Biomedicine & Pharmacotherapy 104 (2018) 343–365

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Phytochemistry and pharmacology of anti-depressant medicinal plants: A review

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ARTICLE INFO

Keywords:
Depression
Medicinal plants
Serotonin
TST
FST
MAO
Antidepressant

ABSTRACT

Stress renders an individual to experience mental pressure and exhaustion which brings about feelings of anxiety, depression, anger and/or other negative emotions. Depression affects a person's state of mind, behaviour, health and is often associated with suicide. The use of anti-depressant drugs as therapeutic agents is associated with symptoms such as, delayed onset of action, side-effects, drug–drug and dietary interactions, sexual dysfunction, cardiac toxicity, *etc.* Thus, there is need to target these issues and improve current treatment options. Medicinal plants have long been used in discovering novel treatment strategies and compounds with promising roles in treating various disease conditions. There has been an increase, worldwide, in the use of medicinal plants and herbs for developing nutraceuticals for treatment of depression and other psychiatric disorders. Medicinal plants in their natural forms are valuable as they are rich in various phytochemical compounds. These phytochemical compounds have pharmacological roles in treating various diseases conditions; apart from being widely available in nature and commercially beneficial. The phytochemical compounds in plants are constantly being explored through various experimental studies to determine the molecular basis of how medicinal plants work in relation to drugs and diseases and to develop neutraceuticals for improving conditions. This review summarizes 110 medicinal plants and their phytochemical constituents that have been shown to possess anti-depressant activity. This review also highlights the various mechanisms of anti-depressant action of some of these plants and their plant parts like roots, stem, leaves, flowers, fruit or whole plant; phytochemical compounds showing anti-depressant activity such flavanoids, steroids, saponins, sugars, lectins, alkaloids, *etc.*; and various anti-depressant screening models used such as tail suspension test, forced swim test, chronic unpredictable stress test, sucrose preference test, monoamine oxidase inhibition assay, learned helplessness test, open field test, hole board test, *etc.* However, mechanistic evaluation of many of these plants still needs to be investigated and explored.

1. Introduction

1.1. Depression and its forms

Depression is a syndrome that is generally comprised of loss of interest, anxiety, disturbance in sleep, loss of appetite, lack of energy and suicidal thoughts, which can be recurrent. Stress is the main trigger of depression that is constant in today's world. It manifests itself as the body's reaction towards a stimulus, displayed in the form of mental, physical and/or an emotional response [1]. Depression is initiated through stress and stressful situations that are difficult to solve and can cause a person to suffer and function poorly in everyday life. Under worst circumstances it can lead to suicide.

According to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) by the World Health Organization (WHO) [2] and the Diagnostic and Statistical Manual (DSM-V) by the American Psychiatric Association [3], there are multiple variations of depression that a person can suffer from. Depending on the number and severity of symptoms, a depressive episode can be categorized as: mild to moderate depression, major to severe depression and bipolar affective disorder.

According to the National Institute of Mental Health (NIMH), depression is also seen to occur in the following forms: perinatal depression, seasonal affective disorder, disruptive mood dysregulation and

Abbreviations: HPA, hypothalamic pituitary adrenocortical axis; SERT, serotonin transporter; NET, norepinephrine transporter; DAT, dopamine transporter; CUMS, chronic unpredictable mild stress test; SPT, sucrose preference test; LH, learned helplessness; OFT, open field test; BrdU, bromodeoxyuridine assay; BDNF, brain-derived neurotrophic factor

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https://doi.org/10.1016/j.biopha.2018.05.044
Received 30 January 2018; Received in revised form 3 May 2018; Accepted 8 May 2018

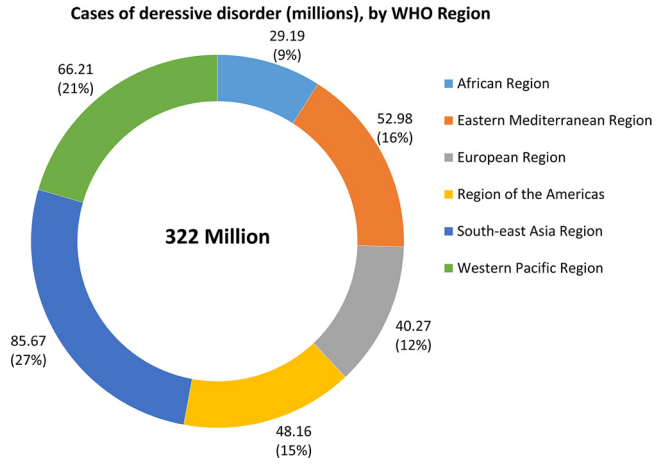

Fig. 1. Cases of depression (in millions) prevalent in different regions of the world [8].

premenstrual dysphoric disorder [4–7].

1.2. Disease burden

Depression is a main cause of distress worldwide. The WHO reports more than 300 million people across the world suffer from depression which accounts for 4.4% of the world's population [8]. Fig. 1 shows cases of depression (in millions) that are prevalent in different regions of the world. There has also been an 18% increase in cases of depression from 2005 to 2015, worldwide. The burden of depression, globally, is seen to be 50% higher for females than in males and is the leading cause of disease burden for women in high, low- and middle-income countries. The WHO Mental Health Action Plan 2013–2020, launched in 2008, ensures that the WHO member states commit themselves to work towards the global target of reducing the suicide rate in countries by 10% by 2020 [8].

