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REVIEW ARTICLE

New Frontiers in Huntington's Disease Treatment: Advances in Pharmacology and Molecular Understanding

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Abstract: ***Background*:** Huntington's Disease (HD) is a progressive neurodegenerative disorder marked by a triad of motor, cognitive, and psychiatric disturbances. The disease is caused by a CAG trinucleotide repeat expansion in the *HTT* gene, leading to the production of a mutant Huntingtin Protein (mHTT) that disrupts multiple cellular processes. Despite the clear genetic basis, HD currently lacks effective disease-modifying treatments. Recent years have witnessed major advancements in understanding the molecular mechanisms involved in HD pathogenesis, including aberrant protein aggregation, excitotoxicity, mitochondrial dysfunction, and impaired neurotrophic signaling, providing new avenues for therapeutic development.

***Objective*:** This review aims to synthesize and critically appraise emerging pharmacological strategies targeting key molecular pathways implicated in Huntington's disease. It focuses on recent preclinical and clinical research to highlight the therapeutic potential and challenges in translating these findings into viable treatments.

***Methods*:** A comprehensive literature review was conducted, encompassing peer-reviewed articles, clinical trial data, and recent developments in HD research. The review evaluates various pharmacological approaches, including gene silencing, modulation of protein homeostasis, neuroinflammation mitigation, and the application of gene-editing technologies such as CRISPR-Cas9. Special attention is given to recent preclinical models and ongoing clinical trials exploring both novel agents and repurposed drugs.

***Results*:** The review reveals that gene silencing strategies, such as Antisense Oligonucleotides (ASOs) and RNA interference (RNAi), show promise in reducing mHTT levels and alleviating disease phenotypes in models. Modulators of protein homeostasis aim to enhance autophagy and reduce toxic aggregates. Anti-inflammatory agents target microglial activation and cytokine dysregulation observed in HD brains. Gene-editing tools, especially CRISPR-Cas9, offer potential to directly correct the underlying genetic mutation. Additionally, several compounds are undergoing clinical trials, demonstrating varying degrees of efficacy in slowing disease progression or alleviating symptoms. Biomarker development and personalized medicine approaches are emerging as critical components for early diagnosis and treatment monitoring.

***Conclusion*:** While significant progress has been made in unraveling the molecular underpinnings of Huntington's disease and developing targeted pharmacological interventions, challenges remain in translating preclinical successes into clinical treatments. Collaborative efforts among academic institutions, pharmaceutical companies, and regulatory bodies are essential to drive forward the development of effective disease-modifying therapies. The integration of precision medicine and validated biomarkers will be key to advancing treatment efficacy and improving patient outcomes in HD.

Keywords: Huntington's disease, cholera, antidopaminergic agents, antipsychotic agents, omega- 3 fatty acids, N-methyl-D-aspartic acid receptor antagonists.

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1. INTRODUCTION

Huntington's Disease (HD) was discovered in East Hampton, Long Island, in 1872. It is a degenerative brain disorder characterized by irrational behavior, emotional distress, and cognitive decline (Cognition) [1]. Another name for it is Huntington's Chorea. Adult-onset Huntington's illness, the most prevalent type, often starts to show symptoms in a person's thirties or forties. Some of the early signs and symptoms include irritation, sadness, slight movement disorders, poor coordination, difficulties learning new information, and difficulty making judgments. Chorea, or uncontrollable jerking or twitching motions, is a common HD symptom. As the illness progresses, these motions become more pronounced [2]. Affected individuals may have difficulties talking, moving, or digesting. Some signs of this disorder include a decline in thinking and reasoning skills as well as personality changes. Adult-onset HD Patients usually survive 15 to 20 years after their symptoms start. A less common teenage form of HD begins in childhood or adolescence. It also causes mental and emotional changes and problems with movement [3]. The juvenile form can also be identified by its slow movements, awkwardness, repeated falls, stiffness, difficulty speaking, and drooling. Academic performance suffers as one's ability to think and reason deteriorates. Seizures are experienced by 30 % to 50% of kids who have this condition. Juvenile HD patients typically have a lifespan of 10 to 15 years from the onset of symptoms, and the disease advances faster than in adults [4].

2. METHODOLOGY

A comprehensive literature review was conducted to identify and evaluate emerging pharmacological strategies targeting key molecular pathways implicated in Huntington's Disease (HD). The search strategy involved querying electronic databases, including PubMed, Scopus, Web of Science, and ClinicalTrials.gov, for peer-reviewed articles, preclinical studies, and clinical trial data published between 2010 and 2025. Search terms included combinations of "Huntington's disease," "mutant huntingtin," "gene silencing," "antisense oligonucleotides," "RNA interference," "CRISPR-Cas9," "neuroinflammation," "autophagy," "protein aggregation," and "pharmacological treatment." Additional manual searches of reference lists from relevant articles were performed to ensure comprehensive coverage of the literature. Study selection was based on predetermined inclusion criteria, focusing on studies that investigated pharmacological interventions targeting the molecular mechanisms of HD in either preclinical models or clinical settings. Only original research articles, clinical trials, and high-quality reviews published in English were included. Exclusion criteria involved studies lacking experimental data, articles not specific to HD, and non-pharmacological or purely behavioral interventions. Both novel and repurposed drug candidates were considered, with special emphasis on those advancing toward or currently in clinical trials. Data extraction and synthesis were performed systematically, with relevant information from selected studies categorized according to therapeutic approach-such as gene silencing, modulation of protein homeostasis, anti-inflammatory strategies, and gene-editing technologies. Key data points included the mechanism of action, study model, dosage and administration, outcomes measured, and reported efficacy or safety concerns. Findings were critically appraised to identify trends, therapeutic potential, limitations, and challenges in translating preclinical findings into clinical success. The synthesis aimed to provide a balanced and up-to-date overview of the current pharmacological landscape in HD research, highlighting both the promise and the complexity of therapeutic development.

3. GENE-SILENCING TECHNOLOGIES AND GENE-EDITING TOOLS AS EMERGING THERAPEUTICS FOR HUNTINGTON'S DISEASE

Huntington's Disease (HD) is caused by a CAG trinucleotide repeat expansion in the Huntingtin (*HTT*) gene, leading to the production of a mutant Huntingtin (mHTT) protein with toxic gain-of-function properties. Since the root cause is a genetic mutation, molecular approaches aimed at reducing mutant protein expression or correcting the defective gene have gained significant attention.

3.1. Gene-Silencing Approaches

The primary aim is to lower the levels of mHTT transcripts and protein, thereby reducing neurotoxicity. Antisense Oligonucleotides (ASOs) are one of the most advanced strategies in this regard. They are short, synthetic nucleic acids designed to bind complementary sequences in the *HTT* mRNA, leading to its degradation *via* RNase H-mediated cleavage. Clinical trials, such as those investigating *tominersen* (developed by Ionis Pharmaceuticals/Roche), have provided important proof-of-concept evidence, although results have been mixed due to challenges with long-term efficacy and tolerability. Another promising silencing approach involves RNA interference (RNAi), where small interfering RNAs (siRNAs) or microRNA (miRNA) mimics are delivered to selectively target and degrade *HTT* transcripts. Viral vector–mediated RNAi delivery into the striatum has shown sustained mHTT suppression in preclinical models. Importantly, allele-selective silencing strategies are being developed to preferentially target the mutant allele while sparing the wild-type *HTT*, which is essential given the normal protein's critical cellular roles.

Gene-editing technologies, particularly CRISPR-Cas9, hold potential to directly modify the underlying mutation. CRISPR-Cas9 can be engineered to selectively excise or contract the expanded CAG repeats within the *HTT* gene, thereby reducing pathogenic protein production. Preclinical studies in HD mouse models have demonstrated that CRISPR-mediated editing reduces mHTT levels and ameliorates behavioral and neuropathological phenotypes. Moreover, newer Cas variants such as Cas12 and Cas13 allow more precise targeting of either DNA or RNA, respectively, broadening therapeutic possibilities. RNA-targeting Cas13, for example, offers transient suppression of mHTT without permanent genome alterations, potentially improving safety. Challenges remain, however, including efficient and safe delivery to neurons, minimizing off-target edits, and ensuring long-term therapeutic benefit.

