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REVIEW ARTICLE

Dapsone, More than an Effective Neuro and Cytoprotective Drug

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ARTICLE HISTORY

Received: April 23, 2021
Revised: June 13, 2021
Accepted: June 13, 2021

DOI:
10.2174/1570159X19666210617143108

Abstract: ***Background*****:** Dapsone (4,4'-diamino-diphenyl sulfone) is a synthetic derivative of sulfones, with the antimicrobial activity described since 1937. It is also a drug traditionally used in dermatological therapies due to its anti-inflammatory effect. In recent years its antioxidant, anti-excitotoxic, and antiapoptotic effects have been described in different ischemic damage models, traumatic damage, and models of neurodegenerative diseases, such as Parkinson's (PD) and Alzheimer's diseases (AD). Finally, dapsone has proven to be a safe and effective drug as a protector against heart, renal and pulmonary cells damage; that is why it is now employed in clinical trials with patients as a neuroprotective therapy by regulating the main mechanisms of damage that lead to cell death.

Objective**:** The objective of this study is to provide a descriptive review of the evidence demonstrating the safety and therapeutic benefit of dapsone treatment, evaluated in animal studies and various human clinical trials

Methods**:** We conducted a review of PubMed databases looking for scientific research in animals and humans, oriented to demonstrate the effect of dapsone on regulating and reducing the main mechanisms of damage that lead to cell death.

Conclusion**:** The evidence presented in this review shows that dapsone is a safe and effective neuro and cytoprotective treatment that should be considered for translational therapy.

Keywords: Dapsone, neuroprotection, cytoprotection, anti-inflammatory, antioxidant, antiexcitotoxic, antiapoptotic.

1. INTRODUCTION

Neuronal damage is a pathological process observed in various neurological diseases such as neurodegenerative diseases, ischemic or hemorrhagic stroke, traumatic brain and spinal cord damage, and epilepsy. Ionic dysregulation is the main mechanism that leads to cell death in those diseases. The intracellular influx of calcium and the release of excitatory amino acids cause excitotoxicity, oxidative stress, inflammation, and apoptosis [1, 2]. In this scenario, it is essential to develop effective neuroprotective therapies that regulate or block the main mechanisms that lead to irreversible damage [3]. As research is looking for new neuroprotective therapies, dapsone appears as a compelling candidate due to its anti-inflammatory effect, particularly to preserve nervous tissue [4-6]. On the other hand, diseases of the central nervous system (CNS) share damage mechanisms similar to others that occur in heart, kidney and lung diseases. Interestingly, those pleiotropic therapeutic mechanisms of dapsone allowed some authors to consider this drug as a potential therapeutic resource in the severe form of the COVID-19 disease [7-10].

1.1. Dapsone

Dapsone (4,4'diaminodiphenylsulfone) was synthesized for the first time in 1908 by Emil Fromm, who is considered the father of sulfones [11]; its chemical structure consists of a central sulfur atom attached to two carbon atoms (Fig. **1**). The use of sulfones as therapeutic agents appeared long after dapsone synthesis. Dapsone is classified as an antibiotic to treat infections due to bacteria, yeasts, and parasites [4, 12]. This sulphone has a general use for the treatment of leprosy

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1570-159X/22 $65.00+.00

(*Mycobacterium leprae*) [13-15] and by having anti-inflammatory effects and inhibiting the production of reactive oxygen species (ROS), reducing the effect of eosinophil peroxidase on mast cells and negatively regulating neutrophil chemotaxis, this allows its use in the treatment of a wide variety of inflammatory and skin conditions. such as dermatitis herpetiformis and acne vulgaris [16] (Fig. **2**).

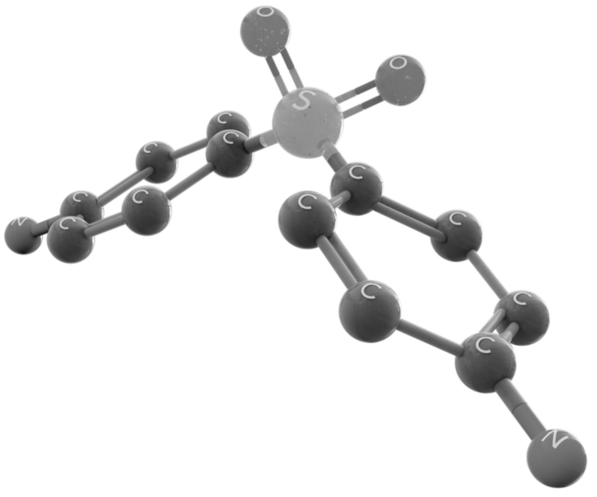

Fig. (1). Dapsone chemical structure. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

Dapsone is rapidly and completely absorbed by the gastrointestinal tract with a bioavailability of nearly 90%. Peak serum concentrations are achieved between 2 to 8 hours after administration and its elimination takes about 20-30 hours [17, 18].

Once inside the body, dapsone passes into the enterohepatic circulation and is metabolized by the liver. Metabolic inactivation is carried out through cytochrome P450 (CYP) in hepatocytes. However, other cells such as polymorphonuclear cells (PMNs) and monocytes can contribute to its metabolism [19]. Dapsone metabolism can occur in two ways in hepatocytes: N-acetylation (by an N-acetyltransferase) or N-hydroxylation (by isoforms of CYP) such as cytochrome P450-2E1 (CYP2E1) and cytochrome P450-2C (CYP2C).

Acetylation generates Monoacetyldapsone (MADDS) [20, 21] and hydroxylation, dapsone hydroxylamine (DDS-NHOH) [22]. Dapsone is distributed into all organs and excreted through urine and a small amount can be excreted in feces [6].

The bacteriostatic effect is given by the regulation of folic acid synthesis (necessary for DNA synthesis) by inhibiting the enzyme dihydropteroate synthetase that incorporates Paraminobenzoic Acid (PABA) into dihydropteroate, which is the immediate precursor of folic acid [23].

The anti-inflammatory effect on PMNs is carried out by the inhibition of the formation of ROS [24], as well as by the inhibition of Myeloperoxidase (MPO), the enzyme responsible for producing Hypochlorous acid (HOCl), a highly reactive and cytotoxic compound [25, 26]. Dapsone also inhibits the cell migration process (adherence to endothelium and chemotaxis) of PMNs; by interfering with chemokine receptors (G protein-coupled receptors; (GPCRs), integrins (CD11b / CD18) [27-29], chemotaxis by Leukotriene B4 (LTB4) [30] and inhibition of the formation of the Interleukin-8 (IL-8) [31, 32]. Other cytokines also identified as a target for dapsone are Interleukin 1 beta (IL-1β) and Tumor Necrosis Factor-alpha (TNF-α) [33] (Fig. **2**).

Dapsone has a well-known safety profile. Adverse effects occur between 0.5-3.6% of people taking dapsone pills for the control of infections [16]. Methemoglobinemia is the main adverse effect of dapsone, and Methemoglobin molecule possesses a high affinity for molecular iron that produces hypoxia by not allowing oxygen release in the tissues [23, 34, 35].

Clinically, hypoxemia manifestations as dyspnea, acrocyanosis, and headache, as well as the presence of hemolysis in laboratory tests, and dissociation between the concentration of oxyhemoglobin in blood and oxygen desaturation using the pulse oximeter characterizes this condition.

