Current Neuropharmacology, 2023, *21*, 867-889

REVIEW ARTICLE

The Emerging Landscape of Natural Small-molecule Therapeutics for Huntington's Disease

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ARTICLE HISTORY

Received: June 30, 2022
Revised: November 12, 2022
Accepted: November 18, 2022

DOI:
10.2174/1570159X21666230216104621

Abstract: Huntington's disease (HD) is a rare and fatal neurodegenerative disorder with no disease-modifying therapeutics. HD is characterized by extensive neuronal loss and is caused by the inherited expansion of the huntingtin (HTT) gene that encodes a toxic mutant HTT (mHTT) protein having expanded polyglutamine (polyQ) residues. Current HD therapeutics only offer symptomatic relief. In fact, Food and Drug Administration (FDA) approved two synthetic small-molecule VMAT2 inhibitors, tetrabenazine (1) and deutetrabenazine (2), for managing HD chorea and various other diseases in clinical trials. Therefore, the landscape of drug discovery programs for HD is evolving to discover disease-modifying HD therapeutics. Likewise, numerous natural products are being evaluated at different stages of clinical development and have shown the potential to ameliorate HD pathology. The inherent anti-inflammatory and antioxidant properties of natural products mitigate the mHTT-induced oxidative stress and neuroinflammation, improve mitochondrial functions, and augment the anti-apoptotic and pro-autophagic mechanisms for increased survival of neurons in HD. In this review, we have discussed HD pathogenesis and summarized the anti-HD clinical and pre-clinical natural products, focusing on their therapeutic effects and neuroprotective mechanism/s.

Keywords: Natural products, Huntington's disease, neuroprotective mechanisms, drug discovery, therapeutic interventions, molecules, huntingtin (HTT).

1. INTRODUCTION

HD is an autosomal dominant progressive neurodegenerative disease with a global incidence of 2.7 per 100, 000 individuals, with western populations having the highest prevalence and Asian populations having the lowest [1, 2]. A few juvenile forms of HD (5% of all cases) with the disease onset by the age of 20 have also been reported [2, 3]. While the typical HD symptoms include movement disorder or chorea and cognitive deficits, juvenile HD patients exhibit mental disturbance rather than chorea [1-8]. Psychiatric symptoms, including obsessive-compulsive disorder, psychosis, and depression, are also prevalent in HD [9].

HD is a complex disease with varied symptoms, including involuntary choreatic motions and motor coordination deficiencies, mild to severe cognitive decline, and psychotic and behavioural deficits [1-7, 10] During the onset of HD, all these symptoms may not appear, but they worsen with age [1-7]. These phenotypes often manifest in middle age with cognitive and psychiatric abnormalities [1-7]. Motor coordination anomalies in HD can be categorized into choreiform movements with gait instability (which manifest early) and motor deficits, like stiffness and bradykinesia (typically appearing later), as the disease progresses [1-7]. Cognitive decline commences with minor disruptions but advances to apparent deterioration with age [1-7]. HD patients also find it difficult to manage basic daily tasks and lose mental agility [1-7]. Finally, HD patients may show signs of apathy, impatience, hyperactivity, and social dissociation, as well as frequent sadness, extreme mood swings, and anxiety [1-7].

HTT is about 350 kDa cytoplasmic protein with limited nuclear localization [9]. The nuclear localization sequence (NLS) of HTT is present at the N-terminus (between 174 to 207 amino acids), facilitating its nuclear interaction with

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karyopherin β2 [9, 10]. This NLS is made up of three consensus sequences: a basic-charged sequence, a proline-tyrosine sequence, and a downstream-conserved arginine [9, 11]. In addition, a nuclear export sequence is present at the COOH terminus of HTT [12]. Additionally, the N-terminus of HTT mediates its nuclear export by interacting with Tpr (a nuclear pore protein) [9, 13]. Of note, poly extensions reduce this interaction and enhance HTT nuclear aggregation [13]. Humans and rodents express HTT throughout the body [9, 13, 14]. However, the utmost expression is observed in the neurons. HTT is mostly localized in the cytoplasm on the vesicular membranes of the neurons [14]. HTT is predominantly abundant in cortico-striatal and large striatal neurons [14].

Existing HD therapeutics focus mainly on managing chorea, psychiatric and cognitive anomalies [1-7]. Tetrabenazine (**1**) and deutrabenazine (**2**) are FDA-approved medicines to treat HD chorea [15, 16]. Psychiatric HD symptoms, such as anxiety, depression, or irritability, are managed with benzodiazepines and SSRIs, while acetylcholinesterase inhibitors are used to treat HD-associated dementia [1-7, 17]. Presently, there is no disease-modifying treatment for HD [1-7]. However, several exciting studies at pre-clinical and clinical levels are being carried out to explore/identify the disease-modifying potential therapies for HD [1-7]. This article will highlight the structure and neuroprotective effects of clinical and pre-clinical natural products for the treatment of HD.

2. PHYSIOLOGICAL FUNCTIONS OF HTT

HTT is necessary during early embryonic development, as HTT knockout mice die before the nervous system develops at day 8.5 [9, 18]. Furthermore, current research indicates that HTT plays an important function in neurogenesis [9]. During the neural induction process, HTT is essential for the lineage maintenance of primitive neuronal stem cells [9, 19]. HTT plays an important function in neurulation-mediated homotypic interactions among neuro-epithelial cells by inactivating metalloproteases like ADAM10 [20]. Of note, the neural tube morphogenesis abnormalities observed in HTT-knockdown embryos of zebrafish were reversed by inhibiting ADAM10 with GI254023X [20].

2.1. HTT Functions as Scaffolding Protein and Transcriptional Control

HTT is a characterized scaffolding protein [9]. During mitosis, HTT localizes to spindle poles, where it controls the orientation of the spindle in mouse neural cells [9, 21]. HTT might also work as a scaffolding molecule, orchestrating the dynein/dynactin complex formation [9, 21]. The nuclear localization of HTT provides insight into its role in transcriptional control [22]. Although several transcription factors have been shown to interact with mHTT, the information about the interactions of transcription factors with the wild-type protein is poorly understood [9]. An excellent example of HTT-mediated transcriptional regulation is that of the brain-derived neurotrophic factor (BDNF) gene [9]. HTT regulates BDNF expression by neuron restrictive silencer factor (NRSF) or repressor element-1 transcription factor (REST), which negatively controls BDNF production, which is sequestered and inhibited in the cytoplasm by wild-type HTT [23]. HTT has recently been demonstrated to interact with methyl-CpG-binding protein 2 in both *in vitro* and *in vivo* HD models, which also regulates the HTT-mediated BDNF expression [9, 24].

2.2. Regulation of Synaptic Plasticity

HTT has emerged as a novel player in the regulation of synaptic plasticity [9]. In the presynaptic terminals, HTT is coupled with the synaptic vesicles and the postsynaptic PSD95 scaffolding protein [9, 14, 25]. Of note, a recent study found that HTT is essential for developing the striatal and cortical excitatory synapses [26]. The role of HTT in synaptic plasticity was further strengthened when silencing of the HTT in developing mouse brain increased the formation of excitatory synapses in the striatum and cortex [9].

3. PATHOGENIC MECHANISMS IN HD

HD is an autosomal dominant genetic disease caused by a poly cytosine-adenine-guanine (CAG) repeat expansion in the HD gene on chromosome 4 (4p16.3) [9]. The HD gene encodes the HTT (HTT) protein, expressed by various tissues and cells throughout the body, including the brain [9]. The mHTT protein generated by poly CAG repeat expansion causes neuronal death by interfering with the biological functions mentioned above. When the expansion of the CAG sequence exceeds the 6-26 repeats, it becomes highly unstable and might continue to expand in subsequent progeny, particularly with paternal transmission [1-7]. People having 27 to 35 repetitions seldom exhibit clinical signs and symptoms [1-7]. The average HD threshold is 36 repetitions, but complete penetrance is rarely visible before 40 repetitions [9]. Higher CAG repeats are responsible for the disease's early onset, fast development, and severity [1-7, 27, 28]. Furthermore, genetic predisposition or epigenetic changes might influence HD pathogenesis and severity [1-7, 27, 28]. When these aggregates clump together, they promote cellular malfunctioning and death, culminating in substantial shrinking of the afflicted brain regions, particularly the striatum [1-7, 27, 29]. Thus, striatal atrophy is considered the neuropathological hallmark of HD [1-7, 27, 29, 30].

Despite the well-defined genetic basis of HD, the frequency and diversity of molecular changes observed in HD are vast and poorly understood [9]. Since it is commonly stated that a gain of function of the mutant protein causes toxicity in HD, and impact of a loss of function of the wild-type protein cannot be ruled out [9] because loss or inactivation of wild-type HTT triggers neurodegeneration [31, 32]. We summarise some of the pathogenic processes that have been revealed to date, with a particular emphasis on those that are linked to prospective therapeutic targets (Fig. **1**).

