B-ICON Proceeding

EVALUATION OF THE ANTI-PHOTOAGING POTENTIAL OF *HYPSIZYGUS MARMOREUS* AQUEOUS CRUDE EXTRACTS: ANTIOXIDANT COMPOUNDS, ACTIVITIES, AND CELL VIABILITY IN NIH/3T3 FIBROBLASTS

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Abstract

Hypsizygus marmoreus (Bunashimeji), a popular edible mushroom in East Asia, is recognized for its therapeutic properties, including antioxidant activity. Ultraviolet (UV) radiation, particularly UVB, induces reactive oxygen species (ROS), accelerating skin aging and elevating cancer risk. This study evaluated the antioxidant and anti-photoaging potential of aqueous crude extracts of H. marmoreus prepared by cold water extraction (CWE) and hot water extraction (HWE). Antioxidant capacity was assessed through total phenolic content (TPC), total flavonoid content (TFC), reducing power, ferrous ion chelating activity, and DPPH radical scavenging assays, while cytotoxicity and protective effects were examined in fibroblast cells using MTT. CWE contained significantly higher phenolic content than HWE ($p < 0.001$), indicating stronger antioxidant potential. No significant differences were observed in TFC and chelating activity ($p > 0.05$). CWE demonstrated greater reducing power at 5–15 mg/mL ($p < 0.05$), while both extracts exhibited concentration dependent DPPH scavenging activity, with CWE showing slightly higher efficacy. Neither extract surpassed the standard in ferrous ion chelation. MTT analysis confirmed non-cytotoxicity of both extracts and revealed enhanced fibroblast viability, suggesting a protective effect against oxidative stress. In conclusion, CWE of *H. marmoreus* exhibited superior antioxidant properties compared to HWE, particularly in phenolic content and reducing power, and supported fibroblast survival. These findings suggest that *H. marmoreus* holds promise as a natural photoprotective agent for anti-aging and skin-care formulations.

Keywords: *Hypsizygus marmoreus*, Antioxidant, Anti Photo-aging, Crude Extrac

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INTRODUCTION

Environmental changes have contributed to increased levels of ultraviolet B (UVB) radiation reaching the Earth's surface, thereby elevating the risk of UVB-induced damage to human skin. This exposure is widely recognized as a key driver of photoaging a form of accelerated aging of the skin resulting from prolonged and repetitive exposure to solar ultraviolet radiation. Grandi and D'Ovidio (2020) highlighted UVB as a catalyst in this process. While often considered primarily a cosmetic concern, photoaging carries significant

implications for long-term health and the risk of chronic illnesses (Pomatto & Davies, 2018).

Despite rising global life expectancy, many individuals tend to underestimate the importance of proactive health maintenance and disease prevention as they age (Haryanto *et al.,* 2020). Over the decades, researchers have advanced more than 300 distinct theories to explain the biological process of aging, yet the pursuit of a universal explanatory model remains challenging and unresolved. One of the most enduring is the free radical theory, which proposes that aging arises from the accumulation of molecular damage caused by reactive oxygen species (ROS). This framework emphasizes declining mitochondrial function and the protective role of endogenous or exogenous antioxidants (Polidori & Mecocci, 2022; Pomatto & Davies, 2018).

Skin Structure and UV Protection

The skin, the body's largest organ and a major component of the innate immune system, has multiple intrinsic protective mechanisms against ultraviolet exposure. At the frontline is the multilayered stratification of the epidermis, which acts as a physical barrier. Within this structure reside immune cells such as Langerhans cells and T lymphocytes, contributing to immune surveillance and response. Melanocytes, which synthesize melanin, provide an additional line of defense: melanin absorbs and scatters UV radiation, thus diminishing its penetration into living epidermal layers. At the molecular level, UV-induced DNA damage can be countered through nucleotide excision repair and base excision repair mechanisms; cell cycle checkpoints and apoptotic pathways are also activated to eliminate severely damaged cells (Mohania *et al.,* 2017; Natarajan *et al.,* 2014).

