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Review Article

Molecular Targeting in Huntington's Disease: Redox Balance, Inflammatory Pathways, and Mitochondrial Regulation by *Aegle marmelo*

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ABSTRACT

Huntington disease (HD) is a hereditary neurodegenerative disease, in which the motor, cognitive, and psychiatric degeneration is caused by mutant huntingtin-mediated oxidative stress, neuroinflammation and mitochondrial dysfunction. The traditional pharmacotherapies provide only symptomatic treatment and do not stop the development of the disease, which indicates the necessity of multitarget treatment methods. This is a comprehensive review in which the molecular interaction between redox disequilibrium, inflammatory signaling, and impaired mitochondria in HD is investigated, and the effects of Aegle marmelos as a medicinal plant enriched with alkaloids, flavonoid, phenolics, and coumarins on these convergent processes are outlined. The antioxidant activity of the phytoconstituents of A. marmelos is associated with the capacity to activate the Nrf2/ARE signaling axis, which enhances endogenous enzymatic protective mechanisms and suppresses oxidative damage. At the same time, NF-kB inhibition and suppression of pro-inflammatory cytokines (TNF-a, IL-1b, and IL-6) can provide a strong anti-inflammatory effect. In addition, by controlling mitochondrial homeostasis via PGC-1a activation, ATP production, biogenesis, and apoptosis are inhibited, respectively, which restores the neuronal homeostasis. Relative assessment with other botanicals such as curcumin, resveratrol, bacopa and ashwagandha demonstrates that A. marmelos provides an integrative action including redox, inflammatory and mitochondrial control. The review also considers the challenges in translating them, biomarker validation, and future clinical perspectives as a need to use standardized formulations and pharmacokinetic optimization. In short, Aegle marmelos is a mechanistically holistic, multi-target phytotherapeutic candidate that has high disease-modifying capability against Huntington disease and other neurodegenerative diseases.

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INTRODUCTION

Huntington disease (HD) is a neurodegenerative disorder that is progressive, autosomal dominant and is typified by severe motor dysfunctions, cognitive impairment, and psychiatric disturbance. It develops as a result of a CAG trinucleotide repeat that is increased in size in the HTT gene in chromosome 4 causing mutant huntingtin protein to be produced [1]. This misfolded protein is subjected to miscellaneous folding, aggregation and deposition in the nuclei and cytoplasm of the neurons, especially the striatal medium spiny neurons and the cortex. The ensuing series of oxidative stress, mitochondrial dysfunction, excitotoxicity, and neuroinflammation, eventually lead to neuronal death and consequent functional impairment. Although much has been achieved in terms of the molecular basis of HD, the disease has not been cured, and the interventions that have been used are more symptomatic than curative [2]. Huntington disease pathophysiology is multifactorial and includes a complicated interrelationship of redox imbalance, dysregulated responses of inflammation and mitochondrial perturbation. The overproduction of reactive oxygen species and reactive nitrogen species in the neuronal cells is also involved in the process of enhancing lipid peroxidation, protein oxidation, and DNA damage, which amplifies neurodegeneration. At the same time, mitochondrial malfunction reduces the production of ATP and calcium homeostasis, thereby increasing neurons to apoptotic signals. Furthermore, microglia and astrocytes become activated releasing pro-inflammatory cytokines (TNF-a, IL-1b, and IL-6), which provide negative feedback of oxidative damage and neuroinflammation. All these molecular processes interfere with cellular homeostasis, resulting in advanced neurodegeneration and motor deficit that characterize HD pathology [3]. In a normal person, the nervous system operates by the synchronized action of neurons, which transfer electric and chemical impulses and facilitates normal movement, mental and emotional control. The genetic information is properly transcribed and translated to synthesize vital proteins that help in the maintenance and survival of neurons [4]. By contrast, Huntington disease HD is an inherited neurodegenerative condition that is progressive and occurs as a result of mutation in the gene HTT that resides on chromosome 4. This mutant causes a defective increase in the CAG trinucleotide repetitions, which causes the production of defective huntingtin protein **Fig.1**. The mutated protein develops in neurons, especially in the basal ganglia and the cerebral cortex, interfering with the normal functioning of neurons, which eventually kills cells [5]. Clinically, HD shows itself in form of triad of motor dysfunctions (chorea, dystonia), cognitive dysfunction and psychiatric symptoms. In contrast to the consistent neuronal communication observed in a healthy brain, Huntington disease causes progressive dementia, changes in behavior, and deterioration of coordination, which badly affect the quality of life of the affected people [6, 7].

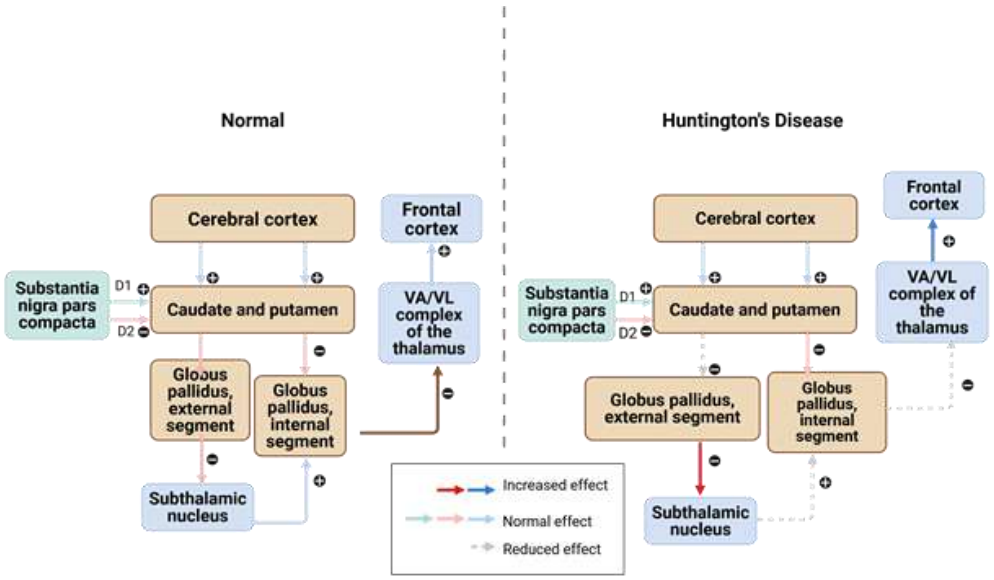


Fig.1: Difference between Normal and Huntington's disease

Even though several pharmacological interventions have been designed to alleviate the symptoms or delay disease progression they do not do much to stop the neurodegenerative cascade. Tetrabenazine and deutetrabenazine are the most popular drugs used to treat choreiform movements and the drugs target the monoamine depletion but not the mechanism of oxidation and inflammatory processes. Other drug candidates, such as glutamate receptor antagonists, histone deacetylase inhibitors and antisense oligonucleotides have demonstrated some efficacy in preclinical or early clinical trials but were biologically restricted by off-target toxicity and lack of long-term effect [8]. Thus, the absence of a curative or disease-modifying therapeutic approach stresses the necessity of the development of alternative therapeutic modalities, able to address several checkpoints on a molecular level and intervene. The trend of the last several years show that there is a growing focus on the use of phytotherapeutics and bioactive of plant-origin compounds to manage complex neurodegenerative conditions [9]. In contrast to single-target synthetic agents, phytochemicals have a multipotential mechanism of action, usually incorporating antioxidant, anti-inflammatory, and mitochondrial-protective actions. This polypharmacological property is especially beneficial in pathologies like Huntington where there are many pathways that are linked with each other and thus lead to neuronal loss. Moreover, a variety of natural products show positive safety profiles, blood-brain barriers permeability, and ability to regulate redox signaling and neuroinflammatory pathways [10]. These include *Aegle marmelos* (Bael) which is a promising candidate because of its high phytochemical profile which consists of marmelosin, aegeline, skimmianine, lupeol, and other flavonoids; it belongs to the Rutaceae family. *A. marmelos*, which is traditionally employed in Ayurvedic medicine due to its anti-inflammatory, antioxidant, and hepatoprotective benefits, has recently been of interest as a possible neuroprotector [10]. Preclinical trials have demonstrated that extracts of *A. marmelos* have high levels of free radical-scavenging capacity, reduce lipid peroxidation, and augment endogenous antioxidant enzyme activity, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. These attributes indicate the ability to replenish the redox balance in neuronal cells effectively overcoming one of the key molecular initiators of Huntington

pathology [5]. This modulation could inhibit glial activity and minimize neuronal injury related to chronic neuroinflammation. Due to these complex effects, a closer understanding of the molecular processes by which *Aegle marmelos* regulates neuronal survival mechanisms can give new knowledge on the therapeutic potential of *Aegle marmelos* [5, 11]. This review attempts to pressure the association between redox homeostasis, inflammatory cascades, and mitochondrial regulation in Huntington disease and how *A. marmelos* can potentially be able to induce these hypothetically joined systems [12].