3.1. mHTT Toxicity

The existence of aggregates in the brain is a defining feature of HD and other polyQ diseases [1-7]. HD aggregates are mostly made up of mHTT but contain ubiquitin, proteasome subunits, and chaperones [1-7]. The amount of these proteins is related to the speed of aggregation and disease manifestation [33]. mHTT aggregation, like other polyQ-containing proteins, occurs *via* nucleated polymerization, with polyQ residues forming a β-sheet stabilized by hydrogen bonding, resulting in a typical amyloidic structure found

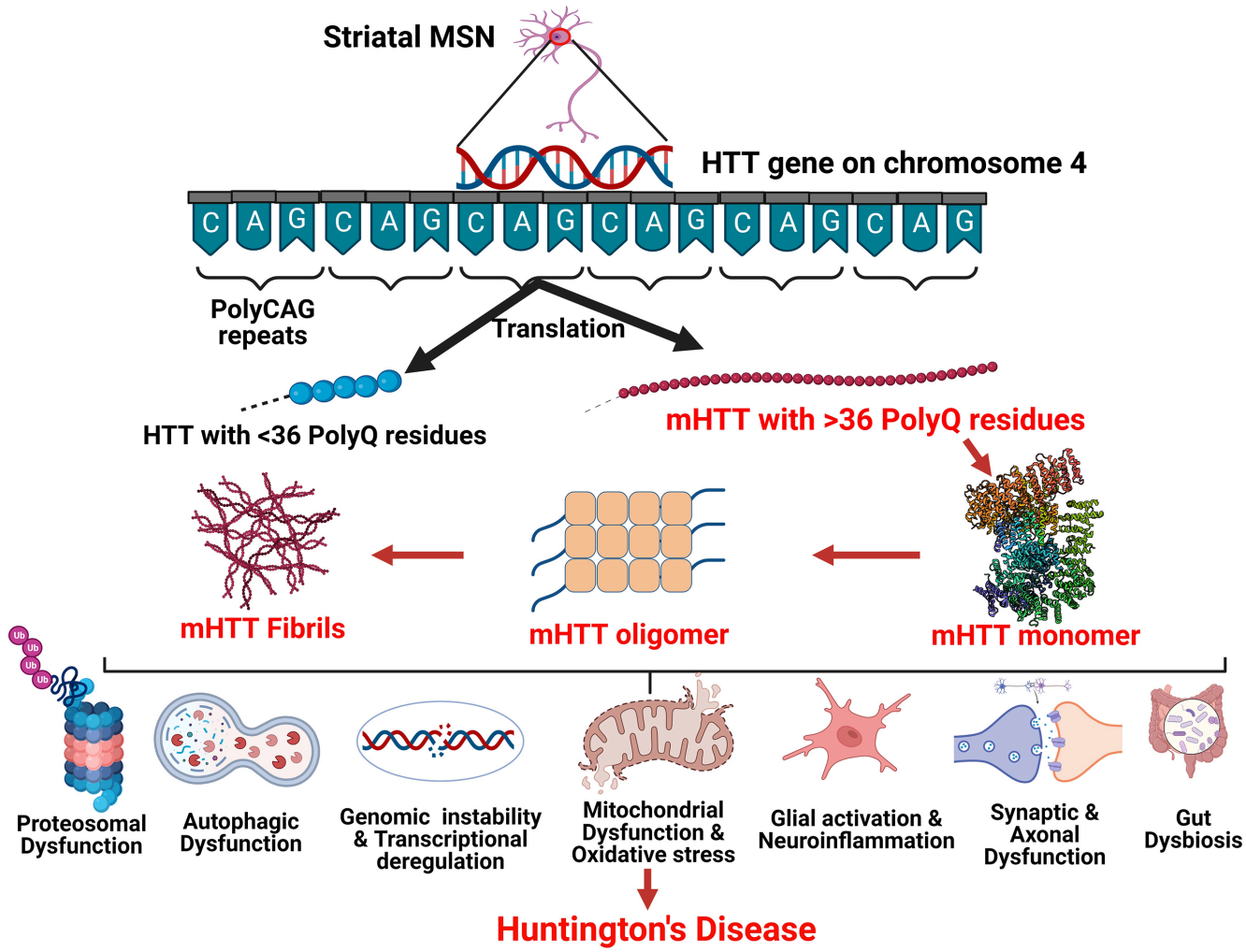

Fig. (1). Schematic diagram depicting the sequel of events/mechanisms in HD pathogenesis. mHTT (PDB: 6X9O) *via* dysregulation of various processes like proteasomal and autophagic degradation, mitochondrial dysfunction and oxidative stress, neuroinflammation, synaptic and axonal transport deregulation, genomic instability, transcriptional dysfunction, and gut dysbiosis results in neurodegeneration and HD pathogenesis. **Abbreviations**: MSN, medium spiny neurons; HD, Huntington's disease; HTT, huntingtin gene; mHTT, mutant Huntington protein. Figure prepared using Biorender software. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

in other degenerative diseases [34-36]. HD aggregates were originally detected in the nucleus of HD brains and then in the cytoplasm and neuronal processes [14, 37]. Further, it was demonstrated that the extent of poly-glutamine residues corresponds with aggregation and the disease onset, implying an unswerving relationship between aggregation and cell toxicity [33, 34, 37, 38].

In HD, the expanded polyQ tract causes mHTT to fold incorrectly, resulting in the formation of cytotoxic oligomers from the soluble monomers of HTT protein [1-7]. These oligomers then act as the starting point for the formation of mHTT fibrils and cytoplasmic and nuclear inclusion bodies [1-7, 14, 39]. Likewise, mHTT oligomers, fibrils, and inclusions have all been observed in HD brains [6, 40, 41]. Recent evidence suggests that mHTT oligomers are cytotoxic, while the inclusion formation might be neuroprotective [6, 42, 43]. PolyQ-containing N-terminal mHTT fragments, produced by either proteolysis or aberrant splicing, accumulate more rapidly than the full-length protein in HD patients [6, 44, 45]. There is also substantial proof that mHTT may propagate between cells since synthesized polyQ peptides are phagocytosed *in vitro*, and mHTT trafficking has been detected between adjoining cells through various mechanisms, including endocytosis, nanotubes, and phagocytosis [6, 44, 45]. However, mHTT seeding in human brains is poorly understood [6, 46-51]. Additionally, various molecular studies have pointed to the role of mHTT aggregates in sequestering the critical transcription factors and co-activators that affect the transcription process [6, 7, 52]. Furthermore, mHTT aggregates also derail organelle trafficking and vesicle transport in glia and neurons [6, 7, 27]. Finally, mHTT aggregates disrupt several mechanistic pathways, leading to genomic instability, mitochondrial dysfunction, synaptic deregulation, and autophagic and proteasomal anomalies [6, 7, 27, 53, 54].

3.2. HTT and Toxic Fragments

The accumulation of pathogenic N-terminal HTT fragments is a hallmark of HD [1-7, 55]. These fragments origi-

nate from various sources, including proteolysis by caspases and calpains [55, 56]. Although both HTT and mHTT are cleaved, mutant fragments are associated with greater toxicity [57]. These fragments differ across tissues, explaining the variations or susceptibility of different cell types [9]. Therefore, hampering the formation of these fragments has been actively explored as a potential HD therapy, such as modifying the cleavage vulnerability of HTT by Cdk5-mediated phosphorylation or phosphorylation of a domain that hampers calpain cleavage [58, 59].

3.3. Transcription Dysregulation

Transcriptional deregulation has been considered an important pathogenic factor in HD [9]. According to DNA microarray research, the expression patterns of several genes are significantly changed in HD [60, 61]. Many transcription factors have activation domains possessing glutamine-rich sequences, implying that they may interact with extended polyQ [9]. Interestingly, mHTT interacts with several transcriptional factors, including cAMP response element-binding protein (CREB), p53, and CREB-binding protein (CBP), which are essential for cell survival and proliferation, and PGC-1α (peroxisome proliferator-activating receptor-coactivator-1 alpha), which is necessary for metabolic control [57, 59, 62-64]. Furthermore, mHTT interacts with Sp1 and its co-activator TAFII130, which influences the transcriptional regulation of genes, like the D2 dopamine receptor [65, 66].

The greater vulnerability of the striatal neurons to neurodegeneration in HD has been linked to the reduction in cortical BDNF levels [9]. The BDNF transcriptional deregulation, impaired BDNF axonal transport, and reduced TrkB expression (BDNF receptor) are known to significantly increase the sensitivity of striatal neurons to neurodegeneration in HD [67-69]. Furthermore, corticostriatal synaptic abnormalities in mice models have recently been linked to BDNF signaling deficits rather than lower BDNF levels by regulating the postsynaptic receptor, p75 neurotrophin, which binds with BDNF [67, 70-73]. Notably, p75 neurotrophin has also been strongly associated with HD pathogenesis [67, 70-73].

3.4. DNA Repair and Genomic Instability

Most neurons are post-mitotic in the adult brain, and repair mechanisms become more important in neurons than in other cells as the neurons might die due to substantial DNA damage [7, 9]. These potentially hazardous and toxic lesions can form during regular neuronal tasks and might become highly toxic if not removed properly [7, 9]. Evidence suggests that DNA repair is hampered by mHTT in neurons, causing DNA damage to accumulate [7, 9]. The widespread occurrence of damaged DNA in HD postmortem brains, particularly in the pre-symptomatic HD mouse brain, suggests that DNA damage/lesions accumulation in HD might contribute to HD pathogenesis rather than being a diagnostic marker for HD [7, 74-76]. Recently, genome-wide association studies have identified numerous genes of DNA damage repair mechanism in neurons for HD pathogenesis (like, MLH1, FAN1, MSH3, LIG1, PMS1, and PMS2) as important determinants of disease severity and onset, implying that a faulty or impaired DNA repair pathway is associated with HD pathophysiology [6, 7, 9, 77, 78]. Of note, transgenic mHTT expression in the mouse brain causes DNA damage before the disease onset [7, 9]. These findings support the notion that failure of neuronal DNA repair processes caused by polyQ expansion might be an essential early contributing element to the downstream degenerative events seen in HD [7, 9].

3.5. Proteasomal Degradation and Autophagy

There are two primary intracellular protein degradation pathways: the ubiquitin-proteasome system (UPS) that rapidly degrades wild-type HTT and the autophagy crucial in degrading the enlarged mHTT proteins [9, 79]. Proteasomes may completely break down the enlarged polyQ, implying that a competent UPS is required in HD [9]. Early results suggested that the enlarged polyQ HTT reduces the proteasome activity due to the confinement of UPS components within inclusions or by the interaction of aggregation-resistant HTT variants and proteasome [14, 56, 80-82]. Additionally, *in vitro* neuronal and *in vivo* animal studies have revealed that an early UPS impairment is followed by the appearance of inclusions, implying proteasomal dysregulation in HD [83, 84].