Nevertheless, the integumentary system remains vulnerable to environmental insults, particularly UVB radiation whose intensity has increased in some regions due to ozone layer depletion. UVB exposure is associated not only with photoaging, but also with photo-immune suppression and photocarcinogenesis. Its higher energy compared with UVA permits deeper tissue impact primarily within the epidermis but the downstream effects extend well beyond. UVB triggers activation of transcription factors, collagen breakdown, and oxidative stress (Haryanto *et al.,* 2020; Decean *et al.,* 2016). The imbalance between pro-oxidant enzymatic activity and the oxidants themselves leads to oxidative stress, which is implicated in a broad spectrum of pathological conditions, including cancers and neurodegenerative disorders (Polidori & Mecocci, 2022).

Mechanisms of Photoaging

Photoaging is a multifactorial process involving altered levels of ROS, disruption of extracellular matrix (ECM) components, upregulation of matrix metalloproteinases (MMPs), and shifts in cytokine profiles (Rittié & Fisher, 2002). Ultraviolet (UV) radiation induces free-radical formation, leading to acute phenomena like immediate pigment darkening and long-term effects like ECM damage (Huang *et al.,* 2016). As the outermost organ, the skin's barrier function is critical it prevents water loss, wards off infection, and buffers physical, chemical and photic insults. UV irradiation undermines barrier integrity by generating ROS and triggering inflammatory responses in skin cells (Baba *et al.,* 2005). Both UVA and UVB promote ROS formation in biological systems (Krutmann *et al.,* 2020).

Specifically, UVB is particularly harmful due to its higher photon energy: it promotes collagen degradation, impairs collagen synthesis, and contributes to wrinkle formation (Kwon *et al.,* 2019; Kang *et al.,* 2019; Myung *et al.,* 2019). UVB also stimulates pro-inflammatory cytokines such as interleukin (IL)–6, IL–8 and MCP-3, which in turn aggravate inflammation and contribute to dermal fat loss hallmark features of skin photoaging (Jung *et al.,* 2022). The overproduction of ROS from UVB activates signaling pathways including mitogen-activated protein kinases (MAPKs) and AKT. These pathways dysregulate collagen biosynthesis genes (e.g., COL1A1), while upregulating MMPs that degrade ECM components (Kammeyer & Luiten, 2015; Hwang *et al.,* 2011; Lee *et al.,* 2021; Choi *et al.,* 2022). Consequently, dermal structural integrity is compromised, driving visible signs of aging such as wrinkles, uneven skin thickness, and laxity.

Although UVA is less energetic than UVB, it penetrates more deeply into the dermis and triggers activation of MAPK and NF-κB pathways, leading to MMP over-expression and enhanced collagen breakdown (Quan *et al.,* 2015). While UVA and UVB differ in depth of penetration and direct vs. indirect DNA damage mechanisms, they converge on ROS generation and MMP-mediated ECM degradation thereby reinforcing oxidative stress as a central driver of photoaging (Watson *et al.,* 2014; Masaki, 2010).

Natural Antioxidants and Therapeutic Potential in Photoaging

In recent years, attention has turned to natural antioxidants particularly polysaccharides derived from edible mushrooms as promising agents to mitigate UV-induced oxidative stress and dermal ECM damage. For example, polysaccharides from *Pholiota nameko* protected fibroblasts from UVA-induced oxidative stress and collagen degradation by down-regulating MMP expression (Lin *et al.,* 2022). Likewise, polysaccharides from *Agaricus blazei Murill* attenuated UVB- induced keratinocyte damage by reducing pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNF- α) and restoring barrier proteins (filaggrin, aquaporin-

3) (Cheng *et al.,* 2024). These findings underscore the therapeutic potential of mushroom-derived compounds to maintain ECM integrity, suppress ROS accumulation, regulate collagen homeostasis, and thus protect against photoaging. Importantly, they engage signaling pathways such as AKT and inflammatory regulators (Jung *et al.,* 2024).