Methemoglobinemia and hemolysis, as the adverse effects of dapsone, may coincide with the genetic deficiency of 6-phosphate dehydrogenase, with chronic use of the drug and in some cases with doses higher than 200 mg/kg. A recent study demonstrated the utility of high doses of dapsone in three patients suffering from relapsing and remitting Lyme disease; they were treated with double doses of dapsone (200 mg/kg/day for a total of 7-8 weeks) showed remission of main Lyme symptoms for a period of 25 to 30 months with no side effects [36]. Furthermore, it is relevant to note that these adverse effects are reversible as medication stops [37-39], and some treatments, such as methylene blue and ascorbic acid, are available to resolve clinical methemoglobinemia [40].

2. METHODS

This review includes clinical trial reports and original studies using experimental models with rats, cats, ferrets and *in vitro* cells. The database consulted was from the National Library of Medicine, National Center for Biotechnology Information (NIH) PubMed, taking as inclusion criteria only works published in English, using the following keywords: Dapsone and Epilepsy, dapsone and excitotoxicity, dapsone and quinolinic acid, dapsone and seizures, dapsone and Parkinson models, dapsone and Alzheimer´s disease, multiple sclerosis and blood-brain barrier and anti-inflammatory treatments review, dapsone and cerebrovascular disease, dapsone and neuroprotection, dapsone and glioblastoma multiforme, cardioprotective effects of dapsone, dapsone and damage, dapsone and acne, dapsone and diabetes mellitus and dapsone and Lung. From 685 retrieved references, 161 articles were reviewed and discussed as they met the inclusion and exclusion criteria.

3. DISCUSSION

3.1. Epilepsy and Status Epilepticus

Epilepsy is one of the most common neurological problems, affecting 1% to 2% of the human world population. The International League Against Epilepsy (ILAE) defined epilepsy as a chronic neurological condition characterized by

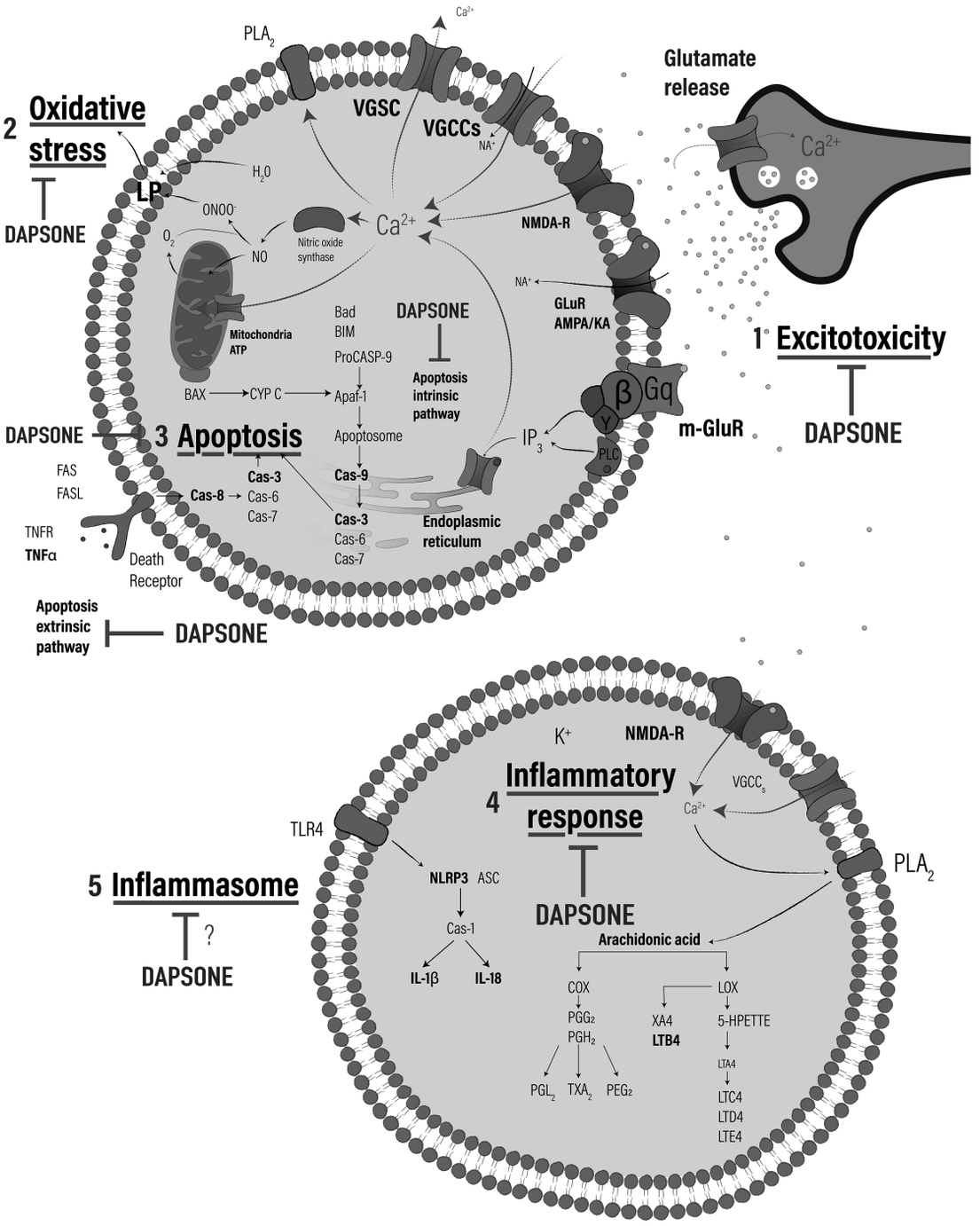

Fig. (2). Neuroprotective and cytoprotective mechanisms of dapsone. **1**) Antiexcitotoxic effect: Regulates glutamate release preventing the activation of metabotropic and ionotropic receptors (m-GluR y NMDA, respectively) as well as Glu receptors (AMPARs) and kainate receptors (KA), which leads to avoid membrane depolarization inhibiting the opening of voltage-gated calcium channels (VGCCs), voltage-dependent sodium channels (VGSC) and voltage gated-potassium channels (VGKC), regulating the signaling cascade and ions liberation. **2**. Antioxidant effect: Decrease the formation of superoxide radical ($O2^-$) and hydrogen peroxide (H_2O_2), produced in mitochondria during the excitotoxic and ischemic process, avoiding cell death and decrease the NO production and peroxynitrite ($ONOO^-$). **3**) Dapsone regulates formation of the multiprotein complex known as inflammasome active by Toll-like receptor 4 (TLR4) attenuating the assembly of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) interacting with the ASC and recruits the Caspase-1 (Cas-1) responsible of formation of proinflammatory interleukins (IL-1β y IL-18). **4**) Antiinflamatory effect: regulates metabolism of arachidonic acid mediated by cyclooxygenase (COX) and lipoxygenase (LOX) through inhibition of phospholipase A2, reducing the formation of chemoattractants as prostaglandins (PGDs), thromboxanes (TXBs) and leukotrienes (LTs). **5**) Antiapoptotic effect: Regulates both the intrinsic as extrinsic way of apoptosis mediated by the activation of several caspases. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

recurrent epileptic seizures. A seizure is a brain dysfunction with transitory paroxysms with a recurrent tendency and spontaneous termination [41]. Some works report that temporal lobe epilepsy in humans and animal models is associated with neuronal loss in the hippocampus during epileptogenesis [42, 43]. On the other hand, status epilepticus (SE) is a severe medical condition defined by the ILAE as a disorder that results from the failure of the mechanisms responsible for the termination or the initiation mechanisms of the crisis, which leads to abnormal and prolonged seizures: It is a condition frequently related with long-term consequences including neuronal death, neuronal damage, and disruption of neural networks, depending on the type and duration of seizures [44].

