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Review Article

A REVIEW ARTICLE ON TREATING HUNTINGTON'S DISEASE: CURRENT AND EMERGING THERAPEUTIC ASPECTS

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ABSTRACT

A rare genetic neurodegenerative disorder called Huntington's disease (HD) causes nerve cells to progressively die. When the trinucleotide CAG repeats are <36, it is regarded as "normal." When the repetitions in the huntingtin gene are >36, polyglutamine (polyQ) tract leads to polyQ poisoning, which in turn causes psychological, genetic, and movement disorders which are hallmarks of HD. One particularly concerning aspect of HD is its controlling inheritance pattern, this indicates that each child born to a parent who exaggerated through the condition has a 50% likelihood of having the lineage of mutated gene that causes the disease. As a result, there is a significant risk that offspring of individuals with HD may also develop the condition. The underlying molecular mechanisms resulting in the visible loss of neurons remain incompletely elucidated, and the current therapeutic approaches primarily aim to alleviate symptoms. Many symptoms can be treated with the HD prescription medications that are currently available. These include prescribed medication for chorea, tranquilizers, calming agents, antidepressants, and non-pharmacological therapy. Additional possible treatments now undergoing clinical research include RNA interference therapies, therapies targeting RNA using tiny molecules, antibody therapies, stem cell therapies, small molecule therapies not targeting RNA, and therapies concentrating on neuroinflammation. Among the potential treatments presently in pre-clinical development stages are zinc-finger protein therapies, transcription activator-like effector nuclease therapies, and rehabilitations involving clustered regularly interspaced short palindromic repeats (CRISPS)/CRISPS-associated system. Therefore, the purpose of this comprehensive review is to discuss the efficacy of current HD medicines and look into the insights of new emerging therapies which are under pre-clinical development stage.

Keywords: Huntington Chorea/Huntington's disease, Genetics, Pathogenesis, Polyglutamine, Zinc-finger protein, Transcription activator-like effector nuclease.

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INTRODUCTION

Huntington's disease is a progressive neurodegenerative disorder that leads to the gradual degeneration of neurons in the brain. It is also referred as Huntington's chorea because it causes unnecessary involuntary jerky movements, behavioral and mental disturbances, depression, and dementia. The Fig. 1 shows it is a genetic disorder with passes from generation to generation and its onset is from middle age groups. Polyglutamine repeats are recurrence that is determined by various factors, including genetic modifications in the huntingtin gene (HTT), which lies on the fourth chromosome. Because its codes for glutamate, an excitatory neurotransmitter gradually destroys neurons through a number of processes [1]. The clinical evolution of HD is categorized in three clear stages. Initially, individuals enter the pre-symptomatic stage, during which no noticeable clinical abnormalities manifest. As the disease progresses, they move into the prodromal phase, characterized by subtle changes in motor skills, cognition, and behavior, typically visible only to those in close proximity. Finally, the manifest stage is followed by the clinical diagnosis, marked by pronounced symptoms such as motor impairments, cognitive decline, and behavioral changes, which worsen over time, affecting functional capacity and overall quality of life. As the disease progresses, it leads to complete dependency in day-to-day life followed by death. The leading causes of death include pneumonia and suicide [2].

EPIDEMIOLOGY

Huntington's disease (HD) is prevalent mostly in Europe and European descendants, such as United States and Australia. It is less prevalent in Japanese, Chinese, and African descent. Age onset typically varies between 35 and 50; the disease is mostly growing with death within 15–20 years after disease commencement. This disease affects 4–8 people/100,000 of European ancestry [3]. In North America, its estimated to affect 9.5 people/100,000. In United States, HD affects about 1 in 10,000–20,000 people. In India, it is usually rare and less prevalent usually 3–7 people/100,000 due to HD [4].

ETIOPATHOGENESIS

Neurodegeneration

The movement-related and neurological signs of HD are caused by abnormalities in the pyramidal or extrapyramidal motor systems, which indicates motor dysfunction rather than sex-linked genetic issue. "As per the report of Huntington's Disease Society of America (HDSA), huntington's disease shows similarity of symptoms with other neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Cerebral Ischemia, and Amyotrophic lateral sclerosis (ADS)". The indications linked to this disease are psychological and psychiatric disturbances, rigidity of muscles, cognitive impairment, dependency, characteristic "choreatic" movements (Abnormal autonomic movements). This occurs due to the genetic aspect associated with the disease progression; it is related with the mutation in the HTT gene [5]. The healthy neurons contain 8–35 repeats, while in mutant huntingtin (mHtt), there are more than 36 CAG repeats during the translation process. This leads to death of the neurons in the central nervous system (CNS) specially those present in the striatum and causes degeneration of neurons and neurotransmitter imbalance in the CNS. Various biochemical parameters are altered such as decline in gamma aminobutyric acid (GABA), acetylcholine, serotonin, and dopamine. After the appearance of symptoms in the affected individual, death occurs after 15–20 years [6].

Mitochondrial dysfunction associated abnormalities

There are number of pathways through which the mHtt gene affects the mitochondrial regulation. The early studies postulated that it interacts with the cyclic AMP response element binding protein and interferes

