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Research Paper

The Role of Medicinal Plants in Protecting Mesenchymal Stromal Cells From Oxidative Stress

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Abstract— Recently, research has focused on mesenchymal stromal cells (MSCs) as one of the most important therapeutic products, which have been effectively used in the treatment of many diseases. However, the functionality and longevity of in vitro expanded MSCs are greatly affected by oxidative stress. Moreover, most of the transplanted MSCs are lost in few days following transplantation, due to the hypoxia and the presence of oxygen-free radicals in the transplant recipient, that increase aging factors. Therefore, strategies that protect MSCs from apoptosis and increase their resistance to oxidative stress are required for optimizing MSC-based therapy. It has been shown recently that some plant compounds can protect MSC from oxidative stress. Therefore, the present review highlights the role of medicinal plants in modulating oxidative stress in MSC. We hope that this review will provide additional information that will facilitate and improve MSC-based therapies.

Keywords— mesenchymal stem/stromal cells, oxidative stress, plant extracts, plant derived compounds, MSC apoptosis.

1. Introduction

Mesenchymal stromal cells (MSCs) are described as cells capable of forming colonies with fibroblast-shaped cells in culture [1].

Minimal criteria were proposed by The International Society for Cellular Therapy (ISCT) to identify human MSC: adhering to plastic surfaces, expression of CD105, CD90 and CD73, lack expression of CD45, CD34, CD19 or CD79a, CD11b or CD14 and HLA-DR surface molecules; and the ability to differentiate into adipocytes, chondroblasts and osteoblasts in vitro [2].

MSCs are easy to isolate from human donors or patients, and the MSCs culture can be rapidly expanded for ≥30 population doublings. Moreover, the differentiation of MSCs is simple under specific conditions. Due to these properties, MSCs have been widely used in therapeutic applications [3].

The use of MSC in therapeutic applications requires in vitro expansion to obtain sufficient cell numbers for treatment [1]. However, the longevity and functionality of in vitro expanded MSCs are greatly affected by oxidative stress (OS) [4]. Excessive reactive oxygen species (ROS) can cause oxidative damage to DNA in MSCs, thereby affecting cell adhesion, migration and proliferation [5], decrease MSC immunomodulation, and induce senescence [4]. Moreover, most of the transplanted MSCs are lost in few days following transplantation, due to the hypoxia and the presence of oxygen-free radicals in the transplant recipient, that increase aging factors and lead to apoptosis [6].

Therefore, strategies to protect MSCs from apoptosis and enhance their ability to counter oxidative stress are important for optimizing MSC-based therapy [7]. A new method under consideration is to precondition cells with different substrates with affinity for MSCs. One such method is the use of medicinal plants that have antioxidant activities [8]. Therefore, the present review highlights the role of medicinal plants in modulating oxidative stress in MSC.

2. Related Work

A previous review discussed the effect of oxidative stress on Leydig cells and the effects of different plant extracts on TM3 Leydig cells [9].

A previous study discussed the anti-oxidant effects of various plant extracts against H2O2-induced oxidative stress in both in-vitro and in-vivo models [10].

A previous study compiled the results of interesting studies that used cancer cell line models to evaluate the effects of plant-derived compounds in modulating oxidative stress [11].

3. Methodology

Data was obtained from online search using the keywords 'mesenchymal stem/stromal cells', 'oxidative stress', 'plant extracts', 'plant derived compounds', using online databases such as Google Scholar and PubMed.

4. Oxidative stress

Oxidative stress (OS) occurs due to an imbalance between oxidant and antioxidant compounds. Oxidant compounds include ROS, reactive sulfur species and reactive nitrogen species [12]. The generation of ROS in the body plays a key role in cellular signaling process. But when large amounts of ROS and free radicals are generated without any neutralization, oxidative damage to DNA, lipids and proteins occurs [13].

Superoxide anion, hydrogen peroxide and hydroxyl radical are the main types of ROS that react with macromolecules, causing cell dysfunction and tissue damage [14]. The reduction of intracellular ROS is regulated by the antioxidant defense mechanisms such as superoxide dismutases, glutathione peroxidases and catalases. The SOD enzyme plays an important role in eliminating ROS as it reduces superoxide (O2) to form hydrogen peroxide (H2O2). CAT enzyme catalyzes the breakdown of H2O2 produced by SOD into water and oxygen, protecting cells from the harmful effects of H2O2 [12]. However, in some cases, the antioxidant system may not be sufficient to maintain a redox balance and will easily reach saturation, causing permanent genomic damage and toxicity [11].

