Review article

Dysfunctional energy and future perspective of low dose H_2O_2 as protective agent in neurodegenerative disease

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ABSTRACT

The number of people with neurodegenerative disease continues to increase every year. A new perspective is needed to overcome this disease. In this review, researchers collected information about dysfunctional energy in neurodegenerative diseases driven by mitochondria. Mitochondrial dysregulation can cause damage to the neuron system. The increase in the amount and interaction of α-synuclein with SAMM50 and GABARAPL1 in the mitochondria is one of the factors causing neurodegenerative disease. As an energy provider in the body, the existence of harmonization in the regulation of mitochondria, specifically the mitochondrial outer membrane, is important. Low-dose hydrogen peroxide (H_2O_2) has neuroprotective abilities to overcome the impairment function of mitochondria in neurodegenerative patients. Based on computational simulation of this case, it can be used as a basic concept for the development of the role of H_2O_2 in neurodegenerative diseases.

1. Introduction

Neurodegenerative disease and the concept of aging are inextricably linked, as aging is an inherent phenomenon in living organisms characterized by a progressive deterioration in cellular, molecular, and physiological capabilities. The aging process is closely intertwined with the pathogenesis of neurodegenerative diseases, establishing a complex interrelationship between these two phenomena [1–3]. The primary focus of this article centers around neurodegenerative diseases (ND) and their intricate connection to energy provision. It is widely recognized that neurons within the brain heavily depend on a steady supply of energy facilitated by mitochondria. Disruption or dysfunction of these mitochondria can lead to impaired brain function, with one prominent factor being the accumulation of α-synuclein within the mitochondrial structure [4–6]. The implementation of low-dose hydrogen peroxide (H_2O_2) represents a potential preventive measure against this condition. Within the brain ischemia model, the utilization of low-dose H_2O_2 has been observed to confer a neuroprotective effect, thus mitigating the occurrence of the aforementioned condition [7–9]. Contradictory outcomes stemming from the application of low-dose hydrogen peroxide (H_2O_2) have been observed across diverse case studies involving cancer models. Notably, in the context of human breast cancer MCF-7, the administration of low-dose H_2O_2 within the range of 50–200 μM exhibits the ability to impede proliferation, thereby highlighting its inhibitory potential [10]. An additional illustration

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pertains to the application of low-dose hydrogen peroxide (H_2O_2) at a concentration of 30 μM, which demonstrates the ability to stimulate migration of A549 cells. This migratory response, in turn, contributes to tissue repair during instances of acute lung injury in human subjects, underscoring its potential therapeutic implications [11]. The primary emphasis of the authors revolves around exploring the intricate interplay among neurodegenerative disease, energy provision, and the significance of low-dose hydrogen peroxide (H_2O_2). This relationship constitutes the central focal point of their investigation.

2. Neurodegenerative disease based on dysfunctional energy and α-synuclein localization

Parkinson's disease (PD) stands as the second-most rapidly advancing neurological movement disorder, surpassed only by Alzheimer's disease. This debilitating condition impacts a substantial global population, with over ten million individuals affected worldwide. The prevalence of Parkinson's disease varies, ranging from 1% in individuals aged 65 years to 4% in those aged 80 years, signifying its notable impact across different age groups [12–14]. Meanwhile, MSA is a condition that involves the combination of several disorders, including striatonigral degeneration (SND), Shy-Drager syndrome, and olivopontocerebellar atrophy (OPCA) [15]. Motor disturbances in affected patients typically manifest as a result of significant neuronal cell loss accompanied by the presence of glial cytoplasmic inclusions (GCI). These pathological features exert their deleterious effects on various structures within the central nervous system, thereby contributing to the observed disruptions in movement [16–18].

Both diseases exhibit a close association with the functionality of mitochondria, which can become compromised due to multiple factors. Environmental influences, genetic factors, or a combination of both, commonly referred to as epigenetic modifications, can contribute to mitochondrial damage. The role of mitochondria as a crucial energy provider in the body cannot be understated. Particularly within neurons, adenosine triphosphate (ATP) production via oxidative phosphorylation is essential. Disruptions in mitochondrial function can impede the generation of ATP, leading to compromised ATP biogenesis. Neuronal survival viability enters a critical phase when mitochondrial dysfunction occurs. Extensive research has explored the correlation between various neurodegenerative diseases and mitochondrial function. The oxidative phosphorylation complex is deficient in some diseases related to the nervous system. NADH dehydrogenase (Complex I) was damaged and found in platelets and substantia nigra patients with Parkinson's disease (PD) [19,20].