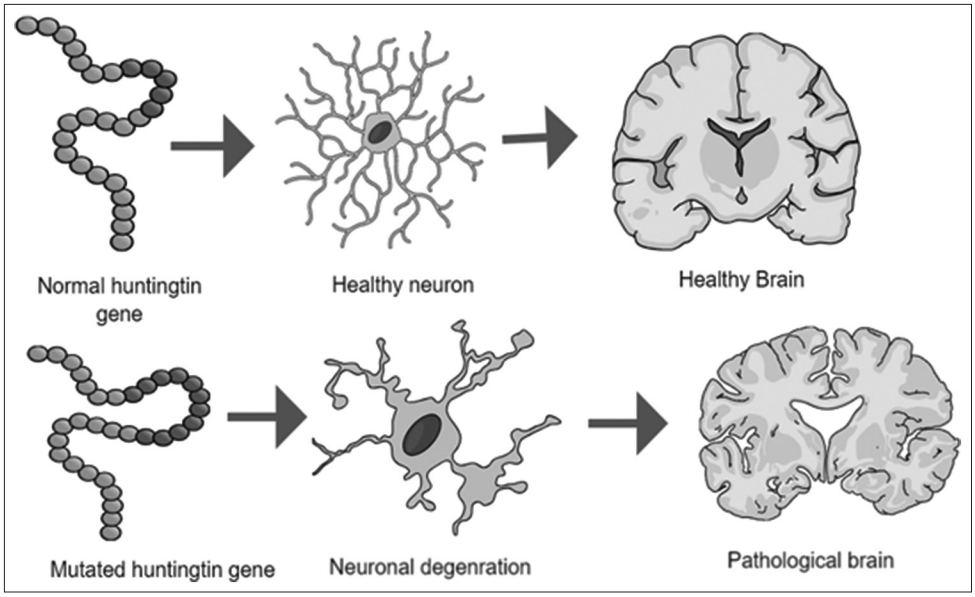

Fig. 1: Huntington's disease pathogenesis

with the CREB binding protein-dependent gene expression by interacting with histone acetyl transferase activity which is necessary for the histone and non-histone acetylation and is crucial in protein activity and chromatin structure and mHtt inhibits its activity. In addition, it induces oxidative damage and interacts with mitochondrial transporter II receptors, both of which result in mitochondrial dysfunction [7]. Another mechanism through which mitochondrial dysfunction occurs in HD is through p53 dysregulation mHtt binds with p53 and enhances the p53 gene expression and transcription process which is responsible for depolarization and excitotoxicity in HD. PGC-1α is a transcriptional coactivator responsible in protein expression in mitochondrial function such as homeostasis, maintenance of glucose, energy (ATP synthesis) lipid regulation. PGC-1α IT also regulates PPARγ receptors and various respiratory genes. Recent evidences provide that mHtt suppresses the activity of PGC-1α and contributes to the mitochondrial dysfunction in HD [8].

Genetic aspect

HD has several genetic reasons, one of which is the triplet that defines the amino acid glutamine, which is repeated at least 40 times. The first exon of the HTT gene, which is found on chromosome 4p16.3, has 20 repetitions of the CAG triplet [9]. The commencement of illness development coincides with the amount of CAG repeats. More than 70 CAG repeats are linked with HD [10].

Cognitive and motor impairment connected to HD

This illness affects the physiology of the CNS generally, resulting in a variety of neurological symptoms as irritability, depression, anxiety, and apathy. Cognitive changes include rapid involuntary movements of face, trunk, limbs (choreatic movements), frank aphasia, agnosia, and apraxia [10]. Certain cognitive impairments seem to manifest gradually with a subtle advancement, while others exhibit a sudden rise, unfolding in a progressive manner during the period surrounding clinical manifestation. For instance, slight alterations in psychomotor function among individuals with the HD mutation, evident years before HD onset, progressing gradually as the disease advanced. Conversely, other alterations, particularly in memory function, emerged around the time of clinical onset and experienced a more noticeable decline [11].

Oxidative stress

The mechanism associated with oxidative stress related to HD pathogenesis is still not clear. Many laboratory analyses provide results that the ROS is responsible for HD pathogenesis. However, the clinical trial studies in humans are unsuccessful in proving the same. It is therefore necessary to highlight the molecular, transcription mitochondrial pathways in HD pathogenesis but still the exact correlation with oxidative stress is not determined. According to hypothesis the mHtt increases the oxidative stress, this causes the free radicals to cause excitotoxicity of neurons by increasing the intracellular influx of Ca^{2+}ions [12]. An additional theory about the pathophysiology of HD involves the removal of oxidized bases (base excision repair enzyme [BER]) enzymes, which are responsible for DNA repair as well as oxidative damage. Oxidized bases, such as 5-hydroxyuracil (5-OH-uracil), 5-hydroxycytosine (5-OHC), and 8-oxoguanine DNA glycosylase, are removed by apyrimidinic endodeoxyribonuclease, Nei-like glycosylase 2, Nei-like glycosylase 3, and other BER enzymes. Thus, removal of these oxidized bases may cause CAG to proliferate, which in turn may initiate the pathophysiology of HD [13].

Biomarkers in HD

Biomarkers are used to determine the disease condition of a patient by evaluating the biological parameters associated with the disease. The Fig. 2 shows the current biomarkers in HD aiming to develop therapies for premanifest HD which requires biomarkers to measure the outcome of the disease therapy [14]. Numerous biomarkers for HD have been explored such as biofluid biomarkers from peripheral blood, plasma biomarkers, structural biomarkers, and clinical biomarkers. Recently, peripheral biofluid biomarkers have increasingly gained attention and have tested for their role as biomarkers in HD because of their potential with minimum invasiveness, high accuracy, and good predictive capacity [15].

CURRENT THERAPEUTIC APPROACHES FOR TREATMENT OF HD

Therapeutic approaches for motor symptoms

These are generally focused on the involuntary choreatic movements which are the hallmark characteristic symptom of the disease. Additional therapeutic strategies for managing motor indications in HD rely on the comprehensive evaluation employing the Unified Huntington's Rating Scale (UHDRS). Motor function, Cognitive function, Behavioral function, and Functional Capacity are the four key categories of clinical functioning that are assessed by this measure [16]. Tetrabenazine (TBZ) and deutetrabenazine (deuTBZ) are drugs prescribed for the choreatic movements. TBZ acts by inhibiting vesicular monoamine transporter 2 (VMAR2) and its first approved by FDA in the treatment of HD. The primary dose-limiting side effects typically associated with TBZ is dizziness, hyperprolactemia, depression, akathisia, constipation, and bruising [17]. The pioneering

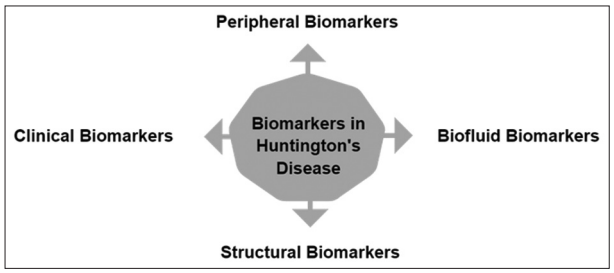

Fig. 2: Overview of biomarkers in HD

multicenter trial executed with Huntington study group with a purpose to analyze the efficiency, optimal dosage, and acceptability of TBZ in individuals with HD exhibiting choreatic symptoms. This double-blind, randomized, and placebo-controlled analysis encompassed in all 84 members, ages ranging through 25–77 years [18]. deuTBZ is an isotopic isomer of TBZ. It is a deuterated version of TBZ which imparts a longer half-life, better tolerability, less frequency of dosing, and higher safety levels. An indirect treatment comparison of TBZ and deuTBZ reported fewer complications such as akathisia and Parkinson's disease with deuTBZ as compared to TBZ [19]. Benzodiazepines were also evaluated for its therapeutic efficacy in chorea induced by anxiety. From surgical perspective, various interventions are considered in the treatment of HD like pallidotomy, deep brain stimulation is being considered as a disease modifying therapeutic options [20].