1.3. Rating scales in diagnosing depression

Two major governing bodies have laid down certain criteria to be considered for a person to be diagnosed as depressed or not. These are the ICD-10 and the DSM-V [2,3]. A number of clinician-rated and patient-rated scales have also been developed as efficacy measures in depression clinical trials for diagnosing depression in patients (Table 1). The Hamilton Rating Scale for Depression and Montgomery-Asberg Depression Rating Scale are the ones that are commonly used by clinicians and researchers in assessing patient symptoms in diagnosis or for checking the efficacy of drugs in therapy [9].

Table 1
List of various clinician-rated and patient-rated scales for depression [9].

Common Rating Scales for Depression	
1.	The Hamilton Rating Scale for Depression (HAM-D or HRSD)
2.	Montgomery-Asberg Depression Rating Scale (MADRS)
3.	Raskin Depression Rating Scale
4.	The Beck Depression Inventory (BDI)
5.	Inventory of Depressive Symptomatology (IDS or QIDS)
Other Rating Scales for Depression	
1.	Centre for Epidemiological Studies - Depression Scale (CES-D)
2.	Center for Epidemiological Studies Depression Scale for Children (CES-DC)
3.	Edinburgh Postnatal Depression Scale (EPDS)
4.	Goldberg Health Questionnaire (GHQ)
5.	Geriatric Depression Scale (GDS)
6.	Hospital Anxiety and Depression Scale (HADS)
7.	Kutcher Adolescent Depression Scale (KADS)
8.	Major Depression Inventory (MDI)
9.	Mood and Feelings Questionnaire (MFQ)
10.	Newcastle Depression Scales (NDS)
11.	Patient Health Questionnaire (PHQ)
12.	Weinberg Screen Affective Scale (WSAS)
13.	Zung Self-Report Depression Scale (Zung SDS)

1.4. Neurochemistry of depression

The monoamine theory of depression has been a major focus of research in the fields of pathophysiology and pharmacotherapy for more than 25 years and most of the antidepressant treatment is based on this theory [10]. This theory states the underlying basis of depression to be as a result of depletion in the monoamine levels of serotonin, norepinephrine, and/or dopamine in the brain [11]. Serotonin, norepinephrine and dopamine are major neurotransmitters in the brain, of which, serotonin or 5-hydroxytryptamine (5-HT) is the neurochemical which primarily affects depression and moods. Serotonin binding sites are located predominantly in the raphe nucleus of the brain and other areas of the brain, including the frontal cortex, the striatum and limbic system, affecting the hypothalamus and hippocampus [12]. Serotonin controls feelings of hunger, appetite, the drive to act, violence, impulsiveness, anxiety, fearfulness, ability to think clearly, perception, *etc.* Norepinephrine promotes vigilance by increasing arousal and alertness. It also enhances memory formation and retrieval. Dopamine functions mainly in motor control, reward-motivated behaviour and in the release of various hormones besides other functions [13]. Fig. 2 illustrates the pathways through which these neurotransmitters function.

1.4.1. Serotonin receptors

The 5-HT receptors control the release of many neurotransmitters and hormones. They also influence biological and neurological processes such as anxiety, appetite, mood, memory, learning, cognition, nausea and sleep [13]. Hence, they have been used as therapeutic targets for various pharmacological drugs. There are seven serotonin receptor classes namely 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, which are further divided into various subclasses: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}; 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_{5A}, 5-HT_{5B}, 5-HT_6 and 5-HT_7. [14].

Studies have reported that patients with major depression show changes in 5-HT_{1A} receptor as well as a reduction in its density at the postsynaptic terminal [15,16]. Genetic studies have also shown that individuals with a high density and activity of 5-HT_{1A} autoreceptors are more prone to mood disorders and respond poorly to antidepressant treatment [17]. This suggests that 5-HT_{1A} receptor antagonists may possess anti-depressant activity. Activation of 5-HT_{1B} heteroreceptors promotes anti-depressant behaviour and 5-HT_{1B} receptor knockout mice have been reported to display highly aggressive behaviour and have increased preference for alcohol [18,19]. Therefore, 5-HT_{1B} receptor activation may play an important role in anti-depressant activity. Unlike the 5-HT_{1A} and 5-HT_{1B} receptors, the clinical significance of other subclasses of 5-HT_1 receptors (5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}) still remains unclear.

Studies have also shown that antipsychotic drugs and antidepressant tricyclic drugs augment the clinical response to SSRIs *via* their interaction with α_2 adrenoceptors and the 5-HT_{2A} receptor in treatment-resistant patients. This indicates the significance of these receptors in anti-depressant activity [20,21]. Lack of 5-HT_{2B} receptors has been shown to be associated with impulsive behaviour in individuals and suicidal intent due to changes in serotonin neurotransmission to certain regions of the brain [22]. This suggests that 5-HT_{2B} receptor agonists may help bring about anti-depressant activity. Preclinical studies have also shown that selective and nonselective 5-HT_{2C} antagonists potentiate the effects of SSRIs on brain serotonin levels and also significantly augment the effect of SSRI drugs in behavioural models of depression [23]. More recently, 5-HT_3 receptor antagonism with drug ondansetron has been reported to potentiate the increase in extracellular 5-HT produced by SSRI citalopram in rat forebrain [24]. Conductier et al., demonstrated the inhibitory response