Together, gene-silencing and gene-editing approaches represent a paradigm shift from symptomatic management

toward disease-modifying therapies. While still in early clinical stages, they highlight the possibility of directly addressing the root genetic cause of HD. Continued optimization of delivery systems (*e.g.*, adeno-associated viral vectors, lipid nanoparticles), improvement in allele selectivity, and rigorous evaluation of safety profiles are critical steps before these innovative therapies can be translated into routine clinical practice.

3.2. Symptoms

HD symptoms are three symptoms: motor, cognitive, and mental that often present between the ages of 30 and 50, though they can occur at any age. In 50% of instances, psychiatric symptoms come on first. The terms early, middle, and late stages, with a prodromal phase earlier, are widely employed to describe their progression. Early symptoms typically come before motor symptoms and include small personality alterations, issues with impatience, physical prowess, emotional swings, and cognitive abilities. Although practically everyone with HD experiences the same physical symptoms over time, there are significant individual differences in the onset, course, and severity of cognitive and behavioral problems [5]. The most obvious early physical sign of chorea is jerking, irregular, and unpredictable movement. Many people struggle with or are unaware of their involuntary movements. A lack of coordination, general restlessness, little unfinished or purposely initiated movements, or slower saccadic eye movements might all be the first signs of chorea. Three years often pass before more glaring symptoms of motor impairment appear. As the disease worsens, symptoms including rigidity, writhing movements, or odd posturing become more obvious. These are symptoms of movement system dysfunction in the brain. As psychomotor abilities decline, any movement that requires concentration decreases [6]. Common side effects include physical unsteadiness, unusual facial expressions, and difficulty speaking, eating, swallowing, and chewing. Other typical symptoms include losing weight and having trouble sleeping. Weight loss due to eating disorders is common and can result in malnutrition. The Westphal type of sluggishness, stiffness, and tremors, as well as seizures, is more prevalent in juvenile HD. Typically, juvenile HD advances more quickly and results in more cognitive deterioration. Dementia develops as cognitive capacities decline over time. Particularly affected are executive processes like planning, cognitive adaptability, abstract thought, rule acquisition, appropriate action initiation, and unsuitable action inhibition. Memory loss is frequent as the illness worsens [7]. There have been reports of difficulty with working memory as well as short-term and long-term memory disorders, procedural memory, and episodic memory (remembering one's life). As neuropsychiatric symptoms, anxiety, depressive disorders, diminished emotional expression, egocentrism, hostility, and compulsive behavior have all been documented. The latter can trigger or exacerbate addictions, including alcoholism, gambling, and hypersexuality. People have reportedly had trouble identifying other people's unpleasant facial expressions. Between studies, there is a large variation in the incidence of these symptoms, with 33 to 76% lifetime prevalence rates for psychiatric illnesses [8]. Early behavioral changes in HD raise the likelihood of suicide. People commonly underestimate chorea, cognitive, and emotional deficits. The body expresses huntingtin, and abnormalities of peripheral tissue brought on by its expression outside of the brain have been related to huntingtin mutations. Testicular atrophy, osteoporosis, decreased glucose tolerance, weight loss, and muscle atrophy are a few of the problems [9].

3.3. Pathophysiology

In HD, there is a decrease in the levels of neurotransmitters like GABA (gamma-aminobutyric acid) and substance P. Additionally, the inhibitory medium spiny neurons in the corpus striatum also experience cell death (Fig. **1**). The amino acid glutamine is coded for by the DNA sequence CAG, which repeats abnormally as a result of a mutation in the gene for Huntingtin (HTT) (on chromosome 4) [10]. Huntingtin, the gene's byproduct, is a large protein with a lengthy stretch of polyglutamine residues that builds up inside neurons and causes disease by an unidentified method. The disease manifests more severely and earlier when there are more CAG repeats. When the mutation is passed down through the father, the amount of Cytosine, Adenine, and Guanine (CAG) repeats can increase with every subsequent generation, leading to families with progressively more severe phenotypes [11]. Various treatments used in HD are shown in Fig. (**2**). The pathophysiology of HD is primarily associated with an abnormal expansion of a specific DNA sequence, Cytosine-Adenine-Guanine (CAG), within the gene. The mutated HTT gene leads to the production of a mutant form of the Huntingtin (mHTT) protein. The accumulation of mHTT disrupts various cellular processes, leading to widespread dysfunction in the brain [12]. One key aspect of HD pathology is the preferential loss of neurons in the striatum, a region involved in motor control and cognition. The mHTT protein is believed to undergo abnormal processing, forming toxic fragments that aggregate within neurons, contributing to cellular dysfunction and eventual neuronal death. Additionally, there is evidence of impaired neurotransmitter regulation, mitochondrial dysfunction, and altered gene expression in HD. The progressive degeneration of neurons, particularly in the striatum and other brain regions, results in the characteristic motor symptoms, cognitive decline, and psychiatric disturbances observed in individuals with HD. The complex interplay of genetic and molecular factors underscores the intricate pathophysiology of Huntington's disease [13].

3.4. Antidopaminergic Agents

An imbalance in dopamine levels in the brain is a hallmark of the genetic neurodegenerative condition HD. Movement abilities depend on the neurotransmitter dopamine, a signaling molecule. Patients with HD are thought to experience chorea, or uncontrollable jerking or writhing motions, as a result of exceptionally high dopamine levels [14]. As the illness worsens, dopamine levels may drastically decline. Unusually low levels of dopamine reduce chorea but result in symptoms resembling Parkinson's disease, such as akinesia, or the loss of voluntary muscle movement. Antidopaminergic medications are used to treat the symptoms of chorea, but they also run the risk of speeding up the disease's course by decreasing dopamine action below a key level (Fig. **3**) [15].

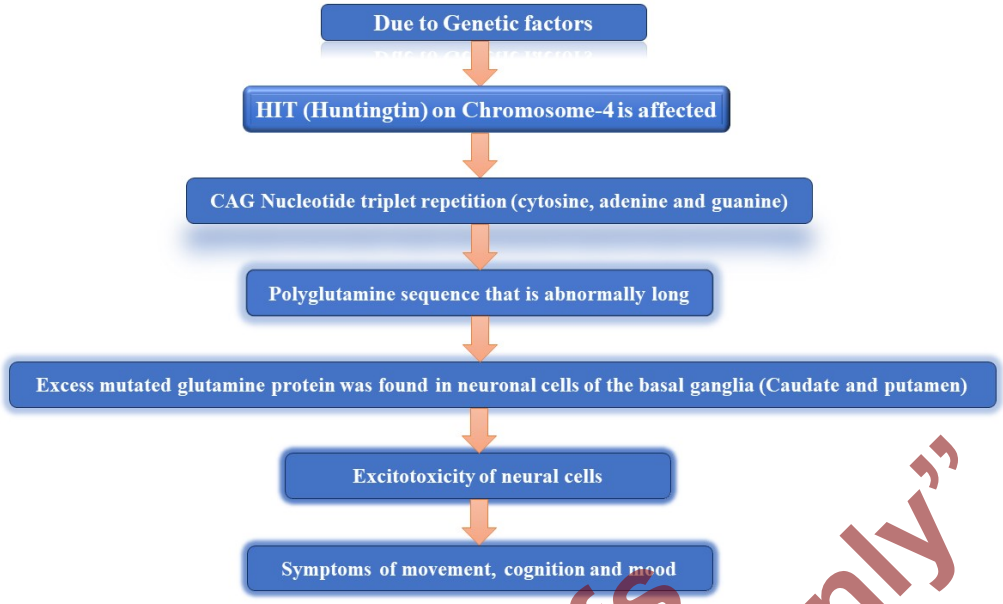

Fig. (1). Visual representation outlining the pathophysiology of Huntington's Disease. This illustration demonstrates the progressive neurodegenerative process involving the striatum and cortical regions, characterized by the loss of neurons, particularly in the medium spiny neurons, resulting from the mutant huntingtin protein's toxic effects, leading to motor, cognitive, and psychiatric manifestations. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