Therapeutic approaches for behavioral symptoms

Behavioral symptoms occur in HD patients even before the cognitive symptoms. Symptoms mainly include irritability, impulsivity, obsessive-compulsive behavior, depression, loss of interest, and apathy. Suicide is more prominent in the pre-manifest stage of disease when the individual becomes dependent for day-to-day activities. Psychosis may also arise later with the progress of pathological condition which can be compared to schizophrenia due to symptoms such as hallucinations, self-harm, mental confusion, and disorientation [21]. The vasopressin 1A receptor antagonist SRX46 and the combination of dextromethorphan and quinidine are being studied as potential treatments for irritability. Bupropion was looked into as a possible treatment for apathy in the case of HD.

Forty participants with HD and clinical manifestations of apathy as measured by the Structured Clinical Interview for Apathy Dementia who did not have depression were randomly assigned to receive either a placebo or bupropion at doses of 150/300 mg daily for 10 weeks in a multicenter, double-blind, placebo-controlled crossover trial [22]. The study's findings concluded that bupropion did not demonstrate efficacy in alleviating apathy in individuals with HD. However, notable placebo effects were observed, underscoring the importance of rigorous control in trials assessing therapeutic interventions for HD [23].

Therapeutic approaches for cognitive symptoms

Cognitive impairment is the characteristic feature of HD. Snowden *et al*. observed that psychomotor changes in HD were associated years before onset of HD. The cognitive impairment worsens as the disease progresses. As the disease progresses, patients find it harder to complete cognitively demanding tasks such as the Tower of London as well as the Wisconsin Card Sorting Test. These tasks call for cognitive flexibility, planning, and stability, all of which are absent in HD patients. As time processes, memory deficits are prominent in HD patients. Various short-term memory related to long-term memory-related discrepancies are seen across patients including episodic memory, declarative memory [23]. According to the neuropsychological pattern described by Zakzanis, frontostriatal dysfunction is associated with impairment in recall and recognition memory. Cognitive impairment usually worsens and is characterized by apathy, depression, and speech impairment. This is usually characterized as subcortical dementia syndrome which is different from what is caused in Alzheimer's disease. As there is a notable consequence observed that is the substantial depletion of acetylcholine and acetylcholine receptors within the striatum and subcortical region of the brain, rivastigmine is indicated for the treatment of cognitive symptoms, but still, more research is required to know the potential clinical therapeutic efficacy [24]. Memantine a non-competitive glutamate agonist is postulate to useful treatment option in glutamate excitotoxicity associated with HD. An initial exploratory open-label study implicated as a potential neuroprotective effect in HD. However, additional thorough investigation is imperative to fully ascertain safety and ascertain the clinical utility of this approach. Hence, it is not approved for the treatment of HD [25].

Psychiatric symptoms

The two psychological symptoms associated with HD that is most devastating are depression and anxiety. It has been demonstrated that the pharmacological advantages of selective serotonin reuptake inhibitors (SSRIs), which include medications such as citalopram and fluoxetine. SSRIs are also used to treat obsessive compulsive disorder which is seen more prominently in HD patients. Anti-epileptic drugs such as carbazepine, lamotrigine, valproate can be used as adjunctive therapy in the form of mood-stabilizing agents [26,27]. The current research endeavors are focused on assessing the efficacy of dextromethorphan/quinidine and a vasopressin 1A receptor antagonist (SRX46) aimed at managing mood swings. Mental illness occurs in approximately 3–4% patients having schizophrenia-like symptoms. The underlying cause of mental illness in HD is not yet elucidated. Many atypical antipsychotics are recommended for the treatment of psychiatric symptoms [27].

LIMITATIONS IN THE CURRENT TREATMENT APPROACHES FOR HD

Till now, there is no complete cure for HD as it is a genetic non-sex-linked inherited disease. Only the symptoms associated with the disease such as anxiety, depression, irritability, muscular abnormalities, difficulty in speaking, and tremor can be controlled by the medications. Various medication of different categories is used to improve the symptoms associated with disease. Drugs such as GABA agonist, acetylcholinesterase inhibitors, antidepressants, dopamine depletors, anti-glutamatergic drugs, and typical and atypical neuroleptics are used in disease treatment. TBZ, aloperidol, and amantadine are drugs used in the management of the chorea.

THERAPEUTIC APPROACHES: RECENT RESEARCH FOR THE TREATMENT OF HD

Treatment options which are presently available are primarily limited to symptomatic treatment which only provide relief during the initial stages of the condition and lessens its intensity without addressing the underlying cause. The requirement for more research on the effectiveness of symptoms-based therapy is highlighted by meta-analyses of clinical studies. To date, only deuterabenazine and TBZ are available medications for the treatment of choreatic episodes. Nevertheless, as there are no disease modifying remedies presently, there is a need to identify effective treatments capable of slowing down disease progression. Major approach is targeting the mutant Htt (mHtt) gene reducing the mutation or blocking mHtt gene. This can be evaluated from the animal studies that the phenotype changes produced by HD can be reduced by blocking the mHtt gene in young and adult animal [28].

ANTISENSE OLIGONUCLEOTIDES (ASO)

The Fig. 3 shows that ASO therapy is a treatment that uses minute portions of DNA or RNA to attach with particular RNA molecules. This is a synthetically made therapy that is designed to target almost any RNA sequence. ASOs offer significant advantages for treating neurological diseases like HD. They are especially advantageous because of their long half-lives and widespread dispersion throughout the brain network (CNS). Within the CNS, ASOs are easily absorbed by neurons, glial, and