Given the well-documented role of UVB-induced ROS in driving photoaging via collagen degradation, MMP activation, and pro-inflammatory cytokine release, strategies that mitigate oxidative stress and restore ECM homeostasis are of vital significance. Natural mushroom polysaccharides have already demonstrated antioxidant, anti-inflammatory, and collagen- protective activities in both fibroblast and keratinocyte models.

Rationale for Investigating *Hypsizygus marmoreus*

Despite the promising data on various mushroom species, research focusing specifically on *Hypsizygus marmoreus* an edible mushroom widely consumed in East Asia, known for its bioactive polysaccharides remains limited. Commercial cultivation of *H. marmoreus* began in Japan in the 1970s and it has since become a key edible fungus in East Asia (Chen *et al.,* 2017). Nutritional analyses indicate that *H. marmoreus* extracts contain various bioactive compounds including indole compounds, glucans, phenolics and other compounds with antioxidant capacity (Sun *et al.,* 2009). Polysaccharide fractions extracted from *H. marmoreus* have been shown to consist of rhamnose, mannose, galactose and glucose, and exhibit antioxidant and anti- inflammatory activities (turn0search6; turn0search0). Moreover, recent work indicates the presence of low molecular weight peptides in *H. marmoreus* hydrolysates that show antioxidant and antibacterial activities (turn0search22).

Given the strong link between ROS, inflammation, ECM degradation and photoaging and the fact that *H. marmoreus* contains bioactive components with antioxidant potential it is scientifically justified to evaluate the antioxidant and anti-photoaging effects of *H. marmoreus* aqueous crude extract in NIH/3T3 fibroblasts. Such investigation may offer novel insights into the therapeutic potential of *H. marmoreus* extracts for skin health and protection against UVB-induced damage.

MATERIALS AND METHODS

Fruiting bodies of *Hypsizygus marmoreus* were collected from Green Garden Life Co., Ltd., Wufeng District, Taichung, Taiwan, and subsequently lyophilized. A comprehensive list of all chemicals and reagents, including their common names, scientific names, chemical formulas, and suppliers (e.g., Sigma-

Aldrich, Merck, Bio Basic), were used for the extraction, compound, and activity assays.

All chemicals used in this research are listed in Table 01

Common name	Scientific name	Chemical formula	Company
BHT (Butylated hydroxytoluene)	2,6-Di-Tert-buty1-4-methylphenol	$C_{15}H_{24}O$	SIGMA-ALDRICH
Caustic soda	Sodium hydroxide	NaOH	BIO BASIC
DPPH (2,2-diphenyl1-1pircry1hydrazyl)	2,2-Diphenyl-l-(2,4,6-trinitrophenyl)hydrazin	$C_{18}H_{12}N_5O_6$	SIGMA-ALDRICH
EDTA	2-({2-Bis (carboxymethyl) amino] ethyl}(carboxymethyl)amino)acetic acid	$C_{10}H_{16}N_2O_8$	BIO BASIC
FCR/GAE	Folin-ciocalteu's phenol reagent		SIGMA-ALDRICH
Ferric chloride	Iron (III) chloride	FeCl	MERCK
Ferrous chloride Tetrahydrate	Iron (II) chloride tetrahydrate	$FeCl.4H_2O$	MERCK
Ferrozine	3-(2-Pyridyl)-5,6-diphenyl-1,2,4-triazine-*p,p'*-disulfonic acid monosodium salt hydrate	$C_{20}H_{13}N_4O_6S_2Na$	SIGMA-ALDRICH
Fetal Bovine Serum	Fetal Bovine Serum		HYCLONE
Gallic acid	3,4,5-trihyoxybenzoic Acid	$C_6H_2(OH)_3COOH$	BIO BASIC
Alcohol	Ethanol (EtOH)	C_2H_5OH	Zhan Mao Trade
Aluminum chloride	Aluminum chloride	$AlCl_3$	ACROS
Aspirin Acetylsalicylic acid	2-acetyloxybenzonic acide	$C_9H_8O_4$	SIGMA-ALDRI.CH