Although HD models have an increased number of autophagosomes, neither mutant nor wild-type HTT alters autophagosome production [85, 86]. Further, HD autophagosomes cannot optimally sequester mHTT substrates due to the proposed role of wild-type HTT as a scaffolding protein for autophagy machinery during autophagy [87]. It is postulated that due to poor axonal transport of autophagosomes, a fusion of autophagosome-lysosome is diminished, which results in reduced mHTT degradation in HD [9, 88, 89].

3.6. Synaptic Dysfunction

Early pathogenic events in HD also include prominent synaptic dysfunctions [90-92]. Pathogenic HTT impairs axonal organelle transport [9, 93]. HTT polyQ-expansion may also indirectly impact synapsis by increasing the phosphorylation of JNK3 [9, 94]. Neuronal homeostasis may be jeopardized not only by reduced expression of neurotransmission and signaling genes but also by abnormalities in protein and organelle distribution in the neuronal axons [9, 93, 95]. mHTT aggregates by obstructing axons or confiscation of motor proteins impair the organelle transport across the axons [88, 95, 96]. In addition, HTT, by acting as a scaffold between microtubules, cargo, and motor proteins, promotes vesicle trafficking, which is disrupted by mHTT in HD [68, 88, 97, 98].

To enable synaptic transmission, axonal transport is essential for proper delivery to neuronal membranes [88, 95, 96]. Failure to supply receptors, such as AMPA (amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) or GABA (A) (g-aminobutyric acid type A), reduces synaptic excitability in HD [9]. mHTT also suppresses the transport and release of cortical BDNF and the retrograde striatal TrkB transport in HD, explaining the highest striatal MSNs degeneration in

HD [9]. Moreover, the studies have demonstrated that the glutamatergic signals selectively affect MSNs due to excitotoxicity *via* NMDA receptor stimulation, further corroborating the increased vulnerability of striatal neurons in HD [9, 90, 99, 100].

3.7. mHTT and Mitochondrial Health

Neurodegeneration in HD is linked with altered mitochondrial activity, which results in abnormalities in ATP synthesis, calcium buffering capability, and apoptotic cell death [101, 102]. mHtt can impair mitochondrial function and is linked to neurodegeneration in HD [101-103]. Mutants may be responsible for respiratory malfunction and neuronal cell death [101-103]. Studies have shown that mHTT interacts with the outer mitochondrial membrane, causing mitochondria calcium dysregulation [101-103]. mHTT also hampers the organelle's axonal trafficking, impairs mitochondrial synaptic transport and ATP generation, and cell death [102, 104, 105]. Further, a reduced PGC-1α expression (a transcriptional co-activator) required for mitochondrial biogenesis and respiration has been observed in HD [63]. Moreover, mHTT also impairs cysteine synthesis, which is necessary for mitochondrial homeostasis leading to dysfunctional mitochondria and neurodegeneration in HD [9, 106]. Furthermore, HTT inhibits TIM23 (inner mitochondrial membrane transport complex component); thus, the protein transport into mitochondria is impaired, resulting in mitochondrial failure and neurodegeneration in HD [9, 107]. Additionally, increased generation of reactive oxygen species (ROS) as a result of mitochondrial dysfunction causes the mitochondria to further deteriorate and increases neurodegeneration by many folds [9, 107]. The post-mortem HD brains and rodent HD models are significantly associated with oxidative damage; thus, antioxidants that can reduce ROS levels and improve mitochondrial functions are being evaluated as an effective therapeutic strategy for HD [9, 108-110].

3.8. Neuroinflammation

Increased release of pro-inflammatory cytokines and chemokines has been found in both late and early presymptomatic HD gene carriers [9, 111, 112]. Neuroinflammation is both a reactive and an active component in HD etiology [9, 111, 112]. Neuroinflammation is increasingly being linked to neurodegeneration in HD [9]. Neurons have more HTT aggregates than non-neuronal glial cells [9, 111, 112]. Glia also play a role in HD pathogenesis, as reactive gliosis is observed in several HD models [9]. Astrocytes are the most common glial cells and nourish neurons along with the glutamate uptake, thereby reducing glutamate-induced excitotoxicity [9]. Concurrent over-expression of mHTT in neurons and astrocytes exacerbated HD symptoms compared to neuronal-specific over-expression [9, 113, 114]. R6/2 and Q175 HD mouse astrocytes had decreased Kir4.1 potassium channel levels, resulting in increased extracellular striatal neuronal potassium and neuronal hyperactivation [115]. Additional abnormalities, such as reduced chemokine CCL5 or BDNF production or loss of BDNF-like activity, may contribute to the disease [115-117].

HTT is expressed in microglia, causing microglial activation and cytokine production due to increased transcription of myeloid-specific factors, like PU.1 and C/EBPs (CCAAT/enhancer-binding proteins) [118]. mHTT influences inflammatory responses in the peripheral immune system by inhibiting NF-kB signalling [118, 119]. Inflammation in HD may potentially be explained by signaling *via* CB2 cannabinoid receptors [120, 121]. Furthermore, mHTT-expressing microglia and peripheral cells show reduced migration in response to chemotactic cues [9]. Likewise, wild-type bone marrow cell transplantation in HD mice restored cytokine and chemokine levels and moderately inhibited HD progression [9, 122, 123].

3.9. Huntington and Other Proteinopathies

mHTT has been linked to several other neurodegenerative brain disorders [9]. For example, α-synuclein, a Lewy body component in Parkinson's disease, is generally associated with HTT aggregates, and higher mHTT aggregation is related to increased a-synuclein expression [124-127]. In line with these findings, knocking down α-synuclein in R6/1 animals decreased the inclusions frequency and slowed HD progression [128]. In contrast, a-synuclein overexpression mitigated autophagy and worsened HD progression in R6/1 and N171-82Q animals [129, 130]. Of note, reducing a-synuclein levels augmented autophagy in R6/1 and N171-82Q animals and slowed down HD progression [129, 131]. Moreover, an imbalance in tau isoform levels, prevalent in AD, with an enhanced three or four microtubule-binding repeats (4R/3R ratio) is enough to induce neurodegeneration [9, 132-134]. This relationship is enhanced in HD mice due to splicing abnormalities and contributes to HD pathogenesis [9, 132, 134]. HD mice models also influence tau phosphorylation, which may affect HD development [9, 133, 135].

3.10. Huntington and Gut Dysbiosis

Apart from the cognitive, motor, and neuropsychiatric symptoms, people with HD exhibit various gastrointestinal abnormalities, including nutrient inadequacies, diarrhoea, gastritis, and unexpected weight loss, as well as alterations in intestinal permeability, motility, and structure [136-139]. Thus, these symptoms are considered an indication of gastrointestinal dysfunction in HD [137-140]. Furthermore, gastrointestinal issues may be secondary repercussions of other progressive illness symptoms, such as cognitive impairment and reduced mobility [137-139]. The majority of research on the pathophysiology of HD has been on brain shrinkage and the associated cognitive, behavioural, and psychiatric symptoms; however, it is still unclear how much peripheral pathology, particularly in the gut, is connected to the illness' core symptoms [137-139, 141]. R6/1 transgenic HD mice express the mutant human HTT transgene and serve as an excellent preclinical model for the disease, displaying progressive cognitive, behavioural, cellular, and molecular deficits that closely resemble those seen in clinical HD [137-139, 141]. These deficits include the onset of gut dysfunction at the earliest stages of the disease, with the potential to get worse as the disease advances [137-139, 141]. This microbiota dysbiosis is observed in several neurodegenerative dis-

eases, such as Alzheimer's and Parkinson's disease [137-139, 141]. More recently, even before the development of motor symptoms, alteration of the gut microbiota has been repeatedly demonstrated in both preclinical and clinical HD [137-139, 141]. Importantly, modifications to the gut microbiota have been shown to be connected to an inflammatory state, cognitive function, and clinical outcomes in HD gene expansion carriers (including symptomatic patients) [137-139, 141]. Given the experimental and clinical evidence of gut dysbiosis in HD, future therapeutic approaches, like fecal matter transfer (FMT), and other forms of gut microbiome modification, like dietary probiotics and prebiotics, are now being developed as potential HD therapeutics.

4. HORMESIS AND NEUROPROTECTION

Regulation of cellular defense mechanisms is a novel treatment option in diseases that cause chronic cellular injury, such as neurodegeneration [142, 143]. Low stress levels may even help prevent further injuries. Hormesis is a biphasic dosage response in which a biologically favourable response is elicited by exposing an organism or cell to small amounts of toxins and other stressors [142-145]. For instance, in the early stages of neurodegenerative disorders, mild or low levels of oxidative stress or ER stress specifically activate the UPR signalling processes, which prevent apoptotic neuronal death [142-145]. Additionally, mitochondrial superoxide and hydrogen peroxide are key players in various cellular processes that can trigger signalling pathways that support cell survival and resistance to disease [142-145]. Superoxide-activating protein kinase C promotes neurite outgrowth, suggesting that mitochondrial ROS may play a role in the recovery following injury [142-145]. It is interesting to note that extracellular regulated kinase activation is necessary for the mechanism through which superoxide increases long-term potentiation in hippocampal CA1 neurons [142-145]. Although the precise molecular processes by which mitochondrial ROS promotes neurohormesis are not entirely known, the transcription factors with regulatory effects may play a significant role.