5. Induction of oxidative stress

Many compounds are used to induce oxidative stress in vitro, such as hydrogen peroxide (H2O2), tert-Butyl hydroperoxide (t-BHP), Monosodium iodoacetate (MIA) and hydroquinone [15]. The main harmful effects are caused by hydroxyl radical ($OH^{\cdot}$) produced by H2O2 and superoxide species ($O2^{-}$) produced in the presence of a redox active transition metal. H2O2 caused a decrease in cell viability by increasing the production of intracellular ROS, resulting in DNA damage and apoptosis [16]. t-BHP has been widely used as model inducer of oxidative stress in a many systems [17].

tBHP has two metabolic pathways, both cause oxidative stress. The first is provided by cytochrome P450 and leads to the generation of peroxyl and alkoxyl radicals. Another pathway uses glutathione peroxidase. tBHP is detoxified to tert-butanol and GSH is depleted to GSSG -its disulphide form- by oxidation [18]. MIA enhances the level of ROS and thus causes membrane potential changes, upregulates caspase-3 activity and enhances cytochrome c release which ultimately leads to apoptosis [15]. Hydroquinone can also redox cycle with its semiquinone radical and produce ROS. Hydroquinone cause cytotoxicity, immunotoxicity, and carcinogenicity, in addition to being immunosuppressive upon prolonged exposure. It also increases apoptosis, damages cellular molecules and increases oxidative stress [19].

6. Medicinal plants

Medicinal plants have been used for therapeutic purposes since ancient times [20]. Plants are important sources of antioxidants [21]. Recent studies have shown that plants can protect cells from oxidative stress, directly through antioxidant activity and/or by regulating the levels of endogenous antioxidant enzymes [22]. As seen in (figure 1), the number of publications, in the PubMed search on the effects of medicinal plants in modulating oxidative stress, has increased markedly over the past 10 years. This demonstrates the interest given to the study of bioactive compounds from plants and oxidative stress [11].

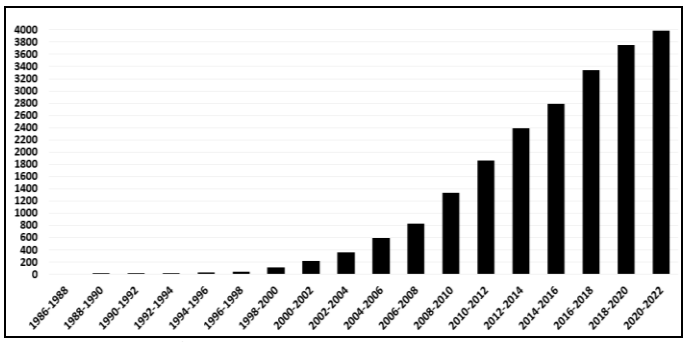

Figure 1. Number of publications related with plant extracts, oxidative stress

Polyphenols are secondary metabolites in plants. These plant-derived compounds have antioxidant effects that affect apoptosis and cell proliferation [23]. Therefore, oxidative stress in MSCs can be prevented by preconditioning with various plant-derived products [24]. Some of medicinal plants and plant derived products that can modulate oxidative stress in MSC are presented in table (1) and table (2).

Table 1. Some medicinal plants that protect MSCs from oxidative stress

Specie/ Family	Extract	Ox. Ag	MSC source	Effects	Ref
Cirsium setidens/ Asteraceae	water	H_2O_2	hADMSCs	The extract suppressed ROS production and increased MSCs survival	[3]
Sarcandra glabra/ Chloranthaceae	ethanolic	FeCl2 plus H_2O_2	rBMSCs (Sprague-Dawley rats)	The extract increased the survival of MSCs and prevented oxidative stress	[25]
Plastrum testudinis/ Testudinidae	ethanolic	H_2O_2	rBMSCs (Sprague-Dawley rats)	The extract repaired oxidative damage, and reduced LPO	[26]
Cladophora glomerata/ Cladophoraceae	methanolic	H_2O_2	eADMSC	The extract decreased oxidative stress, increased the antioxidant enzymes activities, and improved viability	[27]
Mori fructus-Mori ramulus/ Moraceae	aqueous	FeCl2 plus H_2O_2	rBMSCs	The extracts protected MSCs from •OH-induced damage	[4]
Ginkgo biloba/ Ginkgoaceae	-	H_2O_2	rBMSCs	The extract decreased cell death and reversed oxidative stress in diabetic rats	[28]

