

Review

Modulation of the Serotonergic Receptosome in the Treatment of Anxiety and Depression: A Narrative Review of the Experimental Evidence

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Abstract: Serotonin (5-HT) receptors are found throughout central and peripheral nervous systems, mainly in brain regions involved in the neurobiology of anxiety and depression. 5-HT receptors are currently promising targets for discovering new drugs for treating disorders ranging from migraine to neuropsychiatric upsets, such as anxiety and depression. It is well described in the current literature that the brain expresses seven types of 5-HT receptors comprising eighteen distinct subtypes. In this article, we comprehensively reviewed 5-HT₁₋₇ receptors. Of the eighteen 5-HT receptors known today, thirteen are G protein-coupled receptors (GPCRs) and represent targets for approximately 40% of drugs used in humans. Signaling pathways related to these receptors play a crucial role in neurodevelopment and can be modulated to develop effective therapies to treat anxiety and depression. This review presents the experimental evidence of the modulation of the “serotonergic receptosome” in the treatment of anxiety and depression, as well as demonstrating state-of-the-art research related to phytochemicals and these disorders. In addition, detailed aspects of the pharmacological mechanism of action of all currently known 5-HT receptor families were reviewed. From this review, it will be possible to direct the rational design of drugs towards new therapies that involve signaling via 5-HT receptors.

Keywords: 5-HT receptors; anxiety; depression; G protein-coupled receptors; antidepressants; anxiolytics; phytochemicals

1. Introduction

The first two subtypes of serotonergic receptors, serotonin receptors (5-HT) D and M, were discovered in 1957 [1]. Since then, a combination of pharmacological and neurochemical investigations has culminated in the discovery of a diversity of other types of 5-HT receptors. Currently, it has been well established in literature that the brain expresses seven types of 5-HT (5-HT₁₋₇) receptors, comprising a total of eighteen distinct subtypes (Table S1 (Supplementary Material)), although two of these receptors, 5-HT_{1e} and 5-HT_{5b}, keep the denomination in lower case and are classified as gene products, since they have not been associated with a specific function in native cells and/or tissues. Regarding the location of these receptors, most subtypes of 5-HT receptors are found both in the central and peripheral nervous system and in other cell types, such as smooth muscle, gastrointestinal tract, and platelets. The only exceptions are 5-HT_{1e}, 5-HT_{2c}, and 5-HT₆ receptors, for which there is limited expression outside the central nervous system (CNS). This diversity of receptors is comparable to that of more complex neurotransmitter systems, including glutamate and purines. Despite this, a wide range of agonists, antagonists, and selective radioligands are available for each subtype of 5-HT receptors, which has allowed further investigation of their location, signaling properties and functions in the CNS and in the rest of the organism [2].

Given this scenario, this review presents, in a narrative context, the experimental evidence for the modulation of the “serotonergic receptosome” in the treatment of anxiety and depression, as well as demonstrating state-of-the-art research related to phytochemicals and these disorders. In addition, a detailed review of aspects related to the mechanism of action of all currently known families of 5-HT receptors was carried out. The present study represented a crucial milestone to direct the rational development

of drugs and, consequently, new therapies that involve signaling through serotonergic receptors.

2. 5-HT₁ Receptors

2.1. Mechanism of Pharmacological Action

The five subtypes of 5-HT₁ serotonergic receptors are metabotropic coupled to the inhibitory G protein ($G_{\alpha i/o}$); that is, the receptor activation inhibits the adenylate cyclase enzyme (AC) and the formation of adenosine 3',5'-cyclic monophosphate (cAMP) [3].

5-HT_{1A} receptors are distributed in the limbic, cortical, and dorsal and median raphe nucleus (DRN and MRN), and are expressed in the pre- and post-synaptic membrane of neurons, where they act by regulating the extracellular serotonin concentration (5-HT) and transmission of the action potential. As an autoreceptor, it promotes the activation of internal rectifying potassium channels (GIRK), which allow an increase in potassium conductance, leading to neuron hyperpolarization, which in turn inhibits the opening of voltage-dependent calcium channels and the release of 5-HT [2,4]. In the post-synaptic membrane of non-serotonergic neurons, 5-HT_{1A} heteroreceptors, when stimulated by an agonist, activate the signal transduction pathway mediated by the $G_{\alpha i/o}$ protein, which decreases cAMP synthesis and the activation of protein kinase A (PKA), which is responsible for the phosphorylation of proteins and enzymes downstream, such as the cAMP-responsive binding protein (CREB), an intranuclear transcription factor (Figure 1a). The activation of these post-synaptic receptors also promotes hyperpolarization, similar to what occurs in pre-synaptic 5-HT_{1A} receptors, reducing neuronal hyperactivity, important for the treatment of some diseases such as anxiety [5] and schizophrenia [6]. By a mechanism not yet known, the activation of this receptor is also related to an increase in the number of reactive oxygen and nitrogen species, and stimulation of an enzyme similar to nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase) [7–10].

Another mechanism associated with the 5-HT_{1A} receptor activity involves the activation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) and protein kinase B (AKT), with increased dendritic growth in hippocampal neurons after stimulation of serotonergic receptors 5-HT_{1A} and 5-HT₇ [11]. The activation of the receptor leads to the same transduction pathway that culminates in the activation of ERK1/2 and AKT, which are important for the reorganization of the cytoskeleton. The activation of ERK increases the activity of nuclear factor kappa B (NF- κ B), which inhibits caspase 3, preventing cell death. Calmodulin-dependent protein kinase II (CaMKII), which is stimulated by active ERK, is also involved in the signal transduction pathway of the 5-HT_{1A} receptor and can promote the destabilization of microtubules. In turn, after stimulating the 5-HT_{1A} receptor, AKT activation is mediated by phosphatidylinositol-3-kinase (PI3K) and stimulated by negative feedback when there are high levels of active ERK. This increase in active AKT promotes the inhibition of Raf, the kinase responsible for phosphorylating and activating ERK, thus reducing the ERK concentration. In contrast to the anti-apoptotic activity, the activation of 5-HT_{1A} is also related to the increase in the activity of the apoptosis-inducing c-Jun N-terminal kinase protein (JNK). The stimulation of 5-HT_{1A} induces the activation of the Janus kinase 2 protein (JAK2), which phosphorylates calmodulin (CaM), which is associated with the sodium and hydrogen transporter 1 (NHE-1), causing its activation and an increase in intracellular pH with proton output (Figure 1b) [12–14]. It is important to highlight that the balance between these activities and the final effect is dependent on the tissue analyzed.

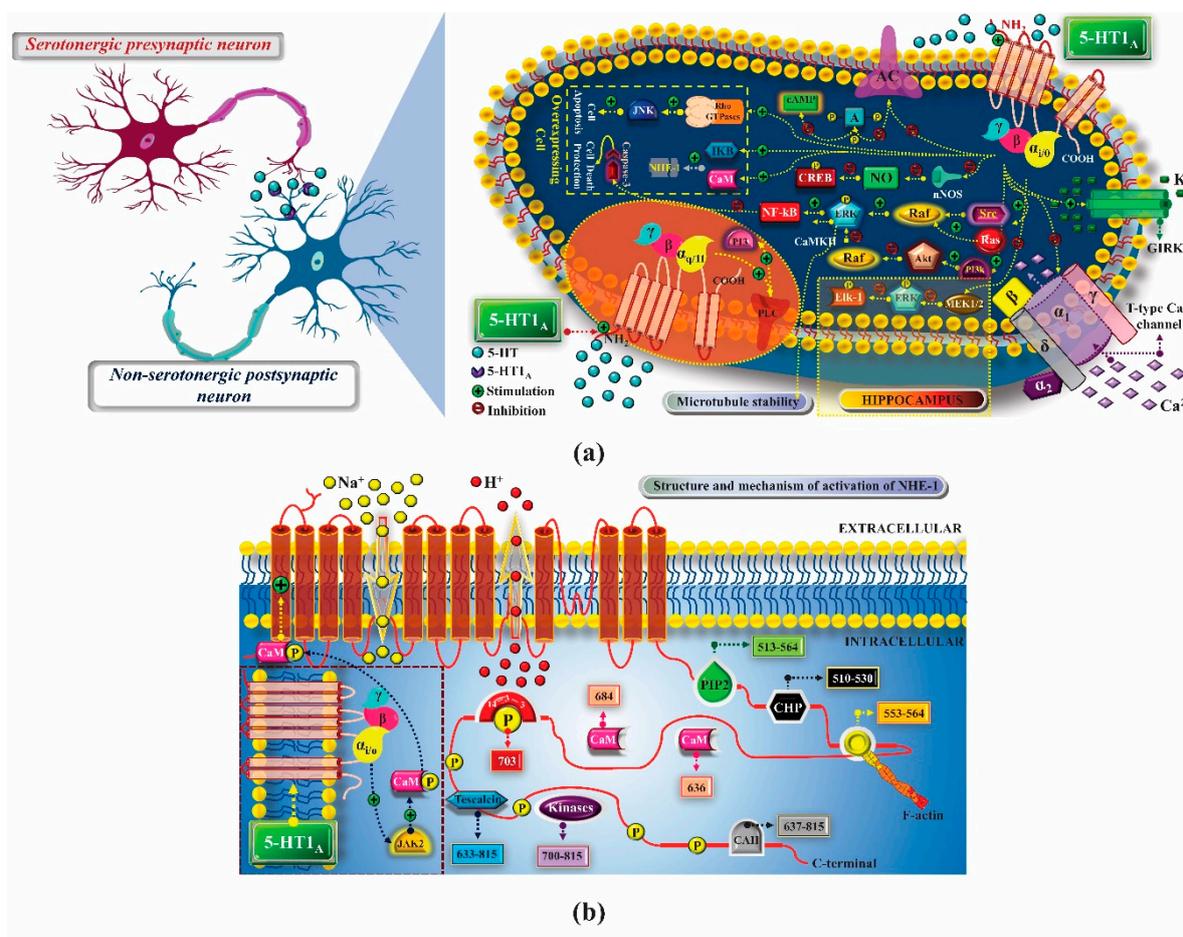


Figure 1. Serotonin (5-HT_{1A}) receptor signaling pathways: (a) The 5-HT_{1A} receptor is coupled to the G $\alpha_{i/o}$ protein. Its activation blocks the adenylate cyclase activity (AC), reducing the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP), which is responsible for the activation of protein kinase A (PKA). The activation of these receptors decreases the release of neurotransmitters in neurons through opposite changes in K⁺ (increase) and Ca²⁺ (decrease) conductances. In addition, stimulation of the 5-HT_{1A} receptor regulates the phosphorylation of the extracellular signal-regulated kinase (ERK). The “atypical” coupling is represented by the orange circle and demonstrates the overexpressing cell Jurkat T-like cell line. The yellow rectangle represents a specific effect on the rat hippocampus, where stimulation of the 5-HT_{1A} receptor reduced MEK1/2 and ERK and Elk-1 phosphorylation. This change in pERK levels was not seen in the cortex [12]; (b) the activation of the 5-HT_{1A} receptor also induces stimulation of the Janus kinase 2 protein (JAK2), which phosphorylates the calmodulin protein, which in turn is associated with the sodium and hydrogen 1 (NHE-1) transporter, activating it. The massive outlet of protons caused by the 5-HT_{1A} activation culminates in an increase in intracellular pH. The numbers represent the amino acids (approximate region) of the cytoplasmic domain of the NHE1 transporter in which the other proteins interact.

The activation of the 5-HT_{1B} serotonergic receptor also promotes the modulation of calcium and potassium channels, increasing the potassium conductance, hyperpolarizing the cell and, indirectly, reducing the calcium influx, which inhibits the release of 5-HT, when the 5-HT_{1B} receptor is expressed in the pre-synaptic membrane. As a post-synaptic receptor, 5-HT_{1B} inhibits AC through the signaling pathway triggered by the G $\alpha_{i/o}$ protein. The activation of 5-HT_{1B} induces the activation of ERK, AKT, and the Rho-kinase (ROCK) pathway, which stimulates the translocation of active ERK to the nucleus. As a way to regulate this signaling pathway, the glycogen synthase kinase 3 protein (GSK3) was associated with a possible phosphorylation of the receptor, increasing its inhibitory potential on AC (Figure 2) [12,15].

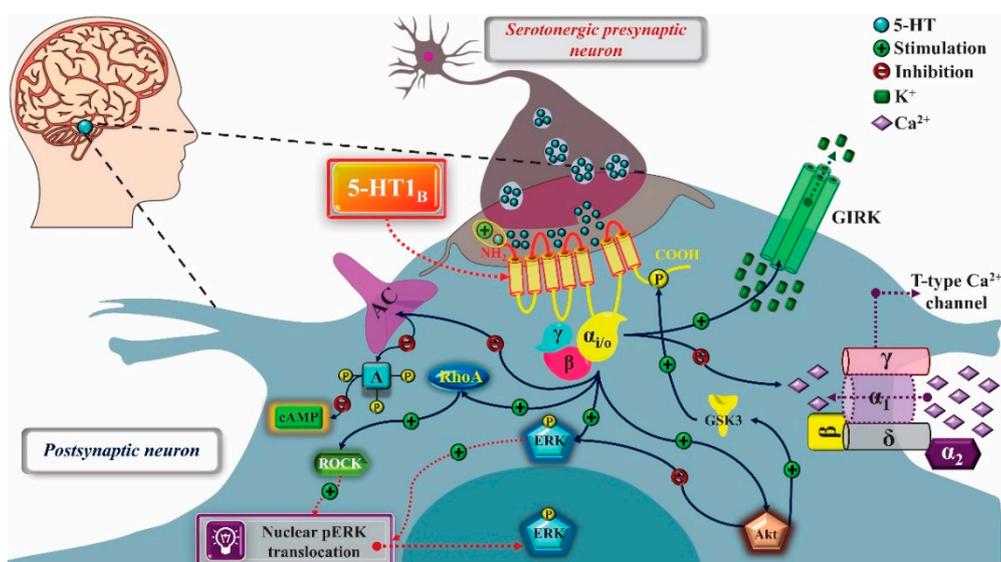


Figure 2. 5-HT_{1B} receptor signaling pathways. The 5-HT_{1B} receptor is coupled to the G $\alpha_{i/o}$ protein. Its activation blocks the activity of adenylyl cyclase (AC), reducing the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP), which is responsible for the activation of protein kinase A (PKA). The activation of these receptors decreases the release of neurotransmitters in neurons through opposite changes in K⁺ (increase) and Ca²⁺ (decrease) conductances. After 5-HT_{1B} activation, a cascade of kinases regulates the translocation of extracellular signal regulated kinase (ERK) (transcription activation) [12]. In addition, kinase B protein (AKT) is stimulated with consequent activation of glycogen synthase kinase 3 (GSK3), which is involved with phosphorylation and regulation of the 5-HT_{1B} receptor activity [16].

The 5-HT_{1D} receptor is expressed on the pre- and post-synaptic membrane of neurons in several regions of the nervous system, such as the nigrostriatal pathway, caudate putamen, globus pallidus, and substantia nigra. As autoreceptors, when activated, they inhibit the release of 5-HT from the pre-synaptic terminal through the same mechanism observed for the other 5-HT_{1A} and 5-HT_{1B} serotonergic autoreceptors, changing potassium conductance and calcium influx. Although the mechanisms resulting from the activation of post-synaptic 5-HT_{1D} receptors have not yet been elucidated, it is known that they act through the inhibition of AC, common among 5-HT₁ receptors and that it is structurally similar to the 5-HT_{1B} receptor [2,17,18]. Likewise, the pharmacological mechanism of action of 5-HT_{1E} and 5-HT_{1F} serotonergic receptors is still unknown. It is believed that 5-HT_{1E} has high affinity for 5-HT and low affinity for 5-HT₂ agonists, and for this reason, it was classified as 5-HT₁. As for the 5-HT_{1F} receptor, its expression in terminals and cell bodies of neurons in the human trigeminal ganglion is known. Its activation is associated with AC inhibition, preventing the release of neuropeptides and neurotransmitters, including the calcitonin gene-related peptide (CGRP) and glutamate. This role has been investigated in the planning of migraine treatments, as it has reduced neuronal hypersensitivity and hyperstimulation [19,20].

2.1.1. Treatment of Anxiety

The stimulation of the pre-synaptic 5-HT_{1A} receptor activity results in an anxiolytic effect by suppressing the release of 5-HT, whose high concentration is associated with the development of anxiety disorders. Based on this mechanism, the 5-HT_{1A} autoreceptor became a target to be explored for the planning of anxiolytic drugs. Examples of these drugs are buspirone and fluoxetine, direct and indirect agonists of this receptor, respectively [21]. Buspirone is a partial agonist of the 5-HT_{1A} autoreceptor, and is used, at low doses, to treat anxiety disorders. High doses of this drug are associated with the opposite clinical effect, the reason has not yet been completely clarified, but it may be related to the affinity of this substance with the 5-HT_{1A} heteroreceptor and the antagonistic activity on pre-synaptic dopamine (DA) D₂ receptors and adrenergic α_1 and α_2 receptors [22]. Another substance, also of the azapirone class and 5-HT_{1A} agonist, is gepirone, which

has anxiolytic and antidepressant activity. Gepirone is still in the development phase and has been an alternative to selective serotonin reuptake inhibitors (SSRIs), constituting a possible treatment for anxiety and depression, without causing sexual dysfunction, a common adverse effect among SSRIs [23]. Tansospirone is a post-synaptic 5-HT_{1A} receptor agonist and exerts its anxiolytic activity by inhibiting adenylate cyclase and activating GIRK, hyperpolarizing neurons from regions associated with anxiety disorders, such as the hippocampus and amygdala, where 5-HT_{1A} receptors are expressed, consequently inhibiting local neuronal activity (Figure 3a–c) [24]. In addition, tansospirone appears to facilitate the elimination of fear and reduce anxiety. This effect is mediated by the indirect increase in DA neurotransmission through the dopaminergic loop in the ventral tegmental area (VTA) hippocampus, which improves the synaptic efficacy in the extinction processes in the animal model of post-traumatic stress disorder (PTSD) [25,26] (Figure 3d).

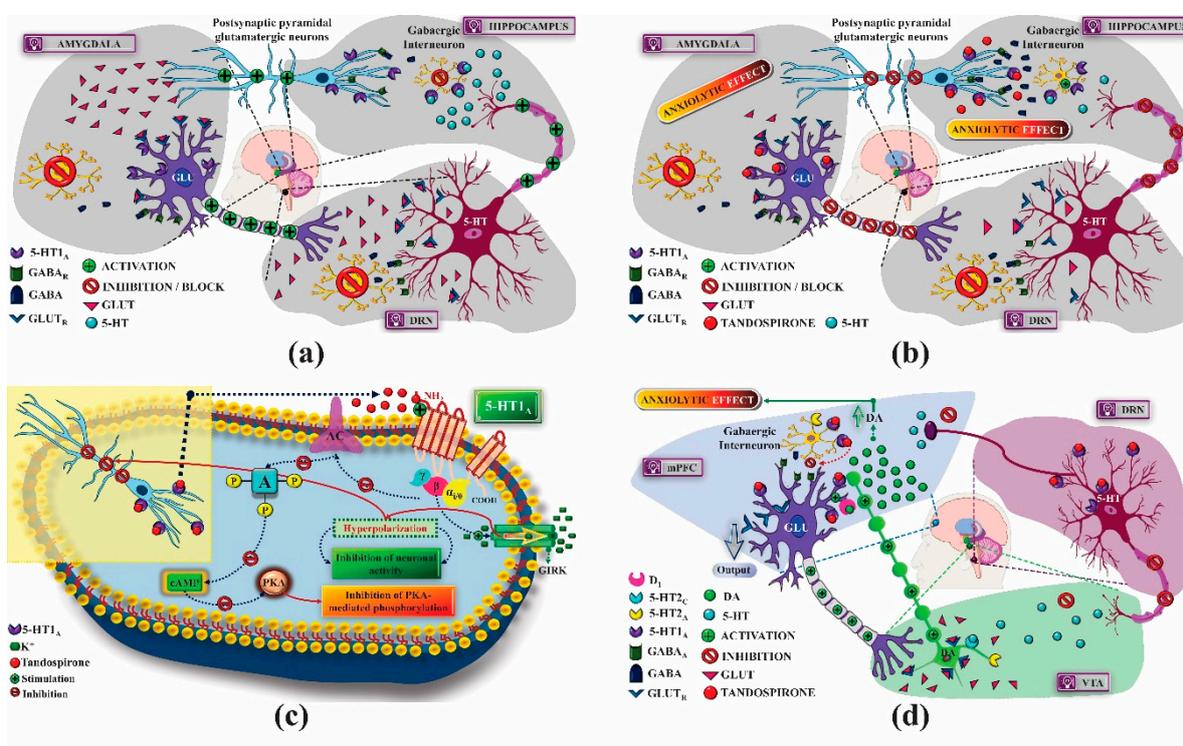


Figure 3. Anxiolytic mechanism of tansospirone. 5-HT_{1A}: (a) Biological factors have been implicated in the pathogenesis of anxiety. Neurochemical evidence suggests that the dysregulation of serotonin, norepinephrine, gamma-aminobutyric acid (GABA), glutamate, and peptides (corticotropin releasing factor, cholecystokinin, neuropeptide Y) transmission systems are strongly correlated with the pathophysiology of anxiety. In the classic concept of stress, homeostasis is threatened by physical and psychological events, known as stressors. Behavior is aimed at assessing the destabilizing potential of the stressor. If the stressor event does not correspond to any cognitive representation based on previous subjective experiences, there is an increase in alertness, hypervigilance, focused attention, and cognitive processing. The interface between sensory information received and the evaluation process is formed in the limbic region of the brain, which comprises structures such as the hippocampus, the amygdala, and the medial prefrontal cortex (mPFC). The components of the human fear circuit, which can be of particular relevance for destabilization produced by the stressor and, consequently, induction of anxiety, include mPFC (subservient fear extinction processes), the amygdala (risk assessment processing), and the hippocampus. The ascending serotonergic pathway that projects from the DRN into the hippocampus may be implicated in the genesis of behavioral inhibition observed in dangerous situations. During episodes of anxiety crisis, it is postulated that these serotonergic inputs in the hippocampus activate 5-HT_{1A} receptors in GABAergic interneurons. In this case, 5-HT_{1A} receptors coupled to the Gai/0 protein block adenylate cyclase (AC), prevent the formation of cyclic adenosine monophosphate (cAMP) and reduce the activation of protein kinase A (PKA) which, once reduced, decrease the permeability of calcium (Ca²⁺) to specific channels located in the cell membrane. This reduction in the calcium influx into the GABAergic interneuron culminates in the blocking the exocytosis of the GABA neurotransmitter. The reduction of the hippocampal GABAergic transmission causes an increase in the number of post-synaptic pyramidal glutamatergic neurons fires, stimulating anxiety-related regions such as the amygdala and the DRN,

which feeds back and over-stimulates the anxiety-related circuit; **(b,c)**; tandospirone has a promising anxiolytic effect, which has been shown in animal models, especially of the generalized anxiety disorder (GAD). Tandospirone acts as an anxiolytic by activating the post-synaptic 5-HT_{1A} receptor coupled to the G α i/o protein, resulting in reduced cAMP formation and PKA inhibition. On the other hand, it activates the G protein-controlled internal rectifying potassium channels (GIRK) by releasing G β γ subunits, leading to intracellular potassium (K⁺) efflux, hyperpolarization of target neurons and, finally, inhibition of the local neuronal activity [24]; **(d)** another mechanism by which tandospirone exerts its anxiolytic effect is by increasing the release of dopamine (DA) in the VTA. In this case, tandospirone activates the 5-HT_{1A} receptor in DRN or mPFC, directly or indirectly, stimulating dopaminergic transmission in VTA [24].

Reference [27] injected the following substances into the dorsal-medial raphe sub-nucleus (dmDR) and neurons in the lateral wings of the raphe dorsal nucleus (lwDR): (1) Kainic acid, an excitatory amino acid; (2) WAY-100635, a 5-HT_{1A} receptor antagonist; and (3) 8-hydroxy-2-(di-n-propylamino) tetraline (8-OH-DPAT), a 5-HT_{1A} receptor agonist. Administration of kainic acid and 8-OH-DPAT reduced anxiety behavior, while administration of the 5-HT_{1A} antagonist produced an anxiogenic effect and accentuated panic symptoms, indicating that the increased anxiety is associated with 5-HT_{1A} inhibitors. To demonstrate the implication of the 5-HT_{1A} receptor as a target for the treatment of anxiety disorders, a study by [28] demonstrated that the activation of serotonergic terminals in the dorsal part of the bed nucleus of the stria terminalis (dBNST) reduces anxiety, while inhibition of these terminals produces anxiogenic effect. In addition, it has been observed that 5-HT induces neuronal hyperpolarization through the 5-HT_{1A} receptor in dBNST, since the administration of an antagonist of these receptors intensifies anxiety-like behavior. Thus, researchers observed that the activation of 5-HT_{1A} is crucial for the anxiolytic effect observed through the activation of the serotonergic terminals in dBNST. An observation about 5-HT_{1A} autoreceptors is their participation in cases of anxiety due to chronic use of SSRIs. Chronic depression treatment with these drugs promotes desensitization of 5-HT_{1A} autoreceptors, preventing them from playing their regulatory role in the serotonergic activity and resulting in anxious behavior induced by neuronal hyperactivity, since 5-HT_{1A} would not be activated to promote hyperpolarization [29].