Regardless of the presence or not of any systemic, cardiovascular, or metabolic complication as well as pre-existing epilepsy, SE produces disseminated neuronal loss and reactive gliosis in the hippocampus, amygdala, the dorsomedial nucleus of the thalamus, in the cerebellar Purkinje cell layer, and the periamigdaloid (piriformis) region.

In patients with SE, the neuronal loss has a similar distribution to that seen in SE induced by domoic acid intoxication in humans and SE induced by Kainic acid and pilocarpine in rats [45].

There is a wide variety of medications used to treat epilepsy. These include sodium, potassium, and calcium transmembrane blockers, N-*methyl*-D-*aspartate* (NMDA) α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) channel blockers, gamma-amino butyric acid (GABA) agonists or enhancers, and synaptic vesicle blockers, all of which improved over time, resulting in a new generation of antiepileptic drugs. The therapeutic success of antiepileptic drugs depends on the tolerability of the drug, adherence to treatment and the reduction of adverse reactions (dizziness, headache, diplopia, and ataxia) [46] as well, in some cases, of the capacity to develop treatment resistance [47]. Most of these drugs have little or no neuroprotective effect; therefore, it seems reasonable to propose new therapeutic strategies with an alternative, complementary and neuroprotective approach with minimal adverse reactions even with prolonged use with not drug resistance (Fig. **2**).

Recent work shows the efficacy of dapsone to treat epilepsy and SE in animals and humans (Table **1**) [48-58]. In support of the above, some authors describe that the acute and chronic administration of dapsone (6.25, 9.375, 12.5 mg/kg) reduces the number of seizures generated by electrical stimulation of the amygdala and hippocampus in cats with no adverse reactions (maximum dose of 40 mg/kg) [48, 49]. On the other hand, the use of dapsone (9,375 and 125 mg/kg) administered 30 min before inducing seizures by kainic acid (AK) (10 mg/kg) decreases the number of seizures and mortality in a dose-dependent manner in rats [50]. Likewise, the use of dapsone and sodium phenobarbital (12.5/30 mg/kg, respectively) alone or in combination diminished KA-induced seizures, decreased lipoperoxidation, and significantly increases neuronal hippocampal viability in rats [51]. Similarly, the combination of dapsone and Diazepam (25/20 mg/kg, respectively) administered during seizures demonstrated therapeutic efficacy in a model of SE induced by KA by significantly reducing the electrical activity associated with this condition; this effect remained up to 24 hours after drugs administration.

A more significant number of viable hippocampal CA-3 pyramidal neurons were also found in animals treated with dapsone than in the control group (untreated). This study indicates that dapsone is not only an anticonvulsant drug but also a neuroprotective one [52]. Dapsone analogs have also been shown to have a neuroprotector effect by decreasing lipoperoxidation, increasing cell viability, preventing GABA reduction, and improving behavioral disturbances, after the application of quinolinic acid, a known agonist of the NMDA receptor. Some of those analogs, with N- substituents, also decreased methemoglobin levels compared to dapsone itself [53, 54] (Fig. **2**).

A clinical study shows the therapeutic effect of dapsone in patients who develop resistance to conventional treatments. Administration of 100 mg/day decreased the frequency of seizures per month by more than 50%, after a follow-up for 3 months. In terms of therapeutic safety, there were no severe adverse effects related to dapsone daily administration. Only symptoms such as methemoglobinemia (at subclinical levels), headaches, drowsiness, and paleness were observed [55]. The studies carried out on the anticonvulsant effect of dapsone *in vivo* models, and one study in drug-resistant epileptic patients have shown encouraging results to consider dapsone and some of its analogs, a potential treatment to decrease the number and intensity of seizures and the consequent degeneration of nervous tissue, necessary for preserving CNS functions.

3.2. Parkinson's Disease

PD is a progressive neurodegenerative disorder characterized by the massive loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNc) [59] and the generalized presence of intracytoplasmic and intraneuritic inclusions of α aggregates-synuclein (Lewy bodies (DLB)), and Lewy Neurites (LN) [60]. PD results from the interaction between genetic susceptibility and some identified environmental factors [61]. After AD, PD is the second most common chronic and systemic neurodegenerative disease in adults [62, 63].

In industrialized countries, the prevalence of this disease ranges between 0.3% and 1% in older than 60 years and reaches 3% in those older than 80 years or more, with incidence rates that vary between 0.08 and 0.18 per 1,000 people/year [64]. The main clinical characteristics of patients with PD are impairments in motor functions such as tremor at rest, rigidity, postural instability, and bradykinesia. It also causes non-motor manifestations, including cognitive, behavioral and pain [65]. Several studies have reported that motor and non-motor problems are related to aging, accelerating neuronal dysfunction, and extended loss of dopaminergic neurons in the SNc. Several studies have reported that motor and non-motor problems are related to aging, accelerating neuronal dysfunction, and extended loss of dopaminergic neurons in the SNc.

Disturbance of protein degradation by the ubiquitin-proteasome system might have a critical role in neurodegeneration. Parkin is a ubiquitin-protein ligase involved in protein degradation as collaborating with the ubiquitin-

Table 1. Excitotoxicity and experimental epilepsy models and pharmacological effects of dapsone and analogs.

Specie	Treatment	Doses	Model	Effect	References
Rat	Dapsone	6.25-12,5 mg/Kg	Amygdaloid kindling model of epilepsy	↓ Seizures	[48]
	Dapsone	6.25, 9.375 y 12.5 mg/Kg	Amygdala-kindled seizures and hippocampal-kindled seizures model	↓ Seizures	[49]
	Dapsone	9.375 y 125 mg/Kg	Temporal lobe epilepsy model (Kainic Acid)	↓ Seizures ↓ Mortality	[50]
	Dapsone	12.5 mg/Kg and 25 mg/Kg	Excitotoxicity model by quinolinic acid (an NMDA agonist of glutamate receptors)- and kainic acid (a non-NMDA agonist of glutamate receptors	↑Functional improvement Prevented the decrease of GABA Neuroprotection	[56]
	Dapsone	12.5 mg/Kg and 25 mg/Kg	Excitotoxicity model by quinolinic acid (an NMDA agonist of glutamate receptors)	↓Lipid peroxidation Prevent the neuronal damage	[57]
	Dapsone analogs (1) 4,4'-diaminodifenylsulfone N,N'-diformaldehyde sulfoxylate (2) 4,4'-diaminodiphenylsulfone N,N'-didextrose sulfonate (3) Sodium dibisulfite 4,4'-biscinamilidenamindiphenyl sulfone (4) N,N'-dimethyl-4,4'-dimethylphenylsulfone	3.12 and 6.25 mg/Kg	Temporal lobe epilepsy model (Kainic Acid)	↓ Seizures Only analogs 3 and 4 showed therapeutic effect	[53]
	Dapsone analogs (1) N,N'-dimethyldapsone (2) N,N'-diethyldapsone (3) N,N'-dipropyldapsone (4) N,N'-dibutyldapsone and N,N'-ditosyldapsone	12.5mg/Kg and equimolar doses respectively	Excitotoxicity model by quinolinic acid	↓ Methemoglobin ↑Functional improvement Prevented the decrease of GABA	[54]
-	Dapsone/ Phenobarbital	12.5/30 mg/Kg	Temporal lobe epilepsy model (Kainic Acid)	↓ Lipid peroxidation ↓ Mortality ↑ Hippocampal neuronal cells viability	[51]
-	Dapsone/ Diazepam	25/20mg/Kg	Status Epilepticus model Kainic Acid	↓ Seizures ↑ Hippocampal neuronal cells viability	[52]
Kat	Dapsone	13-23 mg/Kg	Amygdaloid kindling model of epilepsy	↓ Seizures	[48]
Human	Dapsone	100 mg/día	Open Clinical Trial	↓ Seizures	[55]
-	Dapsone	-	Review	↓ IL-8 ↓ Seizures	[58]

Abbreviations: NMDA: N-methyl-D-aspartate receptor, GABA: Gamma-aminobutyric acid.

conjugating enzyme UbcH7. PD patients show loss of this ubiquitin-protein ligase activity [66, 67].