In addition, proteins related to PD are also related to mitochondria. These proteins include α-synuclein, PINK1, DJ-1, and parkin [21,22]. Another complex is Complex IV, which is cytochrome *c* oxidase, where there is a decrease in activity in people with PD. Meanwhile, ATP synthase (Complex V) in PD patients also experienced a decrease in enzyme activity [21]. Other diseases, such as Alzheimer's disease (AD), also show a decrease in the number of Complex I and II in the mitochondria. Meanwhile, Complex IV in AD patients experienced a decrease in activity [22–26].

Several proteins have a relationship with the mitochondria of AD patients, including the amyloid precursor protein (APP). APP is associated with both outer and inner mitochondrial membrane proteins. Mutations in APP can cause cell death and an increase in mitochondrial fission. Proteins in mitochondrial membranes, such as SAMM50, VDAC, and TOMM20, can directly interact with α-synuclein (see Fig. 1). α-Synuclein is known to be a cause of a wide variety of neurodegenerative diseases. The accumulation of large amounts of α-synuclein triggers the oxidation of proteins in the mitochondria and an increase in reactive oxidant species (ROS) (see Figs. 1 and 2) [27,28].

The α-synuclein protein (see Fig. 2) consists of 140 amino acids (aa), with amino acid residues 1–60 comprising the N-terminal region, which has a positive charge. Amino acids 61–95 are involved in the aggregation of α-synuclein and are referred to as the non-amyloid-beta component (NAC). The last part of this protein (96–140) is the C-terminal domain. The NAC domain is protected by two other parts, which prevent the protein from easily aggregating [29–31].

Mutations caused by environmental conditions in α-synuclein occur due to environmental factors. The six point-mutations are A53E, A53T, E46K, H50Q, A30P, and G51D [32–36]. All mutations are located in the N-domain and do not affect the secondary structure changes of α-synuclein [37]. In A30P mutants, α-synuclein is more easily subjected to oligomerization, whereas in A53T and H50Q, the probability of protein aggregation increases [38,39]. The increase in the amount of α-synuclein in the mitochondria causes the function of complex I to be damaged, whereas if this protein is present in low quantity, then the mitochondrial function can be maintained [40–42]. Oligomers of α-synuclein are able to penetrate lipid bilayers as well as intracellular membrane structures
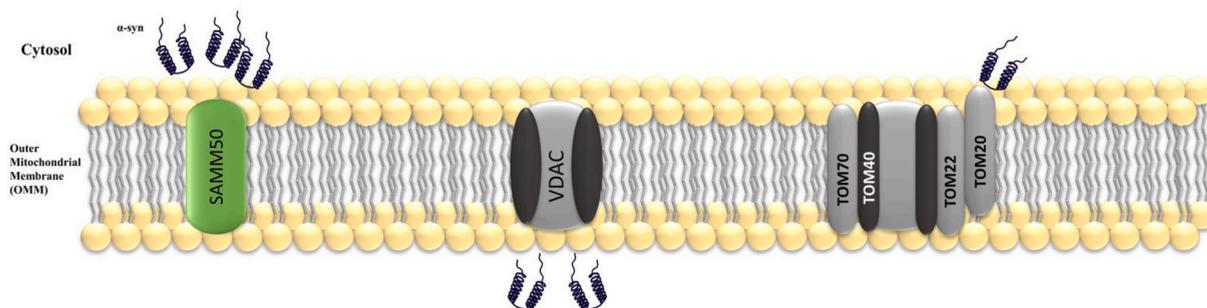
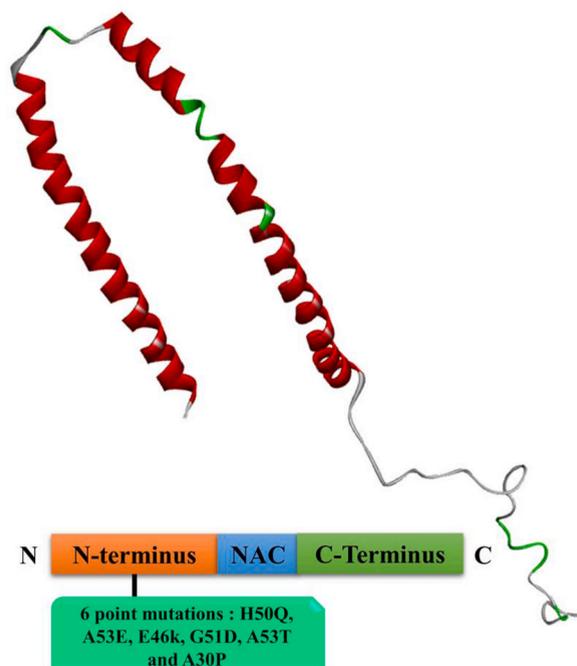

