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Review

Therapeutical strategies for anxiety and anxiety-like disorders using plant-derived natural compounds and plant extracts

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ABSTRACT

Anxiety and anxiety-like disorders describe many mental disorders, yet fear is a common overwhelming symptom often leading to depression. Currently two basic strategies are discussed to treat anxiety: pharmacotherapy or psychotherapy. In the pharmacotherapeutical clinical approach, several conventional synthetic anxiolytic drugs are being used with several adverse effects. Therefore, studies to find suitable safe medicines from natural sources are being sought by researchers. The results of a plethora experimental studies demonstrated that dietary phytochemicals like alkaloids, terpenes, flavonoids, phenolic acids, lignans, cinnamates, and saponins or various plant extracts with the mixture of different phytochemicals possess anxiolytic effects in a wide range of animal models of anxiety. The involved mechanisms of anxiolytics action include interaction with γ-aminobutyric acid A receptors at benzodiazepine (BZD) and non-BZD sites with various affinity to different subunits, serotonergic 5-hydrodytryptamine receptors, noradrenergic and dopaminergic systems, glutamate receptors, and cannabinoid receptors. This review focuses on the use of both plant-derived natural compounds and plant extracts with anxiolytic effects, describing their biological effects and clinical application.

1. Introduction

Anxiety and related disorders are among the most common of mental disorders. The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) principles arranged the anxiety disorder spectrum into separate groups for the classical anxiety disorders, trauma- and stressor-related disorders, obsessive-compulsive and related disorders, and dissociative disorders. Based on DSM-5, the classical anxiety disorders also include selective mutism and separation anxiety disorder [1]. According to large population-based surveys, up to 33.7% of the population are affected by an anxiety disorder during their lifetime; it has higher prevalence than the lifetime prevalence of mood disorders and substance use disorders [2–6]. A broad range of mental declines are included in the definition of anxiety or anxiety-like disorders. They are

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commonly diagnosed using mental questionnaires and by oral interactions with patient. Instrumental tools like magnetic resonance are used to map the focal point of the disease [7]. Neither diagnosis nor therapy is easy, as the sub-conscious and conscious are involved. Understanding the pathophysiology is crucial for accurate diagnosis [8]. Generally, anxiety is a normal human emotion which arises during stress and/or discomfort. However, when left uncontrolled, anxiety can lead to debilitating overwhelming fear. Patients are mentally crippled, expressing a wide variety of symptoms including restlessness, worry, irritability, muscle tension and sleep problems.

Many symptoms are similar to those which occur in depression and anxiety could ultimately lead to depression [9,10]. But, compared to depression, anxiety disorders are rarely self-diagnosed while depression is often recognized by patients. Recently Coles and co-workers reported that 50% of patients recognized depression while only 20% correctly recognized anxiety [11]. The findings of Sun et al. [12] suggest that anxiety, depression, and helplessness are important correlates of obsessive-compulsive disorders in Chinese adolescents and it is evident that these different mental disorders have several common signs. More than half of patients with an anxiety disorder have multiple anxiety disorders [2,13], and almost 30% will have three or more comorbid anxiety or related disorders [2]. Anxiety is often associated with substance use and mood disorders [2,14]. An estimated 52% of patients with bipolar disorder [15], 60% of patients with major depressive disorder [16], and 47% of those with attention deficit hyperactivity disorder [17] will have an anxiety or related a comorbidity. The high frequency of comorbidity must be considered when diagnosing anxiety and related disorders since this can have important implications for diagnosis and treatment [18]. Anxiety disorders associated with other anxiety or depressive disorders are associated with poorer treatment outcomes and greater severity [19–22], increased functional impairment [20], increased health service use [23], and higher treatment costs [24]. Patients with anxiety disorders have a higher prevalence of hypertension and other cardiovascular conditions, gastrointestinal disease, arthritis, thyroid disease, respiratory disease, migraine headaches, and allergic conditions compared to those without anxiety disorders [25]. Anxiety has a considerable economic impact on society as well, being associated with greater use of health care services [4,26] and decreased work productivity [26,27]. Importantly, studies report that about 40% of patients diagnosed with anxiety and related disorder remain untreated [4,28].