Ginkgo biloba/ Ginkgoaceae	-	H_2O_2	rBMSCs	The extract decreased oxidative stress and increased the survival rate of MSCs transplantation	[29]
Aesculus indica/ Sapindaceae	methanolic	MIA	hADMSC	The extract rescued MSCs against oxidative stress, enhanced viability, proliferation, reduced LDH activity and ROS release, and improved cell migration and SOD activity	[8]
Daphne mucronata/ *Thymelaeaceae*	methanolic	MIA	hADMSC	The extract increased the viability and proliferative of MSCs, decreased the LDH, ROS and increased SOD activity	[15]
Ginger/ Zingiberaceae	alcoholic	H_2O_2	rBMSC/ hADMSC	The extract increased the bioavailability of MSC and decreased apoptosis	[6]
encapsulated nanocurcumin-PEGOA/ Zingiberaceae	-	hydroquinone	hBMSCs	It improved the viability, reduced ROS, and the extent of LPO and increased the expression of CAT and hemeoxygenase-1	[13]
Curcumin/ Zingiberaceae	-	H_2O_2	hADMSC	The extract attenuated the oxidative stress	[30]
Mixture of vitamin D, lactobasillus rhamnosus, ginger, curcumin and Boswellia extract/ ginger, curcumin (Zingiberaceae)Boswellia (Burseraceae)	-	H_2O_2	hBMSCs	The extract reduced oxidative stress	[31]
Strawberry-Derived Exosome-Like Nanoparticles/ Rosaceae	-	H_2O_2	hADMSC	They improved MSC survival and prevented oxidative stress	[32]

Ox. Ag: oxidizing agent; **rBMSCs***:* rat Bone Marrow Mesenchymal Stromal Cells, **hBMSC**s: Human Bone Marrow Mesenchymal Stromal Cells, **hADMSC:** Human adipose tissue-derived MSCs, **eADMSC:** equine adipose mesenchymal stromal cells, **MIA**: monosodium iodoacetate, LDH: lactate dehydrogenase, **LPO**: lipid peroxidation, CAT: catalase, SOD: superoxide dismutase.

Table 2. Plant derived compounds that modulate oxidative stress in MSCs

Compound/ class	**Species/ family**	**Ox. Ag**	**MSC source**	**Effects**	**Ref**
Lycopene/ carotenoid	tomatoes/ Solanaceae	H_2O_2	hADMSC	The compound increased manganese SOD expression, decreased ROS levels and attenuated apoptosis	[33]
hydroxysafflor yellow A/ flavonoid	safflower (*Carthamus tinctorius* L.)/ Compositae	β-mercaptoethanol	MSC	The compound improved viability, maintained high level of SOD and GSH, reduced apoptosis and improved the ratio of Bcl/Bax	[34]
Leonurine/ alkaloid	Herba leonuri (traditional Chinese medicine)	H_2O_2	rBMSCs (Sprague-Dawley rats)	The compound decreased apoptosis, ROS, COX2 and NOX4 levels and enhanced the differentiation ability	[35]
Naringin/ flavonoid glycoside	*rhizoma drynariae*/ Polypodiaceae	H_2O_2	hADMSC	Naringin increased viability, reduced cytotoxicity and reversed oxidative stress	[36]
Berberine/ alkaloid	Chinese herb Huanglian	H_2O_2	rBMSCs (Sprague-Dawley rats)	The compound decreased apoptosis, ROS production and increased SOD activity	[37]
Saponins/ saponin	*Tribulus terrestris*/ Zygophyllaceae	H_2O_2	ADMSCs	The compound prevented apoptosis and protected MSCs against oxidative stress	[38]
a member of phytophenol family	*Maclura tinctoria* /Moraceae	Fenton system (Fe^{2+}+ H_2O_2)	rMSC	The compound protected DNA and MSCs against OH-induced damages	[5]
Artemisinin/ sesquiterpene endoperoxide	*Artemisia annua*/Asteraceae	H_2O_2.	rBMSCs (Sprague-Dawley rats)	The compound improved MSC survival, decreased apoptosis, ROS production, Caspase 3 activation, LDH release and increased antioxidant enzyme activities	[39]
Gigantol/ biphenolic compound	stem of *Dendrobium aurantiacum* /Orchidaceae	H2O2	rBMSCs (Sprague-Dawley rats)	The compound inhibited apoptosis	[40]
Geraniin/ Ellagitannin	*Geranium sibiricum* /Geraniaceae	H2O2	rBMSCs (Sprague-Dawley rats)	The compound promoted MSC survival, reduced ROS production and maintained mitochondrial function	[7]
Rosmarinic acid/ phenolic compound	*Blechnum binervatum* /Blechnaceae	H2O2	TMSC	The compound increased the viability and reduced cytotoxicity	[41]
Epigallocatechin-3-gallate/ polyphenolic compound	-	H2O2	hBMSCs	The compound prevented oxidative stress-induced cellular senescence in MSCs	[42]
Quercetin/ flavonoids	-	tBHP	rNPMSCs (Sprague-Dawley	The compound reduced oxidative stress-induced	[43]