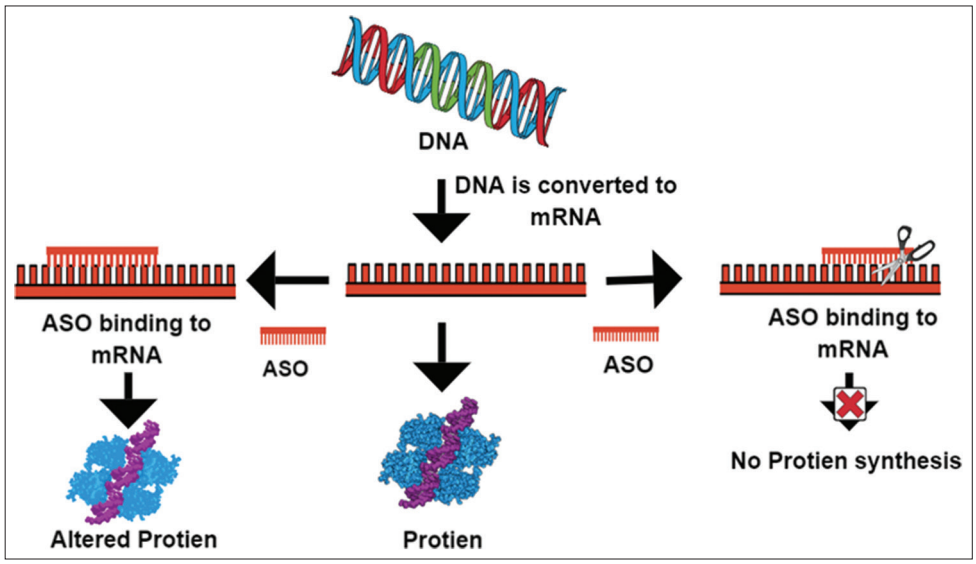

Fig. 3: Basic mechanism of antisense oligonucleotides

ependymal cells without the need for a carrier molecule. They can act by causing RNA cleavage or RNA blockage [29]. ASOs may dramatically change the course of heritable illnesses like HD and have demonstrated to show promising results in treating genetic disorders. Artificial single-stranded DNA analogs are used in this therapy, which are usually 16–22 bases long and are made to specifically attach to the appropriate disease-causing pre-messenger RNA. To avoid being quickly depleted by cellular nucleases, these analogs go through previous chemical modifications. ASO binding to target RNA results in the formation of an RNA-DNA hybrid. RNase H1 then begins to break down messenger RNA (mRNA) [30]. Tominersen is a non-selective stereo-random 2′ MOE gapmer ASO that was created by Ionis Pharmaceuticals and Roche. A phase I/IIa clinical trial, an open-label extension study, and a phase III clinical trial have all been completed on tominersen [31].

DNA TARGETING APPROACHES

Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (CAS9)

CRISPR/Cas9 stands for "Clustered Regularly Interspaced Short Palindromic Repeats. The Fig. 4 shows that CRISPR associated protein Cas9 having characteristic features like bacterial defense system and serves as the foundation for CRISPR-Cas9 genome editing technology". "Cas9 protein is an RNA guided nuclease that cleaves double-strand breaks (DSBs) in specific DNA sites". CRISPR/Cas9 is a viral defense associated system which targets bacteria and destroys the foreign DNA, which plays important role reducing the CAG repeats to silence mHTT expression. Because of a unique characteristic of the enzyme, cas nucleases are exclusive to pathogens because they only target complementary DNA sequences when activated by an RNA guide. There are two main components of the CRISPS/Cas9 system: sgRNA and Cas9 nuclease. By complementary base pairing, the sgRNA gives target DNA sequences specificity. DSBs are formed inside the DNA backbone as a result of the cleavage of DNA caused by the Cas9 protein's binding to the specific location that the sgRNA has directed [32]. Vectors Cas9 and sgRNA are introduced in the cells through recombinant DNA technology. The DNA-based protein recognition domain is not utilized by the Cas9 nuclease in this method. Protein recognition domain based on RNA guides the Cas9 nuclease. RNP, or ribonucleoprotein structure, is created when Cas9 and the RNA protein domain interact and may be directed toward particular DNA locations. Employing the CRISPR/Cas9 technology, gene alterations associated with the CAG-expanded allele are targeted in patient-derived fibroblasts to inactivate mHTT genes [33]. This approach leads to a comprehensive reduction in RNA and mHTT protein levels. CRISPR/Cas9 is an important therapeutic tool used in various neurodegenerative disorders, cancers, and

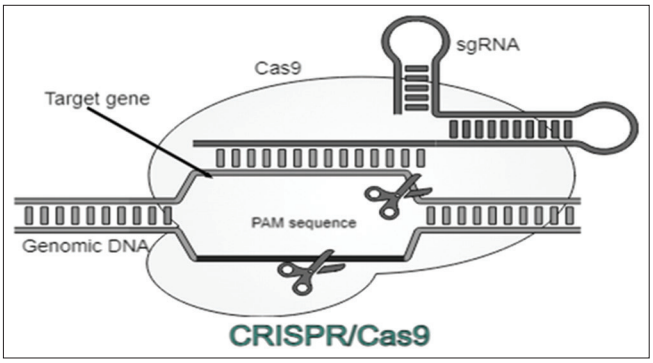

Fig. 4: CRISPR/CRISPR-associated protein 9 methodology. CRISPR: Clustered regularly interspaced short palindromic repeats

cardiovascular disease. The above-said methods are applicable in the determination of COVID-19 [34].

Zinc-finger nucleases (ZFN'S)

ZFN'S was first constructed in 1996 by Kim *et al*. These are the major gene targeting tool in biological research. By adhering to the DNA strand and impeding gene transcription, zinc-finger proteins (ZFPs) lacking nuclease ability may inhibit gene expression [20]. ZFN consists of a three-finger binding domain and a FokI nuclease dissolution area linked together. This technology laid the groundwork for genetic changes in prepared human cells, especially in pluripotent stem cells. However, it comes with several drawbacks, including complexity, challenges with specificity of DNA binding, and a greater risk of missing the effects because of single-nucleotide change or wrong domain interactions. As per recent data, it can possibly used in HD by binding to the expanded CAG repeats without altering the normal proteins. These findings provide impetus for additional investigations aimed at developing allele-specific ZFP repressors and zinc-finger nucleases (ZFNs) as possible curative interventions for HD [35,36].

Transcription activator-like effector nucleases (TALEN)

Plant pathogenic bacteria are the primary source of TALEN, or TALEN, which contain DNA binding proteins known as TALEs. At the beginning, they combine a TAL effector DNA-binding domain with a DNA cleaving domain. At the conclusion of the sequence, TALENs require a particular nucleotide, despite their shown superiority over ZFNs in terms of efficiency and specificity. This requirement could pose a limitation

when targeting certain sequences for genome editing. It is a lot like ZFNs. Two of the tandem recurrence of the 34 amino acids that make up its DNA-binding domain (located on positions 12 and 13) are extremely variable (also known as repeat variable residues, or RVDs), and they are in charge of nucleotide recognition [37]. TALENs have recently acted as a breakthrough editing tool in various organisms and cell lines. The chromosomal double-strand of particular location breaks induced by TALENs substantially enhance the effectivity of gene modification. Fink *et al*. employed TALENs containing an obligate-heterodimeric variant of the FokI endonuclease to correct alleles in human HD adult fibroblasts. Even though TALENs are more potent and specific than ZFNs, they still need a thymine (T) at the target site's 5' terminus. This requirement can limit the range of target sequences that can be effectively edited using TALENs [38,39].

