Review

Melatonin and biological membrane bilayers: a never ending amity

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ABSTRACT

Biological membrane, the most fluidic structure of a cell or an organelle, refrains the cells to progress toward apoptosis by sustaining their optimum environment. This bilayer-membrane equips all machineries required for cellular communication, limits the entry of foreign bodies, selectively transports molecules or ions depending on the need of the system but, it also acts as a first line defense against environmental insults. Due to the presence of a vast number of poly unsaturated fatty acids (PUFA), the biological membrane is highly prone to oxidative stress and as a consequence, acceleration in lipid peroxidation by free radicals, becomes a threat to cellular viability. Alterations in the biophysical state of bilayer caused by oxidative stress frequently occur in the *in vivo* as well as *in vitro* conditions. It has been well documented that the molecule, melatonin, exhibits profound coherence in neutralizing oxidative stress and thus, to normalize fluidity status of biological membranes. Aging associated decline in melatonin level with subsequent ascended lipid peroxidation and membrane viscosity found in almost all organisms further suggest the importance of melatonin in this context. Since disruption of membrane structure or even some modifications will cause a spectrum of diseases, keeping membrane intactness would be an adequate strategy to prevent these diseases. Considering the high permeability, safe and potent antioxidant capacity of melatonin, this molecule can be a superlative choice to alleviate membrane bilayer rigidity and its related ailments.

Key words: Biological membrane, lipid, fluidity, membrane rigidity, melatonin, oxidative stress, free radical

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1. INTRODUCTION

Biological membranes dictate the existence of life. This universal component of cell is the key operator for maintaining cellular homoeostasis. Amphiphilic lipid molecules, the building blocks of membrane bilayer arrange themselves in a wise manner to generate a highly hydrophobic environment at its core, which in turn arrest passage of all molecules irrespective of its chemical moieties. This nature of bilayer fabricates the need of protein transporters that selectively admit the entry of different molecules (1). The fine balance between cellular survival and apoptosis relies on magnificently knitted signal transduction system, the mode of cellular communication. These functional aspects feature the

interweaving between lipids and residing proteins of the membrane bilayers. Furthermore, cellular membranes act as the first line barrier against pathogen entry as it possesses extremely sensitive immune sensors that recognize the pathogens (2). Evolution has made cellular environment more stringent for pathogens or foreign bodies by creating compartmentalization also such as organelle's membrane with lipid bilayer. On that account, it is easily understandable that disassembly in structure and function of biological membrane is a disaster for cells.

Though nature has created the unique structure as a shield for crucial cellular components, being prone to oxidation, lipid molecules suffer from deleterious oxidative stress by free radicals (3). Hydroxyl radical, peroxynitrite are the major form of radicals that trigger the process of peroxidation either by abstracting a hydrogen molecule from residing lipids or by donating single electron and the resultant intermediate peroxyl radical becomes more hazardous by amplifying the peroxidative chain reaction (3). When the biophysical state of lipid bilayer is immensely affected, the phospholipid composition and fatty acid head group position became modified to alter the membrane fluidity (4). Fluidity of membrane is necessary to maintain lipid and protein free diffusion across the leaflets for preservation of bilayer asymmetry. Lipid peroxidation will hamper this membrane harmony and lead to cellular membrane damage. The oxidative stress related membrane damage is associated to many diseases and aging process.

Melatonin, an indoleamine, is considered as a potent broad spectrum antioxidant backed by many rigorous investigations (5). The decrease in melatonin production accompanied by elevated membrane lipid peroxidation with aging has been found almost in all organisms (6, 7). Consequently, composition and structure of cellular membrane are altered with the reduced melatonin level (8). Hence, the attention has been given to this molecule among other antioxidants for having capacity to maintain the biological membrane fluidity at optimum level. Many researches have highlighted the mechanism by which melatonin achieved its protective effects on the cellular membranes. A detailing on those attainments may unfold new research angles to be discovered in near future.

