar depression. Almost all psychotropic medications carry a risk of side effects in pregnant women and may also adversely affect fetal and infant development. CAM therapies are safe alternatives in pregnant women with major depression. Omega-3 fatty acids are also safe for use in children and adolescents with bipolar disorder.

The most commonly observed side effects of omega-3 fatty acids in children are nausea, heartburn, stomach pain, belching, bloating, and diarrhea attributable to higher doses and use of unrefined fish oil preparations. Bleeding episodes due to reduction in platelet aggregation and triggering of mania are other side effects of high doses of omega-3 fatty acids. Use of omega-3 fatty acids should be strictly avoided in patients on anticoagulant therapy and antidiabetic medications. Some omega-3 fatty acids found in fish oil can increase low-density lipoprotein cholesterol, which is bad for the heart.

- Lysine

It has long been postulated that the dysregulation of neurotransmitters may be a cause for anxiety. These neurotransmitters include GABA, serotonin, dopamine and norepinephrine. Amino acids such as L-tyrosine and L-tryptophan are known precursors for specific neurotransmitter. Recent studies in animals have identified two other amino acids, L-lysine and L-arginine which may influence neurotransmitters involved in stress and anxiety. L-lysine has been shown to act as a partial serotonin receptor antagonist, decreasing the brain-gut response to stress as well as decreasing blood cortisol levels. L-lysine and L-arginine combination supplements improved participants' ability to handle induced stress through an increase in cortisol. It seems that the L-lysine and L-arginine combination effectively reduces anxiety scores with no reported side effects [37].

- Magnesium

Magnesium is a positively charged ion, a cation that is involved in many important molecular functions in the body and has been linked to anxiety-related disorders. Three human trials have been conducted that test the anti-anxiety effects of increased magnesium intake in combination therapies and all showed a positive direction of evidence [39]. In the first study, 28-day treatments with a multivitamin that contained large amounts of magnesium, zinc and calcium dramatically decreased psychological distress compared to placebo, which worsened symptoms. Magnesium supplementation is effective at treating anxiety and anxiety-related disorders when used in combination with other vitamins, minerals and herbal extracts.

- Inositol in bipolar disorder

Inositol, a glucose isomer precursor of phosphatidyl inositol linked to the second messenger system, has been found to be more effective than placebo in the treatment

of depression and other psychiatric illnesses, including panic disorder. Inositol, a vitamin-like substance found in many plants and animals, can be produced synthetically. Nierenberg et al suggested that patients with treatment-resistant depression are suitable candidates for inositol augmentation. Another study of 66 bipolar I or II patients with resistant depression examined the benefits of augmenting mood stabilizers with inositol, and found that the rate of recovery was 17.4% with inositol. However, at therapeutic doses, inositol frequently causes flatulence and occasionally induces mania.

- Choline in bipolar disorder

Choline has been used effectively in treating symptoms of mania. A randomized controlled trial of oral choline in rapid cycling bipolar patients treated with lithium reported significantly decreased purine levels in the brain over a 12-week period, which was related to the anti-manic effects of choline. Oral administration of exogenous choline increased synthesis of phospholipids in the cell membrane and corrected the mitochondrial component of diathesis in patients with bipolar disorder inadequately meeting the demand for increased adenosine triphosphate production. Thus, choline supplementation in small studies was effective for improving manic symptoms in bipolar patients, although larger studies are needed before recommending use of oral choline in the treatment of mania in bipolar I disorder [39].

- 5-hydroxy-L-tryptophan in bipolar disorder

5-hydroxy-L-tryptophan is an immediate precursor in the synthesis of serotonin, and deficiency of serotonin can cause major depression. . As a dietary supplement, 5-hydroxy-L-tryptophan is used widely as a self-medication for depression, and has replaced L-tryptophan, which caused eosinophilia myalgia syndrome and was taken off the market [40]. There is some support for 5-hydroxy-L-tryptophan 200–300 mg/day being more effective than placebo when given alone in adults with major depression, although the data are better when it is used to augment antidepressants.

The most common side effects include nausea, vomiting, diarrhea, headache, and insomnia. 5-hydroxy-L-tryptophan was effective when used to supplement antidepressants and mood stabilizers in mood disorders.