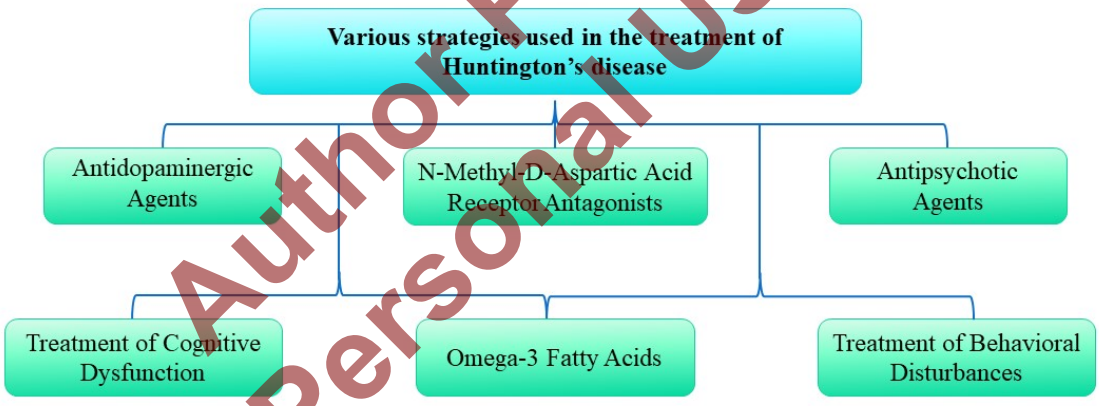

Fig. (2). Overview of diverse treatment strategies employed in Huntington's Disease. This figure highlights multifaceted therapeutic approaches encompassing symptomatic management, pharmacological interventions targeting neurotransmitter systems, gene silencing techniques, and supportive care utilized in addressing motor, cognitive, and psychiatric symptoms associated with Huntington's Disease. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

There are two main ways that antidopaminergic drugs function, and both of them obstruct how dopamine acts in the brain. Nerve cells store dopamine in vesicles until it is released. These vesicles need to contain dopamine, which is packaged inside by a group of proteins known as Vesicular Monoamine Transporters (VMATs). Drugs that are antidopaminergic first bind to the VMAT proteins to stop them from storing a lot of dopamine inside the vesicles. Dopamine release and propagation to additional adjacent neurons are decreased as a result. Dopamine interacts with nerve cells by attaching to dopamine receptors. These substances function in a second way by preventing dopamine from attaching to its receptors [16]. To treat chorea symptoms in HD, the FDA has approved the antidopaminergic drugs Xenazine (tetrabenazine) and Austedo (deutetrabenazine). They work by blocking dopamine receptors and VMAT proteins. Austedo shares a chemical structure with Xenazine; however, it is more stable. A clinical study from the Enroll-HD group in which approximately 500 HD patients being treated with antidopaminergic medication and 500 patients who were not were recruited for assessments of motor, cognitive, and psychiatric measurements. They found that patients taking antidopaminergic medication had a slower progression in chorea and irritability compared with those not taking such medications. However, this same group also displayed a significantly greater rate of decline in a range of cognitive tasks [17].

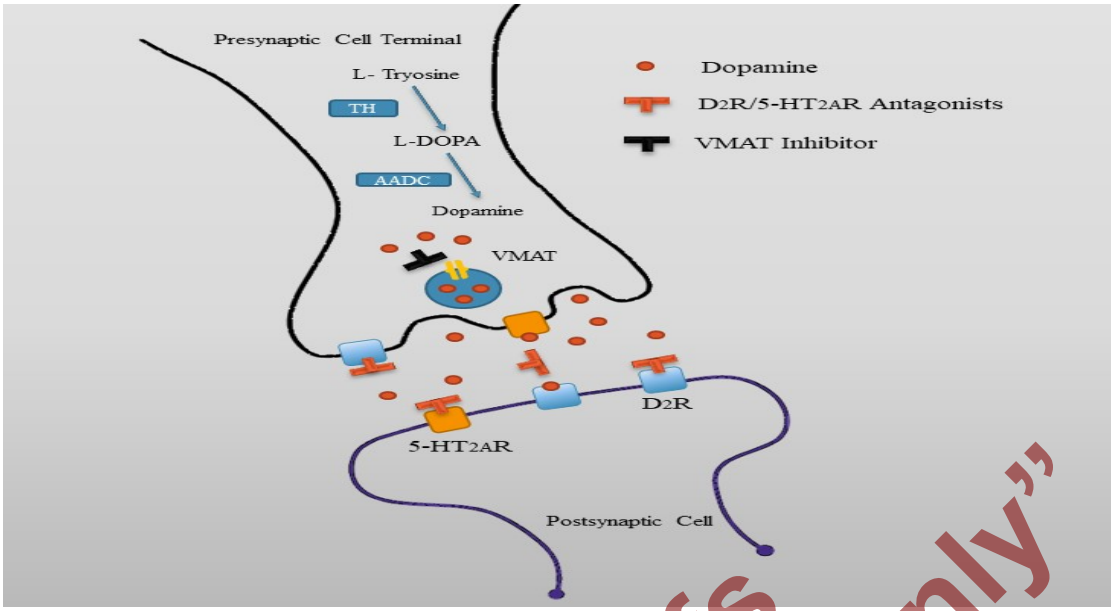

Fig. (3). Schematic representation depicting the mechanism of action of antidopaminergic agents. These compounds inhibit dopamine receptors, thereby modulating neurotransmission and affecting various physiological processes. **Abbreviations:** TH - Tyrosine Hydroxylase, AADC - Aromatic L-amino Acid Decarboxylase, VMAT - Vesicular Monoamine Transporter, D2R - Dopamine D2 Receptor, 5-HT2AR - 5-Hydroxytryptamine 2A Receptor (Serotonin 2A Receptor). *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

3.5. Antipsychotic Agents (APA)

Patients with HD who exhibit psychotic behavior, such as delusions, *etc*. Medications may also be used to manage behavioral problems, including irritability and chorea, which are movement signs of HD. APA can be divided into two categories: conventional APA and atypical APA. The chemical messenger dopamine, which-when it is hyperactive-is thought to produce symptoms of psychosis. A primary generation antipsychotic called Haldol (haloperidol) is used to treat HD [18]. Second-generation APA includes the following: Geodon (ziprasidone), Risperdal, Clozapine, risperidone, quetiapine, aripiprazole, and olanzapine. Antipsychotic medications can cause sleepiness, vertigo, postural hypotension (low blood pressure upon standing from a seated or lying position), abnormal heartbeats, sexual dysfunction, and sudden cardiac arrest. One type of side effect associated with first-generation APA is known as extrapyramidal symptoms. Parkinson's disease symptoms, dystonia symptoms, dyskinesia symptoms, and akathisia symptoms are among these (Fig. **4**) [19].

2nd generation APAs are more likely to have adverse metabolic consequences, such as weight gain, raised blood sugar levels, and increased cholesterol, all of which can result in diabetes mellitus. Patients using APA are often closely monitored due to these adverse effects, and they may need to undergo routine tests to make sure their medicine levels are within safe ranges. Regular use of antipsychotic medicines is recommended. Before symptoms start to get better, taking medication consistently for around six months is necessary [20].

3.6. Omega-3 Fatty Acids

EPA (Eicosapentaenoic Acids: Fig. **5**) is converted into docosahexaenoic acid after that (DHA; Fig. **6**). DHA, which has 22 carbons and 6 double bonds, is considered to be more significant. It has been shown that omega-3 fatty acids alter cell behavior. Signaling and cell membrane shape, ultimately acting as antidepressants (Fig. **5**) [21].