2. THE DECOR OF BIOLOGICAL MEMBRANE

Biological membranes, which institute the existence of life, are naturally sketched by an interweaving of lipids and proteins. Though amphipathic lipid molecules are the main building blocks for membrane bilayer formation, presence of proteins have made the bilayer being able for many biological functions, essential for cell survival (9). The hydrophilic heads of different glycerophospholipids, glycolipids and sterols advantageously arrange themselves in a bilayer while their hydrophobic tails form aggregates to provide a disordered structure with high entropy. This elevated entropy level of membrane allows the phospholipids to diffuse along bilayer leaflets. Phospholipid translocation between leaflets i.e., vertical movements is seldom observed since the hydrophilic heads have to pass through a highly hydrophobic inner environment which requires overcoming a high activation energy barrier (10). However, this translocation seems necessary for cell endocytotic process (11). The all-pervasive phospholipid asymmetry across the bilayer, the resultant of lipid translocation are responsible for conserving cellular mechanical properties. Disruption of this asymmetric distribution leads to disturbed interaction between proteins and lipids in inner leaflet of membrane which triggers the activation of macrophages and, thus promotes apoptosis (12).

Along with the presence of these flexible lipid molecules, membrane proteins also contribute in maintaining the dynamic nature of biological membranes though they possess much slower rates in cis-trans diffusion (13). Apart from maintaining structural integrity of

membrane, proteins are indispensable machineries in allowing or hindering movement of substances within cells, in transducing essential signals for maintaining physiological homoeostasis. The specific position of a particular protein in membrane dictates the assigned function of that protein and hence, the dense network of integral membrane proteins, membrane spanning proteins and peripheral proteins are crucial for maintaining functional status of biological membrane.

The elixir of a properly functional membrane lies within the interaction between those membrane lipids and proteins. The lipid molecules, immediately adjacent to a protein form a shell or annulus where the fatty acyl chains of lipids are intermingled to the grooves and protrusions of protein molecules in order to give a rigid structural appearance (14). Since the interaction energy depends on several weak van der Waals and electrostatic forces, the lipid molecules loosened connection with specific proteins and give an unfavourable membrane conformation. Therefore, the dynamic nature of the bilayer depends on this annular site binding of lipids though the non annular binding i.e., binding of phospholipids with transmembrane alpha helices of proteins provide a glance of discrete binding, where the head groups of lipid molecules are attached with protein moiety through strong hydrophobic interaction (15). This more specific non- annular binding, unlikely to annular binding, is almost devoid of steric hindrance and hence allows entry of lipid molecules by simple diffusion only (15). Not only lipid molecules, but also the proteins can be revamped either by tilting their helices or by rotating their side chains for being adapted within lipidic environment.

Another principal bio-molecule that declines the permeability of membrane is cholesterol, which is accountable for making the membrane less fluidic (16) by interacting with polar head group and hydrocarbon chain of phospholipid through their own hydroxyl group and steroid ring structure respectively. In abstract, an ardent steric and operative synchrony between lipids and proteins furnish the unique ubiquitous structure of biological membrane.

3. PHOSPHOLIPID BILAYER- THE HOTSPOT OF LIPID PEROXIDATION

Lipid peroxidation has been identified as the dominant cause of several detrimental diseases related to cell membrane disruption (17). Cell membrane with abundant lipid molecules is highly susceptible to oxidative stress (18) and hence, it becomes a primary target of peroxidation (19) (Figure. 1).

Principally, poly unsaturated fatty acids (PUFA) are the prime substrates for this autooxidative process initiated by free radicals (19-21). For example, brain tissues are extremely vulnerable to peroxidation due to its high concentrations of PUFA (22). This is also observed in membranes of organelles such as in mitochondria and peroxisome (21). Long chain fatty acids with more than one carbon-carbon double bond (C=C) and with pentadiene moiety are more prone to this oxidative stress (3, 21).