2. Pathophysiology of Huntington's disease

HD is a neurodegenerative disease that is devastating and gradually affects motor, cognitive and psychiatric functions. On the molecular basis, HD is mostly triggered by an enlarged CAG trinucleotide repeat in the exon 1 of the huntingtin gene, which committed an extended polyglutamine repeat in the huntingtin protein [13]. The product of mutant huntingtin protein is aberrantly folded and acquires toxic gain functions that disrupt many cellular functions. In the long run, it leads to neuronal dysfunction especially in striatum and the cortex. Molecular derangements occurring in HD include protein misfolding and excitotoxicity, oxidative injury, chronic neuroinflammation, and mitochondrial dysfunction which are all dynamically interacting to hasten neurodegeneration **Fig.2** [14].

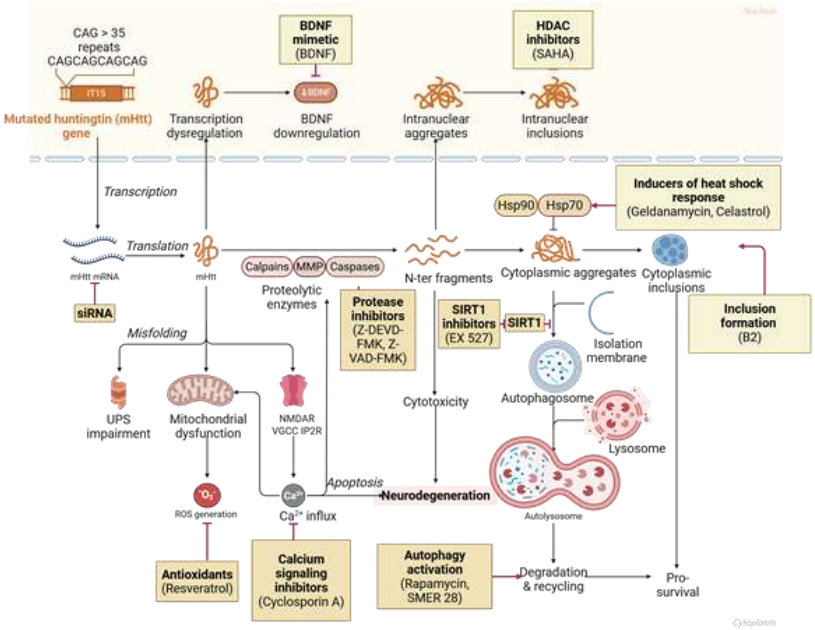


Fig.2: Pathophysiology of Huntington disease

2.1. Protein misfolding and excitotoxicity

Misfolding of mHTT forms a key primary event in the pathogenesis of HD. The increased length of polyQ sequence enhances b-sheet based conformations that accumulate in the form of oligomers, fibrils and inclusion bodies in the neurons [15]. These aggregates disrupt the major cell mechanisms, such as transcriptional regulation, axonal transport and proteostasis. Specifically, mHTT interferes with the ubiquitin-proteasome system (UPS) and autophagy pathways, leading to the appearance of misfolded proteins and cellular strain. Silencing of critical transcriptional factors including CREB-binding protein (CBP) and TATA-binding protein further

down regulates the expression of the genes, attenuating signals of neuronal survival and facilitating apoptosis [16]. Excitotoxicity is also another significant cause of HD pathology, which is the result of overstimulation of glutamate receptors, in particular, the N-methyl-D-aspartate subtype. It is shown that mutant huntingtin can modify the localization and the functionality of NMDA receptors and cause long-lasting calcium influx and the activation of downstream apoptotic pathways [17]. High intracellular calcium levels promote the action of calpains, phospholipases and nitric oxide synthase, which lead to neuronal damage. This pathological glutamatergic transmission is especially deleterious to medium spiny neurons (MSNs) in the striatum that are highly expressive of NMDA receptor subunits and highly vulnerable to calcium-induced excitotoxicity. Excessive stimulation of extrasynaptic NMDA receptors also inhibits the brain-derived neurotrophic factor signaling, which further weaken the resilience of neurons [18].

2.2. Oxidative damage

A classic biomarker of Huntington disease as well as an intermediate in the neuronal death is oxidative stress. The over-production of reactive oxygen species and reactive nitrogen species destroys redox homeostasis, which results in the destruction of proteins, lipids and nucleic acids. Oxidative biomarkers (8-hydroxy-2'-deoxyguanosine (8-OHdG), malondialdehyde and carbonyls of proteins) found in HD striatum and cortical tissues have always been increased in the studies conducted after death [19]. Mutant huntingtin leads to oxidative stress in various ways. The initial one is that mHTT is damaging the electron transport chains complexes within the mitochondria mostly II and III, leading to the release of electrons and generation of superoxide anions. Secondly, mitochondrial ROS generation is aggravated by excitotoxic calcium overload. Third, the compromised antioxidant defense mechanism such as decreased superoxide dismutase, catalase, and glutathione peroxidase activities restricts the capacity of the neurons to eliminate the free radicals [20]. In addition to the fact that oxidative stress causes damage to cellular macromolecules, it increases downstream pathological pathways. Further, oxidative alterations of lipids form reactive aldehydes such as 4-hydroxynonenal (4-HNE), which covalently react with proteins and lead to a loss of enzymatic activity [21]. Equally, DNA oxidation leads to mutations, which undermine the integrity of mitochondrial genome. These are self-perpetuating processes that produce a vicious cycle of oxidative damage and energy failure that causes progressive loss of neurons [22].

2.3. Neuroinflammation

Neuroinflammation has become an important factor in the development of Huntington disease, as an outcome, as well as a cause of neuronal loss. This process involves the activation of glial cells which are microglia and astrocytes. Microglial activation in HD brains is early prior to the actual presence of neuronal loss suggesting a key pathogenic role [23]. Direct activation of the glial cell inflammatory signaling cascades by mutant huntingtin expression. MHTT also induces the release of pro-inflammatory factors through NF-kB and mitogen-activated protein kinase (MAPK) in microglia: tumor necrosis factor-alpha (TNF-a), interleukin-1 beta, and interleukin-6. The microglia activated also secrete nitric oxide (NO) and superoxide that interact to produce peroxynitrite a strong oxidant that can destroy the nearby neurons. Astrocytes, in their turn, become unable to support the homeostasis of glutamate as a result of down-regulation of the glutamate transporter EAAT2 and develop the extracellular

glutamate accumulation and excitotoxic damage [24]. There is also the peripheral immune activation that contributes to HD pathology. Cytokines such as IL-6 and TNF-a have been detected in high plasma concentrations in premanifest and early-stage patients indicating systemic inflammatory condition. Notably, inflammatory milieu is tightly interconnected with oxidative stress and mitochondrion dysfunction. Pro-inflammatory cytokines enhance the production of ROS by activating NADPH oxidase and inducible nitric oxide synthase and oxidative damage continues microglial stimulation. This two-way cross-talk highlights the combined way of redox and inflammatory dysregulation in Huntington disease [25].

2.4. Mitochondrial dysfunction

Mitochondria is also a critical actor in terms of neuronal homeostasis as they control the production of ATP, buffering of calcium and apoptosis. Mitochondrial impairment is a deleterious and one of the most reproducible molecular abnormalities in HD. Mitochondria are directly related to mutant huntingtin, which interferes with their structure and dynamics as well as bioenergetic processes [26]. Mitochondrial respiration with a deficiency in complex II and complex III electron transfer chain has been found in functional analyses of HD models. This will result in a decrease in ATP production, increase ROS production, and depolarization of the mitochondrial membrane potential. The impaired energy supply makes neurons very susceptible to both excitotoxic and oxidative damages [27]. This occurrence induces mobilization of cytochrome c and other pro-apoptotic factors into the cytosol which provokes caspase-mediated cell death. Mitochondrial biogenesis and turnover are also involved. One of the major regulators of mitochondrial activity, transcriptionally repressed by mHTT, is the transcriptional coactivator PGC-1a (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) by disrupting the CREB-binding protein (CBP) and TAF4. The low levels of PGC-1a cause a decrease in the mitochondrial mass and antioxidant capacity. At the same time, compromised mitophagy the selective autophagic deletion of impaired mitochondria leads to accumulation of dysfunctional organelles, which further worsen neuronal injury [28]. All these disturbances result in a condition of chronic energy shortage, increased oxidative stress, and apoptotic vulnerability. Mitochondrial dysfunction, thus, is a cause and a result of other disease mechanisms like oxidative stress and inflammation [29].

