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Review

Anti-oxidant potential of plants and probiotic spp. in alleviating oxidative stress induced by H_2O_2

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ABSTRACT

Cells produce reactive oxygen species (ROS) as a metabolic by-product. ROS molecules trigger oxidative stress as a feedback response that significantly initiates biological processes such as autophagy, apoptosis, and necrosis. Furthermore, extensive research has revealed that hydrogen peroxide (H_2O_2) is an important ROS entity and plays a crucial role in several physiological processes, including cell differentiation, cell signalling, and apoptosis. However, excessive production of H_2O_2 has been shown to disrupt biomolecules and cell organelles, leading to an inflammatory response and contributing to the development of health complications such as collagen deposition, aging, liver fibrosis, sepsis, ulcerative colitis, etc. Extracts of different plant species, phytochemicals, and *Lactobacillus* sp (probiotic) have been reported for their anti-oxidant potential. In this view, the researchers have gained significant interest in exploring the potential plants spp., their phytochemicals, and the potential of *Lactobacillus* sp. strains that exhibit anti-oxidant properties and health benefits. Thus, the current review focuses on comprehending the information related to the formation of H_2O_2, the factors influencing it, and their pathophysiology imposed on human health. Moreover, this review also discussed the anti-oxidant potential and role of different extract of plants, *Lactobacillus* sp. and their fermented products in curbing H_2O_2-induced oxidative stress in both in-vitro and in-vivo models via boosting the anti-oxidative activity, inhibiting of important enzyme release and downregulation of cytochrome c, cleaved caspases-3, − 8, and − 9 expression. In particular, this knowledge will assist R&D sections in biopharmaceutical and food industries in developing herbal medicine and probiotics-based or derived food products that can effectively alleviate oxidative stress issues induced by H_2O_2 generation.

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1. Introduction

Oxidative stress refers to the disrupted equilibrium between the generation and accumulation of reactive oxygen species (ROS) within cells and tissues, and the capacity of the biological system to effectively neutralize and eliminate them [1]. The imbalance between elevated levels of reactive molecules and insufficient endogenous defence mechanisms results in impaired cellular structures and molecules such as lipids, proteins, and DNA. This process ultimately contributes to the development of various diseases, as supported by literature findings [2]. The scientific literature confirms that oxidative stress plays a crucial role in the pathogenesis of diverse diseases, encompassing gastrointestinal and hepatic diseases, atherosclerosis, infertility, neurodegenerative disorders, metabolic syndrome, diabetes, cancer, cardiovascular disease, and renal diseases [2]. This also increases free radicals and decreases anti-oxidant defence mechanisms [1]. Free radicals are oxygen-containing reactive molecules with unpaired electrons. Different free radicals include ROS, singlet oxygen, superoxide anions, hydroxyl radicals, and peroxides [1,3]. Mutations caused by nucleic acid interactions [both in the mitochondria (mtDNA) and in the nucleus (nDNA)] cause oxidative stress, causing DNA strand breaks [3]. The oxidation of lipids by ROS can damage phospholipid cellular membranes and result in cell death at an early stage. The oxidation of amino acids can occur due to interactions with proteins, changing their structure and affecting the ability of proteins to function enzymatically. They play an important role in various physiological processes in cells, such as redox signalling, and are a by-product of mitochondrial respiration [4–6]. The maintenance of appropriate signalling mechanisms in the human body necessitates crucial redox regulation [7]. The regulatory responses entail the interaction between ROS and the amino acid cysteine, which is present within proteins [7]. ROS are essential in regulating cellular proliferation and programmed cell death pathways, thereby maintaining proper control of the cell cycle [7]. Several kinases present in these pathways exhibit interactions with ROS. Among them is the apoptosis signal-regulated kinase 1 (ASK1), which functions as an upstream mitogen-activated protein kinase kinase (MAPKKK) [7]. Further, the ASK1 regulates the functioning of transcription factors like JNK and p38, which elicit the process of apoptosis through the phosphorylation of MAPKK4, MAPKK3, and cGMP-dependent protein kinase (PKG) [7]. Furthermore, the activation of protein kinase A (PKA) is facilitated by ROS, and it is known to play a vital role in mitogen-activated protein kinase (MAPK) signalling. The oxidation of cysteine, which is facilitated by ROS, has the potential to impede the activity of protein phosphatases, thereby hindering their ability to exert inhibitory effects on MAPK signalling [7]. As a result, the redox-dependent regulation extends to manage the transcription factors like p38. The maintenance of optimal growth factor signals is facilitated by the oxidation and consequent inhibition of protein tyrosine phosphatase (PTP) through ROS-mediated mechanisms [7]. The correlation between ROS and tyrosine phosphatases is consistent with the "redox window" theory. Within this framework, moderate levels of H_2O_2 activate tyrosine kinases by oxidising cysteine to sulfenic acid. Conversely, elevated ROS levels cause cysteine to be oxidised into sulfinic and sulfonic acids, which irreversibly modify the catalytic cysteine and lead to the complete inactivation of the phosphatase [8]. The phosphoinositide 3-kinase (PI3K) signalling pathway is another major pathway regulated via ROS through oxidation reactions. Generally, the body maintains ROS at a homeostatic level by ROS-derived products, which activate antioxidant defence genes through mechanisms like PI3K-NFE2-like2 (Nrf2)-antioxidant response element (ARE) signalling [9]. Ref-1, also referred to as redox factor-1, is an endonuclease that is controlled by transcription factors, including p53, nuclear factor kappa B (NFκB), activator protein 1 (AP-1), and hypoxia-inducible factor 1-alpha (HIF-α). Moreover, Upon exposure to ROS and subsequent oxidative stress, cytoplasmic Ref-1 translocates to the nucleus, enabling interactions between redox and transcription factors to initiate the antioxidant defence system [9].

The ROS entity H_2O_2 is particularly important due to its stable but weak reactivity and ability to produce free radicals [10–12]·H_2O_2 is less reactive without transition metal ions than hydroxyl ($OH^{\cdot}$) and superoxide anion (O_2^{-}) radicals and acts as a reducing and oxidising agent [10]. Although H_2O_2 does not easily oxidise proteins, lipids, or DNA, it is involved in numerous physiological processes, including differentiation (apoptosis), immunity mediation, signal transduction, cell growth, and maintenance [13]·H_2O_2 shows detrimental effects on cells when the concentration exceeds 50 μM, while concentrations between 20 μM and 50 μM are found to be comparatively less harmful. The impact of H_2O_2 on a biological system is influenced by several factors, which encompasses cell type, concentration, exposure duration, and physiological state [14,15]. It is noteworthy that H_2O_2 can act as a mediator in redox signalling processes within cells; however, excessive H_2O_2 expression often leads to oxidative damage of tissues and organs, potentially eliciting numerous inflammatory responses [16,17]. Moreover, in the presence of oxygen or redox metal ions like iron and copper (Fenton reaction), H_2O_2 can generate highly reactive OH free radicals [18]. As a result, anti-oxidants are crucial to scavenging free radicals from ROS. Moreover, changes in the endocellular redox status significantly impact immune cell activation and dysfunction [10].