Fig. 1. Outer mitochondrial membrane and α-synuclein.

Fig. 2. α-Synuclein and six point mutations.

[43–45]. Inhibition of tubulin polymerization is also one of the impacts of excess presence of α-synuclein in the system [46]. Over-expression of α-synuclein also results in destabilization of microtubules and cytoskeleton cells [46,47].

Furthermore, with regard to the combination of genetic and environmental factors, it cannot be ruled out that mitochondrial damage, other than due to overexpression and aggregation of α-synuclein, is also related to the mechanism of molecular change that causes alteration in the regulation of various related genes. Such alterations cause neuronal apoptosis and mitochondrial dysfunction [48–50]. In MSA patients, it is known that MicroRNAs (miRNAs) have a role in modulating the expression of MSA-related genes, such as SNCA. The SNCA gene is a gene that plays a role in the encoding of the α-synuclein protein. In addition, it was found that inhibition in miR-34c can cause aggregation of α-synuclein in the model [51].

miR-153 and miR-7 show a similar expression and distribution pattern to α-synuclein. Furthermore, overexpression of these two miRNAs has been demonstrated to drastically decrease the amount of α-synuclein in primary neurons [52]. Meanwhile as we know that Parkinson's disease is a movement disorder that can be characterized by the formation of Lewy bodies involving the localization of α-synuclein and the reduction of dopaminergic neurons in the substantia nigra pars compacta [53]. In Table 1, there is a compilation of various studies related to molecular changes with a focus on mitochondrial function damage and α-synuclein.

As previously stated, the role of mitochondria in supplying energy to the body is crucial. In patients with MSA, mitochondrial dysfunction has been found, resulting in a decrease in the number of Coenzyme CoQ10 [64,65]. Coenzyme CoQ10 plays a vital role as an electron carrier and cellular antioxidant. In the mitochondrial electron transport chain (ETC), CoQ10 carries electrons from

Table 1

Studies overview of PD related to mitochondria and α-synuclein.

Subject	RNA	Effect	Main Result	Target	Reference
Human, MPP$^+$-SH-SY5Y cells	miR-214	↓	Increasing the aggregation of α-synuclein, leads to mitochondrial damage	SNCA	[54]
	miR-34b/c	↓	Increasing the mitochondrial fragmentation and lowering ATP concentration	DJ-1 and Parkin	[55,56]
Norad knockout-mice	LncRNA-Norad	↓	Mitochondrial dysfunction and instability in genomic	PUM2	[57]
MPP$^+$-SH-SY5Y cells	LncRNA-HOTAIR	↑	Inhibiton of miR-205 that leads to apoptosis and mitochondrial damage	miR-205-5p-LRRK2	[58]
Zebrafish	CDR$_{las}$	↑	Upregulate of SNCA (Neuronal Damage)	SNCA	[59]
Transgenic C-elegans model of PD	circSNCA	↓	Accumulation of alpha synuclein (Neuronal Damage)	SNCA	[60]
PGC-1α null mice	miR-485	↑	Accumulation of alpha synuclein	PGC-1α	[61]
MPP$^+$-SH-SY5Y cells	LncRNA-UCA1	↑	Mitochondrial dysfunction and leads to apoptosis	P13K/Akt signaling pathways	[62,63]