Small molecules GPCR 52 antagonists

It has been shown that decreasing the levels of HTT (HD-related protein) in both dermal cells and the brain cells extracted from patients is a successful disease-modifying tactic. This method considerably decreased cerebrospinal fluid (CSF) HTT by 50% in two investigations using animal models; human trials are currently being done to confirm these findings. The strategy involves targeting specific cellular pathways such as protein pathways, G protein-coupled receptor (GPCR) antagonism, and cellular differentiation [40]. GPCRs, particularly the non-odorant receptors, have garnered attention as viable drug targets due to their pharmaceutical targetability and prevalence in the CNS, where neurotransmitters such as dopamine, acetylcholine, glutamine, and serotonin are predominantly expressed. These receptors play a vital role in regulating synaptic transmission of these neurotransmitters, making them potential targets for antipsychotics and drug discovery for CNS-related disorders being abundantly expressed in the striatum of both humans and rodents; GPCR 52 is unique among non-odorant GPCRs because it co-localizes with striatal dopamine D2 receptors. There is hope for enhancing the processing of HTT precursor mRNA through the use of oral medications that can cross the blood–brain barrier (BBB) and other tiny molecules that target RNA [41]. Research has demonstrated that GPCR 52 restriction may function as a disease modifying therapy for HD by reducing the quantities of mHTT synthesis. Using a siRNA screen, preliminary results showed that GPCR 52 modulates mHTT expression *in vitro*. Later studies showed that *in vivo* HD models and neurons generated from patients showed repression of HD-associated traits when GPCR 52 was lowered [42]. Small GTPase Rab39B inactivation causes the proteasomal degradation of mHTT, which is the mechanism by which GPCR 52 regulates HTT production. This signaling is cAMP-dependent but PKA-independent. However, mHTT is shielded from proteasomal destruction by GPCR 52 activation, which makes it easier for mHTT to enter the endoplasmic reticulum (ER) [43]. Targeting GPCR 52 by genetic deletion has demonstrated encouraging effects in lowering mHTT levels and alleviating HD-related abnormalities in a number of mice, despite the intricate nature of the cAMP pathway's function in HD. This emphasizes how intriguing GPCR 52 is as a target for HD treatment. It has been demonstrated that lowering HTT levels in dermal cells and neurons derived from HD patients is a feasible disease-modifying strategy for HD. In two studies using experimental animals, this approach resulted in a notable 50% decrease in CSF. Human trials are presently in progress. The strategy involves targeting specific cellular pathways such as protein pathways, GPCR antagonism, and cellular differentiation [44]. GPCRs, particularly the non-odorant receptors, have garnered attention as viable drug targets due to their pharmaceutical targetability and prevalence in CNS, where neurotransmitters such as dopamine, acetylcholine, glutamine, and serotonin are predominantly expressed. These receptors are pivotal in regulating transmission of these neurotransmitters, making them potential targets for antipsychotics and drug discovery for CNS-related disorders [45]. GPCR 52 is a notable example of a non-odorant GPCR as it co-localizes with striatal dopamine D2 receptors and is widely expressed in both the human and rodent striatum's. Improvements have been observed in the processing of HTT precursor mRNA by small compounds that target RNA, such as orally reachable medicines that pass the BBB [46]. Study findings has demonstrated that inhibiting GPCR 52 could lower the amounts of mHTT synthesis, which might serve as a disease modifying therapy for HD. Implementing a siRNA screen, early outcomes showed that GPCR 52 modulates mHTT expression *in vitro*. Further research showed that *in vivo* HD models and neurons generated from patients showed suppression of HD-associated traits when GPCR 52 was minimized [47]. The process through which GPCR 52 controls HTT production is based on cAMP-dependent but PKA-independent signaling, which causes mHTT to be proteasomally metabolized by inactivating small GTPase Rab39B. On the other hand, activation of GPCR 52 promotes the conveyance of mHTT to the ER and shields it from destruction by proteases [48]. Despite the complexity surrounding the cAMP pathway's involvement in HD, genetic deletion of GPCR 52 has been demonstrated to specifically target the protein with encouraging outcomes, lowering levels of mHtt protein and improving abnormalities associated with HD in a number of animals. This indicates that GPCR 52 may be a viable target for HD therapy [49].

Antibody therapies

Antibody-based therapies are being evaluated for various neurodegenerative disorders which include tau and synuclein proteins in the brain. Along with this, it is also being evaluated for the monogenic disorders associated with CNS like HD. *ANX005* is monoclonal antibody developed by Annexon Biosciences to treat autoimmune disease. It acts by preventing Clq (Chloroquine), cascade inhibition and prevents the synaptic loss and neurodegeneration in HD. ANX005 was at first used for treating Guillain–Barré syndrome (GBS) and AD. Studies suggest that the murine version of ANX005 reduced synaptic loss of neurons and neuroinflammation in HD animal models [50]. ANX005 is been tested in HD clinical stabilization and was reported after biweekly, open-label doses in 23 participants. It was reported that participants had reduced CSF, Clq, and YKL-40 markers of neuroinflammation, at the end of treatment. Experimental investigation indicated increased propensity of binding to ANX005 to C1q in many species, and in rats and monkeys, there was a successful reduction in CSF and serum C1q. Effective suppression of the complement cascade has been shown in both *in vitro* and *in vivo* models of dementia related to Alzheimer's (AD) and Guillain–Barré syndrome (GBS) in mice. Moreover, tolerance, dosage dependence, and safe dosing frequency have been established in rats and monkeys [51]. Pepinemab, also known as IgG4 monoclonal antibody VX15/2503 from Vaccinex, is an inhibitor of the semaphorin 4D (SEMA4D) protein. One protein linked to neuroinflammation is SEMA4D; among other things, it activates glial cells and initiates signaling cascades that cause oligodendrocytes and neural precursor cells (NPC) to die. Vaccinex, Inc. and the Huntington research Group conducted double-blind phase 2 clinical research to examine the pharmacokinetics, safety, and tolerability of VX15/2503. This experiment focused on patients with early signs of HD as well as those in the late prodromal stage. Patients received intravenous monthly doses of VX15/2503 or a placebo and were split into 2 groups: A (1-year treatment) and B (3-year treatment). Among other things, the researchers measured brain volume, motor functioning through magnetic resonance imaging, cognitive functioning, and CSF through the use of biomarkers. In mid-2020, the study came to an end. According to cohort studies, preliminary SIGNAL data (n=36), VX15/2503 was found safe and acceptable. For a total of 150 days (open label), Cohort A received VX15/2503 with a 90-day observation period. However, in cohort B1 with early apparent HD (n=179), VX15/2503 did not significantly improve motor, cognitive, or behavioral performance nor did it arrest the decline in brain volume and metabolic activity [51,52]. The patterns toward cognitive advances that had been noted were validated by a *post hoc* analysis using Clinical Global Imprint of change in an advanced HD subgroup. However, these findings require more study [53].