Transgenic mice were developed that underwent the transformation of omega-6 to omega-3 fatty acids in order to analyze the amounts of omega-3 fatty acids in the brain and their impact on neurogenesis. As a result, their brain's DHA concentration rose, which is associated with improved performance on learning and memory tests and neurogenesis in the hippocampus. Recent research has focused on genetic variants that, when subjected to proinflammatory cytokine therapy, increase the likelihood of experiencing depressive episodes. The occurrence of inflammatory processes when receiving interferon therapy is linked to a higher chance of developing depression. In response to immunological activity, there are known genotypes linked to higher EPA and DHA levels (Fig. **6**) [22]. The TREND-HD study investigated the effects of treating patients with Huntington's Disease (HD) using omega-3 fatty acids. The trial aimed to assess whether these compounds could potentially modify the progression of HD, a neurodegenerative disorder. The results of the TREND-HD study suggested some promising outcomes, although the findings were not definitive. While there were indications of potential benefits in certain aspects of the disease's progression, such as improved cognitive function and motor performance, the overall impact of omega-3 fatty acids on modifying the course of HD remained inconclusive [23]. It is important to note that the study faced certain limitations, including sample size and variations in individual responses to treatment. Therefore, while the TREND-HD study provided some initial insights into the potential benefits of omega-3 fatty acids for HD patients, further research with larger cohorts and longer durations may be necessary to establish more concrete conclusions regarding their efficacy in managing this condition [24].

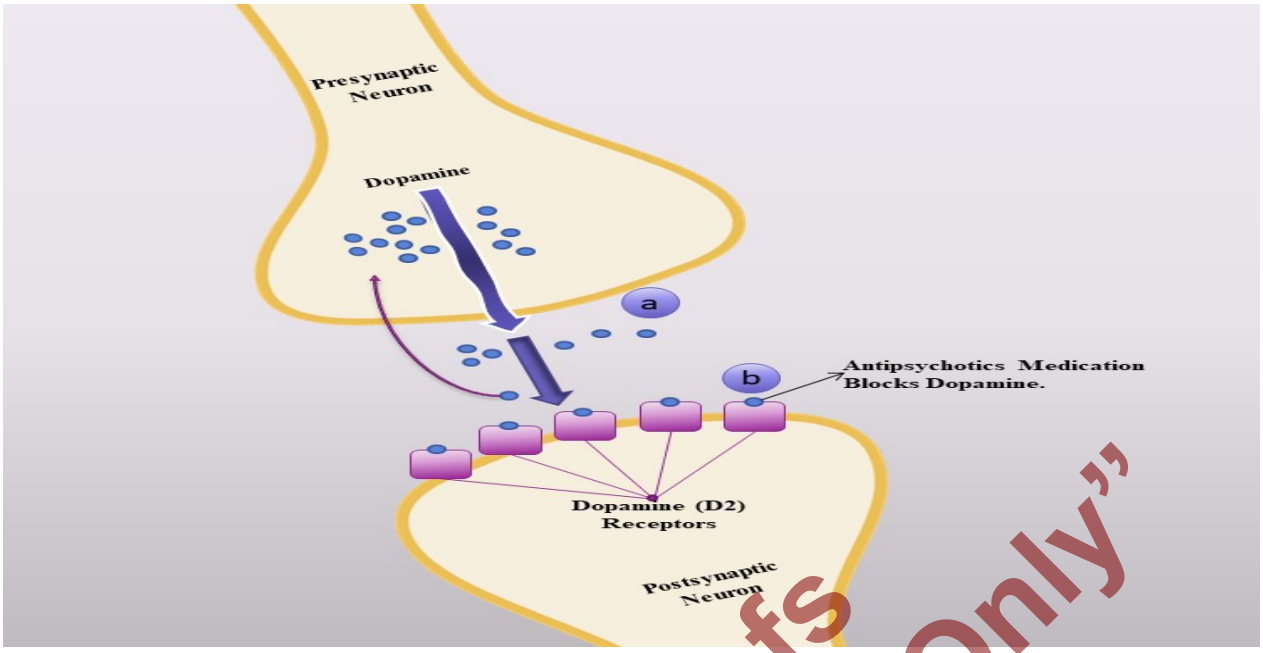

Fig. (4). Illustration outlining the mechanism of action of antipsychotic agents. These medications primarily block dopamine receptors, influencing neurotransmission and mitigating psychotic symptoms by modulating dopaminergic activity in the brain. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

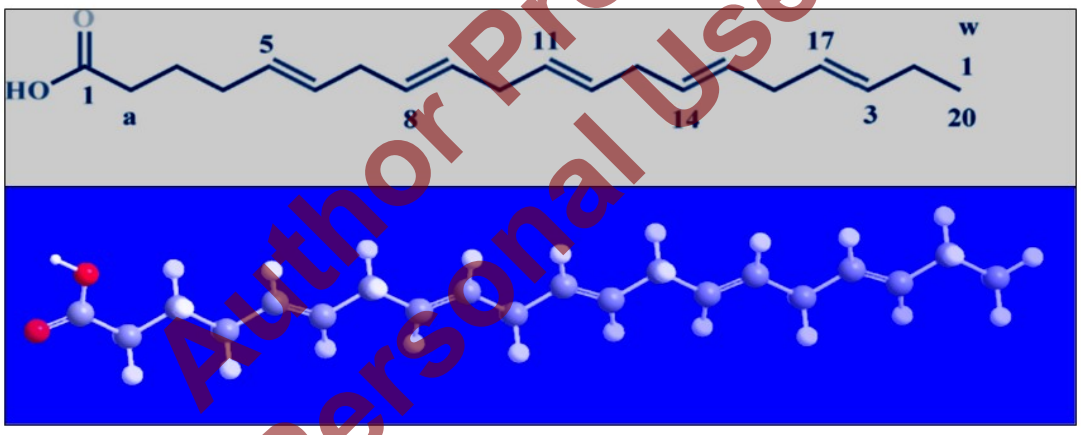

Fig. (5). Three-dimensional molecular structure representation showcasing the optimized geometry of Eicosapentaenoic Acid (EPA), highlighting its spatial arrangement, atomic positions, and structural conformation. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

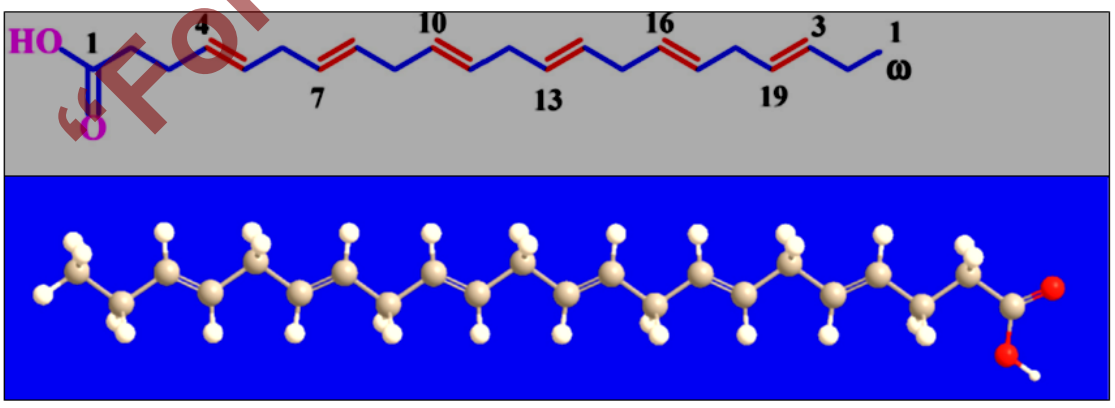

Fig. (6). Visualization of the optimized three-dimensional molecular structure of Docosahexaenoic Acid (DHA), revealing its spatial configuration, atomic arrangement, and structural conformation for scientific analysis and understanding. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

The FADS1 and FADS2 genes are among those with genetic variations that influence omega-3 fatty acid metabolism. Desaturases, which are typical and necessary for the metabolism of omega-3 and omega-6 fatty acids, are encoded by these genes. A higher risk of developing cardiovascular disease and greater inflammation is linked to specific haplotypes. These haplotypes are likely to be in charge of some important inter-individual differences. These haplotypes are likely responsible for certain important inter-individual differences. It is not yet clear whether these genes contribute to the onset of depression or if they can be used to predict antidepressant therapy responses to omega-3 fatty acids. They may also be associated with conditions such as type II Bipolar Disorder (BD II) and Bipolar Spectrum Disorder (BSD). One study examined 20 patients with moderate to severe depression to investigate the correlation between their depression severity and the ratio of omega-3 to omega-6 fatty acid levels in plasma and erythrocyte phospholipids. It was discovered that the degree of depression was highly linked with the ratio of red blood cell arachidonic acid to EPA. A substantial inverse relationship between erythrocyte EPA and depression was also found [25]. However, the scientists concluded that variations in dietary EPA intake did not account for these effects solely. In the rat brain, valproic acid treatment over an extended period of time reduces arachidonate synthesis. A decrease in the formation of lithium arachidonate was correlated with a decrease in the gene expression and activity of the cytosolic phospholipase A2 enzyme, which exclusively releases omega-3 but not arachidonic fatty acids from phospholipids (Fig. **7**).