complex I and II to Complex III [66]. The decrease in Coenzyme CoQ10 levels is due to damage to CoQ2, which encodes coenzyme-Q2-polyprenyltransferase involved in the synthesis of coenzyme Q10 [67]. A decrease in CoQ10 levels was found in the CSF (cerebrospinal fluid), tissues, and plasma of MSA patients [68]. A study in Japan [69] showed a decrease of up to 30% in CoQ10 levels in the plasma of MSA patients compared to controls. Additionally, other studies found a decrease in the number of CoQ10 by 40% in 12 MSA patients [70]. In a 2019 study published by Nature [71], MSA patients in the cerebellar white matter section of Complex I and IV experienced an increase and decrease in Complex II/III, respectively, while in PD patients in the occipital white matter section of Complex II/III, there was a decrease and an increase in Complex I. Both MSA and PD patients did not show any changes in the mitochondrial mass.

The presence of mitochondria is crucial for the survivability of neurons in the human body. Various neurodegenerative diseases experience dysfunctions in energy management associated with mitochondria. The mitochondrial outer membrane (OMM) plays an essential role in the translocation of various proteins related to energy metabolism [72–74]. One of the proteins that is in the OMM and has a direct bond with various proteins, including α-synuclein, is the sorting and assembly machinery (SAM) complex. As previously mentioned, the presence of α-synuclein with large amounts occurs in patients with neurodegenerative diseases such as AD, MSA, and PD (Fig. 3 A & Fig. 3 B) [27,28]. The human body has a mechanism for handling damaged mitochondria, where lysosomes degrade them through a selective process called mitophagy [75–77]. GABARAPL1 is one of the proteins that play an important role in mitophagy [78–80]. Research by Abudu et al. (2021) showed that SAMM50 has a strong interaction with GABARAPL1, allowing the function of mitophagy to work correctly and maintain the body's energy system's harmony [81]. During the process of mitophagy, mitochondria release their components, such as mtDNA with cardiolipin, which are accepted by the body's system as DAMPs (danger-associated molecular patterns) and trigger innate immune signals [82].

3. Low dose H_2O_2 and protective agent in neurodegenerative diseases (in-silico studies)

H_2O_2 molecules are commonly recognized as toxic agents that exert detrimental effects on multiple levels of biological organization, encompassing cellular and tissue domains. Their presence is associated with adverse consequences, contributing to negative outcomes across various facets of life [83,84]. Nonetheless, numerous studies have revealed that the concentration of H_2O_2 plays a critical role in modulating molecular functions within the body. Interestingly, at low concentrations, H_2O_2 exhibits the capacity to confer a diverse array of advantageous effects, unveiling its potential for conferring a broad spectrum of benefits [7–9]. Through the enzymatic action of catalase (CAT), this molecule is enzymatically cleaved into H_2O and ½ O_2. The resulting breakdown products, particularly O_2, can serve as an alternative source within the body, thereby reducing the production of reactive oxidant species. Numerous studies have substantiated the manifold positive functions of the H_2O_2 molecule, particularly its role as a regulatory signal in metabolic pathways, emphasizing its diverse beneficial effects [85–93].

The presence of a minute quantity of hydrogen peroxide (H_2O_2) in the rat brain has been discovered to serve as a modulator of plasticity, as evidenced by studies [94–97]. Furthermore, it possesses the capability to regulate synaptic transmission, as demonstrated by a range of investigations [98–100].

Neuroprotective effect using H_2O_2 found at low concentrations of 10 μM can protect PC12 cell lines from induction of apoptosis, this means that the administration of molecules in low concentrations has a positive impact on mitochondrial functional improvement. In addition, cerebral infarction decreased in H_2O_2 administration by 2 mM [101,102]. Based on the above explanation, the context of α-synuclein abundance in mitochondria, especially SAMM50 protein, will cause impairment of mitochondria which will eventually have implications for neuron damage in ND patients [27,28]. As well as the relationship between GABARAPL1 which is a protein with the role of maintaining mitochondrial function [81], the addition of H_2O_2 molecules in the system will have a neuroprotective impact on the GABARAPL1 and SAMM50 complexes through binding to the α-synuclein protein and the SAMM50 + GABARAPL1 complex (Fig. 4 A and B). Data from string (https://string-db.org) and STICH (http://stitch.embl.de) databases show that the SAMM50, α-synuclein (SNCA) and GABARAPL1 proteins have interactions (Fig. 5).

