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Review

Botanicals for mood disorders with a focus on epilepsy

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ABSTRACT

Mood disorders are among the major health problems that exist worldwide. They are highly prevalent in the general population and cause significant disturbance of life quality and social functioning of the affected persons. The two major classes of mood disorders are bipolar disorders and depression. The latter is assumed to be the most frequent psychiatric comorbidity in epilepsy. Studies published during the second half of the 20th century recognized that certain patients with epilepsy present a depressed mood. Synthesized pharmaceuticals have been in use for decades to treat both mood disorders and epilepsy, but despite their efficiency, their use is limited by numerous side effects. On the other hand, animal models have been developed to deeply study potential botanicals which have an effect on mood disorders. Studies to investigate the potential effects of medicinal plants acting on the nervous system and used to treat seizures and anxiety are increasingly growing. However, these studies discuss the two conditions separately without association. In this review, we present animal models of depression and investigative models (methods of assessing depression) of depression and anxiety in animals. Other classical test models for prediction of clinical antidepressant activity are presented. Finally, this review also highlights antidepressant activities of herbals focusing specially on depression-like behaviors associated with epilepsy. The pharmacological properties and active principles of cited medicinal plants are emphasized. This review, therefore, provides an overview of the work done on botanicals for mood disorders, potential mechanisms of action of botanicals, and the major compounds.

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1. Introduction

Mood disorders are treatable medical conditions in which the emotional symptoms are intense, long-lasting, or recurrent and decrease the ability to function. Some of the major symptoms include low mood, reduced interest or pleasure in all activities, appetite changes, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, worthlessness or excessive guilt, and reduced ability to concentrate [1]. Mood disorders are among the major health problems in the world for two reasons: they are highly prevalent in the general population, and they cause significant disturbance of life quality and social functioning of the affected persons. They are generally classified into two groups, which are bipolar disorders and depression.

Bipolar disorder has traditionally been thought to have a lifetime prevalence of about 1% of the world populace. The term "depression" is suggestive of a single entity; it denotes a very heterogeneous psychiatric disorder with several clinical manifestations, some of which are particular to patients with epilepsy. Depression in epilepsy has been considered, for a long time, as a complication of the underlying seizure disorder. Psychosocial aspects of being diagnosed with epilepsy may contribute to depression associated with epilepsy. Some clinical and experimental evidence suggests that the imbalances in such neurotransmitters as GABA, glutamate, norepinephrine, and serotonin, which are presumed to occur in patients with epilepsy, may concurrently contribute to the development of depression. Major depression and dysthymia are the most common mood disorders experienced by people with epilepsy, and the incidence of depressive disorders in epilepsy ranges between 20% and 80% [2,3]. Indeed, the relationship between mood disorders and epilepsy has been observed for over 2400 years, and studies published during the second half of the XX century also recognized that certain patients with epilepsy present depressed mood [4]. Depression is the most

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frequent psychiatric comorbidity in epilepsy, affecting one out of three patients with epilepsy in population-based studies. It is lower in community-based samples with epilepsy (20–30%) and higher in specialist epilepsy clinics (20–55%). This large variation in epidemiological data is due to the diversity of methodologies across the studies and to the differences in definitions of mood disorder [5]. Yet, despite its high prevalence, depression remains unrecognized and undertreated in patients with epilepsy [6].

Depression as a common comorbidity of temporal lobe epilepsy (TLE) is poorly understood [7,8]. In general, evidence for treatment strategies of mood disorders in epilepsy is lacking, and development of management approaches tends to rely on clinical experience rather than evidence-based trials favoring one treatment over another [9]. Establishment of animal models of this comorbidity is critical for both understanding the mechanisms of the condition and preclinical development of effective therapies.

For instance, the pharmacological mechanisms of many antidepressant drugs have been well documented. However, there is a notable paucity of data on the effectiveness of antidepressants in epilepsy-associated depression. Increasingly, researchers are developing animal models of the comorbidity between depression and epilepsy and to evaluate the effects of herbals on depression in animals with chronic epilepsy induced by *status epilepticus*. This review presents the major experimental models that are in use to test drugs and botanicals for use in mood disorders and an overview of the work done on botanicals for mood disorders, potential mechanisms of action of botanicals, and the major compounds. This review will also focus on animal models for depression associated with epilepsy and on studies that examine whether a commonly used animal model of TLE is characterized by behavioral and biochemical alterations involved in depression. Then, we will look at studies based on the potential of botanicals used as possible treatment modality for epilepsy-associated depression.