Although it is not a determining mechanism for the occurrence of anxious symptoms, the activation of serotonergic neurons in the bed nucleus of the stria terminalis (BNST) can be considered a way to modulate the neuronal hyperactivity observed in anxious patients. In this context, [30] investigated the anxiety modulation by means of 5-HT_{1A} heteroreceptors, expressed in the BNST, in male and female rats. The loss of the 5-HT_{1A} receptor in the region did not increase the anxiety behavior, confirming that this is not a determining mechanism for anxiety; however, this loss promoted an increase in fear conditioning in male rats, but not in female rats, which may be associated with the lower neuronal excitability observed in males, increased by the receptor depletion. It has been recently found that the depletion of 5-HT_{1A} heteroreceptor in the dentate gyrus (DG) of the hippocampus by means of the local elevation of glucocorticoid levels; that is, a chronic stress mechanism, is associated with the development of stress-induced anxiety, demonstrating again the importance of the 5-HT_{1A} receptor in the modulation of the neuronal activity [31].

The 5-HT_{1B} receptor is also an important target when it comes to the treatment of mental disorders. To investigate the role of this receptor on anxiety disorders, [32] used a genetic model to inhibit the expression of the 5-HT_{1B} autoreceptor in rats, which resulted in a reduction in behaviors suggestive of anxiety, demonstrated in the open field (OF) test, and decreased depression, observed in forced swimming and sucrose preference tests. These data indicate that blocking 5-HT_{1B} autoreceptors may be an alternative for the development of new treatments for anxiety and depression. Another study investigated the role of agonists in behavioral modulation after cocaine use. In this case, CP 94.253, a 5-HT_{1B} agonist, was administered via intracranial injection in the lateral habenula region, recently related to the neurobiology of anxiety disorders. The agonist attenuated the emergence of anxiogenic behaviors produced by cocaine. The anxiolytic activity was

stopped after the administration of the selective 5-HT_{1B} antagonist, NAS-181. These results confirm the contribution of this receptor to the effects resulting from cocaine administration and also reaffirm the possibility of making it a target for treatments against anxiety [33].

Studies on the involvement of serotonergic 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} receptors as possible targets for treatments against anxiety are recent and scarce. The ACH-000029 compound is undergoing pre-clinical studies, and showed anxiolytic activity, acting through partial activation of 5-HT_{1A} and 5-HT_{1D} receptors, antagonism on 5-HT_{2A}, and α_{1A} , α_{1B} , and α_{1D} adrenergics. The anxiolytic effect was observed in animal models with predictive validity for anxiolytic drugs, such as the marble burying test and the light–dark box. The compound demonstrated regular regions such as amygdala, paraventricular nucleus of the thalamus, retrosplenial cortex, BNST bed, and locus ceruleus, were implicated in the development of anxious symptoms [34]. Vortioxetine is another example of a therapeutic compound that reduces anxiety-like behavior, with the 5-HT_{1D} receptor as a non-specific target. It is an SSRI, but it also acts as an antagonist of the 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor, and a partial 5-HT_{1B} and 5-HT_{1A} agonist, reducing the exacerbated expression of the fear memory associated with anxiety and depressive disorders [35].

2.1.2. Treatment of Depression

The activation of 5-HT_{1A} serotonergic heteroreceptors with 8-OH-DPAT produces antidepressant effect [36]. This activity was associated with the inhibition of GABAergic neurons of the limbic pathway that express 5-HT_{1A}, which, once activated, induces neuronal hyperpolarization, inhibiting the release of the γ -aminobutyric acid (GABA), an inhibitory neurotransmitter involved in the development of depression and mood disorders, increasing the glutamatergic influence. This factor is associated with the role of 5-HT_{1A} receptors in the pathogenesis of depression since the activation of 5-HT_{1A} autoreceptors inhibits the release of 5-HT and induces depressive symptoms. These receptors are also expressed in afferent nociceptive fibers in the dorsal horn of the spinal cord (DHS); thus, therapies with 5-HT_{1A} autoreceptor antagonists and heteroreceptor agonists increase the available 5-HT concentration and decrease the release of nociceptive neurotransmitters, enabling not only the treatment of depression, but also chronic pain, often associated with mental disorders (Figure 4) [37,38].

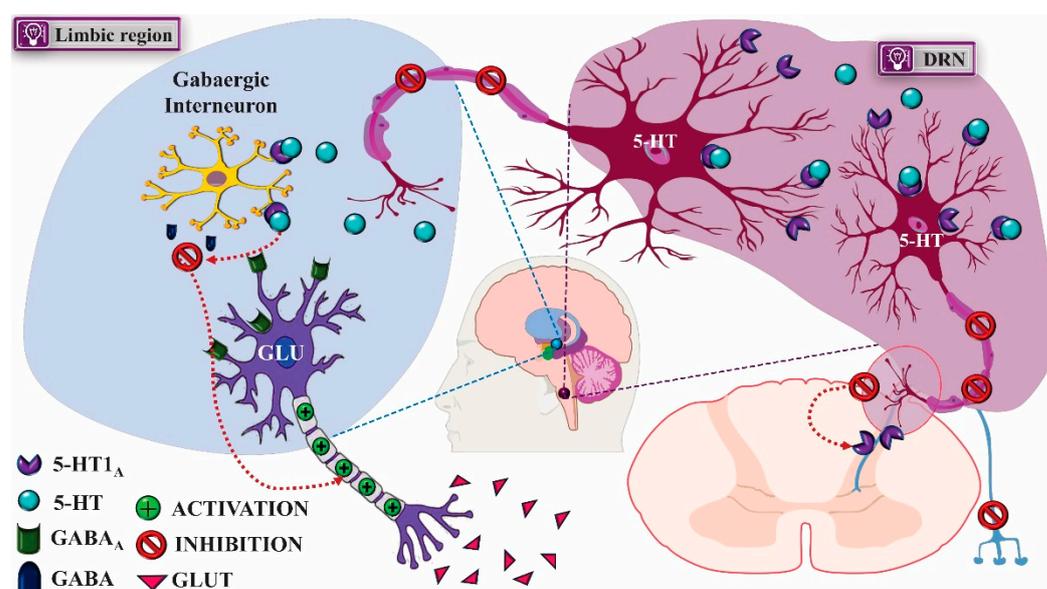


Figure 4. Hypothetical scheme of serotonergic projections resulting from the raphe and innervation of the dorsal horn spinal neurons (DHS) and limbic regions. In the dorsal raphe nucleus (DRN), 5-HT_{1A} receptors activate G protein-controlled internal rectifying potassium channels (GIRK) by releasing G $\beta\gamma$ subunits of the G α_{i0} protein, leading to intracellular potassium

(K⁺) efflux, hyperpolarization of target neurons, and, finally, inhibition of the local neuronal activity. Hippocampus and cortex heteroreceptors are also coupled to GIRK channels. Thus, activation of both 5-HT_{1A} autoreceptors and the hippocampus and cortex heteroreceptors increases the GIRK current, leading to neuronal hyperpolarization. As shown in the figure, the activation of 5-HT_{1A} autoreceptors reduces the release of serotonin (5-HT) in limbic regions or in DHS. However, the activation of 5-HT_{1A} heteroreceptors located in the DHS reduces the release of local 5-HT, consequently decreasing the release of nociceptive neurotransmitters and reducing pain signals (antinociceptive effect). In limbic regions, the stimulation of these receptors activates GIRK in GABAergic interneurons, hyperpolarizing them and consequently decreasing the influence of GABA on local glutamatergic neurons. As a consequence, there is an increase in the excitatory glutamatergic influence on underlying dopaminergic neurons [37].

The important role of 5-HT in mood regulation has made the serotonergic system become a determining target for the treatment of depression. In this sense, SSRIs were among the first treatments aimed at increasing the 5-HT concentration; that is, promoting the opposite reaction to that observed in depressive disorders, in which this concentration is reduced. SSRIs act by inhibiting the 5-HT (SERT) transporter, expressed in the pre-synaptic membrane of serotonergic neurons. The ability of these drugs to block this transporter without affecting other neuroreceptors made them stand out from other antidepressant therapies, with fewer adverse and side effects [39]. Vilazodone is an SSRI and partial 5-HT_{1A} receptor agonist and an alternative for the treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD). Its agonist action on 5-HT_{1A} is possibly responsible for the rapid effect of this substance, different from other SSRIs [40]. Similar to vilazodone, tandospirone is a selective agonist of the 5-HT_{1A} autoreceptor, whose administration, in the short term, promotes a decrease in the release of 5-HT. Chronic tandospirone administration, responsible for its pharmacological outcome, induces the desensitization of these receptors and, consequently, an increase in 5-HT concentration, exhibiting antidepressant activity, with late onset. However, this is not the only way the substance can be used to treat depression. The concomitant administration of tandospirone with SSRI or tricyclic antidepressants (TCAs), is even more effective, enhancing the effect of these drugs and even reducing their adverse effects [24].

Brexipiprazole is a drug used to treat MDD and schizophrenia. This substance acts as an agonist for the following receptors: 5-HT_{1A}; dopaminergic D₂ and D₃, and as an antagonist of the following receptors: 5-HT_{2A}, 5-HT_{2B}, 5-HT₇, and adrenergic α_{1A} , α_{1B} , α_{1D} , and α_{2C} , with greater affinity than aripiprazole, which belongs to the same class and with the absence of akathisia, a characteristic adverse effect. The use of brexipiprazole is recommended as an adjunct to antidepressant therapies, where it acts by enhancing the effect of antidepressants such as fluoxetine. This action can be observed in animal models for the assessment of depression and anxiety, such as the forced swimming test and the Vogel conflict test [41–43].

5-HT_{1B} antagonists have also been considered adjuvants to antidepressant therapy. Monotherapy with these substances does not induce effective results, which can be explained by the fact that 5-HT_{1A} and 5-HT_{1B} autoreceptors have less distribution and less pronounced activity than SERT. Thus, its application as a therapeutic enhancer is more efficient, intensified through the inhibition of the feedback mechanism that prevents the release of 5-HT [44,45]. Although structurally different, 5-HT_{1B} and 5-HT_{1D} may play similar roles in depressive disorders. Both are hypersensitive in patients diagnosed with these disorders; thus, they are easily activated and inhibit the release of 5-HT, a characteristic factor of the condition. Antidepressant vortioxetine acts by antagonizing 5-HT_{1D}, increasing the release of 5-HT [46,47]. As for 5-HT_{1E} and 5-HT_{1F} receptors, there is a lack of studies with antidepressant treatments that target these receptors or that correlate them with the pathogenesis of depression.

3. 5-HT₂ Receptors

3.1. Mechanism of Pharmacological Action

5-HT₂ receptors are coupled to the G $\alpha_{q/11}$ protein and activate phospholipase C (PLC or PLC- β) and phospholipase A₂ (PLA₂). They have three subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. The 5-HT_{2A} receptor is expressed in the cerebral cortex, insula, brain stem, and limbic system. In addition, it mediates contractile responses and regulates the expression of growth factors in these regions. The stimulation of the 5-HT_{2A} receptor promotes the activation of PLC- β , which catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate into inositol 1,4,5-triphosphate (IP₃) and diacylglycerol (DAG), increasing the concentration of these messengers in the intracellular medium. IP₃ acts by increasing the release of calcium from the endoplasmic reticulum (ER). The high calcium concentration can also promote the activation of voltage-dependent L-type calcium channels, which cause calcium influx, being responsible for the increase of intracellular calcium levels, causing contraction in muscle cells that express this receptor. In addition, DAG induces the activation of protein kinase C (PKC), which favors the activation of AC, formation of cAMP, stimulation of PKA, and activation of calcium channels, increasing the influx of this ion in the cell and, consequently, muscle contraction (Figure 5a).

In pyramidal neurons of mPFC, the 5-HT_{2A} receptor can activate p38, which, coupled to G $\alpha_{12/13}$, promotes the activation of PLA₂, inducing the formation of arachidonic acid and stimulating ERK₁ and ERK₂ through the activation of Rho kinase. In these neurons, stimulation of 5-HT_{2A} promotes the inhibition of calcium influx in Ca v1.2-type channels. This effect is mediated by the increase in PKC, IP₃, and stimulation of calcineurin, which not only reduce the calcium concentration but also inhibit the sodium efflux, a mechanism associated with synaptic plasticity. The activation of the 5-HT_{2A} receptor can also induce the activation of protein kinase MEK (mitogen-activated protein kinase), promoting the activation of ERK. In CNS cells, the 5-HT_{2A} receptor interacts with the postsynaptic density protein 95 (PSD-95), which can regulate the receptor expression. The activation of 5-HT_{2A} also increases the activity of PI3K and Akt (Figure 5b) [12].

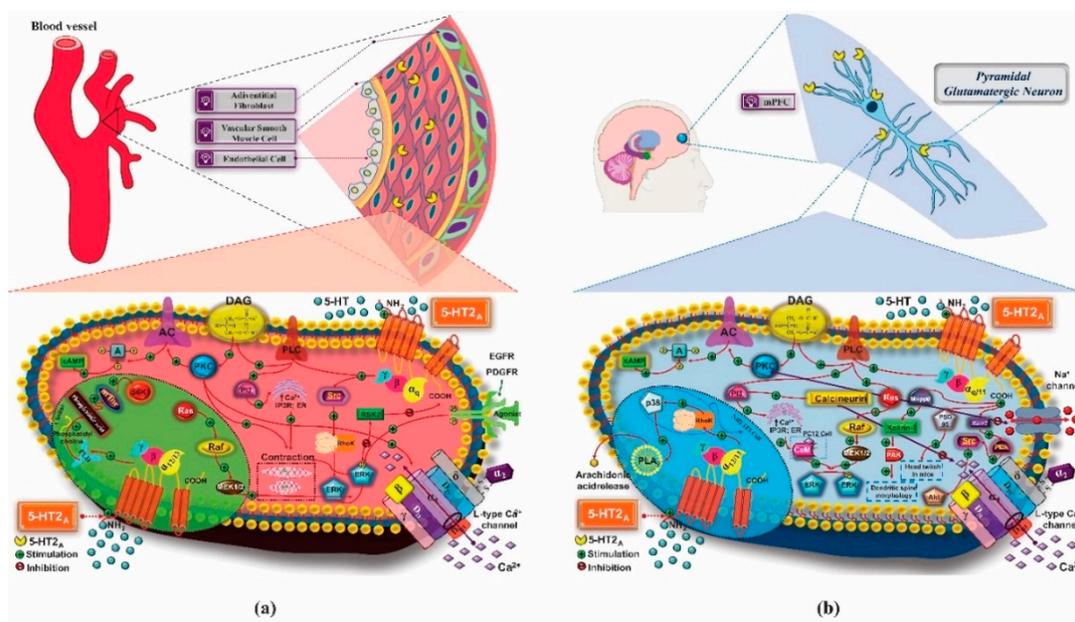


Figure 5. 5-HT_{2A} receptor signaling pathways: (a) In blood vessels (and other smooth muscles), stimulation of the 5-HT_{2A} by 5-HT receptor activates several signal transduction pathways through the G $\alpha_{q/11}$ protein (phospholipase C (PLC)/Diacylglycerol (DAG)/protein kinase C (PKC)/calcium (Ca²⁺) and kinase phosphorylation regulated by extracellular signal (ERK), leading to vascular smooth muscle contraction. The “atypical” coupling represented by the green circle demonstrates the specific signaling of the tracheal tissue mediated by the 5-HT_{2A} receptor, corroborating the hypothesis that the activity of these receptors, as well as the integration of their multiple pathways, varies from one tissue to another.

In the trachea, activation of the 5-HT_{2A} receptor produces its downstream effects primarily through the mammalian target of rapamycin (mTOR)/p70 ribosomal protein S6 kinase (S6K1) pathway [12]. **(b)** In glutamatergic neurons of the medial prefrontal cortex (mPFC), the coupling of 5-HT to the 5-HT_{2A} receptor stimulates the G $\alpha_{q/11}$ protein that activates several signal transduction pathways through PLC/DAG/AC/PKC. These, in turn, produce inhibition of Ca²⁺ and Na⁺ conductances. The “atypical” coupling represented by the blue circle demonstrates the activation of phospholipase A2 (PLA₂) mediated by the 5-HT_{2A} receptor and the subsequent release of arachidonic acid, described as a result of G $\alpha_{12/13}$ -coupled, Rho-mediated, p38 activation in NIH 3T3 cells [48]. Stimulation of PLA₂ causes the release of arachidonic acid. The pathways of several kinases are involved in the modulation of neuron morphology and plasticity through direct interaction between the C terminal portion of the receptor and specific modulating proteins [12].

5-HT_{2A} receptors can be pre- or post-synaptic. Post-synaptic receptors are part of the mechanism of action of some psychotropic and psychedelic drugs. However, pre-synaptic receptors are a recent discovery, and appear to stimulate glutamatergic transmission and memory consolidation. [49] described three main functions associated with the 5-HT_{2A} pre-synaptic receptor: a) The potentiation of NMDA glutamatergic receptor responses; b) involvement in the development of depression; and c) important participation in associative learning. 5-HT_{2A} receptors have a specific characteristic, the interaction with β -arrestin 1 and 2, known to mediate the desensitization of metabotropic receptors and important for cell signaling performed by 5-HT_{2A} receptors. In addition, these receptors have other mechanisms that regulate their signaling, such as the formation of homo and heteromeric complexes with other metabotropic receptors such as mGlu₂ and D₂ [50,51]. The interaction between 5-HT_{2A} and mGlu₂ can be attested by the synergistic effect between 5-HT_{2A} antagonist antipsychotic drugs and mGlu₂ agonists, and also by the documented co-localization of these receptors [52,53].

As for 5-HT_{2A}, signaling induced by the activation of 5-HT_{2B} receptors occurs differently depending on the tissue and ligand. Stimulation of the 5-HT_{2B} receptor induces cell cycle regulation, with the activation of the platelet-derived growth factor receptor (PDGFR) and the Src family kinase. When stimulated, PDGFR promotes the activation of ERK1 and 2, which has an inducing effect on cyclin D₁, while the Src family kinase stimulates cyclin E; both cyclins act in the progression from phase G1 of the cell cycle to phase S. This mechanism is associated with the rapid proliferation of cells of some tissues that express the 5-HT_{2B} receptor. In cells in which MAPK was previously depleted, the expression of cyclin D₁ was reduced, but not of cyclin E, indicating that the MAPK pathway may be involved in this mechanism [54].

Previous studies have shown the mechanism resulting from the activation of the 5-HT_{2B} receptor, expressed in astrocytes, by fluoxetine. The activation of 5-HT_{2B} promotes the activation of PKC and the increase of intracellular calcium concentration. This increase in calcium levels induces the activation of metalloproteinases (MMPs), which act by causing the release of growth factors such as the epidermal growth factor receptor (EGFR) ligand that stimulates the phosphorylation of this receptor, which, once phosphorylated, promotes the activation of ERK via the Ras/Raf/MEK signaling pathway and Akt activation via the PI3K pathway. Activation of ERK induces gene expression of cfos and fosB in astrocytes, while AKT inhibits glycogen synthase kinase-3 β (GSK-3 β), involved not only in metabolic issues, but also in the pathophysiology of mood disorders (Figure 6) [55].

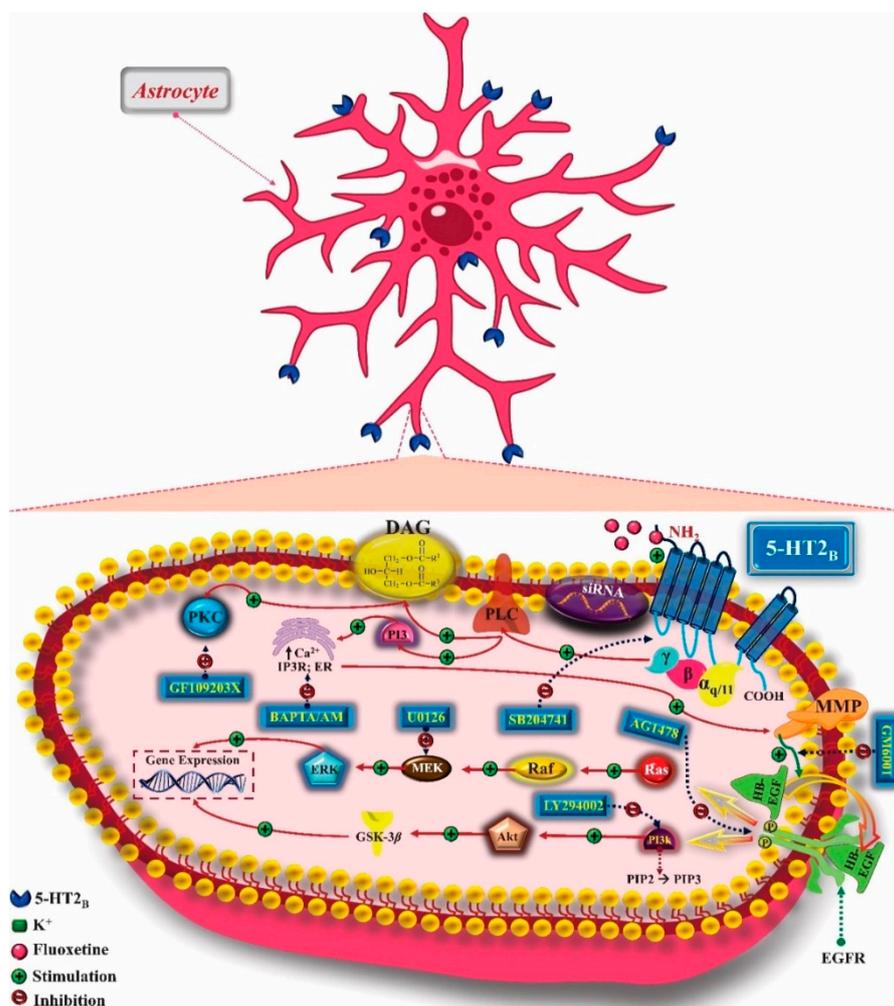


Figure 6. Scheme of pathways that stimulate extracellular signal-regulated kinase (ERK) and phosphorylate protein kinase B (AKT) after stimulation of the 5-HT_{2B} receptor by fluoxetine in astrocytes. Fluoxetine binds and activates 5-HT_{2B} receptors, culminating in the stimulation of G $\alpha_{q/11}$ protein, which stimulates enzyme phospholipase C (PLC), which catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate in inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol (DAG). DAG induces protein kinase C (PKC) activity, while IP₃ increases the intracellular calcium (Ca²⁺) concentration due to the release of Ca²⁺ from endoplasmic reticulum stocks. Ca²⁺ stimulates zinc-dependent metalloproteinases (MMPs) and leads to the release of growth factors. The released epithelial growth factor receptor (EGFR) ligand stimulates EGFR phosphorylation. ERK, the downstream target of EGFR, is phosphorylated via the Ras/Raf/MEK pathway, and AKT is phosphorylated via the phosphoinositide 3-kinase pathway (PI3K). In addition, PIK3 catalyzes the formation of PIP₃ from PIP₂. After fluoxetine administration, ERK and AKT phosphorylation was blocked when iRNA against the 5-HT_{2B} receptor was administered or after administration of inhibitors of this receptor (SB204741) (shown in blue), PKC (GF109293X), intracellular Ca²⁺ homeostasis (BAPTA/AM, an intracellular Ca²⁺ chelator), zinc-dependent MMPs (GM6001), EGFR (AG1478), ERK phosphorylation (U0126, a mitogen-activated protein Kinase (MEK) inhibitor), or AKT pathway (LY294002, a PI3K inhibitor) [55].

The activation of the 5-HT_{2B} receptor in cardiomyocytes induces the activation of PI3K/AKT and ERK pathways, which can control the expression of nuclear genes that directly influence the permeability of the mitochondrial membrane. The PI3K/Akt pathway inhibits the expression of ANT-1, a cell death regulator, and the ERK pathway inhibits Bax, an apoptosis inducer. A study with mice, whose cardiomyocytes did not have the 5-HT_{2B} receptor, revealed that in these animals, caspase activation occurred, which induced apoptosis and destruction of myofibrils, leading to a dilated cardiopathy condition. On the other hand, mice with excessive expression of these receptors showed

intense ANT-1 downregulation, which culminated in increased proliferation and hypertrophic cardiomyopathy. This information suggests that adequate expression of the 5-HT_{2B} receptor promotes a protective effect against heart disease, without inducing uncontrolled proliferation or apoptosis [56]. The activation of the 5-HT_{2B} receptor expressed in transfected cells promotes activation of GTPase and production of IP₃. This stimulus also activates the MAPK, PDGFR, PLA₂, PLC pathway, inducible nitric oxide synthase (iNOS), PI3K and constitutive nitric oxide synthase (cNOS). As a result, activation of ERK 1 and 2, induction of the activity of cyclins D and E, increase in the release of arachidonic acid and production of intracellular cGMP due to the iNOS and cNOS stimulus are observed. PI3K promotes activation of the NF- κ B transcription factor [57].

5-HT_{2C} serotonin receptors are widely distributed throughout the CNS. They have different levels of expression in the cerebral cortex, cerebellum, substantia nigra, cingulate cortex, nucleus accumbens (NAc), ventral pallidum, putamen, caudate nucleus, globus pallidus, amygdala, hippocampal formation, VTA, olfactory system, epithalamus, thalamus, and subthalamus, with greater expression in GABAergic neurons than in glutamatergic neurons. Like the other subtypes, 5-HT_{2C} is coupled to the G $\alpha_{q/11}$ protein and signals the activation of PLC- β , promoting the mobilization of calcium and increasing its levels in the intracellular environment, in addition to inducing the expression of immediate early genes (IEGs). PLC catalyzes the formation of IP₃ and DAG. IP₃ causes the release of calcium reserves in the ER, which, associated with the role of CaM, may be related to the activity of some drugs that act on this receptor, such as antidepressants. DAG induces the activation of PKC, which promotes phosphorylation and activation of ERK 1 and 2. Activation of the 5-HT_{2C} receptor can promote the activation of PLA₂, which leads to the release of arachidonic acid and activation of PLC γ . The G $\alpha_{12/13}$ protein also participates in the coupling and stimulates the PLD activity, which is involved in the activation of ERK 1 and 2 and the G β - γ subunit. G $\alpha_{i/o}$ can participate in 5-HT_{2C} signaling and induce PLA₂ and PI3K, whose signaling cascade involves GSK-3 β and ERK 1 and 2, culminating in the transcription of the β -Arrestin gene, capable of interacting with the 5-HT_{2C} receptor. As for the other subtypes of 5-HT₂ receptors, the mechanisms resulting from their activation are different according to tissue and ligand, making it possible to activate only some of these signaling pathways (Figure 7) [58].