The brain's concentration of prostaglandin E2 and cyclooxygenase-2 is decreased by lithium. This research suggests that arachidonic acid, a component of the inflammatory pathway that is overexpressed in manic states, may be a mechanism by which lithium and anticonvulsants work. DHA and EPA can use two possible mechanisms to inhibit the synthesis of eicosanoids from their precursor arachidonic acid. The first is that they diminish the levels of both cellular and plasma arachidonic acid by combining with it to create membrane-based phospholipids [26]. Another theory is that EPA and arachidonic acid may compete for the cyclooxygenase enzyme system, which would prevent the production of prostaglandin E2, thromboxane B2, and other proinflammatory eicosanoids from arachidonic acid (such as leukotrienes and thromboxanes). Additionally, eicosanoid discharge-influenced proinflammatory cytokine release, which has been associated with depression and bipolar disorder, is inhibited by DHA and EPA. These cytokines include interferon, Tumour Necrosis Factor (TNF), Interleukin (IL)-1, IL-2, and IL-6. EPA may lower IL-1 and TNF- *via* blocking nuclear factor-B, according to some research. Additionally, EPA decreases the activity of the protein 1 transcription factor by blocking the upstream Mitogen-Activated Protein Kinase (MAPK) pathway. Omega-3 fatty acids are thought to control transcription by lowering protein-1 expression by inhibiting JNK, ERK, and MAPK protein phosphorylation. Fatty acids, omega-3, are also suggested to contribute to the inhibition of nuclear factor-B translocation brought on by IB phosphorylation. CYP2C9 and CYP2C19 are two hepatic enzymes that facilitate drug metabolism. The EPA has been shown to have a restrictive effect on both. CYP2D6 and CYP3A4, which are crucial for the metabolism of drugs, may be inhibited at high concentrations [27].

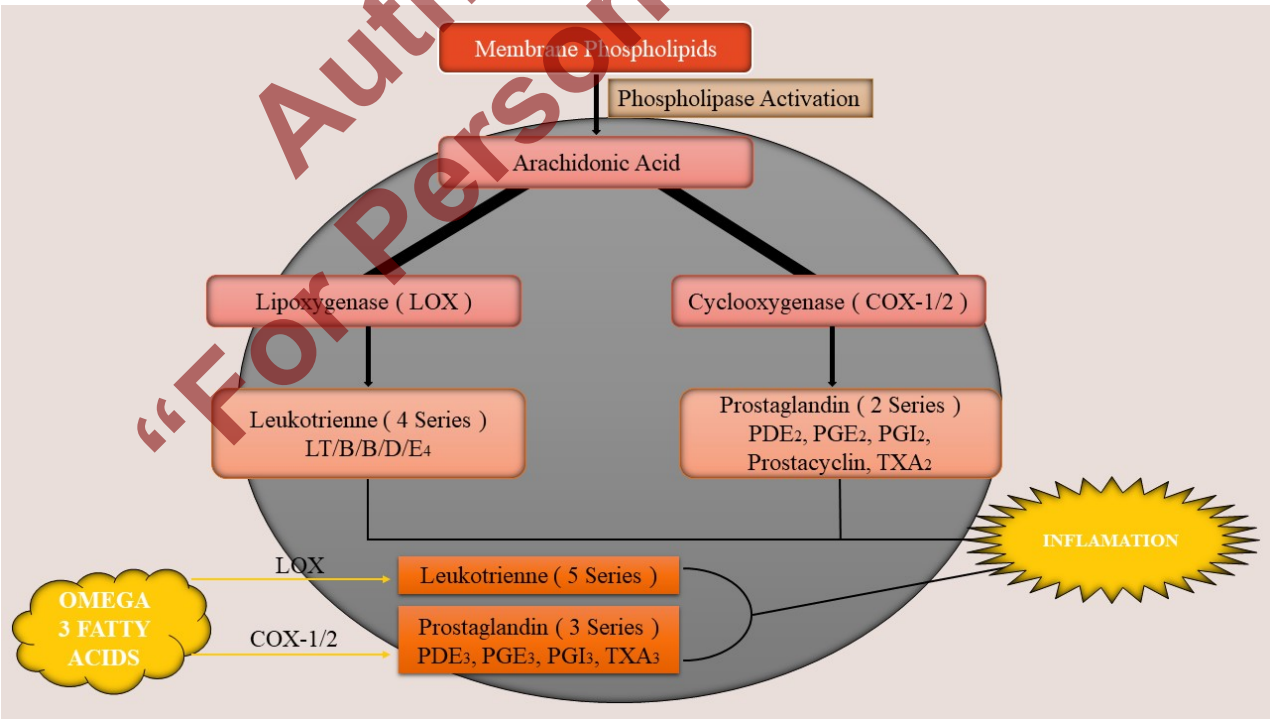

Fig. (7). Schematic representation elucidating the mechanism of action of omega-3 fatty acids in combating inflammation. Omega-3 fatty acids interfere with pro-inflammatory pathways, modulating immune responses and promoting the resolution of inflammation through various molecular mechanisms. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Huntington's Disease (HD) is mostly inherited, and the age when symptoms start and their severity are linked to a genetic factor called CAG repeat length. However, there are other genetic and environmental factors influencing when symptoms appear and how they progress. One such factor is the level of a protein called mHTT. Diet may also play a role in HD, with some evidence suggesting that a diet rich in ω-3 Polyunsaturated Fatty Acids (PUFAs) could be beneficial. The balance between ω-3 and ω-6 PUFAs in the diet seems important. A high ω-6: ω-3 ratio, common in Western diets, is associated with health issues like cardiovascular diseases, cancer, and inflammation. In countries like Japan and Greece, where the ratio is lower, the prevalence of HD is also lower. On the contrary, the United States and the United Kingdom, with high ratios, have a higher prevalence of HD. Research suggests a link between ω-3 PUFA consumption and the incidence of HD in different regions. For instance, countries with lower ω-3 levels, like the U.S. and the U.K., have higher HD rates. Meanwhile, Japan and Greece, with higher ω-3 levels, have lower HD prevalence [28]. However, it is essential to note that this does not prove causation. Apart from potential HD links, ω-3 PUFAs have shown benefits for mental health. They possess anti-inflammatory effects, reducing the risk of neurological and psychiatric diseases like Alzheimer's, Parkinson's, and depression. ω-3 PUFAs also have a history of improving mood disorders, such as anxiety, and may contribute to lower incidences of dementia and better cognitive performance. In the context of HD, patients experience physical impairments affecting body mass and cognitive issues similar to mild cognitive impairment. Additionally, they may suffer from psychological disorders impacting mood and behavior. Therefore, studying the effects of ω-3 PUFAs on HD could be beneficial, given their positive impact on other neurological conditions [29].

3.7. Omega-3 Fatty Acids and their Therapeutic Roles in Huntington's Disease

Omega-3 Polyunsaturated Fatty Acids (PUFAs), particularly Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), have been widely investigated for their neuroprotective effects in neurodegenerative disorders, including Huntington's Disease (HD). These fatty acids are integral components of neuronal cell membranes, where they regulate fluidity, synaptic function, and signaling pathways critical for neuronal survival. Their therapeutic potential in HD arises from multiple mechanisms that target the underlying pathogenic processes of the disease.

