Pharmacological Research 148 (xxxx) xxxx

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Cytotoxicity models of Huntington's disease and relevance of hormetic mechanisms: A critical assessment of experimental approaches and strategies

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ARTICLE INFO

Keywords:
Huntington's disease
Animal models
Chemoprevention
Dose response
Hormesis
Preconditioning

ABSTRACT

This paper assesses *in vivo* cytotoxicity models of Huntington's disease (HD). Nearly 150 agents were found to be moderately to highly effective in mitigating the pathological sequelae of cytotoxic induction of HD features in multiple rodent models. Typically, rodents are treated with a prospective HD-protective agent before, during, or after the application of a chemical or transgenic process for inducing histopathological and behavioral symptoms of HD. Although transgenic and knockout rodent models (1) display relatively high construct and face validity, and (2) are ever more routinely employed to mimic genetic-to-phenotypic expression of HD features, toxicant models are also often employed, and have served as valuable test beds for the elucidation of biochemical processes and discovery of therapeutic targets in HD. Literature searches of the toxicant HD rodent models yielded nearly 150 agents that were moderately to highly effective in mitigating pathological sequelae in multiple mouse and rat HD models. Experimental models, study designs, and exposure protocols (e.g., pre- and post-conditioning) used in testing these agents were assessed, including dosing strategies, endpoints, and dose-response features. Hormetic-like biphasic dose responses, chemoprotective mechanisms, and the translational relevance of the preclinical studies and their therapeutic implications are critically analyzed in the present report. Notably, not one of the 150 agents that successfully delayed onset and progression of HD in the experimental models has been successfully translated to the treatment of humans in a clinical setting. Potential reasons for these translational failures are (1) the inadequacy of dose-response analyses and subsequent lack of useful dosing data; (2) effective rodent doses that are too high for safe human application; (3) key differences between the experimental models and humans in pharmacokinetic/pharmacodynamic features, ages and routes of agent administration; (4) lack of robust pharmacokinetic, mechanistic or systematic approaches to probe novel treatment strategies; and (5) inadequacies of the chemically induced HD model in rats to mimic accurately the complex genetic and developmental origin and progression of HD in humans. These deficiencies need to be urgently addressed if pharmaceutical agents for the treatment of HD are going to be successfully developed in experimental models and translated with fidelity to the clinic.

1. Introduction

Huntington's disease (HD) is an inherited autosomal dominant neurodegenerative disorder caused by expansion of specific nucleotide [cytosine-adenine-guanine (CAG)] repeats in the first exon of the *huntingtin* gene, creating long polyglutamine (PolyQ) repeats in the

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https://doi.org/10.1016/j.phrs.2019.104371
Received 22 February 2019; Received in revised form 22 July 2019; Accepted 23 July 2019

Table 1
Agents shown to prevent and/or delay the onset and severity of Huntington's disease in induced and/or genetic *in vivo* models.

- 17-AAG (17-N-allylamino-17-demethoxygeldanamycin)
- 2,4-Dinitrophenol (2,4-DNP)
- Acetyl-L-carnitine
- Alpha lipoic acid
- Antidepressants
  - Imipramine
  - Trazodone
  - Ventalaxine
- S-allylcysteine
- Acetylcysteine
- ADIOL (5-androstene-3 beta,17 beta-diol) (metabolite of DHEA)
- Agomelatine
- Alpha2-adrenoceptor antagonists
  - Efaroxan
  - Idazoxan
- Arginine
- Azulenyl nitrone
- C5a receptor antagonists
  - PMX53 (Complement component 5a receptor antagonist)
  - PMX205 (Complement component 5a, receptor antagonist)
- *Calendula officinalis*
- Cannabinoids
  - Win55,212-2
  - Arvanil
  - THC (Tetrahydrocannabinol)
  - AM374
  - AM404
  - ACEA (arachidonyl-2-chloroethylamide)
  - HU-308
  - CBD/Cannabidiol
- Sativex
- Carvedilol
- Centella asiatia
- Cereport
- Clorgyline
- Coenzyme Q10
- Copper
- *Convolvulus pluricaulis*
- CPE (*Calendula pluricaulis* extract)
- CPE-Ethyl acetate
- CPE-N-butanol
- CPE-aqueous
- Creatine
- Cyclocreatine
- Curcumin
- Cyclooxygenase (COX-2) inhibitors
  - Naproxen
  - Valdecoxib
- Cyclosporine A
- Cyclosporine A + Cereport
- DEPMPO
- Dichloroacetate
- L-Deprenyl (Selegiline)
- DHEA (dehydroepiandrosterone)
- Dietary restriction
- DMF (dimethylfumarate)
- DMPO (5,5-dimethyl-1-pyrroline N-oxide)
- EGCG (epigallocatechin gallate)
- Electromagnatic field (extremely low frequency)
- Embellin
- Escitalopram
- β-Estradiol
- Essential fatty acid rich diets
- Ethyl pyruvate
- Fenofibrate
- Fisetin
- Fish oil + ferulic acid
- Ferulic acid
- FK506
- Gabapentin
- Galantamine
- Genistein
- *Ginkgo biloba*
- Ginseng-American
- Ginseng (Korean Red)
- Ginseng-Saponins (GTS)-ginsenoides
- Glucocorticoids
  - DEX (dexamethasone)
- Hemeoxygenase-1/Glycogen synthase Kinase #B modulators
  - Hemin
  - Lithium chloride
- Hesperidin
- Hydrotyrosol
- Kaempferol
- Naringin
- Lamatrigine
- Licofelone
- Lipoic acid
- Lithium
- Luehea divaricate (aqueous extract)
- Lycopene + EGCG
- Melatonin
- Memantine
- Methozolamide
- Minocycline + pyruvate
- Mithramycin
- Naringin
- Necrostatin-1
- Nicotine
- NPY (neuropeptide Y)
- NPY13-56
- Olive oil
- Orphenadrine
- Paroxetine
- PDE4 inhibitor (RO-20-1724)
- PDE5 inhibitor (Sidenafil)
- Peroxisome proliferators
  - Fenofibrate
  - Pioglitazone
  - Rosglitazone
- Phenylbutyrate
- Piroxicam
- Probucol
- Protopanaxtriol
- Puerarin
- Quercetin
- Remacemide
- Reseveratrol
- Rice bran extract
- Riluzole
- Rivastigmine
- Rolipram
- Rosiglitazone
- Rutin
- Selenide,Bis
- Selenium
- Serotonin reuptake inhibitor, selective
  - Sertraline
- Sesammol
- Simvastatin
- Sodium buyrate
- SP1411716
- Spermidine
- Succinobucol
- Sun N8075
- Taurine
- Tauroursodeoxycholine (TUDCA)
- TEMP, 4-hydroxy
- Tert-butylhydroquinone
- Testosterone
- Tetramethylpyrazine
- L-Theanine
- Thymoquione
- Tiagbaine
- TMS – Transcranial magnatic stimulation
- Trehalase
- Trolox
- Valdecoxib
- Vanillin
- Vardenafil
- VDM11
- Vitamin C

(*continued on next page*)

Table 1 (*continued*)

Vitamin E
Uridine Pro-drug PN401
Withania somofera
Win 55-212-2

huntingtin protein (CAG > 40) [1]. An individual with ≤35 repeats will usually remain asymptomatic, whereas those with 40–70 repeats tend to develop the disease during adulthood, and those with ≥70 repeats will usually present with clinical symptoms of HD during childhood [2]. This reflects a striking dose-responsive relationship between genotype and phenotype. The brain regions most severely affected by HD are the striatum and cerebral cortex. Clinical signs and symptoms of HD include uncontrollable jerking movements (i.e., involuntary choreic or "dance"-like movements), dementia, and psychiatric disturbances [3]. The choreic movements progressively worsen with time, eventually affecting the entire body. The approximate average onset of HD typically occurs at 40 years of age, with a progression of clinical features extending ~15–20 years. Epidemiologically, HD affects ~5–10 in every 100,000 people worldwide [3].

Given the profound neurodegenerative features of HD, and its inevitably fatal course, there has been considerable cellular and animal preclinical research to identify and evaluate other possible chemopreventive agents. Although transgenic and knockout rodent models (1) have been shown to have relatively high construct and face validity, and (2) are ever more routinely employed to mimic genetic-to-phenotypic expression of HD features, toxicant models are also often employed, and serve as valuable test beds for elucidation of biochemical processes and therapeutic targets in HD. However, there is an urgent need for thorough examinations of the relative value of these toxicant models. In light of this deficiency, the present paper assesses the methods, outcomes and implications of recent *in vivo* cytotoxicity studies employing Wistar, Sprague-Dawley, and Lewis strains of rats, and transgenic mice (e.g., R6/2 and N-171-82Q) to evaluate the efficacy of agents that may be viable for the treatment of HD. Although the majority of studies assessed a single therapeutic agent, combination treatments have been developed and these studies are also evaluated here. This paper specifically addresses the selection criteria of the biological models employed, pre- and post-conditioning treatment protocols, study designs, dosing strategies used to treat the onset and progression of HD-like effects, putative mechanisms of action, and the clinical applicability of the studies and their findings.

2. HD chemopreventive agents/experimental approaches

2.1. Rat models of HD

Table 1 provides a list of agents that delay the onset, progression, or severity of HD features in animal models. Agents that prevent the onset and progression of HD symptoms induced by 3-nitropropionic acid (3-NP), quinolinic acid, and malonate are listed in Tables 2–4. Our analyses reveal that the male Wistar rat has been more frequently used in HD studies than female Wistar rats, male Sprague-Dawley rats, or male Lewis rats. Additionally, 3-NP (Table 2) was used to induce HD in rat models more frequently than either quinolinic acid (Table 3) or malonate (Table 4).

3-NP is an irreversible inhibitor of complex II of the electron transport chain (ETC), which generates oxidative stress. At the appropriate dose, 3-NP can produce selective striatal lesions that mimic many of the histologic, neurochemical, and clinical [4,5] features of HD pathology [6]. Apart from HD induction, 3-NP may also induce a preconditioning response at low doses (typically as single exposures) that protects against the subsequent induction of HD symptoms by a higher dose of 3-NP and other stressor agents (typically administered over multiple days) [7–10]. Furthermore, low doses of 3-NP exert systemic effects, protecting the heart from subsequent massive cardiotoxicities [11,12]. Below, we address protocols and findings of studies employing 3-NP.

2.2. 3-NP – HD study designs

Fig. 1 compares the study designs employed by multiple research groups to induce HD with 3-NP. In these studies, 3-NP was administered prior to, simultaneously with (30 or 60 min post-therapy), or after multiple days of chemopreventive treatment. While these protocols enable testing a range of specific hypotheses, they have evolved without a systematic plan. For example, the extensive research of Kumar and Kumar utilized a 14-day exposure protocol with the chemopreventive agent administered one hour prior to 3-NP. The use of singular chemopreventive agents in separate experiments could be compared with responses to other agents using the same protocol. However, other experimental protocols by this group tested only 2–3 agents. The same agents were usually not tested in different protocols. This diversity of experimental approaches is also evident in the work of other research groups, each with their respective strengths and limitations.

Our analyses revealed that the most commonly employed protocol was the concurrent exposure to 3-NP and chemopreventive treatments. Pretreatment designs were used when studying the effects of curcumin, carediol [13], uridine [14], selenium [15], creatine, cyclocreatinine [16], copper [15], adiol [17], melatonin [18], and probucol [19], but these treatment regimens are less clinically translatable than post-treatment approaches. No agents were tested with different regimens to evaluate the effects on disease onset as compared to disease progression. While each protocol resulted in some measure of clinical benefit in the experimental models, it is possible that such improvements seen in the different protocol-based studies were mediated via different underlying mechanisms even if the same performance endpoints were measured. Further, no reports of classic/traditional post-conditioning protocol use were reported. However, some of the diverse spectrum of preconditioning protocols incorporated treatments during post-toxic (e.g., 3-NP) treatment period. These diverse experimental protocols affect the capacity to provide needed descriptive and mechanistic clarity for the chemical protective effects, since they were not directly compared to each other and across chemical.

3. Transgenic mouse models

Mangiarini et al. [20] developed a transgenic mouse (N171-82Q) model expressing cDNA encoding a 171 amino acid N-terminal fragment of *huntingtin* containing 82 CAG repeats. Similar to the N171-82Q model, the HD transgenic R6/2 mouse model includes CAG repeat expansion, and displays loss of both brain and body weight at about 6 weeks. By 9–11 weeks of age, R6/2 mice exhibit an irregular gait, abrupt shuttering stereotypic movements, resting tremors, and epileptic seizures, as occurs in progressive human HD. Brains from these animals reveal striatal atrophy and neuronal extranuclear inclusions that are immunopositive for *huntingtin* and ubiquitin, the principal histopathological hallmarks of HD. N171-82Q mice show comparable behavioral patterns to R6/2 transgenic mice, but their developmental abnormalities begin later, perhaps because they express approximately 50% fewer CAG repeats. Table 5 lists agents that slow the onset, progression, and severity of HD symptoms in the R6/2 and/or N171-82Q transgenic models. Fig. 2 illustrates the experimental approaches principally using the R6/2 and/or N171-82Q transgenic mouse strains. Other transgenic mouse models [i.e., A17-1 [21]; AR-979 [22]; YAC128 [23]] have been developed and used in chemopreventive studies, but less frequently than the R6/2 and/or N171-82Q models.

Table 2
Chemicals effective in preventing the occurrence and/or progression of Huntington's disease in the male rat following treatment with 3-NP.