Recent studies have demonstrated the effectiveness of phytochemicals (secondary metabolites) in controlling inflammation [19]. Once considered "health-promoting," these compounds can scavenge free radicals or exert direct anti-oxidant effects on cellular biomolecules. Nevertheless, reactive species have been reported to disrupt cellular functions by interfering with vital signalling pathways within cells [20]. In addition, recent research has demonstrated that these molecules interact with receptors, transcription factors, and enzymes [21,22]. *Bifidobacteria* and *Lactobacilli* Probiotic strains have also been shown to possess antioxidative properties [23]. Probiotic strains may release metabolites that promote antioxidative activity. Probiotic metabolites have increased liver antioxidative enzymes and serum antioxidative activity in in-vivo studies [24]. In order to reduce the effects of oxidative stress, probiotic strains, and their fermented products might be considered potential dietary supplements.

Considering the above challenges and complications, this review summarised the general knowledge about H_2O_2 formation, the factors that influence it, and its pathological consequences for humans. It also the anti-oxidant potential and role of plant spp. extract and *Lactobacillus sp.*, and their fermented products in alleviating in vitro and in vivo H_2O_2-induced oxidative stress.

2. Formation of H_2O_2 and factors affecting its production

In addition to $OH^{\cdot}$ radicals and superoxide anion ($O_2^{\cdot-}$), H_2O_2 is a significant component of the ROS group and is a by-product of cellular metabolism [12,25,26]. It is formed in the respiratory chain cascade, and its reactivity targets the lipids, proteins, and DNA as components of ROS, causing oxidative stress [27–29]. Even though H_2O_2 is considered cytotoxic, excessive production has been linked to several fatal diseases. As a second messenger, H_2O_2 plays a vital role in cellular signalling [13, 16,30]. Apart from being generated endogenously in several cellular components like peroxisomes, mitochondria, and endoplasmic reticulum, H_2O_2 is also produced when oxygen is highly utilized. It represents the simplest form of peroxide, characterized by the presence of two oxygen atoms covalently bonded together [11].

Numerous studies have demonstrated that H_2O_2 is a metabolite of $O_2^{\cdot-}$; it acts as a substrate for $OH^{\cdot}$ radical production during cellular metabolism and is formed in the mitochondria during cellular respiration [11,12,30]. Among the most important ROS components are the $O_2^{\cdot-}$ radical (half-life of 10^{-6} s), $OH^{\cdot}$ radical (half-life of 10^{-10} s), and H_2O_2 (stable half-life) [11]. The stable half-life of H_2O_2 makes it non-radical (without transition metal ions). The reactivity of this compound is increased when it is combined with a transition metal ion to form an $OH^{\cdot}$ radical (Fenton reaction) or with $O_2^{\cdot-}$ to form an OH radical (Haber-Weiss

reaction) [18].

peroxidase and catalase), H_2O_2 cannot be detoxified or hydrolysed.

Fenton Reaction

$$Fe^{3+} + O_2^{\cdot-} \longrightarrow Fe^{2+} + O_2 \quad \text{(Auto-oxidation)} \quad (1)$$

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH^{\cdot}$$

Haber- Weiss Reaction

$$Fe^{3+} + O_2^{\cdot-} \longrightarrow O_2 + OH^- + OH^{\cdot} \quad (2)$$

Fenton reaction is initiated by the superoxide radical produced by cellular metabolism. Oxygen (O_2) and erroneous electrons interact to produce (unstable) $O_2^{\cdot-}$, an important component of ROS. In response to an increase in metabolic rate, $O_2^{\cdot-}$, a non-enzymatic substance that oxidises cellular components, is produced more frequently. In cells, low levels of $O_2^{\cdot-}$ can be maintained due to the ability of the metalloprotein enzyme SOD to catabolise $O_2^{\cdot-}$ to H_2O_2, which is then catabolised (detoxified) by the enzymes GPx and catalase to oxygen and water [11].

An electron transport chain (ETC) comprises electron transporters embedded in the mitochondrial membrane. These transporters facilitate the movement of electrons from nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) to molecular oxygen (Fig. 1). Oxygen is oxidised to form water at this stage. Protons are pushed to the intermembrane space from the mitochondrial matrix. The level of $O_2^{\cdot-}$ may occasionally increase after alcohol dehydrogenase (ADH) metabolises alcohol, and NAD^+ produces significant amounts of NADH [10]. Due to the limited supply of enzymes (glutathione

Further, it also interacts with iron (Fe^{2+}) and copper (Cu^+), the transition metal ions present in cells such as ceruloplasmin and ferritin, producing the OH radical, an extremely unstable molecule [31,32]. However, in the Haber-Weiss reaction mechanism, the $OH^{\cdot}$ radical is generated by the reaction of H_2O_2 and $O_2^{\cdot-}$ and is catalysed by iron (Equation 2) [22]. Various studies have demonstrated that H_2O_2 is a major contributor to the generation of $OH^{\cdot}$ radicals that cause oxidative stress and cellular damage [32]. Because of its neutral state, the neutral form of ROS is highly reactive and has a short half-life of approximately 10^{-10} seconds. This unstable molecule has been linked to cellular dysfunctions, alterations, and cell death [33,34].

3. Brief description of the role of H_2O_2 in pathological processes

3.1. Immune responses and collagen deposition

The induction of cytokines and growth factors involves the

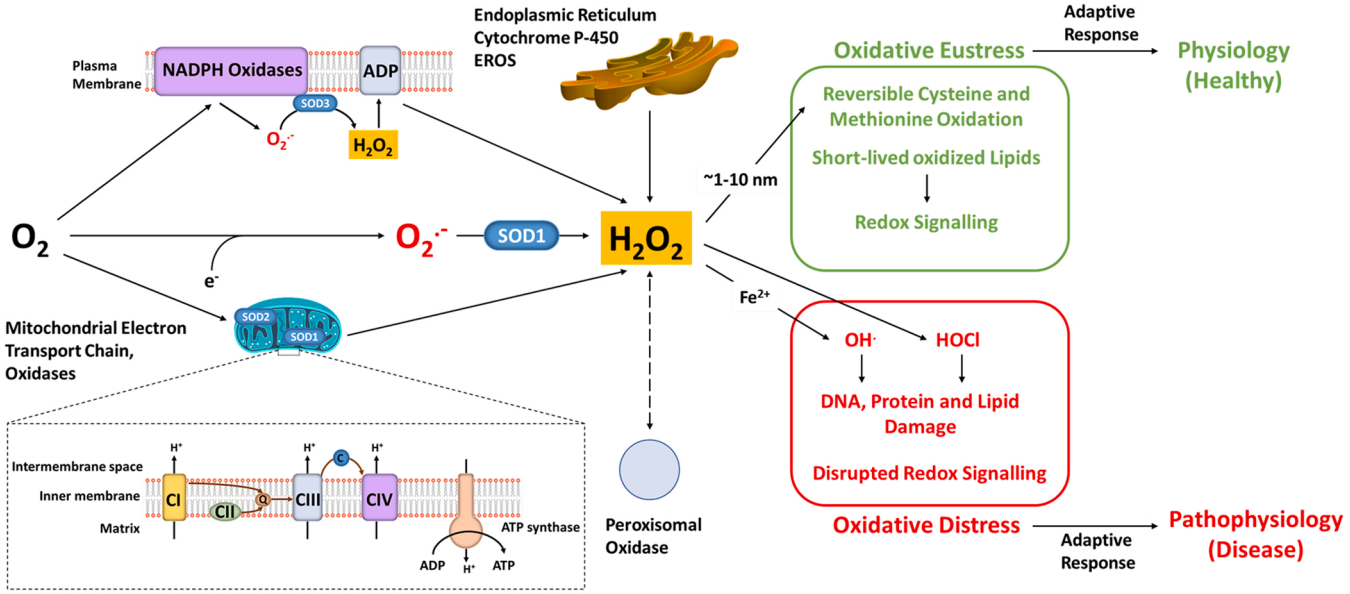

Fig. 1. An illustration of the pivotal role played by hydrogen peroxide (H_2O_2). Left Upper Side: Illustration of endogenous H_2O_2 sources, such as NADPH oxidases and other oxidases (membrane-bound or free), as well as mitochondria. Superoxide radicals (anion) are converted to H_2O_2 via three superoxide dismutases, namely SODs 1, 2, and 3. H_2O_2 diffuses across cell membranes via specific aquaporins called peroxiporins. The right top in green represents redox signalling induced by oxidative eustress or physiological oxidative stress. The right bottom in red represents excessive oxidative stress, which leads to oxidative damage to biomolecules, oxidative distress, and disruption of redox signalling.