The interaction score between SAMM50 and α-synuclein was 0.457 while GABARAPL1 with α-synuclein was 0.680. Interaction analysis shows that directly and indirectly H_2O_2 can interact with all proteins (GABARAPL1, α-synuclein or SAMM50). We also
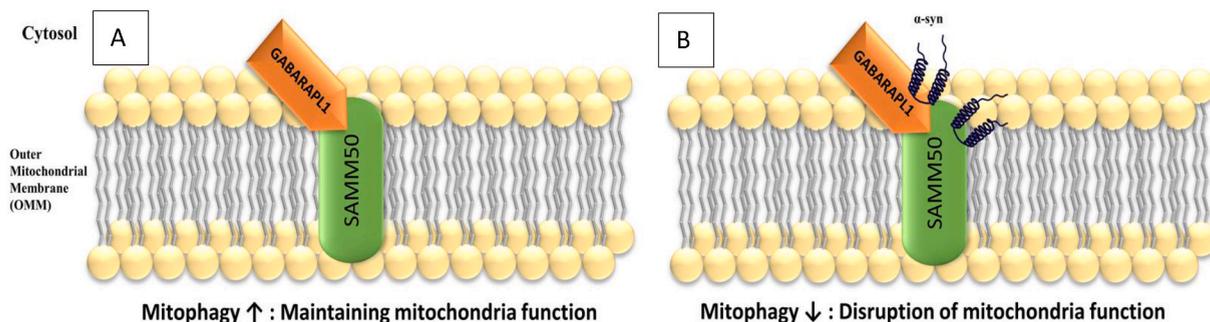
Fig. 3. Schematic model of SAMM50, GABARAPL1 and α-synuclein association (A) Maintaining mitochondria function (B) Disruption of mitochondria function.
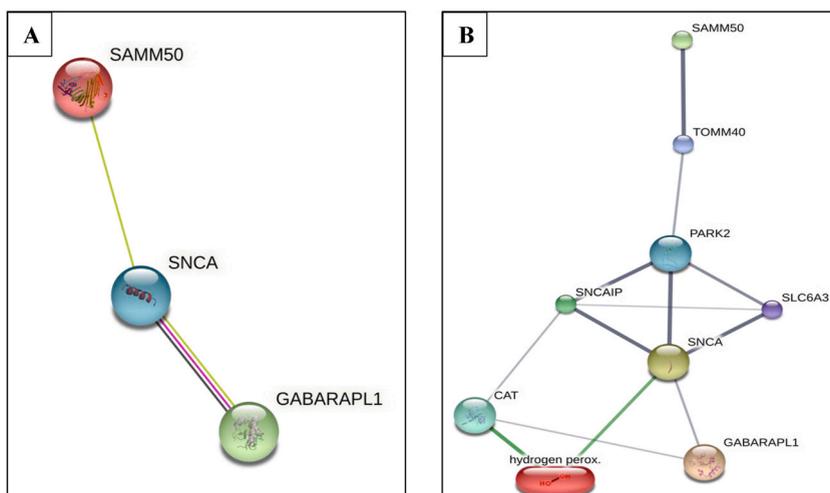
Fig. 4. Overview schematic of H_2O_2 addition to GABARAPL1+SAMM50 and α-synuclein with (A) STRING and (B) STITCH database.

conducted docking studies in order to model the data obtained from the various literature sources above. We used molecular docking analysis using PatchDock and interaction analysis using discovery studio 2016 client, as well as visualization using YASARA.