Male Sprague-Dawley

Agent	Rat model	Reference
3-NP	Sprague-Dawley (male) (N = 3 or 6/group)	Lastres-Becker et al. [115]
ACEA	Sprague-Dawley (male) (N = 5 or 6/group)	Sagredo et al. [116]
ACEA	Sprague-Dawley (male) (N = 6–8/group	Sagredo et al. [117]
AM374	Sprague-Dawley (male) (N = 5 or 6/group)	Lastres-Becker et al. [115]
AM404	Sprague-Dawley (male) (N = 5 or 6/group)	Lastres-Becker et al. [115]
AM630 (3-NP/Malonate)	Sprague-Dawley (male) (N = 5 or 6/group)	Sagredo et al. [118]
Arvanil	Sprague-Dawley (male) (N = 6/group)	De Lago et al. [50]
Cannabidiol	Sprague-Dawley (male) (N = 5 or 6/group)	Sagredo et al. [116]
Capsazepine	Sprague-Dawley (male) (N = 5 or 6/group)	Lastres-Becker et al. [115]
CBD	Sprague-Dawley (male) (N = 5 or 6/group)	Sagredo et al. [116]
CBD	Sprague-Dawley (male) (N = 6–8/group)	Sagredo et al. [117]
Clorgyline	Sprague-Dawley (male) (N = 8/group)	Maragos et al. [119]
CP1 (CP55, 940)	Sprague-Dawley (male) (N = 5–8/group)	Lastres-Becker et al. [115]
Creatine	Sprague-Dawley (male) (N = 8–10/group)	Matthews et al. [16]
Creatine	Sprague-Dawley (male) (N = 10/group)	Shear et al. [120]
Cyclocreatine	Sprague-Dawley (male) (N = 8–10/group)	Matthews et al. [16]
DEPMPO	Sprague-Dawley (male) (N = 8–11/group)	La Fontaine et al. [40]
Deprenyl	Sprague-Dawley (male) (N = 8/group)	Maragos et al. [119]
DMPO	Sprague-Dawley (male) (N = 12/group)	Schulz et al. [6]
Ginseng	Sprague-Dawley (male) (N = 7–8/group)	Lian et al. [121]
Ginseng Saponins	Sprague-Dawley (male) (N = 20/group)	Kim et al. [122]
GTS	Sprague-Dawley (male) (N = 20/group)	Kim et al. [122]
Hu-308	Sprague-Dawley (male) (N = 5 or 6/group)	Sagredo et al. [116]
Melatonin	Sprague-Dawley (male) (N = 4–8/group)	Chakraborty et al. [123]
Melatonin	Sprague-Dawley (male) (N = 8/group)	Nam et al. [124]
N-Acetylcysteine	Sprague-Dawley (male) (N = 8–11/group)	La Fontaine et al. [40]
Protopanaxtriol	Sprague-Dawley (male) (N = not provided)	Gao et al. [125]
Co-enzyme Q10	Sprague-Dawley (male) (N = 9–10/group)	Schulz et al. [6]
Riluzone	Sprague-Dawley (male) (N = 15, treated; N = 10, for controls)	Guyot et al. [126]
Sativex (Δ^9 THC + CBD)	Sprague-Dawley (male) (N = 5 or 6/group)	Sagredo et al. [118]
SP1411716	Sprague-Dawley (male) (N = 5 or 6/group)	Lastres-Becker et al. [115]
THC	Sprague-Dawley (male) (N = 5 or 6/group)	Lastres-Becker et al. [127]
VDMII	Sprague-Dawley (male) (N = 5 or 6/group)	Lastres-Becker et al. [115]

Male Lewis

Agent	Rat model	Reference
Co-enzyme Q	Lewis Rats (male) (N = 15/group)	Yang et al. [128]
Creatine	Lewis Rats (male) (N = 15/group)	Yang et al. [128]
C5 receptor antagonist (PMX53 and PMX205)	Lewis Rats (male) (N = 22 and 19/group)	Woodruff et al. [129]
Galantamine	Lewis Rats (male) (N = 8/group)	Park et al. [130]
Sildenafil	Lewis Rats (male) (N = 9/group)	Puerta et al. [131]
THC	Lewis Rats (male) (N = 7–13/group)	Lastres-Becker [127]
Vardenafil	Lewis Rats (male) (N = 9/group)	Puerta et al. [131]

Male Wistar

Agent	Rat model	Reference
Agomelatine	Male Wistar (N = 8/group)	Gupta and Sharma [132]
17β-Estradiol	Male Wistar (N = 6)	Tunez et al. [133]
AD10L (metabolite of DHEA)	Male Wistar (N = 8/group)	Hanna et al. [17]
Bis selenide (EGb7G1)	Male Wistar (N = 6/group)	Bortolatto et al. [134]
Carediol	Male Wistar (N = 8/group)	Kumar and Kumar [13]
Convolvulus pluricaulis	Male Wistar (N = 8/group)	Malik et al. [135]
Curcumin	Male Wistar (N = 6–8/group; N = 9/group)	Kumar et al. [136]; Singh et al. [137]
Cyclosporine A	Male Wistar (N = 12/group); (N = 4/group)	Kumar et al. [25]; Kumar and Kumar [138]
Dexamethasone	Male Wistar (N = 6)	Montilla et al. [139]
DHEA	Male Wistar (N = 6/group)	Tunez et al. [48]
Electromagnetic fields	Male Wistar (N = 8/group)	Tasset et al. [140]
Epigallocatechin	Male Wistar (N = 6–8/group)	Kumar and Kumar [39]
Embelin	Wistar (gender not mentioned) (N = 6)	Dhadde et al. [141]
Fasudil	Male Wistar (N = 12/group)	Ahmed et al. [35]
Fenofibrate	Male Wistar (N = not depend on)	Grover et al. [45]
Fish oil	Male Wistar (N = 6/group-in each study)	Denny Joseph and Lidhara [107]
FK506	Male Wistar (N = 12/group)	Kumar et al. [142]
Ferulic acid	Male Wistar (N = 6)	Denny Joseph and Lidhara [107]
Ginkgo biloba	Male Wistar (N = 12/group)	Mahdy et al. [34]
Hemin	Male Wistar (N = 6/group)	Khan et al. [28]
Hesperidin	Male Wistar (N = 8/group)	Menze et al. [29]
Imipramine	Male Wistar (N = 10/group)	Kumar et al. [24]

(*continued on next page*)

Table 2 (*continued*)

Male Wistar

Agent	Rat model	Reference
Kaempferol	Male Wistar (N = 10–21)	Lagoa et al. [143]
L-theanine	Male Wistar (N = 6/group)	Thangarajan et al. [36]
Licofelone	Male Wistar (N = 12–15)	Kumar et al. [27]
Lycopene	Male Wistar (N = 10–15/group); (N = 12/group)	Kumar et al. [38]
Melatonin	Male Wistar (N = 8/group); (N = 6/group)	Tasset et al. [41]; Tunez et al. [18]
Memantine	Male Wistar (N = 6/group)	Tozzi et al. [144]
Minocycline	Male Wistar (N = 6/group)	Ahuja et al. [30]
Naproxen	Male Wistar (N = 8/group)	Kumar et al. [145]
Naringen	Male Wistar (N = 10/group); (N = 6/group)	Kumar and Kumar [111]; Gopinath et al. [146]
Nicotine	Male Wistar (N = 6/group)	Tunez et al. [18]
Olive oil	Male Wistar (N = 8/group)	Tasset et al. [51]
PDEA (RO-1724) and PDE5 (Sildenafil)	Male Wistar (N = 8/group)	Thakur et al. [37]
Pioglitazone	Male Wistar (N = not given)	Grover et al. [45]
Probucol	Male Wistar (N = 10/group)	Colle et al. [19]
Puerarin	Male Wistar (N = 6/group)	Mahdy et al. [147]
Rice bran extract	Male Wistar (N = not provided)	Kaur et al. [148]
Rivastignine	Male Wistar (N = 10/group)	Kumar and Kumar [149]
RO-20-1724	Male Wistar (N = 8/group)	Thakur et al. [37]
Rutin	Male Wistar (N = 6)	Suganya and Sumathi [150]
S-Allylcysteine	Male Wistar (N = 6/group)	Perez-De La Cruz et al. [151]; Herrera-Mundo et al. [152]
Selegiline	Male Wistar (N = 8/group)	Wahdan et al. [153]
Sertraline	Male Wistar (N = 9/group)	Kumar and Kumar [154]; Kumar and Kumar [155]
Sesamol	Male Wistar (N = 6/group) (N = 10/group)	Kumar et al. [156]; Kumar et al. [156]
Simvastatin	Male Wistar (N = 12/group)	Ahmed et al. [35]
Spermidine	Male Wistar (N = 9 group)	Jamwal and Kumar [33]
Taurine	Male Wistar (N = 12)	Tadros et al. [157]
Testosterone	Male Wistar (N = 6)	Tunez et al. [158]
Tetramethylpyrazine	Male Wistar (N = 15)	Danduga et al. [159]
Transcranial Magnetic Stimulation (TMS)	Male Wistar (N = 8/group)	Tunez et al. [133]; Tunez et al. [160]
Trazodone	Male Wistar (N = 10/group)	Kumar et al. [24]
Valdecoxib	Male Wistar (N = 8/group)	Kumar et al. [145]
Vanillin	Male Wistar (N = 8/group)	Gupta and Sharma [132]
Venlafaxine	Wistar (gender not mentioned) (N = 8/group)	Kumar et al. [24]
WIN 55-212-2	Male Wistar (N = 5/group)	Maya-Lopez et al. [161]
Withania somnifera	Male Wistar (N = 10/group)	Kumar and Kumar [13]

Female Wistar

Agent	Rat model	Reference
4-Hydroxy tempo	Female Wistar (N = 6/group)	Sandhir et al. [100]
17β-Estradiol	Female Wistar (N = 6/group)	Tunez et al. [162]
Acetyl-L-carnitine	Female Wistar (not mentioned)	Mehrotra et al. [163]
Agomelatine	Female Wistar (N = 8)	Gupta and Sharma [132]
Alpha-lipoic acid (ALA)	Female Wistar (not given)	Mehrotra et al. [163]
Cadendula officinalis	Female Wistar (N = 6/group)	Shivasharan et al. [164]
Escitalopram	Female Wistar (N = 6/group)	Shetty et al. [165]
Lycopene	Female Wistar (N = 6/group)	Sandhir et al. [166]
N-Acetylcyteine (NAC)	Female Wistar (N = 6/group)	Sandhir et al. [167]
Nicotine	Female Wistar (N = 7/group)	Tariq et al. [168]
Quercetin	Female Wistar (N = 6–8/group)	Sandhir and Mehrotra [32]
Tert-butylhydroquinone	Female Wistar (N = 3–5/group)	Silva-Palacios et al. [169]
Testosterone	Female Wistar (N = 6/group)	Tunez et al. [158]
Trolox (analog of vitamin E)	Female Wistar (N = 7/group)	Al Mutairy et al. [170]
Vanillin	Female Wistar (N = 8/group)	Gupta and Sharma [132]

Other

Agent	Rat model	Reference
Genistein	Female Albino (N = 8/group)	Menze et al. [171]
Thymoquinone (TQ-SLNS)	Male Albino (N = 6/group)	Ramachandran and Thangarajan [172]

4. Evaluation of dosage regimens: an insufficiency of dose-response relationships

In designing a rodent study to characterize an effective pharmacological response to a prospective HD chemoprotective agent, it is important to know both the range of doses that elicits a response as well as the specific optimal dose. Knowing the effective dosing range and optimal treatment dose of the test agent will facilitate not only further experimental studies, but also expedite its potential translation into the clinical setting. Such information, however, cannot be effectively obtained without a sufficient number of treatment doses to pharmacologically characterize the response of the rodent to the agent. It is somewhat remarkable then that approximately 50% of the experimental rodent studies used only a single dose of the test agent, while 80% had ≤ 2 doses, and less than 5% had ≥ 4 doses. Although the time and cost of testing additional doses in animal models can become prohibitive, without a dose-response curve, evaluation of the therapeutic versus toxic properties of the intervention is hindered and clinical translation impeded. Furthermore, when only 1 or 2 doses are used, the capacity to rigorously discern dose-response patterns between

Table 3
Chemicals effective in preventing the occurrence and/or progression of Huntington's disease in the male rat following treatment with quinolinic acid.

Agent	Model	Reference
Copper	Male Wistar (N = 10/group)	Santamaria et al. [15]
Efaroxan	Male Sprague-Dawley (N = 22/group)	Martel et al. [46]
Idazoxan	Male Sprague-Dawley (N = 19/group)	Martel et al. [46]
Minocycline and pyruvate	Male Sprague-Dawley (N = 4/group)	Ryu et al. [173]
Pyruvate	Male Sprague-Dawley (N = 5–7/group)	Ryu et al. [174]
Rolipram	Male Wistar (N = 20/group)	DeMarch et al. [175]
Selenium	Male Wistar (N = 9/group)	Santamaria et al. [15]
WIN 55,212-2	Male Wistar	Pintor et al. [176]

Table 4
Chemicals effective in preventing the occurrence and/or progression of Huntington's disease in the male rat following treatment with malonate.

Male Sprague-Dawley and Lewis rats		
Agent	Rat model	Reference
ACEA	Sprague-Dawley (male) (N = 5 or 6/group)	Sagredo et al. [116]
C5A, receptor antagonists: PMX53/PMX205	Lewis (male) (N = 6/group)	Woodruff et al. [129]
Creatine	Sprague-Dawley (male) (N = 10/group; N = 8–10/group)	Matthews et al. [16]; Shear et al. [120]
Cyclocreatine	Sprague-Dawley (male) (N = 8–10/group)	Matthews et al. [16]
Efaroxan	Lewis (N = 5–14/group)	Martel et al. [46]
Ginseng Saponins	Sprague-Dawley (male) (N = 20/group)	Kim et al. [122]
Hu-308 (CB2 receptor agonist)	Sprague-Dawley (male) (N = 5–6/group)	Sagredo et al. [116]
Idazoxan	Lewis (N = 5–14/group)	Martel et al. [46]
Quinolinic acid	Sprague-Dawley (male) (N = 5–14/group)	Martel et al. [46]
Vitamin E	Male Wistar (N = 12/group)	Kalonia et al. [177]

different agents is not possible. For example, Kumar et al. [24] compared the effect of four antidepressant agents (sertraline, venlafaxine, imipramine, trazodone) on HD symptoms in a 14-day 3-NP exposure protocol (10 mg/kg/day). The results indicated that sertraline and venlafaxine reduced oxidative damage more effectively than imipramine and/or trazodone. As assessed by locomotor and rotarod activities, sertraline and venlafaxine were nearly twice as effective as imipramine and trazodone in preventing and recovering from HD-induced symptoms (i.e., approximately 70% recovery for sertraline and venlafaxine, as compared to 35% for imipramine and trazodone). This enhanced protection with sertraline and venlaflaxine may be due to their greater capacity for inhibition of serotonin reuptake and greater potency as antioxidants. However, based on one dose alone, it is impossible to estimate the responses at doses that are ~5–20 fold lower, as is typical of human subjects.

4.1. Magnitude of protection

4.1.1. Locomotor activity performance

Superior recovery in the locomotor activity test was also reported for other agents: FK506 – 66.2% [25], cyclosporine – 89.6% [26], licofelone – 94.3% [27], lycopene – 79.6% [38], and lithium – 88.8% [28]. Similarly, high rates of recovery were also reported by other investigators using hesperidin – 76.0% [29]; minocycline – 103% [30]; piroxicam – 100%; 3-NP (using a Swiss mouse model [31]); quercetin – 70%, 3-NP (using a female Wistar rat model [32]); spermidine – 73.3% [33], and ginkgo biloba extract – 62.3% [34].

4.1.2. Rotarod activity performance

High levels of functional recovery in locomotor activity following therapeutic interventions were generally consistent with effects of therapeutic treatment on the rotarod test results: fasudil – 65.9% [35]; simvastatin – 65.2% [35]; cyclosporine – 47% [25]; L-theanine – 53.3% [36]; FK506 – 55.1% [25]; uridine – 70.8% [14]; lithium chloride – 81.8% [28]; sildenafil – 58.8% [37]; licofelone – 89.7% [27]; lycopene – 94.1% [38]; and minocycline – 63.1% [30].

4.1.3. Behavioral outcomes

Similarly, recovery rates were also observed with other behavioral endpoints, such as: lycopene: memory testing – 101% (i.e., exceeding nondamaged control value [39]); epigallocatechin gallate (EGCG): memory testing – 93% [39]; withania: memory testing – 69.9% [13].