ADDITIONAL THERAPIES TARGETED TARGETING NEUROINFLAMMATION

Minocycline

Many therapies that target inflammation have been anticipated in response to the chronic inflammation that has been identified

in HD. One such suggested treatment that had anti-inflammatory and anti-apoptotic qualities was minocycline, a medication of the second generation of tetracyclines. The behavioral performance of diseased mice administered with a lesser dose of minocycline (5 mg/kg/day) was better than that of animals not receiving therapy [54]. Minocycline dosage of 100 and 200 mg/day was bearable for 48 days according to clinical research. Using a random assignment method, 60 individuals were included in the research and given one of three doses of minocycline: 200 mg/day, 100 mg/day, or placebo (n=19). Nevertheless, no efficacy was noted, and no impact on the UHDRS notches [55]. During a 2-day clinical trial, participants given with 100 mg/day of minocycline exhibited notable decreases in mental symptoms, alongside the stabilization of overall cognitive and motor symptoms [56].

Cannabinoids

The endogenous cannabinoids administration has brought significant attraction in therapeutic prospects for various medical conditions in recent years. It has a role in several physiological and many well-known functions, including blood pressure regulation, energy balancing, hunger stimulation, memory, learning, immunity, and control over nausea and vomiting. It also plays a protective role in pathological circumstances. Modifications in endocannabinoid levels have been linked to a number of neurodegenerative diseases [57]. Depending on numerous preclinical researches, the endocannabinoid system is expressed differentially in the areas implicated in HD, which may have an effect on the disease course. Research on post-mortem HD patients revealed a significant reduction (almost 97.5%) in CB1 receptors in basal ganglia regions, particularly in the pallidus globe [58]. Despite using 10 mg/kg/day of oral cannabidiol (CBD) for 6 weeks, individuals with HD did not see any improvement in any of the indicators; nevertheless, the usage of nabilone appeared to lessen behavioral difficulties and choreatic symptoms. Enhanced research is necessary to provide the possible application of cannabis in HD [59].

Stem cell therapies

Another option for HD medication in the future is stem cell therapy. Their primary benefits include the potential to enhance regeneration, supply pro-survival factors, and transfer destroyed nerve cells as a result of HD disease. Moreover, if stem cells were induced into brain microenvironment of the patient, some long-term advantages might be possible. However, there are also uncertainties that these treatments could cause immunological responses or rejection [60,61].

Cellavita

Neural Stem Cells or NPCs generated from embryonic stem cells (ESCs) have shown to be the significant promise aimed at curing nerve cell illnesses, even HD, in stem cell therapies [62]. Many *in vitro* investigations have been carried out to examine various forms of ESCs, such as neural and mesenchymal; some of these researches have demonstrated significant promise as potential treatments for neurodegenerative diseases. Human iPSC-derived neural progenitor cells through animal experiments have shown to develop into normal neuronal cells when implanted into the brain, hence facilitating the restoration of behavior and motor function. At present, few clinical attempts are ongoing for measuring the dose of cellavita safety and efficacy. Patients with HD can get intravenous stem cell delivery using ionis maptrx and tofacitinib [63].

NANOPARTICLES AND NANOTECHNOLOGY-BASED TREATMENT

The restricted capacity of numerous substances to cross the BBB presents a significant hurdle that constrains the utilization of various possible therapeutic strategies for managing HD and other neurodegenerative conditions [64]. In addition, the efficacy of delivery strategies is significantly hindered by severe swelling and injury to brain, including BBB, caused by ongoing nerve cell breakdown mechanisms. One potential approach to circumvent these challenges is by employing nanotechnology to securely transport neuroprotective drugs to the impacted areas of the brain. In 2015, Bhatt *et al*. employed SLN for 4 rosmarinic acid, derivative of caffeic acid having anti-inflammatory and antioxidant characteristics, into the brains of rats with 3-NP lesions. When administered intranasally (as opposed to intravenously). 4 rosmarinic acid-loaded nanoparticles dramatically corrected cognitive impairments and decreased free radical stress in rats given with 3NP [65]. While the utilization of nanotechnology and nanoparticles for HD is still relatively novel, it offers a compelling and promising avenue for delivering safe and effective drugs to specific brain area. In addition, it holds potential for advancing genomic or personalized medicine [66,67]. However, before this innovative technology can be considered a viable option for administering medications and other biomolecules in therapeutic settings, further optimization and refinement are needed. Specifically, it will be essential to thoroughly comprehend and consider the distribution patterns of nanoparticles and their payloads within the brain, the breakdown of various nanocarriers, and its real implications on delivering these molecules. Therefore, widespread investigation is mandatory to properly comprehend the techniques and applications of the technology in relation to HD and other neurodegenerative disorders [68,69].

CONCLUSION

There are various advances in the field of HD therapy. Clinical treatment guidelines for HD are getting better. Both HTT and genetic modifier targets are in the best position since genetically validated targets have an overall greater development success rate. Success in medication development is contingent upon both the benefit-risk ratio and efficient delivery to the brain, in addition to target validation. Various approaches such as small molecules, CRISPR/Cas9, Stem cell therapies, and nanoparticles are being developed. The advancement of novel vectors, encompassing both viral and non-viral vectors, along with the evolution of gene editing techniques, holds the potential for revolutionary advancements in gene therapy. A new generation of HD therapeutics is considered to be on the horizon, though, as many of the most recent advancements are promising.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES