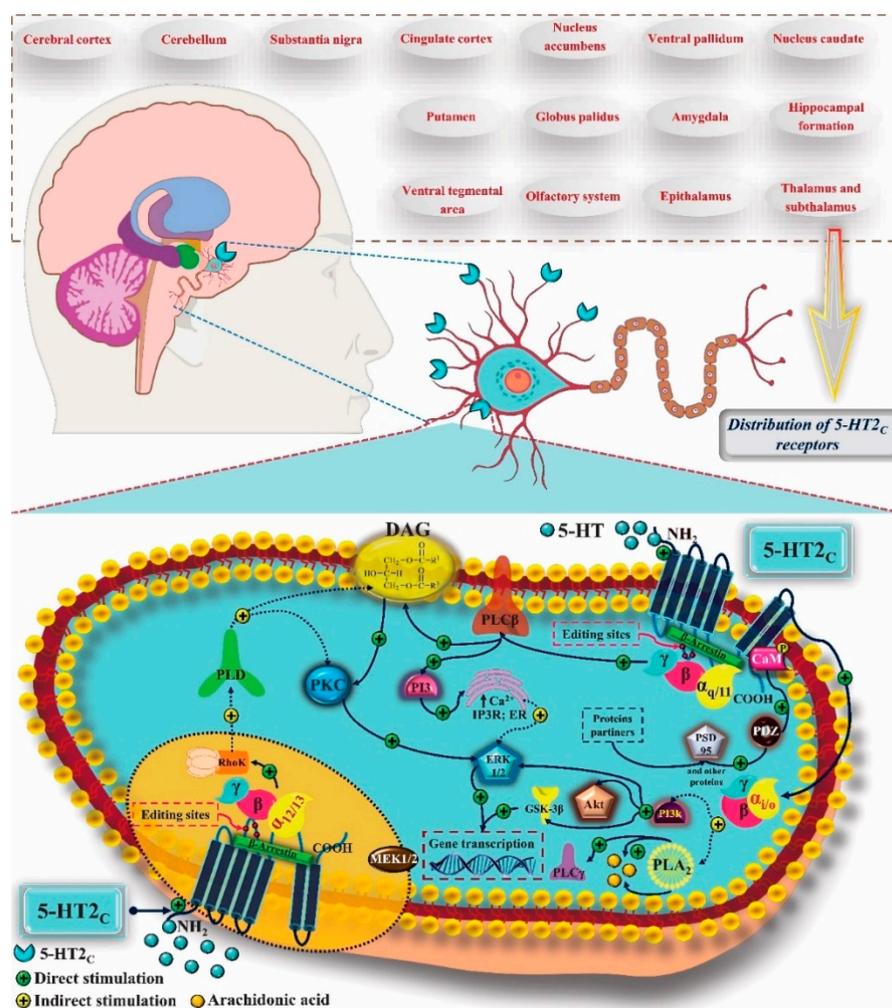


Figure 7. 5-HT_{2c} receptor signaling. After activation of the 5-HT_{2c} receptor by 5-HT, the G $\alpha_{q/11}$ protein is activated and subsequently stimulates phospholipase C (PLC) activity. PLC catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate into inositol 1,4,5-triphosphate (IP₃) and diacylglycerol (DAG). IP₃ diffuses through the cytoplasm and stimulates the release of calcium (Ca²⁺) from the endoplasmic reticulum and DAG activates protein kinase C (PKC), leading to the phosphorylation of various cellular substrates, which in turn activate several intracellular biochemical cascades. The activation of the 5-HT_{2c} receptor can also stimulate the activity of enzyme phospholipase A₂ (PLA₂), which is responsible for the synthesis of arachidonic acid (causing its release in the intracellular space). The “atypical” coupling represented by the orange circle demonstrates that through the coupling of the G $\alpha_{12/13}$ protein, the activation of the 5-HT_{2c} receptor stimulates phospholipase D (PLD), whose activity converges to PKC activation, which subsequently activates extracellular signal-regulated kinases 1 and 2 (ERK1/2). Another ERK activation pathway is provided through G $\alpha_{i/o}$, which induces the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/glycogen synthase kinase-3 β (GSK-3 β) cascade. Finally, this signal transduction system controls genetic transcription [58]. The β -Arrestin protein interacts with 5-HT_{2c} receptors and creates a steric impediment that blocks the coupling of heterotrimeric G proteins to the receptor, preventing the activation of G α proteins.

3.1.1. Treatment of Anxiety

The 5-HT_{2A} receptor is involved in behavioral responses and plays an important role in the development of behaviors similar to anxiety and depression. 5-HT_{2A} antagonists can control anxious symptoms, and although the mechanism of their activity is unclear, the role of ERK signaling for this purpose has been suggested [59]. Based on the influence of the intestinal microbiota on immunity and behavior, a study that tested the use of the neonatal probiotic (BGOS) showed that the administration of lipopolysaccharides (LPS) and induction of acute inflammation in mice promote increased expression of the 5-HT_{2A}

receptor. This increase was associated with post-inflammatory anxiety behavior, showed by the submission of these animals to anxiety assessment models [60]. The antagonism of 5-HT_{2A} by ritanserin, ketanserin, R59022, and R59949 inhibits the formation of IP3 and DAG. However, ritanserin and R59022 also exhibit another activity, the specific inhibition of the diacylglycerol kinase alpha enzyme (DGK α), which catalyzes the conversion of DAG into phosphatidic acid (PA) [61]. The analysis of the injection of 5-HT_{2A}/5-HT_{2C}, DOI agonist in PAG, in hippocampus CA1, CA2, and CA3 subregions, in basolateral amygdala (BLA), and in the lateral LA, demonstrates that the compound produces an anxiolytic effect only with administration in the CA2 subregion. This compound had an opposite effect on the amygdala and PAG compared to that observed in the hippocampus. In the latter, intense anxiolytic activity was observed, while in the others, the effect was anxiogenic [62,63].

In a study using an animal model with zebrafish, 2,5-dimethoxy-4-bromo-amphetamine hydrobromide (DOB), and para-methoxyamphetamine (PMA) showed anxiolytic activity, which was blocked by the administration of the 5-HT_{2A}/5-HT_{2C} antagonist, ritanserin, demonstrating that the mechanism of action of DOB and PMA involves these receptors [64]. Analysis conducted by [65] verified the activity of the 5-HT_{2A} agonist, TCB-2, and 5-HT_{2A} antagonist, MDL 11,939, on anxiety and acquisition of conditioned defeat memories in Syrian hamsters. These substances were administered by injection into the nucleus of the BLA. When the same substances were administered to other regions of the brain, they did not produce the same results, indicating a determinant function of the 5-HT_{2A} receptor over local control. These receptors are expressed in pyramidal neurons and GABAergic interneurons in BLA, and their role is to directly or indirectly inhibit the activity of neurons in that region. Thus, the stress-induced downregulation of 5-HT_{2A} receptors increases neuronal excitability and, consequently, fear and anxiety. The administration of the agonist can lead to desensitization of the receptor, which, like downregulation, causes anxiety, while the antagonist avoids desensitization and downregulation, decreasing the anxiety triggered by stress. Although most animal models use rodents, dogs with pathological anxiety were submitted to analysis that verified the 5-HT_{2A} receptor binding index in these animals. A lower binding index and reduced expression of 5-HT_{2A} receptors was observed in these animals, indicating that there is a role for these receptors in the pathophysiology of anxiety disorders, which still needs to be investigated, so that new anxiolytic therapies can be proposed [66].

The administration of the 5-HT_{2B}/5-HT_{2C} receptor agonist, mCPP, in PAG, reduced anxiety-like behavior in mice. However, after treatment with ketanserin, a 5-HT_{2A}/5-HT_{2C} antagonist, mCPP administration did not produce the same effect, indicating that the 5-HT_{2C} receptor plays an important role in modulating anxiety in PAG, since its activation induced an anxiolytic effect [67]. There are few studies that describe the 5-HT_{2B} receptor as a possible target for the treatment of anxiety, and some previous analyses indicate the anxiolytic activity of 5-HT_{2B} agonists, such as BW723C86, which demonstrated this effect in the Vogel conflict and Geller–Seifter test [68] (tests based on associative learning), but was ineffective in the elevated plus-maze (EPM) test [69,70] (ethologically-based model).

There are disagreements about the role of the 5-HT_{2C} receptor in anxiety disorders, since the results of its activation or blockage are different according to the CNS region submitted to analysis. Recent studies have shown that the administration of the 5-HT_{2B}/5-HT_{2C} agonist in the dorsal hippocampus (DH) of rats induced anxiety, but the administration of selective 5-HT_{2C} agonists, MK-212 and RO-600175, promoted an anxiolytic effect, indicating that local activation of 5-HT_{2C} causes the opposite effect of local activation of 5-HT_{2B}. As expected, the 5-HT_{2C} antagonist, SB-242084, demonstrated anxiogenic activity. These results were observed in the Vogel conflict, elevated T maze, and in the light–dark box tests. This study also verified the influence of the 5-HT_{2C} receptor on the activity of the tricyclic imipramine antidepressant, and it was then observed that the blockade of 5-HT_{2C} by SB-242084 in DH did not alter its anxiolytic effect [71].

This 5-HT_{2C} receptor is also involved in the development of alcohol withdrawal anxiety. In this context, increase in neuronal excitability and negative regulation of type M potassium channels are observed in LHb, a region known for its role in the pathophysiology of anxiety disorders. Stimulation of the 5-HT_{2C} receptor in LHb, with selective WAY161503 agonist, contributed to the negative regulation of M channels and induced anxious symptoms, while blocking the receptor with SB242084 attenuated these symptoms [72].

Agomelatine, a selective agonist of melatonergic MT₁ and MT₂ receptors, 5-HT_{2C} antagonist, acts by modulating the GABAergic pathway and modulating monoamine levels in depressed patients. Its application for the treatment of GAD is recommended by some studies, whose clinical tests indicate improvement of the condition and safety in use. The administration of agomelatine promotes the regulation of plasma levels of vasopressin in men and women and oxytocin in women, which are altered in animals with behavior similar to anxiety [73,74]. Desensitization of the 5-HT_{2C} receptor in the cerebral cortex is capable of attenuating anxious behavior; thus, its activation can promote this behavior. To block this effect, 5-HT_{2C} antagonists such as SB-242084 are proposed, which had an acute effect similar to that of SSRI on the electroencephalogram (EEG), providing further evidence of the therapeutic potential of this compound [75].

Although there are studies describing that the use of 5-HT_{2C} antagonists produces an anxiolytic effect, male 5-HT_{2C} knockout mice exhibit behavior similar to anxiety. In an attempt to explain these observations, a study analyzed the levels of c-Fos, a neuronal activation marker, in 5-HT_{2C} knockout mice. The study reported high levels of this marker in the BNST and in the central nucleus of the amygdala (CeA), regions with high density of neurons secreting the corticotrophin-releasing hormone (CRH), which means that the high secretion of this hormone is also associated with intensification of the anxious behavior. These data may support the development of new studies and therapies based on the important role of the 5-HT_{2C} receptor in modulating anxiety [76].

3.1.2. Treatment of Depression

5-HT₂ serotonergic receptors have been associated with the pathophysiology of a variety of mental disorders, including depression. Investigation of the binding rate and activation of 5-HT_{2A}, 5-HT_{1A}, and SERT receptors in the auditory cortex of patients with MDD, compared to a control group, demonstrates that patients with MDD do not present changes in the binding rate of 5-HT_{1A} and SERT receptors, but there is a significant reduction in the binding rate to the 5-HT_{2A} receptor [77]. Nefazodone is an antidepressant that acts as a postsynaptic 5-HT_{2A} receptor antagonist. The use of nefazodone has significant efficacy for clinical conditions consistent with the depressive state, including acute non-psychotic bipolar depression from moderate to severe intensity [78]. Despite not having adverse effects common to other antidepressants, such as sexual dysfunction and intestinal constipation, nefazodone induces hepatotoxicity by compromising the mitochondrial function of hepatocytes [79]. Currently, this medication is indicated only for cases in which the patient is refractory to other antidepressants. In addition to blocking 5-HT_{2A}, nefazodone also produces a moderate inhibition of 5-HT and norepinephrine (NE) reuptake and can interact with other drugs, as it inhibits the CYP3A4 isoenzyme of the P450 cytochrome microsomal system located in hepatocytes [80,81].

Mirtazapine is also an antidepressant that acts on 5-HT_{2A} receptors. Its mechanism of action includes antagonism of pre- and post-synaptic α_2 adrenergic receptors and antagonism of 5-HT_{2C} and 5-HT₃ receptors. Blocking the pre-synaptic α_2 autoreceptors promotes an increase in the available NE concentration, as well as antagonism of 5-HT_{2C} and 5-HT₃ serotonergic receptors, and induces an increase in 5-HT (Figure S1a,b (Supplementary Material)) [82]. In cases of individuals who do not respond to other antidepressants, or when there is depression in comorbidity with other mental diseases, it has been proposed that mirtazapine would be associated with other drugs, such as SSRIs or selective 5-HT and NE reuptake inhibitors (SNRIs). A phase III clinical study tested this

hypothesis with SSRI and SNRI for MDD; however, the results do not indicate a benefit for the association, but considerable adverse effects were observed [83]. In addition to the possibility of antidepressant treatments with substances that act on 5-HT_{2C} receptors, and the potentiation mechanism of other antidepressants, there is evidence that ritanserin, a 5-HT_{2A}/5-HT_{2C} antagonist, significantly reduces extrapyramidal side effects of other antidepressants [84].

The administration of DOI, a 5-HT_{2A}/5-HT_{2C} agonist, in the orbitofrontal cortex (OFC), induces the following responses: (1) Depression-like behaviors; (2) reduced expression of Kalirin-7 (Kal7), an essential component of excitatory synapses; and (3) reduced expression of PSD-95, a protein capable of modulating 5-HT_{2A} receptor expression. In addition, reduction in the density of dendritic spines was observed. This information corroborates the statement that the 5-HT_{2A} receptor plays an important role in the synaptic plasticity and neurobiology of depression, as well as its interaction with PSD-95. The administration of ketanserin, a 5-HT_{2A} antagonist, reverses these effects, reinforcing information about its performance [85,86].

The 5-HT_{2B} receptor expressed in astrocytes is involved in the development of depression in mice with Parkinson's disease induced by the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP treatment causes downregulation of 5-HT_{2B} receptors, while fluoxetine promotes the upregulation of these receptors and improvement of the depressive state [87]. An analysis of the interaction between SSRIs and the 5-HT_{2B} receptor in astrocytes shows the possible mechanism of SSRI action on glial cells, which do not express SERT, the main target of these substances. SSRIs have dose-dependent affinity and promote the activation of ERK 1 and 2 and PLA₂, mediated by 5-HT_{2B}. Paroxetine is an SSRI antidepressant, the administration of which caused the activation of the astrocytic 5-HT_{2B} receptor, responsible for the signaling that activates MMP, PLA₂, EGFR, and ERK. Like paroxetine, sertraline, fluvoxamine, fluoxetine, and citalopram are also SSRIs used in the treatment of depression. These drugs acted similarly on the astrocytic 5-HT_{2B} receptor, inducing the same signaling pathway. However, the therapeutic effect occurred about 3 weeks after starting treatment, indicating that acute administration has no significant efficacy [88,89].

Reference [90] conducted a study that investigated the role of 5-HT_{2B} receptors in depression and the SSRI activity. 5-HT_{2B} knockout mice showed depressive symptoms after 4 weeks of isolation. SSRI administration did not alleviate the symptoms, demonstrating that 5-HT_{2B} is a considerable target for depression therapy. In addition to these data, stimulating 5-HT_{2B} expression has been shown to have antidepressant activity. Treatment with fluoxetine in association with leptin causes an increase in the expression of these receptors in astrocytes, and this increase is able to mitigate the symptoms of MDD associated with sleep deprivation. The effects of this treatment demonstrate one more possibility of modulating these receptors to treat depression through monotherapy with 5-HT_{2B} agonists or combined therapy [91].

As for the 5-HT_{2C} receptor, studies indicate the possibility for the treatment of obesity and disorders associated with the consumption of psychostimulant drugs through the activation of this receptor, and for the treatment of anxiety, depression, and schizophrenia using 5-HT_{2C} antagonists. The development of positive allosteric modulators (PAM) allows the modulation of the affinity and efficacy of the ligand of this receptor. PNU-69176E is a selective PAM for 5-HT_{2C} and its application increases the release of calcium in the intracellular medium, which is stimulated by the activation of the receptor [92]. Agomelatine is a 5-HT_{2C} antidepressant antagonist and agonist of melatonin receptors M₁ and M₂. The existence of a cluster between M₂ and 5-HT_{2C} receptors has been proposed, which would explain the higher G $\alpha_{i/0}$ /G $\alpha_{q/11}$ activation ratio promoted by agomelatine, compared to melatonin and 5-HT. In addition, the regulation of the circadian rhythm associated with the role of melatonin is involved in controlling mood and intensity of depressive symptoms [86,93,94]. Selective antagonists of the 5-HT_{2C} receptor, SB242084 and RS 102221, are capable of enhancing the action of SSRIs, as well as ketanserin, a non-

selective antagonist of this receptor. This action is observed by the increase in the levels of available serotonin, the increase of which is even more intense than that observed only with the administration of SSRI alone [95]. The intensification of the effect of citalopram on the levels of 5-HT and DA in ATV and NAc by SB242084 is another evidence of the enhancement of SSRIs by 5-HT_{2C} receptor antagonists. This association not only promoted an increase in 5-HT and DA levels, but also optimized the onset of action of citalopram. This effect was associated with the inhibition of tonic DA release induced by signaling the 5-HT_{2C} receptor blocked by SB242084 [96].

Mirtazapine is an atypical antidepressant that acts as an antagonist of 5-HT_{2C}, 5-HT_{2A}, and 5-HT₃ receptors; post-synaptic α_2 adrenergic; and histaminergic H₁. This action increases the levels of 5-HT and NE. This high concentration of available 5-HT interacts with the 5-HT_{1A} receptor, whose activation promotes a reduction in depressive symptoms. Thus, the antidepressant effect of mirtazapine occurs indirectly. In addition, by blocking the 5-HT_{2C} receptor, mirtazapine differs from other antidepressants that have adverse effects such as akathisia and sexual dysfunction [97,98]. Substance S32006 is a potent 5-HT_{2C}/5-HT_{2B} antagonist that exhibited antidepressant activity in the forced swimming and marble burying tests and showed anxiolytic activity, observed in the Vogel conflict test [99].

Compound S32212 is an inverse agonist of the 5-HT_{2C} receptor, which makes it different from other substances that act on this receptor and have antidepressant activity. S32212 is also a α_2 adrenergic receptor antagonist and although the mechanisms related to its activity have not yet been clarified, its administration induced an antidepressant effect, demonstrated in the forced swim and preference for sucrose tests. In addition, an increase in DA and acetylcholine (ACh) levels and anxiolytic activity was observed in the Vogel conflict test [100]. The 5-HT_{2C} receptor agonist, WAY-163909, exhibited rapid onset antidepressant activity, with similar behavior to that promoted by SSRI in the forced swimming test and also in the resident-intruder and olfactory bulbectomy models. This activity was inhibited by the administration of the selective 5-HT_{2C} receptor antagonist SB242084 [101]. These studies serve as a basis for the development of new research that explores the potential of 5-HT_{2C} receptors as a target for the treatment of depression and as an alternative to joint therapy with other antidepressants.

4. 5-HT₃ Receptors

4.1. Mechanism of pharmacological Action

5-HT₃ receptors are coupled to ion channels composed of five subunits: 5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}, 5-HT_{3D}, and 5-HT_{3E}. These receptors are expressed in the CNS and peripheral nervous system (PNS), including the enteric system. All receptors have the 5-HT_{3A} subunit, but the other subunits are not always expressed [102]. The receptor was characterized in the homomeric form, presenting only the 5-HT_{3A} subunit and in the heteromeric form with 5-HT_{3A} and 5-HT_{3B}. 5-HT_{3B} and 5-HT_{3C} subunits are not capable of forming a homomeric receptor, and 5-HT_{3D} and 5-HT_{3E} subunits have not yet been characterized in terms of their expression and function. Homomeric 5-HT_{3A} and heteromeric 5-HT_{3A} and 5-HT_{3B} forms are found in peripheral and central neurons, mononuclear cells, lymphocytes, and enterochromaffin cells. In the CNS, the 5-HT₃ receptor is involved in integration processes of the vomiting reflex, pain processing, reward, and anxiety systems. This receptor can be pre- or post-synaptic. The activation of the pre-synaptic 5-HT₃ receptor, accompanied by neuronal depolarization, promotes calcium influx and the mobilization of intracellular calcium reserves, causing the exocytosis of the neurotransmitter. Activation of the post-synaptic receptor promotes sodium influx, inducing depolarization (Figure S2 (Supplementary Material)). 5-HT_{3A} and 5-HT_{3B} heteromeric receptors have low permeability to calcium ions and less sensitivity to 5-HT, unlike homomeric 5-HT_{3A} receptors, allowing the distinction between them [103].

The location of the 5-HT₃ receptor defines its effect and the activation of this receptor in raphe neurons causes the release of 5-HT, which acts on 5-HT_{1A} autoreceptors in the DRN, exerting inhibitory activity and reducing the neuronal firing rate. The 5-HT₃ receptor is expressed in GABAergic interneurons of the hippocampus and PFC. The activation of these receptors in the hippocampus causes the depolarization of local GABAergic neurons and release of GABA, an inhibitory effect. In PFC, the 5-HT₃ receptor is mainly expressed in GABAergic neurons. Increasing the serotonin concentration activates 5-HT₃ receptors, but in the long run, these receptors are desensitized, and 5-HT activates the 5-HT_{2A} receptor, with excitatory activity. In the striatum and NAc, 5-HT₃ activation promotes an increase in the DA release, an effect blocked by antagonists, which reduces nerve activity, a mechanism for controlling mood disorders, such as anxiety [104].

4.1.1. Treatment of Anxiety

Activation of the 5-HT₃ receptor induces anxious symptoms, but blocking this post-synaptic receptor in the hippocampus and NAc produces anxiolytic effect [103]. Compound (4-benzylpiperazine-1-yl)-(3-methoxyquinoxaline-2-yl) methanone is a 5-HT₃ antagonist, whose anxiolytic activity was tested in the EPM, light–dark box, and OF test, using mice. The administration of the compound together with fluoxetine reduced anxiety symptoms induced by LPS in all tested models. Increase in serotonin levels was also observed, which could intensify such symptoms; however, it was possibly prevented by the action of the 5-HT₃ antagonist [105]. 5-HT₃ receptor antagonists have an advantage over benzodiazepines for the treatment of anxiety, as they do not present sedative or hypnotic activity and there is no evidence of dependence. These data suggest that the 5-HT₃ receptor blockade does not stimulate GABAergic activity; on the contrary, this blockage reduces the release of GABA, indicating that its anxiolytic action does not occur by mechanisms that activate GABA signaling [106]. The 5-HT₃ antagonist, N-n-propyl-3-ethoxyquinoxaline-2-carboxamide (6n), also decreased anxiety in rats, whose behavior was observed in the marble burying test, EPM, sucrose preference test, and OF test [107].

Blocking the 5-HT₃ receptor in the amygdala and DRN reduces anxiety, as does the downregulation of that receptor in the hypothalamus, LA, CeA, and BNST. Tropisetron is a 5-HT₃ receptor antagonist, which has an anxiolytic effect and reduces NO and iNOS levels in pathological conditions. These two effects can be correlated since mitochondrial dysfunction and high concentrations of reactive oxygen species can be stress products and are associated with the pathophysiology of anxiety and mood disorders. Thus, the anxiolytic activity of tropisetron may be associated with improved mitochondrial function [108]. In addition, neuroinflammation is an immune mechanism that participates in the pathogenesis of anxiety disorders. Tropisetron has been shown to inhibit the release of pro-inflammatory cytokines and chemokines and LPS-induced microglia proliferation. Tropisetron, like most 5-HT₃ antagonists, reduces the release of substance P, whose interaction with NK1 receptors favors the inflammatory response in the CNS, nuclear NF- κ B translocation and stimulates the production of cytokines by the microglia. All of these events are inhibited after tropisetron administration (Figure S3 (Supplementary Material)) [109].

Through mechanisms not yet elucidated, 5-HT₃ antagonists alosetron [110], ondansetron [111], and zacopride [112] demonstrated anxiolytic activity in animal models of anxiety assessment. N-cyclohexyl-3-methoxyquinoxaline-2-carboxamide (QCM-13) is a 5-HT₃ antagonist that showed potent anxiolytic activity in the light–dark box, EPM and OF tests. This activity was related to the increased availability of serotonin after blocking 5-HT₃ receptors; they are possibly receptors located in GABAergic interneurons, since this blockade would cause disinhibition of underlying serotonergic neurons. In addition, the 5-HT₃ post-synaptic receptor can be expressed in adrenergic, GABAergic, and dopaminergic neurons, whose neurotransmission modulation can promote anxiolytic effects. Similarly, other compounds such as N-(3-chloro-2-methylphenyl)-quinoxaline-2-carboxamide (4i) [113] act by antagonizing 5-HT₃ receptors and as a result, attenuate

anxiety-like behavior. The location of the 5-HT₃ receptor is crucial for its function, and the antagonism of this receptor in the amygdala and DRN causes a decrease in local neuronal activity and reduces anxious symptoms [106]. Blocking this receptor is a significant pharmacological strategy with few reported adverse effects. Studies that investigate the efficacy and safety of therapeutic agents, 5-HT₃ antagonists, for the treatment of anxiety, are innovative and should be expanded.