Firstly, omega-3 fatty acids exhibit anti-inflammatory properties by modulating microglial activation and reducing pro-inflammatory cytokine release. This is particularly relevant to HD, where chronic neuroinflammation contributes to striatal and cortical neurodegeneration. Secondly, omega-3s exert antioxidant effects, reducing oxidative stress by scavenging reactive Oxygen Species (ROS) and enhancing mitochondrial function, both of which are disrupted in HD pathology. DHA, in particular, has been shown to stabilize mitochondrial membranes, improve energy metabolism, and reduce excitotoxic damage.

Another important role is in synaptic plasticity and neurogenesis. Omega-3 supplementation has been associated with increased expression of Brain-Derived Neurotrophic Factor (BDNF), a critical molecule for neuronal survival and synaptic maintenance that is markedly reduced in HD. By enhancing BDNF signaling, omega-3s may promote neuronal resilience and slow disease progression. Additionally, EPA and DHA have been implicated in modulating neurotransmitter systems, including dopamine and glutamate, thereby potentially ameliorating motor and cognitive symptoms of HD.

Clinical studies, though limited, provide supportive evidence. For example, trials of ethyl-EPA supplementation have suggested modest improvements in motor scores and neuropsychiatric symptoms in HD patients, though larger, long-term studies are required for conclusive results. Importantly, omega-3 fatty acids are generally safe, well-tolerated, and can be delivered through dietary supplementation, making them attractive adjunctive therapies.

Overall, while omega-3 fatty acids are not curative, their multi-targeted neuroprotective actions-spanning anti-inflammatory, antioxidant, mitochondrial, and neurotrophic effects-make them promising candidates for slowing HD progression and improving quality of life. Continued preclinical and clinical investigations are warranted to establish optimal dosing, formulation, and treatment duration.

3.8. N-Methyl-D-Aspartic Acid Receptor Antagonists

We no longer need to limit our understanding of depression psychopharmacology to the route of the serotonin receptor. The NMDA and opioid receptor signalling pathways, among others, have lately been found to be important in the neurophysiology of depression (Fig. **8**). Numerous studies have demonstrated the effectiveness of the phencyclidine compound ketamine in treating depression [30].

Ketamine, a drug with two primary categories of mechanisms, is under consideration. These include the alteration of neurotransmitters and the intracellular signaling or modulation of neurotrophic factors. Table **1** displays synthetic drugs with appropriate mechanisms of action and side effects for treating Huntington's Disease (HD). The use of NMDAR (N-methyl-D-aspartate receptor) antagonists in Huntington's Disease (HD) has garnered considerable attention as a potential therapeutic approach. Numerous studies have highlighted the relevance of NMDARs as a target for HD treatment, emphasizing their involvement in the pathophysiology of the disease. Several preclinical studies have demonstrated the dysregulation of NMDAR-mediated signaling pathways in HD, contributing to excitotoxicity and neuronal damage. This has spurred interest in exploring NMDAR antagonists as a means to mitigate these effects and potentially slow down the progression of the disease [31].

Clinical trials investigating NMDAR antagonists, such as memantine, in HD patients have been conducted. For instance, the trial carried out by Forrest Pharmaceuticals in 2010 aimed to evaluate the efficacy and safety of memantine in treating HD. Memantine, an NMDAR antagonist commonly used in Alzheimer's disease, was hypothesized to have potential neuroprotective effects in HD due to its ability to modulate glutamate transmission [32]. However, despite

initial enthusiasm, results from some of these clinical trials have been mixed, with varying degrees of success in demonstrating significant benefits in HD patients. Some trials showed modest improvements in certain symptoms like cognitive function or motor abilities, while others did not achieve the desired outcomes. The complexity of HD and the multifaceted nature of NMDAR involvement in the disease's progression present challenges in developing effective treatments. While NMDAR antagonists like memantine hold promise, further research is needed to understand their mechanisms of action better, optimize dosing regimens, and identify specific subgroups of HD patients who might benefit most from this type of intervention. This ongoing exploration underscores the need for continued clinical trials and research efforts to elucidate the potential of NMDAR antagonists as a viable therapeutic avenue for HD [33].

Investigated the treatment of a disease called HD using various plants. In Table **2**, they list different kinds of plants that were used in the treatment. It was found that all parts of these plants were helpful in treating HD, and most researchers preferred using a model of HD induced by something called 3NP. These plants have different natural compounds in them, like primary and secondary metabolites, that are responsible for fighting the disease. For future researchers, these plants could be a good starting point to explore for potential treatments. Table **3** shows some of these medicinal plants, how they might work to treat the disease, and the models they were tested on, like animals or cells in a lab [35].

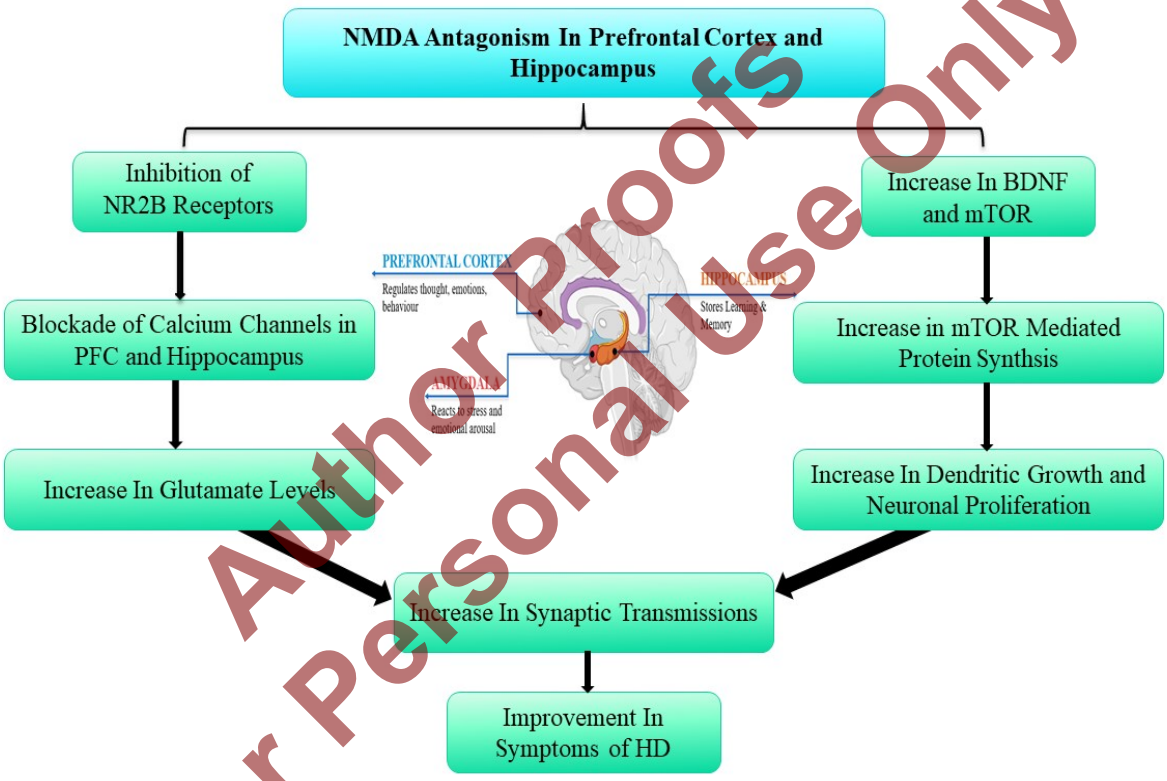

Fig. (8). Visual representation detailing the mechanism of action of NMDA (N-Methyl-D-aspartate). NMDA functions as a receptor for the neurotransmitter glutamate, playing a crucial role in synaptic plasticity, learning, and memory by regulating calcium influx and neuronal excitability. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 1. List of synthetic drugs with proper MOA and side effects to treat HD.