Even though mitochondrial H_2O_2 may stimulate neurons' adaptive stress response processes, it also has the potential to protect other cell types against neurodegenerative diseases [142-145]. Recent research has clarified the molecular processes and cellular signalling pathways that govern the hormetic adaptation response, which often entails the production of numerous stress-resistance proteins as by-products of vitagenes, a set of genes dedicated to maintaining homeostasis under stressful circumstances [142-145]. The vitagenes family includes the heat shock proteins (Hsp) Hsp32, Hsp70, Hsp60, heme-oxygenase-1 (HO-1), thioredoxin system, and sirtuin proteins [142-145]. Of note, the antioxidant response element (ARE) is present in single or multiple copies in the regulatory regions of the vitagenes [142-145]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is the most important transcription factor that binds to the ARE [142-145]. Under homeostatic settings, cytoprotective gene expression is minimal due to low Nrf2 intracellular levels regulated by Kelch-like ECH-associated protein 1 (Keap1) [142-145]. However, numerous stressors, such as mitochondrial oxidative stress, activate the Keap1/Nrf2/ARE pathway, resulting in the activation of vitagenes that result in the transcriptional upregulation of cytoprotective proteins and prevent cellular injury and damage (Fig. **2**) [142-145]. Initial exposure to low-dose stressors (exogenous and endogenous inducers) to improve mitochondrial functions and prevent neurotoxicity is being evaluated as an effective therapeutic strategy for HD because mHtt-induced mitochondrial oxidative stress and mitochondrial dysfunction are linked to neurodegeneration in HD [142-145]. For instance, the neuroprotective properties of hormetic phytochemicals, such as polyphenols, which activate the Keap1/Nrf2-ARE pathway, are thought to be prospective molecules or compounds for anti-HD treatment [142-145]. In the subsequent section of the paper, these hormetic phytochemicals will be discussed in more detail.

5. THERAPIES AGAINST HD

There are various approaches for treating HD, including small molecules, CRISPR/CRISPR-associated protein 9 (Cas9), RNA interference, antisense oligonucleotides, monoclonal antibodies, small molecules, and zinc finger repressors [6]. These therapies work either by HTT gene editing, HTT RNA targeting, or inhibiting the aggregation of mHTT protein [146]. According to ClinicalTrials.gov, approximately 256 clinical trials have been registered for treating HD, including 64 observational and 192 interventional studies (accessed on June 25, 2022). Among the interventional trials, 105 studies have been completed, and 20 others have been terminated for various reasons. The majority of interventional studies, 157 trials, are without results, and only 35 studies have results. These interventional studies are at different stages of clinical development (phase I = 52, phase II = 68, and phase III = 28).

5.1. Overview of Synthetic Small Molecule Therapeutics for Treating HD

In the last two decades, small molecules have emerged as potential therapeutics for treating HD [147]. There are various advantages of using small molecules, such as their small size, longer shelf life, cost-effective production, ease of modification, oral bioavailability, high pharmacological properties, and capability of crossing the blood-brain barrier (BBB) [148, 149]. As a result, tetrabenazine (**1**), a vesicular monoamine transporters 2 (VMAT2) inhibitor, was approved by FDA in 2008 for managing the chorea associated with HD (Fig. **3**) [147]. Similarly, deutetrabenazine (**2**) was approved by FDA in 2017 for the same indication. Deutetrabenazine (**2**) is an isotopic isomer of tetrabenazine (**1**) with enhanced tolerability and metabolic stability (Fig. **3**) [147].

Besides these two FDA-approved drugs, several other off-label small-molecule-based medicines are used to manage various HD symptoms. Similarly, numerous novel small molecules and earlier approved drugs (drug repurposing) are currently under clinical investigation for managing HD. These

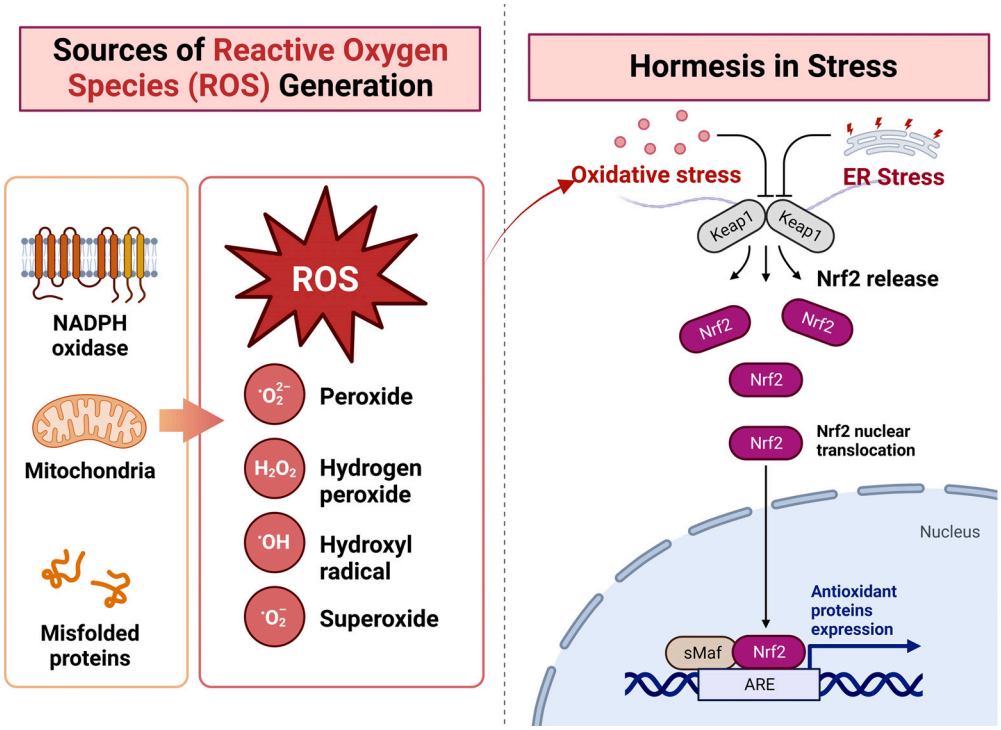

Fig. (2). Schematic diagram depicting the numerous stressors, such as mitochondrial oxidative stress, by the activation of Keap1/Nrf2/ARE pathway, to promote neurohormetic response *via* transcriptional upregulation of cytoprotective proteins and prevent neuronal injury and death. Figure prepared using Biorender software. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

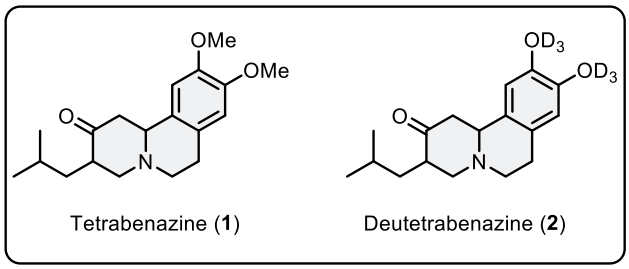

Fig. (3). Chemical structure of FDA-approved drugs to manage chorea associated with HD.

small molecules include synthetic compounds and natural products [147, 150]. These small molecules ameliorate HD by targeting the HTT gene, splicing and CAG repeat of mutant RNA, and mHTT aggregation, modulating several other critical drivers involved in HD pathogenesis [6]. We have summarized the important synthetic small molecules (**3**-**21**) in Fig. (**4**), which are currently performing well in clinical trials for HD management. In Fig. (**4**), we have skipped those molecules discontinued from the clinical trials. Due to the several unwanted side effects of synthetic small molecules HD therapeutics, increased attention is being given to adopting complementary and alternative therapies based on natural products [151].

5.2. Neuroprotective Mechanisms and Anti-HD Effects of Natural Products

Though HD is a rare neurodegenerative disease, due to the autosomal dominant nature of HD, the diagnosis and accurate modeling of the disease are possible [150, 152-156]. Interestingly, various nutraceuticals have exhibited the potential to treat HD by delaying the symptomatic onset of the disease *in vitro* and *in vivo* [157]. These natural products exert their effect by acting as free radical scavengers, antioxidants, anti-inflammatory and anti-apoptotic agents, reducing oxidative stress, inducing autophagy, and improving mitochondrial functions, as depicted in Fig. (**5**) [150-156].

Besides isolated natural products, extracts from various medicinal plants have been evaluated to check neuroprotection *in vitro* and *in vivo*. Most of these plant extracts show potential against HD due to antioxidant properties, *e.g.*, plant extract from *Calendula officinalis, Celastrus paniculatus, Centella asiatica, Convolvulus pluricaulis, Luehea divaricate,* and *Withania somnifera* [158-164]. Extracts from other medicinal plants exhibit neuroprotective activity due to their free radical scavenging, cholinesterase, MAPKs, and NF-κB inhibitory activities [165-167]. This review summarizes the naturally occurring small molecules under clinical and preclinical investigations for managing HD.