Interestingly, long-term treatment with dapsone (2 mg/kg) restores parkin levels through its up-regulation. Furthermore, chronic treatment with dapsone prevents neuronal loss related to normal aging and reduces oxidative stress in mice with MPTP-induced PD [68].

On the other hand, a study on cellular aging, using an animal aging and lifespan model in worms (*C. elegans*) treated with paraquat (free radical-generating compound, used as a model of Parkinson´s disease), dapsone (5 mg/kg) reduces the production of free radicals and increased life expectancy and motor activity [69].

3.3. Dementia and Alzheimer's Disease

Dementia is a state of progressive cognitive impairment that leads to loss of independent functions and significant disruption of daily living activities [70]. More than 70 conditions cause the clinical syndrome of dementia [71]. Of these, AD represents 60-80% of all cases, followed by vascular dementia and other neurodegenerative dementias such as DLB dementia, dementia-Parkinson complex, and frontotemporal dementia [72]. Around 35.6 million people worldwide are affected by AD, mainly affecting people over 65 [73]. Therefore, AD should be suspected in a patient older than 60 years who suffers from cognitive impairment and progressive short-term memory impairment. Although AD definitive diagnosis requires a histopathological or postmortem study [74], biological markers are now available to make an early diagnosis. Among these, quantification of total Tau protein (Tau), Phosphorylated Tau isoforms (P-Tau181 and P-Tau231), and β-amyloid peptide (Ab42), in cerebrospinal fluid, showed sensitivity and specificity of 80-90% [75].

Drugs used to treat AD, and other forms of degenerative dementia can resolve biochemical abnormalities due to neuronal loss but do not modify the underlying neuropathology or its progression. Cholinesterase inhibitors partially restore the acetylcholine deficiency that arises from the loss of neurons in the nucleus basalis of Meynert and the central septum area, projecting to the cortical regions. Memantine as an NMDA receptor inhibitor eventually attenuates the toxic effects of glutamate released by degenerating neurons, although its exact mechanism of action is uncertain. No drug has shown neuroprotective potential in humans [76].

Chronic inflammatory processes are related to the progression of different degenerative diseases, including AD. There is evidence that dapsone treatment by regulating brain cells' inflation decreases the progression of cognitive disorders in patients with AD [71]. A clinical study demonstrated that leprosy patients treated with dapsone had a lower incidence of dementia than tuberculosis treatment [77] and without treatment [78]. Dapsone does not seem to have a direct effect on the degenerative neuronal process once it shows high levels of β-amyloid in cell cultures and patients with AD [79, 80]; therefore, it is possible that dapsone does not modify the progression of the disease in advanced phases. However, a recent review [81] suggests that it is necessary to develop a combined drug therapy to attenuate chronic inflammation and confer neuroprotection in AD. In this report, it is proposed that the mechanisms to neuroprotect against AD must include: anti-inflammatory actions, show drug permeability through the Blood-Brain Barrier (BBB), evidence of an efficacy in blocking oxidative damage and the chemotactic response mediated by activated microglia; Evidence indicates that dapsone possesses these effects in different conditions both in clinical and experimental studies, and this strategy could be used to delay the progression of AD (Fig. **3**).

Given these data, it is important to consider of interest to carry out new research to determine if the anti-inflammatory effect of dapsone is useful or not to modify the course of the disease.

3.4. Cognitive Dysfunction and Depression

Yang *et al.* (2017) [82] evaluated the effect of propofol on cognition in aged rats treated or not with dapsone, since this anesthetic commonly produces postoperative cognitive dysfunction in elderly patients. The results showed that propofol produces alterations in learning and memory in rats, associated with decreased autophagy in the hippocampus and that pretreatment with dapsone at a dose of 5 mg / kg or 10 mg / kg of body weight significantly improved the behavioral disorder and positively regulated the inhibited autophagic response.

Propofol is frequently related to postoperative cognitive dysfunction in elderly patients. Yang *et al.* (2017) [82] evaluated propofol's effect on cognition in aged rats treated or not with dapsone. They confirmed that propofol produces alterations in learning and memory in rats, associated with decreased autophagy in the hippocampus, and pretreatment with dapsone at a dose of 5 mg / kg or 10 mg / kg of body weight significantly improved the behavioral disorder and positively regulated the inhibited autophagic response.

Dapsone has also been proposed as an antidepressant treatment in experimental models of aged mice undergoing abdominal surgery since it has been described that depression induced by surgical stress and anxiety are common complications in patients after surgery, as well as recent studies have shown that oxidative stress is involved in the pathophysiology of depression and anxiety induced by surgical stress [83]. As dapsone is known to possess antioxidant properties, Zhang *et al.* (2015) [84] evaluated the effect of dapsone on depressive and anxious behavior and brain oxidative stress in a surgical stress model. The results demonstrated depressive and anxiety-like behaviors accompanied by elevated brain oxidative stress in aged mice undergoing abdominal surgery and that pretreatment with dapsone 5 mg / kg significantly improved the mice's behavior and decreased brain oxidative stress. They also observed that surgical stress increased the level of NADPH oxidase in the brain, while pretreatment with dapsone blocked the elevation of NADPH oxidase triggered by surgical stress. Therefore, the authors suggest that dapsone is effective in preventing oxidative damage to the brain induced by surgical stress by downregulating the level of NADPH oxidase in elderly mice.

Furthermore, because depression induced by surgical stress and anxiety are common complications in patients after surgery, dapsone has also been proposed as an antidepressant treatment in experimental models of aged mice undergoing abdominal surgery.