3. Oxidative stress in Huntington's disease

Oxidative stress is a main pathogenic hallmark of Huntington disease (HD), which is closely connected with the mitochondrial dysfunction, excitotoxicity, and neuroinflammation. It is caused by the disequilibrium between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the effectiveness of antioxidant cellular defense mechanisms. This imbalance in the susceptible neuron populations of the striatum and cortex leads to oxidative damage of macromolecules, defective energy metabolism and ultimately loss of neurons. An increasing literature suggests that oxidative state does not only contribute to the development of neurodegeneration, but it is a precursor to the clinical manifestation, which indicates that it has an early and causative role in the pathophysiology of HD [30].

3.1. Sources of reactive oxygen and nitrogen species

Various sources of ROS and RNS in HD include mitochondria, as the most important source.

Mitochondrial electron transport chain (ETC) is also predisposed to the leakage of electrons, especially in complexes I and III, and leads to partial reduction of oxygen to superoxide anions. Superoxide dismutase neutralizes these species under physiological conditions to form hydrogen peroxide (H_2O_2), which is catalyzed by catalase and glutathione peroxidase to water. In HD, however, mutant huntingtin disrupts ETC functioning and affects mitochondrial membrane potential by significantly increasing ROS generation [31]. The further aggravation of oxidative stress is supplied with calcium dysregulation. NMDA receptors are sensitized by mutant huntingtin resulting in the excessive calcium influx and calcium overload in mitochondria. The condition induces the tricarboxylic acid cycle as well as the production of NADH and FADH2 flux to the ETC enhancing electron leakage. Calcium overload in mitochondria also causes the mitochondrial permeability transition pore (mPTP) to open and causes membrane depolarization, release of cytochrome c and further production of ROS [32]. Outside mitochondria, there exist a number of enzymatic systems that contribute to the oxidative burden in HD. Superoxide is produced by NADPH oxidase (NOX), which is mainly expressed in activated microglia and which transfers electrons of NADPH to oxygen [33] [34].

3.2. Lipid peroxidation and DNA damage

Among the diverse consequences of oxidative stress in HD, lipid peroxidation and DNA oxidation are particularly destructive. Neuronal membranes are rich in polyunsaturated fatty acids, which are highly susceptible to ROS-mediated peroxidation. Superoxide and hydroxyl radicals attack membrane lipids, forming lipid peroxyl radicals that propagate chain reactions, ultimately generating toxic aldehyde byproducts such as malondialdehyde and 4-hydroxynonenal [35]. These aldehydes can covalently modify proteins, leading to the formation of cross-linked aggregates and loss of enzymatic activity. Post-mortem studies on HD patients have revealed significantly elevated MDA and 4-HNE levels in the striatum and cortex, confirming extensive lipid peroxidation in affected brain regions. Lipid peroxidation products also act as secondary signaling molecules, amplifying neuroinflammatory cascades. For instance, 4-HNE can activate NF-κB and mitogen-activated protein kinases (MAPKs), inducing transcription of pro-inflammatory genes. Moreover, the alteration of membrane fluidity and integrity impairs ion channel function, synaptic transmission, and receptor trafficking factors that are critical for neuronal excitability and survival [32]. DNA damage constitutes another major outcome of oxidative stress. Both mitochondrial DNA (mtDNA) and nuclear DNA are vulnerable to ROS attack. The hydroxyl radical readily oxidizes guanine bases, forming 8-hydroxy-2'-deoxyguanosine, a well-established biomarker of oxidative DNA damage. Damage to mtDNA results in defective respiratory chain subunits, further reducing ATP production and enhancing ROS leakage, thereby perpetuating a vicious cycle of oxidative injury [36].

3.3. Antioxidant defense impairment

Oxidative vulnerability of the neurons in HD is further intensified by the compromising of natural defense mechanisms against oxidative processes. In healthy physiological situations, neurons ensure a fragile redox balance by enzymatic and non-enzymatic antioxidants. The significant enzymatic antioxidants are superoxide dismutase, catalase, glutathione peroxidase, whereas non-enzymatic anti-oxidants are reduced glutathione (GSH), vitamin E, vitamin C, and coenzyme Q10.

Nevertheless, differences in the genome expression and activity of these antioxidant elements have been reported in HD models and patient tissues in several studies [37]. Transcriptional dysregulation is an action by which mutant huntingtin suppresses the expression of antioxidant genes. Of importance is the downregulation of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1a), which is a master regulator of mitochondrial biogenesis and antioxidant enzyme production. The lowered PGC-1a level results in down-regulation of SOD2, catalase and GPx transcription, which reduces the ability of the cell to counteract the ROS. Also, mHTT captures transcription factors like CREB-binding protein and specificity protein 1, which inhibit the actification of antioxidant response factors [38]. The glutathione system which is an important part of the redox regulation is also drastically impaired [39]. The non-enzymatic systems are also affected by impairment of the antioxidant defenses. Coenzyme Q10 levels which are crucial elements of the mitochondrial ETC and antioxidant molecule are lower in HD brains. Coenzyme Q10 deficiency has been shown to be of significance in experimental neuroprotective studies when supplemented in experimental animals in part [40]. Together, the inability of non-enzymatic and enzymatic antioxidants mechanisms creates a chronic oxidative stress which worsens mitochondrial dysfunction and neuroinflammation. This redox regulation deficiency converts oxidative stress into the second consequence to the main cause of neuronal loss [41].

4. Neuroinflammation in Huntington's disease

Neuroinflammation is an auto-central and self-promoting process in Huntington disease pathogenesis. Having initially been regarded as a secondary effect of neuronal death, it can currently be defined as a primary and active cause of neurodegeneration. The appearance of mutant huntingtin protein in neurons and glial cells triggers a chronic inflammatory condition with the activation of microglia, astrocytic maladaptation, and excessive secretion of cytokines and chemokines. Such chronic state of inflammation does not only increase the rate of neuronal damage but also enhances oxidative stress, dysfunctioning of mitochondria, and excitotoxicity. The complexity of molecular crosstalk of glial activation, cytokine signaling, and redox imbalance is imperative in defining possible therapeutic targets in HD [42].

4.1. Microglial and astrocytic activation

Microglia, which are the endogenous immune cells within the central nervous system, are critical in ensuring neural homeostasis by pruning off synapses, clearing the area, and the release of neurotrophic factors. The activation of microglia in Huntington disease, however, is chronic, and they change their homeostatic state to a pro-inflammatory one. This change can be observed at premanifest HD stages, which indicates that microglial activation goes before overt neuronal loss. Increased activity in the immune system evidenced by post-mortem analyses and neuroimaging research has shown higher microglial density and translocator protein binding in the striatum and cortex of HD patients [43]. Microglia expressing mutant huntingtin can directly affect their activation status, mHTT interferes with the cytoskeletal organization, impairs autophagy, and predisposes microglia to overproduction of reactive oxygen species and reactive nitrogen species. Microglia release a variety of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-1 beta (IL-1b), interleukin-6 (IL-6) and nitric oxide

(NO) under facilitation of inducible nitric oxide synthase (iNOS). These mediators facilitate neuronal damage by oxidative stress, glutamate excitotoxicity and apoptosis. Persistent microglial activation, in this way, maintains a pathogenic microclimate, which promotes neuronal impairment [40]. In parallel with the active process of the microglia, astrocytes, the most numerous glial cell type also play an important role in neuroinflammation associated with HD. The physiological role of astrocytes includes supporting neurons, which are achieved through maintaining the extracellular ionic balance, the provision of metabolic substrates, and the elimination of extra-cellular glutamate via excitatory amino acid transporters (EAAT1 and EAAT2) [44]. The two-way interaction of the microglia and astrocytes increases neuroinflammation. Microglia stimulated by this release IL-1a, TNF-a and complement component C1q which result in astrocyte conversion into the A1 neurotoxic subtype. These A1 astrocytes lose their capacity to aid in the development of synapses and rather unleash components that encourage neuronal demise. Therefore, glial activation is not a by-product but a central pathologic process, which leads to progressive neurodegeneration via feed-forward processes of inflammatory loops [45].