The manifestation of anxiety and anxiety-like disorders involves a coordinated activity of numerous brain signalling pathways involving different neurotransmitters. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter which is known to counterbalance the action of the excitatory neurotransmitter glutamate. Other neurotransmitters that modulate complex anxiety responses in the amygdala, including serotonin, opioid peptides, endocannabinoids, neuropeptide Y, oxytocin, and corticotrophin-releasing hormone [29]. GABAergic inhibition is essential for maintaining a balance between neuronal excitation and inhibition in the central nervous system (CNS) [29]. Neuronal inhibition by GABA is mediated by two distinct classes of GABA receptors. Ionotropic $GABA_A$ receptor is fast-acting ligand-gated chloride channel responsible for rapid inhibition [30]. $GABA_B$ receptor is coupled indirectly via G-proteins to either calcium or potassium channels to produce slow and prolonged inhibitory responses which is involved in the processes of myorelaxation [31]. The $GABA_A$ receptor is a transmembrane hetero-oligomer with pentameric structure (α_1, α_2, β_1, β_2, and γ subunits) located in the neuronal membrane as is showed in Fig. 1. Activation of $GABA_A$ receptors causes an immediate and substantial rise in chloride conductance across the cell membrane, which renders the neuron unable to raise an action potential and leads to “phasic” inhibition of the neuron [32,33]. Preclinical studies demonstrated that the α_2 subunit of $GABA_A$ receptor is particularly relevant for the manifestation of anxiety [34]. The neural circuits involved in anxiety comprise inhibitory networks of principally GABAergic interneurons. It is supposed that the presence of allosteric sites on the GABAA receptor allows the level of inhibition of the neuron to be regulated with exquisite precision using different classes of anxiolytic and sedative–hypnotic drugs such as benzodiazepines, barbiturates, or neurosteroids. However, these allosteric sites can be modulated also by wide spectrum of plant natural compounds. Consequent changes in the subunit composition and conformation of the $GABA_A$ receptor may represent mechanisms whereby the level of neuronal activity may be affected in pathological anxiety states [29].

1.1. Pharmacotherapy of anxiety using synthetic drugs

Anxiety can be controlled by pharmacotherapy and/or psychotherapy. Antianxiety agents (anxiolytics) are used in pharmacotherapy [35–37]. The commonly recommended pharmacological agents for treatment of different anxiety and related disorders are benzodiazepines (BDZ), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and reversible inhibitors of monoamine oxidase A (RIMAs). BDZ are the first-line pharmacological anxiolytics drugs, and advanced psychoactive medications were developed in the last 45 years. However, their long-term use is impaired by tolerance development and abuse liability [38–40]. BDZ may be useful as adjunctive therapy early in treatment, particularly for acute anxiety or agitation, to help patients in times of acute crises, or while waiting for onset of adequate efficacy of SSRIs or other antidepressants [18]. Recent clinical outcomes have shown that SSRIs are effective on various anxiety disorders but have a slow onset of action [41–45]. SSRIs and SNRIs are usually preferred as initial treatments, since they are generally safer and better tolerated than TCAs or MAOIs [18]. Several anticonvulsants and atypical antipsychotics have demonstrated efficacy in some anxiety and related disorders, but for various reasons, including side effects, as well as limited trial data and clinical experience, these agents are generally recommended as adjunctive therapies. The choice of medication should take into consideration the evidence for its efficacy and safety/tolerability for the treatment of the specific anxiety and related disorder, as well as for any comorbid conditions the patient might have, in both acute and long-term use [18]. Although benzodiazepines, SSRIs, SNRIs and other anxiolytics are often effective, it is clear there is a need for rapidly acting, better tolerated medications with a greater and more sustained response. In this regard, there are also neurosteroids that are powerful allosteric modulators of $GABA_A$ and glutamate receptors which lack the unwanated side effects of benzodiazepines [46]. Based on findings from a wide range of preclinical and clinical studies, it is proposed that opioid ligands and its receptors are involved in physiological and dysfunctional forms of anxiety [47]. Many neuropeptides are plenteously expressed in specific brain regions which are involved in emotional processing and anxiety behaviours. In this regard, the various neuropeptides represent awaited candidates for new therapeutic ways against anxiety and anxiety-like disorders [48]. Moreover, glutamate-based anxiolytic ligands, which act through decreasing the activity of glutamatergic neurotransmission, may attenuate excitation in the CNS, thus resulting in anxiolysis [49]. Over the last two decades, some of the most promising molecules in pharmacological studies were addressed as prospective substances for development of new anxiolytics. Fig. 2 summarizes the mechanisms of action of prospective molecules with anxiolytic effects, such as Δ^9-tetrahydrocannabinol, modulators of metabotropic glutamate receptors and acid-sensing ion channels, and polyamines that are potentially new substances for the treatment of anxiety [50–58].

1.2. Animal models of anxiety disorders

Animal models are often used for the evaluation of molecular