5.2.1. Natural Products Against HD with Anti-oxidant and Anti-inflammatory Activities

A plethora of neurodegenerative diseases, including HD, have the predominant feature of oxidative stress and neuroinflammation, marked by increased ROS production, depletion of cellular antioxidants, and increased release of pro-inflammatory mediators [6, 46-51]. Interestingly, some of these natural products are currently elevated as potential anti-HD candidates at various phases of clinical trials (Fig. **6**). For instance, ubiquinol (**22**) is a reduced form of coenzyme Q10, which is known for boosting cell energy and free radical scavenging

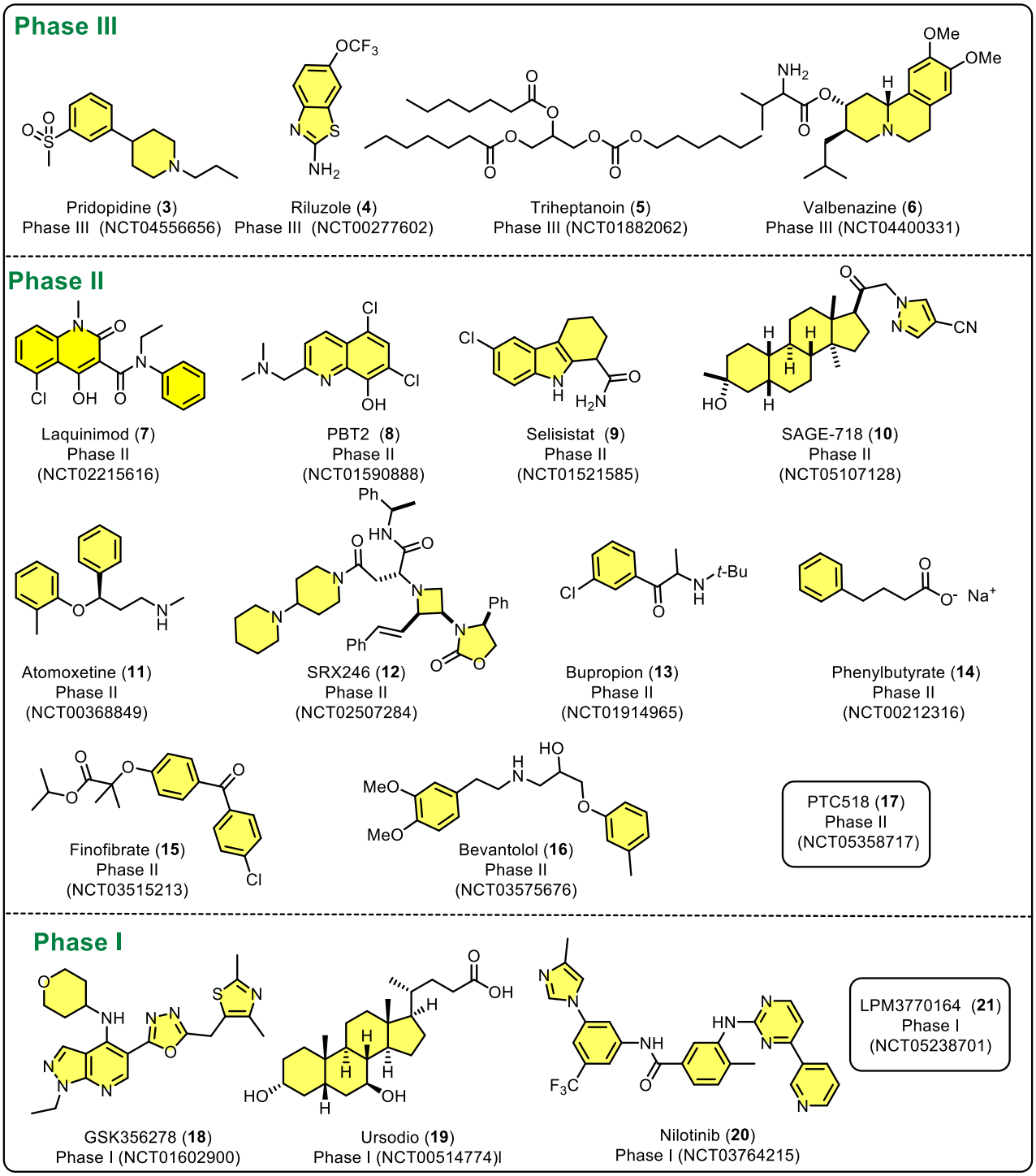

Fig. (4). Structures of synthetic small-molecule-based clinical candidates to manage HD.

property. Ubiquinol (**22**) was found to be safe and well-tolerated in phase III clinical trials in patients with early-stage HD (NCT00608881). However, no significant benefit in terms of slowing down the progression of HD of high-dose of ubiquinol (**22**) was observed in the treated group [168]. The striatum is responsible for motor control, one of HD's most affected brain areas. Notably, the striatum is rich in cannabinoid receptors (CBRs), which control neuronal function and neuroinflammation in neurons and microglia [169, 170]. These CBRs diminish in the early stage of HD progression [169, 170]. Interestingly, cannabinoid treatment improved the levels of BNDF, brain lesions, and overall phenotypes in the animal model of HD [169]. The safety and efficacy of a combination of cannabinoids, delta-9-tetrahydrocannabinol (**23**) and cannabidiol (**24**), are being evaluated in phase II clinical trial (NCT01502046). Melatonin (**25**) is a neurohormone known for its antioxidant and anti-inflammatory effects and shows neuroprotection in HD. Further, a change in melatonin (**25**) levels has been observed during HD pathogenesis [171]. The University of Texas

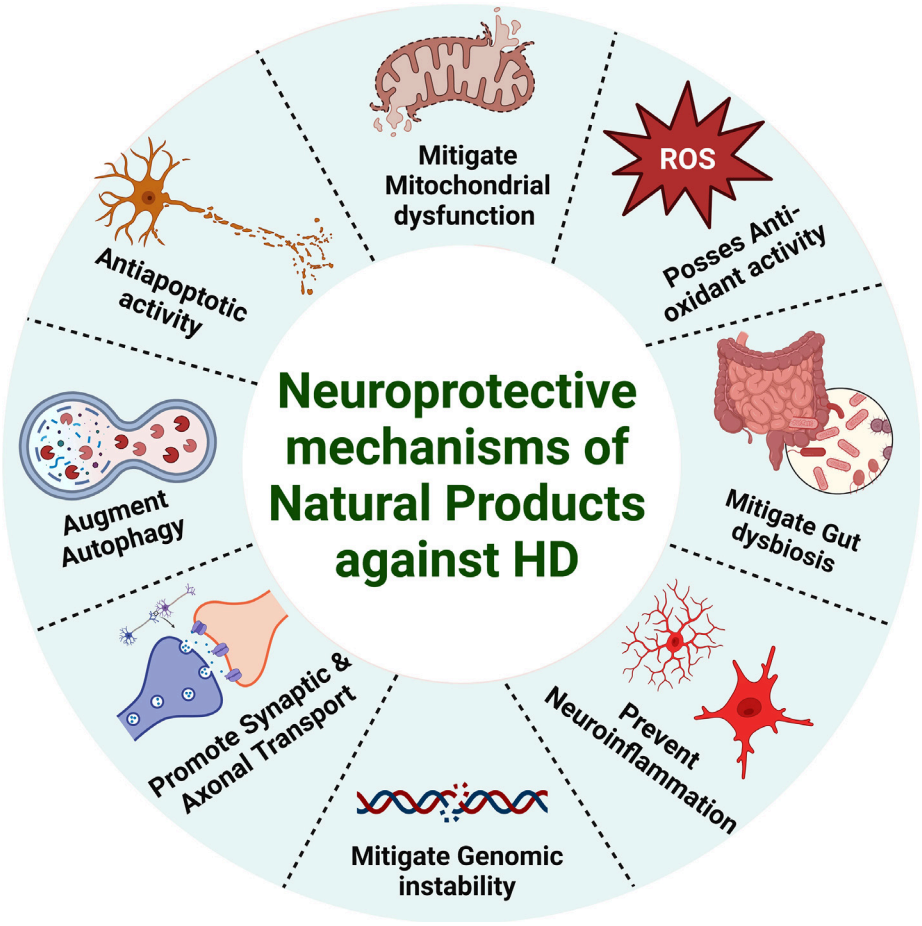

Fig. (5). Overview of the putative neuroprotective mechanisms of natural products against HD. Figure was prepared by using Biorender software. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

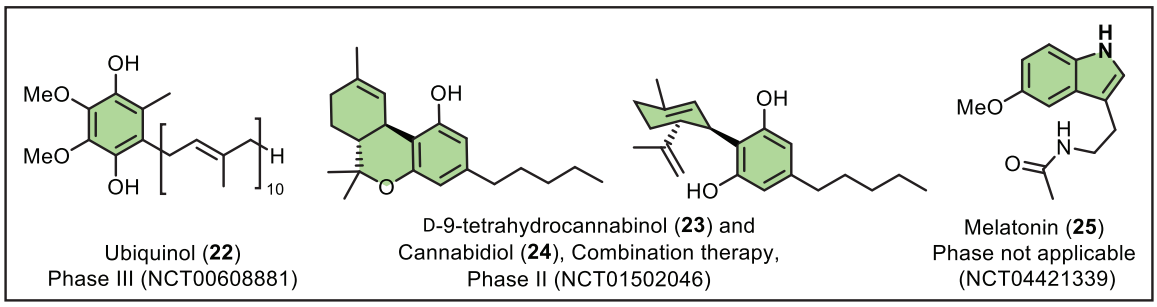

Fig. (6). Clinical natural products with anti-oxidant and anti-inflammatory activities to manage HD.

Health Science Center (Houston) is currently recruiting to examine the efficacy of melatonin (**25**) supplements for enhancing sleep quality in HD patients (NCT04421339).