4.2. Neurological damage

High degrees of agent-mediated protection were reported for various types of neurological damage. 5-(diethylphosphono)-5-methyl-1-pyrroline N-oxide (DEPMPO), striatal lesion volume – 75.0% [40]; melatonin, striatal neurodegeneration – 98% [41]; simvastatin, neuronal damage score – 83.6% [35]; fasudil, neurological damage score – 92.9% [35]; and Korean red ginseng, neuronal degeneration – 76.1% [42].

4.3. Dosing in experimental HD may not translate to the human condition

Most agents successful at delaying HD onset, progression, and severity in animal models have failed to successfully translate to effective therapies in human patients. Factors that have impeded the translation of preclinical findings include the limitations in the dosages, drug delivery routes, time/disease stage at which the drug is administered, and the lack of attention to comorbidities and other biological variables, such as age and gender, in animal models.

It is important to note, that, when standardized by body weight, most agents in HD animal models are tested at doses that significantly exceed those recommended for human use. Table 6 summarizes effective doses for various agents in HD animal models compared to those doses recommended by various human health organizations for use in humans. Furthermore, agents are most commonly administered by intraperitoneal injection in animals (Table 7), as opposed to the oral route typically employed for human treatments. This combination of significantly higher doses (based on a body weight allometric framework) and varying routes of administration in animals is inherently difficult to relate qualitatively and quantitatively to human outcomes. These concerns have been left largely unaddressed in the published literature.

A

Research Team: Kumar and Kumar

#1 Study Design[1]

HD Induction Agent
3-NP
(days 5 to 8)

Chemoprotective Treatment
(days 1 to 8)

1	2	3	4	5	6	7	8
Days							

Data Endpoint Collection Days:	**5**	**6**		**9**

Endpoints Measured: behavior, learning, motor (e.g., locomotion)

Agents Tested: curcumin (Kumar et al., 2007); carvedilol (Kumar and Kumar, 2008)

#2 Study Design

HD Induction Agent
3-NP
(days 1 to 4)

Chemoprotective Treatment
(days 1 to 8)

1	2	3	4	5	6	7	8
Days							

Data Endpoint Collection Days:	**5**	**6**		**9**

Endpoint Measured: Behavior, learning, motor (e.g., locomotion)

Agents Tested: COX-2 inhibitors, naproxen, valdecoxib (Kumar et al., 2007a)

#3 Study Design

HD Induction Agent
3-NP
(days 1 to 14)

Chemoprotective Treatment
(day 1 to 14)

1	2	3	4	5	6	7	8	9	10	11	12	13	14
Days													

Data Endpoint Collection Days:	**5**	**10**	**15**

Endpoints Measure: rotarod, locomotion

Agents Tested: FK-506 (Kumar et al., 2010b); lycopene (Kumar et al., 2009; antidepressants-sertraline, venlafaxine, trazodone, and imipramine (Kumar et al., 2011); cyclosporine A (Kumar et al., 2010b); EGCG (Kumar and Kumar, 2009); semamol (Kumar et al., 2012a); hemin (Kumar et al., 2015); lithium chloride (Kumar et al., 2015); hesperidine (Kumar and Kumar, 2010); naringen (Kumar and Kumar, 2010); licofelone (Kumaret al., 2011); Withenia (Kumar and Kumar, 2008); gabapentin and lamotrigine (Kumar et al., 2012b)

#4 Study Design

HD Induction Agent
3-NP
(days 1 to 21)

Chemoprotective Treatment
(days 1 to 21)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Days																				

Data Endpoint Collections Days:	**1**	**7**	**14**	**21**

Endpoints Measured: rotarod, grip strength, locomotion

Agents Tested: spermidine (Jamwal and Kumar, 2016; rice bran extract (Kaur et al., 2015); curcumin (Kumar et al., 2007b)

Fig. 1. The use of multiple study designs with rat Huntington's disease models by various leading research teams. [1] In each study design, the chemical treatment was administered 30 min or 1 h prior to the 3-NP.

B

Research Team: Sandhir

#1 Study Design[1]

HD Induction Agent
3-NP
25 mg/kg
(days 1 to 4)

Chemoprotective Treatment
(days 1 to 15)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

Days

Data Endpoint Collection Days: **15**

Endpoints Measured: memory, motor scores

Agents Tested: lycopene (Sandhir et al., 2010)

#2 Study Design

HD Induction Agent
3-NP
Twice per day (7.5 mg/kg) for 2 days; 37.5 mg – 7 days; 2 mg/kg last 8 days
(days 1 to 17)

Chemoprotective Treatment
(days 1 to 21)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

Days

Data Endpoint Collection Days:	**1**	**7**	**14**	**21**

Endpoints Measured: motor score, memory scores

Agents Tested: ALA and ALCAR (Mehrotra et al., 2015); 4-hydroxytempo (Sandhir et al., 2015); and quercetin (Sandhir and Mehrotra, 2013)

Research Team: Sandhir

#3 Study Design

HD Induction Agent
3-NP
(days 1 to 12)

Chemoprotective Treatment
(days 1 to 12)

1	2	3	4	5	6	7	8	9	10	11	12

Days

Data Endpoint Collection Days:	**5**	**12**

Endpoints Measured: cognition, motor

Agents Tested: NAC (Sandhir et al., 2012)

Fig. 1. (*continued*)

Despite the generally high doses in animal studies, notable exceptions are doses used for 2,4-DNP (i.e., 50 to 60-fold lower than human doses), and phenylbutyrate (i.e., 5-fold lower than human doses) (see Table 6).

Typically, young male and female mice and rats have been used in studies of chemopreventive HD treatments. The rats are usually 2.5–4.0 months old when the studies are initiated. Transgenic HD mice survive only for 3–6 months, and the experimental chemopreventive treatments are usually initiated at 6–10 weeks of age. However, the average age of HD onset in humans is approximately 40 years, with the disease progressing for another 15–20 years [2]. Thus, the experimental subjects in the preclinical models are far too young in age, and not representative of the age-dependent natural history of HD. It is well known that the induction of adaptive responses—such as various types of preconditioning— is age-dependent, declining significantly in both older animals and humans [43]. Preconditioning adaptive responses may also be affected by comorbidities (such as obesity), even in very young experimental rodent models. Healthy, non-obese young rats typically display far greater adaptive capabilities than obese, old animals in preconditioning protocols. Thus, aside from the recapitulation of classic HD pathology and the extensive inter-individual variation found in human patients, *in vivo* animal studies of HD fail to accurately represent and assess the effect(s) of age and/or other comorbidities [44]. These limitations are exacerbated by the small sample sizes and lack of genomic heterogeneity in studies of inbred laboratory animals.

4.4. Rationale for dose selection in animal studies of chemopreventive agents

Dose evaluation involves an assessment of the rationale and justification for dose selection, and the relevance of selected experimental

C

Research Team: Khalifa

#1 Study Design[1]

HD Induction Agent
3-NP
20 mg/kg
(days 3 to 6)

Chemoprotective Treatment
(days 1 to 2)

1	2	3	4	5	6

Days

Data Endpoint Collection Days:	**1**	**4**	**6**

Endpoints Measured: locomotion

Agents Tested: ADIOL (Hanna et al., 2015)

#2 Study Design

←HD Induction Agent→
3-NP
20 mg/kg
(days 1 to 5)

← Chemoprotective Treatment →
(days 1 to 5)

1	2	3	4	5

Days

Data Endpoint Collection Days:	**1**	**2**	**5**

Endpoints Measured: locomotion

Agents Tested: hesperidin (Menze et al., 2012); puerarin (Mahdy et al., 2014)

Research Team: Khalifa

#3 Study Design

HD Induction Agent
3-NP
20 mg/kg
(days 1 to 13)

Chemoprotective Treatment
(days 1 to 15)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

Days

Data Endpoint Collection Days:	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**

Endpoints Measured: locomotion

Agents Tested: ginkgo biloba (Mahdy et al., 2011)

#4 Study Design

HD Induction Agent
3-NP
(days 4 to 7)

Chemoprotective Treatment
(days 1 to 7)

1	2	3	4	5	6	7

Days

Data Endpoint Collection Days:	**1**	**4**	**5**	**7**

Endpoints Measured: locomotion

Agents Tested: selegilline (Wahdan et al., 2017)

Research Team: Khalifa

#5 Study Design

HD Induction Agent
3-NP
(days 4 to 7)

Chemoprotective Treatment
(days 1 to 3)

1	2	3	4	5	6	7	8

Days

Data Endpoint Collection Days:	**2**	**4**	**6**	**8**

Endpoints Measured: motor scores, mortality

Agents Tested: uridine prodrug (Saydoff et al., 2003)

Fig. 1. (*continued*)

D

Research Team: Tunez

#3 Study Design

HD Induction Agent 3-NP (days 1 to 4)

Chemoprotective Treatment (days 1 to 21)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

Days

Data Endpoint Collection Days: 21

Endpoints Measured: neurotrophic factors, neuronal density

Agents Tested: melatonin (Tasset et al., 2011); electromagnetic fields (Tasset et al., 2012)

#4 Study Design

HD Induction Agent 3-NP (days 11 to 14)

Chemoprotective Treatment (days 1 to 10)

1	2	3	4	5	6	7	8	9	10	11	12	13	14

Days

Data Endpoint Collection Days: 15

Endpoints Measured: behavioral measurements

Agents Tested: Olive oil (Tasset et al., 2011)

Research Team: Tunez

#1 Study Design[1]

HD Induction Agent 3-NP (days 5 to 8)

← Chemoprotective Treatment → (days 1 to 8)

1	2	3	4	5	6	7	8

Days

Data Endpoint Collection Days: 8

Endpoints Measured: brain oxidative damage

Agents Tested: DHEA (Tunez et al., 2005); dexamethasone (Montilla et al., 2004); melatonin (Tunez et al., 2004); TMS (Tunez et al., 2006), testosterone (Tunez et al., 2007)

#2 Study Design

HD Induction Agent 3-NP (days 1 to 4)

Chemoprotective Treatment (days 1 to 8)

1	2	3	4	5	6	7	8

Days

Data Endpoint Collection Days: 8

Endpoints Measured: brain oxidative damage, cell death

Agents Tested: estradiol (Tunez et al., 2006)

E

Research Team: Colle

#1 Study Design

HD Induction Agent 3-NP 25 mg/kg IP (6 days)

← Chemoprotective Treatment → (2 months)

2 Months	**6 Days**

Data Endpoint Collection Days: Day 7

Endpoints Measured: rotarod (24 hours after last 3-NP treatment), locomotion motor behavioral, biochemical changes, body weight (every two weeks)

Agents Tested: probucol (Colle et al., 2013b)

Fig. 1. (*continued*)

doses to possible applications in humans. Table 8 lists agents that have demonstrated protective effects in standard rat models, but for which no justification for the selection of dosages was provided. Table 8 provides similar information on studies with transgenic HD mouse models. On the other hand, Table 9 lists agents and references where authors provided a justification for the selection of doses. Each of the cited studies were subdivided into three groups (Table 9): (1) Group 1 – cited other studies upon which their dosages were largely based (Table 10); (2) Group 2 – doses were selected based upon preliminary dose range studies or physiological/pharmacological factors (Table 11); and (3) Group 3 – doses were based on either an approximation of human exposure or as a proportion of the ingested diet. The basis and relative soundness of these approaches to dose selection are considered in turn below.

4.4.1. Group 1: Evaluation of dose selection based on the literature

Researchers might base their dosing strategy upon other publications, particularly when cited studies used the same species, strain, gender, route of administration, and/or dosing protocol. Apropos of such criteria, the 22 studies in Group 1 were evaluated (Table 10). Despite their citation of prior publications for dose selection, these studies most often based their dosing scheme upon studies that utilized different animal models, genders, or routes of delivery. None of the 22 listed studies (Table 10) provided justification for the dose selection, even when there were significant differences between their study and the protocols employed in the cited work. Although not listed in Table 10, within this same category are studies of fenofibrate and pioglitazone [45]. The authors mentioned that the doses of these agents were based on their capacity to induce neuroprotective effects in “other studies”, but no citation was provided.

4.4.2. Group 2A: Physiological/pharmacological bases for dose selection

A limited number of studies reported that dose selections were based on biological factors (Table 11). For example, doses of efaroxan and idazoxan were selected that optimally blocked alpha adrenoceptors and elicited effects in the rat CNS [46]. Doses for copper were based on the rate of copper uptake into the rat hypothalamus [15], whereas doses for lithium chloride were selected that slightly exceeded the dose needed to treat bipolar disorder in humans [47]. DHEA dosage was based on the treatment regimen that protected against oxidative stress in rat synaptosomes [48]. Cyclosporin A doses induced immunosuppression [49], and arvanil doses were based on multiple pharmacodynamic characteristics [50]. With the exception of lithium chloride, none of the physiologically based/derived doses related to studies of human subjects.

4.4.3. Group 2B: Doses based on preliminary testing

Doses for several agents, including ADIOL, creatine, cyclocreatine, tBHQ (tert-butylhydroquinone), and cystamine were selected based on a variety of preliminary dose ranging studies. For example, several agents were first tested over a range of 6–8 doses, with an optimal dose based on toxicity and other effects of interest.

4.4.4. Group 3: Dose based on proportion found in human diet

Some studies utilized therapeutic dosages designed to be a proportion of the consumed diet or based on a range of known human exposures. For example, doses selected for probucol and sildenafil were similar to those used by humans on a mg/kg body weight basis. However, olive oil was administered at 10% of the total caloric intake of a standard rat diet, which would far exceed human consumption [51]. Cannabigerol doses were selected based on the level of other phytocannabinoids, without specific quantitative documentation [52]. Phenylbutyrate was administered to mice at a dose which was approximately $1/5^{th}$ that given to humans in a cancer treatment trial, albeit via a different route (ip in mouse vs po in humans [53]). Wu et al. [54] used doses of 2,4-DNP that were 50 to 60-fold lower (2–5 mg/day) than doses for obese human subjects in the 1930s (~300 mg/day).

More than 50% of the cited chemoprotective studies failed to include a scientific basis for dosage selection. Taken together, these observations suggest that future studies should emphasize the dose selection criteria used, and must design dosing regimens that are based upon sound scientific rationale. Such changes would be expected to improve reproducibility and the potential for clinical translation.