4.2. Cytokine and chemokine imbalance

Pro-inflammatory and anti-inflammatory mediators occur in a significant imbalance that characterizes the inflammatory microenvironment in HD. High plasma levels and cerebrospinal fluid (CSF) concentrations of TNF-a, IL-1b, IL-6 and interferon-gamma have been consistently observed in HD patients, prior to the onset of clinical symptoms [46]. Tumor necrosis factor-alpha (TNF-a), an important cytokine in the pathology of HD, has pleiotropic effects via TNFR1 and TNFR2 receptors. TNFR1 activation sets in motion the NF-kB and caspase cascades which stimulate the inflammatory expression of genes as well as the apoptotic signaling. TNF-a also impairs mitochondrial activity and increases the production of ROS, which connects the process of inflammation and oxidative stress [43]. Interleukin-6 (IL-6) enhances chronic neuroinflammation by signaling JAK/STAT3 pathway which induces pro-inflammatory gene expression and inhibits the production of neurotrophic factors. The IL-6 signaling overactivation disrupts synaptic plasticity and enhances gliosis [42]. Interestingly, anti-inflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-b (TGF-b) are significantly decreased in HD and this means that there is an inability to regulate immune response in a compensatory manner. The similarity between peripheral and central inflammation is that monocytes of HD patients show they respond to lipopolysaccharide (LPS) with an exaggerated cytokine response indicating the role of systemic immune control in disease progression. In sum, dysregulation of cytokines and chemokines are components of a self-perpetuated inflammatory feedback mechanism worsening neuronal stress, oxidative damage, and synaptic dysfunction in Huntington disease [34]. Microglia, which are the endogenous immune cells within the central nervous system (CNS), are critical in ensuring neural homeostasis by pruning off synapses, clearing the area, and the release of neurotrophic factors. This change can be observed at premanifest HD stages, which indicates that microglial activation goes before overt neuronal loss. Increased activity in the immune system evidenced by post-mortem analyses and neuroimaging research has shown higher microglial density and translocator protein (TSPO) binding in the striatum and cortex of HD patients [47]. Microglia expressing mutant huntingtin can

directly affect their activation status, mHTT interferes with the cytoskeletal organization, impairs autophagy, and predisposes microglia to overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Microglia release a variety of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-1 beta (IL-1b), interleukin-6 (IL-6) and nitric oxide (NO) under facilitation of inducible nitric oxide synthase (iNOS). These mediators facilitate neuronal damage by oxidative stress, glutamate excitotoxicity and apoptosis. Persistent microglial activation, in this way, maintains a pathogenic microclimate, which promotes neuronal impairment [48] [49].

4.3. NF-κB signaling in neurodegeneration

NF-kB signaling pathway should be regarded as a hub to connect oxidative stress, inflammation, and neurodegeneration in HD. NF-kB is a complex of transcription factor that controls the expression of many genes that have been associated to immune responses, apoptosis, and cell survival. NF-kB dimers (usually p65/p50) remain in the cytoplasm of resting cells under an inhibitory action of the IkB proteins. The IkB kinase (IKK) complex induces IkB phosphorylation upon stimulation with inflammatory signals or oxidative stress and subsequent ubiquitination and degradation of IkB. This enables NF-kB to move to the nucleus and start target gene transcription, such as TNF-a, IL-1b, IL-6, COX-2 and iNOS [50]. Both glial cells and neurons show aberrant NF-kB activity in the Huntington disease. Mutant huntingtin binds directly to IKKg/NEMO which increases IKK activity and attracts long-term NF-kB signaling. This constitutive NF-kB-activation of microglia and astrocytes promotes chronic cytokine and ROS-generation. Although, NF-kB activation is protective in its early stages because of triggering antioxidant and anti apoptotic genes, prolonged activation turns into pro-inflammatory and neurotoxic phenotype [46]. NF-kB can be induced by oxidative stress and mitochondrial dysfunction which are powerful. Redox-sensitive cysteine residues in IKK are activated by ROS generated by mitochondrial respiration or NADPH oxidase to cause NF-kB nuclear translocation. NF-kB, in turn, also improves the expression of iNOS and NOX2, producing more ROS and RNS [42]. NF-kB is a therapeutic target of interest owing to its central position. It has been demonstrated that pharmacological inhibition of NF-kB with natural compounds, small molecules, or genetically has the ability to reduce the production of inflammatory cytokines, as well as enhance neuronal survival in HD models. Interestingly, anti-inflammatory phytochemicals like flavonoids and coumarins of *Aegle marmelos* were also shown to regulate NF-kB activation and inhibit transcription of pro-inflammatory genes. This underscores the possible potential in the NF-kB axis as a mode of inhibiting neurodegeneration caused by inflammation in Huntington disease [42, 51].

5. Mitochondrial dysfunction in Huntington's disease

The dysfunction of mitochondria is one of the most typical and disastrous changes in Huntington disease, which forms the basis of neuronal energy impairment, oxidative dysbalance, and a form of apoptotic signals that lead to the development of the disease. Mutant huntingtin protein protein has a direct interaction with mitochondrial membranes and proteins that control their structure, dynamics, and bioenergetic efficiency. Since neuron ATP production is highly reliant upon mitochondrial ATP production as a means of synaptic transmission, calcium buffering, and axonal transport, even subtle mitochondrial perturbation may have severe pathological effects. There is an

accumulating amount of literature indicating that the abnormalities that take place in the mitochondria are early in HD before the onset of neurodegeneration and the appearance of symptoms. These changes include impaired bioenergetics, mitochondrial DNA damage, calcium dysregulation, and apoptosis pathways activation [52].

5.1. Impaired bioenergetics

The defective bioenergetics is one of the first and greatest mitochondrial abnormalities in HD. Both HD patients and transgenic animal models show a severe impaired ability of oxidative phosphorylation, especially of complexes II (succinate dehydrogenase) and III (cytochrome bc1 complex) of the electron transport chain (ETC). Maladaptive ETC activity impairs ATP generation causing energy deficits resulting in the impairment of neuronal maintenance and signal propagation. This energy deficiency particularly hurts the medium spiny neurons (MSNs) of the striatum which demand much energy and have little glycolytic ability [37]. The oxidative stress is also facilitated due to the impaired activity of ETC complexes which aid in the leaking and formation of reactive oxygen species (ROS). Mutant huntingtin disrupts the mitochondrial protein importation and transcriptional regulation of nuclear-encoded mitochondrial genes and only worsens bioenergetic degradation. The down regulation of PGC-1a leads to and decreases production of critical metabolism enzymes and antioxidant proteins, and exacerbates inefficiency and oxidative susceptibility in the mitochondrion [53, 54].

5.2. Mitochondrial DNA damage

Mitochondrial DNA is especially vulnerable to oxidative damage as it is located very near to the electron transport chain, which is the main ROS generator, and is not surrounded by protective histones. Oxidative stress results in the presence of even more lesions of the mitochondrial DNA in HD, such as base alterations, deletions and strand breaks. The most common oxidative damage, 8-hydroxy-2'-deoxyguanosine (8-OHdG), is significantly increased in HD neurons, which show that there is a great deal of oxidation of the mtDNA. This damage impairs the process of transcription and replication of the mitDNA leading to the malformation of respiratory chain subunits and poor mitochondrial respiration [26]. Mutant huntingtin increases the susceptibility of the mitochondrial DNA in several ways. To begin with, mHTT binds to mitochondrial transcription factor A (TFAM) and mitochondrial RNA polymerase, affecting the transcription and replication of the mitochondrial DNA [55]. The damages in the mitochondrial DNA not only destroy the bioenergetic efficiency but also elicit the innate immune responses. The ability of the oxidized fragments of the Mitochondrial DNA to leak into the cytosol or extracellular space and activate pattern recognition receptors (cGAS) and toll-like receptors (TLRs), triggers inflammatory cascades. This activation of the immune system through the mediation of the mTDNA also adds to the neuroinflammatory condition of HD. Therefore, the destruction of the mitochondrial and neuronal functions in Huntington disease is not only a marker but also a driver of the process facilitated by the destruction of the mitochondrial and neuronal DNA [56].