Drug Class	Examples	Mechanism of Action (MOA)	Side Effects
ACE Inhibitors (Angiotensin-Converting Enzyme Inhibitors)	Lisinopril, Enalapril, Ramipril, Captopril	Inhibit the ACE enzyme, reducing the conversion of angiotensin I to angiotensin II, leading to vasodilation, decreased blood volume, and lower blood pressure	- Dry cough- Hyperkalemia- Hypotension- Dizziness- Angioedema (rare)- Fatigue [34]
Angiotensin II Receptor Blockers (ARBs)	Losartan, Valsartan, Irbesartan, Olmesartan	Block Angiotensin II Receptors (AT1), preventing angiotensin II from constricting blood vessels, leading to vasodilation and reduced blood pressure	- Dizziness- Hyperkalemia- Fatigue- Headache- Angioedema (rare)

(Table 1) Contd…

Drug Class	Examples	Mechanism of Action (MOA)	Side Effects
Calcium Channel Blockers (CCBs)	Amlodipine, Diltiazem, Verapamil, Nifedipine	Inhibit calcium entry into vascular smooth muscle and cardiac muscle, leading to vasodilation and decreased heart rate (depending on subtype)	- Peripheral edema- Dizziness- Constipation (especially with verapamil)- Flushing- Headache
Diuretics (Thiazide Diuretics)	Hydrochlorothiazide, Chlorthalidone, Indapamide	Inhibit sodium reabsorption in the distal tubules of the kidneys, leading to increased excretion of sodium, water, and a reduction in blood volume	- Hypokalemia- Dehydration- Hyperuricemia (can lead to gout)- Dizziness- Hyperglycemia (rare)
Beta-Blockers	Metoprolol, Atenolol, Carvedilol, Bisoprolol	Block beta-adrenergic receptors in the heart, reducing heart rate and cardiac output, leading to reduced blood pressure	- Fatigue- Bradycardia- Dizziness- Depression- Sexual dysfunction- Cold extremities
Alpha-1 Blockers	Doxazosin, Prazosin, Terazosin	Block alpha-1 adrenergic receptors in vascular smooth muscle, causing vasodilation and reducing peripheral resistance	- Orthostatic hypotension (especially after the first dose)- Dizziness- Fatigue- Reflex tachycardia
Direct Vasodilators	Hydralazine, Minoxidil	Directly relaxes the smooth muscles of blood vessels, causing vasodilation and lowering blood pressure	- Tachycardia- Fluid retention (edema)- Headache- Dizziness- Lupus-like symptoms (hydralazine)
Renin Inhibitors	Aliskiren	Inhibit renin, an enzyme that activates the renin-Angiotensin-Aldosterone System (RAAS), leading to vasodilation and reduced blood pressure	- Diarrhea- Hyperkalemia- Dizziness- Cough (rare)- Rash
Central Alpha-2 Agonists	Clonidine, Methyldopa	Stimulate alpha-2 adrenergic receptors in the brainstem, reducing sympathetic outflow, causing vasodilation, and lowering blood pressure	- Sedation- Dry mouth- Dizziness- Bradycardia- Rebound hypertension if abruptly stopped

Table 2. Plants reported in Huntington's disease treatment.

Plant Name	Active Component(s)	Mechanism of Action	Reported Effects	References
Hypericum perforatum (St. John's Wort)	Hypericin, Hyperforin	Modulates neurotransmitter activity (serotonin, dopamine, and norepinephrine), and exhibits antioxidant effects	- Potential neuroprotective effects- Antidepressant effects (may help manage mood disorders in HD)	- NAMI *et al*. 2007
Ginkgo biloba	Flavonoids (quercetin, kaempferol), Terpenoids	Antioxidant, anti-inflammatory, and neuroprotective effects. Enhances cerebral blood flow and regulates neurotransmitter activity	- Cognitive enhancement- Improved blood flow to the brain- Neuroprotective effects	- Muthuraman *et al*. 2017
Withania somnifera (Ashwagandha)	Withanolides	Neuroprotective, reduces oxidative stress, modulates neurotransmitter levels, and enhances brain function	- Reduces oxidative stress- Potential neuroprotective effects- Improves motor coordination	- Zeng *et al*. 2015, Chopra *et al*. 2019
Curcuma longa (Turmeric)	Curcumin	Potent antioxidant and anti-inflammatory. Inhibits neuroinflammation and reduces oxidative stress	- Neuroprotective effects- Reduces inflammation- Potential to slow neurodegeneration	- Lee *et al*. 2011, Hsieh *et al*. 2012
Panax ginseng	Ginsenosides	Modulates dopaminergic and other neurotransmitter systems and has neuroprotective and anti-inflammatory effects	- Cognitive function improvement- Antioxidant effects- Potential neuroprotective effects	- Lee *et al*. 2012
Boswellia serrata (Frankincense)	Boswellic acids	Exhibits anti-inflammatory effects *via* 5-lipoxygenase inhibition and reduces neuroinflammation	- Anti-inflammatory- Reduces oxidative stress- Potential neuroprotective effects	- Prakash *et al*. 2012
Silybum marianum (Milk Thistle)	Silymarin (silibinin)	Antioxidant, anti-inflammatory, and hepatoprotective effects. Potential to reduce oxidative damage in the brain.	- Neuroprotective- Reduces oxidative damage- May help mitigate liver damage in HD patients	- Kim *et al*. 2016
Valeriana officinalis (Valerian)	Valerenic acid	Displays GABAergic activity and modulates neurotransmitter systems	- Reduces anxiety- Promotes relaxation- Sleep aid (potentially useful for managing HD-related insomnia)	- Zeng *et al*. 2015

(Table 2) Contd…

Plant Name	Active Component(s)	Mechanism of Action	Reported Effects	References
Crocus sativus (Saffron)	Crocin, Safranal	Modulates serotonin and dopamine pathways, has antioxidant and neuroprotective effects.	- Neuroprotective- Enhances mood- Potential improvement in cognitive function	- Sanjeev *et al.* 2013
Mucuna pruriens	L-dopa, Mucuna alkaloids	Provides a natural source of L-DOPA, modulates the dopaminergic system, and has potential neuroprotective effects	- Increases dopamine levels- Reduces motor dysfunction- Potential neuroprotective effects	- Ranjan *et al*. 2016
Nicotiana tabacum (Tobacco)	Nicotine	Modulates acetylcholine and dopamine systems and has neuroprotective effects by enhancing synaptic plasticity and reducing neuroinflammation	- Potential neuroprotective effects- May improve motor and cognitive function (controversial)	- Li *et al*. 2013
Salvia officinalis (Sage)	Rosmarinic acid, Carnosic acid, Carnosol	Antioxidant, anti-inflammatory, and neuroprotective. Enhances cholinergic function and reduces oxidative stress	- Potential cognitive enhancement- Reduces neuroinflammation- Antioxidant effects	- McKinney *et al*. 2012
Zingiber officinale (Ginger)	Gingerol, Shogaol, Zingerone	Anti-inflammatory, antioxidant effects. Modulates the neuroinflammatory response, and has potential neuroprotective effects	- Reduces inflammation- Antioxidant effects- Potential neuroprotective effects	- Lee *et al*. 2016
Fucus vesiculosus (Bladderwrack)	Fucoidan, Iodine	Anti-inflammatory, antioxidant, and potentially neuroprotective	- May help protect against oxidative stress- Potential benefits for neurodegenerative diseases	- van de Laar *et al*. 2011
Glycyrrhiza glabra (Licorice)	Glycyrrhizin	Anti-inflammatory and neuroprotective, modulates cortisol levels, and reduces oxidative stress	- Neuroprotective- Reduces inflammation- Potential improvement in cognitive function	- Murakami *et al*. 2010
Tyrphostin (T. muscosa)	Muscimol (GABAergic)	GABA receptor activity, neuroprotective, modulates neurotransmitter activity	- Potential cognitive enhancement- May modulate neurotransmitter systems in HD	- da Costa *et al*. 2011
Annona muricata (Graviola)	Annonaceous acetogenins, Alkaloids	Exhibits Antioxidant and anti-inflammatory properties and reduces neuroinflammation and oxidative stress	- Neuroprotective effects- May reduce oxidative stress- Anti-cancer properties (caution in long-term use)	- Rodriguez *et al*. 2012
Avena sativa (Oats)	Avenanthramides, Saponins	Exhibits Antioxidant and anti-inflammatory effects and promotes brain health by enhancing neuroplasticity.	- Cognitive enhancement- Anti-inflammatory- Antioxidant effects	- Fu *et al*. 2014

Table 3. List of medicinal plants, proposed mechanism, and animal model/cell culture.