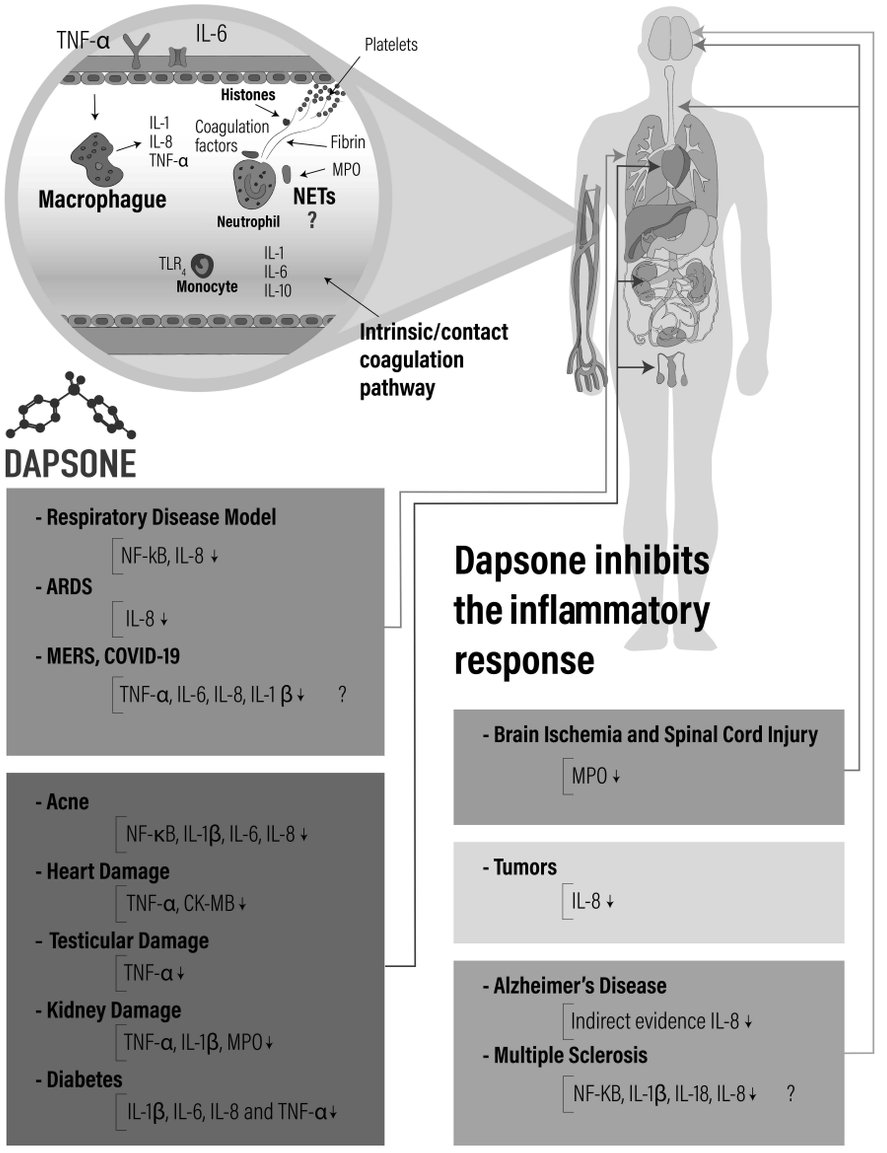

Fig. (3). Anti-inflammatory effect of dapsone in several diseases. Alzheimer's disease and dementia syndrome the evidence shows that dapsone decreased levels of IL-8. Multiple sclerosis, it is proposed that due to the histopathological characteristics of the disease, dapsone treatment may decrease the levels of various pro-inflammatory cytokines (IL-1β, IL-18 and IL-8) and the expression of the transcription factor NFkB. Respiratory disease model a decrease in IL8 and expression of the transcription NFkB factor were observed. Acute respiratory distress syndrome (ARDS), Middle East respiratory syndrome (MERS) and coronavirus disease 2019 (COVID-19), by pathophysiological characteristics the dapsone may be decrease the levels of various proinflammatory cytokines (IL-1β, IL-6, IL-8 and TNFα). Acnes showed diminished of IL-1β, IL-6, IL-8 and NFkB factor. Heart damage TNFα and Creatine kinase-myocardial (CK-MB) diminished levels. Testicular damage (TNFα diminished level). Kidney ischemia damage (TNFα, IL-1β and Myeloperoxidase (MPO) decreased levels). Diabetes (IL-1β, IL-8, IL-18 and TNFα diminished levels). Brain ischemia and Spinal cord injury MPO decreased level. Tumors IL-8 decreased level. Blood vessels the dapsone lowers the levels of IL-8, IL-6 and TNFα by blocking the inflammatory response mediated by macrophages and neutrophils present in the blood vessels, an effect that may prevent the formation of extracellular neutrophil networks (NETs) traps and the disseminated thrombosis characteristic of the COVID-19 disease. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

Recent studies have shown that oxidative stress is involved in the pathophysiology of depression and anxiety induced by surgical stress [83]. As dapsone is known to possess antioxidant properties, Zhang *et al.* (2015) [84] evaluated the effect of dapsone on depressive and anxious behavior and brain oxidative stress in a surgical stress model. The results demonstrated depressive and anxiety-like behaviors accompanied by elevated brain oxidative stress in aged mice undergoing abdominal surgery and that pretreatment with dapsone 5 mg/kg has a significant improvement on the mice behavior and decreased brain oxidative stress. They also observed that surgical stress increased NADPH oxidase's level in the brain, while pretreatment with dapsone blocked the elevation of NADPH oxidase triggered by surgical stress. Therefore, the authors suggest that dapsone effectively prevents oxidative damage to the brain induced by surgical stress by downregulating the level of NADPH oxidase in elderly mice.

3.5. Multiple Sclerosis and Other Autoimmune Diseases

Multiple Sclerosis (MS) is a chronic inflammatory disorder of the CNS characterized by demyelination and axonal and neuronal degeneration [85]. MS affects more than 2 million people worldwide [86], presenting itself as the most common cause of non-traumatic disability in young adults [87]. The most common symptoms include visual loss in one eye due to optic neuritis, limb weakness, sensory dysfunction due to transverse myelitis, double vision due to brain stem dysfunction, or ataxia due to cerebellar injury. These lesions occur throughout the white matter of CNS as focal areas of demyelination, inflammation, and glial reaction [86]. Activation of the inflammasome and the breakdown of the BBB seems to play fundamental roles in the autoimmune and pro-inflammatory responses in various neurological diseases, including MS and autoimmune encephalitis, since the excessive induction of Caspase-1 (Cas-1) leads to a programmed cell death process called pyroptosis characterized by the rapid induction of an inflammatory response leading to cell lysis [88]. As mentioned previously, MS is a demyelinating disease of the CNS and remains the most common autoimmune disorder affecting the CNS [86]. Although the cause of MS remains unclear, the pathological mechanisms present can be due to damage to myelin-producing cells (oligodendrocytes) or direct damage to the myelin layer by autoimmune T cells. Recent advances have indicated that inflammasomes contribute to the etiology of MS [89]. In this way, inflammasomes are multiprotein complexes of the innate immune response involved in the processing of Cas-1, the activation of the pro-inflammatory cytokines IL-1β and IL-18, as well as the mechanism of pyroptosis mediated by cell death and activation of the adaptive immune response [90]. Inhibition of the inflammasome is a therapeutic strategy used in patients with MS. Interferon- β (IFNβ) is one of the first-line treatments for MS and can inhibit the inflammasomes NLRP1 and NLRP3 [91]. Based on this information, dapsone may be useful in patients with MS since it can covalently compete with proteins that activate the NLRP3 inflammasome and to decrease the nuclear factor -kappa B (NF-kB) signaling that drives transcription of inflammatory cytokines and chemokines, including IL-1β, IL-18, and IL-8, and priming the expression of NLRP3 to its functional level [71]. On the other hand, the BBB rupture contributes to the development of the disease because the autoaggressive T cells cross this barrier, causing demyelination that eventually leads to progressive disability [92]. The BBB integrity maintenance represents a fundamental pillar for the correct functioning of the CNS; some misfunctioning of this barrier are associated with various neurodegenerative diseases [93, 94]. The BBB has high selective permeability to peripheral molecules and cells, which allows maintaining CNS homeostasis [95]. Endothelial Cells (EC) are the hallmark of this barrier. Specific proteins in the CE of the CNS allow tight junctions between the BBB cells, preventing a possible leakage of molecules or cells potentially damaging to the tissue. These proteins are claudins, occludins, and Zonula Occludens (ZO) cytoplasmic proteins [96, 97]. An experimental study using a model of disruption of BBB in rats by administering lipopolysaccharide demonstrated that the administration of 0.5 mg/kg, 2 mg/kg and 5 mg/kg of dapsone managed to normalize the BBB in a dose-dependent effect by regulating the levels of the Zonula occludens-1 (ZO-1), occludin and claudin-5, which are responsible for generating the tight junctions of the BBB [98]. In another similar study, dapsone induced recovery of the BBB integrity in a model of injury generated by a high-fat diet in mice. The continuous administration of dapsone reversed the lipid peroxidation induced by this diet and the loss of tight junction proteins after eight weeks [99].