F

Research Team: Tariq						
#1 Study Design						
←HD Induction Agent→ 3-NP 25 mg/kg IP (days 1 to 7)						
← Chemoprotective Treatment → (days 1 to 7)						
1	2	3	4	5	6	7
Days						
Data Endpoint Collection Days:						8
Endpoints Measured: grip strength, motor balance, limb withdrawal, behavioral scores						
Agents Tested: trolox (Al Mutairy et al., 2010); nicotine (Tariq et al., 2005)						

G

Research Team: Santamaria (Perez-DeLa Cruz et al., 2006)						
#1 Study Design						
	←HD Induction Agent→ 3-NP Single injection 30 minutes apart					
Chemoprotective Treatment (days 1 to 7)						
1	2	3	4	5	6	7
Days						
Data Endpoint Collection Days:						7
Endpoints Measured: brain lipid peroxidation, brain mitochondrial function						
Agents Tested: S-allylcysteine (SAC) (Herrera-Mundo et al., 2006)						
#2 Study Design						
	←HD Induction Agent→ quinolinic acid Single injection (140 nmol/L) into right corpus striatum					
Chemoprotective Treatment (days 2 to 5)						
1	2	3	4	5	6	7
Days						
Data Endpoint Collection Days:						7
Endpoints Measured: lipid peroxidation, SOD levels						
Agents Tested: selenium (Santamaria et al., 2003)						

Fig. 1. (*continued*)

5. Chemoprotective agents: dose response features

Hormetic dose responses as shown in Fig. 3 were observed in a diverse range of HD experimental protocols, including the use of pre- and post-conditioning agents. Regardless of the experimental model used, exposure protocol, and/or endpoints of interest, the quantitative features of the dose response are similar in their display of hormetic-like features. Although the majority of *in vivo* HD studies of chemopreventive agents used relatively few doses, 21 studies were capable of addressing the dose-response characteristics of a number of agents, with several studies using up to ten doses of agents selected. Of these 21 studies, nine involved *in vivo* rodent experimentation, five employed *in vitro* neuronal cells, five involved cellular models often employed in the assessment of HD, and two used alternative models (i.e., *C. elegans* and yeast), with extrapolation/application to some aspects of HD (see Fig. 3A–R). The general features of the hormetic dose response indicate that the maximum stimulatory response is modest, typically about 30–60% greater than the control group. The hormetic response may also be represented by J-shaped dose responses, depending upon the endpoint. Hormetic dose responses can be elicited by direct stimulation, and via preconditioning or postconditioning protocols, which are commonly used for studies on chemopreventive agents in HD experimental models. Detailed assessment of the frequency of hormetic dose responses [55,56] and of hormetic mechanisms [57] in the biological/

H

Research Team: Denny Joseph													
#1 Study Design													
HD Induction Agent 3-NP 25 mg/kg (days 1 to 4)													
Chemoprotective Treatment (days 1 to 14)													
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Days													
Data Endpoint Collection Days:						**7**							**14**
Endpoints Measured: behavioral scores, motor													
Agents Tested: fish oil (Denny Joseph and Lidhara, 2013 & 2014)													

I

Research Team: Beal														
#1 Study Design														
														Malonate HD Induction Day 1
Chemoprotective Treatment (days 1 to 14)														
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Days														
Data Endpoint Collection Days:								**22**						
Endpoints Measured: striatic lesions, striatal energy metabolites														
Agents Tested: creatine (Matthews et al., 1998); cyclocreatine (Matthews et al., 1998)														

Fig. 1. (*continued*)

biomedical literature has been reported. The quantitative features of the hormetic dose-response are independent of the biological model used, endpoint measured, inducing agent, potency of the inducing agent, hierarchy of biological system (cell, tissue, organ, organism), and/or mechanism of action [58,59]. Evidence supporting the hormetic dose response is found in several neuroscience studies [60], which encompass a broad range of anxiolytic [61], anti-seizure [62], and memory-enhancing effects [63]. Specific applications of the hormetic dose-response effects have also been reported in studies of Alzheimer's disease [63] and Parkinson's disease [64,65].

While the present paper focuses on *in vivo* rodent studies, of particular interest is the report of Wang et al. [66], which assessed chemopreventive agents and their dose response features on cell survival in an *in vitro* ST14A HD cell line. ST14A cells are striatal cells that stably express a mutant *huntingtin* (mhtt) gene fragment. All of the compounds tested were known to inhibit the release of mitochondrial cytochrome C, a key biomarker in HD toxicity/damage. In subsequent testing, 19 of 20 agents reduced cell death. However, many showed a biphasic dose-response, with low doses stimulating cell survival and high doses eliciting cell death (Fig. 3R). Similar hormetic-like biphasic dose responses were reported in *in vitro* studies for the cannabinoid VCE-003 in HiBg neuronal cell lines ([67]; Fig. 3D.1) and Neuro2a cell lines (Fig. 3D.2), for riluzole in NG108-15 cells ([68]; Fig. 3L), and in *in vivo* studies of *C elegans* ([69]; Fig. 3C).

Mammalian *in vivo* studies demonstrate similar hormetic biphasic dose responses, most notably in mouse [70], rat [16,71–75], and gerbil models [76]. These studies typically involved the use of a pretreatment study design, which led to responses that were hormetic/biphasic and protective. These findings were further supported by *in vitro* studies using low doses in pretreatment protocols [77–80]. Although it was generally found that low doses of the chemopreventive agents reduced toxicity/damage, this was not the case with spermidine [73]. Instead, low doses of spermidine enhanced contralateral rotations induced by the striatal injection of quinolinic acid, and reduced the number of rotations at higher doses (Fig. 3P). It was hypothesized that low doses of spermidine stimulated the NMDA receptor-mediated response, whereas higher doses inhibited excitotoxicity.

6. General chemopreventive strategies and interventions

The conclusions of Kumar and Ratan [81] are consistent with a hormesis-related perspective that harmful oxidative stress in HD develops because of direct repression of adaptive gene expression by mutant *huntingtin* htt (mhtt). They noted that continued repression of adaptive responses to oxidative stress resulted in persistent and uncontrolled stress at multiple levels of biological organization. Within this mechanistic framework, it was posited that hormetic agents would act to derepress homeostatic responses, leading to the activation of large numbers of genes to restore and sustain redox homeostasis in HD. This is consistent with the prior work of Dunah et al. [82], which proposed that gene repression may follow from the engagement of mhtt with co-activators, or by direct effects of mhtt on redox-regulated transcription factors.

Chemoprotective agents for HD listed in this review act through molecular and cellular mechanisms that target macromolecular damage and mitochondrial oxidative stress, disruption of proteostasis, age-related decreases in autophagy and ubiquitin proteasome degradation, extracellular matrix remodeling, apoptosis, and the bioavailability of nitric oxide. These general chemopreventive processes will be discussed in the following context of caloric restriction (CR), intermittent fasting (IF), and effects of resveratrol.

Caloric restriction (CR) is widely recognized as one of the most robust general interventions to prolong lifespan and delay the onset of age-associated diseases such as HD. CR affects biomarkers of

Table 5
Transgenic Huntington's disease mouse models.

A. R6/2 model

Agent	Dose	Rotarod days tested	Rotarod % increase	Control lifespan (days)	Treatment lifespan (days)	Lifespan % increase	Age at start of exposure	Reference	Ratio rotarod/lifespan increase
Clioquinol (CQ)	30 mg/kg	63	81	78	92	17.9	3 weeks	Nguyen et al. [178]	4.5
CQ10	0.2%, diet	84	127	96	114	18.7	42 days	Ferrante et al. [44]	6.8
CQ10	30 mg/kg	84	200	101	118	16.8	3 weeks	Yang et al. [128]	11.9
Creatine	2%, diet	84	116	101	118	16.8	3 weeks	Yang et al. [128]	6.9
Cystamine	112.5 and 225 mg/kg	80	145	92	120	30.4	3 weeks	Dedeoglu et al. [179]	4.8
Dichloroacetate	100 mg/kg	90	100	97.2	103.9	6.9	4 weeks	Andreassen et al. [180]	N/A
DMF	30 mg/kg	84	41	92	103	11.9	4 weeks	Ellrichmann et al. [181]	3.4
Fisetin	0.5–25 mg/kg	91	71	104	139	33.6	42–45 days	Maher et al. [182]	2.1
Laquinimod	0.5–25 mg/kg	84	100	86.6	99.8	15.5	30–32 days	Ellrichmann et al. [70]	6.4
Lipoic acid	100 mg/kg	N/A	N/A	97.3	104.2	'7.1	4 weeks	Andreassen et al. [183]	N/A
Lithium	16 mg/kg	63	55	96	110	14.6	37 days	Wood and Morton [47]	3.8
Methozolamide	20 and 40 mg/kg	168	28	168	203	20.8	6 weeks	Wang et al. [66]	1.3
Mithramycin	50–150 mg/kg	84	150	100	126	26	3 weeks	Ferrante et al. [184]	5.8
Necrostatin-1	0.05%, diet	N/A	N/A	82.2	89.3	8.6	Not provided	Zhu et al. [185]	N/A
Remacemide	0.007%, diet	84	144	96	114	18.7	42	Ferrante et al. [44]	7.7
Remacemide (equals)	0.007% diet, 14 mg/kg/day	84	140	96	114	18.7	3 weeks	Ferrante et al. [44]	7.5
Sertraline	5 and 10 mg/kg	70	66	84.3	101.9	19.8	6 weeks	Peng et al. [186]	3.3
Sodium buyrate	100–1200 mg/kg	77	38	100	123	23	3 weeks	Ferrante et al. [184]	1.6
Sun N8075	30 mg/kg/day	90	71	96	140	45.8	4 weeks	Noda et al. [187]	1.5
Tiagabine	2 and 5 mg/kg/day	84	380	80	102	27.5	6 weeks	Masuda et al. [188]	13.8
Trehalase	2% water	77	68	100	110	10	3 weeks	Tanaka et al. [189]	6.8

B. N171-82Q model

Agent	Dose	Rotarod days tested	Rotarod % increase	Control lifespan (days)	Treatment lifespan (days)	% Increase	Age at start of exposure	Reference	Ratio rotarod/lifespan increase
Creatine (male/female), 2% diet	2% diet	125	62	131	156.4	18.6	4 weeks	Andreassen et al. [190]	3.3
Dichloroacetate	100 mg/kg	120	118%	127.1	139.5	9.8%	4 weeks	Andreassen et al. [180]	12.4
Dietary restriction	N/A	N/A	N/A	98	143.8	46.7	8 weeks	Duan et al. [191]	N/A
Lipoic acid	100 mg/kg	N/A	N/A	129.5	140.3	10.8	4 weeks	Andreassen et al. [183]	N/A
Paroxetine	5 mg/kg/day	112	28	Male – 122; Female – 134	Male – 134; Female – 150	Male – 9.8; Female – 11.9	8 weeks ~ 56 days	Duan et al. [192]	2.85
Phenylbutyrate	100 mg/kg/day	N/A	N/A	120	153.2	27.7	75 days	Gardian et al. [53]	N/A
Resveratrol	25 mg/mouse/day	133	−15	158	158	0.0	75 days	Ho et al. [193]	N/A
Rosiglitazone	10 mg/kg/day	140	67	Not determined	ND	ND	8 weeks	Jin et al. [194]	N/A
Sertraline	20 mg/kg/day	112	80	119	164.5	38.5	12 weeks	Duan et al. [195]	2.1
Tiagbaine	5 mg/kg/day	112	102	140	161	15	8 weeks	Masuda et al. [188]	6.8

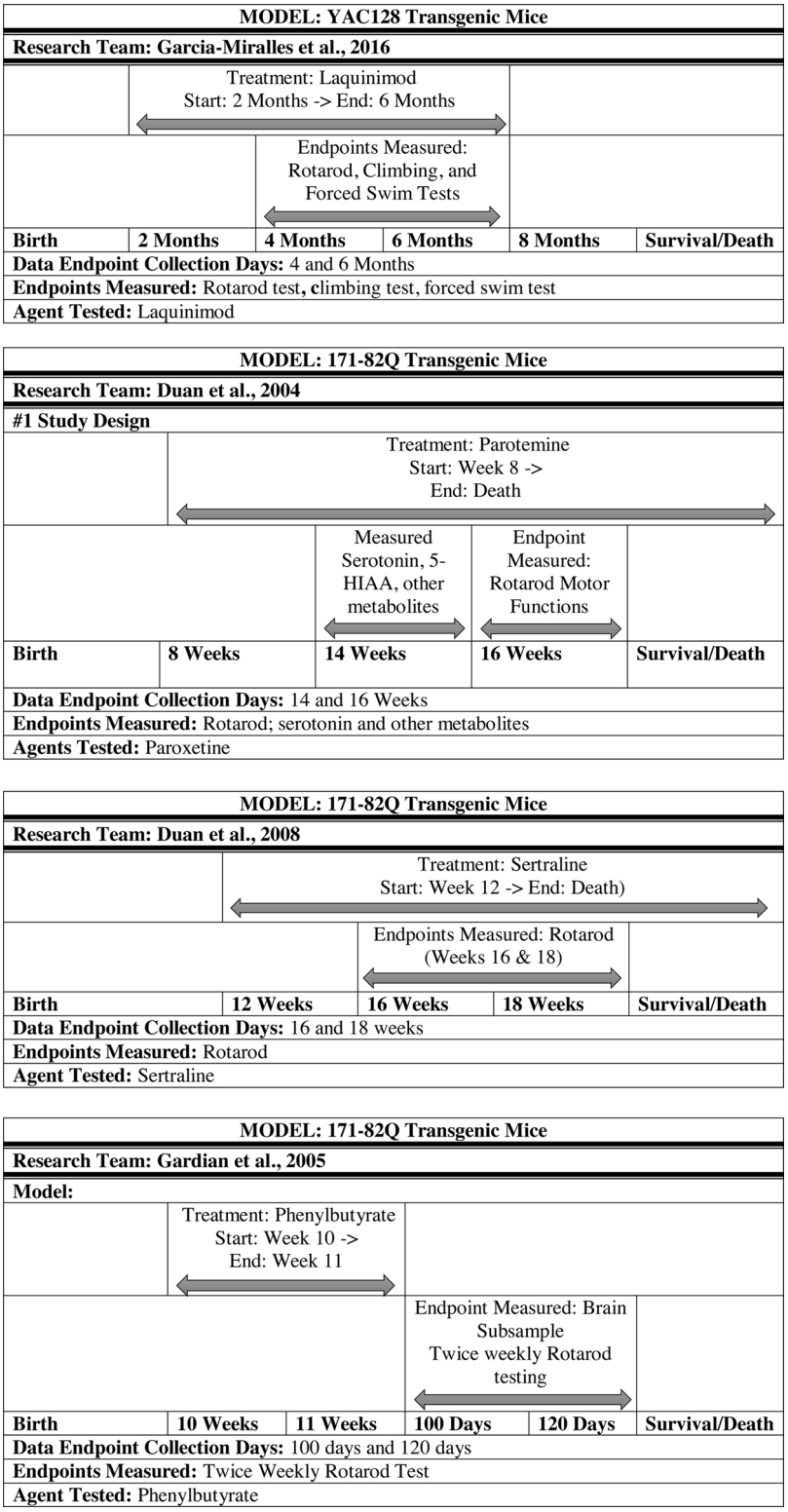

Fig. 2. Use of multiple study designs with transgenic mice.

cardiovascular disease (CVD) and neurological aging, specifically by decreasing circulating C-reactive protein (as well as other indicators of inflammation), and by stimulating endogenous anti-oxidative and anti-inflammatory mechanisms linked to activation of the redox-sensitive master transcription factor, Nrf2 [83].