4.1.2. Treatment of Depression

Some antidepressants widely used in clinical practice have an affinity for the 5-HT₃ receptor, such as fluoxetine, which can interact with 5-HT₃ antagonists and have their antidepressant activity enhanced. Granisetron is an antagonist of this receptor and its activity can alleviate gastrointestinal disorders associated with the use of SSRIs. At low doses, an increase in the antidepressant action of fluoxetine is also observed when administered in conjunction with granisetron [114]. A previous study has shown that other antidepressants such as imipramine, phenelzine, and iproniazid are able to inhibit the serotonergic current mediated by the 5-HT₃ receptor, blocking its action. This effect has not been elucidated so far, but 5-HT₃ receptor antagonism is constantly associated not only with gastroprotective activity, but also with antidepressant action [115].

Ondansetron is a 5-HT₃ antagonist, which, administered in combination with the SSRI paroxetine, enhanced its antidepressant activity. The authors of this study propose that this effect occurred through the inhibition of 5-HT₃ receptors in hippocampal GABAergic interneurons, which, when activated, act to inhibit the release of 5-HT by serotonergic neurons. In this case, the blockade caused by ondansetron increases the 5-HT concentration, enhancing the SSRI action [116]. Another study revealed that ondansetron inhibits the depressive and anxious phenotype in diabetic mice by blocking the 5-HT₃ receptor. Mice showed high levels of 5-HT and intense oxidative stress, which was attenuated by treatment with ondansetron, which increased the expression of antioxidant factors, such as glutathione (GSH), and increased levels of 5-HT, producing results comparable to fluoxetine, a widely used antidepressant [111,117].

Compound N-(benzo [d] thiazol-2-yl)-3-methoxyquinoxaline-2-carboxamide is a potent 5-HT₃ receptor antagonist. This substance reduced the resignation that is considered a depressive-like behavior in mice. The chronic administration of this compound reduced the depressive behavior and oxidative stress induced by the mild and unpredictable chronic stress protocol, with an increase in the activity of antioxidant enzymes and reduction in the levels of corticosterone. Thus, the antidepressant action may occur due to its antioxidant and regulatory activity of the hypothalamic–pituitary–adrenal (HPA) axis [118].

The val66met genetic polymorphism in the pro-domain of the BDNF gene causes reduction in the secretion of the brain-derived neurotrophic factor (BDNF); the subsequent mechanisms are still unknown. However, in mice with this profile, downregulation of 5-HT_{3A} homomeric receptors and upregulation of 5-HT_{2C} receptors were observed, which inhibited long-term depression in the hippocampus, increasing synaptic activity. This effect was blocked by the administration of a 5-HT_{3A} agonist [119].

HBK-14 and HBK-15 are 5-HT₃, 5-HT_{1A} and 5-HT₇ receptor antagonists. The administration of HBK-15 in combination with fluoxetine or ketamine resulted in antidepressant and anxiolytic activity in mice with corticosterone-induced depression. This combination also prevented a decrease in the levels of neural growth factor (NGF) and BDNF, whose levels tend to be reduced in individuals with mood disorders. In turn, HBK-14 showed anxiolytic activity in this model. Mice that participated in the analysis were submitted to the sucrose preference test, forced swimming test, and EPM. These results have advantages for the association of antidepressants with 5-HT₃ antagonists, which have been shown to be able to intensify their antidepressant action [120].

A study described some pathological pathways common to obesity and depression, such as hyperactivity of the HPA axis, oxidative imbalance, increased levels of

inflammatory mediators, leptin, and insulin resistance, reduced BDNF levels and serotonergic signaling dysregulation. These common factors are influenced by serotonergic signaling and explain the fact that 5-HT₃ receptor antagonists reduce appetite and depressive behavior through mechanisms that involve modulating the HPA axis, reducing inflammatory cytokines and increasing BDNF levels [121].

Vortioxetine is an antidepressant that acts as a 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, partial 5-HT_{1B} agonist, 5-HT_{1A} agonist, and SERT inhibitor. In [122], the authors presented a hypothesis for the involvement of 5-HT₃ receptors in the antidepressant activity of vortioxetine. According to the study, this antidepressant promotes an increase in monoamine levels, greater than that promoted by SSRIs. The antagonism of 5-HT₃ receptors in GABAergic interneurons blocks the inhibitory effect of these neurons on glutamatergic and monoaminergic neurons, increasing neurotransmission in the forebrain, which results in a decrease in depressive symptoms. A double-blind study of patients with MDD compared the results of administering vortioxetine with placebo. Treatment with vortioxetine for two weeks caused significant improvement in the clinical condition, with an onset of action observed in the first 24 h [123].

Tropisetron has been shown to be able to attenuate depressive behavior in mice submitted to juvenile social isolation stress. This effect is mediated by inhibiting iNOS activity and reducing oxidative stress, which is associated with the depressive phenotype. This activity was confirmed after aminoguanidine administration, a specific iNOS inhibitor that enhances the action of tropisetron [124]. This suggests that the mechanism of action of tropisetron may be correlated with the nitrergic system and the pathophysiology of mood disorders.

Some piperazine analogs of naphthyridine-3-carboxamides and indole-2-carboxamides are known to act as 5-HT₃ receptor antagonists and have demonstrated antidepressant activity in the forced swim test [125]. Other compounds that showed similar antidepressant activity in animal models for assessing depressive disorders are: N-(3-chloro-2-methylphenyl)-quinoxaline-2-carboxamide (4i) [113], 3-methoxy-Np-tolylquinoxaline-2-carboxamide (QCM-4) [126], Nn-propyl-3-ethoxyquinoxaline-2-carboxamide (6n) [107], and (4-phenylpiperazin-1-yl) (quinoxalin-2-yl) methanone (4a) [127].

5. 5-HT₄ Receptors

5.1. Mechanism of Pharmacological Action

The 5-HT₄ receptor can be found in central areas such as the limbic system, basal ganglia, olfactory tubercle, hippocampus, pre-Bötzinger complex, and in the periphery, in the gastrointestinal tract, urinary bladder, myocardium, and adrenal glands. It has eight isoforms identified so far, which differ from each other by their carbonic terminals: 5-HT_{4A}, 5-HT_{4B}, 5-HT_{4C}, 5-HT_{4D}, 5-HT_{4E}, 5-HT_{4F}, 5-HT_{4G}, and 5-HT_{4H}. The 5-HT₄ receptor is coupled to the G protein through which it stimulates the activity of AC and PKA, increasing the cAMP concentration. The 5-HT₄ (b) isoform is capable of inhibiting the AC activity through its interaction with the G α_{i0} protein and the 5-HT_{4A} isoform interacts with the G α_{13} protein, activating the Ras homolog family member A (RhoA), which stimulates the actin expression and activates the serum response factor (SRF) complex, which regulates the gene expression of factors that participate in processes of cell proliferation, differentiation and development. The interaction with G α_{13} also activates PKA, independently of cAMP, through the A-kinase anchoring protein (AKAP110) (Figure S4 (Supplementary Material)) [128,129].

The activation of this receptor can trigger different mechanisms, according to the cell type in which it is expressed. The activation of 5-HT₄ in cholinergic neurons, followed by increase in cAMP, is a mechanism associated with neurodegenerative diseases, such as Alzheimer's disease. In this case, the elevation of cAMP levels causes activation of the

CREB and BDNF expression, which acts in the formation of memory. The activation of 5-HT₄ in neurons also induces the blockage of potassium channels and mobilization of intracellular calcium, causing the release of the neurotransmitter in the synaptic slit [130]. When expressed in enterocytes and enteroendocrine cells, activation of 5-HT₄ and increase of cAMP favor intestinal motility and secretion of fluid and mucus [131].

5.1.1. Treatment of Anxiety

The activation of the 5-HT₄ receptor can promote a response similar to that produced by treatment with fluoxetine. RS67333 is a partial 5-HT₄ agonist, which exhibited anxiolytic activity with the onset of action faster than fluoxetine. The activation of the 5-HT₄ receptor by RS67333 caused the release of 5-HT in the DRN, which activates 5-HT_{1A} receptors, reducing neuronal hyperactivation and anxious symptoms. RS67333 also stimulated neurogenesis; that is, neuronal proliferation and maturation. The anxiolytic activity of this substance was observed through EPM and OF tests [132]. Prevention of psychiatric diseases, such as mood disorders, can occur by increasing the ability to tolerate stressful events. Stressful stimuli can promote anxiety disorders. In [133], the authors tested the effectiveness of prophylaxis with 5-HT₄ agonists against anxiety and depression. RS67333 was effective in prophylaxis against anxiety, but not against depression. Prucalopride, a selective high-affinity 5-HT₄ agonist, and PF-04995274, a partial agonist of this receptor, prevented depressive behavior, but not anxiety. The neurobiological mechanisms that can explain the difference in action of these compounds have not yet been clarified.

A study investigated the effect of administering RS 39604, a 5-HT₄ receptor antagonist, and RS67333. The substances were administered to rats submitted to elevated zero maze (EZM), an animal model for assessing anxiety. As expected, the 5-HT₄ agonist RS67333 attenuated the anxious behavior, as well as the 5-HT₄ antagonist, which, paradoxically, showed anxiolytic activity. The authors suggested that the 5-HT₄ receptor does not have a direct relationship with the pathophysiology of anxiety disorders. The performance of new comparative tests using other animal models could confirm or refute these results. However, agonists and antagonists have been tested in isolation in other studies, showing similar results; that is, both antagonism and activation of the 5-HT₄ receptor cause anxiolytic effect [134]. An example is the result of a study that analyzed the effect of two selective 5-HT₄ receptor antagonists, SB204070 and GR113808. Both compounds showed dose-dependent anxiolytic activity. The animals that participated in the study were evaluated in the EPM test [135].

The anxiolytic effect of RS67333 can occur through the activation of 5-HT₄ in mPFC receptors and in the DRN. This activation is accompanied by the inhibition of cortical glutamatergic neurons in the DRN, which may have been induced through the activation of GABAergic neurons present in this region. These neurons are able to modulate the activity of other glutamatergic cells through the inhibitory effect of GABA [136]. Reference [137] suggested that the 5-HT₄ receptor is important for the anxiolytic action of SSRIs, such as fluoxetine. To test this hypothesis, these authors observed the activity of fluoxetine on knockout mice for the 5-HT₄ receptor. In mice that express this receptor, fluoxetine induces reduction in BDNF expression, but in knockout mice, this effect did not occur, and the anxiolytic activity was not observed in this case. This information indicates that the 5-HT₄ receptor is essential for the anxiolytic action of fluoxetine and that the role of 5-HT₄ on the BDNF expression is a point that should be explored to explain this relationship. Research with compounds that act on the 5-HT₄ receptor to promote the anxiolytic effect are still inconsistent and with unknown mechanism of action and safety profile, impairing the development of new anxiolytic treatments that target this receptor.

5.1.2. Treatment of Depression

5-HT₄ receptors are involved in the pathophysiology of depression and their participation can be modulated by casein kinase 2 (CK2), which acts by phosphorylating

specific transcriptional regulators of the brain. CK2 α knockout mice have an antidepressant phenotype. The upregulation of 5-HT $_4$ receptors in PFC was observed in these animals. The overexpression of this receptor, and the consequent increase in signaling, may be responsible for the phenotype exhibited in these animals [138]. 5-HT $_4$ receptors participate in the therapeutic response to SSRIs, as observed after fluoxetine administration to 5-HT $_4$ knockout mice, in which fluoxetine did not exhibit antidepressant or anxiolytic activity. Similarly, 5-HT $_4$ receptor antagonism also prevents fluoxetine action. In this sense, tests with 5-HT $_4$ agonists could show positive results, since their antagonism or lack of expression causes the opposite effect [139].

The administration of the 5-HT $_4$ agonist RS67333 for three days was able to attenuate the immobility behavior of mice in the forced swim test. In addition, some brain parameters that are modified after chronic treatment with other antidepressants have been observed after three days of treatment with RS67333, such as desensitization of 5-HT $_{1A}$ autoreceptors, increased tonus of 5-HT $_{1A}$ heteroreceptors in the hippocampus, and increased phosphorylation of CREB and hippocampal neurogenesis. To improve this comparison, SSRI citalopram was administered for three days; however, no effect was observed. 5-HT $_4$ activation demonstrated not only its effectiveness on depressive symptoms, but also faster action compared to the most common antidepressants currently commercialized [140].

Another study that also analyzed the antidepressant potential of RS67333 reported the same effects described above after treatment for three days and described the results of the administration of this 5-HT $_4$ agonist for seven days. In this case, AC desensitization and a more significant increase in BDNF, CREB, AKT, and hippocampal neurogenesis were observed. The complete reversal of the anhedonic state, characteristic of depression, was also observed [141]. Although there are not many studies that clarify the mechanism of action, effectiveness of 5-HT $_4$ agonists as antidepressants or therapeutic adjuvants and the investigation of the pharmacological potential of these compounds have attracted the attention of researchers in the area. The proposal for an antidepressant treatment with the association of SSRI and 5-HT $_4$ agonist showed positive results, enhancing the action of the agonist. The combined treatment with citalopram and RS67333 intensified the phosphorylation capacity of CREB in the hippocampus and increased tonus of 5-HT $_{1A}$ hippocampal heteroreceptors. Therefore, the combination of RS67333 with fluvoxamine, citalopram, or fluoxetine showed better results in the forced swim test, compared to monotherapy with these substances alone [142].

6. 5-HT $_5$ Receptors

6.1. Mechanism of Pharmacological Action

The 5-HT $_{5A}$ serotonergic receptor is a member of the 5-HT $_5$ receptor family. This family of receptors is composed of 5-HT $_{5A}$, which is expressed in humans, rats, and mice, and 5-HT $_{5B}$, expressed in rats and mice [143]. In rodents, the 5-HT $_{5A}$ receptor is widely distributed in regions such as the hippocampus, cortex, cerebellum, olfactory bulb, habenula, and spinal cord. Due to its location, this receptor may be involved in the processes of memory consolidation, learning, motor control and in pathophysiology of psychiatric disorders [143]. The 5-HT $_{5A}$ receptor is the least understood receptor in the entire family of serotonergic receptors. The scarcity of studies focusing on its functional characterization is a reason for this. To elucidate the function of this receptor, the effects of the depletion of 5-HT $_{5A}$ receptor and its antagonism on the cortex of mice were observed. The study revealed that 5-HT $_{5A}$ receptors produce internal rectifying potassium current. This current was not observed in mice that received the 5-HT $_{5A}$ antagonist SB-699551 and in 5-HT $_{5A}$ knockout mice; in these animals, an increase in another inhibitory current mediated by 5-HT $_{1A}$ receptors was observed, which suggests an interaction between them. Regarding behavior, 5-HT $_{5A}$ knockout mice did not show anxiety symptoms, unlike the 5-HT $_{1A}$ knockout mice. Activation of the 5-HT $_{1A}$ receptor is a

pharmacological strategy for the treatment of mood disorders. Thus, as a possible interaction between receptors has been demonstrated, studies with selective 5-HT_{5A} agonists can better clarify the function of this receptor and the level and mechanism of interaction with the 5-HT_{1A} receptor [144,145].

The 5-HT_{5A} receptor is coupled to the G $\alpha_{i/0}$ protein through which it promotes the inhibition of AC activity and blocks cAMP production. These receptors have been found in the hippocampus, cerebellum, hypothalamus, thalamus, amygdala, and striatum, but can also be expressed in other regions where they have not yet been identified. LSD and 5-carboxamidotriptamine (5CT) are 5-HT_{5A} receptor agonists; the first is a partial agonist and the second is an agonist with affinity and potency superior to 5-HT itself. The coupling of this receptor to the G $\alpha_{i/0}$ protein results not only in the blocking of cAMP production and consequent reduction in PKA activity, but also in the inhibition of the adenosine diphosphate enzyme ADP-ribosyl cyclase, which is responsible for the synthesis of the calcium-mobilizing messengers, the cyclase ADP-ribosyl (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP). Thus, the activation of 5-HT_{5A} and inhibition of cyclase ADP-ribosyl inhibit the mobilization of intracellular calcium [146,147]. However, this mobilization can still occur due to the activity of IP₃, which stimulates the release of calcium reserves in the ER, increasing the intracellular calcium concentration. This increase can stimulate the potassium output currents through a GIRK1 channel that is also coupled to the 5-HT_{5A} receptor. These potassium currents are inhibited by antagonists of that receptor (Figure S5 (Supplementary Material)) [12].

6.1.1. Treatment of Anxiety

There are few studies indicating that the 5-HT_{5A} receptor plays important roles in the neurobiology of anxiety disorders. Fear memory and fear conditioning are associated with the anxious phenotype. Individuals with social anxiety and specific phobias tend to have memories of fear situations and exposure to constant danger, such as images of personal and social fear and fear of physical dangers, which seem to have great potential to occur. A recent study proposed that blocking 5-HT_{5A}, 5-HT₆, and 5-HT₇ serotonergic receptors in BLA can facilitate the extinction of fear memories, which would alleviate the anxious condition. This hypothesis was also tested with the same receptors but located in the CA1 region of the hippocampus; however, no benefits were observed. The 5-HT_{5A} antagonist SB699551, the 5-HT₆ antagonist SB-271046A, and the 5-HT₇ antagonist SB269970 were used. The combined administration of these substances in BLA favors the extinction of the contextual fear conditioning implicated in anxiety disorders [148,149].

SB699551-A and A-843277 are 5-HT_{5A} antagonists and were administered to rats submitted to tests in anxiety assessment models. SB699551-A showed anxiolytic properties, while A-843277 demonstrate antidepressant-like activity. In the OF test, both compounds produced a sedative effect, with depression of the motor system. Animals that received o-843277 squirmed, which suggests abdominal pain. In the forced swim test, SB699551-A produced no effect and A-843277 despite reducing mobility, caused contortions, which may be responsible for reducing mobility. Although interesting results have been observed for the exploration of the anxiolytic potential of 5-HT_{5A} antagonists, these data are still inconclusive, since the reduction in anxious behavior was not observed for both compounds in all tests [150].

6.1.2. Treatment of Depression

5-HT_{5A} receptors may be involved in signaling triggered by antidepressants such as SSRIs. In [151], the authors investigated this hypothesis by analyzing the activity of 5-HT_{5A} receptors expressed in the parvalbumin interneurons, GABAergic neurons found in the DG of the hippocampus. Chronic SSRIs administration promotes the translocation of 5-HT_{5A} receptors to the membrane, where they acquire the active form. Stimulation of these receptors reduces cAMP levels and PKA activity, which results in the inhibition of Kv3.1 β potassium channels and, consequently, reduction of parvalbumin neuron firing. Through

this mechanism, 5-HT_{5A} receptors can delay or reduce behavioral and physiological responses to antidepressants. Thus, 5-HT_{5A} antagonists could induce the opposite action, generating or intensifying antidepressant activity. An example of this is the action of the 5-HT_{5A} antagonist A-843277, which exhibited antidepressant-like activity in rats submitted to the forced swim test [150]. There is lack of studies that investigate the antidepressant potential of compounds that act on the 5-HT_{5A} receptor, even though there are analyses that correlate it to the neurobiology of depression, which makes this receptor a potential target, but recent and little have explored the possibilities of new antidepressant therapies [70,152].

7. 5-HT₆ Receptors

7.1. Mechanism of Pharmacological Action

The 5-HT₆ serotonergic receptor is expressed in greater density in regions of the CNS such as olfactory tubercle, frontal and entorhinal cortex, hippocampus, NAc and striatum, and in lower density in the hypothalamus, amygdala, substantia nigra, and diencephalic nuclei. The 5-HT₆ receptor is coupled to the G α_s protein, through which it stimulates AC activity, increasing the cAMP production and PKA activity. The carboxylic terminal of the 5-HT₆ receptor interacts with Fyn-tyrosine kinase, a protein which is part of the Src family of non-receptor kinases. Through the interaction with Fyn-tyrosine kinase, the 5-HT₆ receptor signals the activation of ERK 1 and 2. Fyn-tyrosine kinase is able to interact with Tau, a protein associated with the microtubule that is involved in the development of neurodegenerative diseases. When ERK1 is active, it participates in the phosphorylation of the Tau protein, enabling an association between 5-HT₆ receptor modulation and the pathophysiology of neurodegenerative diseases. The 5-HT₆ receptor also interacts with protein-1 linked to the Jun activation domain (Jab-1). The activation of 5-HT₆ induces the translocation of Jab-1 to the nucleus, favoring the interaction between Jab-1 and c-Jun. The activation of the 5-HT₆ receptor also generates inhibition of GIRK channels, reducing potassium currents (Figure S6 (Supplementary Material)) [12,153].

The 5-HT₆ receptor is capable of interacting with mTOR, intensifying its signaling pathway. The administration of a 5-HT₆ agonist stimulated the mTOR pathway in PFC neurons, mainly GABAergic neurons. The 5-HT₆ receptor interacts with proteins in the mTOR pathway, including the mTOR regulatory protein (Raptor), mTOR itself, and G β L, a positive regulator of the mTOR pathway, which together form the rapamycin-sensitive mTOR complex 1 (mTORC1). This interaction stimulates the mTOR pathway, which is involved in the development of psychiatric diseases such as schizophrenia [154]. 5-HT₆ receptors are found on the post-synaptic membrane of GABAergic neurons. Blocking the 5-HT₆ receptor in these neurons inhibits the release of GABA, increasing cholinergic, glutamatergic, and monoaminergic neurotransmission [155].

7.1.1. Treatment of Anxiety

Dorsomedial PFC (dmPFC) is a brain region with a high expression of 5-HT₆ receptors. This region participates in information processing and may be involved in anxiety modulation mechanisms. In an attempt to investigate the importance of this region for the development and treatment of anxiety disorders, and the 5-HT₆ receptors expressed in it, the 5-HT₆ agonist EMD386088 and the SB271046 antagonist were injected into the dmPFC of mice. EMD386088 caused an anxiolytic effect in the OF, EPM, and social interaction tests, with intense reduction in spontaneous excitatory post-synaptic currents (EPSCs) and, to a lesser extent, reduction in spontaneous inhibitory post-synaptic currents (IPSCs). This imbalance results in increased levels of GABAergic transmission. The regulation of anxiety through dmPFC may occur due to its glutamatergic projections for BNST and CeA, cerebral structures implicated in the neurobiology of anxiety. Thus, the increase in GABAergic transmission in dmPFC inhibits the excitatory transmission that starts from dmPFC towards BNST and CeA, reducing the activity of the amygdala. In

contrast, SB271046 exhibited the opposite effect, with anxiogenic symptoms in the OF, EPM, and social interaction tests [156].

Similarly, the intra-hippocampal administration of the 5-HT₆ agonist EMD386088 promoted anxiolytic and antidepressant effects in rats in forced swim, EPM, and Vogel conflict tests. The 5-HT₆ antagonist SB399885 was also injected into the hippocampus and exhibited an anxiogenic effect in these tests [157,158]. Conversely, DNA1184 is an antagonist of 5-HT₆ and 5-HT₇ receptors and has been tested in mice submitted to four-plates, EPM, marble burying, and Vogel conflict tests. The compound exhibited anxiolytic activity in all animal models evaluated; however, a more pronounced activity was observed in the Vogel conflict test [159].

The 5-HT₆ antagonist SB399885 has been tested to treat symptoms of PTSD, an anxiety disorder. Intraperitoneal administration of SB399885 reduced 5-HT levels in the amygdala, inhibiting local neuronal overactivity, without affecting motor activity. This anxiolytic effect was observed in the EPM test [160]. 5-HT₆ agonists WAY-208466 and WAY-181187 were subcutaneously administered to rats, which were subsequently submitted to evaluation in the forced swimming, marble burying, and in the novelty-induced hypophagy tests. Both compounds showed anxiolytic and antidepressant activity in all tests, with advantages over drugs available so far, with rapid onset of action [161]. Intra-hippocampal administration of the selective 5-HT₆ receptor antagonist SB-258585 induced an effect of the antidepressant and anxiolytic types in rats. These properties were observed in the Vogel conflict and forced swim tests. The mechanism of anxiolytic action of 5-HT₆ receptor antagonists and agonists has yet to be elucidated. It is known that these receptors are involved in the modulation of GABAergic, glutamatergic, cholinergic and monoaminergic neurotransmission; however, it is not yet possible to attribute to any of these pathways, in particular, the observed effects, which may vary according to the injection site, compounds, location, and density of receptors [162].

7.1.2. Treatment of Depression

To learn about the role of 5-HT₆ agonists and antagonists on depression, more specifically, on depression associated with Parkinson's disease, [163] tested the 5-HT₆ receptor agonist WAY208466 and SB258585 antagonist. The activation of the 5-HT₆ receptor in the pre-limbic cortex through WAY208466 in rats with depressive phenotype resulted in an antidepressant effect. However, the administration of the same compound in rats that did not have a depressive phenotype had the opposite effect. In turn, the receptor blockade induced by SB258585 showed antidepressant activity in rats without a depressive phenotype and increased depressive behavior in rats with this phenotype. This study showed an increase in glutamate production induced by 5-HT₆ agonist WAY208466, and reduction in that production after treatment with the SB258585 antagonist.