Medicinal Plant	Proposed Mechanism	Animal Model/Cell Culture
Ashwagandha (*Withania somnifera*)	Neuroprotective, antioxidant, anti-inflammatory	R6/2 transgenic mice, PC12 cell line
Bacopa (*Bacopa monnieri*)	Antioxidant, anti-inflammatory, neuroprotective	3-Nitropropionic acid (3-NP) induced rat model
Blueberries (*Vaccinium spp.*)	Antioxidant, anti-inflammatory, neuroprotective	R6/2 transgenic mice, HdhQ111 mouse model
Cat's Claw (*Uncaria tomentosa*)	Neuroprotective, anti-inflammatory	R6/2 transgenic mice
Chinese Skullcap (*Scutellaria baicalensis*)	Anti-inflammatory, neuroprotective	R6/2 transgenic mice
Cinnamon (*Cinnamomum verum*)	Antioxidant, anti-inflammatory, neuroprotective	R6/2 transgenic mice
Curcumin (*Curcuma longa*)	Antioxidant, anti-inflammatory, neuroprotective	R6/2 transgenic mice, HdhQ111 mouse model
Ginkgo (*Ginkgo biloba*)	Antioxidant, neuroprotective	R6/2 transgenic mice, HdhQ111 mouse model
Ginseng (*Panax ginseng*)	Neuroprotective, anti-inflammatory	R6/2 transgenic mice
Gotu Kola (*Centella asiatica*)	Neuroprotective, antioxidant	R6/2 transgenic mice
Green Tea (*Camellia sinensis*)	Neuroprotective, antioxidant	R6/2 transgenic mice, HdhQ111 mouse model

(Table 3) Contd…

Medicinal Plant	Proposed Mechanism	Animal Model/Cell Culture
Huperzine A (*Huperzia serrata*)	Acetylcholinesterase inhibitor, neuroprotective	R6/2 transgenic mice
Lemon Balm (*Melissa officinalis*)	Neuroprotective, antioxidant	R6/2 transgenic mice
Milk Thistle (*Silybum marianum*)	Antioxidant, anti-inflammatory, neuroprotective	R6/2 transgenic mice
Olive Oil (*Olea europaea*)	Neuroprotective, antioxidant, anti-inflammatory	R6/2 transgenic mice
Peony (*Paeonia lactiflora*)	Neuroprotective, antioxidant, anti-inflammatory	R6/2 transgenic mice
Resveratrol (*Polygonum cuspidatum*)	Neuroprotective, antioxidant, anti-inflammatory	R6/2 transgenic mice
Rhodiola (*Rhodiola rosea*)	Neuroprotective, antioxidant, anti-inflammatory	R6/2 transgenic mice
Sage (*Salvia officinalis*)	Neuroprotective, antioxidant, anti-inflammatory	R6/2 transgenic mice
Schisandra (*Schisandra chinensis*)	Neuroprotective, antioxidant, anti-inflammatory	R6/2 transgenic mice
St. John's Wort (*Hypericum perforatum*)	Neuroprotective, antidepressant	R6/2 transgenic mice
Turmeric (*Curcuma longa*)	Antioxidant, anti-inflammatory, neuroprotective	R6/2 transgenic mice, HdhQ111 mouse model
Valerian (*Valeriana officinalis*)	Neuroprotective, anxiolytic	R6/2 transgenic mice
Vinpocetine (*Vinca minor*)	Neuroprotective, anti-inflammatory	R6/2 transgenic mice
Wormwood (*Artemisia absinthium*)	Neuroprotective, antioxidant	R6/2 transgenic mice
Yerba Mate (*Ilex paraguariensis*)	Neuroprotective, antioxidant, anti-inflammatory	R6/2 transgenic mice
Ziziphus (*Ziziphus jujuba*)	Neuroprotective, antioxidant	R6/2 transgenic mice
Licorice (*Glycyrrhiza glabra*)	Neuroprotective, anti-inflammatory	R6/2 transgenic mice
Mucuna (*Mucuna pruriens*)	Neuroprotective, antioxidant	R6/2 transgenic mice
Passionflower (*Passiflora incarnata*)	Neuroprotective, anxiolytic	R6/2 transgenic mice

CONCLUSION

The pharmaceutical treatment of Huntington's Disease (HD) has advanced significantly in recent years, giving patients and their families renewed hope. While a treatment for HD is still lacking, tremendous progress has been made in creating medications that target different components of the condition and offer much-needed symptom alleviation. The aberrant amplification of CAG repeats in the huntingtin gene, which results in the creation of mutant huntingtin protein, has been an important area of study in determining the molecular processes behind HD. Promising treatment approaches that aim to reduce mutant huntingtin production or mitigate its negative consequences have been developed. By selectively suppressing the mutant huntingtin gene, gene silencing techniques like RNA interference (RNAi) and Antisense Oligonucleotides (ASOs) have shown promise. Clinical studies for these novel approaches are now being conducted, boosting hopes for efficient and disease-modifying therapies. Another important factor in the aetiology of HD has been identified as neurotransmitter imbalance. Dopamine and glutamate receptor-targeting medications have demonstrated promise in controlling chorea associated with HD and offering neuroprotection. The study of anti-inflammatory drugs and antioxidants with possible neuroprotective benefits emerged from the examination of neuroinflammation and oxidative stress as factors in HD development. Treatment for HD still heavily relies on symptom management. HD patients' quality of life has improved thanks to medications that address their motor symptoms, mental problems, and cognitive deficits. It is important to note that many of these therapies are still in the experimental stage or are just effective in treating symptoms. Despite these encouraging advancements, further research is imperative to validate the efficacy and safety of these emerging therapies in larger-scale clinical trials. The road to finding effective treatments for HD is challenging, requiring meticulous investigation and collaboration between researchers, clinicians, and patients. Looking ahead, the future prospects in the pharmacological management of HD are promising. Continued research into novel therapies and molecular targets may lead to disease-modifying treatments, providing real hope for a cure. Additionally, advancing technologies in drug delivery systems and personalized medicine approaches hold the potential to optimize treatment outcomes and minimize side effects. In conclusion, there have been significant advances in the field of pharmacological therapy of Huntington's disease that aim to address the illness's fundamental processes. These developments raise hopes for bettering the lives of HD sufferers. Even while there is still much to be done, current research initiatives are laying the groundwork for improved therapies and, eventually, the long-awaited solution for this debilitating neurodegenerative condition. Together, we continue to be committed to pursuing a future in which people with HD may live lives free from its responsibilities and where families can take comfort in the prospect of a better future.

STUDY LIMITATIONS

Despite the comprehensive analysis of emerging pharmacological strategies for Huntington's Disease (HD), several limitations must be acknowledged. First, much of the evidence presented is derived from preclinical models, which, although informative, may not fully replicate the complex pathophysiology of HD in humans. This translational gap poses a significant challenge, as many therapies that show promise in animal studies fail to demonstrate efficacy in clinical trials. Additionally, the clinical data available for some of the newer approaches, such as gene-editing technologies and gene-silencing therapies, remain limited in terms of long-term safety and efficacy. The heterogeneity of patient responses observed in ongoing clinical trials further complicates the development of standardized treatment protocols. Moreover, while advancements in biomarker discovery and precision medicine are promising, these tools are still in early stages and not yet fully integrated into clinical practice. This limits the ability to accurately diagnose, monitor, and personalize treatments for HD patients. Finally, the multifactorial nature of HD pathogenesis-encompassing protein aggregation, mitochondrial dysfunction, and neuroinflammation-suggests that single-target therapies may be insufficient, underscoring the need for combination approaches and more holistic treatment strategies.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: Study conception and design: S K and J K G.; Data collection: M G; Analysis and interpretation of results: N T, R, and R D; Draft manuscript: A G, S J, P M, S S, and L Y. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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DECLARATION

The English language of the article was improved with ChatGPT.

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