Dietary restriction by way of intermittent (i.e., alternate day) fasting (IF) represents a type of hormetic stress. A study by Moreno et al. [84] using the transgenic YAC128 mouse HD model demonstrated that IF reversed/corrected a spectrum of HD features: increasing body weight, decreasing blood glucose, and improving impaired motor function. The authors hypothesized that dietary restriction could possibly reduce a range of symptoms of HD—and increase lifespan—in humans. These findings raise many new questions, including whether dietary restriction may interact with other chemopreventive modulators to further diminish HD progression.

Resveratrol, a natural polyphenol, activates SIRT1 (and transcriptional responses that are similar to CR-mediated SIRT1 activation) in

MODEL: 171-82Q Transgenic Mice							
Research Team: Jin et al., 2013							
	Treatment: Rosiglitazone Start: Week 8 -> End: Week 32						
		Endpoint Measured: Brain sampling					
Birth	**8 Weeks**		**14 weeks**		**32 Weeks**		
Data Endpoint Collection Days:							
Endpoints Measured: motor performance, brain sampling (week 14); week 32 mice sacrificed							
Agent Tested: Rosiglitazone							
MODEL: 171-82Q Transgenic Mice							
Research Team: Pouladi et al., 2012							
	Treatment: NP03-YAC128e Start: 2 Months -> End: Death						
	Endpoint Measured: Motor testing/rotarod every two months						
Birth	**2 Months**	**4 Months**	**6 Months**	**8 Months**	**10 Months**	**12 Months**	**Survival/Death**
Data Endpoint Collection Days: Every two months							
Endpoints Measured: motor testing/rotarod							
Agent Tested: NP03 – YAC128							
MODEL: Typical R6/2 Mice							
Research Team: Duan et al., 2008; Peng et al., 2008a, b; Masuda et al., 2008							
	Treatment: Sertraline; Tiagabine Start: 6 Weeks -> End: Death						
			Endpoint Measured: Rotarod				
Birth	**1 Week**	**6 Weeks**	**10 Weeks**	**12 Weeks**	**Survival/Death**		
Data Endpoint Collection Days: Motor testing/rotarod every two months							
Endpoints Measured: Rotarod							
Agent Tested: Sertraline; Tiagabine							

MODEL: Typical R6/2 Mice						
Research Team: Ellrichmann et al., 2011, 2017; Fatoba et al., 2018						
	Treatment: Laquinimod, dimethylfumarate (DMF) Start: 4 Weeks -> End: Death					
	Endpoint Measured: Every other week a series of behavioral test - Rotarod, clasping scores, vertical pole					
Birth	**4 Weeks**	**6 Weeks**	**8 Weeks**	**10 Weeks**	**12 Weeks**	**Survival/Death**
Data Endpoint Collection Days: Motor testing/rotarod every two months						
Endpoints Measured: Every other week a series of behavioral tests - Rotarod, clasping scores, vertical pole						
Agent Tested: Laquinimod, dimethylfumarate (DMF)						
MODEL: Typical R6/2 Mice						
Research Team: DeMarch et al., 2008						
	Treatment: Rolipram Start: 4 Weeks -> End: Death					
	Endpoints Measured: Weekly body weights; neurological abnormalities, histology subsample at 12 Weeks					
Birth	**4 Weeks**			**12 Weeks**	**Survival/Death (15 weeks)**	
Data Endpoint Collection Days: weekly						
Endpoints Measured: Measured: Weekly body weights; neurological abnormalities (clasping, behavior), histology subsample at 12 Weeks						
Agent Tested: Rolipram						

Fig. 2. (*continued*)

humans and enhances cell survival and p53 activation [85]. These responses enhance cerebro-microvascular function [86], increase cerebro-microvascular density [87], and prevent cerebral microhemorrhages [88] to enhance neuroprotection in HD models. In order to overcome the limitations in its clinical use and due to some unfavorable properties, including poor cellular uptake and excessively rapid metabolism,

Table 6
Dose comparison: chemproventive doses in animal models versus commonly recommended human doses (mg/kg): Note – use of commercial websites for recommended dose is useful for comparison purposes but should not be assumed to be a dose recommended by the authors.

Human vs animal dose comparisons	Reference(s)
Human exposure (>) greater than animal protective dose	Probucol, 2-fold (drugs.com); 2,4-DNP, 50–60-fold [54]; phenylbutyrate, 5-fold [53]
Human exposure is comparable to the animal protective dose	Licofelcone (drug development-technology.com); cyclosporine (drugs.com); neproxan (drugs.com)
Human exposure is less (<) than animal protective dose (~2 to < 10-fold)	Quercetin (rxlist.com); ginkgo biloba (drugs.com); sildenafil (drugs.com); ethyl pyruvate; genistein (healthcare.com); curcumin (Webmd.com); ALA (drugs.com); THC (drugs.com); sertraline (drugs.com); TBH; fish oil (omega3inorations.com)
Human exposure is less (<) than animal protective dose (> 10 to < 30-fold)	Minocycline (drugs.com); fisudil (Vicari et al. [196]); resveratrol (webmd.com); nicotine (drugs.com); venlafaxine (drugs.com); uridine (drugs.com); imipramine (drugs.com); Ginseng (drugs.com); trazodone (drugs.com); lycopene (drugs.com); vardenafil (drugs.com); FK506 (drugs.com); withania sonifera (examine.com)
Human dose is less (<) than animal protective dose (> 30 to < 100-fold)	Simvastatin (drugs.com); galantamine (drugs.com); valdenefil (drugs.com); hydroxtyrosol; L-theanine (drugs.com); piroxicam (drugs.com)
Human dose is less (<) than animal protective dose (≥100-fold)	Rosiglitazone (drugs.com); melatonin (drugs.com); spermidine (Schwartz et al. [197]); puerarin (drugs.com); hesperidin (webmd.com)

some resveratrol conjugates possessing improved stability and bioavailability have been developed and studied [89]. Resveratrol also enhances Nrf2, which sustains redox homeostasis [90–92] and proteasome activity, while increasing the clearance of proteins damaged by free radical toxicity [93]. In addition, Nrf2 activity decreases with age [94], which may contribute to the age-related increased risk of HD progression.

Evidence suggests a critical role for mitochondrial ROS in neuronal aging and neurodegeneration [95–97]. Mice over-expressing the mitochondrial antioxidant enzyme catalase displayed an 18% increase in lifespan [98,99]. These findings led to the development of mitochondria-targeted antioxidants, such as hydroxyTEMPO [100]. The anti-aging effects of polyunsaturated fatty acids (PUFAs) in HD models may act by membrane modifications, regulation of inflammatory gene activity, and modulation of products of bioactive lipid mediators of 3-PUFAs [101].

Hashimoto et al. [102] proposed that amyloidogenic proteins (APs) may be of clinical value for coping with a spectrum variety of CNS stressors. These authors posited that the heterogeneous structure of APs may correspond to a particular type of environmental stressor agent, thereby reflecting a hormetic adaptive response in the brain. They further proposed that the transgenerational transmission of stress-specific APs via germ cells may affect preconditioning responses in the brain of offspring (i.e., an epigenetic effect). These epigenetic features of APs are heritable and enhance neuronal survival in offspring, which may help to explain why APs have survived natural selection processes, despite their neurotoxic properties. In examining APs as a molecular framework, Hashimoto et al. [102] extended this analogy to the role of elongated polyQ sequences (epolyQ) in the spectrum of polyglutamine (polyQ) diseases (e.g., HD). Specifically, they suggested that the heterogeneity of epolyQ may functionally relate to a set of diverse stressors, affecting hormetic responses in the brains of both adults and (transgenerational) offspring.

7. Discussion

The present analyses reveal that preclinical research in cellular and animal models of HD has led to the identification of approximately 150 agents with apparent disease-preventive capacities. Over 120 of these agents have been tested in either one or more *in vivo* cytotoxicity rodent models and/or transgenic mouse models. In transgenic mice, many of the agents tested extended survival by 10–20%. A number of therapeutic agents tested in rat models of HD induced by 3-NP, quinolionic acid, or malonate typically displayed greater than 60% effectiveness across a spectrum of clinically relevant endpoints.

The diverse range of chemoprotective agents (Table 1) that have been tested include antidepressants, cannabinoids, peroxisome proliferators, COX-2 inhibitors, AChE inhibitors, heme oxygenase inducers, selective immune inhibitors, statins, phosphodiesterase inhibitors, traditional Asian medicines, agents associated with the Mediterranean diet (e.g. olive oil and its constituents), polyphenols (including various flavonoids), and other types of anti-inflammatory and antioxidant substances. Regardless of the considerable structural and mechanistic diversity of these agents, all have generally been successful in delaying the onset and minimizing the severity of HD in animal models. However, with few exceptions, the same agent was not tested systematically in multiple models, and results may not be generalizable to differing species and strains, or to HD induced by multiple mechanisms. According to the standardization fallacy, the more heterogenous the experimental platforms, the more likely a finding will generalize across models to the human condition [103,104].

The chemopreventive agents were typically administered via gavage, diet, intraperitoneal, or less frequently, the subcutaneous route. The male Wistar rat model using 3-NP for the induction of HD symptoms was employed in most studies, with protocol durations lasting from ~4 to 21 days. In experimental protocols wherein the chemopreventive agent and 3-NP were administered simultaneously, the chemopreventive agents were typically delivered 30–60 min prior to 3-NP (see Kumar et al 2010b – 14-day protocol, Fig. 1A, study design #3). This timeframe is confounded by the potential non-specificity of the chemopreventive agents, which may diminish the effect of 3-NP-induced damage that is typical in HD animal models. This raises serious questions regarding whether the pretreatment protocol allows the agent to directly reduce or interfere with the 3-NP model itself. If the HD model cannot be established and cell death processes are not initiated, then the speculation or claim that the "pre-conditioning" agent actually blocks cell death is unfounded. An additional limitation is that chemically-induced HD—and the corresponding therapeutic interventions—was generally acute in nature in rat models, thereby failing to capture the characteristically slow neurodegeneration of clinical HD.

When normalized to body weight (mg/kg), the doses of chemoprotective agents used in these studies often exceeded the doses recommended for human use (Table 6). Dose responses occurring in animal models are pharmacokinetically augmented when administered via subcutaneous and intraperitoneal routes. Similarly, if actions of agents administered to animals via the oral route are to be translated for clinical utility, the dose required may far exceed clinically applicable ranges in humans [e.g., olive oil (10% [51])]. Furthermore, if an individual ingests 10–12 commercially available supplements daily

Table 7
Route of administration for chemopreventive agents in HD animal models.

IP (N = 57)	SC (N = 7)	Oral (N = 49)
Acetyl-L-carnitine	β-Estradiol	Agomalatine
Alpha lipoic acid	DHEA	C5a receptor antagonist: PMX53, PMX205
Antidepressants: imipramine, trazodone, ventalaxine	DMPA	*Calendula officinalis*
S-allylcysteine	Nicotine	Carvedilol
ADIOL (metabolite of DHEA)	PPN	Centella asiatia
Alpha2-adrenoceptor antagonists: efaroxan, idazoxan	SPBN	Coenzyme Q10
Azulenyl nitrone	Testosterone	*Convolvulus pluricaulis* (CPE): ethyl acetate, n-butanol, aqueous
Cannabinoids: Win55,212-2, Arvanil, THC, AM404, ACEA, HU308, Sativex		Creatine
Cereport (IV)		Cyclocreatine
Clorgyline		Curcumin
Copper		COX-2 inhibitors: naproxen, valdecoxib
Cyclosporine A + Cereport		Cyclosporine A
L-Deprenyl (selegiline)		Dichloroacetate
DEPMPO		EGCG
Ethyl pyruvate		Embellin
Galantamine		Escitalopram
Genistein Ginkgo Biloba		Faudil
Ginseng-American		Fish oil: ferulic acid, quercetin
Ginseng-Saponins		FK506
Glucocorticoids: DEX		Ginseng (Korean Red)
Hemo-oxygenase-1/glycogen synthase kinase #B modulator: hemin, LiCl		Hesperidin
Kaempferol		Naringin
Melatonin		Licofelone
Minocycline + pyruvate		Lipoic acid
NAC		Lycopene
Nicotine		Olive oil: EVOO, hydroxtyrosol
Orphenadrine		Peroxisome proliferators: fenofibrate, pioglitazone
PDE4-RO-20-1721		Probucol
Peroxisome proliferator: rosglitazone		Protopanaxtriol
Piroxicam		Quercetin
Puerarin		Remacemide
Riluzule		Resveratrol
Rolipram		Rice bran extract: ethanol extract, hexane extract
Selenide, Bis		Rivastigmine
Selenium		Rutin
Sildenafil		Sertraline
Taurine		Simvastatin
TUDCA		Spermidine
Tertbutylhydroquinone		L-Theanine
Tetramethylpyrazine		Thymoquione
Vardenafil		Trolox
Withania somofera		Vanillin
		Vitamin C
		Vitamin E
		Uridine pro-drug PN401

(i.e., a considerable amount of supplements) at the doses recommended to elicit chemoprotective effects in HD models as reported here (e.g., coenzyme Q10, curcumin, EGCG, fish oil, gensing, gingko biloba, lycopene, melatonin, olive oil/olive oil leave extracts, resveratrol, and others), the collective proportion by weight of the diet that these agents would comprise would be far below 1/1000th of the total daily diet, even if some agents were taken twice per day. This raises the question of how animal findings may be functionally translated to the clinic and rigorously evaluated.

The protective findings reported in experimental rat models entail a broad range of protocols, albeit with similarly quantitative results

Table 8
No justification for dosing selection/strategy in chemically induced rat and transgenic mouse models of HD.