Interestingly, numerous natural products with anti-oxidant and anti-inflammatory activities are under the pre-clinical stage of development to manage HD (Fig. **7**). Natural products, like protopanaxatriol (**26**), naringin (**27**), and solanesol (**28**), due to their anti-oxidant activities, like scavenging of free radicals, inhibition of ROS generation by NADPH oxidase, *etc*., are effective in the mitigation of HD pathogenesis in both *in vitro* and *in vivo* conditions [6, 46-51]. The potent antioxidant activity of these compounds might also be due to the induction of the inherent anti-oxidant defense mechanisms, for example, activation of the Nrf2 pathway, which increases the level of anti-oxidants like CAT, SOD, GSH, *etc*., to prevent ROS-mediated cellular injury and apoptosis [6, 46-51]. Moreover, by mitigating lipid peroxidation, these compounds limit cellular damage in HD [150, 163, 172, 173]. Additionally, natural compounds prevent the activation of the NFκB pathway (major neuroinflammatory pathway), reduce the glial activation and subsequent release of pro-inflammatory mediators, and thus prevent neurodegeneration in HD models [150, 163, 172, 173]. Protopanaxatriol (**26**) is one of the ginsenosides isolated from *Panax*

ginseng. The antioxidant nature (free radical scavenger) of protopanaxatriol (**26**) protects striatal neurons *in vitro* and reduces 3-NP-induced oxidative stress *in vivo* [174, 175]. Celastrol (**29**) is a triterpene isolated from the root and bark of *Tripterygium wilfordii*, and is known for its antioxidant and anti-inflammatory action. Celastrol (**29**) protects from 3-NP-triggered neurotoxicity and increases the expression of HSP70 *in vivo* [176]. On the other hand, dihydromyricetin (**30**) is a flavonoid isolated from *Ampelopsis grossedentata*. Dihydromyricetin (**30**) exhibited neuroprotection *in vivo* through an antioxidant defense system [177]. Similarly, praeruptorin C (**31**) is an anti-depressant and neuroprotective natural product, which reduces the 3-NP-triggered neural defects [178, 179]. Moreover, embelin (**32**) is well known for its antioxidant, anti-inflammatory, and anticonvulsant activities, and protects from 3-NP-induced neurotoxicity *in vivo* due to its free radical scavenging nature [180]. Natural products, such as esculetin (**33**), forskolin (**34**), genistein (**35**), and nicotine (**36**), have also displayed neuroprotective activities in various HD models due to their inherent antioxidant and free radical scavenging nature [156, 181-183]. Gintonin (**37**) is a complex anti-inflammatory molecule, which enhances striatal cell survival by reducing mitochondrial dysfunction and inhibiting MAPKs and NF-κB [184]. Carotenoids, like lutein (**38**) and lycopene (**39**), are well-known natural antioxidants that relieve symptoms associated with HD *in vivo* [185, 186]. Several other isolated natural products with anti-oxidant and anti-inflammatory neuroprotective properties, such as spermidine (**40**), sulforaphane (**41**), tetramethylpyrazine (**42**), α-mangostin (**43**), L-theanine (**44**), quercetin (**45**), sesamol (**46**), luteolin (**47**), puerarin (**48**), and S-allylcysteine (**49**), have been reported in the literature [155, 150, 187-194].

5.2.2. Natural Products Inhibiting mHTT Aggregation, Excitotoxicity, and RNA Splicing to Manage HD

We have summarized the natural products inhibiting mHTT aggregation, excitotoxicity, and RNA splicing in Fig. (**8A**). Epigallocatechin-3-gallate (EGCG, **50**) and ellagic acid (**51**) have been shown to reduce mHTT aggregation and cytotoxicity in HD [150, 195, 187]. Interestingly, EGCG (**50**) improved photoreceptor degeneration and motor function in transgenic HD flies [195]. Currently, Charite University is evaluating the efficacy, tolerability, and effects on HD biomarkers using an EGCG (daily dose of 1200 mg) supplement in a phase II clinical trial (NCT01357681). Further, T1-11 (**52**), isolated from *Gastrodia elata*, reduces the mHTT aggregation and protects against apoptotic cell death in HD [196]. Further, a combination of dextromethorphan (NMDA antagonist) and quinidine (**53**) is being evaluated in phase III clinical trial to mitigate the excitotoxicity in the HD brain (NCT03854019). Quinidine (**53**), an inhibitor of CYP2D6 and which improves the bioavailability of dextromethorphan (NMDA receptor antagonist), is being evaluated for HD-linked excitotoxicity [197]. The RNA-binding protein and cytoplasmic polyadenylation element binding protein (CPEB) shorten or lengthen the poly(A) tails of CPE-containing transcripts to suppress or stimulate translation, respectively [198]. Druggable SLC19A3 (thiamine transporter-2) is the key deadenylated transcript linked to striatal atrophy in HD, and high-dose thiamine (**54**) and biotin (**55**) therapy mitigated the neuropathological and motor HD-like phenotypes in HD mice [198]. Currently, a phase II clinical trial is evaluating a combination of thiamine (**54**) and biotin (**55**) to reduce the progression of symptoms in early-stages HD patients (NCT04478734).

5.2.3. Natural Products Improving Mitochondrial Functions and BDNF Synthesis to Manage HD

Mitochondrial dysfunction, characterized by the alteration in ATP synthesis, mitochondrial ROS production, mitochondrial biogenesis, degradation, and fragmentation, is the common pathological marker shared by all neurodegenerative diseases, including HD [150, 163, 191, 192]. It is well established that mHTT promotes mitochondrial dysfunction in HD [150, 163, 172, 173]. Resveratrol (**56**) is currently under clinical trial to reduce neurodegeneration by improving energy profiles in patients with HD (NCT02336633). Notably, resveratrol (**56**) exhibits diverse biological activities ranging from cancer to neurological disorders. Resveratrol (**56**) improves energy metabolism and mitochondrial functions by modulating several neuroprotective and neurodegenerative therapeutic targets, including AMPK, Sirtuin 1, and PGC-1α (Fig. **8B**) [199, 200]. Cysteamine (RP103, **57**), a natural molecule with low molecular weight, has been reported to enhance the levels of BNDF and show beneficial effects in numerous animal models of HD. In phase II/III clinical trial, cysteamine (**57**) was found to be safe and well tolerated, but there was no evidence of efficacy in HD patients (NCT02101957) [201]. Interestingly, EGCG (**50**), by augmenting enzyme activities of cytochrome oxidase, NADH, ATP synthase, *etc*., also promotes ATP synthesis and rescues mitochondrial functions in HD [150, 202]. In addition, naringin (**27**) and genistein (**35**), in addition to their anti-oxidant activities, mitigate NMDA-induced ATP loss and mitochondrial dysfunction [150, 156, 203-205]. Further, naringin (**27**) (flavanone glycoside isolated from grapefruits) also exhibits neuroprotection by improving mitochondrial functions *via* activating Nrf2 [203-205]. Solanesol (a precursor of coenzyme Q10, **28**) also reduces mitochondrial dysfunction by enhancing the levels of ATP and protecting the brain from inflammation by exerting its antioxidant effect [206].

5.2.4. Natural Products Modulating Apoptosis and Autophagy to Manage HD

The natural compounds, such as dihydromyricetin (**30**), praeruptorin C (**31**), genistein (**35**), *etc*., besides their antioxidant activities, show anti-apoptotic activity mainly by increasing the expression of anti-apoptotic factor Bcl2 and down-regulation of pro-apoptotic factors, like Bax and Bad, thereby preventing the release of cytochrome c and subsequent caspase activation [150, 152-156, 178, 179]. Further, these compounds also increase neuroprotective peptides like BDNF, which mitigate apoptosis in both *in vitro* and *in vivo* models [150, 152-156]. Since striatal neurons are most vulnerable to apoptosis in HD, natural compounds, by reducing the levels of catecholamines, like norepinephrine and serotonin, show anti-apoptotic activity in HD models [150, 152-156].

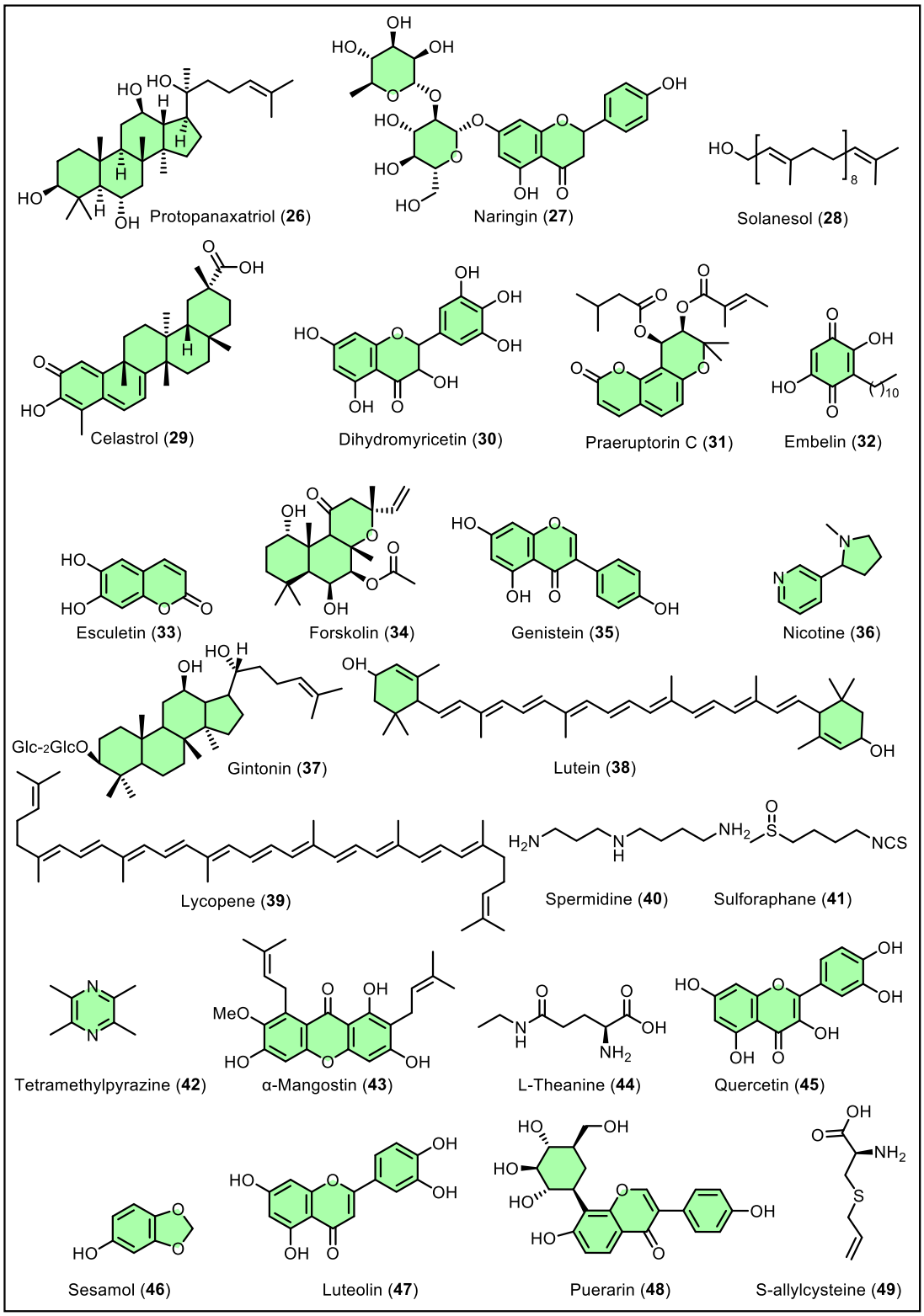

Fig. (7). Preclinical natural products with anti-oxidant and anti-inflammatory activities to manage HD.