EMD386088 is a partial 5-HT₆ receptor agonist. The acute and chronic intraperitoneal administration of this substance in rats exhibited antidepressant activity. This effect was noticed in the forced swimming and OF tests, performed 30 min and 24 h after EMD386088 administration. The administration of the selective 5-HT₆ receptor antagonist SB271046 blocked the antidepressant activity of the compound [164]. Another study analyzed neurochemical data collected after analyses in animals that received EMD386088 and exhibited antidepressant activity. The activation of the 5-HT₆ receptor promotes increased activation of the dopaminergic system, but not of serotonergic and adrenergic systems. In addition, EMD386088 has considerable activity on the DA transporter, which is inhibited by the compound. These data indicate an important involvement of dopaminergic signaling in the antidepressant mechanism of EMD386088, which is confirmed by the abolition of the antidepressant activity after the administration of the dopaminergic receptor antagonist D₁ SCH23390 and D₂ sulpiride antagonist [165].

Subchronic ketamine administration to mice induces depression-like behavior. This behavior was reversed by acute treatment with E-6837, 5-HT₆ agonist, and SB-271046, 5-HT₆ antagonist. Both substances significantly reduced immobility in tail suspension and

forced swimming tests, indicating an antidepressant effect. The authors of this study suggest that 5-HT₆ receptor agonists may enhance the release of GABA in the limbic system. The increased activity of GABAergic interneurons can restore the activity of the mesocortical pathway, compromised by the depressive condition. This restoration involves the connection between GABAergic and dopaminergic neurons of the VTA. The antidepressant activity of both compounds is contradictory to the theoretically paradoxical action between 5-HT₆ agonists and antagonists. This similarity of results may occur due to the varied location of 5-HT₆ receptors in different neurons, including cholinergic, GABAergic, and glutamatergic. New studies that investigate the signaling pathways involved in the activation and blockade of the 5-HT₆ receptor in each type of neuron could clarify the occurrence of the same effect for agonists and antagonists of that receptor [166].

8. 5-HT₇ Receptors

8.1. Mechanism of Pharmacological Action

The 5-HT₇ serotonergic receptor is coupled to the G α_s protein, through which it stimulates AC activity and promotes an increase of cAMP levels and PKA activation. This signaling induces AKT and ERK activation through the Ras protein. AKT and ERK participate in several intracellular processes, among them, gene transcription, cytoskeleton formation, and neuroprotection. Although AKT activation is generally mediated by an increase in cAMP and calcium levels, while an increase in calcium inhibits ERK activation, in the case of 5-HT₇ receptor activation, no changes in calcium concentration were observed, but AKT and ERK were activated. The 5-HT₇ receptor also interacts with the G α_{12} protein, which stimulates the signaling pathway of Rho GTPases, important for stabilizing microtubules and actin reorganization. The stimulation of proteins in Rho pathway occurs through the activation of the guanine nucleotide exchange factor (GEF), which stimulates cell division cycle 42 (Cdc42) proteins, which activates the SRF, whose role involves the stimulation of the serum response element (SRE). In addition to these proteins, G α_{12} also interacts with heat shock protein 90 (HSP90), A-kinase anchoring proteins (AKAPs), proteins from the ezrin–radixin–moesin family (ERM), non-receptor tyrosine kinases (nRTKs), cadherins, phosphatases, and proteins in the occlusive zone. Thus, activation of the 5-HT₇ receptor may be necessary for neurogenesis and reorganization of the dendritic morphology (Figure S7 (Supplementary Material)) [167,168].

The 5-HT₇ receptor is widely expressed in the nervous system in regions such as spinal cord, thalamus, hypothalamus, hippocampus, PFC, *striatum*, and amygdala. Due to its location, the 5-HT₇ receptor is associated with the regulation of the circadian rhythm, thermoregulation, nociception, and memory processing. Its role in CNS morphogenesis was assessed after stimulation with the selective 5-HT₇ agonist LP-211. The activation of this receptor caused a decrease in the number of dendritic spines in striatal and cortical neurons, confirming its role on the neurogenesis and density of dendritic spines. These activities were mediated by the Cdc42 protein, whose activation was increased by stimulation of the 5-HT₇ receptor [169].

8.1.1. Treatment of Anxiety

There are few studies that have investigated the role of 5-HT₇ receptors on anxiety. To assess the performance of these receptors in anxiety associated with Parkinson's disease, 5-HT₇ agonist AS19 and 5-HT₇ antagonist SB269970, administered via pre-limbic intra-cortex, were tested. AS19 agonist showed anxiolytic activity, observed in OF and EPM tests. AS19 increased the DA, 5-HT, and NE levels in the mPFC, ventral hippocampus, and amygdala, while SB269970 decreased monoamine levels in these regions and triggered the anxiogenic effect [170]. Compounds PZ-1417 and PZ-1150 are 5-HT₇ receptor antagonists and were intraperitoneally administered in male albino and

Swiss mice and in male Wistar rats. Antidepressant and anxiolytic properties of both compounds were observed in the forced swim, tail suspension, and four-plates tests. This activity was compared to the activity of SB269970, a 5-HT₇ receptor antagonist, used as reference. However, the effect observed for PZ-1417 and PZ-1150 was greater than that observed for SB269970 [171].

The antidepressant and anxiolytic activities of SB269970 were also compared to the effect of diazepam and imipramine antidepressants. SB269970 showed anxiolytic and antidepressant effect in the four-plates, EPM, and Vogel conflict tests, and antidepressant activity in the forced swim test. However, the effect observed was less intense than that promoted by the drugs used as reference [172]. The antagonism of the 5-HT₇ receptor by SB269970 was also able to reduce prenatal stress, which is related to behavior like anxiety and depression. Stress induces an increase in EPSCs and decrease in IPSCs, stimulating neuronal excitability in DRN. Blocking the 5-HT₇ receptor by SB269970 decreases cortical glutamatergic transmission and contributes to restoring balance between EPSCs and IPSCs, reducing neuronal overactivation induced by prenatal stress [173]. Directly or indirectly, 5-HT₇ receptor antagonists appear to trigger anxiolytic effects. Although the mechanism responsible for this effect is still unknown, the influence of this receptor on monoamine levels and on the excitatory/inhibitory balance, which modulate neuronal excitability, which is critical for the development of anxious symptoms, is known.

8.1.2. Treatment of Depression

5-HT₇ knockout mice exhibited antidepressant behavior in the forced swim test. This observation supported the hypothesis that blocking this receptor may attenuate depression-like behavior. The selective 5-HT₇ receptor antagonist SB269970 showed antidepressant activity in the tail suspension test and the forced swim test. 5-HT₇ knockout mice were submitted to the same tests and the results were similar, indicating that inhibition of the 5-HT₇ receptor is a potential pharmacological strategy for the treatment of depressive disorders [174].

This antidepressant action that results from blocking the 5-HT₇ receptor may occur due to the capacity of this receptor to modulate monoamine levels. An increase in the release of 5-HT was observed after SB269970 administration. This compound can exert antidepressant activity administered as monotherapy, but its association with other antidepressants has been investigated and shown to be even more advantageous. Combined therapy using SB269970 and citalopram proved to be effective for the treatment of depression, since the SSRI action was enhanced by the administration of the 5-HT₇ antagonist, promoting a marked increase in the available 5-HT concentration. This effect was quantified by the decrease of the immobility duration [175].

Another association with SB269970, which exhibited intense antidepressant activity, was the combined therapy with imipramine, which had its effects enhanced by SB269970 [176]. The calcium-binding protein S100B reduces cAMP production in astrocytes. Overexpression of this protein disrupts the cAMP pathway and induces behaviors similar to depression, observed in the forced swim test. SB269970 administration and the consequent blocking of the 5-HT₇ receptor neutralizes the effects of overexpression of this protein, leading to an antidepressant effect, which suggests that the action of S100B on cAMP levels may occur through an interaction with the receptor 5-HT₇ [177].

Another 5-HT₇ receptor antagonist, JNJ-18038683, exhibited antidepressant activity in the tail suspension test, with increased serotonergic transmission observed after administration of the compound. JNJ-18038683 was also able to intensify the action of citalopram, both in rats and in humans [178]. The ability of 5-HT₇ receptor antagonists to increase the release of 5-HT is effective in reducing depressive symptoms and is even more useful when this activity is associated with the effect of SSRIs, whose antidepressant action is enhanced.

9. Phytochemical Compounds of Natural Origin Acting via 5-HT Receptors: Preclinical and Clinical Research and Future Perspectives in the Treatment of Anxiety and Depression

The role of herbal medicine in the treatment of anxiety and depressive disorders has been established over the years, especially the use of *Hypericum perforatum* (St. John's wort) [179] and *Piper methysticum* (Kava) [180], among others, as phytotherapeutic preparations that present respectable clinical evidence. The aim of this section is to summarize evidence from the last 5 years of research in preclinical studies and clinical trials involving medicinal plants with potentially positive effects on anxiety and depressive disorders. Studies involving up to three herbal medicines were included and studies detailing secondary analyses of primary data were not included.

Tables 1 and 2 present some isolated phytochemicals and plant extracts, respectively, that produce antidepressant-like or anxiolytic-like effects on pre-clinical animal models. The first table (Table 1) shows the names of phytochemicals and their plant source, animal models and specimen assayed, administration scheme, major findings, and, if possible, the mechanism of action evaluated in studies. The second table (Table 2) presents plant extracts, compounds detected, animal models and specimen assayed, administration scheme, major findings, and, if possible, the mechanism of action evaluated in studies. The structural formulas of these phytochemicals cited in Tables 1 and 2 are presented in Figure 8.

Tables S2 and S3 (Supplementary Material) present isolated phytochemicals and herbal medicines, respectively, submitted to clinical trials to verify their antidepressant and/or anxiolytic effectiveness. The first table (Table S2) described the names of phytochemicals and their plant source, disorder or symptoms, diagnostic instruments, posology, and major findings. The second table (Table S3) presents herbal medicines and the marker compound, disorders or symptoms, diagnostic instruments, posology, and major findings. The structural formulas of phytochemicals cited in tables S1 and S2 are presented in Figure S8 (Supplementary Material).

As can be observed, pre-clinical and clinical studies using plant extracts or herbal medicines are more frequent, exploring a variety of different specimens. Concerning clinical trials, only four phytochemicals (crocin, curcumin, l-theanine, and valeric acid) have been recently investigated. About herbal medicines, an emerging interest regarding two specimens has been noted: *Crocus sativus* in depressive disorders and *Lavandula angustifolia* in anxiety disorders.

Table 1. Phytochemicals that produce antidepressant-like or anxiolytic-like effects on animal models.

Compound	Plant/Extract	Model/Test Used	Animal Species	Administration	Major Findings	Mechanisms of Action	Reference
Cannabidiol	<i>Cannabis sativa</i> /not informed	Elevated plus-maze and novelty suppressed feeding tests	Male C57BL/6 mice	Intraperitoneal administration (30 mg/kg) 2 h after daily stressor for 14 days	Anxiolytic effectiveness	Not assayed	[181]
Chrysin	Not informed	Splash, rota-rod, and tail suspension tests	C57B/6J mice	Oral administration (10 ml/kg) 30 min before tests	Antidepressant effectiveness	Decrease in the levels of 5-HT in the hippocampus	[182]
Dehydrojuncuenin A (4)	<i>Juncus setchuensis</i> /ethanolic extract	Elevated plus maze	Male CD-1 mice	Oral administration (5, 10, or 20 mg/kg) 30 min before test	Anxiolytic effectiveness	Not assayed	[183]
Dehydrojuncusol (2)	<i>Juncus setchuensis</i> /ethanolic extract	Elevated plus maze	Male CD-1 mice	Oral administration (2.5, 5, or 10 mg/kg) 30 min before the test	Anxiolytic effectiveness	Not assayed	[183]
Juncuenin A (3)	<i>Juncus setchuensis</i> /ethanolic extract	Elevated plus maze	Male CD-1 mice	Oral administration (2.5, 5, 10, or 20 mg/kg) 30 min before test	Anxiolytic effectiveness	Not assayed	[183]
Juncuenin H (1)	<i>Juncus setchuensis</i> /ethanolic extract	Elevated plus maze and locomotor test	Male CD-1 mice	Oral administration (5, 10, or 20 mg/kg) 30 min before tests	Anxiolytic effectiveness	Reductions in the levels of 5-HT and 5-HT/DA metabolites in the cerebral cortex and hippocampus.	[183]
Paeoniflorin	Not informed	Elevated plus maze test	Male Sprague–Dawley rats	Intraperitoneal administration (5, 10, and 20 mg/kg) 1 h before test	Anxiolytic effectiveness	Increased levels of 5-HT and 5-HIAA in the hippocampus	[184]
S-(+)-linalool	<i>Cinnamomum osmophloeum</i> /essential oil	Elevated plus maze test	Male ICR mice	Oral administration (250 and 500 mg/kg) 1 h before tests for 14 days	Anxiolytic effectiveness	Anxiolytic effect via modulation of 5-HT	[185]

Abbreviations: 5-HT = 5-hydroxytryptamine, 5-HIAA = 5-hydroxyindoleacetic acid, DA = dopamine.

Table 2. Plant extracts that produce antidepressant-like and/or anxiolytic-like effects in animal models.

Plant/Extract	Model/Test Used	Animal Species	Administration	Major Findings	Mechanisms of Action	Reference
<i>Achyranthes aspera</i> /methanolic extract	Hole cross, OF, forced swimming, tail suspension, elevated plus maze, and light/dark	Mice	Oral administration (50, 100, and 200 mg/kg) 30 min before tests	Anxiolytic and antidepressant effectiveness	Not assayed	[186]
<i>Aloysia triphylla</i> /methanolic, dichloromethane and hexanic extracts	Elevated plus maze test	Male ICR mice	Oral administration (125, 250, 500, and 750 mg/kg) 30 min before test	Anxiolytic effectiveness	Interaction with serotonergic transmission	[187]
<i>Annona vepretorum</i> /essential oil	Elevated plus-maze, hole-board, open-field, rota-rod, and tail suspension tests	Male albino Swiss mice	Intraperitoneal administration (25, 50, and 100 mg/kg)	Anxiolytic and antidepressant effectiveness	Not assayed	[188]
<i>Camellia euphlebia</i> /aqueous extract	Light/dark box, elevated plus maze, forced swimming, tail suspension, and open-field tests	Male Kunming mice	Intragastrical administration (100, 200, or 400 mg/kg) 1 h before tests for 7 days	Anxiolytic and antidepressant effectiveness	Not assayed	[189]
<i>Camellia sinensis</i> /aqueous and ethanolic extracts	Elevated plus maze and OF tests	Male C57BL/6J mice	Oral administration (50 and 100 mg/kg) 1 hour before test	Anxiolytic effectiveness	Activation of serotonin 5-HT _{1A} receptors	[190]
<i>Cananga odorata</i> /essential oil	Open field, elevated plus maze, and light/dark box tests	ICR mice	10 mL inhalation 10 min before tests	Anxiolytic effectiveness	Increased 5-HT concentration in the hippocampus of male mice	[191]
<i>Capparis thoningii</i> /methanolic extract	Forced swimming, tail suspension, hole-board, light/dark, and elevated plus maze tests	Swiss albino mice	Oral administration (500–4000 mg/kg) 1 h before tests	Anxiolytic and antidepressant effectiveness	5-HT ₂ receptor inhibition	[192]
<i>Carthamus tinctorius</i> /ethanolic extract	Elevated plus maze and forced swim tests	White albino rats	Oral administration (100 and 200 mg/kg) 1 h before tests	Anxiolytic and antidepressant effectiveness	Not assayed	[193]

<i>Cocos nucifera</i> /hydroalcoholic extract	Elevated plus maze, hole-board, forced swimming, tail suspension, and open-field tests	Swiss mice	Oral administration (50, 100, or 200 mg/kg) 1 h before tests	Anxiolytic and antidepressant effectiveness	Inhibition of the 5-HT system	[194]
<i>Coriandrum sativum</i> /aqueous extract	Elevated plus-maze test and light/dark transition	Male Swiss albino mice	Oral administration (100, 200, or 400 mg/kg) 2 hours/day for 14 days	Anxiolytic effectiveness	Decrease in levels of NE, DA, and 5-HT in cortex, hippocampus, cerebellum, and brain stem	[195]
<i>Cuscuta reflexa</i> /methanolic extract	Elevated plus maze and light/dark box tests	Swiss albino mice	Oral administration (200 and 400 mg/kg) 30 min before tests for 14 days	Anxiolytic effectiveness	Not assayed	[196]
<i>Hoodia gordonii</i> /aqueous extract	Forced swim and OF tests	Male Swiss mice	Oral administration (25 and 50 mg/kg) 1 h before tests	Antidepressant effectiveness	Results showed that only 5-HT monoamine was significantly increased after acute <i>H. gordonii</i> administration	[197]
<i>Maerua angolensis</i> /crude extract	Novel tank and light/dark box tests	Zebrafish	1.0, 0.3, 0.1 mg/ml diluted in water 20 min before tests	Anxiolytic effectiveness	Direct or indirect effect on the activation of GABA _A and 5-HT ₁₋₃ receptor	[198]
<i>Morinda citrifolia</i> /methanolic extract	Elevated plus maze, light/dark transition, and tail suspension tests	Male Swiss albino mice	Oral administration (0.5, 1, 3 g/kg) 1 h before tests	Anxiolytic and antidepressant effectiveness	Not assayed	[199]
<i>Newbouldia laevis</i> /hydroethanolic extract	Hole-board, open-field, elevated plus maze, light/dark box exploration, social interaction, forced swim, and tail suspension tests	Mice	Intraperitoneal administration (50, 100, 200, 400, and 800 mg/kg)	Anxiolytic and antidepressant effectiveness	Not assayed	[200]

<i>Paederia foetida</i> /aqueous, ethanolic, and ethyl acetate extracts	Hole cross, OF, and elevated plus maze tests	Albino mice	Oral administration (400 mg/kg)	Anxiolytic effectiveness	Not assayed	[201]
<i>Pimpinella anisum</i> /aqueous and ethanolic extracts	Forced swimming, tail suspension tests	Mice	Intraperitoneal administration (50, 100, and 200 mg/kg)	Antidepressant effectiveness	Not assayed	[202]
<i>Salvia miltiorrhiza</i> /essential oil	Elevated plus maze, social interaction, and rota-rod tests	Male Sprague–Dawley rats	Oral administration (50, 100, and 200 mg/kg) 1 h before tests	Anxiolytic effectiveness	Reduction of monoamine and 5-HT system levels in the cerebral cortex	[203]
<i>Solanum melongena</i> /aqueous extract	Elevated plus maze, forced swimming, and tail suspension tests	Male albino mice	Oral administration (100 and 200 mg/kg)	Anxiolytic and antidepressant effectiveness	Increase of 5-HT levels	[204]
<i>Tagetes erecta</i> /aqueous extract	Hole-board, open-field, and exploration cylinder tests	Male Swiss Webster mice	Intraperitoneal administration (10, 30, 100 mg/kg) 1 h before tests	Anxiolytic and sedative effectiveness	Not assayed	[205]
<i>Tagetes lucida</i> /aqueous extract	Forced swimming	Male Wistar rats	Intragastric administration (50, 100, and 200 mg/kg) 72, 48, 24, 18, and 1 h before test	Antidepressant effectiveness	Modulating the release/reuptake of serotonin by interaction with 5-HT _{1A} and 5-HT _{2A} receptors	[206]
<i>Tanacetum parthenium</i> /aqueous extract	Burying behavior, elevated plus maze, forced swimming, and OF tests	Male Swiss Webster mice	Oral administration (0.5, 1.0, 5, 10, 20, and 40 mg/kg) 30 min before tests	Anxiolytic and antidepressant effectiveness	Not assayed	[207]
<i>Tilia americana</i> /hexanic, ethyl acetate, and methanolic extracts	Elevated plus maze and hole-board tests	Male CD-1 mice	Intraperitoneal administration (100 mg/kg) 50 min before test	Anxiolytic and sedative effectiveness	Production of the anxiolytic effect reversed in the presence of 5-HT _{1A} receptor antagonists	[208]
<i>Ziziphus mucronata</i> /hydromethanolic extract	Elevated plus maze, light/dark, and forced swim tests	Adult male Wistar rats	Oral administration (300 mg/kg) 30 min before tests	Anxiolytic and antidepressant effectiveness	Modulation of serotonergic and noradrenergic systems	[209]

Abbreviations: 5-HT = 5-hydroxytryptamine, DA = dopamine, GABA = gamma-aminobutyric acid, GABA_A = GABA type A receptor, NE = noradrenaline, OF = open-field.

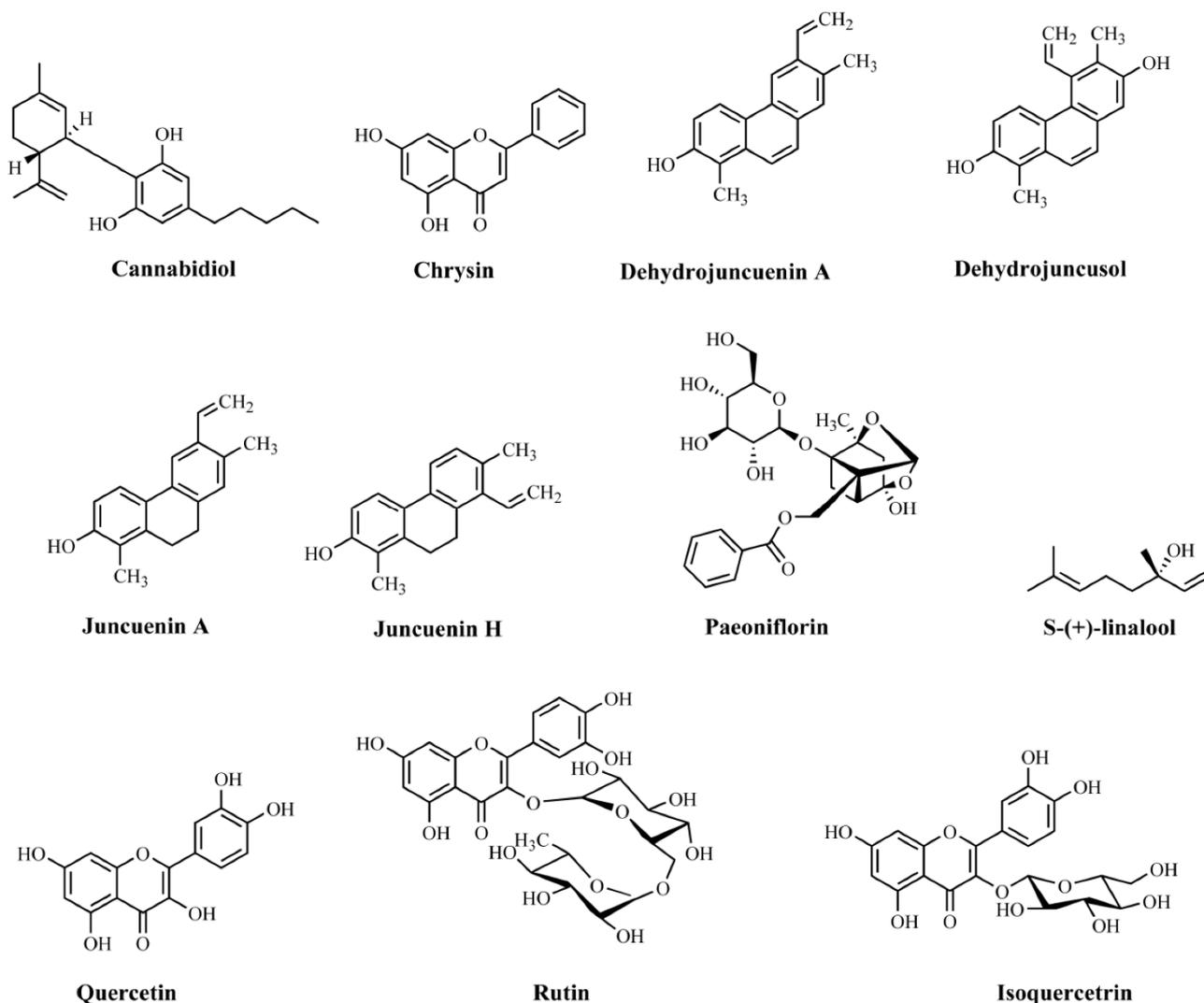


Figure 8. Structural formulas of phytochemicals cited in Tables 1 and 2.

Evidence that supports the effect of herbal medicines on anxiety and depressive disorders has grown in the past years, and many of these featured only in isolated, short-term, and small sample studies. Therefore, it is still required to conduct further robust and larger studies [179,180,210]. In addition, the co-prescription of certain herbal medicines with pharmaceuticals should provide beneficial and additional effectiveness, as seen in Tables 2 and S2, and this approach remains an area of potential future research.

10. Conclusions

Over the past twenty years, there has been an important advancement regarding the understanding of the “serotonergic receptorsome” signaling mechanisms, both receptors coupled to the G protein and receptors coupled to ion channels, and their correlations with the treatments of anxiety and depression. As for GPCRs, an advancement that is still crucial in the field of pharmacology and neurochemistry is the precise determination of where 5-HT receptors activate G proteins in cells and the activation dynamics of these proteins. In addition to G protein signaling, the identification of regions of interaction of serotonergic receptors using genetic or proteomic strategies is effective for the understanding of new signaling pathways related to these receptors. As an example, the

new signaling pathways related to 5-HT₆ and 5-HT₇ receptors that play a crucial role in neurodevelopment can be highlighted.