Dapsone is a proven effective treatment for subacute cutaneous lupus erythematosus, particularly in refractory drug cases [100]. The potential mechanisms for this efficacy are attributed to the inhibition of the myeloperoxidase enzyme by dapsone, its inhibitory effect on the synthesis and release of prostaglandins, the inhibition of the production of leukotrienes C4 and the inhibition of the adherence of neutrophils to cells vascular endothelial cells and their subsequent extravasation through the endothelial vascular wall, thus preventing the migration of neutrophils to the injury sites [101].

Furthermore, dapsone has been tested to treat bullous systemic lupus erythematosus, a rare bullous condition associated with systemic lupus erythematosus [102]. The results showed that dapsone was effective in 90% of the cases to diminished dermal infiltration of polynuclear neutrophils, alignment of these cells at the basal membrane zone and leukocytoclastic. Therefore, the authors conclude that dapsone is the first-choice option for this disease.

Finally, the therapeutic efficacy of dapsone has been tested in autoimmune diseases such as pemphigus and pemphigoid, two variants of the autoimmune mucocutaneous bullous dermatoses [103]. The anti-inflammatory action of dapsone lies in its ability to suppress neutrophils migration and production of toxic secretory products that cause skin damage [6, 28]. Therefore, it is effective in various skin disorders associated with abnormal neutrophils accumulation such as dermatitis herpetiformis, linear IgA bullous dermatosis, pyoderma gangrenosum, PV, BP, sweet's syndrome and vasculitis [5, 6]. All the patients showed a satisfactory response to dapsone, achieving disease remission in a short period with no serious side-effects necessitating treatment cessation.

3.6. Dapsone in Ischemic and Traumatic Diseases of the Central Nervous System

3.6.1. Cerebrovascular Diseases

Cerebrovascular disease (CVD) is a temporary or permanent alteration of the functioning of one or more parts of the brain caused by a circulatory disorder [104]. Clinically characterized as an acute-onset focal neurological deficit, which includes cerebral infarction, intracerebral hemorrhage and subarachnoid hemorrhage. The frequency of stroke subtypes is variable, while ischemic stroke occurs in approximately 70% of cases, and hemorrhagic stroke in 30% in different series [105]. In some reports, data from different hospitals showed that ischemic stroke occurs in 57% of cases, intracranial hemorrhage in 28%, and subarachnoid hemorrhage in 12.0%, and cerebral venous thrombosis in 3% [106].

The occlusive phenomenon originating ischemic stroke has different causes; large artery atherosclerosis, cardioembolism, small artery disease, and in some cases, the cause cannot be determined [107]. In this patient group, comorbidi-

ty is the rule; in people older than 60 years, arterial hypertension, diabetes mellitus, hyperlipidemia, heart disease and altered coagulation states (including transitory states such as pregnancy and the puerperium) are known risk factors and as well-defined causative agents [108].

Regardless of the etiology, interruption of blood flow to the brain triggers chemical events that alter tissue homeostasis, produce neurotoxicity and changes in gene expression, which lead to cell death, loss of nerve connections [109] and apoptosis [110]. That is why restoring cerebral blood flow in the shortest possible time is a priority, and thrombolytic therapy and thrombectomy have marked a before and after in patients' prognosis [111]. Unfortunately, full and timely recanalization is often not achieved, and in this clinical scenario is crucial to continue and propose new treatments with different approaches to efficiently decrease the degradation of nervous tissue [112]. In this sense, in an experimental study, the effect of dapsone at doses of 9.375 mg/kg and 12.5 mg/kg was evaluated in a model of cerebral ischemia in Wistar rats, the results allowed to demonstrate in the experimental group with dapsone, a smaller infarction area, better physical performance and they presented lower mortality than control rats [113]. In the effort of translational science, a pilot study was performed in patients who suffered from an ischemic stroke, using dapsone (200 mg) as treatment within the first 10 hours of evolution after stroke. The treated patients presented lower neurological deficits and better capacity to carry out daily living activities after 60 days of follow-up [114].

Dapsone has an antioxidant, anti-inflammatory and antiapoptotic effect proven in an ischemia/reperfusion model [115]. In other similar experimental models of ischemia, dapsone demonstrated a beneficial effect by achieving, in the experimental group, attenuation of different markers of nerve tissue damage such as edema, generation of ROS, area of infarction (injured tissue), neurological deficit and transcription factors associated with oxidative stress such as Nuclear factor-erythroid 2 related factor 2 (Nrf-2) [116]. Finally, in a recent work, using a model of occlusion of the middle cerebral artery in rats, the administration of dapsone, even six h after the injury, reduced the area of cerebral infarction and improved neurobehavioral performance (Fig. **3**).

On the other hand, the results of an *in vitro* model of excitotoxicity with glutamate, demonstrated that dapsone could reduce neuronal damage by inhibiting the pro-apoptotic proteins c-Jun N-terminal kinase (JNK), Phosphatidyl 3,4,5-triphosphate 3 phosphatase (PTEN), calpain, caspase-3 (Cas-3), together with the activation of the survival protein Brain derived neurotrophic factor (BDNF), concluding that the treatment with dapsone can be an effective treatment with a wide therapeutic window [117].

3.6.2. Spinal Cord Injury

Spinal Cord Injury (SCI) is a serious condition that in most cases produces permanent disability and irreversible damage. The annual incidence of SCI depends on the geographical area and the socioeconomic environment, being approximately 10 to 80 patients per million inhabitants, with a prevalence of 235-1800 victims per million inhabitants [118, 119]. The clinical spectrum of SCI includes loss of voluntary mobility, decreased range of motion [120], autonomic dysfunction, peripheral vasodilation, alteration of thermoregulation, respiratory deficiencies [118] and alteration of sensitivity [120]. The SCI has complex pathophysiology, including neurotoxic processes, apoptosis, oxidative stress, inflammation and excitotoxicity [121, 122], making it difficult to develop new treatments focused on neuroprotection.