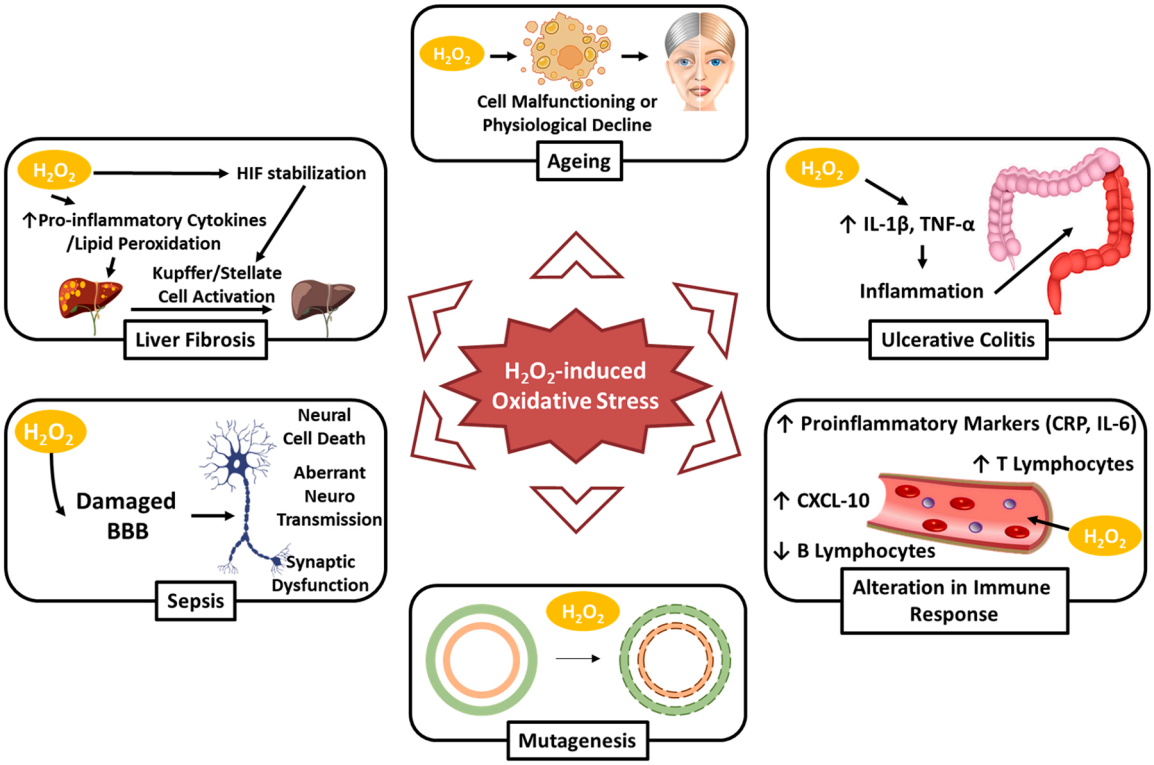

Fig. 2. Diagram illustrating the major detrimental effects of H_2O_2 on the human body.

expression of various molecules by hydrogen peroxide (H_2O_2). This includes connective tissue growth factor, acute phase cytokine interleukin-6 (IL-6), and transforming growth factor-beta (TGF-β) (Fig. 2) [35–39]. Additionally, H_2O_2 is involved in the mechanisms of action of several cytokines and growth factors [40,41]. As a result, autocrine and paracrine loops are formed where one ROS leads to the generation of other ROS [42]. However, the effects of the same ROS can vary depending on the cell type. For example, H_2O_2 induced by TGF-β1 inhibits epithelial cell proliferation, while H_2O_2 acting as a second messenger induced by platelet-derived growth factor (PDGF)-BB promotes cell proliferation [40,43]. In situations such as tumour necrosis factor (TNF)-α-induced apoptosis, H_2O_2 plays a significant role in cell death [44]. Furthermore, inflammatory cells can induce trans halogenation reactions at sites of inflammation via H_2O_2, Br- (Cl-) ions, and myeloperoxidase, leading to the mutagenic and cytotoxic bromination (chlorination) of nucleotides [45–47]. Moreover, H_2O_2 is involved in the excessive collagen deposition by myofibroblasts mediated by acetaldehyde- and TGF-β1 due to the up-regulation of the col1a1 gene [35,36].

3.2. Aging

In general, both H_2O_2 and oxidative stress contribute to aging. The direct contribution of H_2O_2 to its pathophysiology is poorly understood [48]. Studies conducted with cultured cells, where ROS replicate and accelerate age-related changes, have concluded that H_2O_2 is a causal agent of aging [48]. Human diploid fibroblasts undergo biochemical and morphological changes consistent with aging during three days of subtoxic H_2O_2 exposure. Among these changes are increased stress fibers and changes in paxillin and vinculin distribution. Rather than being restricted to the edges of cells, these proteins disperse randomly throughout the body. It has been hypothesised that TGF-β, retinoblastoma protein (Rb), and the need for de novo protein synthesis all contribute to these morphological alterations that simulate aging [49]. The endothelial cells of the umbilical vein undergo the following changes after being exposed to H_2O_2: the rearrangement of F-actin, the movement of filamin from the membrane to the cytosol, the formation of intercellular gaps, the drop in cyclic adenosine monophosphate (cAMP) levels, and the rise in phosphatidylinositol 4,5-bisphosphate levels in a Ca^{2+} dependent manner (PIP2). All of these approaches work to block the H_2O_2-dependent alterations in the cytoskeleton, such as inhibitors of phospholipase C, inhibitors of phosphoinositide turnover, or peptides that bind PIP2 with synthetic peptides [50].

Human mesenchymal stem cells (hMSCs) have the self-renewal ability and the potential to differentiate into different cell types, making them promising for cell therapy and regenerative medicine [51,52]. *In-vitro* studies have shown that hMSCs can undergo stress-induced premature senescence when exposed to oxidative stress or ionizing radiation [53–58]. Prematurely senescent hMSCs exhibit similar molecular and functional characteristics to replicative senescent cells, including enlarged flat morphology, irreversible cell cycle arrest, and increased senescence-associated β-galactosidase activity [59,60]. Under standard culture conditions, hMSCs have a limited capacity for cell divisions. To investigate the mechanisms and characteristics of cellular senescence and aging in hMSCs, H_2O_2 treatment is commonly employed as a model to assess susceptibility to oxidative stress. Accumulating evidence suggests that hMSCs can manage oxidative stress induced by H_2O_2 [56,61]. Recent findings indicate that hMSCs derived from the endometrium undergo premature senescence in response to H_2O_2-induced oxidative stress. This senescence is accompanied by cellular changes like upregulation of p21, loss of proliferative potential, and irreversible cell cycle arrest. Additionally, it has been observed that the resistance of hMSCs to H_2O_2 correlates with increased expression of genes encoding enzymes involved in ROS elimination, like cytosolic superoxide dismutase, mitochondrial superoxide dismutase, and glutathione peroxidase 1 [56]. These findings align with reports demonstrating high antioxidant activity in hMSCs and other cell types like mouse embryonic stem cells [61,62]. This antioxidant activity is ascribed to the upregulation of stress-inducible and antioxidant genes, conferring greater resistance to oxidative stress in contrast to differentiated cells [62]. However, recent studies have reported that certain types of hMSCs with low antioxidant

Table 1
In vitro studies using cell lines that demonstrate anti-oxidative properties of plant species against H_2O_2-induced oxidative stress.