Autophagy is the cellular process through which cells degrade and remove defective proteins, protein aggregates, and defective organelles [207, 208]. However, autophagic dysregulation and inhibition have been observed in many neurodegenerative diseases, including HD [207, 208]. It has been demonstrated that natural compounds, like neferine (**58**), mitigate neurotoxicity by activating autophagy *via* the mTOR/AMPK pathway [207]. *Nelumbo nucifera* is a medicinally important plant, and its seed embryo possesses a non-toxic alkaloid called neferine (**58**) (Fig. **8C**). Of note, the upregulation of autophagic activity promoted neuroprotection and improved cognitive functions *via* increased mHTT

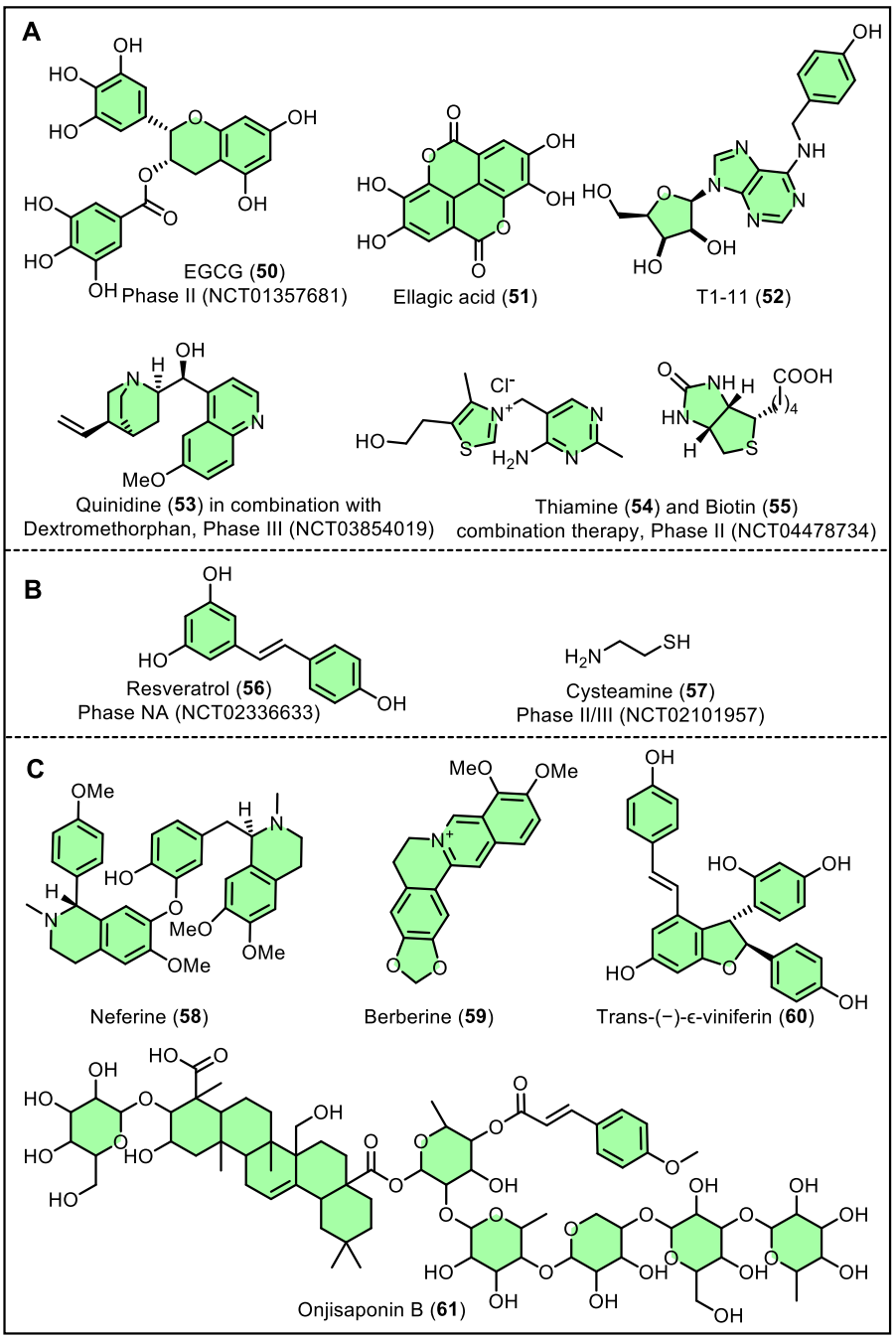

Fig. (8). Natural products to manage HD (**A**) by inhibiting mHTT aggregation, excitotoxicity, and RNA splicing; (**B**) by improving mitochondrial functions and BDNF synthesis; and (**C**) by modulating apoptosis and autophagy.

degradation [207, 208]. Additionally, the strategies that promote the activation of molecular chaperones, like HSP70, impart neuroprotection in HD models [209]. Berberine (**59**), isolated from *Coptis chinensis*, is an alkaloid used to treat various diseases [148, 210]. Berberine (**59**) has exhibited neuroprotection across multiple HD models [210]. It improves motor function by modulating Nrf2 and MAO-B, and degrades the mHTT by increasing autophagy [210]. Trans-(−)-ϵ-viniferin (**60**), by activating AMPK, induces autophagy and promotes neuroprotection in HD [150]. On the other hand, onjisaponin B (**61**) is present in the roots of *Polygala tenuifolia*, and has a high molecular weight. Neferine (**58**) and onjisaponin B (**61**) provided neuroprotection to PC-12 cells against mHTT-toxicity by disrupting autophagy [207, 208].

5.2.5. Natural Products Against HD that Promote Neurohormetic Response by Activation of the Vitagenes

Natural products make up a large portion of the Keap1/Nrf2/ARE pathway inducers (Fig. **9**) [142-144, 211]. The growing body of data supporting biphasic dosage response effects of external "toxins" in living organisms implies that phytonutrients from edible plants may also exhibit biphasic dose responses and contribute to the well-known health advantages of plant-rich diets [142-144, 211]. The antioxidant

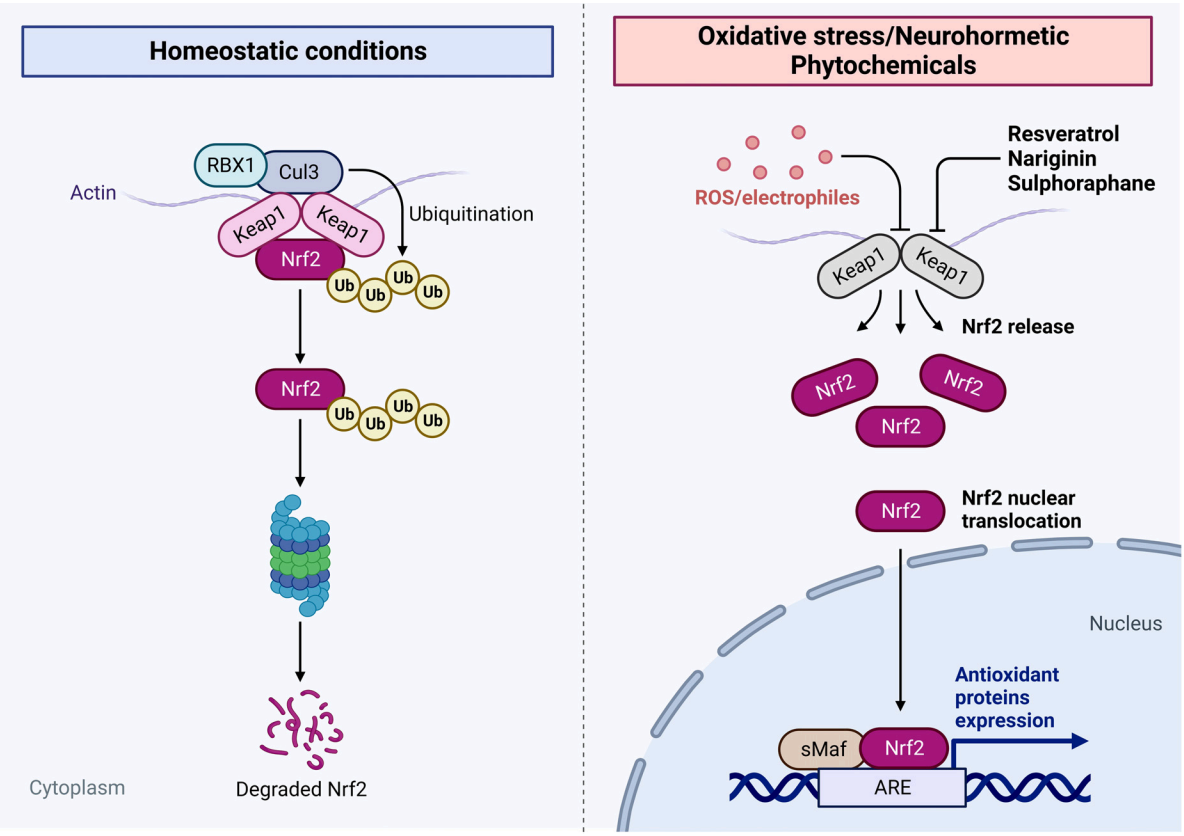

Fig. (9). Natural products promote neurohormetic response by activation of the Keap1/Nrf2/ARE signalling pathway. Figure prepared using Biorender software. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