5.3. Calcium dysregulation

Another significant typical feature of mitochondrial dysfunction in HD is disrupted calcium homeostasis. Calcium ions are important in the neuronal signaling, synaptic plasticity and energy metabolism. In healthy cells, the mitochondria maintain the cytosolic level of

calcium via mitochondrial calcium uniporter (MCU), which is associated with calcium inflow coupled to stimulation of dehydrogenases in the TCA cycle, thus interconnection between calcium dynamics and ATP generation. During HD, however, this well-coordinated system gets grossly out of control [19]. NMDA receptors are changed by mutant huntingtin and cause calcium channels to be open longer and to cause excess calcium to enter the neurons. Higher cytosolic calcium exceeds the buffering capacity of the mitochondrion leading to pathological accumulation of calcium in the organelle [57]. Abnormal connection of ER and mitochondria, which is triggered by changes in mitofusin-2 and inositol 1,4,5-trisphosphate receptor (IP3R) interactions, increases calcium release into mitochondria, increasing oxidative and apoptotic signals. Taken together, calcium dysregulation sets the pathological connection between excitotoxicity, oxidative stress, and mitochondrial dysfunction that propel a series of bioenergetic malfunction and cell demise [58].

5.4. Apoptosis pathways

Mitochondrial dysfunction finally leads to activation of apoptotic pathways which plays a key role in the loss of neurons in Huntington disease. The loss of mitochondrial membrane integrity and pro-apoptotic factors released into the cytosol cause the activation of the intrinsic (mitochondrial) apoptotic pathway. The cascade leads to a structural and regulatory protein cleavage, DNA fragmentation and cell death [59]. Mutant huntingtin alarms neurons to apoptotic stimulus by distorting the equilibrium between pro- and anti-apoptotic Bcl-2 family members. It stimulates the expression of pro-apoptotic proteins Bax and Bak and inhibits the expression of anti-apoptotic Bcl-2 and Bcl-xL. Bax translocation to mitochondria increases the outer membrane permeabilization, accelerating the cytochrome c release. Moreover, ROS and calcium co-operate to enhance the apoptotic signaling by oxidative altering the Bcl-2 protein family and the activation of the stress kinases such as c-Jun N-terminal kinase and p38 MAPK [60].

6. Phytochemistry and Pharmacological Basis of *Aegle marmelos*

Aegle marmelos (L.) Corr., is a holy plant and medicine with medicinal significance, which belongs to the Rutaceae family, and is traditionally used in Ayurvedic and Unani systems of medicine. All the plant parts, such as leaves, fruits, roots, and the bark also have extraordinary therapeutic potential due to the variety of secondary metabolites. In the last decades, the pharmacological effects of *A. marmelos* have been proven by scientific studies, with high antioxidant, anti-inflammatory, hepatoprotective, and neuroprotective properties observed. A diversified pharmacodynamic profile that can tune redox signaling, inflammatory pathways, and mitochondrial stability is attributed to the intricate interaction of its phytoconstituents, which are mostly alkaloids, flavonoids, phenolics, and coumarins **Fig.3**. These complex biological functions make *A. marmelos* a good phytotherapeutic choice in the treatment of neurodegenerative diseases such as Huntington disease [61].

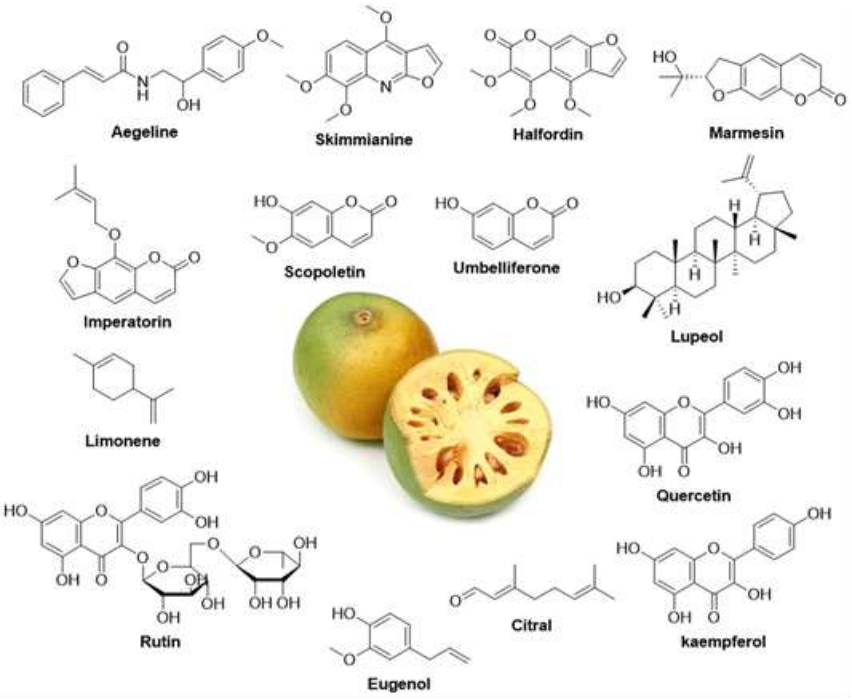


Fig.3: Phytoconstituents of *Aegle marmelos* and their molecular targets

6.1. Bioactive compounds of *Aegle marmelos*

The phytochemical richness of *A. marmelos* encompasses a wide spectrum of structurally diverse compounds. These include alkaloids, flavonoids, phenolic acids, coumarins, terpenoids, and essential oils, many of which contribute synergistically to its pharmacological efficacy. The bioactive profile varies across plant parts and developmental stages, reflecting complex metabolic diversity [37].

6.1.1. Alkaloids

One of the most important groups of compounds in *A. marmelos* is represented by alkaloids, which have diverse bioactivities. Of them, aegeline, marmesinine and skimmianine are common. Aegeline is an N-acyl amine derivative, which is reported to be having antioxidant, antidiabetic properties and cardioprotective. Mechanistically, it regulates lipid peroxidation, increases endogenous antioxidant enzyme, and stabilizes mitochondrial membrane. Skimmianine is a quinoline alkaloid with significant anti-inflammatory and neuroprotective effects, and it suppresses the cyclooxygenase (COX) and lipoxygenase (LOX) pathways. It also inhibits the activation of microglial through the down-regulation of TNF-a and IL-1b. Marmesinine is an aporphine alkaloid that adds to the effects of CNS depressants and antioxidants, scavenging free radicals, and chelating redox-active metal ions. The combination of these alkaloids gives *A. marmelos* its basic neuroprotective and anti-inflammatory base [54].

6.1.2. Flavonoids

Another essential phytochemical group in *A. marmelos* is flavonoids that are characterized by strong anti-oxidant, anti-apoptotic, and anti-inflammatory properties. Some of the major flavonoids that have been identified in *A. marmelos* are rutin, quercetin, kaempferol, isorhamnetin and luteolin [62]. The following are some of the neuroprotective effects of these compounds: Rutin and quercetin are effective scavengers of reactive oxygen and nitrogen species, lipid peroxidation, as well as the

restoration of depleted glutathione levels. Flavonoids regulate several crucial transcriptional factors like nuclear factor erythroid 2-related factor 2 (Nrf2), which increases the transcription of antioxidant enzymes (SOD, catalase and heme oxygenase-1). They also inhibit the activation of nuclear factor kappa B (NF-kB) and subsequent pro-inflammatory mediators, thus inhibiting overactivation of microglia. Quercetin and kaempferol have also been shown to maintain mitochondrial activity, stabilize membrane potential and inhibit apoptosis through Bcl-2 up-regulation and caspase-3 suppression in neuronal models. These characteristics are closely related to the pathophysiology of the Huntington disease where oxidative stress and neuroinflammation are taking major function [5].

6.1.3. Phenolic compounds

These phenolic acids and their derivatives contribute a lot to the antioxidant and the ability to scavenge free radicals of *A. marmelos*. The main phenolics have been found to be ferulic acid, gallic acid, caffeic acid, ellagic acid, and chlorogenic acid. Phenolic compounds take part in redox modulation by: Hydrogen donation-based direct quenching of ROS and RNS [63]. Chelation of metal, which inhibits Fenton and Haber-Weiss reactions which lead to the formation of hydroxyl radicals. Increase in glutathione metabolism and phase II detoxifying enzymes by activating the Nrf2-ARE pathway. In addition to antioxidant activity, these phenolics prevent inflammatory enzymes like COX-2 and inducible nitric oxide synthase (iNOS) and inhibit the production of pro-inflammatory products like prostaglandin and nitric oxide. In addition, they can cross blood-brain barrier and thus, have direct neuroprotective effects hence they are especially important in neurodegenerative diseases [64].