New neuropharmacological studies should be carried out to improve the understanding of the function of the 5-HT system in the CNS and, mainly, in the periphery of the human body, as well as to elucidate the biological responses associated with total, partial, and inverse agonists and 5-HT receptor antagonists and their functional selectivity. Additional data are needed to determine the interest in specific diseases of the CNS and other organ systems. In the present study, we encourage researchers in the field to investigate new anxiolytic and antidepressant therapies based on the modulation of the “*Serotonergic Receptosome*”, once many 5-HT receptors are potential and little explored targets for the possibilities of new therapies for mood disorders.

Supplementary Materials: The following are available online at www.mdpi.com/1424-8247/14/2/148/s1, Figure S1: Mechanism of action of mirtazapine, Figure S2: The pentameric structure of the 5-HT₃ receptor, Figure S3: Mechanism of anti-inflammatory action of tropisetron, Figure S4: 5-HT₄ receptor signaling pathways, Figure S5: 5-HT_{5A} receptor signaling pathways, Figure S6: 5-HT₆ receptor signaling pathways, Figure S7: 5-HT₇ receptor signaling pathways, Figure S8: Structural formulas of phytochemicals cited in tables 4 and 5, Table S1: 5-HT receptors and their subtypes: central signaling and signal transduction systems, Table S2: Phytochemicals submitted to clinical trials to verify their antidepressant and/or anxiolytic effectiveness, Table S3: Herbal medicines submitted to clinical trials to verify their antidepressant and/or anxiolytic effectiveness.

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References

1. Gaddum, J.H.; Picarelli, Z.P. Two kinds of tryptamine receptor. *Br. J. Pharmacol. Chemother.* **1957**, *12*, 323–328, doi:10.1111/j.1476-5381.1957.tb00142.x.
2. Sharp, T.; Barnes, N.M. Central 5-HT receptors and their function; present and future. *Neuropharmacology* **2020**, *177*, 108–155, doi:10.1016/j.neuropharm.2020.108155.
3. Giulietti, M.; Vivenzio, V.; Piva, F.; Principato, G.; Bellantuono, C.; Nardi, B. How much do we know about the coupling of G-proteins to serotonin receptors? *Mol. Brain* **2014**, *7*, 49, doi:10.1186/s13041-014-0049-y.
4. Montalbano, A.; Corradetti, R.; Mlinar, B. Pharmacological Characterization of 5-HT_{1A} Autoreceptor-Coupled GIRK Channels in Rat Dorsal Raphe 5-HT Neurons. *PLoS ONE* **2015**, *10*, e0140369, doi:10.1371/journal.pone.0140369.
5. Niedzielak, T.; Ravenelle, R.; Joseph, M.; Calhoun, C.; Plotkin, B.; Jones, R.; Herrera, M.; Tiffany Donaldson, S. 5-HT_{1A} and α ₂ adrenergic receptor levels are associated with high anxiety-like patterns and impulsivity in selectively bred Long Evans rats. *Behav. Brain Res.* **2020**, *383*, 112522, doi:10.1016/j.bbr.2020.112522.
6. Da Silva, N.R.; Gomes, F.V.; Sonogo, A.B.; da Silva, N.R.; Guimarães, F.S. Cannabidiol attenuates behavioral changes in a rodent model of schizophrenia through 5-HT_{1A}, but not CB₁ and CB₂ receptors. *Pharmacol. Res.* **2020**, *156*, 104749, doi:10.1016/j.phrs.2020.104749.
7. Chilmonczyk, Z.; Bojarski, A.; Pilc, A.; Sylte, I. Functional Selectivity and Antidepressant Activity of Serotonin 1A Receptor Ligands. *Int. J. Mol. Sci.* **2015**, *16*, 18474–18506, doi:10.3390/ijms160818474.
8. Albert, P.R.; Vahid-Ansari, F. The 5-HT_{1A} receptor: Signaling to behavior. *Biochimie* **2019**, *161*, 34–45, doi:10.1016/j.biochi.2018.10.015.
9. Xie, F.; Fan, Q.; Li, B.X.; Xiao, X. Discovery of a Synergistic Inhibitor of cAMP-Response Element Binding Protein (CREB)-Mediated Gene Transcription with 666-15. *J. Med. Chem.* **2019**, *62*, 11423–11429, doi:10.1021/acs.jmedchem.9b01207.
10. Qiu, Y.; Wang, Y.; Wang, X.; Wang, C.; Xia, Z. Role of the hippocampal 5-HT_{1A} receptor-mediated cAMP/PKA signalling pathway in sevoflurane-induced cognitive dysfunction in aged rats. *J. Int. Med. Res.* **2018**, *46*, 1073–1085, doi:10.1177/0300060517744037.
11. Rojas, P.S.; Aguayo, F.; Neira, D.; Tejos, M.; Aliaga, E.; Muñoz, J.P.; Parra, C.S.; Fiedler, J.L. Dual effect of serotonin on the dendritic growth of cultured hippocampal neurons: Involvement of 5-HT_{1A} and 5-HT₇ receptors. *Mol. Cell. Neurosci.* **2017**, *85*, 148–161, doi:10.1016/j.mcn.2017.09.009.
12. Masson, J.; Emerit, M.B.; Hamon, M.; Darmon, M. Serotonergic signaling: Multiple effectors and pleiotropic effects. *Wiley Interdiscip. Rev. Membr. Transp. Signal.* **2012**, *1*, 685–713, doi:10.1002/wmts.50.
13. De Deurwaerdere, P.; Bharatiya, R.; Chagraoui, A.; Di Giovanni, G. Constitutive activity of 5-HT receptors: Factual analysis. *Neuropharmacology* **2020**, *168*, 107967, doi:10.1016/j.neuropharm.2020.107967.
14. Cui, W.-Q.; Sun, W.-S.; Xu, F.; Hu, X.-M.; Yang, W.; Zhou, Y.; Du, L.-X.; Zhang, W.-W.; Mao-Ying, Q.-L.; Mi, W.-L.; et al. Spinal Serotonin 1A Receptor Contributes to the Analgesia of Acupoint Catgut Embedding by Inhibiting Phosphorylation of the N-Methyl-d-Aspartate Receptor GluN1 Subunit in Complete Freund's Adjuvant-Induced Inflammatory Pain in Rats. *J. Pain* **2019**, *19*, 16.e1–16.e16, doi:10.1016/j.jpain.2018.07.011.
15. Nishijo, T.; Momiyama, T. Serotonin 5-HT_{1B} receptor-mediated calcium influx-independent presynaptic inhibition of GABA release onto rat basal forebrain cholinergic neurons. *Eur. J. Neurosci.* **2016**, *44*, 1747–1760, doi:10.1111/ejn.13273.
16. Polter, A.M.; Li, X. Glycogen Synthase Kinase-3 is an Intermediate Modulator of Serotonin Neurotransmission. *Front. Mol. Neurosci.* **2011**, *4*, 31, doi:10.3389/fnmol.2011.00031.
17. Goddard, A.W.; Shekhar, A.; Whiteman, A.F.; McDougale, C.J. Serotonergic mechanisms in the treatment of obsessive-compulsive disorder. *Drug Discov. Today* **2008**, *13*, 325–332, doi:10.1016/j.drudis.2007.12.009.
18. McGowan, O.O.; Reynolds, G.P. Functional pharmacogenetics of serotonin receptors in psychiatric drug action. In *Handbook of Behavioral Neuroscience*; Elsevier: Amsterdam, The Netherlands, 2020; Volume 31, pp. 941–957, ISBN 9780444641250.
19. Marin, P.; Bécamel, C.; Chaumont-Dubel, S.; Vandermoere, F.; Bockaert, J.; Claeysen, S. Classification and signaling characteristics of 5-HT receptors: Toward the concept of 5-HT receptosomes. In *Handbook of Behavioral Neuroscience*; Elsevier: Amsterdam, The Netherlands, 2020; Volume 31, pp. 91–120, ISBN 9780444641250.
20. Clemow, D.B.; Johnson, K.W.; Hochstetler, H.M.; Ossipov, M.H.; Hake, A.M.; Blumenfeld, A.M. Lasmiditan mechanism of action—review of a selective 5-HT_{1F} agonist. *J. Headache Pain* **2020**, *21*, 71, doi:10.1186/s10194-020-01132-3.
21. Soria-Fregozo, C.; Perez-Vega, M.I.; Rodríguez-Landa, J.F.; Germán-Ponciano, L.J.; García-Ríos, R.I.; Mora-Perez, A. Association of 5-HT_{1A} Receptors with Affective Disorders. In *Serotonin—A Chemical Messenger Between All Types of Living Cells*; InTech: Rijeka, Croatia, 2017.
22. Balaj, K.; Nowinski, L.; Walsh, B.; Mullett, J.; Palumbo, M.L.; Thibert, R.L.; McDougale, C.J.; Keary, C.J. Buspirone for the treatment of anxiety-related symptoms in Angelman syndrome. *Psychiatr. Genet.* **2019**, *29*, 51–56, doi:10.1097/YPG.0000000000000218.
23. Gill, A.K.; Bansal, Y.; Bhandari, R.; Kaur, S.; Kaur, J.; Singh, R.; Kuhad, A.; Kuhad, A. Gepirone hydrochloride: A novel antidepressant with 5-HT_{1A} agonistic properties. *Drugs Today* **2019**, *55*, 423–437, doi:10.1358/dot.2019.55.7.2958474.
24. Huang, X.; Yang, J.; Yang, S.; Cao, S.; Qin, D.; Zhou, Y.; Li, X.; Ye, Y.; Wu, J. Role of tandospirone, a 5-HT_{1A} receptor partial agonist, in the treatment of central nervous system disorders and the underlying mechanisms. *Oncotarget* **2017**, *8*, 102705–102720, doi:10.18632/oncotarget.22170.

25. Saito, Y.; Matsumoto, M.; Yanagawa, Y.; Hiraide, S.; Inoue, S.; Kubo, Y.; Shimamura, K.I.; Togashi, H. Facilitation of fear extinction by the 5-HT_{1A} receptor agonist tandospirone: Possible involvement of dopaminergic modulation. *Synapse* **2013**, *67*, 161–170, doi:10.1002/syn.21621.
26. Li, X. Using the conditioned fear stress (CFS) animal model to understand the neurobiological mechanisms and pharmacological treatment of anxiety. *Shanghai Arch. Psychiatry* **2012**, *24*, 241–249, doi:10.3969/j.issn.1002-0829.2012.05.001.
27. Spiacci, A.; Pobbe, R.L.H.; Matthiesen, M.; Zangrossi, H. 5-HT_{1A} receptors of the rat dorsal raphe lateral wings and dorsomedial subnuclei differentially control anxiety- and panic-related defensive responses. *Neuropharmacology* **2016**, *107*, 471–479, doi:10.1016/j.neuropharm.2015.06.015.
28. Garcia-Garcia, A.L.; Canetta, S.; Stujenske, J.M.; Burghardt, N.S.; Ansorge, M.S.; Dranovsky, A.; Leonardo, E.D. Serotonin inputs to the dorsal BNST modulate anxiety in a 5-HT_{1A} receptor-dependent manner. *Mol. Psychiatry* **2018**, *23*, 1990–1997, doi:10.1038/mp.2017.165.
29. Turcotte-Cardin, V.; Vahid-Ansari, F.; Luckhart, C.; Daigle, M.; Geddes, S.D.; Tanaka, K.F.; Hen, R.; James, J.; Merali, Z.; Béique, J.; et al. Loss of Adult 5-HT_{1A} Autoreceptors Results in a Paradoxical Anxiogenic Response to Antidepressant Treatment. *J. Neurosci.* **2019**, *39*, 1334–1346, doi:10.1523/JNEUROSCI.0352-18.2018.
30. Marcinkiewicz, C.A.; Bierlein-De La Rosa, G.; Dorrier, C.E.; McKnight, M.; DiBerto, J.F.; Pati, D.; Gianessi, C.A.; Hon, O.J.; Tipton, G.; McElligott, Z.A.; et al. Sex-Dependent Modulation of Anxiety and Fear by 5-HT_{1A} Receptors in the Bed Nucleus of the Stria Terminalis. *ACS Chem. Neurosci.* **2019**, *10*, 3154–3166, doi:10.1021/acscchemneuro.8b00594.
31. Zhu, L.; Xu, C.; Ren, J.; Chang, L.; Zhu, X.; Sun, N.; Meng, G.; Liu, M.; Zhang, J.; Li, Y.; et al. Dentate nNOS accounts for stress-induced 5-HT_{1A} receptor deficiency: Implication in anxiety behaviors. *CNS Neurosci. Ther.* **2020**, *26*, 453–464, doi:10.1111/cns.13269.
32. Nautiyal, K.M.; Tritschler, L.; Ahmari, S.E.; David, D.J.; Gardier, A.M.; Hen, R. A Lack of Serotonin 1B Autoreceptors Results in Decreased Anxiety and Depression-Related Behaviors. *Neuropsychopharmacology* **2016**, *41*, 2941–2950, doi:10.1038/npp.2016.109.
33. Klein, A.K.; Purvis, E.M.; Ayala, K.; Collins, L.; Krug, J.T.; Mayes, M.S.; Ettenberg, A. Activation of 5-HT_{1B} receptors in the Lateral Habenula attenuates the anxiogenic effects of cocaine. *Behav. Brain Res.* **2019**, 357–358, 1–8, doi:10.1016/j.bbr.2018.04.014.
34. Azevedo, H.; Ferreira, M.; Costa, R.W.; Russo, V.; Russo, E.; Mascarello, A.; Guimarães, C.R.W. Preclinical characterization of ACH-000029, a novel anxiolytic compound acting on serotonergic and alpha-adrenergic receptors. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2019**, *95*, 109707, doi:10.1016/j.pnpbp.2019.109707.
35. Hatherall, L.; Sánchez, C.; Morilak, D.A. Chronic Vortioxetine Treatment Reduces Exaggerated Expression of Conditioned Fear Memory and Restores Active Coping Behavior in Chronically Stressed Rats. *Int. J. Neuropsychopharmacol.* **2016**, *20*, 316–323, doi:10.1093/ijnp/pyw105.
36. Hu, B.; Doods, H.; Treede, R.-D.; Ceci, A. Duloxetine and 8-OH-DPAT, but not fluoxetine, reduce depression-like behaviour in an animal model of chronic neuropathic pain. *Neurosci. Lett.* **2016**, *619*, 162–167, doi:10.1016/j.neulet.2016.03.019.
37. Haleem, D.J. Targeting Serotonin_{1A} Receptors for Treating Chronic Pain and Depression. *Curr. Neuropharmacol.* **2019**, *17*, 1098–1108, doi:10.2174/1570159X17666190811161807.
38. Duman, R.S.; Sanacora, G.; Krystal, J.H. Altered Connectivity in Depression: GABA and Glutamate Neurotransmitter Deficits and Reversal by Novel Treatments. *Neuron* **2019**, *102*, 75–90, doi:10.1016/j.neuron.2019.03.013.
39. Lattimore, K.A.; Donn, S.M.; Kaciroti, N.; Kemper, A.R.; Neal, C.R.; Vazquez, D.M. Selective Serotonin Reuptake Inhibitor (SSRI) Use during Pregnancy and Effects on the Fetus and Newborn: A Meta-Analysis. *J. Perinatol.* **2005**, *25*, 595–604, doi:10.1038/sj.jp.7211352.
40. Stuiynga, M.; Giltay, E.J.; Cools, O.; Roosens, L.; Neels, H.; Sabbe, B. Evaluation of vilazodone for the treatment of depressive and anxiety disorders. *Expert Opin. Pharmacother.* **2019**, *20*, 251–260, doi:10.1080/14656566.2018.1549542.
41. McKeage, K. Adjunctive Brexpiprazole: A Review in Major Depressive Disorder. *CNS Drugs* **2016**, *30*, 91–99, doi:10.1007/s40263-016-0320-0.
42. Stahl, S.M. Mechanism of action of brexpiprazole: Comparison with aripiprazole. *CNS Spectr.* **2016**, *21*, 1–6, doi:10.1017/S1092852915000954.
43. Cha, D.S.; Luo, X.; Ahmed, J.; Becirovic, L.; Cha, R.H.; McIntyre, R.S. Brexpiprazole as an augmentation agent to antidepressants in treatment resistant major depressive disorder. *Expert Rev. Neurother.* **2019**, *19*, 777–783, doi:10.1080/14737175.2019.1653759.
44. Gardier, A.M.; Trillat, A.-C.; Malagie, I.; David, D.; Hascoët, M.; Colombel, M.-C.; Jolliet, P.; Jacquot, C.; Hen, R.; Bourin, M. Récepteurs 5-HT_{1B} de la sérotonine et effets antidépresseurs des inhibiteurs de recapture sélectifs de la sérotonine. *Comptes Rendus l'Académie Sci.-Ser. III-Sci. Vie* **2001**, *324*, 433–441, doi:10.1016/S0764-4469(01)01332-4.
45. David, D.J.; Gardier, A.M. Les bases de pharmacologie fondamentale du système sérotoninergique: Application à la réponse antidépressive. *Encephale* **2016**, *42*, 255–263, doi:10.1016/j.encep.2016.03.012.
46. Orsolini, L.; Tomasetti, C.; Valchera, A.; Iasevoli, F.; Buonaguro, E.F.; Vellante, F.; Fornaro, M.; Fiengo, A.; Mazza, M.; Vecchiotti, R.; et al. New advances in the treatment of generalized anxiety disorder: The multimodal antidepressant vortioxetine. *Expert Rev. Neurother.* **2016**, *16*, 483–495, doi:10.1586/14737175.2016.1173545.
47. Araldi, D.; Ferrari, L.F.; Levine, J.D. Gi-protein-coupled 5-HT_{1B/D} receptor agonist sumatriptan induces type I hyperalgesic priming. *Pain* **2016**, *157*, 1773–1782, doi:10.1097/j.pain.0000000000000581.
48. Kurrasch-Orbaugh, D.M.; Parrish, J.C.; Watts, V.J.; Nichols, D.E. A complex signaling cascade links the serotonin_{2A} receptor to phospholipase A₂ activation: The involvement of MAP kinases. *J. Neurochem.* **2003**, *86*, 980–991, doi:10.1046/j.1471-4159.2003.01921.x.

49. Bécamel, C.; Berthou, C.; Barre, A.; Marin, P. Growing Evidence for Heterogeneous Synaptic Localization of 5-HT_{2A} Receptors. *ACS Chem. Neurosci.* **2017**, *8*, 897–899, doi:10.1021/acschemneuro.6b00409.
50. Fuxe, K.; Tarakanov, A.; Romero Fernandez, W.; Ferraro, L.; Tanganelli, S.; Filip, M.; Agnati, L.F.; Garriga, P.; Diaz-Cabiale, Z.; Borroto-Escuela, D.O. Diversity and bias through receptor–receptor interactions in GPCR heteroreceptor complexes. Focus on examples from dopamine D₂ receptor heteromerization. *Front. Endocrinol.* **2014**, *5*, 71, doi:10.3389/fendo.2014.00071.
51. Guiard, B.P.; Di Giovanni, G. Central serotonin-2A (5-HT_{2A}) receptor dysfunction in depression and epilepsy: The missing link? *Front. Pharmacol.* **2015**, *6*, 1–17, doi:10.3389/fphar.2015.00046.
52. Wischhof, L.; Koch, M. 5-HT_{2A} and mGlu_{2/3} receptor interactions. *Behav. Pharmacol.* **2016**, *27*, 1–11, doi:10.1097/FBP.0000000000000183.
53. Hámor, P.U.; Šírová, J.; Páleníček, T.; Zaniewska, M.; Bubeníková-Valešová, V.; Schwendt, M. Chronic methamphetamine self-administration dysregulates 5-HT_{2A} and mGlu₂ receptor expression in the rat prefrontal and perirhinal cortex: Comparison to chronic phencyclidine and MK-801. *Pharmacol. Biochem. Behav.* **2018**, *175*, 89–100, doi:10.1016/j.pbb.2018.09.007.
54. Nebigil, C.G.; Launay, J.-M.; Hickel, P.; Tournois, C.; Maroteaux, L. 5-Hydroxytryptamine 2B receptor regulates cell-cycle progression: Cross-talk with tyrosine kinase pathways. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 2591–2596, doi:10.1073/pnas.050282397.
55. Hertz, L.; Rothman, D.L.; Li, B.; Peng, L. Chronic SSRI stimulation of astrocytic 5-HT_{2B} receptors change multiple gene expressions/editings and metabolism of glutamate, glucose and glycogen: A potential paradigm shift. *Front. Behav. Neurosci.* **2015**, *9*, 1–17, doi:10.3389/fnbeh.2015.00025.
56. Nebigil, C.G.; Maroteaux, L. Functional Consequence of Serotonin/5-HT 2B Receptor Signaling in Heart. *Circulation* **2003**, *108*, 902–908, doi:10.1161/01.CIR.0000081520.25714.D9.
57. Doly, S.; Diaz, S.L.; Belmer, A.; Roumier, A.; Maroteaux, L.; Becamel, C.; Marin, P.; Bockaert, J. 5-Hydroxytryptamine Receptor 2B. In *Encyclopedia of Signaling Molecules*; Choi, S., Ed.; Springer: New York, NY, USA, 2012; pp. 2–12, ISBN 978-1-4419-0461-4.
58. Chagraoui, A.; Thibaut, F.; Skiba, M.; Thuillez, C.; Bourin, M. 5-HT_{2C} receptors in psychiatric disorders: A review. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2016**, *66*, 120–135, doi:10.1016/j.pnpbp.2015.12.006.
59. Xiang, M.; Jiang, Y.; Hu, Z.; Yang, Y.; Du, X.; Botchway, B.O.; Fang, M. Serotonin receptors 2A and 1A modulate anxiety-like behavior in post-traumatic stress disorder mice. *Am. J. Transl. Res.* **2019**, *11*, 2288–2303.
60. Savignac, H.M.; Couch, Y.; Stratford, M.; Bannerman, D.M.; Tzortzis, G.; Anthony, D.C.; Burnet, P.W.J. Prebiotic administration normalizes lipopolysaccharide (LPS)-induced anxiety and cortical 5-HT_{2A} receptor and IL-1 β levels in male mice. *Brain. Behav. Immun.* **2016**, *52*, 120–131, doi:10.1016/j.bbi.2015.10.007.
61. Boroda, S.; Niccum, M.; Raje, V.; Purow, B.W.; Harris, T.E. Dual activities of ritanserin and R59022 as DGK α inhibitors and serotonin receptor antagonists. *Biochem. Pharmacol.* **2017**, *123*, 29–39, doi:10.1016/j.bcp.2016.10.011.
62. Masse, F.; Petit-Demouliere, B.; Dubois, I.; Hascoët, M.; Bourin, M. Anxiolytic-like effects of DOI microinjections into the hippocampus (but not the amygdala nor the PAG) in the mice four plates test. *Behav. Brain Res.* **2007**, *188*, 291–297, doi:10.1016/j.bbr.2007.11.005.
63. Petit-Demouliere, B.; Bourin, M. Temporal parameters of one-trial tolerance to benzodiazepines in four-plate test–retest. *Behav. Brain Res.* **2007**, *183*, 222–225, doi:10.1016/j.bbr.2007.06.005.
64. Ponzoni, L.; Sala, M.; Braidà, D. Ritanserin-sensitive receptors modulate the prosocial and the anxiolytic effect of MDMA derivatives, DOB and PMA, in zebrafish. *Behav. Brain Res.* **2016**, *314*, 181–189, doi:10.1016/j.bbr.2016.08.009.
65. Clinard, C.T.; Bader, L.R.; Sullivan, M.A.; Cooper, M.A. Activation of 5-HT_{2a} receptors in the basolateral amygdala promotes defeat-induced anxiety and the acquisition of conditioned defeat in Syrian hamsters. *Neuropharmacology* **2015**, *90*, 102–112, doi:10.1016/j.neuropharm.2014.11.016.
66. Vermeire, S.T.; Audenaert, K.R.; Dobbeleir, A.A.; De Meester, R.H.; De Vos, F.J.; Peremans, K.Y. Evaluation of the Brain 5-HT_{2A} Receptor Binding Index in Dogs with Anxiety Disorders, Measured with 123I-5I-R91150 and SPECT. *J. Nucl. Med.* **2009**, *50*, 284–289, doi:10.2967/jnumed.108.055731.
67. Nunes-de-Souza, V.; Nunes-de-Souza, R.L.; Rodgers, R.J.; Canto-de-Souza, A. 5-HT₂ receptor activation in the midbrain periaqueductal grey (PAG) reduces anxiety-like behaviour in mice. *Behav. Brain Res.* **2008**, *187*, 72–79, doi:10.1016/j.bbr.2007.08.030.
68. Kennett, G.; Trail, B.; Bright, F. Anxiolytic-like actions of BW 723C86 in the rat Vogel conflict test are 5-HT_{2B} receptor mediated. *Neuropharmacology* **1998**, *37*, 1603–1610, doi:10.1016/S0028-3908(98)00115-4.
69. Kennett, G.A.; Bright, F.; Trail, B.; Baxter, G.S.; Blackburn, T.P. Effects of the 5-HT_{2B} receptor agonist, BW 723C86, on three rat models of anxiety. *Br. J. Pharmacol.* **1996**, *117*, 1443–1448, doi:10.1111/j.1476-5381.1996.tb15304.x.
70. Żmudzka, E.; Sałaciak, K.; Sapa, J.; Pytka, K. Serotonin receptors in depression and anxiety: Insights from animal studies. *Life Sci.* **2018**, *210*, 106–124, doi:10.1016/j.lfs.2018.08.050.
71. Sant’Ana, A.B.; Vilela-Costa, H.H.; Vicente, M.A.; Hernandes, P.M.; de Andrade, T.G.C.S.; Zangrossi, H. Role of 5-HT_{2C} receptors of the dorsal hippocampus in the modulation of anxiety- and panic-related defensive responses in rats. *Neuropharmacology* **2019**, *148*, 311–319, doi:10.1016/j.neuropharm.2019.01.026.
72. Fu, R.; Mei, Q.; Shiwalkar, N.; Zuo, W.; Zhang, H.; Gregor, D.; Patel, S.; Ye, J.-H. Anxiety during alcohol withdrawal involves 5-HT_{2C} receptors and M-channels in the lateral habenula. *Neuropharmacology* **2020**, *163*, 107863, doi:10.1016/j.neuropharm.2019.107863.