Regarding dapsone, the administration of (2.5 mg/kg to rats, up to 3 or 5 hours after the injury, managed to decrease the damage of the nervous tissue by diminishing the area of injured tissue, lipid peroxidation, the inflammatory response (decrease of neutrophil MPO activity) and contributing significantly to functional recovery. Furthermore, when testing a therapeutic window of 3 hours after the injury, this effect was more evident [123]. Subsequent studies demonstrated that treatment with dapsone reduces apoptosis in spinal cord tissue by reducing Caspase-9 (Cas-9), Caspase-8 (Cas-8) and Cas-3 [124]. In a recently published review work, the mechanisms and neuroprotective targets that lead to the therapeutic success of dapsone and other antibiotics after SCI are analyzed and synthesized, with evidence of the anti-inflammatory, antiapoptotic, antiexcitotoxic and antioxidant effects of the sulfone (Fig. **3**). This review provides information on the role of dapsone in translational medicine to manage SCI and its complications [125].

3.7. Cancer

Cancer is an anormal and uncontrolled cellular growth in any organ or body structure [126]. Current cancer research focuses on early recognition of a malignant lesion delimiting the patient's healthy tissue and implementing radio and medical therapy. The knowledge of the tumor microenvironment allows for describing and predicting cancer cells' behavior and response to a specific treatment. This microenvironment is composed of fibroblasts, immune cells, cells that form new blood vessels, and the proteins produced by all cells present in the tumor that promote the growth of cancer cells [127].

In Glioblastoma (GB), the tumoral CE abnormally generates IL-8 and increases neutrophil recruitment. Neutrophils, in turn, produce Vascular Endothelial Growth Factor (VEGF), inducing angiogenesis and more CE that produce more IL-8 and greater recruitment of neutrophils as a vicious circle [128, 129]. This accumulation of neutrophils in the tumor tissue is a biological marker of poor prognosis [130, 131].

It has been suggested [132] that dapsone is potentially useful for the treatment of GB multiforme by inhibiting neutrophil accumulation, migration, and response to IL-8, as well as the production of IL-8, [133]. Furthermore, dapsone and its analogs have an antiproliferative effect in glioma cell cultures [134].

3.8. Dapsone as Cytoprotective Drug

3.8.1. Cardiac Damage Model

Doxorubicin, a drug frequently used in cancer treatment [135], has been associated with adverse effects such as ROS generation, inflammation, and cell death; damaging various organs such as the heart, brain, kidney and liver [136]. In an

experimental study with rats, dapsone was applied at doses of 1, 3, and 10 mg/kg, 30 min after the administration of doxorubicin (2.5 mg/kg) for two weeks. Results showed that dapsone prevented damage to cardiac tissue by decrease lipid peroxidation, inflammatory response (decrease of TNFα expression) and diminished Creatine Kinase-myocardial (CK-MB), associated with destabilization of cardiac cell membranes, and a marker of cardiac cells´ damage [137].

3.8.2. Testicle Damage Model

Testicular ischemia occurs in patients with torsion of the spermatic cord. This pathology requires prompt attention to avoid irreversible ischemic damage that causes sterility and a possible orchiectomy [138, 139]. In an experimental study of testicular torsion in rats, dapsone, when administered (12.5 mg/kg) 30 min before testis torsion, showed a decrease of inflammatory cytokines (TNFα), lipid peroxidation and diminished lesion of the tissue [140].

3.8.3. Kidney Damage Model

Ischemic and reperfusion damage occurs in the kidney of patients with kidney transplantation, hydronephrosis, nephrectomy and acute kidney damage [141-143]. In an experimental study in rats, dapsone (20 mg/kg) administration significantly decreased kidney scars after pyelonephritis. This protective effect of the sulfone was due to its anti-inflammatory effect through MPO inhibition [144]. It is also possible to observe the protective effect of dapsone on the kidneys when this drug is administered 30 min before (1, 3 and 10 mg/kg) the production of ischemia. The levels of inflammatory cytokines (TNFα, IL-1β), cell death and tissue damage due to necrosis and hemorrhage, all decreased due to the use of dapsone [145].

3.8.4. Diabetes Model and Acne In Vitro Models

Another potential use of dapsone can be in wound healing of patients with diabetes, which undergo an intense inflammation process. Treatment with dapsone (30 mg/kg) improves wound healing in streptozotocin-induced diabetic rats, through the diminution of both IL-8 mediated neutrophil infiltration and oxidative stress [146]. In non-obese mice, treatment with dapsone allowed a lower possibility of developing insulin-dependent diabetes mellitus than in controls. The diminution of ROS by this drug can delay the onset of the disease and prevent lymphocytic infiltration of the islets of Langerhans in mice [147]. In this effect, the participation of dapsone-induced prevention of the over-activity of NADPH oxidase (Nox) generated by an increase in oxidative stress was reported [148]. Likewise, there are reports indicating that the use of dapsone (0.4 μg/mL, 4 μg/mL and 40 μg/mL) favors the recovery of the lesions and the inflammatory process induced by acne (Cutibacterium) by reducing the levels of IL-8 in human epidermal keratinocytes and IL-1β, Interleukin-6 (IL-6), IL-8, and TNFα in primary neonatal epidermal keratinocyte cells and human monocytes in response to Cutibacterium [149].

3.8.5. Dapsone in Models of Lung Damage

Experimental evidence in lung damage models demonstrates that IL-8 is an important activator and chemoattractant for neutrophils, produced by normal human bronchial epithelial cells through the p65 pathways of the Mtogen-Activated Protein kinase (MAPK) and NF-κB. Based on this information, Kanoh *et al.* (2011) [31] designed a study of lipopolysaccharide-induced lung damage in ferrets to evaluate the anti-inflammatory effect of dapsone. The study was conducted as follows: ferrets were exposed to intratracheal Liposaccharide (LPS) for five days to produce tracheal inflammation. Once inflammation was established, oral or nebulized dapsone was administered for five days. Histological tracheal tissue samples demonstrated that dapsone inhibited the secretion of IL-8 and decreased the level of IL-8 mRNA induced by LPS and decrease in phosphorylation of the transcription factor NF-κB p65; this is an essential mechanism since the activation of NF-κB p65 exacerbates the inflammatory response and consequent oxidative stress [150].

The protective effect of dapsone was tested in a lung damage model with paraquat in mice [151]. Results showed a reduction of lung damage due to the treatment with dapsone and low local expression of mRNA transcripts encoding molecules related to inflammation, including Endothelin-1 (ET-1), Macrophage Inflammatory Protein-1α (MIP-1α), and transforming growth factor β (TGF-β), decreased the expression of Nox mRNA and the activation of Protein kinase Cμ (PKCμ), induced by paraquat. Also, a decrease the oxidative stress was observed after dapsone, evaluated as a decreased generation of superoxide anions induced by paraquat. Based on this information, the authors propose that dapsone is an effective protective treatment against tissue damage induced by oxidative stress and inflammation (Fig. **3**).

3.8.6. Acute Respiratory Distress Syndrome, Middle East Respiratory Syndrome CoV and COVID-19 Acute Respiratory Diseases

Acute Respiratory Distress Syndrome (ARDS) is associated with high fatality and high levels of IL-8. The IL-8 neutrophile attraction activity contributes to the alveolar damage of the ARDS, whereas neutrophil infiltration into alveoli is present in ARDS-related coronavirus infections (SARS-CoV) and the Middle East Respiratory Syndrome CoV (MERS-CoV) [152].

Regarding COVID-19 infection and SARS-CoV-2 syndrome, the viral infection process began when the viral spike protein bound to the receptor for Angiotensin Converting Enzyme 2 (ACE2), expressed in various types of cells; Type II pneumocytes, macrophages, and CE. Once the cell is infected, begins a highly inflammatory cell death process called pyroptosis, which results in the release of Damage-Associated Molecular Patterns (DAMP), leading to a hyper-inflammatory response [153], mediated by hyperactivated monocytes and activated monocyte-derived macrophages that release massive amounts of pro-inflammatory cytokines [154].