Glucose	D-(+)-Glucose	$C_6H_{12}O_6$	SIMGA-ALDRICH
Glycine Hydrochloric acid	2-aminoacetic acid Hydrochloric acid	$C_2H_5NO_2$	Gene Mark MERCK
Methyl Alcohol MTT	Methanol (MeOH) 3-(4,5-Dimethylthiazol-2-yl)-2,5-disphenyltetrazolium Bromide tetrazole	CH_3OH $C_{18}H_{16}BrN_5S$	AENCORE BIO BASIC
PBS Penicillin- Streptomycin	Phosphate Buffered Saline Penicillin -Streptomycin		Gene Mark HYCLONE
Phenol	Phenol	C_6H_6O	Union Chemicals
Potassium acetate	Potassium acetate	CH_3COOK	SIGMA-ALDRICH
Potassium ferricyanide	Potassium Hexacyanoferrate (III)	$K_3Fe(CN)_6$	Thermo Scientific
Potassium phosphate	Dipotassium hydrogen phosphate	K_2HPO_4	BIO BASIC
Potassium hydrate	Potassium hydroxide	KOH	Life Science
Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one	$C_{15}H_{10}O_72H_2O$	SIGMA-ALDRICH
SDS Sodium pyruvate	Sodium dodecyl sulfate Sodium;2-oxopropanoate	$CH_3(CH_2)_{11}O SO_3Na$ $C_3H_3NaO_3$	MP Biomedicals HYCOLNE
Sulfuric acid	Sulfuric acid	H_2SO_4	Union Chemicals

TCA	2,2,2-trichloroacetic acid	$C_2HCl_3CO_2$	Thermo Scientific
Tris	2-Amino-2-hydroxymethyl-propane-1,3-diol	$C_7H_{17}NO_3$	Gene Mark
Trypan blue	(3Z,3'Z)-3,3-[(3,3'-diamethyl-biphenyl-4,4'-diyl)di (1Z) hydrazine-2-yl-l-ylidene]bis(5-amino-4-oxo-3,4-dihydrona-phthalene-2,7-dislfonic acid)	$C_{34}H_{28}N_6O_{14}S$	Gibco
Trypsin	Trypsin		HYCLONE

Preparation and Extraction of *Hypsizygus marmoreus*

Dried HM was ground into a powder of approximately 150-200 mesh. The powder was extracted using a modified water extraction method at a ratio of 1:10 (HM powder to deionized water).

1. **Hot Water Extraction (HWE):** Mixture was heated in a water bath at 94°C for 3 hours, vortexed every 10 minutes.
2. **Cold Water Extraction (CWE):** Mixture was placed in a refrigerator at 4°C for 24 hours.

Both mixtures were centrifuged at 10,000 rpm for 10 minutes to separate the soluble supernatant. The supernatant was then lyophilized for three days in a freeze-dryer for preservation.

Antioxidant Compound Quantification

1. **Total Phenolic Content (TPC):** Analyzed using the Folin-Ciocalteau method. Gallic acid was the standard. Absorbance was measured at 750 nm. Results were expressed as Gallic acid equivalent (mg per gram of crude HM extracts).
2. **Total Flavonoid Content (TFC):** Determined using the colorimetric aluminum chloride assay. Quercetin was the standard. Absorbance was measured at 430 nm.
3. **Total Water-Soluble Polysaccharide Content:** Determined using a colorimetric method by DuBois

et al. Glucose was the standard. Absorbance was measured at 490 nm.

All assays were carried out in triplicate (different batches of HM extracts) and expressed as mean value ±SD.