73. Buoli, M.; Grassi, S.; Serati, M.; Altamura, A.C. Agomelatine for the treatment of generalized anxiety disorder. *Expert Opin. Pharmacother.* **2017**, *18*, 1373–1379, doi:10.1080/14656566.2017.1359257.
74. Harvey, B.H.; Regenass, W.; Dreyer, W.; Möller, M. Social isolation rearing-induced anxiety and response to agomelatine in male and female rats: Role of corticosterone, oxytocin, and vasopressin. *J. Psychopharmacol.* **2019**, *33*, 640–646, doi:10.1177/0269881119826783.
75. Papp, N.; Koncz, S.; Kostyalik, D.; Kitka, T.; Petschner, P.; Vas, S.; Bagdy, G. Acute 5-HT_{2C} Receptor Antagonist SB-242084 Treatment Affects EEG Gamma Band Activity Similarly to Chronic Escitalopram. *Front. Pharmacol.* **2020**, *10*, 1636, doi:10.3389/fphar.2019.01636.
76. Heisler, L.K.; Zhou, L.; Bajwa, P.; Hsu, J.; Tecott, L.H. Serotonin 5-HT_{2C} receptors regulate anxiety-like behavior. *Genes, Brain Behav.* **2007**, *6*, 491–496, doi:10.1111/j.1601-183X.2007.00316.x.
77. Steinberg, L.J.; Underwood, M.D.; Bakalian, M.J.; Kassir, S.A.; Mann, J.J.; Arango, V. 5-HT_{1A} receptor, 5-HT_{2A} receptor and serotonin transporter binding in the human auditory cortex in depression. *J. Psychiatry Neurosci.* **2019**, *44*, 294–302, doi:10.1503/jpn.180190.
78. Goldberg, J.F. A preliminary open trial of nefazodone added to mood stabilizers for bipolar depression. *J. Affect. Disord.* **2013**, *144*, 176–178, doi:10.1016/j.jad.2012.04.037.
79. Krajnc, E.; Visentin, M.; Gai, Z.; Stieger, B.; Samodelov, S.L.; Häusler, S.; Kullak-Ublick, G.A. Untargeted metabolomics reveals anaerobic glycolysis as a novel target of the hepatotoxic antidepressant nefazodone. *J. Pharmacol. Exp. Ther.* **2020**, doi:10.1124/jpet.120.000120.
80. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet] - Nefazodone Available online: <https://www.ncbi.nlm.nih.gov/books/NBK548179/> (accessed on Feb 11, 2020).
81. Davis, R.; Whittington, R.; Bryson, H.M. Nefazodone: A Review of its Pharmacology and Clinical Efficacy in the Management of Major Depression. *Drugs* **1997**, *53*, 608–636, doi:10.2165/00003495-199753040-00006.
82. Watanabe, N.; Omori, I.; Nakagawa, A.; Cipriani, A.; Barbui, C.; McGuire, H.; Churchill, R.; Furukawa, T.A. Mirtazapine versus other anti-depressive agents for depression. In *Cochrane Database of Systematic Reviews*; Watanabe, N., Ed.; John Wiley & Sons, Ltd: Chichester, UK, 2007.
83. Kessler, D.S.; MacNeill, S.J.; Tallon, D.; Lewis, G.; Peters, T.J.; Hollingworth, W.; Round, J.; Burns, A.; Chew-Graham, C.A.; Anderson, I.M.; et al. Mirtazapine added to SSRIs or SNRIs for treatment resistant depression in primary care: Phase III randomised placebo controlled trial (MIR). *BMJ* **2018**, *363*, k4218, doi:10.1136/bmj.k4218.
84. Tatara, A.; Shimizu, S.; Shin, N.; Sato, M.; Sugiuchi, T.; Imaki, J.; Ohno, Y. Modulation of antipsychotic-induced extrapyramidal side effects by medications for mood disorders. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2012**, *38*, 252–259, doi:10.1016/j.pnpbp.2012.04.008.
85. Xu, C.; Ma, X.-M.; Chen, H.-B.; Zhou, M.-H.; Qiao, H.; An, S.-C. Orbitofrontal cortex 5-HT_{2A} receptor mediates chronic stress-induced depressive-like behaviors and alterations of spine density and Kalirin7. *Neuropharmacology* **2016**, *109*, 7–17, doi:10.1016/j.neuropharm.2016.02.020.
86. Villas Boas, G.R.; Boerngen de Lacerda, R.; Paes, M.M.; Gubert, P.; Almeida, W.L. da C.; Rescia, V.C.; de Carvalho, P.M.G.; de Carvalho, A.A.V.; Oesterreich, S.A. Molecular aspects of depression: A review from neurobiology to treatment. *Eur. J. Pharmacol.* **2019**, *851*, 99–121, doi:10.1016/j.ejphar.2019.02.024.
87. Zhang, X.; Song, D.; Gu, L.; Ren, Y.; Verkhatsky, A.; Peng, L. Decrease of gene expression of astrocytic 5-HT_{2B} receptors parallels development of depressive phenotype in a mouse model of Parkinson's disease. *Front. Cell. Neurosci.* **2015**, *9*, 1–13, doi:10.3389/fncel.2015.00388.
88. Zhang, S.; Li, B.; Lovatt, D.; Xu, J.; Song, D.; Goldman, S.A.; Nedergaard, M.; Hertz, L.; Peng, L. 5-HT_{2B} receptors are expressed on astrocytes from brain and in culture and are a chronic target for all five conventional 'serotonin-specific reuptake inhibitors.' *Neuron Glia Biol.* **2010**, *6*, 113–125, doi:10.1017/S1740925X10000141.
89. Peng, L.; Gu, L.; Li, B.; Hertz, L. Fluoxetine and all other SSRIs are 5-HT_{2B} Agonists-Importance for their Therapeutic Effects. *Curr. Neuropharmacol.* **2014**, *12*, 365–379, doi:10.2174/1570159X12666140828221720.
90. Diaz, S.L.; Narboux-Nême, N.; Boutourlinsky, K.; Doly, S.; Maroteaux, L. Mice lacking the serotonin 5-HT_{2B} receptor as an animal model of resistance to selective serotonin reuptake inhibitors antidepressants. *Eur. Neuropsychopharmacol.* **2016**, *26*, 265–279, doi:10.1016/j.euroneuro.2015.12.012.
91. Li, X.; Liang, S.; Li, Z.; Li, S.; Xia, M.; Verkhatsky, A.; Li, B. Leptin Increases Expression of 5-HT_{2B} Receptors in Astrocytes Thus Enhancing Action of Fluoxetine on the Depressive Behavior Induced by Sleep Deprivation. *Front. Psychiatry* **2019**, *9*, 734, doi:10.3389/fpsy.2018.00734.
92. Wold, E.A.; Wild, C.T.; Cunningham, K.A.; Zhou, J. Targeting the 5-HT_{2C} Receptor in Biological Context and the Current State of 5-HT_{2C} Receptor Ligand Development. *Curr. Top. Med. Chem.* **2019**, *19*, 1381–1398, doi:10.2174/1568026619666190709101449.
93. Kamal, M.; Gbahou, F.; Guillaume, J.-L.; Daulat, A.M.; Benleulmi-Chaachoua, A.; Luka, M.; Chen, P.; Kalbasi Anaraki, D.; Baroncini, M.; Mannoury la Cour, C.; et al. Convergence of Melatonin and Serotonin (5-HT) Signaling at MT₂/5-HT_{2C} Receptor Heteromers. *J. Biol. Chem.* **2015**, *290*, 11537–11546, doi:10.1074/jbc.M114.559542.
94. Palacios, J.M.; Pazos, A.; Hoyer, D. A short history of the 5-HT_{2C} receptor: From the choroid plexus to depression, obesity and addiction treatment. *Psychopharmacology* **2017**, *234*, 1395–1418, doi:10.1007/s00213-017-4545-5.

95. Cremers, T.I.F.H.; Giorgetti, M.; Bosker, F.J.; Hogg, S.; Arnt, J.; Mørk, A.; Honig, G.; Bøgesø, K.-P.; Westerink, B.H.C.; den Boer, H.; et al. Inactivation of 5-HT_{2C} Receptors Potentiates Consequences of Serotonin Reuptake Blockade. *Neuropsychopharmacology* **2004**, *29*, 1782–1789, doi:10.1038/sj.npp.1300474.
96. Visser, A.K.D.; Kleijn, J.; van Faassen, M.H.J.R.; Dremencov, E.; Flik, G.; Kema, I.P.; Den Boer, J.A.; van Waarde, A.; Dierckx, R.A.J.O.; Bosker, F.J. Serotonin-2C antagonism augments the effect of citalopram on serotonin and dopamine levels in the ventral tegmental area and nucleus accumbens. *Neurochem. Int.* **2015**, *81*, 10–15, doi:10.1016/j.neuint.2014.12.006.
97. Jilani, T.N.; Gibbons, J.R.; Faizy, R.M.; Saadabadi, A. Mirtazapine Available online: <https://www.ncbi.nlm.nih.gov/books/NBK519059/> (accessed on Feb 11, 2020).
98. Naguy, A. Mirtazapine for Major Depression Developed After Hyperemesis Gravidarum. *Am. J. Ther.* **2019**, *26*, e661–e662, doi:10.1097/MJT.0000000000000860.
99. Dekeyne, A.; Mannoury la Cour, C.; Gobert, A.; Brocco, M.; Lejeune, F.; Serres, F.; Sharp, T.; Daszuta, A.; Soumier, A.; Papp, M.; et al. S32006, a novel 5-HT_{2C} receptor antagonist displaying broad-based antidepressant and anxiolytic properties in rodent models. *Psychopharmacology* **2008**, *199*, 549–568, doi:10.1007/s00213-008-1177-9.
100. Dekeyne, A.; Brocco, M.; Loiseau, F.; Gobert, A.; Rivet, J.-M.; Di Cara, B.; Cremers, T.I.; Flik, G.; Fone, K.C.F.; Watson, D.J.G.; et al. S32212, a Novel Serotonin Type 2C Receptor Inverse Agonist/ α 2 -Adrenoceptor Antagonist and Potential Antidepressant: II. A Behavioral, Neurochemical, and Electrophysiological Characterization. *J. Pharmacol. Exp. Ther.* **2012**, *340*, 765–780, doi:10.1124/jpet.111.187534.
101. Rosenzweig-Lipson, S.; Sabb, A.; Stack, G.; Mitchell, P.; Lucki, I.; Malberg, J.E.; Grauer, S.; Brennan, J.; Cryan, J.F.; Sukoff Rizzo, S.J.; et al. Antidepressant-like effects of the novel, selective, 5-HT_{2C} receptor agonist WAY-163909 in rodents. *Psychopharmacology* **2007**, *192*, 159–170, doi:10.1007/s00213-007-0710-6.
102. Thompson, A.J.; Lummis, S.C.R. 5-HT₃ receptors. *Curr. Pharm. Des.* **2006**, *12*, 3615–3630.
103. Faerber, L.; Drechsler, S.; Ladenburger, S.; Gschaidmeier, H.; Fischer, W. The neuronal 5-HT₃ receptor network after 20 years of research—Evolving concepts in management of pain and inflammation. *Eur. J. Pharmacol.* **2007**, *560*, 1–8, doi:10.1016/j.ejphar.2007.01.028.
104. Bétry, C.; Etiévant, A.; Oosterhof, C.; Ebert, B.; Sanchez, C.; Haddjeri, N. Role of 5-HT₃ receptors in the antidepressant response. *Pharmaceuticals* **2011**, *4*, 603–629, doi:10.3390/ph4040603.
105. Bhatt, S.; Mahesh, R.; Devadoss, T.; Jindal, A. Neuropharmacological evaluation of a novel 5-HT₃ receptor antagonist (4-benzylpiperazin-1-yl)(3-methoxyquinoxalin-2-yl) methanone (6g) on lipopolysaccharide-induced anxiety models in mice. *J. Basic Clin. Physiol. Pharmacol.* **2016**, *28*, 101–106, doi:10.1515/jbcpp-2016-0083.
106. Fakhfour, G.; Rahimian, R.; Dyhrfeld-Johnsen, J.; Zarak, M.R.; Beaulieu, J.-M. 5-HT₃ Receptor Antagonists in Neurologic and Neuropsychiatric Disorders: The Iceberg Still Lies beneath the Surface. *Pharmacol. Rev.* **2019**, *71*, 383–412, doi:10.1124/pr.118.015487.
107. Bhatt, S.; Mahesh, R.; Jindal, A.; Devadoss, T. Neuropharmacological and neurochemical evaluation of N-n-propyl-3-ethoxyquinoxaline-2-carboxamide (6n): A novel serotonergic 5-HT₃ receptor antagonist for co-morbid antidepressant- and anxiolytic-like potential using traumatic brain injury model in rats. *J. Basic Clin. Physiol. Pharmacol.* **2017**, *28*, 93–100, doi:10.1515/jbcpp-2016-0057.
108. Amiri, S.; Amini-Khoei, H.; Haj-Mirzaian, A.; Rahimi-Balaei, M.; Naserzadeh, P.; Dehpour, A.; Mehr, S.E.; Hosseini, M.-J. Tropicsetron attenuated the anxiogenic effects of social isolation by modulating nitrenergic system and mitochondrial function. *Biochim. Biophys. Acta-Gen. Subj.* **2015**, *1850*, 2464–2475, doi:10.1016/j.bbagen.2015.09.009.
109. Yu, Y.; Zhu, W.; Liang, Q.; LIU, J.; Yang, X.; Sun, G. Tropicsetron attenuates lipopolysaccharide induced neuroinflammation by inhibiting NF- κ B and SP/NK1R signaling pathway. *J. Neuroimmunol.* **2018**, *320*, 80–86, doi:10.1016/j.jneuroim.2018.05.001.
110. Mayer, E.A.; Bradesi, S. Alosetron and irritable bowel syndrome. *Expert Opin. Pharmacother.* **2003**, *4*, 2089–2098, doi:10.1517/14656566.4.11.2089.
111. Kurhe, Y.; Mahesh, R. Ondansetron attenuates co-morbid depression and anxiety associated with obesity by inhibiting the biochemical alterations and improving serotonergic neurotransmission. *Pharmacol. Biochem. Behav.* **2015**, *136*, 107–116, doi:10.1016/j.pbb.2015.07.004.
112. Costall, B.; Domeney, A.M.; Gerrard, P.A.; Kelly, M.E.; Naylor, E.J. Zacopride: Anxiolytic profile in rodent and primate models of anxiety. *J. Pharm. Pharmacol.* **1988**, *40*, 302–305, doi:10.1111/j.2042-7158.1988.tb05254.x.
113. Gupta, D.; Radhakrishnan, M.; Thangaraj, D.; Kurhe, Y. Antidepressant and anti-anxiety like effects of 4i (N-(3-chloro-2-methylphenyl) quinoxalin-2-carboxamide), a novel 5-HT₃ receptor antagonist in acute and chronic neurobehavioral rodent models. *Eur. J. Pharmacol.* **2014**, *735*, 59–67, doi:10.1016/j.ejphar.2014.04.008.
114. Costescu, M.; Paunescu, H.; Coman, O.; Coman, L.; Fulga, I. Antidepressant effect of the interaction of fluoxetine with granisetron. *Exp. Ther. Med.* **2019**, *5108–5111*, doi:10.3892/etm.2019.8141.
115. Fan, P. Mepacrine-induced inhibition of the inward current mediated by 5-HT₃ receptors in rat nodose ganglion neurones. *Br. J. Pharmacol.* **1994**, *112*, 745–748, doi:10.1111/j.1476-5381.1994.tb13141.x.
116. Bétry, C.; Overstreet, D.; Haddjeri, N.; Pehrson, A.L.; Bundgaard, C.; Sanchez, C.; Mørk, A. A 5-HT₃ receptor antagonist potentiates the behavioral, neurochemical and electrophysiological actions of an SSRI antidepressant. *Pharmacol. Biochem. Behav.* **2015**, *131*, 136–142, doi:10.1016/j.pbb.2015.02.011.

117. Gupta, D.; Radhakrishnan, M.; Kurhe, Y. Ondansetron, a 5HT₃ receptor antagonist reverses depression and anxiety-like behavior in streptozotocin-induced diabetic mice: Possible implication of serotonergic system. *Eur. J. Pharmacol.* **2014**, *744*, 59–66, doi:10.1016/j.ejphar.2014.09.041.
118. Gupta, D.; Radhakrishnan, M.; Kurhe, Y.; Thangaraj, D.; Prabhakar, V.; Kanade, P. Antidepressant-like effects of a novel 5-HT₃ receptor antagonist 6z in acute and chronic murine models of depression. *Acta Pharmacol. Sin.* **2014**, *35*, 1493–1503, doi:10.1038/aps.2014.89.
119. Hao, R.; Qi, Y.; Hou, D.-N.; Ji, Y.-Y.; Zheng, C.-Y.; Li, C.-Y.; Yung, W.-H.; Lu, B.; Huang, Y. BDNF val66met Polymorphism Impairs Hippocampal Long-Term Depression by Down-Regulation of 5-HT₃ Receptors. *Front. Cell. Neurosci.* **2017**, *11*, 1–10, doi:10.3389/fncel.2017.00306.
120. Pytka, K.; Głuch-Lutwin, M.; Kotańska, M.; Waszkielewicz, A.; Kij, A.; Walczak, M. Single Administration of HBK-15—a Triple 5-HT_{1A}, 5-HT₇, and 5-HT₃ Receptor Antagonist—Reverses Depressive-Like Behaviors in Mouse Model of Depression Induced by Corticosterone. *Mol. Neurobiol.* **2017**, *55*, 3931–3945, doi:10.1007/s12035-017-0605-4.
121. Kurhe, Y.; Mahesh, R. Mechanisms linking depression co-morbid with obesity: An approach for serotonergic type 3 receptor antagonist as novel therapeutic intervention. *Asian J. Psychiatr.* **2015**, *17*, 3–9, doi:10.1016/j.ajp.2015.07.007.
122. Riga, M.S.; Sánchez, C.; Celada, P.; Artigas, F. Involvement of 5-HT₃ receptors in the action of vortioxetine in rat brain: Focus on glutamatergic and GABAergic neurotransmission. *Neuropharmacology* **2016**, *108*, 73–81, doi:10.1016/j.neuropharm.2016.04.023.
123. Vieta, E.; Florea, I.; Schmidt, S.N.; Areberg, J.; Ettrup, A. Intravenous vortioxetine to accelerate onset of effect in major depressive disorder. *Int. Clin. Psychopharmacol.* **2019**, *34*, 153–160, doi:10.1097/YIC.0000000000000271.
124. Haj-Mirzaian, A.; Amiri, S.; Amini-Khoei, H.; Rahimi-Balaei, M.; Kordjazy, N.; Olson, C.O.; Rastegar, M.; Naserzadeh, P.; Marzban, H.; Dehpour, A.R.; et al. Attenuation of oxidative and nitrosative stress in cortical area associates with antidepressant-like effects of tropisetron in male mice following social isolation stress. *Brain Res. Bull.* **2016**, *124*, 150–163, doi:10.1016/j.brainresbull.2016.04.018.
125. Dhar, A.K.; Mahesh, R.; Jindal, A.; Bhatt, S. Piperazine Analogs of Naphthyridine-3-carboxamides and Indole-2-carboxamides: Novel 5-HT₃ Receptor Antagonists with Antidepressant-Like Activity. *Arch. Pharm.* **2015**, *348*, 34–45, doi:10.1002/ardp.201400293.
126. Kurhe, Y.; Mahesh, R.; Devadoss, T. Novel 5-HT₃ receptor antagonist QCM-4 attenuates depressive-like phenotype associated with obesity in high-fat-diet-fed mice. *Psychopharmacology* **2017**, *234*, 1165–1179, doi:10.1007/s00213-017-4558-0.
127. Kurhe, Y.; Mahesh, R.; Gupta, D.; Thangaraj, D. Effect of (4a) a novel 5-HT₃ receptor antagonist on chronic unpredictable mild stress induced depressive-like behavior in mice: An approach using behavioral tests battery. *J. Basic Clin. Physiol. Pharmacol.* **2015**, *26*, 25–33, doi:10.1515/jbcpp-2013-0160.
128. Richter, D.W.; Manzke, T.; Wilken, B.; Ponimaskin, E. Serotonin receptors: Guardians of stable breathing. *Trends Mol. Med.* **2003**, *9*, 542–548, doi:10.1016/j.molmed.2003.10.010.
129. Hilenski, L.L.; Griendling, K.K. Vascular Smooth Muscle. In *Vascular Medicine: A Companion to Braunwald's Heart Disease*; Elsevier, 2013; pp. 25–42 ISBN 9781437729306.
130. Ahmad, I.; Nirogi, R. 5-HT₄ Receptor Agonists for the Treatment of Alzheimer's Disease. *Neurosci. Med.* **2011**, *2*, 87–92, doi:10.4236/nm.2011.22013.
131. Wohlfarth, C.; Schmitteckert, S.; Härtle, J.D.; Houghton, L.A.; Dweep, H.; Fortea, M.; Assadi, G.; Braun, A.; Mederer, T.; Pöhner, S.; et al. miR-16 and miR-103 impact 5-HT₄ receptor signalling and correlate with symptom profile in irritable bowel syndrome. *Sci. Rep.* **2017**, *7*, 14680, doi:10.1038/s41598-017-13982-0.
132. Mendez-David, I.; David, D.J.; Darcet, F.; Wu, M.V.; Kerdine-Römer, S.; Gardier, A.M.; Hen, R. Rapid Anxiolytic Effects of a 5-HT₄ Receptor Agonist Are Mediated by a Neurogenesis-Independent Mechanism. *Neuropsychopharmacology* **2014**, *39*, 1366–1378, doi:10.1038/npp.2013.332.
133. Chen, B.K.; Mendez-David, I.; Luna, V.M.; Faye, C.; Gardier, A.M.; David, D.J.; Denny, C.A. Prophylactic efficacy of 5-HT_{4R} agonists against stress. *Neuropsychopharmacology* **2020**, *45*, 542–552, doi:10.1038/s41386-019-0540-3.
134. Bell, R.; Duke, A.A.; Gilmore, P.E.; Page, D.; Bègue, L. Anxiolytic-like effects observed in rats exposed to the elevated zero-maze following treatment with 5-HT₂/5-HT₃/5-HT₄ ligands. *Sci. Rep.* **2015**, *4*, 3881, doi:10.1038/srep03881.
135. Silvestre, J.S.; Fernández, A.G.; Palacios, J. Effects of 5-HT₄ receptor antagonists on rat behaviour in the elevated plus-maze test. *Eur. J. Pharmacol.* **1996**, *309*, 219–222, doi:10.1016/0014-2999(96)00457-8.
136. Faye, C.; Hen, R.; Guiard, B.P.; Denny, C.A.; Gardier, A.M.; Mendez-David, I.; David, D.J. Rapid Anxiolytic Effects of RS67333, a Serotonin Type 4 Receptor Agonist, and Diazepam, a Benzodiazepine, Are Mediated by Projections From the Prefrontal Cortex to the Dorsal Raphe Nucleus. *Biol. Psychiatry* **2020**, *87*, 514–525, doi:10.1016/j.biopsych.2019.08.009.
137. Amigó, J.; Díaz, A.; Pilar-Cuellar, F.; Vidal, R.; Martín, A.; Compan, V.; Pazos, A.; Castro, E. The absence of 5-HT₄ receptors modulates depression- and anxiety-like responses and influences the response of fluoxetine in olfactory bulbectomised mice: Adaptive changes in hippocampal neuroplasticity markers and 5-HT_{1A} autoreceptor. *Neuropharmacology* **2016**, *111*, 47–58, doi:10.1016/j.neuropharm.2016.08.037.
138. Castello, J.; LeFrancis, B.; Flajolet, M.; Greengard, P.; Friedman, E.; Rebolz, H. CK2 regulates 5-HT₄ receptor signaling and modulates depressive-like behavior. *Mol. Psychiatry* **2018**, *23*, 872–882, doi:10.1038/mp.2017.240.
139. Murphy, S.E.; de Cates, A.N.; Gillespie, A.L.; Godlewska, B.R.; Scaife, J.C.; Wright, L.C.; Cowen, P.J.; Harmer, C.J. Translating the promise of 5HT₄ receptor agonists for the treatment of depression. *Psychol. Med.* **2020**, 1–10, doi:10.1017/S0033291720000604.