Cell line used	Plant species and forms used	Dose	H_2O_2 dose	Positive effects	Refs.
Caco-2	*Cornus sericea* (red-osier dogwood) and leaves extract	100 μg/ml	1.0 mM	↑ Cell viability, HO-1, SOD, GSH-Px, Nrf-2, ZO-1, and claudin-3	[134]
	Fengdan bai (tree peony) and flower extract	0.5, 1, 10, 50, and 100 μg/ml	0.8 and 2.0 mM	↑ GSH-Px, SOD, ZO-1, and claudin-3	[135]
	Terminalia ferdinandiana (salty plum) and aqueous extract	10, 25, 50, 100, 200, and 400 μg/ml	10, 25, 50, 100, 200, and 400 μM	↑ *SOD-2* ↓ *iNOS*, *sICAM*, and *COX-2*	[136]
HEK-293	*Artabotrys odoratissimus* Blume (ylang-ylang vine) and stem and bark ethanol extract	62.5, 125, 250, 500, and 1000 μg/ml	1.0 mM	Cell viability > 70% Reduction in nitric oxide concentration	[137]
	Phyllanthus phillyreifolius and aerial acetone and ethanol extracts	31.25, 62.5, 125, and 250 μg/ml	100 μM	↑ SOD-2	[138]
	Moringa oleifera (drumstick) and branches and leaves aqueous extract	15.6, 31.3, and 62.5 μg/ml	1.0 mM	↑ *Bcl-2* and *Bcl-xL* ↓ *Caspase 3*, *BAX*, *p53* Cleaved caspase 9, cytochrome c and *PARP*	[139]
HepG2	*Alternanthera sessilis* Red and leaves ethanol and ethyl acetate extract	15.63, 31.25, 62.50, 125, 250, and 500 μg/ml	400 μM	↓ ROS × Lipid peroxidation	[140]
	Asparagus officinalis L. (green asparagus) and root extract	0.03125, 0.0625, 0.125, 0.25, 0.5, and 1 mg/ml	500 mM	× LDH leakage	[141]
	Coix lacryma-jobi L (adlay) and seed extract	0.2, 0.3, 0.4, and 0.5 mg/ml	0.2 mM	↑ GSH-PX, γ-GCS, CAT, GCLC and HO-1	[142]
	Carica papaya L. (papaya) and seed methanol and hexane extracts	50, 100, 250, and 500 μg/ml	500 μM	↑ SOD, CAT, GPx, activities and GSH	[143]
PC12	*Hypericum perforatum* L. (St John's wort) and flavonoid-rich extract	3.125, 6.25, 12.5, 25, and 50 μg/ml	300 μM	↑ Cell viability ↓ LDH release	[144]
	Glechoma hederacea L. (ground ivy) and whole plant water extract	3.125, 6.25, 12.5, 25, and 50 μg/ml	75 μM	× Release of cytochrome c and AIF ↓ MDA	[145]
IMR32	*Bacopa monnieri* (water hyssop) and whole plant methanol, ethanol and water extracts	1.5, 3.1, 6.25, 12.5, 25, and 50 μg/ml	250 μM	Alleviated the expression of NF200, HSP70, and mortalin	[146]
HT22	*Perilla frutescens* Bitton var. acuta Kudo (Korean perilla) and polysaccharide extract	31.25, 62.5, 125, 250, and 500 μg/ml	500 μM	↑ SOD, PARP, and Bcl-2 ↓ MDA, Bax, and cytochrome c Cleaved caspases-3, − 8, and − 9	[147]
C6 glioma	*Nardostachys jatamansi* (Indian nard) and rhizome methanol, ethanol and water extracts	1.5, 3.1, 6.25, 12.5, 25, and 50 μg/ml	125 μM	↑ CAT, Cu-ZnSOD, GPx, and GSH ↓ GFAP, HSP70, and mortalin	[148]
SH-SY5Y	*Fructus Ligustri Lucidi and fractions of* chloroform, ethyl acetate, n-butanol, and water	NS	1 mM	↑ GSH and anti-oxidant enzymes ↓ Caspases-3	[149]

SOD, superoxide dismutase; HO-1, heme oxygenase 1; GSH-Px, glutathione peroxidase; Nrf-2, nuclear factor (erythroid-derived 2)-like 2; ZO-1, zonula occludens-1; iNOS, inducible nitric oxide synthase; sICAM, soluble cell adhesion molecule; COX-2, cyclooxygenase-2; Bcl-2, B-cell lymphoma 2; BAX, bcl-2-like protein 4; Bcl-xL, B-cell lymphoma-extra-large; p53, tumour protein 53; PARP, poly (ADP-ribose) polymerase; ROS, reactive oxygen species; LDH, lactose dehydrogenase; CAT, catalase; γ-GCS, γ-glutamylcysteine synthetase; GCLC, gamma-glutamylcysteine synthetase; AIF, apoptosis-inducing factors; MDA, malondialdehyde; NF200, neurofilament protein 200; HSP70, heat shock protein; Cu-ZnSOD, Copper- and zinc-containing superoxide dismutase; GPx, glutathione peroxidase; GSH, glutathione; GFAP, glial fibrillary acidic protein; NS, not specified

enzyme activity exhibit increased sensitivity to H_2O_2 exposure [55,63]. For example, human umbilical cord blood-derived MSCs are particularly susceptible to oxidative stress and ionizing radiation, but their sensitivity can be mitigated by exogenous supplementation of antioxidants in the culture media [55]. Additionally, treatment of hMSCs with polyphenols or other antioxidants can repress intracellular free radicals to protect cells from H_2O_2-induced DNA damage and augment antioxidant enzyme activities, providing a potential strategy to maintain hMSC potency and viability for clinical applications [64].