6.1.4. Coumarins and related compounds

Coumarins are a very singular and pharmacologically active group of chemicals found in large quantities in *A. marmelos*. The main ones are psoralen, umbelliferone, marmelosin (imperatorin) and scopoletin. Marmelosin has been shown to possess a good anti-inflammatory and antioxidant effect, which is operated via preventing NF-kB and MAPK signalling pathways. It inhibits the activity of activated glial cells and macrophages in the production of TNF-a, IL-6, and IL-1b [89]. Scopoletin has neuroprotective and anti-apoptotic properties that result in the regulation of calcium homeostasis and improvement of mitochondrial integrity. It also increases the BDNF (brain-derived neurotrophic factor), which facilitates neuronal survival and synaptic plasticity. The other antioxidant properties and DNA-protective properties are in the form of umbelliferone and psoralen which inhibit the oxidative DNA damage caused by ROS. These coumarins acting together equip A. marmelos with an unprecedented biochemical arsenal that activates both redox and inflammatory axes - two common primary features of Huntington pathology [65].

6.2. Antioxidant properties of *Aegle marmelos*

The antioxidant activity of *A. marmelos* has widely been reported in both in vitro and in vivo experiments. Leaf, fruit, and root extracts of it have high antioxidant power, reducing power, and metal chelation ability. Its polyphenolic and flavonoid compounds work together to neutralize ROS effectively like superoxide, hydroxyl radicals and hydrogen peroxide. The experimental research has established that administration of extracts of *A. marmelos* is capable of restoring enzymatic functional antioxidant defense systems, such as SOD, catalase and GPx, in oxidative stress models. At the same time, it restores the depleted glutathione (GSH) and lowers malondialdehyde

(MDA), an indicator of antioxidants that are used to detect lipid peroxidation. These effects are especially useful in neurodegenerative disorders, in which oxidative stress is the major contributor to cell dysfunction [66].

A. marmelos mechanistically triggers the Nrf2-Keap1 signaling pathway, a central controller of antioxidant defense in the cell. When activated, Nrf2 translocates to the nucleus and binds the antioxidant response element (ARE) which enhances the transcription of cytoprotective genes including HO-1, NQO1 and GCLM. This cascade does not only increase the inherent antioxidant ability, but it also supports redox stability in mitochondria. Maintaining the Nrf2 axis helps A. marmelos to counteract the neurotoxic ROS effects and mitochondrial depolarization-induced neuronal death, which is directly connected with the oxidative pathophysiology of Huntington disease [67].

6.3. Anti-inflammatory properties of *Aegle marmelos*

Oxidative stress is highly interconnected with inflammation in neurodegenerative diseases. Anti-inflammatory properties of the *A. marmelos* are due to its ability to regulate major molecular mediators of glial stimulation and cytokine communication. NF-kB is prevented by the alkaloid skimmianine and coumarin marmelosin, thus down-regulating the production of pro-inflammatory cytokines (NF-kB, TNF-a, IL-1b and IL-6), as well as enzymes (COX-2, iNOS). *A. marmelos* inhibits chronic inflammatory signaling by inhibiting phosphorylation of IkB -a and nuclear translocation of NF-kB. At the same time, it inhibits the MAPK pathways (ERK1/2, JNK and p38) that also regulate inflammatory gene expression. Microglial and astrocytic activation is also suppressed by *A. marmelos*, preventing the release of nitric oxide and ROS by these cells. Its use in the neuroinflammation of animal models decreases the number of microglia and inhibits the astrocyte metabolic transition to the neurotoxic A1 phenotype. Neuronal preservation and functional recovery involves the glial activity modulation [68]. Notably, *A. marmelos* induces the anti-inflammatory balance through the expression of the anti-inflammatory cytokines, including IL-10 and TGF-b. In this dual regulation, it restores homeostasis in the neuroimmune setting. These results confirm the hypothesis that the *A. marmelos* is capable of suppressing the neuroinflammatory cascade in Huntington disease by regulating redox-sensitive cascades of inflammatory signaling [69]. *Aegle marmelos* has a combined antioxidant and anti-inflammatory action and the synergistic neuroprotective activity of this plant is very useful in the pathophysiology of the Huntington disease. Simultaneously scavenging free radicals, activating Nrf2, inhibiting NF-kB, and stabilizing the work of mitochondria, *A. marmelos* affects several pathological nodes at once oxidative stress, neuroinflammation, and apoptosis [70].

7. Target-based mechanistic insights of *Aegle marmelos* in Huntington's disease

Huntington disease pathogenesis is difficult due to the fact that it occurs due to a violation of redox balance, chronic neuroinflammation, and mitochondrial dysfunction [71]. All these mechanisms are interconnected, and they enhance one another, leading to progressive neuronal damage and apoptosis. Traditional single-target pharmacological therapies have not been very effective since they only focus on single pathological processes [72]. By comparison, phytochemicals including those found in Aegle marmelos have multitarget properties, and can improve oxidative, inflammatory, and mitochondrial responses simultaneously [73]. *A.*

marmelos has therapeutic potential due to its novel ability to regulate molecular defenses, which ensure neuronal homeostasis. The most important of them are the Nrf2/ARE signaling pathway that regulates redox, the NF-kB axis that regulates inflammatory response, and the mitochondrial network of PGC-1a that is deemed to be important in maintaining bioenergetic stability and anti-apoptotic defense. The sections below expound on the target-based mechanistic understanding where *A. marmelos* can counter the neurodegenerative cascade in Huntington disease [5].

7.1. Redox Modulation: Nrf2/ARE Signaling Pathway

Oxidative stress is essential in the pathophysiology of HD which damages cellular macromolecules and causes apoptotic signaling. Nuclear factor erythroid 2-related factor 2 is a transcription factor that is a master regulator of antioxidant defence and cytoprotection. When oxidative or electrophilic stress occurs, cysteine residues on Keap1 are oxidized resulting in conformational changes that liberate Nrf2. The released Nrf2 translocates to the nucleus and engages the transcription of the target genes, which participates in detoxification and redox homeostasis (heme oxygenase-1 (HO-1), NADPH quinone oxidoreductase-1 (NQO1), glutamate-cysteine ligase (GCL), and glutathione peroxidase (GPx)). In Huntington, disease Nrf2 signaling is also highly disrupted by oxidative alteration of Keap1 and transcriptional suppression by the mutant huntingtin (mHTT). Subsequently, this decreases the Nrf2 nuclear translocation and the expression of antioxidant enzymes, which causes sustained oxidative stress. This malfunction increases the dysfunction of the mitochondria and enhances neuronal death. Nrf2 reactivation, thus, is a key therapeutic objective in HD [74].

Aegle marmelos has a significant stimulation of the Nrf2/ARE pathway, and it is mainly caused by its polyphenolic and flavonoid components that include quercetin, rutin, marmelosin, and scopoletin [75]. Moreover, *A. marmelos* increases the glutathione redox cycle by activating the glutamate-cysteine ligase (GCL) activity, which restores the intracellular GSH depletion and cellular redox balance. *A. marmelos* protects lipid peroxidation, oxidation of proteins and oxidation of DNA, which is typical of HD neurons by strengthening the endogenous antioxidant network. Notably, the Nrf2 activation of *A. marmelos* can not only suppress the oxidative stress, but also mitochondrial biogenesis and inflammation. Nrf2 cooperates with PGC-1a in regulating mitochondrial antioxidant defense genes, and in parallel blocks NF-kB signaling by claiming transcriptional coactivators, including CBP/p300. Therefore, the Nrf2 stimulation by *A. marmelos* offers a holistic defense mechanism that is integrated to involve redox regulation, mitochondrial defense and anti-inflammatory regulation. Together, the redox modulatory effects of *Aegle marmelos* via Nrf2/AREs can provide a molecular mechanism by which the compound is able to disrupt oxidative cascades and neuronal integrity in Huntington disease [76].