properties of sulforaphane (**41**), naringin (**27**), and resveratrol (**56**) are now supported by a variety of lines of research (Fig. **9**) [142-144, 211]. Even while some of the health advantages of certain phytochemicals may be attributed to their antioxidant potential, the vast majority of individuals do not eat enough fruits and vegetables to attain the significant amounts of antioxidants needed to scavenge free radicals efficiently [142-144, 211]. Additionally, there is no evidence from clinical trials that antioxidant supplements, like vitamins E and C, have any positive effects on health [142-144, 211]. New findings indicate that the health advantages of phytochemicals could be best explained by stimulation of the Keap1/Nrf2/ARE pathway than by their free radical scavenging activities (Fig. **9**) [142-144, 211]. The activation of adaptive cellular stress response processes by a variety of phytochemicals has been demonstrated to cause the transcription of hundreds of genes producing protein chaperones, neurotrophic factors, antioxidant enzymes, and other neuroprotective proteins [142-144, 211]. Because they work through the induction of transcription-mediated signalling, stimulators of the Keap1/Nrf2/ARE cascade have longer-lasting effects than direct antioxidants (like vitamin C) with short half-lives [142-144, 211].

Recent research suggests that similar mechanisms that promote neuroprotective effects due to calorie restriction and exercise mediate phytochemical-linked adaptive cellular stress responses [142-144, 211]. It has been observed that widely ingested phytochemicals might promote moderate stress in neurons, improving the nervous system's capacity to handle stress and improving neuronal health [142-144, 211]. Similar to exercise and calorie restriction, neurohormetic phytochemicals intake occurs intermittently, allowing cells to switch between recovery/growth and stress for cellular growth and repair [142-144, 211]. In a few recent studies, it has been discussed as to how neurohormetic phytochemicals, like sulforaphane (**41**), naringin (**27**), lycopene (**39**), EGCG (**50**), and resveratrol (**56**), might activate stress-resilient cellular pathways linked to oxidative stress, for example, Nrf2-ARE and nuclear factor kappa β (NFkB) pathways [142-144, 211]. Further, these phytochemicals also modulate other stress-resilient pathways, like adenosine monophosphate-activated protein kinase (AMPK), sirtuins (*e.g.*, resveratrol), insulin-like growth factor 1 (*e.g.*, lycopene), and mammalian target of rapamycin (mTOR) (*e.g.*, EGCG), which are recognized to be essential in the adaptive response to oxidative stress [142-144, 211].

CONCLUSION

Natural products have always attracted much attention due to their biocompatibility and higher physicochemical properties. In this review, we have summarized the current status of small-molecule therapeutics for treating HD. In particular, we have emphasized discussing therapeutic effects and mechanisms of neuroprotection of natural products. Recently, numerous naturally occurring small-molecule therapeutics with anti-inflammatory and antioxidant properties have been reported, which exhibit neuroprotection by improving mitochondrial function, inducing autophagy, and

reducing apoptosis. For instance, EGCG (**50**), resveratrol (**56**), and melatonin (**25**) are currently being evaluated in clinical trials. Combination therapy, in which a natural molecule in combination with another natural molecule or synthetic molecule, is also being adopted for HD therapeutics, for example, delta-9-tetrahydrocannabinol (**23**) with cannabidiol (**24**), quinidine (**53**) with dextromethorphan, and thiamine (**54**) with biotin (**55**) are performing well in the clinical trials. Nevertheless, relatively few natural products have been translated into clinical trials, and the success rate in clinical studies is low. For example, no significant benefit of ubiquinol (**22**) and cysteamine (**57**) treatment has been observed in patients with HD under the phase III clinical trial. However, numerous natural products with higher neuroprotective effects have been identified as the understanding of HD pathogenesis has increased, and are currently in the preclinical stage of development.

Nearly 50% of HD patients exhibit depression as one of the most common psychiatric symptoms [212, 213]. HD-related depression raises the risk of suicide, with nearly 30% of patients attempting suicide once [213-215]. Identifying the genesis and pathology of depression seems important for early diagnosis of HD-linked depression and improved clinical diagnosis and outcome. One of these important diagnostic indicators of depression is the disruption of the serotonin (5-HT) signalling system [213, 216, 217]. Additionally, enterochromaffin cells (ECs) in the gut produce nearly 95% of the body's 5-HT, a hormone with autocrine, paracrine, and endocrine effects [217-219]. Reduced serotonin receptor expression and the prevalence of altered depressive-related behaviours in HD are consistent with other forms of depression [213, 216, 217]. This shows that reduced serotonergic signalling underpins the genesis of depressive-like traits in HD [213, 216, 217]. It is worth noting that 5-HT production in the gut might alter vasculature (membrane) permeability across the body and the blood-brain barrier (BBB) [217-220]. Dysbiosis that disrupts 5-HT levels has also been linked to depression, posttraumatic stress disorder (PTSD), autism spectrum disorder (ASD), anxiety, Parkinson's, Alzheimer's diseases, *etc*. [139, 218, 221]. Of note, the antioxidant properties of natural products, such as polyphenols, have recently received increased attention due to their capacity to lower oxidative/inflammatory stress signalling, boost neuroprotective signalling molecules, and modulate gut flora [222-224]. Notably, polyphenols can modify the human gut microbiota *in vivo*, and this association can be efficacious in brain neuroplasticity [222-224]. Importantly, natural products, such as polyphenols, decrease gut dysbiosis, which may help to reduce inflammation, depressed behaviour, serotonin (5-HT) signalling dysfunction, and clinical outcomes in HD [222-224]. Given the experimental and clinical evidence of gut dysbiosis in HD and its regulation by natural products, future treatment techniques, such as faecal matter transfer (FMT), and other forms of gut microbiome modification, such as dietary probiotics, prebiotics, and natural chemicals (for example, polyphenols), should be investigated as possible HD therapeutics.

Despite the enormous potential to vastly improve the drug discovery program for HD therapies, due to the scarcity of clinical trials, the translation of preclinical investigations to the clinics remains a key barrier. The failure of these experimental investigations to be translated can be due to several factors, including inadequate solubility, limited bioavailability, dose variations, inferior metabolic and chemical stability, therapeutic window and target selection, and so on, because one of the key limitations of these natural products is their decreased bioavailability owing to the BBB; future nutraceuticals in conjunction with nano-carriers should be used for brain-specific delivery of these natural chemicals for efficient translation from experimental research to clinics. Furthermore, those nano-carriers that, in addition to boosting bioavailability, will also limit drug metabolism to improve the stability of natural chemicals should be used. Additionally, artificial intelligence-based strategies for biomarker identification should be used so that disease progression and severity, as well as the beneficial outcome of natural products, can be monitored for the efficient and timely translation of promising preclinical natural compounds to clinics.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
ADAM10	=	A Disintegrin and Metalloproteinase Domain-containing Protein 10
AMPA	=	Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AMPK	=	AMP-activated Protein Kinase
ATP	=	Adenosine Triphosphate
BBB	=	Blood-brain Barrier
BDNF	=	Brain-derived Neurotrophic Factor
CBRs	=	Cannabinoid Receptors
CCL5	=	Chemokine Ligand 5
CNS	=	Central Nervous System
CAG	=	Cytosine-adenine-guanine
CAT	=	Catalase
C/EBPs	=	CCAAT/Enhancer-binding Proteins
CREB	=	cAMP Response Element Binding Protein
Cdk5	=	Cyclin-dependent Kinase 5
CRISPR	=	Clustered Regularly Interspaced Short Palindromic Repeats
Cas9	=	CRISPR Associated Protein 9
CYP2D6	=	Cytochrome P450 2D6
DNA	=	Deoxyribonucleic Acid
EGCG	=	Epigallocatechin Gallate
FDA	=	Food and Drug Administration
GABA(A)	=	γ-aminobutyric Acid Type A
GSH	=	Glutathione
HSP70	=	Heat Shock Protein 70
HTT	=	Huntingtin
HD	=	Huntington’s Disease
JNK3	=	c-jun N-terminal Kinase 3
MAPKs	=	Mitogen-activated Protein Kinases

mTOR = Mammalian Target of Rapamycin
MAO-B = Monoamine Oxidase B
MSN = Medium Spiny Neurons
mHTT = Mutant Huntingtin
NLS = Nuclear Localization Sequence
NRSF = Neuron Restrictive Silencer Factor
3-NP = 3-nitropropionic Acid
NF-κB = Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells
NMDA = N-methyl-D-aspartate
NRF2 = Nuclear Factor Erythroid 2-related Factor 2
PGC-1α = Peroxisome Proliferator-activating receptor-coactivator-1 Alpha
polyQ = Polyglutamine
PSD95 = Postsynaptic Density Protein 95
REST = Repressor Element-1 Transcription Factor
ROS = Reactive Oxygen Species
RNA = Ribonucleic Acid
SOD = Superoxide Dismutase
SSRI = Selective Serotonin Reuptake Inhibitors
Sp1 = Specificity Protein 1
TAFII130 = TATAbinding Protein (TBP)-associated Factor II 130
TIM23 = Translocase of the Inner Membrane 23
UPS = Ubiquitin-proteasome System
VMAT2 = Vesicular Monoamine Transporters 2

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

The authors acknowledge the infrastructural facilities provided by Department of Zoology, Aligarh Muslim University, Aligarh, India, and CSIR-Central Drug Research Institute, Lucknow, India, respectively. The CSIR-CDRI Communication Number of this manuscript is 10548.

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