1. Gatto EM, Rojas NG, Persi G, Etcheverry JL, Cesarini ME, Perandones C. Huntington disease: Advances in the understanding of its mechanisms. Clin Park Relat Disord 2020;3:100056.
2. Shafie A, Ashour AA, Anwar S, Anjum F, Hassan MI. Exploring molecular mechanisms, therapeutic strategies, and clinical manifestations of Huntington's disease. Arch Pharm Res 2024;47:571-95.
3. McColgan P, Tabrizi SJ. Huntington's disease: A clinical review. Eur J Neurol 2018;25:24-34.
4. Mendez MF. Huntington's disease: Update and review of neuropsychiatric aspects. Int J Psychiatry Med 1994;24:189-208.
5. Gil JM, Rego AC. Mechanisms of neurodegeneration in Huntington's disease. Eur J Neurosci 2008;27:2803-20.
6. Andhale R, Shrivastava D. Huntington's disease: A clinical review. Cureus 2022;14:e28484.
7. Van Duijn E, Kingma EM, Van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J Neuropsychiatry Clin Neurosci 2007;19:441-8.
8. Novak MJ, Tabrizi SJ. Huntington's disease: Clinical presentation and treatment. Int Rev Neurobiol 2011;98:297-323.
9. Imarisio S, Carmichael J, Korolchuk V, Chen CW, Saiki S, Rose C, *et al*. Huntington's disease: From pathology and genetics to potential

therapies. Biochem J 2008;412:191-209.
10. Dumas EM, Van den Bogaard SJ, Middelkoop HA, Roos RA. A review of cognition in Huntington's disease. Front Biosci (Schol Ed) 2013;5:1-18.
11. Montoya A, Price BH, Menear M, Lepage M. Brain imaging and cognitive dysfunctions in Huntington's disease. J Psychiatry Neurosci 2006;31:21-9.
12. Kumar A, Ratan RR. Oxidative stress and Huntington's disease: The good, the bad, and the ugly. J Huntingtons Dis 2016;5:217-37.
13. Van Eimeren T, Giehl K, Reetz K, Sampaio C, Mestre TA. Neuroimaging biomarkers in Huntington's disease: Preparing for a new era of therapeutic development. Parkinsonism Relat Disord 2023;114:105488.
14. Browne SE, Ferrante RJ, Beal MF. Oxidative stress in Huntington's disease. Brain Pathol 1999;9:147-63.
15. Morena E, Romano C, Marconi M, Diamant S, Buscarinu MC, Bellucci G, *et al*. Peripheral biomarkers in manifest and premanifest Huntington's disease. Int J Mol Sci 2023;24:6051.
16. Yero T, Rey JA. Tetrabenazine (Xenazine), An FDA-approved treatment option for huntington's disease-related chorea. P T 2008;33:690-4.
17. Saft C, Burgunder JM, Dose M, Jung HH, Katzenschlager R, Priller J, *et al*. Symptomatic treatment options for Huntington's disease (guidelines of the German Neurological Society). Neurol Res Pract 2023;5:61.
18. Pérot JB, Brouillet E, Flament J. The contribution of preclinical magnetic resonance imaging and spectroscopy to Huntington's disease. Front Aging Neurosci 2024;16:1306312.
19. Paleacu D. Tetrabenazine in the treatment of Huntington's disease. Neuropsychiatr Dis Treat 2007;3:545-51.
20. Dash D, Mestre TA. Therapeutic update on Huntington's disease: Symptomatic treatments and emerging disease-modifying therapies. Neurotherapeutics 2020;17:1645-59.
21. Quintanilla RA, Johnson GV. Role of mitochondrial dysfunction in the pathogenesis of Huntington's disease. Brain Res Bull 2009;80:242-7.
22. Paulsen JS. Cognitive impairment in Huntington disease: Diagnosis and treatment. Curr Neurol Neurosci Rep 2011;11:474-83.
23. Vinther-Jensen T, Larsen IU, Hjermind LE, Budtz-Jørgensen E, Nielsen TT, Nørremølle A, *et al.* A clinical classification acknowledging neuropsychiatric and cognitive impairment in Huntington's disease. Orphanet J Rare Dis 2014;9:114.
24. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP Jr. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol 1985;44:559-77.
25. Ogilvie AC, Schultz JL. Memantine Use and cognitive decline in Huntington's disease: An enroll-HD study. Mov Disord Clin Pract 2023;10:1120-5.
26. Snowden JS. The neuropsychology of Huntington's disease. Arch Clin Neuropsychol 2017;32:876-87.
27. Rosenblatt A, Leroi I. Neuropsychiatry of Huntington's disease and other basal ganglia disorders. Psychosomatics 2000;41:24-30.
28. Caron NS, Dorsey ER, Hayden MR. Therapeutic approaches to Huntington disease: From the bench to the clinic. Nat Rev Drug Discov 2018;17:729-50.
29. Aronin N, DiFiglia M. Huntingtin-lowering strategies in Huntington's disease: Antisense oligonucleotides, small RNAs, and gene editing. Mov Disord 2014;29:1455-61.
30. Rook ME, Southwell AL. Antisense oligonucleotide therapy: From design to the huntington disease clinic. BioDrugs 2022;36:105-19.
31. Leavitt BR, Tabrizi SJ. Antisense oligonucleotides for neurodegeneration. Science 2020;367:1428-9.
32. Alkanli SS, Alkanli N, Ay A, Albeniz I. CRISPR/Cas9 mediated therapeutic approach in Huntington's disease. Mol Neurobiol 2023;60:1486-98.
33. Shin JW, Kim KH, Chao MJ, Atwal RS, Gillis T, MacDonald ME, *et al*. Permanent inactivation of Huntington's disease mutation by personalized allele-specific CRISPR/Cas9. Hum Mol Genet 2016;25:4566-76.
34. Ekman FK, Ojala DS, Adil MM, Lopez PA, Schaffer DV, Gaj T. CRISPR-Cas9-Mediated genome editing increases lifespan and improves motor deficits in a Huntington's disease mouse model. Mol Ther Nucleic Acids 2019;17:829-39.
35. Garriga-Canut M, Agustín-Pavón C, Herrmann F, Sánchez A, Dierssen M, Fillat C, *et al*. Synthetic zinc finger repressors reduce mutant huntingtin expression in the brain of R6/2 mice. Proc Natl Acad Sci U S A 2012;109:E3136-45.
36. Bashir H. Emerging therapies in Huntington's disease. Expert Rev Neurother 2019;19:983-95.
37. Malankhanova TB, Malakhova AA, Medvedev SP, Zakian SM. Modern genome editing technologies in Huntington's disease research. J Huntingtons Dis 2017;6:19-31.
38. Fink KD, Deng P, Gutierrez J, Anderson JS, Torrest A, Komarla A, *et al*. Allele-specific reduction of the mutant Huntingtin allele using transcription activator-like effectors in human Huntington's Disease fibroblasts. Cell Transplant 2016;25:677-86.
39. Komatsu H. Innovative therapeutic approaches for Huntington's disease: From nucleic acids to GPCR-targeting small molecules. Front Cell Neurosci 2021;15:785703.
40. Song H, Li H, Guo S, Pan Y, Fu Y, Zhou Z, *et al*. Targeting Gpr52 lowers mutant HTT levels and rescues Huntington's disease-associated phenotypes. Brain 2018;141:1782-98.
41. Ali S, Wang P, Murphy RE, Allen JA, Zhou J. Orphan GPR52 as an emerging neurotherapeutic target. Drug Discov Today 2024;29:103922.
42. Cowan CM, Raymond LA. Selective neuronal degeneration in Huntington's disease. Curr Top Dev Biol 2006;75:25-71.
43. Smalley JL, Breda C, Mason RP, Kooner G, Luthi-Carter R, Gant TW, *et al*. Connectivity mapping uncovers small molecules that modulate neurodegeneration in Huntington's disease models. J Mol Med (Berl) 2016;94:235-45.
44. Ferguson MW, Kennedy CJ, Palpagama TH, Waldvogel HJ, Faull RL, Kwakowsky A. Current and possible future therapeutic options for Huntington's disease. J Cent Nerv Syst Dis 2022;14:11795735221092517.
45. Rigamonti D, Bauer JH, De-Fraja C, Conti L, Sipione S, Sciorati C, *et al*. Wild-type huntingtin protects from apoptosis upstream of caspase-3. J Neurosci 2000;20:3705-13.
46. Rodrigues FB, Wild EJ. Huntington's disease clinical trials corner: April 2020. J Huntingtons Dis 2020;9:185-97.
47. Wang X, Zhu S, Drozda M, Zhang W, Stavrovskaya IG, Cattaneo E, *et al*. Minocycline inhibits caspase-independent and -dependent mitochondrial cell death pathways in models of Huntington's disease. Proc Natl Acad Sci U S A 2003;100:10483-7.
48. Ahamad S, Bhat SA. The emerging landscape of small-molecule therapeutics for the treatment of Huntington's disease. J Med Chem 2022;65:15993-6032.
49. Wang C, Zhang YF, Guo S, Zhao Q, Zeng Y, Xie Z, *et al*. GPR52 antagonist reduces huntingtin levels and ameliorates Huntington's disease-related phenotypes. J Med Chem 2021;64:941-57. Erratum in: J Med Chem 2021;64:1220-1.
50. Jurcau A, Jurcau MC. Therapeutic strategies in Huntington's disease: From genetic defect to gene therapy. Biomedicines 2022;10:1895.
51. Raymond LA, André VM, Cepeda C, Gladding CM, Milnerwood AJ, Levine MS. Pathophysiology of Huntington's disease: Time-dependent alterations in synaptic and receptor function. Neuroscience 2011;198:252-73.
52. Denis HL, David LS, Cicchetti F. Antibody-based therapies for Huntington's disease: Current status and future directions. Neurobiol Dis 2019;132:104569.
53. Lansita JA, Mease KM, Qiu H, Yednock T, Sankaranarayanan S, Kramer S. Nonclinical development of ANX005: A humanized anti-c1q antibody for treatment of autoimmune and neurodegenerative diseases. Int J Toxicol 2017;36:449-62.
54. Gupta H, Sahi S. High-throughput virtual screening of potential inhibitors of GPR52 using docking and biased sampling method for Huntington's disease therapy. Mol Divers 2024;28:3331-47.
55. Feigin A, Evans EE, Fisher TL, Leonard JE, Smith ES, Reader A, *et al*. Pepinemab antibody blockade of SEMA4D in early Huntington's disease: A randomized, placebo-controlled, phase 2 trial. Nat Med 2022;28:2183-93. Erratum in: Nat Med 2024;30:606.
56. Yao Y, Cui X, Al-Ramahi I, Sun X, Li B, Hou J, *et al*. A striatal-enriched intronic GPCR modulates huntingtin levels and toxicity. Elife 2015;4:05449.
57. Atwal RS, Xia J, Pinchev D, Taylor J, Epand RM, Truant R. Huntingtin has a membrane association signal that can modulate huntingtin aggregation, nuclear entry and toxicity. Hum Mol Genet 2007;16:2600-15.
58. Sagredo O, Pazos MR, Valdeolivas S, Fernandez-Ruiz J. Cannabinoids: Novel medicines for the treatment of Huntington's disease. Recent Pat CNS Drug Discov 2012;7:41-8.
59. Bhat SA, Ahamad S, Dar NJ, Siddique YH, Nazir A. The emerging landscape of natural small-molecule therapeutics for Huntington's disease. Curr Neuropharmacol 2023;21:867-89.
60. Thomas M, Le WD, Jankovic J. Minocycline and other tetracycline derivatives: A neuroprotective strategy in Parkinson's disease and Huntington's disease. Clin Neuropharmacol 2003;26:18-23.
61. Conner LT, Srinageshwar B, Bakke JL, Dunbar GL, Rossignol J. Advances in stem cell and other therapies for Huntington's disease: An update. Brain Res Bull 2023;199:110673.