Agent	Reference
Rat models	
4-Hydroxy tempo	Sandhir et al. [100]
17-β-Estradiol	Tunez et al. [162]
ALA	Mehrotra et al. [163]
ALCAR	Mehrotra et al. [163]
Antidepressant: sertraline; venlafaxine, traxodone	Kumar et al. [24]
Cannabinoid: AM404	Lastres-Becker et al. [198]; Lastres-Becker et al. [115]
Clorgyline	Maragos et al. [119]
C5a receptor antagonists: PMX53, PMX205	Woodruff et al. [129]
Curcumin	Singh et al. [137]
Cyclosporine A	Kumar et al. [26]
DEX	Montilla et al. [139]
DMPO	Schulz et al. [6]
EGCG	Kumar and Kumar [199]
Escitalopram	Shetty et al. [165]
Fish oil/olive oil	Morales-Martinez et al. [200]
Ginseng Saponins	Kim et al. [122]
Ginseng	Lian et al. [121]
Ginseng (Korean Red)	Jang et al. [201]
Hemin	Khan et al. [28]
Hydroxytyrosol	Tasset et al. [51]
L-Theanine	Thangarajan et al. [36]
Licofelone	Kumar et al. [27]
Melatonin	Tunez et al. [18]; Nam et al. [124]; Tasset et al. [41]
N-acetyclsteine (NAC)	Sandhir et al. [167]
Naringin	Gopinath et al. [146]
Nicotine	Tunez et al. [18]
Protopanaxtriol	Gao et al. [125]
Quercetin	Sandhir and Mehrotra [32]
Rice bran extract	Kaur et al. [148]
Riluzole	Guyot et al. [126]
Rivastigmine	Kumar and Kumar [149]
Rolipram	DeMarch et al. [175]
RRO kinase inhibitor: fasudil, simvastatin	Ahmed et al. [35]
S-allylcysteine (SAC)	Herrera-Mundo et al. [152]
Selegiline (deprenyl)	Wahdan et al. [153]
Selenium	Santamaria et al. [15]
Sertraline	Kumar and Kumar [199]; Kumar and Kumar [39]
Spermidine	Jamwal and Kumar [33]
Taurine	Tadros et al. [157]
Testosterone	Tunez et al. [158]
Tetramethylpyrazine	Danduga et al. [159]
Thymoquinone (TQ-SLN-1)	Ramachandran and Thangarajan [172]
Trolox	Al Mutairy et al. [170]
Uridine prodrug	Saydoff et al. [14]
Vitamin E	Kalonia et al. [177]
Win 55,212-2	Maya-Lopez et al. [161]
Transgenic mice models	
2,4-Dinitrophenol	Wu et al. [54]
17-AAG	Waza et al. [22]
Arginine	Deckel et al. [202]
Clioquinol	Nguyen et al. [178]
Coenzyme Q10	Yang et al. [128]; Ferrante et al. [44]
Creatine	Yang et al. [128]; Ferrante et al. [203]; Andreassen et al. [190]
Dichloroacetate	Andreassen et al. [180]
DMF (dimethylfumarate)	Ellrichmann et al. [181]
Fisetin	Maher et al. [182]
Laquinimod	Ellrichmann et al. [70]; Garcia-Miralles et al. [23]
Lipoic acid	Andreassen et al. [183]
Methazolamide	Wang et al. [66]
Necrostatin	Zhu et al. [185]
NP03/LiCl (low dose lithium formulation)	Pouladi et al. [204]

(*continued on next page*)

Table 8 (*continued*)

Agent	Reference
Paroxetine	Duan et al. [192]
Phenylbutyrate	Gardian et al. [53]
Remacemide	Ferrante et al. [44]
Resveratrol	Ho et al. [193]
Rolipram	DeMarch et al. [205]
Rosiglitazone	Jin et al. [194]
Sertraline	Peng et al. [186]; Duan et al. [195]
Trehalose	Tanaka et al. [189] Davies et al. [21]
TUDCA	Keene et al. [206]

across paradigms used. Despite distinct experimental designs, the studies often failed to exploit dose and mechanistic differences that could shed light on possible distinctions of treatment efficacies. These observations suggest that high doses, as used for many chemopreventive agents, may have masked/overwhelmed the capacity to elicit more subtle responses to the diverse experimental protocols utilized.

Table 9
Basis for dose selection provided for chemically-induced Huntington's disease animal model.

Agent	Reference
Rat models	
17 β-estradiol	Menze et al. [171]
ACEA	Sagredo et al. [116]
ADIOL	Hanna et al. [17]
AE (aqueous extract – CPE)	Malik et al. [135]
Agomelatine	Gupta and Sharma [132]
Arvanil	Maya-Lopez et al. [161]
BE (butanol extract – CPE)	Malik et al. [135]
BHQ	Silva-Palacios et al. [169]
Bis selenide	Bortolatto et al. [134]
Carvediol	Kumar and Kumar [13]
CBD	Sagredo et al. [116]
Cereport	Borlongan et al. [49]
COE (*Calendula officinalis* extract)	Shivasharan et al. [164]
CPE (*C. pluricaulis* extract)	Malik et al. [135]
Creatine	Matthews et al. [16]
Cyclocreatine	Matthews et al. [16]
Cyclosporin	Kumar and Kumar [138]
Cyclosporin A	Borlongan et al. [49]
Cycloxygenase inhibitors: naproxan, valdecorib	Kumar et al. [136]
DHEA	Tunez et al. [48]
EAE (ethyl acetate fraction – CPE)	Malik et al. [135]
Efaroxan	Martel et al. [46]
EGCG	Kumar and Kumar [199]
Embelin	Dhadde et al. [141]
Fenfibrate	Grover et al. [45]
Fish oil	Denny Joseph and Lidhara [106]; Denny Joseph and Lidhara [107]
FK506	Kumar et al. [26]; Kumar and Kumar [138]
Genistein	Menze et al. [171]
Ginkgo Biloba	Mahdy et al. [34]
Hesperidin	Kumar and Kumar [111]
HU-308	Sagredo et al. [116]
Idazoxan	Martel et al. [46]
Kaemphenol	Lagoa et al. [143]
Korean Red Ginseng	Tian et al. [42]
Lycopene	Kumar and Kumar [199]; Kumar and Kumar [39]; Sandhir et al. [166]
Minocycline	Ryu et al. [173]; Ahuja et al. [30]
Nesperidin	Menze et al. [29]
Nicotine	Tariq et al. [168]
Olive oil (virgin)	Tasset et al. [41,51]
Pioglitazone	Grover et al. [45]
Piroxicam	Jadiswani et al. [31]
Probucol	Colle et al. [19]
Puevarin	Mahdy et al. [147]
Pyruvate	Jang et al. [71]; Ryu et al. [173]

Table 9 (*continued*)

Agent	Reference
Quercetin	Denny Joseph and Lidhara [106]; Denny Joseph and Lidhara [107]; Sandhir and Mehrotra [32]
Sativex	Sagredo et al. [118]
Sesamol	Kumar et al. [142]
Sildenafil	Puerta et al. [131]
THC	Lastres-Becker et al. [127]
Vanillin	Gupta and Sharma [132]
Withania	Kumar and Kumar [199]
Transgenic mice models	
2,4-DNP	Wu et al. [54]
Arginine	Deckel et al. [202]
Cannabigenol	Valdeolivas et al. [52]
Cystamine	Dedeoglu et al. [179]
Doxycycline	Smith et al. [207]
LiCl	Wood and Morton [47]
Lithium formulation	Pouladi et al. [204]
Minocycline	Smith et al. [207]
NPY	Fatoba et al. [208]
NPY 13-56	Fatoba et al. [208]
Phenylbutyrate	Gardian et al. [53]
Rosiglitazone	Jin et al. [194]
Sodium butyrate	Ferrante et al. [209]
SUN N8075	Noda et al. [187]

In the studies reviewed, authors often provided information about the effect of the chemopreventive treatment on the upregulation of antioxidant enzyme systems. However, the optimal dose range and temporal integrative features of these adaptive processes were generally not well defined. These limitations were exacerbated by low sample sizes (n = 5–6 rats per group) in many of the studies.

Preconditioning protocols used in chemopreventive animal HD studies varied widely in the preconditioning periods, biological model, and therapeutic agent used. Despite the number of studies showing protective effects, the diversity of approaches and endpoints used negatively affects generalization to other models of HD.

8. Chemopreventive mechanisms

The majority of published studies of chemopreventive agents in HD addressed the mechanism of action (see Table 12). Several agents affected more than one mechanism. Fig. 4 provides a schematic representation of the biochemical substrates of cytopathologic changes in HD that may afford key targets for therapeutic interventions against disease progression and severity.

Chemopreventive approaches principally affect antioxidant and anti-inflammatory mechanisms that prevent molecular damage (e.g., protein damage). Strategies for reducing oxidative stress have involved the use of both non-specific antioxidants as well as the targets of redox-modulatory agents, to prevent early-stage damage [81,105]. Complementary prevention strategies also involve the induction of processes to remove damaged proteins and related macromolecules, and facilitation of adaptive processes (e.g. upregulation of brain derived neurotrophic factor to improve neuronal function and/or prevent cellular apoptosis by increasing the Bcl2/Bax ratio).

While efforts were made to combine two chemopreventive agents [e.g., fish oil and quercetin [106] or fish oil and ferulic acid [107]], these were not strategically linked within a mechanistic framework. A chemopreventive treatment may contain a complex mixture of agents which may function as a type of chemopreventive cocktail (e.g., rice bran extract), the concentration of each agent being dependent upon

Table 10
Evaluation of dose selection process by studies that based their decisions on cited literature.

Reference	Model			Gender		Route		Dose		Agent	Notes
	Same	Different		Same	Different	Same	Different	Similar (within 50%)	Different (> difference than 50%)		
		Species	Strain								
Shivasharan et al. [164] vs Ahuja et al. [30]	X				X	X		X		COE	
Shivasharan et al. [164] vs Cetkovic et al. [210]										COE	Could not determine from use of review papers
Sagredo et al. [117] vs Hanus et al. [211]		X			X	X		X		Hu-308	Only tested 1 of 3 agents
Sagredo et al. [117] vs Hillard et al. [212]		X		X		X		X		ACEA	Only tested 1 of 3 agents
Kumar et al. [136] vs Padi and Kulkarni [213]	X			X			X	X		Neproxen	
Kumar et al. [136] vs Dhir et al. [214]		X		X			X	X		Valdecoxib	
Tunez et al. [48] vs Aragno et al. [215]	X			X			X	X		DHEA	
Kumar and Kumar [138] vs Singh et al. [216]	X			X		–	–	–	–	Cyclosporin	Singh et al., did not study cyclosporin
Kumar and Kumar [138] vs Akula et al. [217]		X		X		–	–	–	–	Cyclosporin	Akyla et al., did not study cyclosporin
Kumar and Kumar [13] vs Padi and Chopra [218]	X			X	X		X	X		Carvediol	Both models used
Kumar et al. [25] vs Singh et al. [216]	X			X		X		X		FK506	
Kumar et al. [219] vs Kumar and Goyal [220]		X		N/A	N/A		X	X		Gabapentin	The experimental protocols were strikingly different
Borlongan et al. [49] vs Borlongan et al. [221]			X		X		X	X		Cyclosporin	
Borlongan et al. [49] vs Borlongan et al. [222]			X		X		X	X		Cyclosporin	
Borlongan et al. [49] vs Borlongan et al. [223]	X			X			X	X		Cyclosporin	
Tunez et al. [48] vs Aragno et al. [215]	X			X			X	X		DHEA	
Dhadde et al. [141] vs Thippeswamy et al. [224]	X			–	–	X		X		Embellin	Gender not mentioned
Denny Joseph and Lidhara [107] vs Denny Joseph and Lidhara [106]	X			X		X		X		Fish oil	
Menze et al. [171] vs Bagheri et al. [225]		X			X		X	X		Genistein	
Mahdy et al. [34] vs Kim et al. [226]			X	X			X		X	Ginkgo Biloba	
Mahdy et al. [34] vs Ahmad et al. [227]	X			X			X		X	Ginkgo Biloba	
Kumar and Kumar [155] vs Kaur et al. [228]	X			X		X			X	Hesperidin/naringin	
Kumar and Kumar [155] vs Akula et al. [217]		X		X		–	–	–	–	Hesperidin/naringin	Compounds not tested in reference used to justify
Kumar and Kumar [155] vs Kumar and Kumar [138]	X			X		–	–	–	–	Hesperidin/naringin	Compounds not tested in reference used to justify
Kumar et al. [38] vs Kuhad et al. [229]	X			X			X	X		Lycopene	
Kumar et al. [38] vs Ahuja et al. [30]		X		X		–	–	–	–	Lycopene	Did not test compounds in reference in dose selection
Sandhir et al. [166] vs Kumar et al. (2009e)	X				X	X		X		Lycopene	
Sandhir et al. [166] vs Upaganlawar et al. [230]	X				X	X		X		Minocycline pyruvate	
Ryu et al. [173] vs Popovic et al. [231]	X				X	X		X		Minocycline	
Ryu et al. [173] vs Popovic et al. [231]	X			X		X		X		Pyruvate	
Ryu et al. [173] vs Popovic et al. [231]	X			X			X		X	Minocycline	
Ryu et al. [173] vs Popovic et al. [231]			X		X	X		X		Minocycline	
Ahuja et al. [30] vs Wu et al. [232]	X			X			X	X		Minocycline	
Ahuja et al. [30] vs Yrjanheikki et al. [233]		X		X			X	X		Minocycline	
Jadiswami et al. [31] vs Soliman et al. [234]		X		X		–	–	X		Piroxicam	
Mahdy et al. [147] vs Xu et al. [235]		X		X		X		X		Puerarin	
Mahdy et al. [147] vs Pan and Li [236]	X			X	X	X		X		Puerarin	Both genders used
Jin et al. [194] vs Fatehi-Hassanabad and Tasker [237]			X	X			X	X		Rosiglitozone	
Jin et al. [194] vs Carta et al. [238]			X	X			X	X		Rosiglitozone	

Table 11
Physiological/pharmacological factors affecting dose selection in Huntington's disease animal models.

Agents		References
Arvanil	Dose selected based on pharmacodynamic characteristics of this agent	De Lago et al. [50]
Copper	Dose selected on the basis of rapid copper accumulation in the rat hypothalamus	Santamaria et al. [15]
Cyclosporin A	Selected dose based on inducing immunosuppression	Borlongan et al. [49]
DHEA	Selection based on doses that protected against oxidative stress in rat "synaptosomes"	Tunez et al. [48]
Efavoxan and idazoxan	Dose selection based on optimal blocking of alpha adrenoceptor mediated effects in the rat CNS	Martel et al. [46]
Lithium chloride	Given at dose that slightly exceeds that employed for bipolar disease	Wood and Morton [47]

the type of extracting agent and extraction procedures employed. If translated to human use, the formulation of such a therapeutic cocktail should be rationally guided by multiple pharmacokinetic and mechanistic features ([108]; see below).

A potentially important consideration that has received little attention is that many chemoprotective agents that reduce HD progression in rodent models are also highly effective in retarding cardiovascular aging [109]. Despite this, none of the HD studies reviewed here have addressed or explored effects on cardiovascular aging and how cardiovascular protective effects may interact with CNS protection in the HD models. This issue may become more important given the noted increased prevalence of cardiac abnormalities in HD patients [110].

Another consideration that is not typically discussed is the effect of HD on the microbiome. The studies reviewed here did not provide information on the effects of 3-NP or other neurotoxins that induce HD symptoms on gut microflora. Yet, it is well-known that gastrointestinal tract metabolism increases the bioavailability of some of the therapeutic agents studied (i.e., various polyphenols). The influence of HD (e.g., via 3-NP) on the bioavailability of dietary/oral chemopreventive agents (and vice versa) is currently unknown. Additionally, 3-NP-induced acute effects may incur other systemic responses, including multi-organ toxicity and compensatory adaptive responses.

The rat model of chemically induced HD is of short duration, typically lasting about two, but not more than three weeks. In human subjects, HD tends to first present in middle age; yet the majority of *in vivo* experimental research uses young adult animals. As previously discussed, the induction of adaptive responses decreases with aging, and, therefore, testing HD chemopreventive agents in young rats does not account for age-related loss of adaptive mechanisms. For example, the efficacy of preconditioning can drop precipitously in mice and rats older than 16–18 months of age [43]. As aging is a risk factor for HD, the limited duration of rat studies precludes our capacity to evaluate the interventions over time. Inducing adaptive responses in young rodents and extrapolating to older individuals is thus likely to be problematic at the least, if not outright erroneous at worst.