7.2. Inflammatory regulation: NF-κB and cytokine control

Another significant pathological axis in Huntington disease is neuroinflammation. Continuous stimulation of microglia and astrocytes results in production of pro-inflammatory cytokines like TNF-a, IL-1b and IL-6 that consequently cause oxidative damage and neuronal apoptosis [107]. The nuclear factor kappa B (NF-kB) pathway, which is a transcriptional regulator involved in the coordination of immune and stress reactions, is central to this inflammatory

signalling [77]. NF-kB binds to kB motifs in promoters of target genes in the nucleus, which triggers the transcription of inflammatory mediators, including COX-2, iNOS and cytokines. Mutant huntingtin interacts abnormally with IKKg / NEMO in HD, and both neurons and glial cells constitutively activate NF-kB signaling. This sustained activation is the cause of a loop of inflammation and oxidative stress, which enhances neurodegeneration [78]. *Aegle marmelos* phytochemicals have high NF-kB signaling inhibitory activities, thus restoring immune homeostasis. Simultaneously, COX-2, iNOS and TNF-a are suppressed and IL-10 and TGF-b are up-regulated by *A. marmelos*, and cytokine balance is restored by the neuroimmune environment. Also, flavonoids rutin and quercetin regulate the MAPK signaling cascade, suppressing the phosphorylation of ERK1/2, JNK, and p38 MAPK [37]. The extracts of *A. marmelos* also reduce the microglial density considerably, inhibit the astrocytic hypertrophy, and suppress the expression of GFAP and Iba1 - glial activation markers. These results demonstrate its ability to inhibit the neuroinflammation in the central and peripheral locations. The therapeutic importance of *A. marmelos* in chronic neurodegenerative disorders is anchored on the ability to ameliorate cytokine storms and glial-mediated neurotoxicity [79].

7.3. Mitochondrial protection: ATP synthesis, biogenesis, and anti-apoptotic effects

Mitochondria are central to neuronal health, providing energy, regulating calcium homeostasis, and controlling apoptotic signalling [80]. In Huntington's disease, mutant huntingtin interferes with mitochondrial dynamics, electron transport chain function, and calcium buffering capacity, resulting in energy failure and apoptosis. Restoring mitochondrial function, therefore, constitutes a vital therapeutic objective. *Aegle marmelos* exerts robust mitochondrial protection through several complementary mechanisms [36].

(a) Enhancement of ATP Synthesis

A. marmelos enhances electron flow through the respiratory chain by mitigating oxidative, inhibitory actions on mitochondrial complex II and III, which enhances oxidative phosphorylation and generation of ATP. Its bioactive constituents scavenge ROS its mitochondrion, stabilize the mitochondrial membrane potential (Dpsm), and inhibit the mitochondrial permeability transition pore (mPTP). This does not lose efficiency in ATP synthesis and ensures neuronal survival in the presence of oxidative stress. Experimental models have demonstrated that the *A. marmelos* treatment enhances the activity of major mitochondrial enzymes; succinate dehydrogenase, cytochrome c oxidase and NADH dehydrogenase which validate its power to restore mitochondrial bioenergetics [51].

(b) Promotion of mitochondrial biogenesis

PGC-1a is the main transcriptional coactivator that controls the process of mitochondrial biogenesis, including nuclear respiratory factors (NRF-1, NRF-2) and mitochondrial transcriptional factor A. In HD, mHTT suppresses the PGC-1a causing a decrease in mitochondrial mass and antioxidant capacity. *Aegle marmelos* overcomes this repression, as it increases the expression of PGC-1a and its subsequent signaling pathway. This stimulation improves production of mitochondrial proteins, replication of mitochondrion DNA and creation of new mitochondria, which regenerates the cellular energy network. There is further mutual activation- Nrf2 stimulation activates PGC-1a transcription and PGC-1a stimulation leads to a decline in ROS which stabilizes Nrf2 signalling. This bidirectional synergy leads to the

long-term mitochondrial biogenesis and redox homeostasis [42].

(c) Anti-apoptotic regulation

The end result of mitochondrial dysfunction is the activation of intrinsic apoptotic pathways. The prevention of this is done by *Aegle marmelos*, which regulates key apoptosis factors. Its constituents increase anti-apoptotic proteins, Bcl-2 and Bcl-xL, and decrease pro-apoptotic ones of Bax, Bak and caspase-3. Mitochondrial membrane stabilization prevents the release of cytochrome c and caspase cascade activation. Additionally, *A. marmelos* suppresses importation of apoptosis-inducing factor (AIF) to the nucleus, which suppresses caspase-independent cell death. Re-lesion of mitochondrial integrity is also coincided with the restoration of calcium homeostasis, because A. marmelos inhibits calcium overload by regulating the mitochondrial calcium uniporter and enhancing endoplasmic reticulum-mitochondrial communication. Together, these responses provide all-inclusive mitochondrial protection including energy conservation, structural stability, and prevention of apoptotic signalling [81].

Table 1: Molecular targets in Huntington's disease and modulation by *Aegle marmelos*

Molecular Target / Pathway	Role in Huntington's Disease	Phytoconstituents from *Aegle marmelos*	Mechanism of Modulation / Effect	Pharmacological Outcome	References
Mutant Huntingtin Protein	Aggregation of mutant huntington leads to neuronal toxicity and cell death.	Scopoletin, Aegeline, Lupeol	Reduce protein misfolding and aggregation by antioxidant and proteasomal activation pathways.	Decreased neuronal toxicity; enhanced protein clearance.	[4]
Oxidative Stress (ROS, RNS)	Excess reactive oxygen and nitrogen species damage neuronal membranes and DNA.	Quercetin, Rutin, Scopoletin, β-sitosterol	Enhance activity of antioxidant enzymes (SOD, CAT, GPx) and scavenge free radicals.	Reduction in oxidative stress; protection of neuronal integrity.	[1]
Mitochondrial Dysfunction	Impaired energy metabolism contributes to neuronal death.	Lupeol, Aegeline, β-sitosterol	Stabilize mitochondrial membrane potential and improve ATP synthesis.	Improved neuronal energy metabolism and survival.	[36]
Inflammatory Pathways (NF-κB, COX-2, TNF-α, IL-6)	Chronic neuroinflammation accelerates neuronal loss in HD.	Scopoletin, Lupeol, Skimmianine, Imperatorin	Inhibit NF-κB activation and downregulate pro-inflammatory cytokines (TNF-α, IL-1β, IL-6).	Reduced neuroinflammation; protection of neurons.	[77]
Excitotoxicity (Glutamate Receptor Overactivation)	Overstimulation of NMDA receptors leads to calcium overload and neuronal apoptosis.	Quercetin, Scopoletin	Modulate glutamate receptor signaling and reduce Ca^{2+} influx.	Prevention of excitotoxic neuronal injury.	[3]

Apoptotic Pathways (Caspase-3, Bcl-2, p53)	Overactivation of apoptotic proteins contributes to neuronal degeneration.	Lupeol, Imperatorin, Quercetin	Inhibit caspase-3 activation and upregulate anti-apoptotic Bcl-2 expression.	Suppression of apoptosis; enhanced neuronal survival.	[2]
BDNF (Brain-Derived Neurotrophic Factor)	Decreased BDNF expression impairs neuronal plasticity and survival.	Aegeline, Scopoletin, Rutin	Upregulate BDNF and TrkB signaling via antioxidant and anti-inflammatory effects.	Improved neuronal growth and synaptic plasticity.	[82]
AMPK/PPAR -γ Pathway	Dysregulated energy metabolism and lipid accumulation worsen HD pathology.	β-sitosterol, Lupeol, Aegeline	Activate AMPK and PPAR-γ signaling to improve metabolic regulation.	Enhanced energy homeostasis and neuroprotection.	[83]
MAPK / JNK Pathway	Overactivation contributes to stress-induced neuronal apoptosis.	Quercetin, Scopoletin	Inhibit JNK and p38 MAPK signaling cascades.	Attenuation of stress-mediated neuronal damage.	[84]
Cholinergic and Dopaminergic Systems	Neurotransmitter imbalance causes motor and cognitive dysfunction.	Scopoletin, Rutin, Quercetin	Modulate acetylcholinestera se (AChE) and dopamine levels in the brain.	Improved cognitive and motor performance.	[52]

8. Comparative insights with other botanicals in Huntington's disease

Natural products and botanicals have a classic history of investigation as neuroprotective agents because of their pleiotropic effects and lack of toxicity in chronic neurodegenerative diseases. Huntington disease (HD), as a multifactorial disease, with oxidative stress, dysfunction of the mitochondria, and neuroinflammation as its pathophysiological mechanisms, requires an intervention that has the ability to respond to these interconnected pathways. In these regards, there are a number of phytochemicals that show therapeutic potential, including curcumin, resveratrol, bacopa and ashwagandha, which are promising therapeutics. Their molecular mechanisms can be compared and give useful information on how *Aegle marmelos* fits or even exceeds these botanicals in hitting HD pathology [52].