Apart from PUFA, glycolipids and cholesterol are also the victims of deleterious oxidative stress (18, 23). Lipid peroxidation usually occurs with abstraction of a hydrogen molecule from a PUFA (24) by free radical attack. Hydroxyl radical or hydroperoxyl radical attack causes conjugation of the double bonds. The resultant alkyl radical, being nonpolar easily got soluble within hydrocarbon and reacts with oxygen to generate peroxyl radical, the key propagator of peroxidation, functioning by abstracting allylic hydrogen from the lipid molecule at adjacent vicinity (25). Theoretically, this process can continuously go on to spread in all membrane if it is not terminated by some interventions.

Since physiological as well as biophysical aspects of biological membrane like polarity and permeability are dependent on in-house lipid molecules (26), the ionic permeability modification in artificial membrane is an obvious consequence of lipid peroxidation (23).

Lipid peroxide induced dismantled lipid assembly, composition alterations and dynamic changes within membrane lead to loosening of the integrity of biological membrane (3). Mario Diaz *et al.* have reported the altered lipid-lipid interaction, amended membrane fluidity and permeability when membrane was subjected to lipid peroxidation (4). An escalation in phospholipid bilayer rigidity owing to lipid peroxidation has been reported (27, 28) due to the formation of cross-linking between lipid molecules (29) and loss of freedom of motion in bilayer (27, 29, 30). Additionally, this peroxidation process also affects membrane bound enzyme activity (31). The key cause behind such adverse actions of peroxides on biological membrane has been presumed to be the re-orientation of lipid molecules toward water-lipid head interface leading to reduction in the thickness of membrane (32) along with impeded biological action (33).

4. MEMBRANE DAMAGE AND DISEASES- A THREAT TO CELL VIABILITY

A strong nexus between membrane lipid peroxidation and diseases has been reported in several studies (34, 35). As lipids are essential in maintaining cellular integrity, hampered lipid homoeostasis contributes to disordered cellular as well as organelle membrane structure (36) leading to the cellular aging and related diseases (37). When the rate of lipid peroxidation surpasses the potential of endogenous antioxidant capacity, the pathological alterations are the outcomes (38, 39).

Abnormal chemical and physical alterations in bilayer are the core causes behind those disorders. These alterations will impede the functions of membrane receptors, transportation proteins along with subsequent modifications in lipid composition and membrane permeability to cause muscular dystrophy and cystic fibrosis (36). The two major toxic lipid peroxidation products i.e., malondialdehyde (MDA) and 4-hydroxy-2-noneal (4-HNE) are the major culprits (37) to promote destruction of bilayer structure (32) and to hamper interaction of membrane with its proteins (40). Hydrolysis of membrane phospholipids by activation of phospholipase and subsequent free fatty acid generation in pathological conditions cause abated phospholipid frequency (41) which affect membrane fluidity and ruin receptor clustering (37) and thus jeopardize bilayer function. Elevated lipid peroxidation has been linked to neurodegenerative diseases, atherosclerosis, diabetes, cardiovascular, liver, chronic kidney diseases and arthritis (42-49). 4-HNE is reported to associate with hyperglycaemia and diabetes (50). Cognitive deficiency with aging is also related to the altered composition and distribution of lipids within brain (51, 52).

Not only lipids, membrane proteins can also be attacked by free radicals to jeopardize the cytoskeletal architecture and protein distribution (53), probably due to oxidative protein carbonylation (54). For example, the erythrocytes have typical structure with a diverse range of membrane proteins and thus, they are the easy targets of peroxidation to form excessive glycosylated haemoglobin (55) which cause decline in elasticity and their lifespan (56). Mitochondrial membrane is another easy target of peroxidation due to its distinct architecture with cardiolipin, phosphatidylethanolamine. Its peroxidation causes excessive cytochrome C release and apoptosis (57).