- *N*-acetylcysteine in bipolar disorder

N-acetylcysteine, a precursor of glutathione, is an important antioxidant in the brain and reduces oxidative stress. Increased oxidative stress and altered glutathione metabolism have been reported in bipolar and major depressive disorder. A randomized controlled trial in bipolar patients on mood stabilizers found that those who were given adjunctive *N*-acetylcysteine 2 g/day showed a significant improvement in depression, mania, quality of life, and social and occupational functioning compared with placebo. The therapeutic effect of *N*-acetylcysteine in psychiatric disorders, including bipolar disorder, and found it to be beneficial in patients with bipolar depression.

- Hormones in mood disorders

Dehydroepiandrosterone (DHEA) is an androgen produced by the adrenal glands, levels of which tend to decrease during mid-life in men and women. Lower levels of DHEA have been reported in patients with major depression, and use of DHEA has been associated with improved mood. Lower levels of DHEA have been reported in patients with major depression, and use of DHEA has been associated with improved mood. An increase in DHEA sulfate, the primary metabolite of DHEA, has also been associated with improvement in depression and dysthymia. Patients taking DHEA also showed improvement in sexual function.¹⁵⁸ DHEA has been used effectively in patients with human immunodeficiency virus/acquired immune deficiency syndrome and subsyndromal depression or chronic dysthymia [41].

- Ayurvedic medicine in mood disorders

Ayurvedic medicine is an ancient healing system used in India, which is now practiced worldwide. Ayurveda denotes longevity. The theory of Ayurveda is based on balancing the individual's three constitutional "doshas", ie, vata, pitta, and kappa, which arise from five elements of ancient philosophy, being fire, water, air, earth, and space. It is believed that health or sickness depends on the presence or absence of a balanced state. Both intrinsic and extrinsic factors, such as an indiscriminate diet, undesirable habits, not observing the rules of healthy living, seasonal abnormalities, lack of exercise, and misuse of body and mind can result in lack of balance in the body. With accurate tailoring of herbal preparations, herbal therapy can be powerful in effecting change in the balance of body and mind. Example: with mood disorders that often have complex multifactorial origins. Patients who are intolerant to prescription medications fare are better with Ayurvedic

interventions, including panchakarma detoxification. Small preliminary studies of major depression treated with herbs, herbal mixtures, and Rasayanas (a special branch of Ayurveda aiming to rejuvenate and nourish the body at all levels and comprises several products manufactured from a combination of herbs) have demonstrated improvement in depression scores.

10.0 Herbal supplements for anxiety and anxiety related disorder

Over the past several decades, complementary and alternative medications have increasingly become a part of everyday treatment. With the rising cost of prescription medications and their production of unwanted side effects, patients are exploring herbal and other natural remedies for the management and treatment of psychological conditions. Psychological disorders are one of the most frequent conditions seen by clinicians, and often require a long-term regimen of prescription medications. Approximately 6.8 million Americans suffer from generalized anxiety disorder. Many also suffer from the spectrum of behavioural and physical side effects that often accompany its treatment. It is not surprising that there is universal interest in finding effective natural anxiolytic (anti-anxiety) treatments with a lower risk of adverse effects or withdrawal.

Based on the available evidence, it appears that nutritional and herbal supplementation is an effective method for treating anxiety and anxiety-related conditions without the risk of serious side effects [42]. There is the possibility that any positive effects seen could be due to a placebo effect, which may have a significant psychological impact on participants with mental disorders. However, based on this systematic review, strong evidence exists for the use of herbal supplements containing extracts of passionflower or kava and combinations of L-lysine and L arginine as treatments for anxiety symptoms and disorders. Magnesium-containing supplements and other herbal combinations may hold promise, but more research is needed before these products can be recommended to patients. St. John's wort monotherapy has insufficient evidence for use as an effective anxiolytic treatment.

10.1 Passionflower



Passionflower or *Passiflora incarnata* Linn is a woody, hairy, climbing vine and is reputed to have sedative/anxiolytic properties and has been used widely as an ingredient of herbal remedies, chiefly in the form of a liquid extract tincture. Between the 1970s and 1990s, passionflower was listed as an official plant drug by the pharmacopoeias of America, Britain, Germany, France, Switzerland, Egypt and India; its wide use has made it an acceptable treatment for restlessness and nervousness. The commission E approved the internal use of passion flower for nervous restlessness and the British Herbal Compendium indicates its use for sleep disorders, restlessness, nervous stress, and anxiety.