140. Lucas, G.; Rymar, V.V.; Du, J.; Mnie-Filali, O.; Bisgaard, C.; Manta, S.; Lambas-Senas, L.; Wiborg, O.; Haddjeri, N.; Piñeyro, G.; et al. Serotonin₄ (5-HT₄) Receptor Agonists Are Putative Antidepressants with a Rapid Onset of Action. *Neuron* **2007**, *55*, 712–725, doi:10.1016/j.neuron.2007.07.041.
141. Pascual-Brazo, J.; Castro, E.; Díaz, Á.; Valdizán, E.M.; Pilar-Cuéllar, F.; Vidal, R.; Treceño, B.; Pazos, Á. Modulation of neuroplasticity pathways and antidepressant-like behavioural responses following the short-term (3 and 7 days) administration of the 5-HT₄ receptor agonist RS67333. *Int. J. Neuropsychopharmacol.* **2012**, *15*, 631–643, doi:10.1017/S1461145711000782.
142. Lucas, G.; Du, J.; Romeas, T.; Mnie-Filali, O.; Haddjeri, N.; Piñeyro, G.; Debonnel, G. Selective Serotonin Reuptake Inhibitors Potentiate the Rapid Antidepressant-Like Effects of Serotonin₄ Receptor Agonists in the Rat. *PLoS ONE* **2010**, *5*, e9253, doi:10.1371/journal.pone.0009253.
143. O’Leary, O.F.; Cryan, J.F. The Behavioral Genetics of Serotonin: Relevance to Anxiety and Depression. In *Handbook of Behavioral Neuroscience*; Elsevier B.V.: Amsterdam, The Netherlands, 2010; Volume 21, pp. 749–789, ISBN 9780123746344.
144. Blackburn, T.P. Serotonin (5-Hydroxytryptamine; 5-HT): Receptors. In *Encyclopedia of Neuroscience*; Elsevier: Amsterdam, The Netherlands, 2009; pp. 701–714, ISBN 9780080450469.
145. Goodfellow, N.M.; Bailey, C.D.C.; Lambe, E.K. The Native Serotonin 5-HT_{5A} Receptor: Electrophysiological Characterization in Rodent Cortex and 5-HT_{1A}-Mediated Compensatory Plasticity in the Knock-Out Mouse. *J. Neurosci.* **2012**, *32*, 5804–5809, doi:10.1523/JNEUROSCI.4849-11.2012.
146. Noda, M.; Yasuda, S.; Okada, M.; Higashida, H.; Shimada, A.; Iwata, N.; Ozaki, N.; Nishikawa, K.; Shirasawa, S.; Uchida, M.; et al. Recombinant human serotonin 5A receptors stably expressed in C6 glioma cells couple to multiple signal transduction pathways. *J. Neurochem.* **2003**, *84*, 222–232, doi:10.1046/j.1471-4159.2003.01518.x.
147. Hofer, A.M. Signal Transduction and Second Messengers. In *Cell Physiology Source Book*; Elsevier: Amsterdam, The Netherlands, 2012; pp. 85–98, ISBN 9780123877383.
148. Cuthbert, B.N.; Lang, P.J.; Strauss, C.; Drobos, D.; Patrick, C.J.; Bradley, M.M. The psychophysiology of anxiety disorder: Fear memory imagery. *Psychophysiology* **2003**, *40*, 407–422, doi:10.1111/1469-8986.00043.
149. Brasil, E.S. de A.; Furini, C.R.G.; Rodrigues, F. da S.; Nachtigall, E.G.; Behling, J.A.K.; Saenger, B.F.; Farias, C.P.; Myskiw, J. de C.; Izquierdo, I. The blockade of the serotonergic receptors 5-HT_{5A}, 5-HT₆ and 5-HT₇ in the basolateral amygdala, but not in the hippocampus facilitate the extinction of fear memory. *Behav. Brain Res.* **2019**, *372*, 112055, doi:10.1016/j.bbr.2019.112055.
150. Kassai, F.; Schlumberger, C.; Kedves, R.; Pietraszek, M.; Jatzke, C.; Lendvai, B.; Gyertyán, I.; Danysz, W. Effect of 5-HT_{5A} antagonists in animal models of schizophrenia, anxiety and depression. *Behav. Pharmacol.* **2012**, *23*, 397–406, doi:10.1097/FBP.0b013e3283565248.
151. Sagi, Y.; Medrihan, L.; George, K.; Barney, M.; McCabe, K.A.; Greengard, P. Emergence of 5-HT_{5A} signaling in parvalbumin neurons mediates delayed antidepressant action. *Mol. Psychiatry* **2020**, *25*, 1191–1201, doi:10.1038/s41380-019-0379-3.
152. Thomas, D. 5-HT_{5A} receptors as a therapeutic target. *Pharmacol. Ther.* **2006**, *111*, 707–714, doi:10.1016/j.pharmthera.2005.12.006.
153. Ramírez, M.J. 5-HT₆ receptors and Alzheimer’s disease. *Alzheimers. Res. Ther.* **2013**, *5*, 15, doi:10.1186/alzrt169.
154. Meffre, J.; Chaumont-Dubel, S.; Mannoury la Cour, C.; Loiseau, F.; Watson, D.J.G.; Dekeyne, A.; Séveno, M.; Rivet, J.; Gaven, F.; Délérís, P.; et al. 5-HT₆ receptor recruitment of mTOR as a mechanism for perturbed cognition in schizophrenia. *EMBO Mol. Med.* **2012**, *4*, 1043–1056, doi:10.1002/emmm.201201410.
155. Dawson, L.A. The Central Role of 5-HT₆ Receptors in Modulating Brain Neurochemistry. In *International Review of Neurobiology*; Elsevier Inc.: Amsterdam, The Netherlands, 2011; Volume 96, pp. 1–26, ISBN 9780123859020.
156. Geng, F.; Tian, J.; Wu, J.-L.; Luo, Y.; Zou, W.-J.; Peng, C.; Lu, G.-F. Dorsomedial prefrontal cortex 5-HT₆ receptors regulate anxiety-like behavior. *Cogn. Affect. Behav. Neurosci.* **2018**, *18*, 58–67, doi:10.3758/s13415-017-0552-6.
157. Nikiforuk, A.; Kos, T.; Wesołowska, A. The 5-HT₆ receptor agonist EMD 386088 produces antidepressant and anxiolytic effects in rats after intrahippocampal administration. *Psychopharmacology* **2011**, *217*, 411–418, doi:10.1007/s00213-011-2297-1.
158. Wesołowska, A.; Nikiforuk, A. Effects of the brain-penetrant and selective 5-HT₆ receptor antagonist SB-399885 in animal models of anxiety and depression. *Neuropharmacology* **2007**, *52*, 1274–1283, doi:10.1016/j.neuropharm.2007.01.007.
159. Partyka, A.; Wasik, A.; Jastrzębska-Więsek, M.; Mierzejewski, P.; Bierkowski, P.; Kołaczkowski, M.; Wesołowska, A. ADN-1184, a monoaminergic ligand with 5-HT_{6/7} receptor antagonist action, exhibits activity in animal models of anxiety. *Naunyn. Schmiedeberg’s Arch. Pharmacol.* **2016**, *389*, 593–602, doi:10.1007/s00210-016-1229-3.
160. Abraham, R.; Nirogi, R.; Shinde, A.; Benade, V. Therapeutic Potential of 5-HT₆ Antagonist SB399885 in Traumatic Stress Disorder. *Drug Res.* **2014**, *65*, 442–445, doi:10.1055/s-0034-1390418.
161. Carr, G.V.; Schechter, L.E.; Lucki, I. Antidepressant and anxiolytic effects of selective 5-HT₆ receptor agonists in rats. *Psychopharmacology* **2011**, *213*, 499–507, doi:10.1007/s00213-010-1798-7.
162. Wesołowska, A.; Nikiforuk, A.; Stachowicz, K. Anxiolytic-like and antidepressant-like effects produced by the selective 5-HT₆ receptor antagonist SB-258585 after intrahippocampal administration to rats. *Behav. Pharmacol.* **2007**, *18*, 439–446, doi:10.1097/FBP.0b013e3282d28f9c.
163. Zhang, Y.-M.; Zhang, L.; Wang, Y.; Sun, Y.-N.; Guo, Y.; Du, C.-X.; Zhang, J.; Yao, L.; Yu, S.-Q.; Liu, J. Activation and blockade of prefrontal 5-HT₆ receptors produce different effects on depressive-like behaviors in unilateral 6-hydroxydopamine-induced Parkinson’s rats. *Neuropharmacology* **2016**, *110*, 25–36, doi:10.1016/j.neuropharm.2016.07.014.
164. Jastrzębska-Więsek, M.; Siwek, A.; Partyka, A.; Szewczyk, B.; Sowa-Kućma, M.; Wasik, A.; Kołaczkowski, M.; Wesołowska, A. Antidepressant-like activity of EMD 386088, a 5-HT₆ receptor partial agonist, following systemic acute and chronic administration to rats. *Naunyn. Schmiedeberg’s Arch. Pharmacol.* **2015**, *388*, 1079–1088, doi:10.1007/s00210-015-1141-2.

165. Jastrzębska-Więsek, M.; Siwek, A.; Partyka, A.; Antkiewicz-Michaluk, L.; Michaluk, J.; Romańska, I.; Kołaczkowski, M.; Wesołowska, A. Study of a mechanism responsible for potential antidepressant activity of EMD 386088, a 5-HT₆ partial agonist in rats. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2016**, *389*, 839–849, doi:10.1007/s00210-016-1245-3.
166. Suárez-Santiago, J.E.; Briones-Aranda, A.; Espinosa-Raya, J.; Picazo, O. Agonist E-6837 and antagonist SB-271046 of 5-HT₆ receptors both reverse the depressive-like effect induced in mice by subchronic ketamine administration. *Behav. Pharmacol.* **2017**, *28*, 582–585, doi:10.1097/FBP.0000000000000327.
167. Volpicelli, F.; Speranza, L.; di Porzio, U.; Crispino, M.; Perrone-Capano, C. The serotonin receptor 7 and the structural plasticity of brain circuits. *Front. Behav. Neurosci.* **2014**, *8*, 1–6, doi:10.3389/fnbeh.2014.00318.
168. Guseva, D.; Wirth, A.; Ponimaskin, E. Cellular mechanisms of the 5-HT₇ receptor-mediated signaling. *Front. Behav. Neurosci.* **2014**, *8*, 1–8, doi:10.3389/fnbeh.2014.00306.
169. Speranza, L.; Labus, J.; Volpicelli, F.; Guseva, D.; Lacivita, E.; Leopoldo, M.; Bellenchi, G.C.; di Porzio, U.; Bijata, M.; Perrone-Capano, C.; et al. Serotonin 5-HT₇ receptor increases the density of dendritic spines and facilitates synaptogenesis in forebrain neurons. *J. Neurochem.* **2017**, *141*, 647–661, doi:10.1111/jnc.13962.
170. Du, C.X.; Guo, Y.; Zhang, Q.J.; Zhang, J.; Lv, S.X.; Liu, J. Involvement of prefrontal 5-HT₇ receptors in the regulation of anxiety-like behaviors in hemiparkinsonian rats. *Neurol. Res.* **2018**, *40*, 847–855, doi:10.1080/01616412.2018.1493962.
171. Canale, V.; Kurczab, R.; Partyka, A.; Satała, G.; Lenda, T.; Jastrzębska-Więsek, M.; Wesołowska, A.; Bojarski, A.J.; Zajdel, P. Towards new 5-HT₇ antagonists among arylsulfonamide derivatives of (aryloxy)ethyl-alkyl amines: Multiobjective based design, synthesis, and antidepressant and anxiolytic properties. *Eur. J. Med. Chem.* **2016**, *108*, 334–346, doi:10.1016/j.ejmech.2015.11.040.
172. Wesołowska, A.; Nikiforuk, A.; Stachowicz, K.; Tatarczyńska, E. Effect of the selective 5-HT₇ receptor antagonist SB 269970 in animal models of anxiety and depression. *Neuropharmacology* **2006**, *51*, 578–586, doi:10.1016/j.neuropharm.2006.04.017.
173. Sowa, J.; Hess, G. Prenatal stress-related alterations in synaptic transmission and 5-HT₇ receptor-mediated effects in the rat dorsal raphe nucleus are ameliorated by the 5-HT₇ receptor antagonist SB 269970. *Eur. J. Neurosci.* **2020**, *ejn.14778*, doi:10.1111/ejn.14778.
174. Hedlund, P.B.; Huitron-Resendiz, S.; Henriksen, S.J.; Sutcliffe, J.G. 5-HT₇ Receptor Inhibition and Inactivation Induce Antidepressant-like Behavior and Sleep Pattern. *Biol. Psychiatry* **2005**, *58*, 831–837, doi:10.1016/j.biopsych.2005.05.012.
175. Bonaventure, P.; Kelly, L.; Aluisio, L.; Shelton, J.; Lord, B.; Galici, R.; Miller, K.; Atack, J.; Lovenberg, T.W.; Dugovic, C. Selective blockade of 5-hydroxytryptamine (5-HT)₇ receptors enhances 5-HT transmission, antidepressant-like behavior, and rapid eye movement sleep suppression induced by citalopram in rodents. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 690–698, doi:10.1124/jpet.107.119404.
176. Wesołowska, A.; Kowalska, M. Influence of serotonin 5-HT₇ receptor blockade on the behavioral and neurochemical effects of imipramine in rats. *Pharmacol. Rep.* **2008**, *60*, 464–474.
177. Stroth, N.; Svenningsson, P. 5-HT₇ interacts with the serotonin 5-HT₇ receptor to regulate a depressive-like behavior. *Eur. Neuropsychopharmacol.* **2015**, *25*, 2372–2380, doi:10.1016/j.euroneuro.2015.10.003.
178. Bonaventure, P.; Dugovic, C.; Kramer, M.; De Boer, P.; Singh, J.; Wilson, S.; Bertelsen, K.; Di, J.; Shelton, J.; Aluisio, L.; et al. Translational Evaluation of JNJ-18038683, a 5-Hydroxytryptamine Type 7 Receptor Antagonist, on Rapid Eye Movement Sleep and in Major Depressive Disorder. *J. Pharmacol. Exp. Ther.* **2012**, *342*, 429–440, doi:10.1124/jpet.112.193995.
179. Ng, Q.X.; Venkatanarayanan, N.; Ho, C.Y.X. Clinical use of *Hypericum perforatum* (St John's wort) in depression: A meta-analysis. *J. Affect. Disord.* **2017**, *210*, 211–221, doi:10.1016/j.jad.2016.12.048.
180. White, C.M. The Pharmacology, Pharmacokinetics, Efficacy, and Adverse Events Associated With Kava. *J. Clin. Pharmacol.* **2018**, *58*, 1396–1405, doi:10.1002/jcph.1263.
181. Fogaça, M.V.; Campos, A.C.; Coelho, L.D.; Duman, R.S.; Guimarães, F.S. The anxiolytic effects of cannabidiol in chronically stressed mice are mediated by the endocannabinoid system: Role of neurogenesis and dendritic remodeling. *Neuropharmacology* **2018**, *135*, doi:10.1016/j.neuropharm.2018.03.001.
182. Filho, C.B.; Jesse, C.R.; Donato, F.; Del Fabbro, L.; de Gomes, M.G.; Goes, A.T.R.; Souza, L.C.; Giacomeli, R.; Antunes, M.; Luchese, C.; et al. Neurochemical factors associated with the antidepressant-like effect of flavonoid chrysin in chronically stressed mice. *Eur. J. Pharmacol.* **2016**, *791*, doi:10.1016/j.ejphar.2016.09.005.
183. Sun, L.; Zhang, C.; Xue, C.; Liu, C.; Wang, Y.; Chen, L.; Deng, Y.; Huang, J.; Zhai, H. Anxiolytic effect of a novel 9,10-dihydrophenanthrene, juncuenin H, is associated with metabolic changes in cortical serotonin/dopamine levels in mice. *Fitoterapia* **2019**, *134*, 165–171, doi:10.1016/j.fitote.2019.02.030.
184. Qiu, Z.-K.; He, J.-L.; Liu, X.; Zeng, J.; Xiao, W.; Fan, Q.-H.; Chai, X.-M.; Ye, W.-H.; Chen, J.-S. Anxiolytic-like effects of paeoniflorin in an animal model of post traumatic stress disorder. *Metab. Brain Dis.* **2018**, *33*, 1175–1185, doi:10.1007/s11011-018-0216-4.
185. Cheng, B.-H.; Sheen, L.-Y.; Chang, S.-T. Evaluation of anxiolytic potency of essential oil and S-(+)-linalool from *Cinnamomum osmophloeum* ct. linalool leaves in mice. *J. Tradit. Complement. Med.* **2015**, *5*, 27–34, doi:10.1016/j.jtcme.2014.10.007.
186. Mannan, M.A.; Abir, A.B.; Rahman, M.R.; Khatun, A.; Datta, B. Analgesic, antidepressant and anxiolytic effects of the methanolic extract of *Achyranthes aspera* leaves in mice. *Stamford J. Pharm. Sci.* **2019**, *9*, 11–35.

187. Jiménez-Ferrer, E.; Santillán-Urquiza, M.A.; Alegría-Herrera, E.; Zamilpa, A.; Noguerón-Merino, C.; Tortoriello, J.; Navarro-García, V.; Avilés-Flores, M.; Fuentes-Mata, M.; Herrera-Ruiz, M. Anxiolytic effect of fatty acids and terpenes fraction from *Aloysia triphylla*: Serotonergic, GABAergic and glutamatergic implications. *Biomed. Pharmacother.* **2017**, *96*, 320–327, doi:10.1016/j.biopha.2017.10.024.
188. Diniz, T.C.; de Oliveira Júnior, R.G.; Miranda Bezerra Medeiros, M.A.; Gama e Silva, M.; de Andrade Teles, R.B.; dos Passos Menezes, P.; de Sousa, B.M.H.; Abrahão Frank, L.; de Souza Araújo, A.A.; Russo Serafini, M.; et al. Anticonvulsant, sedative, anxiolytic and antidepressant activities of the essential oil of *Annona vepretorum* in mice: Involvement of GABAergic and serotonergic systems. *Biomed. Pharmacother.* **2019**, *111*, 1074–1087, doi:10.1016/j.biopha.2018.12.114.
189. He, D.; Wang, X.; Zhang, P.; Luo, X.; Li, X.; Wang, L.; Li, S.; Xu, Y. Evaluation of the Anxiolytic and Antidepressant Activities of the Aqueous Extract from *Camellia euphlebia* Merr. ex Sealy in Mice. *Evidence-Based Complement. Altern. Med.* **2015**, *2015*, 618409, doi:10.1155/2015/618409.
190. Kurauchi, Y.; Devkota, H.P.; Hori, K.; Nishihara, Y.; Hisatsune, A.; Seki, T.; Katsuki, H. Anxiolytic activities of Matcha tea powder, extracts, and fractions in mice: Contribution of dopamine D1 receptor- and serotonin 5-HT1A receptor-mediated mechanisms. *J. Funct. Foods* **2019**, *59*, 301–308, doi:10.1016/j.jff.2019.05.046.
191. Zhang, N.; Zhang, L.; Feng, L.; Yao, L. The anxiolytic effect of essential oil of *Cananga odorata* exposure on mice and determination of its major active constituents. *Phytomedicine* **2016**, *23*, 1727–1734, doi:10.1016/j.phymed.2016.10.017.
192. Ishola, I.; Olayemi, S.; Yemitan, O.; Umeh, E. Antidepressant and Anxiolytic Effects of the Methanol Root Extract of *Capparis thoningii*: Involvement of Monoaminergic, Cholinergic and GABAergic Systems. *Drug Res.* **2014**, *65*, 205–213, doi:10.1055/s-0034-1376963.
193. Qazi, N.; Khan, R.A.; Rizwani, G.H. Evaluation of antianxiety and antidepressant properties of *Carthamus tinctorius* L. (Safflower) petal extract. *Pak. J. Pharm. Sci.* **2015**, *28*, 991–995.
194. Lima, E.B.C.; de Sousa, C.N.S.; Meneses, L.N.; e Silva Pereira, Y.F.; Matos, N.C.B.; de Freitas, R.B.; Lima, N.B.C.; Patrocínio, M.C.A.; Leal, L.K.A.M.; Viana, G.S.B.; et al. Involvement of monoaminergic systems in anxiolytic and antidepressant activities of the standardized extract of *Cocos nucifera* L. *J. Nat. Med.* **2017**, *71*, 227–237, doi:10.1007/s11418-016-1053-6.
195. Sahoo, S.; Brijesh, S. Anxiolytic activity of *Coriandrum sativum* seeds aqueous extract on chronic restraint stressed mice and effect on brain neurotransmitters. *J. Funct. Foods* **2020**, *68*, 103884, doi:10.1016/j.jff.2020.103884.
196. Thomas, S.; Shrikumar, S.; Velmurugan, C.; Kumar, B.S.A. Evaluation of anxiolytic effect of whole plant of *Cuscuta reflexa*. *World J. Pharm. Pharm. Sci.* **2015**, *4*, 1245–1253.
197. Citó, M.C.O.; Silva, M.I.G.; Santos, L.K.X.; Fernandes, M.L.; Melo, F.H.C.; Aguiar, J.A.C.; Lopes, I.S.; Sousa, P.B.; Vasconcelos, S.M.M.; Macêdo, D.S.; et al. Antidepressant-like effect of *Hoodia gordonii* in a forced swimming test in mice: Evidence for involvement of the monoaminergic system. *Brazilian J. Med. Biol. Res.* **2015**, *48*, 57–64, doi:10.1590/1414-431x20144215.
198. Benneh, C.K.; Biney, R.P.; Mante, P.K.; Tandoh, A.; Adongo, D.W.; Woode, E. Maerua angolensis stem bark extract reverses anxiety and related behaviours in zebrafish—Involvement of GABAergic and 5-HT systems. *J. Ethnopharmacol.* **2017**, *207*, 129–145, doi:10.1016/j.jep.2017.06.012.
199. Narasingam, M.; Vijeeppallam, K.; Mohamed, Z.; Pandey, V. Anxiolytic- and antidepressant-like activities of a methanolic extract of *Morinda citrifolia* Linn. (noni) fruit in mice: Involvement of benzodiazepine-GABAergic, serotonergic and adrenergic systems. *Biomed. Pharmacother.* **2017**, *96*, 944–952, doi:10.1016/j.biopha.2017.11.148.
200. Murtala, A.A.; Akindele, A.J. Anxiolytic- and antidepressant-like activities of hydroethanol leaf extract of *Newbouldia laevis* (P.Beauv.) Seem. (Bignoniaceae) in mice. *J. Ethnopharmacol.* **2020**, *249*, 112420, doi:10.1016/j.jep.2019.112420.
201. Billah, M.M.; Hasan, M.R.; Nawrin, K.; Mohiuddin, M.; Habib, M.R. Evaluation of Analgesic and Sedative-anxiolytic Potential of *Paderia foetida* Leaf Extract. *Am. J. Biomed. Sci.* **2015**, *7*, 98–104, doi:10.5099/aj150200098.
202. Shahamat, Z.; Abbasi-Maleki, S.; Motamed, S.M. Evaluation of antidepressant-like effects of aqueous and ethanolic extracts of *Pimpinella anisum* fruit in mice. *Avicenna J. Phytomedicine* **2016**, *6*, 322–328.
203. Liu, A.D.; Cai, G.H.; Wei, Y.Y.; Yu, J.P.; Chen, J.; Yang, J.; Wang, X.; Che, Y.W.; Chen, J.Z.; Wu, S.X. Anxiolytic effect of essential oils of *Salvia miltiorrhiza* in rats. *Int. J. Clin. Exp. Med.* **2015**, *8*, 12756–12764.
204. Jawaid, T.; Tiwari, N.; Kamal, M.; Alkamees, O.A.; Alaseem, A.M.; Al Shagha, W.M.; Alsanad, S.M. Evaluation of Antidepressant and Anxiolytic Activity of *Solanum melongena* L. Fruits Aqueous Extract via Monoaminergic and GABAergic Pathway. *J. Pharm. Res. Int.* **2020**, doi:10.9734/jpri/2019/v31i630371.
205. Pérez-Ortega, G.; Angeles-López, G.E.; Argueta-Villamar, A.; González-Trujano, M.E. Preclinical evidence of the anxiolytic and sedative-like activities of *Tagetes erecta* L. reinforces its ethnobotanical approach. *Biomed. Pharmacother.* **2017**, *93*, 383–390, doi:10.1016/j.biopha.2017.06.064.
206. Bonilla-Jaime, H.; Guadarrama-Cruz, G.; Alarcon-Aguilar, F.J.; Limón-Morales, O.; Vazquez-Palacios, G. Antidepressant-like activity of *Tagetes lucida* Cav. is mediated by 5-HT1A and 5-HT2A receptors. *J. Nat. Med.* **2015**, *69*, 463–470, doi:10.1007/s11418-015-0909-5.
207. Cárdenas, J.; Reyes-Pérez, V.; Hernández-Navarro, M.D.; Dorantes-Barrón, A.M.; Almazán, S.; Estrada-Reyes, R. Anxiolytic and antidepressant-like effects of an aqueous extract of *Tanacetum parthenium* L. Schultz-Bip (Asteraceae) in mice. *J. Ethnopharmacol.* **2017**, *200*, 22–30, doi:10.1016/j.jep.2017.02.023.
208. Aguirre-Hernández, E.; González-Trujano, M.E.; Terrazas, T.; Herrera, J.; Guevara-Fefer, P. Anxiolytic and sedative-like effects of flavonoids from *Tilia americana* var. *mexicana*: GABAergic and serotonergic participation. *Salud Ment.* **2016**, *39*, 37–46, doi:10.17711/SM.0185-3325.2015.066.

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209. Keugong Wado, E.; Kubicki, M.; Ngatanko, A.H.H.; Léa Blondelle, K.D.; Jorelle linda, D.; Roland, R.N.; Balbine, K.; Lamshoeft, M.; Assongalem, A.E.; Foyet, H.S. Anxiolytic and antidepressant effects of *Ziziphus mucronata* hydromethanolic extract in male rats exposed to unpredictable chronic mild stress: Possible mechanisms of actions. *J. Ethnopharmacol.* **2020**, *260*, 112987, doi:10.1016/j.jep.2020.112987.
 210. Sarris, J. Herbal medicines in the treatment of psychiatric disorders: 10-year updated review. *Phyther. Res.* **2018**, *32*, 1147–1162, doi:10.1002/ptr.6055.