Cellular membrane oxidative damage is considered as the major contributor of aging and Alzheimer's disease (AD) (58). Mecocci *et al.* have reported an increased viscosity and a concomitant decrease in mitochondrial membrane fluidity in different lobes of AD patient's brain (59), further confirming the involvement of peroxides in declined fluidity (29) and lipid order in cellular membrane (60, 61). Accumulation of Aβ peptide in mitochondrial membrane (Aβ peptide) can initiate peroxidation, membrane protein damage and jeopardizes mitochondrial structure and function (62, 63). Lipid peroxidation induced reorientation in membrane phospholipid composition and distribution in AD brain also confirmed the

observation of membrane alteration occurring in AD (64, 65). Apart from this neurodegenerative disease, mitochondrial lipid peroxidation induced lung injury and cardiomyocyte pathology also have been reported (66, 67).

5. MEMBRANE PERMEABILITY AND MELATONIN

Literature review provides convincing evidence considering lipid peroxidation as the prime factor in biological membrane damage and hence prevention of lipid peroxidation appears as a suitable protective strategy to maintain membrane in its healthy state. Antioxidants, the molecules which provide primary line of defense against such destructive action of free radicals (3), generally overpower other possible preventive measures, due to the ability of membrane phospholipids in facilitating the interaction of antioxidants with membrane lipids (17). Successful retention of this membrane disorder depends on several factors and among them melatonin excels over others by positioning themselves favourably as a membrane protector (68). Hence, exploiting paired advantages of being an antioxidant and maintaining membrane order, melatonin preserves the proper cellular structures and functions by different mechanisms.

Costa *et al.* in 1995 tied up this antioxidative property of melatonin to its profound membrane permeability (69). This also parallels to the observations of melatonin's interaction in the nucleus by easy access through the nuclear membrane (70, 71) and its high aqueous membrane solubility (72). Although previous studies focussed on hydrophobic moieties of the indole (73), Reiter *et al.* then, enlightened its hydrophilic nature also by confirming its non-receptor mediated action (71). Not only its membrane permeability, but melatonin also exhibits high lipid membrane association constant (69) that enable it to nullify free radicals immediately after generation on site (74, 68). Costa *et al.* (75) further studied distribution pattern of melatonin within lipid bilayers using spin labelling technique. They confirmed membrane binding site of melatonin both in membrane interface and in depth of bilayer also. This amphiphilic nature of melatonin along with its favourable distribution in membrane stabilizes microsomal membrane (19), and greatly contributes to its cell protection (76). Microsomal membrane is also protected by either pinoline-melatonin (77) or tamoxifen-melatonin (20) combinations where melatonin enhances the efficacies of these molecules by scavenging both aqueous and lipophilic membrane radicals (68).

Melatonin can prevent UV induced skin damages (78). This photoprotective action of melatonin is attributed to its ability to scavenge UV-triggered free radicals in L-α-dimyristoylphosphatidylcholine, residing in the peroxide attack prone intracellular spaces (79). Admittance of melatonin to red blood cell membrane prevents haemoglobin denaturation and haemin release when erythrocytes were exposed to cumene hydroperoxide (80).

A step forward, Bongiorno *et al.* have investigated the pattern and site of melatonin binding in bio-membrane using reversed micelles which mimic the *in vivo* membrane conditions, as surfactants form aggregates in apolar solvents by burying their polar heads in internal core (81). This study uncovered the preferential location of melatonin which is near micellar head groups irrespective of its presence in apolar solvent or in water (82). de Lima *et al.* have also observed protective ability of melatonin in the egg phosphatidylcholine liposome, no matter how melatonin was supplied; either in incubation or incorporated within liposome (83, 84). When melatonin was infused within liposome to enhance its membrane or intracellular compartment occupancy, it provided 40% more protection on hydroxyl radical and peroxynitrite induced membrane damage (83). Melatonin administration can significantly reduce blood brain barrier permeability (85) and this is attributed to its excellent membrane permeability (86).