H_2O_2 can provide neuroprotective effects by enlarging the bond energy required by the α-synuclein protein (1XQ8) to bind to GABARAPL1+SAMM50 (6YOO). When the H_2O_2 molecule binds to 6YOO it requires energy of −14.47 kcal/mol while in 1XQ8 it is −8.30 kcal/mol (Fig. 6 A and 6 B). Docking analysis [103–106] means that if the hydrogen peroxide molecule is in the system, H_2O_2 will more easily bind to the GABARAPL1 + SAMM50 protein complex first and then to α-synuclein. Then the impact of the binding of such molecules to the protein complex causes a change in the bond energy between the proteins α-synuclein and the GABARAPL1+SAMM50 complex. Before being given hydrogen peroxide molecules the bond between 1XQ8 and 6YOO was −199.93 kcal/mol. Then after being given the H_2O_2 molecule on α-synuclein the energy of interaction with the GABARAPL1+SAMM50 complex becomes −96.09 kcal/mol. While the addition of molecules to the GABARAPL1 + SAMM50 complex has a bond energy of −42.42 kcal/mol.

The increase in energy requirements for binding means that H_2O_2 reduces the probability of binding α-synuclein in the mitochondrial complex so that the mitochondrial function as an energy producer for neurons is maintained. The binding site between protein-protein amino acids may explain the role of H_2O_2 in the 1XQB and 6YOO complexes (Fig. 7). In patients with neurodegenerative disease α-synuclein binds to the SAMM50 and GABARAPL1 protein complexes have interactions between the amino acids PRO33(B) and GLU32(B) of GABARAPL1+SAMM50 and GLY73(A) and VAL77(A) in α-synuclein. Whereas after H_2O_2 administration the bonding site has two different effects between its complexes, where in α-synuclein + H_2O_2 when binding with GABARAPL1+ SAMM50 experienced a decrease in the number of bonding sites to two where only PRO33(B) remained the same as native (before
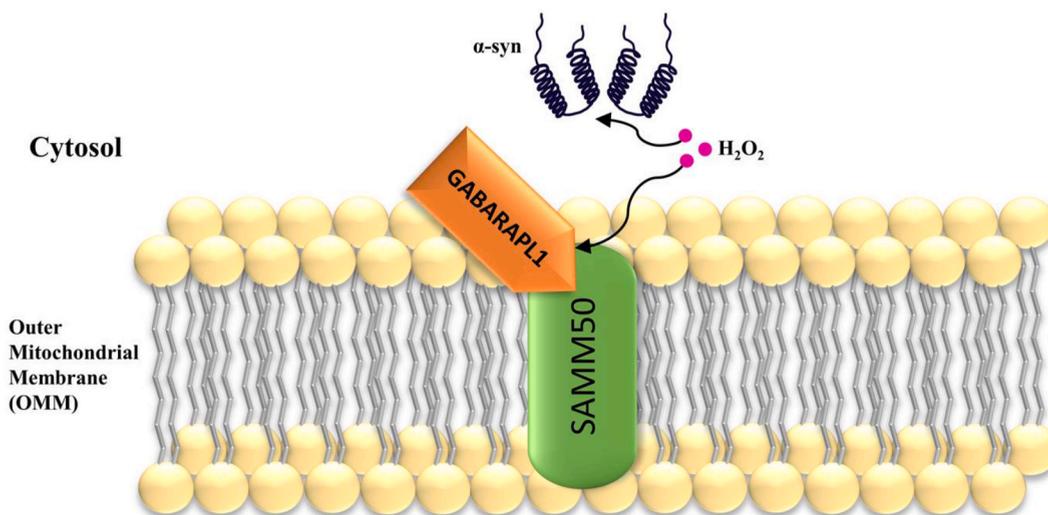
Fig. 5. Proposed interaction between molecules H_2O_2 and proteins (α-synuclein, GABARAPL1 and SAMM50) based on protein-protein interaction networks.
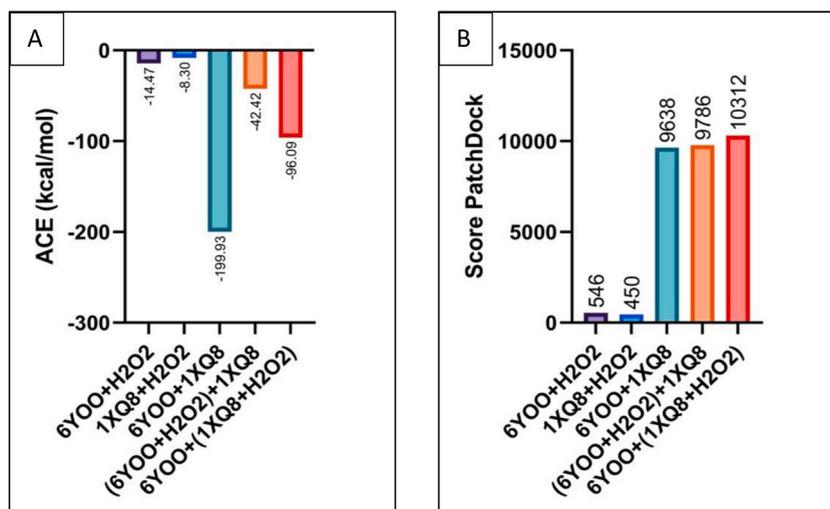
Fig. 6. PATCHDOCK score (A) ACE (Atomic Contact Energy) and (B) Docking score.