3.3. Liver fibrosis

Oxidative stress, particularly involving H_2O_2, plays a substantial role in the development of liver cirrhosis in humans and animals [65–67]. In rats fed alcohol, liver response to oxidative stress occurs prior to fibrosis. Choline-deficient rats, prone to liver fibrosis and hepatocarcinoma, showed mitochondrial dysfunction characterized by reduced NADH-dependent oxygen consumption and increased H_2O_2 production. These findings underscore the involvement of H_2O_2 and oxidative stress in liver cirrhosis progression [68]. Alcohol causes the liver to respond to oxidative stress in several different ways. 1) The primary enzyme in ethanol metabolism, alcohol dehydrogenase, produces acetaldehyde, which increases the build-up of H_2O_2 by an unknown mechanism. Due to this ROS, hepatic stellate cells can activate both types I collagen genes in in-vitro conditions [36]. Moreover, H_2O_2 plays an important role in the control of TGF-1 expression, thereby forming an autocrine fibrogenic loop [69]. 2) In the presence of Fe^{2+} or Cu^{+}, H_2O_2 is converted to OH radicals, which result in lipoperoxidation and the production of many aldehydes, including malondialdehyde (MDA) 4-hydroxynonenal. These aldehydes have the same effect as acetaldehyde in enhancing collagen gene expression and H_2O_2 production in cultured fibroblasts and hepatic stellate cells [70–72]. 3) Ethanol metabolite acetaldehyde leads to hepatic cell damage that triggers an inflammatory response. Kupffer cells are stimulated, and inflammatory cells are attracted to the injury site. As a result, these inflammatory cells produce TGF-1, a fibrogenic cytokine that utilises H_2O_2 as a second messenger and ROS via the NADPH oxidase [35,43,73–75]. 4) Chronic liver damage increases iron reserves, which exacerbate liver damage when combined with H_2O_2 produced during the metabolism of ethanol [66]. Over the long term, ethanol consumption leads to a hypermetabolic state and an increase in oxygen consumption. Since H_2O_2 is produced as a by-product of the mitochondrial respiratory chain, increased O_2 consumption may lead to excess production of H_2O_2. Glutathione levels in mitochondria may be reduced by ethanol, which may significantly increase this toxicity [76,77].

Table 2
In vitro studies using cell lines that demonstrate anti-oxidative properties of plant phytocompounds against H_2O_2-induced oxidative stress.

Cell line used	Phytocompounds used	Dose	H_2O_2 dose	Positive effects	Refs.
C6 astrocyte	Resveratrol	100 μM	1.0 mM	↑ HO-1, and extracellular GSH	[154]
HUVEC	Resveratrol	50 μM	100 μM	↑ Endothelial SirT1	[155]
TM3 Leydig cells	Resveratrol	5–100 μM	300 and 600 μM	↑ Cell membrane integrity, and lysosome activity	[156]
HLEB-3 cells	Resveratrol	2.5–25 μM	100 μM	↑ HO-1, SOD, and CAT	[157]
IMR-90 cells	Tannic acid, gallic acid, ellagic acid, and propyl gallate	10 μg/ml	200 μM	Suppressed 8-oxoguanine	[158]
HepG2	Quercetin	10, and 100 μM	800 μM	Chelated the Cu^{2+}	[159]

HO-1, heme oxygenase 1; GSH, glutathione; SirT1, silencing information regulator; SOD, superoxide dismutase; CAT, catalase

3.4. Ulcerative colitis

Colonocytes, which are colon epithelial cells, can transport extracellular H_2O_2 via their cell membrane [78]. The oxidative degradation of tight junction proteins in the colonic epithelium plays a significant role in colonic inflammation and ulcerative colitis. This process is facilitated by the distinctive characteristics of H_2O_2, like its strong oxidizing potential, chemotactic attraction of neutrophils, ability to permeate cell membranes, and long lifespan [79]. Evidence from different studies demonstrates that the induction of ulcerative colitis in humans and animals occurs on exposure to H_2O_2 in the colon [80,81]. Animals lacking glutathione peroxidase that cannot neutralise H_2O_2 develop a build-up of H_2O_2 in the colon and develop ulcerative colitis, similar to human ulcerative colitis [82].

3.5. Sepsis

Almost all of the energy required to power increased metabolic activity, a hallmark of critical illnesses such as sepsis, is provided by adenosine triphosphate (ATP) [78]. The majority of cellular ATP is generated via oxidative phosphorylation, a process that produces H_2O_2 as a by-product in the ETC reaction. Usually, the presence of H_2O_2 is proficiently eliminated. However, during unexpected and significant increases in cellular bioenergetic demands, the cell experiences a substantial influx of H_2O_2 that must be promptly neutralized to prevent its accumulation and subsequent cell death.

In a hypermetabolic condition, prolonged supraphysiological H_2O_2 production may overwhelm the cellular reductive (antioxidant) mechanisms, increasing H_2O_2 levels in tissues and blood [78]. A build-up of H_2O_2 in the body can harm cells and result in severe bioenergetic malfunctions. Prolonged exposure to H_2O_2 has been reported to disrupt redox homeostasis, which eventually results in the breakdown of cellular balance. This imbalance can also lead to potentially fatal septic shock, microvascular dysfunction, and organ failure [78]. Evidence of glutathione depletion, the key agent responsible for reducing H_2O_2, in skeletal muscle and lung suggests that these organs have transitioned into net generators of H_2O_2. This may account for increased blood H_2O_2 in sepsis [83,84]. Whole blood reductive capacity (ability to eliminate H_2O_2) is decreased due to elevated systemic H_2O_2 production [85]. The loss of systemic reductive ability portends a poor prognosis according to a study that found significantly lower levels of erythrocyte glutathione in no survivors of sepsis compared to survivors ($p < 0.0001$) [86].

3.6. Cancer

Accruing experimental evidence indicates that an elevation in cellular H_2O_2 concentration can contribute to cancer hallmarks [87]· H_2O_2 is known to be associated with mutations, genetic instability, and DNA damage [88–93]. The induction of DNA damage by H_2O_2 is thought to be interceded by OH·generated during the Fenton reaction [88,92,93]. Numerous studies have shown that H_2O_2 can trigger cell proliferation, promote angiogenesis and invasion, and confer resistance to apoptosis and metastasis [94–102]. In fact, these studies have shown that increasing levels of detoxifying enzymes of H_2O_2 inhibit invasion, attenuate cell proliferation, metastasis, and angiogenesis, and enhance apoptosis. The initiation of hypoxia-inducible factor-1α (HIF-1α) by means of H_2O_2 also contributes to the underlying mechanisms of these cancer hallmarks. Evidence suggests that major oncogenic and tumour-suppressor pathways converge on HIF-1α activation, which in turn plays a crucial role in angiogenesis, invasion/metastasis, immortalization, and apoptosis resistance [103–107]. Therefore, it can be concluded that the overexpression of HIF-1α in different human cancer types is linked with increased patient death [104,105,108].

H_2O_2 is also reported to play a critical role in carcinogenesis, which is supported by experiments showing that cancer cells often exhibit elevated H_2O_2 levels [94,109–111]. For example, the study by Szatrowski and Nathan [109] stated that multiple cell lines of the tumour, presenting different tissue types, consistently produce notable amounts of H_2O_2. They noted that the expanding amount of H_2O_2 generated by these tumour cells over 4 h was comparable to the amount generated by an equivalent number of phorbol ester-stimulated neutrophils. It has also been unveiled that H_2O_2 can induce transformation in malignant

Table 3
In-vitro studies using cell lines demonstrate the anti-oxidative activity of probiotic sp. in the presence of H_2O_2-induced oxidative stress.