Given that HD is caused by a CAG/glutamine repeat expansion in HTT that leads to cellular dysfunction and degeneration, transgenic and knockout models have been used to reflect the genotype-to-phenotype expression of HD-like features. The use of the transgenic mouse models may address—and compensate for—some of the limitations of rat cytotoxicity models by (1) providing genotypic bases that are more representative of human disease etiology, and (2) enabling evaluations of iterative disease progression and longevity/survival, thereby (3) creating the opportunity for longitudinal studies of a useful—albeit perhaps limited—set of parameters. Chemopreventive treatments were shown to induce improvements in rotarod performance that were greater than for survival/longevity in the same mice (Table 5). The net increase in longevity was typically only 10–20%; although this enhanced survival is modest in mice, it could perhaps translate to several years of lifespan extension in humans.

The simultaneous administration of multiple agents, each possessing distinctly different but complementary mechanisms of action to counteract HD, could serve as a potentially powerful combinatorial treatment strategy for HD. Unfortunately, to date few experimental animal studies have been conducted that investigate the therapeutic feasibility and efficacy of adopting such a combinatorial approach for HD treatment. Chandran et al. [108] were a notable exception in that they employed a combinatorial therapy of antioxidants to decrease secondary brain damage and to improve functional recovery following brain injury induced by the apocynin-inhibition of NOX2 and the tBHQ-activation of Nrf2. The authors claimed that the generation and clearance of ROS-induced damage were key manifestations of oxidative stress and the stress response it triggered, which enabled the recovery.

It was further argued that a cocktail-like therapy that significantly diminished ROS formation and simultaneously enhanced the disposal of ROS-damaged protein would greatly promote recovery following traumatic brain injury. This type of combinatorial therapy may prove to be a viable and valuable strategy for the treatment of HD in patients. It is also noteworthy that most of the chemoprotective agents in this study yielded significant experimental improvements in HD even though they were administered to animals as a bolus and without optimizing the dosing regimen within a 24-h diurnal cycle. Theoretically, it appears that significant protection may be mediated via multiple agents with different complementary mechanisms that are activated at different rates [108]. Thus, future HD treatments may require the specialized concoction of a chemoprotective cocktail of agents that is based (1) on multiple complementary mechanisms to target multiple molecular pathways and (2) on the rational exploitation of favorable pharmacokinetics (e.g., absorption, distribution, metabolism and excretion) to realize optimal dosing (in magnitude and duration).

Complex diseases such as HD require a multifaceted therapeutic approach that targets the spectrum of cellular dysfunctions, and also activates integrative recovery processes. The use of single agents to prevent the onset, progression, and severity of HD signs and symptoms in animal models has been successful, but only to a limited extent. In general, successful experiments extend survival by approximately 10–30 days in transgenic mice with mitigation of behavioral deficits preceding death by a few weeks. Given that at least 150 highly diverse agents have such notable, but limited, success in experimental animals, the probability that a single targeted chemopreventive agent will protect the CNS and extend lifespan seems low. It may well be that an alternative, cocktail strategy [111] might leverage an integrated mechanistic approach, especially if guided by more precise engagement of pharmacokinetics throughout a 24-hour period and/or dosing cycle. When combined with intermittent fasting and exercise, such an alternative approach may be more likely to confer therapeutic benefits throughout the 24-hour circadian period and, thereby, perhaps decrease the progression and severity of HD [112].

9. Conclusions

1. Over 150 mechanistically diverse agents can significantly reduce signs and symptoms of HD in a variety of *in vivo* mouse and rat models.
2. The doses used in the majority of these animal studies far exceed those for human use (on a mg/kg/day basis), as recommended by various health advisory groups.
3. For each of the 150 agents addressed, there has been little consideration to date whether extrapolation of animal-to-human dosing should be based upon body weight or surface area. This

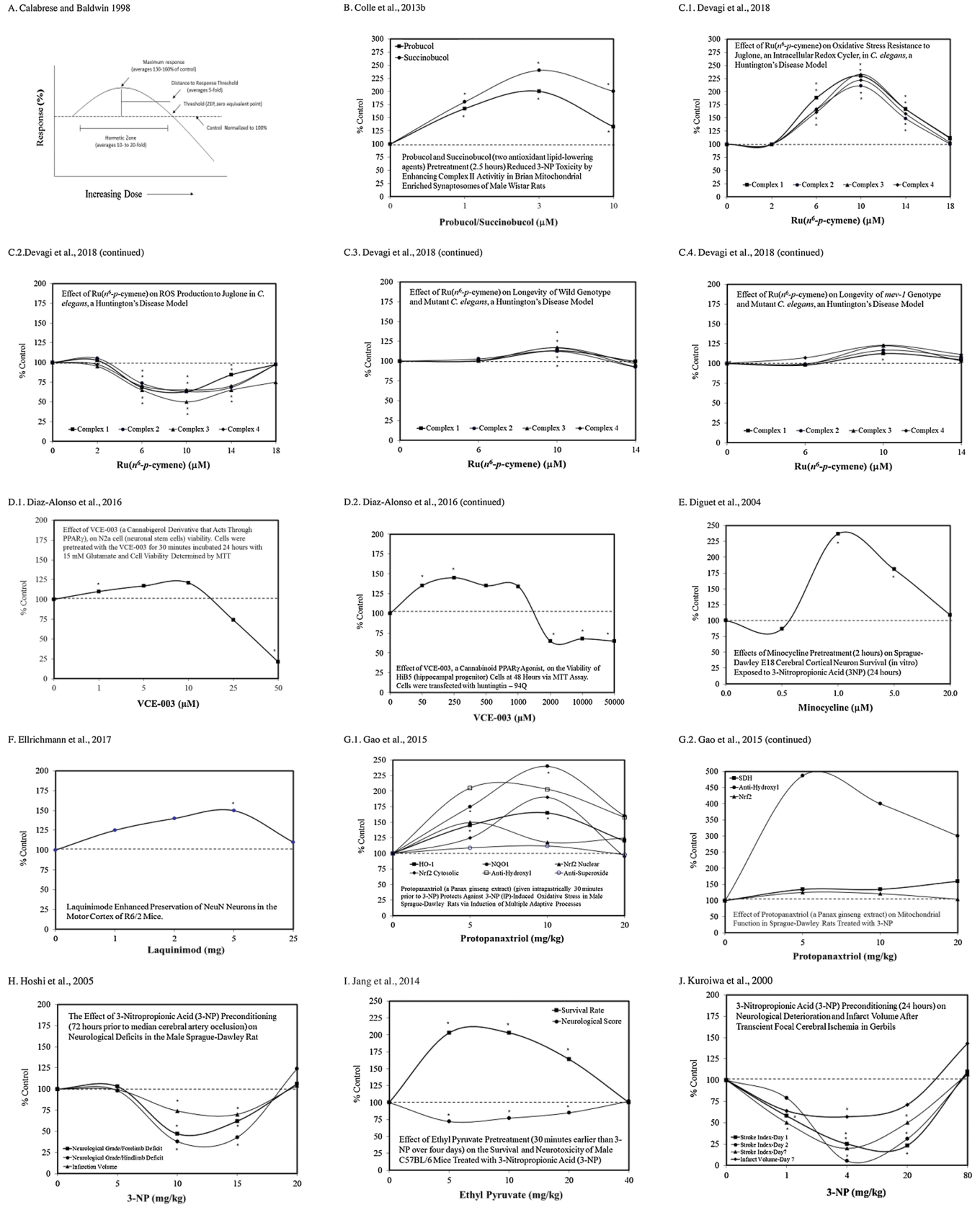

Fig. 3. Hormesis: Chemotherapeutic responses in Huntington's Disease models [113,114].

could be problematic as many of these agents are commercially available to consumers without prescription and may therefore be used by patients to self-medicate their condition.

4. Most of the dose-response studies of HD agents on experimental animals consisted of only 1 or 2 high doses, thereby being inadequate for the purpose of conducting a credible dose-dependent

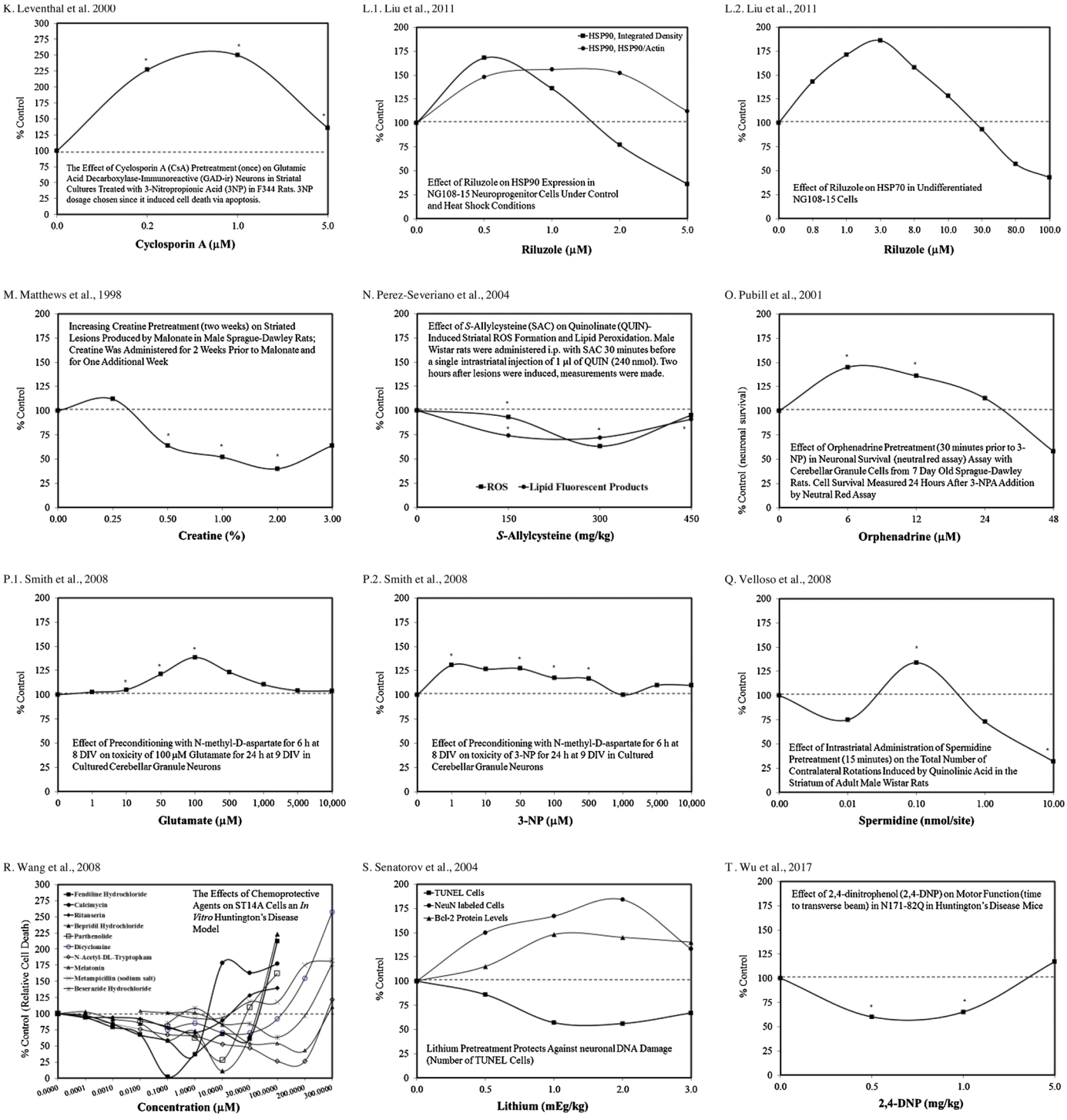

Fig. 3. (*continued*)

evaluation of chemoprotective efficacy.

5. Another related consequence of inadequate dose-response studies is the increased likelihood of failing to obtain optimal dosing regimens and, thus, hindering a rational translation of treatment options from animals to humans.
6. Published studies typically neglected to incorporate pharmacokinetic factors that could enhance pharmacological effects over a 24-hour period and/or more extended periods. There appeared to be little to no attempt at implementing various systematic, mechanistic or pharmacokinetic approaches to discover novel treatment strategies, such as designing cocktails of multiple agents to prevent the progression, signs and/or symptoms of HD.
7. Chemical inductions of HD-like features (by agents such as 3-NP) in rodents dominate the literature. While such animal models permit insight to the prevention of particular signs and symptoms of HD, they are of ambiguous extrapolative value to the human situation, given their lack of genetic and developmental authenticity vis-à-vis the origin and progression of HD in humans.
8. The experimental animal models of HD nearly always consist of young adult rodents that are often administered agents via intraperitoneal injection, while human patients with HD are usually advanced middle age to elderly and treated via oral ingestion.

Table 12
Chemopreventive mechanisms for Huntington's disease.