H_2O_2 administration).

Meanwhile in α-synuclein when binding with (GABARAPL1 +SAMM50)+H_2O_2 there is an addition of amino acid bond sites, but the results of energy analysis show that the energy required of α-synuclein becomes much higher. This means the probability of α-synuclein for binding with GABARAPL1+SAMM50 becomes lower. Low dose usage of H_2O_2 is widely studied in cancer case. One of them is the usage of 100 μM H_2O_2 prevented the migration of H460 large lung cancer cells; superoxide anion and hydrogen peroxide downregulated Cav-1 expression and prevented cell migration and invasion. The action of superoxide anion and hydrogen peroxide on Cav-1 was mediated by a transcription-independent mechanism [107]. Exploiting neuroprotective strategies based on H_2O_2 through mitochondria concept is really possible for future research [94–102]. It needs to be underlined is that the concept of alpha-synuclein is not the only source of the cause of MSA or PD so the roles of other causes besides alpha-synuclein can occur. So that the research direction on neurodegenerative diseases is expected to be more comprehensive in the future.

4. Future perspectives

The evidence presented in our discussion is intriguing and suggests that the accumulation of α-synuclein and its interaction with mitochondria play critical roles in regulating neurodegeneration in neurodegenerative diseases. The future perspective research on the neuroprotective effects of H_2O_2 suggests that it can enlarge the bond energy required by the α-synuclein protein (1XQ8) to bind to GABARAPL1+SAMM50 (6YOO), thus reducing the probability of binding in the mitochondrial complex and maintaining its function as an energy producer for neurons. However, it should be noted that the concept of α-synuclein is not the only source of the cause of MSA or PD, so the research direction on neurodegenerative diseases is expected to be more comprehensive in the future. In low dose usage, H_2O_2 is widely studied in cancer cases, and exploiting neuroprotective strategies based on H_2O_2 through the mitochondria concept is possible for future research.

5. Conclusions

New perspectives to understand the condition of neurodegenerative disease are needed in order to build a concept in the management of the disease. It has been explained that in ND the role of mitochondria and dysfunctional energy can be used as a basis for thinking. There are many factors involved in ND disease, but new focuses such as improving mitochondrial function as energy suppliers for neurons are very interesting to be studied further in the future. In the present review we summarized the relationship of mitophagy in carrying out mitochondrial functional harmony by GABARAPL1 with the mitochondrial OMM protein, namely SAMM50. This functional can be undermined by the presence as well as the α-synuclein interaction in the system. To overcome this, the use of H_2O_2 can be tried in small concentrations. Low dose H_2O_2 is proven to be a paradox in the overall concept of ND, where in large quantities it is able to promote various kinds of damaging pathways while in small concentrations it promotes survival pathways. The use of low dose H_2O_2 function as a neuroprotective agent can be one of the important studies in the future.