Cell line used	Probiotic species and forms used	Dose	H_2O_2 dose	Positive effects	Refs.
HUVECs	*L. plantarum*	7000 cells	800 μM	↑ SOD ↓ iNOS, MDA, caspases-3, − 9 × Changes in mitochondrial permeability	[172]
IPEC-J2	*L. rhamnosus* GG (exopolysaccharides)	1.25, 2.5, 5, 10, 25, 50, 100, and 200 μg/ml	200 μM	↑ ZO-1, occludin, claudin-1, and Nrf2 ↓ Caspase-3, Bax/Bcl-2 ratio, and Keap1	[173]
HT-29	*L. asei zhang*, *L. rhamnosus*, *L. gasseri* and *L. acidophilus* (surface layer protein)	25, 50, 100, and 200 μg/ml	800 μM	↑ SOD and CAT ↓ MDA	[174]
3A-sub-E cells	*L. crispatus* (extracellular vesicles)	10^{10} particles/ml	500 μM	↑ Mitochondrial fusion	[175]
H-29, and SH-SY5Y	*L. plantarum* 200655 (heat-killed)	10^7-10^8 cfu/well	500 μM	↑ BDNF, TH ↓ Bax/Bcl-2 ratio	[176]

SOD, superoxide dismutase; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; ZO-1, zonula occludens-1; CAT, catalase; BDNF, brain-derived neurotrophic factor; BAX, bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2

tumours and that the elevated expression of detoxifying enzymes of H_2O_2, such as glutathione peroxidase or catalase, can inverse the malignant phenotype in cancer cells [112–117]. For instance, introducing the ROS-generating system Nox1 into normal NIH3T3 fibroblasts led to the development of malignant characteristics in these cells, which led to the formation of tumours in the athymic mice model. The transformed cells demonstrated a significant 10-fold increase in H_2O_2 levels. However, the introduction of human catalase into these transformed cells resulted in a reduction of H_2O_2 concentration. This reduction was accompanied by the restoration of normal cell morphology, normalization of the growth rate, and the absence of tumour formation in a mouse model lacking T cells [114]. These compelling findings strongly indicate that H_2O_2 plays a crucial role in carcinogenesis.

4. Anti-oxidant potential of extracts from plants spp

Plant polyphenols, characterized by hydroxyl groups binding to aromatic rings, are secondary metabolites found in higher plants, embracing edible ones [118]. They are classified into flavonoids (anthocyanidins, chalcones, flavanones, flavones, flavanols, and flavonols) and non-flavonoids (tannins, saponin, phenolic acids, and stilbene). The antioxidant activity of plant polyphenols has attracted significant attention owing to their potential to fight oxidative stress-related diseases. Numerous studies have demonstrated the antioxidative effects of plant polyphenols against various oxidative stress conditions [118–120]. Etsassala et al. [121] identified abundant terpenoids, particularly abietane diterpenes, and triterpenes, in the methanolic extract of Salvia africana-lutea. This extract exhibited potent antioxidant and antidiabetic properties in in-vitro conditions, signifying its potential for preventing or alleviating symptoms of diabetes mellitus. Hyperglycemia-induced oxidative stress contributes to vascular damage and inflammation associated with atherosclerosis [122]. Song et al. [123] demonstrated that *Carpinus turczaninowii* extract reduced inflammation and attenuated the arterial damage induced by high glucose levels. The extract contained various phenolic compounds, including ellagic acid, myricitrin, and quercetin, exhibiting antioxidant and anti-inflammatory properties.

Aprile et al. [124] evaluated the total polyphenolic content and the antioxidant potential of olive fruits from the "Cellina di Nardò" cultivar, a widespread olive tree variety in Southern Italy. They found that fully matured olives had the highest polyphenol content, indicating that this stage is optimal for obtaining table olives with high polyphenolic levels. However, treatments employed to remove bitterness and stabilize olives for consumption led to a loss of phenolic substances and antioxidant activity. Martínez et al. [125] explored the use of olive fruits hydroxytyrosol extract as a preservative for patties made from fish. Chen et al. [126] provided evidence that almond skins derived polyphenols have the ability to provide protection against cardiovascular disease triggered by oxidative stress. The consumption of almond skin polyphenols was found to enhance the activity of antioxidant enzymes and inhibit the oxidation of low-density lipoprotein, which is known to play a significant role in the development of cardiovascular diseases. Alzheimer's disease, another chronic condition associated with oxidative stress, has been studied in relation to the protective effects of polyphenols [127]. Diaz et al. [128] explored the in-vivo protective properties of epicatechin against neuronal damage induced by oxidative stress. They observed that administering epicatechin resulted in a decrease in neurotoxicity, oxidative stress, and inflammation in the hippocampus of rats that were injected with Aβ25–35. The treatment also improved spatial memory function and reduced neuronal death in the hippocampus region, i.e., Cornu Ammonis 1 (CA1).

Tea is widely recognized for its preventive properties against chronic diseases, mainly attributed to the antioxidant potential due to the presence of polyphenolic constituents [129]. Currently, researchers are focussing on investigating the chemical composition and bioactive properties of tea, with particular emphasis on the wide range of tea varieties grown under different soil and climatic conditions. These environmental factors have been found to significantly impact tea's characteristics and beneficial effects [129]. Tang et al. [130] conducted a study in which they extracted fractions of polyphenolic compounds from 30 varieties of Chinese teas. The antioxidant capacity of these fractions was evaluated, revealing that oolong and yellow teas have high antioxidant potential and higher levels of polyphenols, including catechins such as epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate; in contrast to black, white and dark teas.

5. Role of plant species in ameliorating H_2O_2-induced oxidative stress in vitro and in vivo

5.1. Role of plant extracts

Pandareesh et al. [131] conducted a study to evaluate the cytoprotective properties of *Bacopa monniera* extract (BME) against oxidative stress induced by H_2O_2 in PC12 and L132 cells. The study demonstrated that BME exhibited significant antioxidant activity, with IC_{50} values of 226.19, 15.17, 30.07, and 34.55 μg/ml against ROS in different cell types. BME also showed protective effects against H_2O_2-induced damage to mitochondrial and plasma membranes in both cell lines, as evidenced by MTT and lactate dehydrogenase leakage assays [131]. Harishkumar et al. [132] investigated the cardioprotective activity of the methanolic leaf extract of *Nelumbo nucifera Gaertn.* against H_2O_2-induced oxidative stress in H9c2 cells. The study revealed that pre-treatment with *N. nucifera* extract at a concentration of 50 μg/ml effectively mitigated H_2O_2-induced oxidative stress in cardiomyocytes, as indicated by the estimation of antioxidants, DNA fragmentation, and lipid peroxidation assay [132]. Sreelatha and Padma [133] examined the protective effects of *Moringa oleifera* leaf extracts against H_2O_2-induced DNA damage, cytotoxicity, and lipid peroxidation in human tumour KB cells. The leaf extracts exhibited significant inhibition of lipid peroxidation and enhanced the activity of antioxidative enzymes, such as catalase (CAT) and superoxide dismutase (SOD) (Table 1). Furthermore, the extracts reduced the incidence of DNA damage and increased the viability of oxidant-stressed KB cells, indicating their cytoprotective activity. These effects were ascribed to the antioxidant properties of phenolic compounds present in the extracts [133].

Ajila and Rao [150] investigated the protective effects of peel extracts from unripe and ripe mango fruits (varieties: Raspuri and Badami) against H_2O_2-induced oxidative damage in rat erythrocytes. The mango peel extract exhibited a dose-dependent inhibition of oxidative haemolysis and protected against membrane protein degradation and morphological changes induced by H_2O_2. The IC_{50} values for inhibition of lipid peroxidation on erythrocyte ghost membrane ranged from 4.5 to 19.3 μg gallic acid equivalents [150]. Sam et al. [151] studied the protective effects of *Zingiber zerumbet* rhizome ethyl acetate extract against H_2O_2-induced damage in red blood cells (RBCs) isolated from male Sprague-Dawley rats. The study demonstrated that pre-treatment with the extract at a concentration of 6.25 μg/ml significantly reduced the percentage of haemolysis and oxidative damage, as indicated by decreased levels of malondialdehyde (MDA) and protein carbonyls (PC) in H_2O_2-treated RBCs. Further, the electron microscopic examination confirmed the protective effects of the extract on H_2O_2-induced morphological changes in RBCs. The major constituent of the extract was determined to be zerumbone, which attributes to its protective effects [151]. Jawaid et al. [152] evaluated the antioxidant potential and protective effects of four Indian medicinal plants (*Boerhavia diffusa, Boswellia serrata, Centratherum anthelminticum,* and *Orchis latifolia*) against H_2O_2-induced haemolysis and lipid peroxidation in human red blood cells. Methanolic extracts of these plants were fractionated into dichloromethane, ethyl acetate, and n-hexane fractions. Oxidative stress was induced in the RBCs using 100 μM H_2O_2. The results demonstrated that all fractions of the plant extracts preserved the integrity of the cell membranes, leading to a reduction in haemolysis and lipid peroxidation