The permeability of melatonin to membrane also exhibits concentration dependent manner. Dies *et al.* have observed the co-existence of melatonin enriched domain along with pure lipid domain at low concentration of melatonin (0.1-1mM) while an ordered uniform structure has been found at high melatonin concentration (10mM) (87) which is similar to the observation reported by Sahin *et al.* (88). Melatonin molecules were reported to align themselves in parallel to phospholipid acyl chains or lipid bilayers at the head group regions in low and high concentrations, respectively without disrupting the lipid matrix. Though higher melatonin concentration provides a more ordered state of membrane, it seems to inhibit the insertion of amyloid peptides in anionic lipid membrane (89). This observation provoked an idea of increased fluidification induced hindrance in insertion of peptides in highly rigid bilayer of AD patients (90). Attribution of cholesterol in progression of AD along with membrane rigidity has been well established (87). Hence, protective action of melatonin for AD may relate to a competitive interaction between melatonin and cholesterol, i.e., cholesterol appears to pull melatonin outwards from membrane core while melatonin with its unique nature possesses permeability from one leaflet to other at different cholesterol concentrations (91). This ever pervasive nature of melatonin depends on transition between its folded and extended states that need a free energy change to attain their favourable configuration depending on concentration of cholesterol (92). In support of these, Yu *et al.* observed melatonin bearing 1.7μm/sec membrane permeability, even higher than that of serotonin (93). The specific filling-emptying method revealed equilibration of cytoplasmic and extracellular melatonin at a median of 3.5 seconds (range of 3 to 7 seconds) period, indicating high penetrable power of this tiny indole molecule.

6. REACTION OF MELATONIN WITH MEMBRANE LIPID PEROXIDES

The ubiquitous presence of melatonin due to its amphiphilic and easy membrane permeable property, has garnished the indole as a superior antioxidant. It acts to stabilize cellular structures by detoxifying ROS and modulating redox enzymes (5). Besides scavenging oxygen-centred radicals, nitrogen-based toxicants and stimulating antioxidant enzymes, this molecule functions as physiological barrier to hinder all stages of membrane lipid peroxidation and thus effectively limits the oxidative burden of an organism. It not only blocks initiation of lipid peroxidation (94), but also acts as the chain breaking antioxidant similar to vitamin E (95). Thus, melatonin is also referred as lipid peroxyl radical scavenger to suppress the propagation of lipid peroxidation (96, 97).

The preservative effects of melatonin on cell membrane structure from peroxidation have been observed both *in vivo* (98-100) and *in vitro* conditions (101-103). For example, it protects against the deleterious effects of peroxides on liver microsomal membrane (84). To be specific, melatonin preserves the long chain PUFA from peroxidation (104) as a broad spectrum of radical scavenger (105, 106). In addition to act as a powerful hydroxyl radical scavenger (106-108) it also neutralizes peroxynitrite and peroxide degradation product, alkoxyl radical which add more feathers to its antioxidative strength (109, 110). The antioxidative nature of melatonin is conserved through evolution as its existence has been confirmed in PUFA rich thylakoid membrane, where it is assumed to protect against oxidative damage (21, 111). Melatonin protects against phenylhydrazine (PHZ) triggered cell membrane damage (112) via its effects on membrane permeability and membrane bound enzyme activity (31). Moreover, melatonin derivatives also possess antioxidative activity. Its direct metabolite, cyclic-3-hydroxymelatonin (c3OHM), exhibits even greater efficacy than melatonin in scavenging peroxyl radical probably by mechanisms of radical adduct formation, single electron transfer and hydrogen transfer (113) in both lipid and aqueous environment (114). Electron donation has made melatonin (115) and c3OHM (116) highly