The anxiolytic effects of passionflower are well documented in mice. To date, three human trials have documented the efficacy of passionflower as a treatment for anxiety-related disorders. One double-blind, placebo-controlled study analysed the difference in efficacy between oxazepam, a prescription benzodiazepine used to treat chronic anxiety symptoms, and passionflower in patients (n = 36) who met the criteria for GAD. The results showed no difference between the two anxiolytics with regard to the treatment of GAD, suggesting that passionflower is as effective as benzodiazepines in eliminating anxiety symptoms. This anxiolytic effect was also seen in two other subsets of patients: those undergoing surgery (n = 60) who were treated. With passionflower monotherapy, and those diagnosed with adjustment disorder with anxious mood (n = 182) who were treated with passionflower in combination with crataegus oxyacantha, ballota foetida, valeriana officinalis, colanitida and paullinia cupana [43]. This preliminary evidence suggests that passionflower may have a role in the treatment of anxiety and warrants future research.

Table 1 Trials testing passionflower [43]

Reference	Study Design	Sample Population	Intervention	Control	Length of Treatment	Outcomes	Direction of Evidence	Reported Adverse Events
Bourin (1997)	Randomized; Double blind; Parallel Group	182 outpatients with adjustment disorder with anxious mood	Euphytose; 2 tablets, 3 times a day	Placebo tablets	28 days	Significant reduction in HAMA scores (from D7 to D28) in favour of Euphytose treatment	+	No serious AEs. Dry mouth Headache Constipation Drowsiness
Akhondzadeh (2001)	Randomized; Doubleblind; Parallel group	36 outpatients with DSM-IV for GAD for at least 6 months	45 drops/day of Passiflora extract plus placebo tablet	Oxazepam 30 mg/day plus placebo drops	4 weeks	Decrease in HAMA for both treatments; overall no significant difference in efficacy between treatments	+	Higher impairment of job performance in oxazepam group; overall no significant difference in total side effects ³
Movafegh (2008)	Randomized; Doubleblind; Parallel Group	60 patients undergoing inguinal herniorrhaphy	Oral Passiflora incarnata (500 mg, Passipy™ IranDarouk)	Placebo	Given as premedication 90 minutes before surgery	NRS anxiety scores were significantly lower in the passiflora group	+	Not reported

10.2 Kava



Kava is a drink that is prepared from the plant *Piper methysticum*. It has been consumed in many cultures because it is known to relieve anxiety, restlessness and insomnia for centuries. Several studies in animals have also demonstrated the kava plant’s abilities as an anxiolytic agent. The attractiveness of kava is that it is anxiolytic but not sedative or mentally impairing, which are typical side effects caused by benzodiazepines. The biochemical mechanism of kava’s anxiolytic activity has been postulated to occur through enhanced ligand binding to GABA type A receptors, blockage of voltage-gated sodium channels and calcium ion channels, norepinephrine and dopamine reuptake inhibition, and reversible inhibition of monoamine oxidase (MAO) B. The first randomized, placebo-controlled, double-blind study of kava for the treatment of patients who were diagnosed with anxiety disorder was conducted in 1997. The subjects (n = 101) were given either an extract of kava or a placebo for 25 weeks. The participants who were given the kava extract showed improvement in the primary and secondary anxiety symptoms based on the HAMA – a method of patient self-reporting – and CGI, which was determined by physicians. Primary anxiety is described as the inability to regulate stress and anxiety since early childhood [44]. Secondary anxiety, which develops later in life, can be caused by clinical disorders. The researchers concluded that when kava is used, an anxiolytic alternative to benzodiazepines or tricyclic antidepressants, individuals typically suffer from less side effects. Of the 435 clinical trial participants taking kava supplements in our review, some at high doses, no liver issues were reported. Therefore, the current review supports the conclusion that liver toxicity is indeed a rare side effect.