Agent	Reference
Mechanism: 5-LOX inhibition	
Licofelone	Kumar et al. [24,27]
Quercetin	Dharmanada – www.itmonline.org/arts/lox.htm
Mechanism: acetylcholine receptor	
Galantamine	Park et al. [130]
Mechanism: ACHE inhibitor	
CPE	Malik et al. [135]
Escitolopram	Shetty et al. [165]
Fish oil	Denny Joseph and Lidhara [106]; Denny Joseph and Lidhara [107]
Rivastigmine	Kumar and Kumar [149]
Rutin	Suganya and Sumathi [150]
Tetramethylpyrazine (TMP)	Danduga et al. [159]
Withania	Kumar and Kumar [13]; Kumar and Kumar [199]
Mechanism: Alpha2-adrenoceptor antagonist	
Efaroxan	Martel et al. [46]
Idazoxan	Martel et al. [46]
Mechanism: BAX/BCl2	
Antidepressants: trazodone, imipramine, venlafaxine	Kumar et al. [24,27]
Fasudil	Ahmed et al. [35]
Galantanine	Park et al. [130]
Ginkgo Biloba	Mahdy et al. [34]
Puerarin	Mahdy et al. [34]
Selegiline (L-deprenyl)	Wahdan et al. [153]
Simvastatin	Ahmed et al. [35]
Mechanism: BDNF upregulation	
Antidepressants: imipramine, trazodone, venlafaxine	Kumar et al. [24,27]
Escitolopram	Shetty et al. [165]
Melatonin	Tasset et al. [41,51]
Nicotine	Tariq et al. [168]
Sertraline	Kumar et al. [24]; Peng et al. [186]
Sildenafil	Puerta et al. [131]
Antidepressants: imipramine, trazodone, venlafaxine	Kumar et al. [24,27]
Extreme low-frequency electromagnetic fields	Tasset et al. [140]
Escitalopram	Shetty et al. [165]
Hesperidin	Menze et al. [29]
Probucol	Colle et al. [239]
Sildenafil	Puerta et al. [131]
Mechanism: C5a receptor antagonists	
PMX53	Woodruff et al. [129]
PMX205	Woodruff et al. [129]
Mechanism: calcineurin inhibition	
Copper	Santamaria et al. [15]
FK506	Kumar et al. [25]
Fish oil	Denny Joseph and Lidhara [106]; Denny Joseph and Lidhara [107]
Sertraline	Kumar and Kumar [155]
Mechanism: cannabinoid receptor upregulation	
AM404	Lastres-Becker et al. [115]
Cannabidiol	Lastres-Becker et al. [115]
Win 55,121-2	Maya-Lopez et al. [161]
THC	Lastres-Becker et al. [127]; Diaz-Alonso et al. [67]
Mechanism: catalase upregulation	
CPE (Convolvulus pluricaulic)	Malik et al. [135]
EGCG	Kumar and Kumar [39]
Melatonin	Tasset et al. [41,51]; Nam et al. [124]
Nicotine	Tariq et al. [168]
Sertraline	Kumar and Kumar [154]; Kumar and Kumar [155]
Mechanism: cellular antioxidant enzyme upregulation	
4-Hydroxy tempo	Sandhir et al. [100]
ADIOL	Hanna et al. [17]
Embelin	Dhadde et al. [141]
Trodox	Al Mutairy et al. [170]
Mechanism: CB1 receptor mediation	
AM404	Lastres-Becker et al. [127]
THC	Lastres-Becker et al. [127]
Mechanism: cGMP upregulation	
Sildenafil (striatum/cortex, hippocampus)	Puerta et al. [131]
Mechanism: Complex II restriction inhibition prevention	
Agomelatine	Gupta and Sharma [132]
Protopanaxtriol	Gao et al. [125]
Rice bran extract	Kaur et al. [148]
Succinobucol	Colle et al. [19]
Uridine	Saydoff et al. [14]
Vanillin	Gupta and Sharma [132]
Mechanism: COX-2 inhibition	
Curcumin	Singh et al. [137]
EGCG	Hussain et al. [240]
Extreme low-frequency electromagnetic fields	Tasset et al. [140]
Ethyl pyruvate	Jang et al. [71]
Fasudil	Ahmed et al. [35]
Fish oil	Denny Joseph and Lidhara [106]
Genistein	Willenberg et al. [241]
Kaempferol	Liang et al. [242]
Licofelone	Kumar et al. [27]
Lycopene	Kumar and Kumar [39]
Microcycline	Ryu et al. [173]
Naproxan	Kumar et al. [136]
Olive oil	Corona et al. [243]
Piroxicam	Jadiswami et al. [31]
Pyruvate	Ryu et al. [173]
Resveratrol	Dharmananda (www.itmonline.org; Subbaramaiah and Dannenberg [244])
Rice bran extract	Kaur et al. [148]
Rutin	Suganya and Sumathi [150]
Valfecoxib	Kumar et al. [136]
Mechanism: CREB upregulation (cAMP response element binding protein)	
Rolipram	DeMarch et al. [175]
Sertraline	Kumar and Kumar [154]; Kumar and Kumar [155]
Sildenafil	Puerta et al. [131]
Mechanism: cytochrome C – decrease prevention	
4-Hydroxy tempo	Sandhir et al. [100]
Calendula officianalis	Shivasharan et al. [164]
Ginko Biloba	Mahdy et al. [34]
Methazolamide	Wang et al. [66]
Minocycline	Ahuja et al. [30]
Puerarin	Mahdy et al. [147]
Selegiline (L-deprenyl)	Wahdan et al. [153]
Mechanism: estrogen receptor mediated	
Calendula officinalis (COE)	Shivasharan et al. [164]
Mechanism: free radical scavengers	
CoEQ10	Beal and Shults [245]
Curcumin	Kumar et al. [145]
DHEA	Tunez et al. [48]
Ferulic acid	Denny Joseph and Lidhara [107]
Ginkgo Biloba	Ahmad et al. [227]
Hesperidin	Menze et al. [29]
Melatonin	Nam et al. [124]
Naringen	Gopinath et al. [146]
Rutin	Suganya and Sumathi [150]
Mechanism: GABA upregulation	
ADIOL	Hanna et al. [17]
CBD	Sagredo et al. [116]
L-Theanine	Thangarajan et al. [36]
Rice bran extract	Kaur et al. [148]
Tetramethylpyrazine (TMP)	Danduga et al. [159]
Thymoquinone	Ramachandran and Thangarajan [172]
Withania	Kumar and Kumar [199]
Mechanism: glutamate uptake - enhanced	
Creatine	Matthews et al. [16]
Cyclocreatine	Matthews et al. [16]
Mechanism: GNDF upregulation	
Melatonin	Tasset et al. [41,51]
Mechanism: GSH upregulation	
ADIOL	Hanna et al. [17]
Carvedilol	Kumar and Kumar [13]
Convolvulus pluricaulis extract (CPE)	Malik et al. [135]

(*continued on next page*)

Table 12 (*continued*)

Agent	Reference
Curcumin	Kumar et al. [145]
EGCG	Kumar and Kumar [39]
Embelin	Dhadde et al. [141]
Ethyl pyruvate	Jang et al. [71]
Extreme low-frequency electromagnetic fields	Tasset et al. [140]
Ferulic acid	Denny Joseph and Lidhara [106]
Fish oil	Denny Joseph and Lidhara [106]
Lycopene	Sandhir et al. [166]
NAC	Sandhir et al. [167]
Nicotine	Tariq et al. [168]
Olive oil	Tasset et al. [41,51]
Probucol	Colle et al. [239]
Selegiline	Wahdan et al. [153]
Selenide	Bortolatto et al. [134]
Sesamol	Kumar et al. [142]
Taurine	Tadros et al. [157]
Thymoquinone	Ramachandran and Thangarajan [172]
Transcranial magnetic stimulation	Tunez et al. [133]
Trolox	Al Mutairy et al. [170]
Mechanism: HO-1 upregulation	
Protopanaxtriol	Gao et al. [125]
Hemin and LiCi	Khan et al. [28]
TMS	Tunez et al. [160]
Mechanism: immune suppression	
Cyclosporine A	Leventhal et al. [80]
Cyclosporine	Kumar et al. [25,26,142]
FK 506	Kumar et al. [25,26,142]
Mechanism: iNOS inhibition	
ADIOL	Hanna et al. [17]
EGCG	Kumar and Kumar [39]
Ethyl pyruvate	Jang et al. [71]
Fish oil	Denny Joseph and Lidhara [106]
Naringin	Menze et al. [29]
Rice bran extract	Kaur et al. [148]
Mechanism: MAO-A/B inhibition	
Clorgyline/deprenyl	Maragos et al. [119]
Ginkgo Biloba	Ahmad et al. [227]
Mechanism: melatonin agonist	
Agomalatine	Gupta and Sharma [132]
Mechanism: microglial activation inhibition	
Ethyl pyruvate	Jang et al. [71]
Fasudil	Ahmed et al. [35]
Minocycline	Wu et al. [232]
Mechanism: mitochondrial alterations – biogenesis enhancement	
Rosiglitazone	Carta et al. [238]
Quercetin	Sandhir and Mehrotra [32]
Mechanism: mitochondrial alterations – deletion transport	
CoEQ10	Schulz et al. [6]
Mechanism: mitochondrial alterations – functional enhancement	
ALA/ALCAR	Mehrotra et al. [163]
Ginseng	Tian et al. [42]
Ginkgo Biloba	Mahdy et al. [34]
Melatonin	Tunez et al. [18]
Quercetin	Sandhir and Mehrotra [32]
Mechanism: mitochondrial alterations – NMDA circuit	
DEPMPO	La Fontaine et al. [40]
Spermidine	Jamwal and Kumar [33]
Mechanism: mitochondrial permeability transition inhibition	
Cyclosporine A	Borlongan et al. [49]; Leventhal et al. [80]
Escitalopram	Shetty et al. [165]
Minocycline	Ahuja et al. [30]
NAC	Sandhir et al. [167]
Mechanism: Nf-KB down regulation	
Licofelone	Kumar et al. [27]
Puerarin	Mahdy et al. [147]
Spermidine	Jamwal and Kumar [33]
Thymoquinone	Ramachandran and Thangarajan [172]
Withania	Kumar and Kumar [199]
Mechanism: nicotine ACH receptor mediation	
Galantamine	Park et al. [130]
Mechanism: nitric oxide pathway	
Korean Red Ginseng	Tian et al. [42]
Lycopene	Sandhir et al. [166]
Microcycline	Ahuja et al. [30]

Table 12 (*continued*)

Agent	Reference
Mechanism: NMDA modulation	
ADIOL	Hanna et al. [17]
Carvedilol	Kumar and Kumar [13]
Copper	Santamaria et al. [15]
DEPMPO	La Fontaine et al. [40]
Orphenadrine	Pubill et al. [79]
Co-enzyme Q10	Schulz et al. [6]
Remacemide	Ferrante et al. [44]
Spermidine	Jamwal and Kumar [33]
Ginseng	Kim et al. [122]; Jang et al. [201]
Riluzone	Guyot et al. [126]
Orphenadrine	Pubill et al. [79]
Mechanism: NQO1	
Protopanaxtriol	Gao et al. [125]
Mechanism: Nrf2 upregulation	
Tertbutylhydroquinone (tBHQ)	Silva-Palacios et al. [169]
Mechanism: peroxisome proliferation upregulation	
Cannabigerol	Valdeolivas et al. [52]
Fish oil	Kjaer et al. [246]
Rosiglitazone	Carta et al. [238]
Pioglitozone	Grover et al. [45]
Fenofibrate	Grover et al. [45]
Mechanism: PGC-1a upregulation	
Fasudil	Ahmed et al. [35]
Resveratrol	Ho et al. [193]
Rosiglitazone	Jin et al. [194]; Carta et al. [238]
Simvastatin	Ahmed et al. [35]
Mechanism: phospholipid/carbohydrate maintenance	
Uridine	Saydoff et al. [14]
Mechanism: RHO kinase inhibition	
Fasudil	Ahmed et al. [35]
Simvastatin	Ahmed et al. [35]
Mechanism: SDH preservation	
Carvediol	Kumar and Kumar [13]
Curcumin	Kumar et al. [145]
Ethyl pyruvate	Jang et al. [71]
Fish oil	Denny Joseph and Lidhara [106]
Fo + quercitin combination	Denny Joseph and Lidhara [106]
L-Deprenyl	Maragos et al. [119]
L-Theanine	Thangarajan et al. [36]
Olive oil	Tasset et al. [51]
Quercetin	Sandhir and Mehrotra [32]
Transcranial magnetic stimulation (TMS)	Tunez et al. [160]
Tetramethylpyrazine (TMP)	Danduga et al. [159]
Mechanism: SOD upregulation	
4-Hydroxy tempo	Sandhir et al. [100]
CPE	Malik et al. [135]
SAC	Herrera-Mundo et al. [152]
Sertaline	Kumar and Kumar [39,138,149,154,155,199]
Mechanism: TNFa suppression	
ADIOL	Hanna et al. [17]
Ethyl pyruvate	Jang et al. [71]
Puerarin	Mahdy et al. [147]
Mechanism: vanillin agonist mediation	
Vanillin	Gupta and Sharma [132]
Mechanism: VR1 (endovanilloid) systems mediation	
AM404 endocannabinoid	Lastres-Becker et al. [115]
Nrf2 activation	Silva-Palacios et al. [169]
Korean Ginseng	Tian et al. [42]
Resveratrol	Ho et al. [193]

Because of species, age, and route of administration differences, the predictive human value of the HD experimental models is likely of questionable relevance, both qualitatively and quantitatively.

9. The published literature on experimental animal models of HD generally reflects multi-laboratory efforts toward broad-based screening, with some mechanistic focus. Well over 150 agents from these experimental studies were shown to significantly reduce signs and symptoms of HD in animals, but none has successfully translated to the clinic for human application. If an important measure of success for an experimental animal model is its potential to

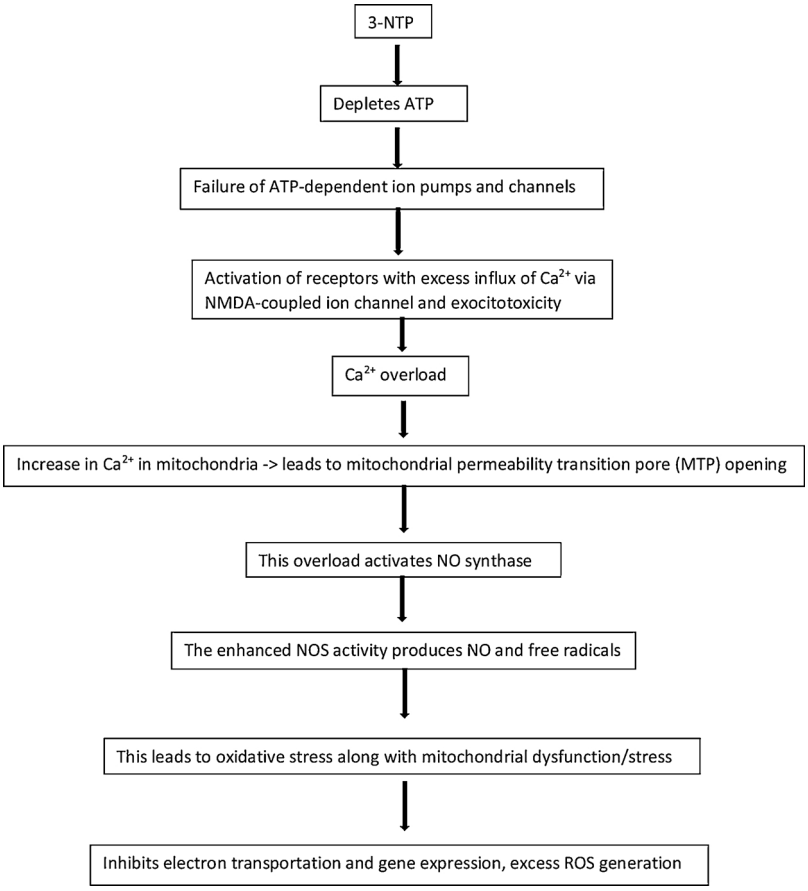

Fig. 4. Biochemical pathways involved in cytopathology of HD.

translate agents to the clinic, then it logically follows that the utility of continuing such studies needs to be carefully examined.

10. In light of the above criticisms, there is a need to rethink the predictive utility of current and proposed screening models, to deepen insight to the differential effect(s) of various treatment routes and dosing regimens, and to develop models that will have greater direct clinical/translational applicability. In this context, it seems important to align the pharmacokinetics and temporal characteristics of particular pathognomic features of HD, such that drug treatments optimally target the most critical disease mechanisms.

Declaration of interests

None.

Acknowledgements

EJC acknowledges longtime support from the U.S. Air Force (AFOSR FA9550-13-1-0047) and ExxonMobil Foundation (< GN2 > S18200000000256 < /GN3 >). The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon. JG is supported by federal funds UL1TR001409 from the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through the Clinical and Translational Science Awards Program (CTSA), a trademark of the Department of Health and Human Services, part of the Roadmap Initiative, "Re-Engineering the Clinical Research Enterprise". The views and conclusions contained herein are those of the author and should not be interpreted as necessarily representing policies or endorsement, either expressed or implied. Sponsors had no involvement in study design, collection, analysis, interpretation, writing and decision to and where to submit for publication consideration.

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