efficient in scavenging while other two metabolites of melatonin including N^1-acetyl-5-methoxykynuramine (AMK) and N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) exhibit their maximum potency in scavenging singlet oxygen and hydroxyl radical, respectively (117, 118) to block their direct reaction with C=C and subsequent peroxide generation (119). AMK has been recognised as a nitric oxide ($NO^{\cdot}$) scavenger; however, melatonin is more potent than AMK to scavenge $NO^{\cdot}$ (120). The potent efficacy of melatonin has been attributed to its actions on conservation and reorganization of membrane lipids to preserve membrane fluidity (121) as well as its antioxidative property (19, 20, 78, 122) (Figure 1). Hence, interdependency of radical scavenging activity and membrane fluidity regulating activity of melatonin make this indole a saviour of organelles, cells and broadly lives.

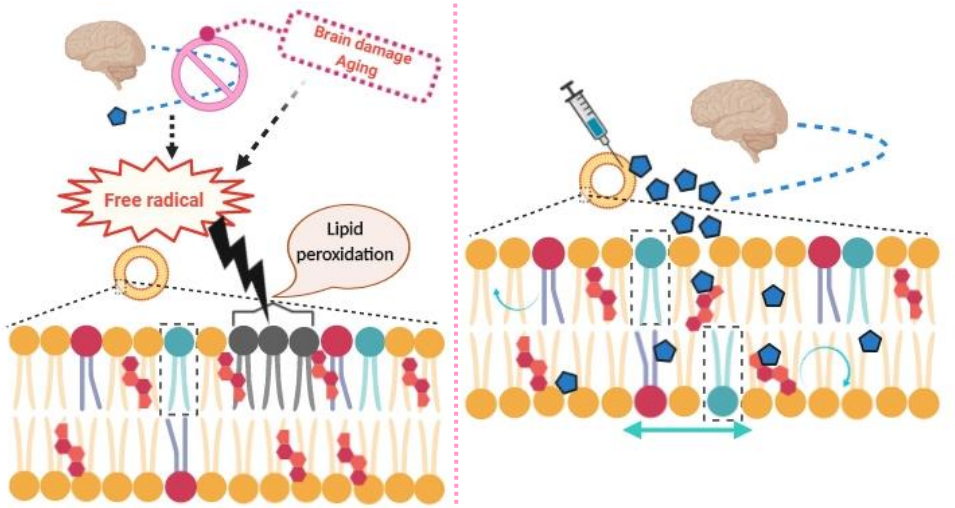

Fig. 1. Illustration of the protective mechanisms of melatonin on cellular membrane.

Left panel: the biophysical state of membrane under the scarcity of melatonin in aging brain. The increase in free radical generation attacks the bilayer phospholipid molecules to cause lipid peroxidation (shown in 'Black'). Profuse cholesterol concentration (shown as 'Red sterol structure') and peroxidation increase membrane rigidity hampering fluidic state. The phospholipids (shown in 'Blue') become incapable to translocate in other leaflet with impeded motions of lipid head groups and tails on their own axis. Right panel: a normal status of membrane with sufficient melatonin. In presence of sufficient melatonin (Shown as 'Blue pentagon'), optimum membrane fluidity has been achieved that allow free movement and rotation of phospholipid molecules (shown with 'Blue arrows'). In particular, the phospholipid (shown in 'Blue' within square) became capable to translocate in otherleaflet. Moreover, melatonin has shown to compete with cholesterol to maintain fluidic state of bilayer.

7. MELATONIN PREVENTS MEMBRANE FLUIDITY IMPAIRMENT INDUCED BY OXIDATIVE STRESS

Several important factors including fatty acid compositions, length and degree of saturation, cholesterol concentration and phospholipid/cholesterol ratio determine the membrane fluidity (123-126). Fluidity refers to the mobility of membrane components vs. membrane viscosity (127, 128). Fluidity is a crucial factor for functional membrane which allows free intra and inter-leaflet diffusion of lipids and proteins within bilayer to maintain the asymmetry of functional proteins including transporters, signal transducers etc. across the leaflets (129). Conservation of optimal membrane fluidity is the basic criterion for

transmembrane solute transport, signal transduction and membrane bound enzyme activities of cells (17, 130, 131). Membrane signal transduction, the basis of every physiological process would be hampered with severe alteration in membrane fluidity (132). Optimal fluidity determines the communicative efficiency between β-adrenergic receptor and G-protein. Several pathological situations are correlated with dismantled membrane fluidity (130, 133-135). Dismantled bilayer fluidity will disrupt perception of environmental signals by cells and influences genetic modifications in response to different environmental conditions (136).