Authors contributions
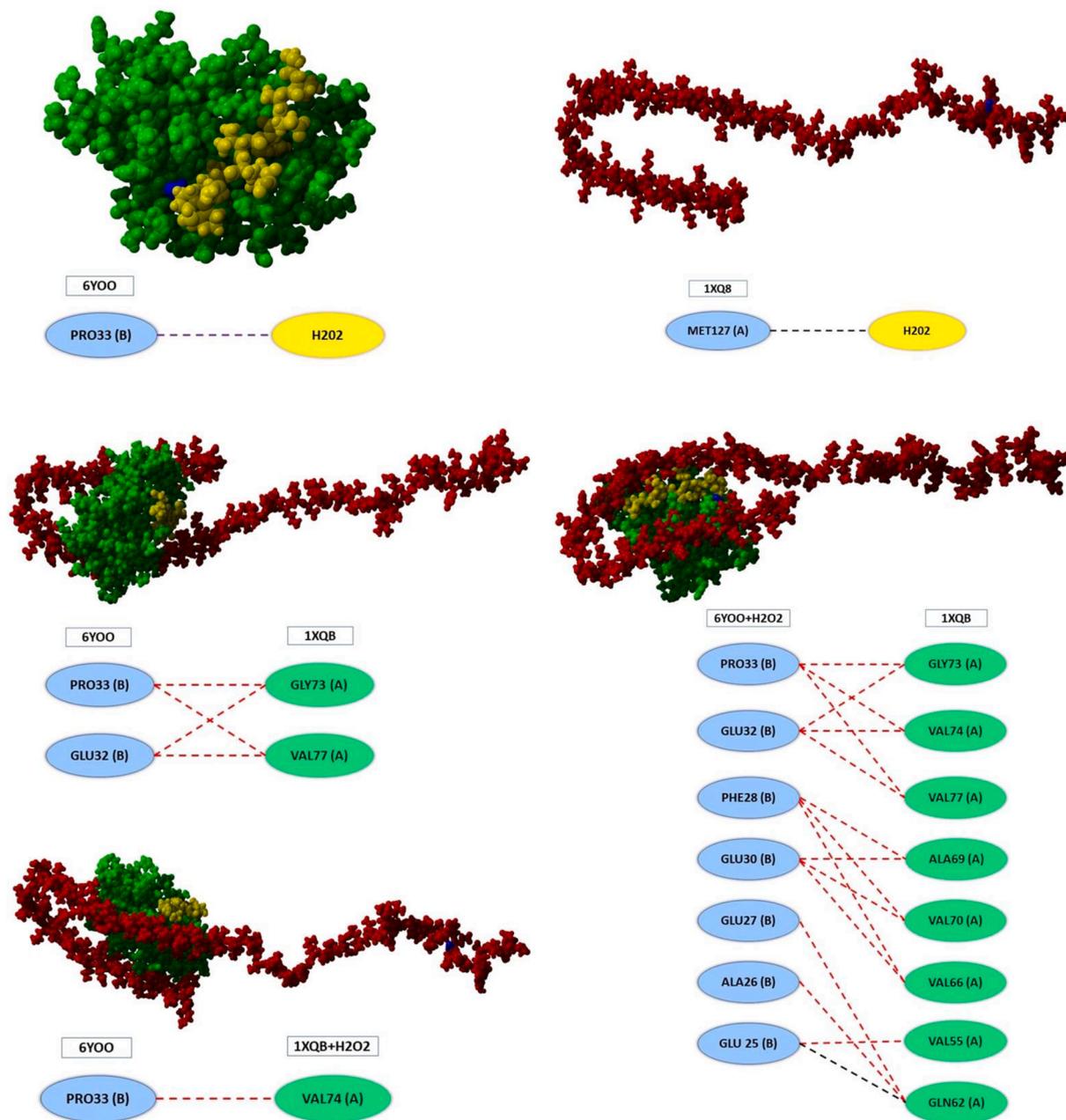
Fig. 7. Interaction between 1XQB (α-synuclein protein), 6YOO (GABARAPL1+SAMM50) and H_2O_2. Colours description: 6YOO (Green: GABAR-APL1; Yellow: SAMM50; Blue: H_2O_2), 1XQB (Red: α-synuclein; Blue: H_2O_2) and Arrows (Red lines: Hydrophobic Bond; Black line: Hydrogen Bond). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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Declaration of competing interest

The authors declare that no potential conflict of interest that could have appeared to influence the work reported in this paper.

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