Table 2 Trials testing kava [44]

Reference	Study Design	Sample Population	Intervention	Control	Length of	Outcomes	Direction of	Reported Adverse

					Treatment		Evidence	Events
Volz (1997)	Randomized; Double-blind; Parallel Group	101 outpatients with anxiety of non-psychotic origin ¹	Kava-kava extract WS 1490 (90- 110 mg dry extract = 70 mg kl per capsule)	Placebo	24 weeks	Significant reduction in anxiety (HAMA, CGI, SCL-90-R, AMS) in favour of kava-kava treatment.	+	Excellent tolerability, similar to placebo; no clinically relevant changes in laboratory results. Stomach upset.
Scherer (1998)*	Open-label; Uncontrolled Observational study	52 outpatients with nonpsychotic anxiety	Kava preparation (no dose reported in abstract)	N/A	Not reported in abstract	42 patients (80.8%) rated kava treatment as "very good" or "good".	+	Rare
Malsch (2001)	Randomized; Double-blind; Parallel group	40 adult outpatients with non-psychotic nervous anxiety, tension and restlessness, impairing work	Pre-treatment with benzodiazepines (tapered off over two weeks) followed by capsules of 50 mg/day of dry extract standardized	Pre-treatment with benzodiazepines (tapered off over two weeks) followed by placebo for three weeks	5 weeks	Significant reduction in anxiety (HAMA, Bf-S, EAAS, CGI) in kava-treated group.	+	No serious adverse events

		performanc e, normal social activities and relationship s	to 35 mg kava lactone for three weeks					
Watkins (2001)	Randomize d; Double- blind; Parallel Group	13 patients with GAD	Kava 280 mg/day (standardized to 30% kavalactones)	Placebo	4 weeks	Significant improvement in baroreflex control of heart rate in kava- treated group; respiratory sinus arrhythmia did not respond to kava treatment.	+	Not reported
Connor (2002)	Randomize d; Double- blind; Parallel Group	38 adults with DSM-IV GAD ₃	Kava (standardized to 70 mg kavalactones [kl]). Treatment initiated at 149 mg kl/day and increased to 280 mg kl/day for	Placebo	4 weeks	No significant difference to placebo ⁴	-	Well tolerated. No evidence of withdrawal or sexual side effects.

			the next 3 weeks.					
Boerner (2003)	Randomized; Double-blind; Parallel Group	129 outpatients diagnosed with GAD (GAD; ICD-10: F41.1)	400 mg/day Kava extract LI 150 (standardized to 30% kavapyrones, extraction solvent 96% ethanol in water, drug-extract ratio 13-20:	(1) 10 mg/day Buspirone or (2) 100 mg/day Opipramol	8 weeks	Kava was shown to be as effective as reference treatments; 75% of patients responded (50% reduction of HAMA score).	+	1 treatment-related adverse event. No systematic difference between treatments. No liver toxicity Reported

10.3 St. John's wort:



Hypericum perforatum, or St John's wort (SJW), is derived from the flowering tops of a perennial shrub. It has been used in traditional medicine for centuries to treat a wide range of disorders and is licensed in Germany to treat anxiety, depression and sleep disorders. St John's wort is a reuptake inhibitor of serotonin, dopamine and noradrenaline, which are chemicals in the brain that are linked

to depression and anxiety. Recent clinical trials have found that St John’s wort was superior to placebo, or as effective as standard antidepressants (e.g. Prozac, Tofranil and Zoloft). There are numerous hypotheses for its anxiolytic effects based on the binding affinity of at least 10 different extracts, including naphthodianthrones like hypericins, flavonoids, xanthenes, and bioflavonoids, for adenosine, GABAA, GABAB and glutamine receptors, as well as the inhibition of monoamine oxidase-A and –B activity and synaptosomal uptake of serotonin, dopamine and noradrenaline (norepinephrine). SJW is probably most recognized for its use in depression. A meta-analysis published in 1996, showed that SJW was more effective than placebo in treating mild to moderate clinical depression.

There has been little study of the effectiveness of SJW in treating anxiety disorders specifically, with only four RCTs and two uncontrolled observational studies. A small 12-week observational study (n = 13) of patients with OCD showed that SJW caused significant improvements, with results comparable to those seen in clinical trials with SSRIs [45]. However, a larger 12-week RCT (n = 60) showed no significant difference between patients treated with SJW (at doses higher than the observational study) or those treated with placebo. For this reason, these negative results were probably due to lack of response to SJW treatment rather than the high placebo response rates noted in the negative kava trials.