Curtis *et al.* have identified oxidative stress as a principal factor to modify the order in the membrane bilayer by reflecting mean angular deviation of fatty acids from its residing bilayer plane (137). This oxidative stress induced structural disorientation leads to molecular motion disruption within membrane (138). Lipid peroxidation induced altered membrane fluidity has been reported in rat frontal cortex (139) and also in endoplasmic reticulum membrane of brain (140). Both cellular and organelle membrane fluidity are altered by free radical assault. Erythrocyte and microsomal membrane lipid peroxidation cause similar alterations of diminished membrane fluidity (141, 142). Both fluorescence and electron spin resonance spectroscopy methods showed the covalent cross-link formation between adjacent lipids as the foremost cause of elevated membrane rigidity (143).

As to the preservative effects of melatonin on membrane fluidity, the studies are summarized in the table 1. Initially, Garcia *et al.* have reported melatonin protects membrane fluidity against oxidative stress (19, 20). Dose responsive studies indicate that the relatively high concentration of melatonin provides better safeguard to membrane. Melatonin and its metabolites lower bilayer rigidity by limiting both cholesterol concentration and incorporation of saturated fatty acids (144). It is found that the less mobile lipid bilayer is prone to radical attack (145) and melatonin has the capability of lowering microviscosity in platelet membrane by shielding lipid molecules from peroxide attack (146). This ability of melatonin to protect membrane fluidity has been confirmed in artificial dimyristoylphosphatidylcholine (DMPC) membrane as well as in erythrocyte membrane of cardiopulmonary patients with high surgical risk (80, 147, 148).

The interplay of melatonin and bio-membrane have been further studied in microsome and hepatocyte membrane challenged by PHZ, lead and CCl_4, respectively and the protective effects of melatonin on membrane fluidity have been confirmed again (113, 149, 150). Significantly abated microsomal membrane fluidity along with rise in 8-hydroxy-2-oxyguanosine concentration in hepatocytes from rats exposed to ionizing radiation, are successfully counteracted by pre-administered melatonin (122) showing constancy in sustaining dynamic state of membrane. Toxic α-Naphtylisothiocyanate (ANIT) induced lipid peroxidation and ensuing hepatic microsomal membrane damage leading to cholestasis was overturned by this indole treatment (151).

On other hand, the potential association of aging related low membrane fluidity and reduced melatonin production has already been apprehended (152, 153). Reiter and his co-workers inferred the altered melatonin level along with escalated membrane rigidity in pinealectomized rats (154). Membrane cholesterol concentration also increases with aging (144) leading to modifications in membrane permeability and fluidity, while active competition of melatonin with cholesterol in order to normalize biophysical state of bilayer by dislodging bound cholesterol has been pre-endorsed (155, 156) (Figure. 1). This implies that cholesterol modifies membrane status to be more rigid in the condition of melatonin scarcity with aging. Furthermore, membrane rigidity has been discerned as an inevitable outcome due to elevated lipid peroxidation (82). These cross-links again bring attention to melatonin for maintaining steady state of biological membrane. Moroni *et al.* (157) observed the decreased erythrocyte membrane rigidity in aged rats with the grafted pineal gland from

young rats. When the senescence accelerated mice (SAM) were treated with melatonin, their brain membrane fluidity was significantly improved (22). Since authors identified a better outcome in mitochondrial membrane, the major seat of free radicals, they proposed the antioxidant activity of melatonin as the core foundation of its membrane shielding effect, supported by decreased age dependent dysfunction in cardiac mitochondria in melatonin supplemented SAM (158).