62. Duncan RS, Riordan SM, Gernon MC, Koulen P. Cannabinoids and endocannabinoids as therapeutics for nervous system disorders: Preclinical models and clinical studies. Neural Regen Res 2024; 19:788-99.
63. Lescaudron L, Naveilhan P, Neveu I. The use of stem cells in regenerative medicine for Parkinson's and Huntington's Diseases. Curr Med Chem 2012;19:6018-35.
64. Van de Roovaart HJ, Nguyen N, Veenstra TD. Huntington's disease drug development: A phase 3 pipeline analysis. Pharmaceuticals (Basel) 2023;16:1513.
65. D'Egidio F, Castelli V, Lombardozzi G, Ammannito F, Cimini A, D'Angelo M. Therapeutic advances in neural regeneration for Huntington's disease. Neural Regen Res 2024;19:1991-7.
66. Valadão KM, Luizeti BO, Yamaguchi MU, Issy AC, Bernuci MP. Nanotechnology in improving the treatment of Huntington's disease: A systematic review. Neurotox Res 2022;40:636-45.
67. Kim A, Lalonde K, Truesdell A, Gomes Welter P, Brocardo PS, Rosenstock TR, *et al*. New avenues for the treatment of Huntington's disease. Int J Mol Sci 2021;22:8363.
68. Singh S, Hema, Sharma N, Sachdeva M, Behl T, Zahoor I, *et al*. Focusing the pivotal role of nanotechnology in Huntington's disease: An insight into the recent advancements. Environ Sci Pollut Res Int 2022;29:73809-27.
69. Khan A, Özçelik CE, Begli O, Oguz O, Kesici MS, Kasırga TS, *et al*. Highly potent peptide therapeutics to prevent protein aggregation in Huntington's disease. ACS Med Chem Lett 2023;14:1821-6.