under artificially induced oxidative stress conditions [152]. Pargi et al. [137] investigated the phytochemical profiling, antioxidative properties, and cytoprotective effects of the stem bark ethanol extract (BEE) and fruit ethanol extract (FEE) of *Artabotrys odoratissimus* Blume, a traditional medicinal shrub native to Eastern Asia, on human RBCs. After inducing oxidative stress in the RBCs using H_2O_2, the researchers measured a decrease in haemolysis after treatment with BEE and FEE extracts [137]. BEE exhibited an inhibition rate of 87.38% at a concentration of 500 μg/ml, while FEE showed an inhibition rate of 89% at 1000 μg/ml. These effects may be attributed to the presence of active compounds such as gamma-butyrolactone, furanone, and pyrrole, which likely play a vital role in the antioxidant activities of the extracts [137].

5.2. Role of phytocompounds

Catechins are the predominant polyphenols found in green tea, while black tea is characterized by the presence of theabrownins (TB), theaflavins (TF), and thearubigins (TR), which are pigments formed via the oxidation of catechins and their gallates during the fermentation process of black tea production [153]. In a study conducted by Yang et al. [153], the researchers examined the ability of oxidized phenolic compounds present in black tea to repress the formation of free radicals and provide protection against H_2O_2-induced oxidative damage in HPF-1 cells (embryonic human lung fibroblasts). The HPF-1 cells were exposed to 600 μM H_2O_2. Pre-treatment with different concentrations (0.72, 1.43, 2.87, 5.73, and 11.5 μg/ml) of TB, TF, and TR resulted in a dose-dependent improvement in cell viability. Moreover, the oxidized phenolic compounds exhibited a significant protective effect against H2O2-induced damage in HPF-1 cells ($p < 0.05$), with a roughly 10% increase in cell viability in contrast to the positive control group treated with epigallocatechin gallate (EGCG) [153]. (Table 2). ROS are the chief contributors to oxidative stress, leading to a decrease in cell viability. The level of 2',7'-dichlorofluorescein (DCF) fluorescence acts as an indicator of ROS production. When HPF-1 cells were exposed to 600 μM H_2O_2, it led to the generation of harmful ROS. After 1 h of H_2O_2 exposure, the intensity of DCF fluorescence was recorded to be increased by approximately 60–70% in contrast to the negative control. Moreover, the co-treatment of the cells with varying concentrations of EGCG, TB, TF, and TR partially reduced the increase in DCF fluorescence intensity. The reduction in fluorescence intensity exhibited a dose-dependent relationship. TB and TF showed a stronger ability to decrease fluorescence intensity than EGCG at concentrations ranging from 0.96 to 3.84 μg/ml [153].

Porres-Martíne et al. [160] conducted a study to investigate the antioxidant and protective effects of α-pinene and 1,8-cineole, two monoterpenes, against oxidative stress induced by H_2O_2 in PC12 cells. The researchers observed that pre-treatment with these monoterpenes resulted in the preservation of cell viability and the prevention of morphological changes in the cells. Additionally, the monoterpenes inhibited intracellular ROS production and significantly upregulated the expression of various antioxidant enzymes, including CAT, GPx, GR, HO-1, and SOD. Moreover, the monoterpenes showed a decrease in apoptosis, as evidenced by reduced caspase-3 activity. The antioxidant mechanisms of α-pinene and 1,8-cineole involved ROS scavenging and activation of the nuclear factor Nrf2. Kwon et al. [161] explored the mechanisms by which 3',4',7-trihydroxyflavone (THF) protected neuronal cells from oxidative stress, which led to cell death due to the neurotoxin effect of H_2O_2. Pre-treatment with THF resulted in a noteworthy enhancement in cell viability and reduction in H_2O_2-triggered lactate dehydrogenase (LDH) release, CAT activity, GSH content, ROS production, SOD activity, and mitochondrial membrane potential (MMP) loss. Western blot analysis revealed that THF inhibited the up-or down-regulation of Bax, Bcl-xL, Bcl-2, cleaved caspase-3 and − 9, along with cleaved poly-ADP-ribose polymerase (PARP) induced by H_2O_2. Moreover, THF attenuated the release of cytochrome c from the mitochondria to the cytosol, which was also triggered by H_2O_2. Furthermore, THF mitigated the rapid and significant phosphorylation of phosphatidylinositol 3-kinases (PI3K)/Akt, c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK) induced by H_2O_2. THF also obstructed nuclear factor-κB (NF-κB) translocation to the nucleus downstream of the H_2O_2-induced phosphorylation of PI3K/Akt and MAPKs [161]. Ismail et al. [162] conducted a study to investigate the neuroprotective potential of thymoquinone (TQ)-rich fraction (TQRF) and commercially obtained TQ against H_2O_2-stimulated neurotoxicity in human SH-SY5Y cells (differentiated). For evaluation, the fraction of TQRF was obtained through supercritical fluid extraction, whereas TQ was procured from the market. Further, the impact of TQRF and TQ on H_2O_2-induced neurotoxicity was assessed by evaluating cell viability, multiplex gene expression, morphological changes, and intracellular ROS levels. The results obtained from the study demonstrated that both TQ and TQRF effectively protected the SH-SY5Y cells from H_2O_2-induced damage. They preserved the activity of mitochondrial metabolic enzymes, maintained the cellular morphology, reduced intracellular ROS levels, and modulated the expression of genes associated with antioxidant defence mechanisms (catalase, SOD1, and SOD2) as well as signalling pathways (AKT1, ERK1/2, JNK, NF-κβ, p38MAPK, and p53) [162].

6. Antioxidant properties of Lactobacillus sp

Kim and his colleagues [163] conducted a study to assess the protective effect of *Lactobacillus gasseri* NLRI 312 against oxidative damage to DNA and cellular membrane lipids in Jurkat cell lines. The supplementation of this *Lactobacillus* strain resulted in a defensive effect against Jurkat cell lines by shielding them from oxidative damage. Interestingly, the supplementation did not affect the production of malondialdehyde (MDA), a marker of oxidative stress [163]. *Lactobacillus helveticus* cluster of differentiation-6 (CD6) was found to play a crucial role in the synthesis of 5-methyl tetrahydrofolate (5-MeTHF), a folic acid derivative, which exhibits antioxidant activity [164]. Intracellular free extracts (ICFE) of *L. helveticus* CD6 demonstrated an antioxidant effect by inhibiting ascorbate auto-oxidation by 27.5%. Furthermore, *L. helveticus* CD6 exhibited superior chelation ability for Fe^{2+} than Cu^{2+} ions. The intact cells of *L. helveticus* CD6 also showed hydroxyl radical scavenging activity of 20.8% and 2,2-diphenyl-1-picrylhydrazyl (DPPH) activity of 24.7%, demonstrating their antioxidative potential [164]. Yoon and Byun [165] reported that *Lactobacillus casei* HY 2782 exhibited a noteworthy cellular glutathione (GSH) level among the tested probiotic strains. They found a significant positive correlation between cellular GSH content and antioxidant potential.