Table1. The chronological list of researches related to melatonin and biological membrane.

Author's Name	Year of Publication	Investigated Cell/Tissue/Organelle	Reference
Costa *et al.*	**1995**	Multilamellar asolectin vesicles	**69**
Daniels *et al.*	**1996**	Platelet membrane	**146**
Costa *et al.*	**1997**	DMPC	**75**
Garcia *et al.*	**1997**	Hepatic microsomal membrane	**19**
Garcia *et al.*	**1998**	Hepatic microsomal membrane	**20**
Garcia *et al.*	**1999**	Hepatic microsomal membrane	**77**
Reiter *et al.*	**1999**	Melatonin deficient rat	**154**
Rudzite *et al.*	**1999**	Rat liver tissue	**144**
Tesoriere *et al.*	**1999**	Human erythrocytes	**80**
Karbownik *et al.*	**2000**	Hepatic microsomal membrane	**112**
Karbownik *et al.*	**2000**	Rat	**149**
Karbownik *et al.*	**2000**	Hepatic microsomal membrane of ionized rat	**122**
Calvo *et al.*	**2001**	Hepatic microsomal membrane	**151**
Saija *et al.*	**2002**	DMPC	**79**
Ochoa *et al.*	**2003**	Erythrocytes of cardiopulmonary surgical patients	**147**
Bongiorno *et al.*	**2004**	Reversed micelles	**81**
Moroni *et al.*	**2004**	Pineal tissue grafting	**157**
Schaffazick *et al.*	**2005**	Melatonin loaded nanoparticles	**121**
Severcan *et al.*	**2005**	DMPC in multilamellar vesicle	**148**
De Lima *et al.*	**2007**	Egg phosphatidylcholine liposome	**83**
Aranda *et al.*	**2010**	Membrane isolated from liver	**150**
Garcia *et al.*	**2011**	Senescence accelerated mice	**22**
Yu *et al.*	**2016**	Cultured cell, isolated from pineal gland of Sprague-Dawley rat	**93**

8. MELATONIN: THE FUTURE AND THE EPILOGUE

Nature and evolution have furnished the tiny indole molecule, melatonin with utmost antioxidative property which becomes more realistic when mitochondria have been named as major site of its synthesis and metabolism among other organelles (159). Moreover, other than simple diffusion process, facilitation of melatonin transport within cells by glucose transporters and solute carriers provides this molecule more favour in order to maintain cellular system in homoeostasis (160). With assistance of those transporters, melatonin can

accumulate at an extremely high level in mitochondria. This high level of melatonin will maintain mitochondrial membrane potential at most favourable level. In addition, physiological homoeostasis conservation by controlling voltage gated channels and ion gradients have been verified as an obligatory action of melatonin (161). These unique characteristics of melatonin facilitate it in positioning at the apex of several remedies accessible for membrane associated disorders. This review attempts to present potency of melatonin in lessening severity of membrane damage and related disorders underlining its antioxidative and biophysical properties. However, currently, researchers have explored the potentiality of melatonin in diminishing rigorousness of cancer, emphasizing its ability to cross bilayer membrane through glucose transporters by which they can limit nutrient uptake by cancerous cells (162). Assimilation of melatonin through glucose transporters within prostate cancer cells also bring ray of hope in cancer treatment (163), which all require existence of healthy membrane bilayer. Hence, melatonin becomes esteemed *per se* as a familiar accessory in everyday's life by decoding complications of critical ailments.

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AUTHORSHIP

DB and AC contributed to conception, revised the manuscript critically and approved it. AB prepared, drafted and edited the manuscript and figure.

CONFLICT OF INTEREST

Authors declare no conflict of interests.

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