2. Integrative description of experimental models used to test drugs and botanicals

2.1. Tests of depression and anxiety based on behavioral changes or environmental challenges

2.1.1. Tests to assess depression in animals

Depression is diagnosed on the basis of a cluster of highly variable symptoms [1]. In addition to depressed or irritable mood, depression includes cognitive symptoms (guilt, ruminations, and suicidality), emotional symptoms (anhedonia), homeostatic or 'neurovegetative' symptoms (for example, abnormalities in sleep, appetite, weight, and energy), and psychomotor agitation or retardation. Only a subset (homeostatic symptoms, anhedonia, and psychomotor behavior) can be measured objectively in rodents. Studies that attempted to develop valuable animal models of comorbidity between epilepsy and depression focused on behavioral alterations in animal models of epilepsy classically linked to depression.

Most animal models of depression are based either on environmental challenges or on manipulation of sensory and integrative functions of the brain [10]. Two of the major symptoms in depression are despair and anhedonia [4]. In rodents, the behavioral equivalents to these emotional states are accessed by the forced swim test, the saccharin or sucrose taste preference test, and the tail suspension test, based on the observation that animals exposed to uncontrolled or unpredictable aversive events for a sufficient period of time will develop long-lasting deficits in escape performance [11].

The forced swim test (FST) is a well-characterized model used to screen the effectiveness of antidepressant drugs in rodents. The FST assesses the adaptive behavior of rodents when confronted to a stressful situation. The swim test involves the scoring of active (swimming and climbing) or passive (immobility) behavior when rodents are forced to swim in a cylinder from which there is no escape [12]. There are two versions that are used, namely, the traditional and modified FSTs, which differ in their experimental setup. For both versions, a pretest of 15 min (although a number of laboratories have used a 10-min pretest with success) is included, as this accentuates the different behaviors in the 5-min swim test following drug treatment. Immobility period is regarded as the time spent by the rats to float in water with no struggle and making only those movements necessary to keep their head above the water. Reduction in passive behavior (duration of immobility) is interpreted as an antidepressant-like effect of the manipulation, provided that it does not increase general locomotor activity, which could provide a false positive result in the FST [13].

In the sucrose taste preference test, when given access to tap water and sweet solution, rodents naturally and strongly prefer the latter. However, animals submitted to experimental stress show a decrease in consumption of the sweet solution. Some studies have demonstrated that rats in which seizures have been induced by kainite, lithium–pilocarpine, or electrical kindling spent a significantly longer time immobile in the forced swim test and exhibited loss of preference for saccharin solution when compared with nonepileptic animals [4].

In the tail suspension test (TST) [14], which relies on similar assumptions and interpretations as the FST, the mice are individually hung upside down by their tails on the edge of a table, 50 cm above the floor by using adhesive tape placed approximately 1 cm from the tip of their tails. The total period of immobility is recorded manually for 6 min. An animal is considered to be immobile when it does not show any body movement, hangs passively, and is completely motionless. The time spent immobile is evaluated.

Other classical test models for prediction of clinical antidepressant activity are as follows: apomorphine antagonism and reserpine-induced hypothermia. Apomorphine (in higher doses) and reserpine induce syndromes like hypothermia, the reversal of which is used as a reliable initial method to detect antidepressant activity. In fact, imipramine-like tricyclic antidepressants antagonize hypothermia induced by apomorphine in mice [15].

5-Hydroxytryptophan (5-HTP) potentiation of head twitches in mice is one test model used to assess therapeutic action of antidepressant drugs, which in part reduce functional activity of some central 5-HT systems. The 5-HT precursor produces typical behavioral responses in rodents. The effect in rats designated "wet dog shakes", comprising intermittent body movements including a shaking of the head, whereas, in mice, predominantly rapid and intermittent head twitches are the effect. Jobe et al. [16] and Kondziella et al. [17] have shown that serotonin (5-HT) deficiency is not only a mechanism of depression but also a defining approach in the treatment of the disease through the use of selective serotonin reuptake inhibitors (SSRIs). On the other hand, dysfunction of serotonergic transmission has been reported under conditions of TLE [18]. It was suggested that impairments in serotonergic transmission represent a pathophysiological link between epilepsy and depression [16,19]. The action of a given substance in apomorphine, reserpine-induced hypothermia, and 5-HTP potentiation of head twitch models can, therefore, show that this substance might have effect on serotonin reuptake inhibition to exert its antidepressant activity.

2.1.2. Tests to assess anxiety in animals

Anxiety, which has also been reported as a psychological disorder common in people with epilepsy, has been described as an unpleasant emotional state for which the cause is either not readily identified or perceived to be uncontrollable or unavoidable [20].