			rats)	senescence	
Chlorogenic acid/ quinic acids and derivatives	-	H2O 2	rBMSCs (Sprague Dawley rats)	The compound protected MSCs against apoptosis and oxidative stress	[44]
7β-13-dihydroxypodocarpa-8,11,13-trien-15-oic acid/ abietic acid/ I. Tricyclic diterpenes	The resin from *Daemonorops draco*/Asterecaceae	tBHP	MSC	It decreased apoptosis and showed good recovery against oxidative stress	[24]
Eudesmane and Eremophilane /II.esquiterpenes	*Alpinia oxyphylla* Fruits/ Zingiberaceae	tBHP	mADMSC	The treatment reverted the damage of tBHP on MSCs and improved the viability	[45]

Ox. Ag: oxidizing agent; **rBMSCs***:* rat Bone Marrow Mesenchymal Stromal Cells, **hBMSC**s: Human Bone Marrow Mesenchymal Stromal Cells, **rNPMSCs:** rat nucleus pulposus-derived mesenchymal stromal cell, **hADMSC:** Human adipose tissue-derived MSCs, **TMSC**: Teeth Mesenchymal Stromal Cells, **mADMSCs**: mice adipose mesenchymal stromal cells, **tBHP**: tert-butyl hydroperoxide, **LDH**: lactate dehydrogenase.

7. What is the mechanism of action of medicinal plants in modulating oxidative stress in MSCs?

Most medicinal plants have been used for therapeutic purposes, but the precise mechanism of action on MSCs has been proven for only a few plant extracts [2]. It has been reported that the protection against oxidative stress is due to the ROS-scavenging effect (especially •OH scavenging) of phytochemicals [4].

However, several signaling pathways have been indicated as being involved in the mechanism of action, such as miR-34a/SIRT1 [43], mitogen-activated protein kinase (MAPK) [29], c-Raf-Erk1/2-p90rsk-CREB [39], Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) [8], phosphoinositide 3-kinase (PI3K) [44], PI3K/Akt [7, 33, 40], PI3K/Akt/mTOR pathways [35].

Nuclear factor-erythroid 2-related factor 2 (Nrf2) and p53/p21 have also been reported to be involved in the protective effect against oxidative stress-induced hMSCs senescence [42]. In addition, there is indication that FOXO subfamily (FOXO1, FOXO3, FOXO4, and FOXO6) represent main downstream targets of the PI-3K/AKT pathway in response to apoptotic stimulation, which is associated with inactivation of pro-apoptotic proteins and attenuation of ROS increase. A previous study suggested that chlorogenic acid can suppress the ROS increase by activation of Akt phosphorylation, and increase FOXO family genes and the expression of anti-apoptotic protein (Bcl-2) in MSCs cultured under oxidative stress [44].

8. Conclusion

Generally, this review showed that plant extracts and plant derived compounds can modulate the oxidative stress in MSCs. Although there are many studies that have identified the molecular pathways involved in the mechanism of action of plant compounds, further studies are still needed to precisely determine the mechanism and the optimal dosage of natural compounds, and also to prove these effects in vivo through clinical trials. We hope that this review will provide useful information that will improve MSC-based therapy.

Data Availability

Data are available from the corresponding author upon demand.

Statements & Declarations

"The authors declare that no funds, grants, or other support were received during the preparation of this manuscript."

Author's Contribution

The idea for the article was suggested by Dr. Ruba joujeh. The literature search was performed by Dr. Dima joujeh. Data analysis was performed by Dr. Ruba joujeh and Dr. Dima joujeh.

Conflict of interest

The authors declare no conflict of interest.

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