Lactobacillus rhamnosus GG exhibited superior superoxide anion radical scavenging potential compared to *Escherichia coli, Bifidobacterium* BB12, *Lactobacillus acidophilus* LA, *L. paracasei* YEC, and *L. rhamnosus* Lc 705 [166]. *Lactobacillus fermentum* strains FTL10BR and FTL2311, isolated from miang (traditional fermented tea leaves), showed potent antioxidant potential [167]. These strains effectively scavenged hydroxyl, DPPH, and superoxide radicals. At population levels of 10^6 and 10^9 colony-forming units (CFU)/ml, their scavenging activities against superoxide, hydroxyl, and DPPH radicals ranged from 12.86% to 80.56%, 7.35–91.84%, and 64.26–87.89%, respectively [168]. In the study by Kapila and his teammates [169], they assessed the antioxidant activity of intracellular free extracts (ICFE) from 13 strains of Lactobacillus via the linoleic acid peroxidation method and the microsome-thiobarbituric acid (MS-TBA) assay. Among the tested strains, *Lactobacillus casei* ssp. *casei* 19 exhibited the highest antioxidant capacity, followed by *Lactobacillus acidophilus* 14, *Lactobacillus* sp. L13, *L. casei* ssp. *casei* 63, *L. helveticus* 6, and *Lactobacillus delbreuckii* ssp. *bulgaricus* 4. The remaining strains displayed antioxidant activity below 50% [123]. Explicitly, *L. casei* ssp. *casei* 19 showed the highest linoleic acid peroxidation at 72.04%, followed by *L. acidophilus* 14 (51.74%) and *Lactobacillus* sp. L13 (51.38%). However, all other strains exhibited

peroxidation activity below 50% [169].

6.1. The role of Lactobacillus sp. and their fermented products in ameliorating H_2O_2-induced oxidative stress in vitro

The anti-oxidant capacity and *Lactobacillus plantarum* ZLP001 mechanism of action was investigated by Wang et al. [170] using in vitro intestinal porcine epithelial cells (IPEC-J2). The cells were preincubated for 3 h with and without *L. plantarum* ZLP001 before being exposed to H_2O_2 for 4 h. Results indicated that pre-treatment with *L. plantarum* ZLP001 reduced apoptosis induced by H_2O_2 and protected IPEC-J2 cells from oxidative damage. Compared to H_2O_2 treatment alone, *L. plantarum* ZLP001 pre-treatment reduced ROS production, increased malondialdehyde concentrations, and enhanced mitochondrial membrane potential, indicating that *L. plantarum* ZLP001 enhances redox homeostasis. Lee and Kang [171] assessed the antioxidative potential of *Lactococcus lactis* MG5125 cell-free supernatant against H_2O_2-induced oxidative stress in the HepG2 cell line. When exposed to 1 mM H_2O_2, 2% CFS demonstrated cytoprotective effects on cells. Furthermore, the levels of glutathione and superoxide dismutase were modulated, and lipid peroxidation and glutathione levels were increased, resulting in a reduction in H_2O_2-induced oxidative stress (Table 3).

The Nrf2-antioxidant response element (ARE) pathway primarily regulates cellular antioxidative responses. Using a new fatty acid metabolite derivative of linoleic acid produced by *Lactobacillus plantarum*, a gut lactic acid bacterium, Furumoto et al. [177] conducted a study on the Nrf2-ARE pathway. They investigated the protective effects of 10-Oxo-trans-11-octadecenoic acid (KetoC), an enzyme derived from *Lactobacillus plantarum* AKU1009a, against H_2O_2-induced cytotoxicity in HepG2 cells. The result obtained from the study unveiled that KetoC treatment effectively shielded the HepG2 cells from H_2O_2-induced cytotoxicity. They found that KetoC enhanced the expression of imperative antioxidative enzymes like NAD(P)H: quinone oxidoreductases 1 (NQO1), glutamate-cysteine ligase modifier subunits (GCLM), and heme oxygenase-1 (HO-1), in HepG2 cells. Additionally, KetoC triggered the activation of ARE-dependent transcription, signifying its involvement in the Nrf2-ARE pathway. These findings recommend that KetoC exerts a protective effect against oxidative stress by activating antioxidant enzymes and modulating the Nrf2-ARE pathway in HepG2 cells. Wu et al. [178] examined the phenolic transition of the individual components from unfermented barley to fermentation with *L. plantarum* P-S1016. In this study, lactic acid bacteria were used to explore the extensive use of hulless black barley and how they improved the capacity of phenolic compounds to protect liver cells from oxidative stress induced by H_2O_2. During fermentation, black barley's bacterial counts and free phenol content increased to 9.54 ± 0.22 log cfu/ml and 5.61 ± 0.02 mg GAE/ml, respectively. Nine isoflavones, two nitrogenous compounds, and eleven phenolic compounds were identified by UPLC-QTOF-MS, among which hordatine, pelargonidin aglycone, and epicatechin were significantly enriched. Additionally, free phenolic extracts from fermented barley were more effective than those from unfermented barley in neutralising DPPH radicals, converting Fe^{3+} into Fe^{2+}, and boosting oxygen radical absorption. In addition to enhancing cell viability, SOD activity, membrane integrity, and non-enzymatic GSH redox status, F-BPE inhibited ROS formation more effectively in hepatocarcinoma cells.

7. Conclusion

Although ROS plays an essential role in the normal and coordinated functioning of organs, apoptosis, mitochondrial dysfunction, and inflammation have been associated with ROS, such as H_2O_2. Nevertheless, their overexpression can induce mutagenesis, alter immune responses, liver fibrosis, sepsis, aging, and ulcerative colitis. Various therapeutic approaches have been developed to combat the complications caused by H_2O_2, including those targeting inflammation, oxidative stress, and mitochondria. Due to their health-promoting properties and anti-oxidant capabilities, natural anti-oxidants derived from plant extract, phytochemicals, and *Lactobacillus sp.* (probiotics) have gained importance in recent decades. As natural antioxidants, these compounds have been reported to have significant anti-oxidant properties by regulating enzyme activity, scavenging free radicals, and chelating pro-oxidative metal ions, which are ultimately responsible for redox equilibrium in the body and the improvement of health. However, the mechanisms of action of these natural anti-oxidants are unclear, and further research is necessary to identify their active target sites. Further, plant extracts, phytochemicals, and *Lactobacillus sp.* could be biofortified to improve and develop enriched foods and their derivatives to maintain health and prevent disease. Additionally, using natural anti-oxidants from plant extracts, phytochemicals, and *Lactobacillus sp.* may provide researchers with new avenues for uncovering their potential to ameliorate the complications resulting from H_2O_2-induced oxidative stress and increase life expectancy.

CRediT authorship contribution statement

The manuscript's initial draft was written by Harsh Kumar. Whereas, Rajni Dhalaria, Shivani Guleria and Ruchi Sharma contributed to the literature collection. Formal analysis was done by Daljeet Singh Dhanjal, Reena Singh, Vijay Kumar and Talwinder Kaur. The original proposal was amended, proofread and improved by Richard Cimler, Shahida Anusha Siddiqui, Marian Valko, Eugenie Nepovimova, Ashok Kumar Pathera, Narinder Verma, Sivakumar Manickam, Suliman Y. Alomar, and Kamil Kuca. The final submitted version of the manuscript has been seen and approved by all authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2023.115022.

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