8.1. Curcumin (*Curcuma longa*)

Curcumin is a polyphenolic product of *Curcuma longa* with one of the most thoroughly investigated phytochemicals in neurodegenerative diseases. It has general-spectrum antioxidant, anti-inflammatory and anti-aggregatory effects. Curcumin prevents the toxicity of mutant huntingtin in HD models through the modification of various molecular targets [83]. Mechanically, curcumin stimulates the Nrf2/ARE pathway that augments the expression of antioxidant enzymes like HO-1, NQO1 and SOD, which ultimately decrease the level of ROS. It simultaneously

suppresses the NF-kB signaling preventing the secretion of TNF-a, IL-1b, and IL-6 by the activated microglia and astrocytes [85]. It has been demonstrated in preclinical studies that curcumin improves locomotor coordination and decreases the inclusion formation in neurons in HD mouse models [53]. Furthermore, some *A. marmelos* coumarins, including marmelosin, have been shown to be more effective as a mitochondrial protector than curcumin, so it could be more effective in maintaining the energy metabolism of the neurons [86].

8.2. Resveratrol (*Vitis vinifera*)

Resveratrol is a neuroprotective and anti-aging polyphenol that is a stilbene and is abundant in red wine and grapes. Its therapeutic benefit in Huntington disease operates mainly through the SIRT1 activation which is a NAD+ deacetylase, which controls mitochondrial genesis, oxidative stress reaction, and apoptosis. Resveratrol activates SIRT1, which causes the deacetylation and activation of PGC-1a, which increases mitochondrial performance and ATP production [87]. Also, SIRT1 controls the expression of FOXO and p53 transcription factors, facilitating cell survival and expression of antioxidant genes [88]. Resveratrol has a drawback though in that glucuronidation and sulfation occur quickly reducing its oral bioavailability. *Aegle marmelos*, comparatively, recapitulates the effects of resveratrol on PGC-1a-mediated mitochondrial biogenesis, but in a dual manner through the activation of both Nrf2 and PGC-1a, hence offering a more complete peri-oxidative and apoptotic protective effect. As opposed to resveratrol, *A. marmelos* does not solely depend on the activation of SIRT1, which enables it to provide its benefits along a wider redox-inflammation-energetics spectrum [89, 90].

8.3. Bacopa (*Bacopa monnieri*)

Bacopa monnieri, which is referred to as Brahmi in Ayurveda has a long history of being a cognitive stimulant and neuroprotectant. Its primary active constituents, bacosides A and B, are also reported to enhance synaptic transmission, anti-oxidant ability and mitochondrial functionality [91]. Bacopa has been demonstrated to have free radical-scavenging activity and increase endogenous antioxidants like SOD, catalase, and GPx in experimental models of HD and other neurodegenerative diseases. It regulates cholinergic neurotransmission by elevating the production of acetylcholine and decreasing the activity of acetylcholinesterase, which helps in enhancing cognitive functioning [61]. These actions are similar to *A. marmelos* that also reinstates mitochondrial membrane integrity and inhibits caspase activity. Although bacopa mainly works by antioxidant and cholinergic mechanisms, *A. marmelos* has a more global molecular effect, and can act on Nrf2, NF-kB, and PGC-1a. In addition, *A. marmelos* coumarins and flavonoids provide other advantages of mitochondrial biogenesis and calcium control less evident in bacopa. Therefore, *A. marmelos* can be of better use in case of energy-degraded neuronal systems like that of HD [92].

8.4. Ashwagandha (*Withania somnifera*)

Another Ayurvedic medicine, *Withania somnifera* (ashwagandha), exhibits very strong neuroprotective and adaptogen effects, which are due to its steroidal lactones called withanolides. Aswagandha has been reported to prevent mHTT aggregation, oxidative stress, and rescue neuronal dysfunction in HD models[93]. Mechanistically, withanolides increase Nrf2 and downstream antioxidants just like *A. marmelos*, and regulate heat shock proteins (HSP70 and HSP90) which help in adequate protein folding and clearance of morphologically variant mHTT aggregates. These

translate to the mitochondrial stabilizing effects of *A. marmelos*. Nevertheless, ashwagandha proves to be superior in proteostasis and the regulation of stress response but its impact on mitochondrial biogenesis (PGC-1a induction) is less proven. By contrast, *A. marmelos* provides an integrated control of redox homeostasis, inflammatory signaling and mitochondrial dynamics, which provides a more holistic therapeutic model [94].

9. Future directions and clinical perspectives

Although there is overwhelming preclinical data to suggest the neuroprotective potential of Aegle marmelos, much translational challenges arise before the potential of this nutrient in clinical contexts can be achieved in Huntington disease (HD). The pathophysiology of HD as a multifactorial process with a combination of oxidative stress, neuroinflammation, and mitochondrial dysfunction requires interventions capable of acting at multiple of the hierarchies of molecules, and *A. marmelos*, with its multitargeted effects embodied by the activation of Nrf2/ARE, suppression of NF-kB, control of PGC-1a, provides exactly this kind of integrative action. Nonetheless, the shift of experimental validation to clinical translation necessitates a systematic maximization in a number of areas. First, the pharmacological consistency of bioactive constituents of *A. marmelos* extracts should be reached by standardization and characterization because the variability of phytochemical because of geographical, extraction method, and choice of plant part can modify the biological activity. The development of sophisticated nanocarrier systems e.g. lipid nanoparticles, phytosomes and polymeric micelles can provide better bioavailability, targeted delivery and sustained release, which improve therapeutic outcome with less systemic toxicity. Biomarker validation perspective Biomarker discovery of consistent molecular signatures that indicate redox homeostasis, mitochondrial fitness, and neuroinflammatory control will be essential in the translation of preclinical findings into quantifiable clinical outcomes.

Aegle marmelos has the potential of clinical application due to the unique pharmacological versatility and safety profile. In comparison to synthetic single-target agents, *A. marmelos* provides a multitiered strategy with potential to reestablish redox balance, chronic inflammation, and mitochondrial transcription of rejuvenated mitochondrial activities, a core process underlying the development of diseases. It has a good basis to be explored clinically because of its known safety in traditional medicine and good tolerability in its preclinical toxicity investigations. The preclinical trials may be conducted as adjunctive therapy with evaluation of *A. marmelos* supplementation in combination with the current symptomatic treatment including tetrabenazine or deutetrabenazine to evaluate the additive or synergist neuroprotective effects.

CONCLUSION

Huntington disease is a multifactorial neurodegenerative condition in which oxidative stress, neuroinflammation, and mitochondrial dysfunction are convergent factors that promote progressive neuronal death. The traditional pharmacotherapies have not been very effective in offering disease-modifying effects, and hence the dire need to develop multi-targeted therapeutic approaches. The current review indicates that *Aegle marmelos* has a potential to be a valuable phytotherapeutic candidate that can interfere with these key molecular pathways. A. marmelos is rich in alkaloids, flavonoids, phenolics, and coumarins that are known to have strong antioxidant properties because of their stimulation of the Nrf2/ARE signalling path pathway to boost the

antioxidant defences of the body and therefore redox homeostasis. The combination of these measures is the result of the opposite to the disease developmental pathological processes. Comparative data suggests that in the context of other botanicals like curcumin, resveratrol, bacopa and ashwagandha, which confer partial protection, *A. marmelos* is likely the only botanical to integrate redox modulatory effects, inflammatory control, and mitochondrial protection into a neuroprotective system. The safety profile and CNS permeability of the plant have solid clinical exploration potential, but the standardized formulations, biomarker-based validation, and optimization of pharmacokinetic processes are important steps to take next. Overall, *Aegle marmelos* represents a mechanistically integrated and pharmacologically effective neuroprotective strategy with novel insights into the design of multi-target therapy of Huntington disease and has the potential to apply this potential to extend to other neurodegenerative settings.

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