Patients with COVID-19 present thrombotic events that include activation of platelets leading to an overexpression of the coagulation cascade in a distinct manner from those seen with bacterial sepsis-induced coagulopathy and disseminated intravascular coagulation. COVID-19 infection blockage the conversion of angiotensin 2 to angiotensin 1-7, decreasing endothelial Nitric oxide (NO) production and its

vasodilator and platelet aggregation blocking effect, allowing the accumulation of endothelial von Willebrand factor, that, in turn, increases thrombus production and platelet activation, by increasing D-dimer and fibrinogen levels with minimal abnormalities in prothrombin time and platelet count [155].

Furthermore, high levels of IL-1β and IL-6 in COVID-19 infection induce thrombocytosis and hyperfibrinogenemia. The hypercoagulable state due to sustained inflammation is named thromboinflammation. An interesting topic in the COVID-19 infection is the poor regulation of the so-called extracellular neutrophil networks (NETs) formed by chromatin, microbicidal proteins and oxidizing enzymes released by neutrophils to contain an infection. Inadequate regulation of NETs propagates inflammation and produces disseminated microvascular thrombosis [156]. The presence of NET remnants in the serum of patients hospitalized for COVID-19 is related to an increased risk of thrombotic events and increased mortality [157]. In *in vitro* studies, it is possible to demonstrate NET formation when neutrophils from healthy people are exposed to the serum of patients with COVID 19 [157]. COVID-19 patients also show high levels of some inflammatory cytokines such as IL-6, Interleukin-10 (IL-10), and TNFα and chemokines (XCL10/IP-10, CCL2/MCP-1 and CCL3/MIP-1α), however, the expression of this elevation depends on the disease's evolution and severity.

On the other hand, patients who develop severe illness from COVID-19 show an increase in the IL-8 concentration and, due to its chemotactic effect, a more than double increase of the number of neutrophils in the blood (10.6 x 109/L), compared to those patients who did not require intensive care (4.4 x 109/L) [158]. Changes in plasma levels of Cytokines, Chemokines, and Growth Factors (CCGF) and how these are related depend on the severity of COVID-19 disease. Xu *et al.* (2020) highlight the considerable elevation of IL-8 and IL-6 in COVID-19 patients with a fatal outcome, suggesting that the reduction in the levels of these cytokines is a possible therapeutic target [159].

Regarding those changes observed in patients with COVID-19, some authors have recently proposed the therapeutic benefit of dapsone [7,8] as a treatment in patients with lung damage generated by the SARS-CoV-2 virus, since it could modulate the production of pro-inflammatory cytokines [160], the secretion of IL-8 from bronchial epithelial cells, by regulating TNFα from activated mononuclear cells and the decrease in MPO activity [161]. Finally, Schön, *et al.*, (2020) [10], in a recent review, discussed the therapeutic benefit of various immunological therapies that regulate the main inflammatory mechanisms in COVID-19, from a basic aspect and its clinical translational implications. In this review, they included dapsone because it can inhibit cytokine storm and neutrophil chemotaxis in the lungs (Fig. **3**). Our group suggests dapsone as a potential, safe drug to be tested in patients developing severe COVID-19 infection by SARS-CoV2.

CONCLUSION

The neuro and cytoprotective effect of dapsone has been tested both in experimental models and in clinical studies in neurodegenerative, traumatic, and ischemic diseases of the CNS such as dementia, PD, AD, epilepsy, SE, cerebral infarction, spinal cord trauma, as well as in conditions such as diabetes mellitus, ischemic testicular damage, heart damage, kidney ischemia and lung damage, all associated to exacerbated inflammatory responses. After reviewing the literature, it is concluded that dapsone regulates or decreases the main mechanisms of damage such as oxidative stress, excitotoxicity, inflammation and various mechanisms of cell death. Likewise, its therapeutic safety has been demonstrated both in experimental and clinical studies as its anti-inflammatory efficacy has been widely demonstrated, proposing its use in acute diseases such as acute respiratory distress syndrome, MERS, and COVID-19. Therefore, we conclude that dapsone is a safe and effective neuro and cytoprotective treatment that must be considered translational therapy.

LIST OF ABBREVIATIONS

ACE2	=	angiotensin converting enzyme 2
AD	=	Alzheimer's disease
AK	=	Kainic acid
AMPA	=	α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid
ARDS	=	Acute respiratory distress syndrome
BBB	=	Blood-brain barrier
BDNF	=	Brain Derived Neurotrophic Factor
Cas-1	=	Caspase-1
Cas-3	=	Caspase-3
Cas-8	=	Caspase-8
Cas-9	=	Caspasa-9
CE	=	Endothelial cells
CCGF	=	growth factors
CK-MB	=	Creatine kinase-myocardial
CNS	=	Central nervous system
CVD	=	Cerebrovascular disease
CYP	=	Cytocrome P450
CYP2C	=	Cytocrome P4502C
CYP2E1	=	Cytocrome P4502E1
DAMP	=	damage-associated molecular patterns
DDS-NHOH	=	Dapsone hydroxylamine
DLB	=	Lewy bodies
ET-1	=	Endothelin-1
GABA	=	Gamma-amino butyric acid
GB	=	Glioblastoma
GPCRs	=	G protein-coupled receptors
HOCl	=	Hypochlorous acid
IFNβ	=	Interferon- β
ILAE	=	International League Against Epilepsy
IL-1β	=	Interleukin 1β

IL-6	=	Interleukin-6
IL-8	=	Interleukin-8
IL-10	=	Interleukin-10
JNK	=	c-Jun N-terminal kinase
LTB_4	=	Leukotriene B_4
LN	=	Lewy Neurites
LPS	=	Liposaccharide
MADDS	=	monoacetyldapsone
MAPK	=	mitogen-activated protein kinase
MERS-CoV	=	East respiratory syndrome CoV
MIP-1α	=	protein-1α
MPO	=	Myeloperoxidase
MS	=	Multiple sclerosis
NETs	=	Extracellular Neutrophil Networks
NF-kB	=	Nuclear factor -kappa B
NMDA	=	N-methyl-D-aspartate
NO	=	Nitric oxide
Nox	=	Nicotinamide adenine dinucleotide phosphate oxidase
Nrf-2	=	Nuclear factor-erythroid 2 related factor 2
PABA	=	Paraminobenzoic acid
PD	=	Parkinson's disease
PKCμ	=	activation of protein kinase Cμ
PMNs	=	Polymorphonuclear cells
PTEN	=	Phosphatidyl 3,4,5-triphosphate 3 phosphatase
ROS	=	Reactive oxygen species
SARS-CoV	=	coronavirus infections
SE	=	Status epilepticus
SNc	=	Substantia Nigra pars compacta
SCI	=	Spinal Cord Injury
Tau	=	Tau protein
TGF-β	=	transforming growth factor β
TNF-α	=	Tumor Necrosis Factor alpha
VEGF	=	Vascular Endothelial Growth Factor
ZO	=	Zonula occludens
ZO-1	=	Zonula occludens-1

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This review was partially sponsored by Servicios al Enfermo Neurológico S.C., Mexico.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

We thank Michel Nader Sayun for preparing and correcting the final version of the illustrations.

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