Table 3 Trials testing St. John’s wort [45]

Reference	Study Design	Sample Population	Intervention	Control	Length of Treatment	Outcomes	Direction of Evidence	Reported Adverse Events
Taylor (2000)	Open-label; Uncontrolled; Observational	13 subjects with a primary DSM-IV diagnosis of OCD of at least 12 month duration	Fixed dose of 900 mg/day of hypericin (a psychoactive compound in	N/A	12 weeks	Significant improvement in YBOCS scores in SJW group (comparable to those seen in clinical	+	Diarrhea Restless sleep

			Hypericum)			trials with SSRIs).		
Volz (2002)	Randomized; Double-blind; Parallel Group	149 outpatients diagnosed with somatization Disorder ² , undifferentiated somatoform Disorders ³ , or somatoform autonomic Dysfunctions	Hypericum extract LI 160 (600 mg/day)	Placebo	6 weeks	Significant reduction in anxiety (HAMA SOM, CGI, HAMA-T, HAMAPSY, HDS, SCL-90-R, SCL-90-R-ANX) in favour of SJW treatment.	+	Verywell tolerated. Mild/moderate: Abdominal pain Arthritis Arrhythmia Bronchitis Cystitis Headache Neuralgia
Muller (2003)	Open label; uncontrolled observational	500 patients diagnosed with depression comorbid with anxiety ((1) 500 mg valerian extracts and 600 mg/day St John's Wort (2) 1,000 mg valerian extract and 600 mg/day St John's wort	N/A	6 weeks	Significant reduction in anxiety disorder symptoms (HAMA) in both treatment groups. Higher dosage results in greater improvements.		Allergy Bad dreams Sleep disorders Dysphoria
Kobak (2005)	Randomized; Double-blind; Parallel Group	40 subjects with GAD	St John's wort; flexible dose (600-1800 mg/day), mean dose at week 12 was	Placebo	12 weeks	No significant difference to placebo (LSAS) - Similar to Placebo		Similar to placebo. Mild/moderate: Gastrointestinal upset Dizziness

			1676 mg/day					Insomnia Fatigue
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11.0 Herbal Medicine for Market Potential in India:

Recently there has been a shift in universal trend from synthetic to herbal medicine, which we can say 'Return to Nature'. Medicinal plants have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention of diseases and ailments. Nature has given our country with an enormous wealth of medicinal plants; therefore India has often been referred to as the Medicinal Garden of the world. Countries with ancient civilizations such as China, India, South America, Egypt, etc. are still using several plant remedies for various conditions. In this regard India has a unique position in the world, where a number of recognized indigenous system of medicine viz., Ayurveda, Siddha, Unani, Homeopathy, Yoga and Naturopathy are being utilized for the health care of people. No doubts that the herbal drugs are popular among rural and urban community of India. The one reason for the popularity and acceptability is belief that all natural products are safe. Now a days, there is a revival of interest with herbal-based medicine due to the increasing realization of the health hazards associated with the indiscriminate use of modern medicine and the herbal drug industries is now very fast growing sector in the international market. But unfortunately, India has not done well in this international trade of herbal industry due to lack of scientific input in herbal drugs. So, it would be appropriate to highlight the market potential of herbal products and that would open floodgate for development of market potential in India [48].

12.0 Conclusion

It appears that nutritional and herbal supplements are effective methods for treating anxiety and anxiety-related conditions without the risk of serious side effects. All three studies of passion flower, kava and St. John's wort showed a positive benefit for treatment with passionflower, providing good evidence of its effectiveness as an anxiolytic agent for depression. Also treatment for depression by lifestyle medicine and complementary therapies and medicine produced effective

treatment for the person suffering from depression and thus causing less side effects. Herbal medicines hold an important place in the history of medicine, as most of our current remedies, and the majority of those to be discovered in the future, will contain phytochemicals derived from plants. While locating the active ingredients in herbal substances is pivotal to being able to produce effective supplements, understanding the quantity needed and potency of different ways of extracting and preparing the phytochemicals is vital to creating a standard measure of their effectiveness. In addition, the dangers of overconsumption and interactions with prescription medications and over-the-counter medications need to be further analyzed. This understanding of the standards for effective preparation further minimizes the chance of side effects from herbal medicines and helps to create an undisputable body of evidence for their effectiveness.

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