Antioxidant Activity Assays

1. **Scavenging Activity on DPPH Radicals:** Measured by mixing HM extracts with a fresh 1mM DPPH solution in 95% methanol. BHT was the standard. Absorbance was measured at **517 nm**. Radical Scavenging (%) was calculated using the equation:

$$\text{Radical Scavenging (\%)}: \left(1 - \frac{(\text{Asample} - \text{Ablank})}{\text{Acontrol}}\right) \times 100\ \%$$

2. **Ferric-Reducing Antioxidant Power (FRAP):** Determined using the method of Yıldırım *et al.*. BHT was the control. Reducing power was measured via the formation of the Fe^{+2} ferricyanide complex, with absorbance measured at 700 nm.
3. **Ferrous Ions Chelating Capacity:** EDTA was used as the control. Chelating capacity was measured by monitoring the formation of the Fe^{+2} ferrozine complex. The Chelating ability (%) was calculated by the equation

$$\text{Chelating ability (\%)}: \frac{(\text{Asample} - \text{Ablank})}{(\text{Acontrol})} \times 100\ \%$$

All assays were carried out in triplicate and expressed as mean value ± SD.

Cell Cultures

A preliminary cytotoxicity study was conducted using the **mouse fibroblast (NIH/3T3)** cell line, purchased from the Bioresource Collection and Research Center (BCRC, Taiwan). Cells were maintained in DMEM supplemented with 10% FBS, 1% sodium pyruvate, and 1% penicillin- streptomycin in a CO_2 incubator (37^0C, 5% CO_2). HM extracts were prepared at concentrations of 0.5, 1, 2, 4, and 8 mg/mL by dilution in culture medium and filtered using a 0.45µm filter.

Table 02: Cell Line and Characteristics

Cell Strain Name	**NIH/3T3**
Organism	*Mus musculus*
Disease	Normal
Growth properties	Adherent
Morphology	Fibroblast
Growth Condition	5% CO_2, 37°C
Medium	DMEM + 10% FBS + 1% sodium pyruvate + 1% penicillin streptomycin

Effect of HM Extract on Cell Viability

The effect of HM extracts on cell viability was measured by a MTT assay using NIH/3T3 cells ($5x10^4$cells/mL) cultured for 24 and 48 hours. The MTT reagent was added, followed by the addition of SDS-HCL to dissolve the formazan crystals. Absorbance was measured at 595 nm.

Cell viability was calculated using the following equation: Cell viability (%):$(\frac{\text{Asample}}{\text{Acontrol}}) \times 100\ \%$. Assays were carried out in triplicate.

Statistical Analysis

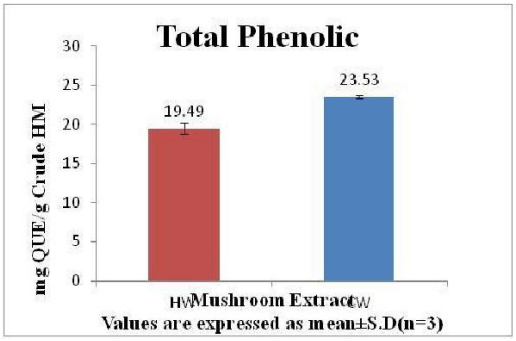
Statistical comparisons for antioxidant compounds and activities were conducted using one-way analysis of variance (ANOVA) followed by Tukey's B post-hoc test. For the MTT experiments, one-way ANOVA and Dunnett's post-hoc test were used to compare treatment groups with the control. A significance level of *$p < 0.05$ and **$p < 0.001$ was considered statistically significant.

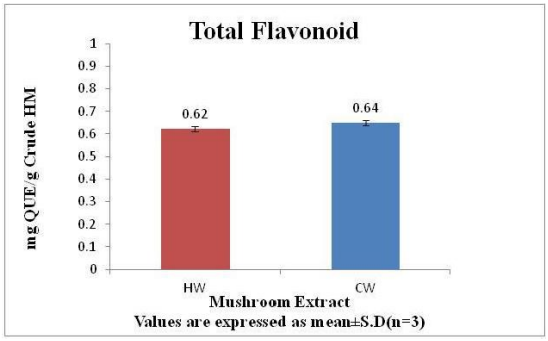
RESULTS AND DISCUSSION

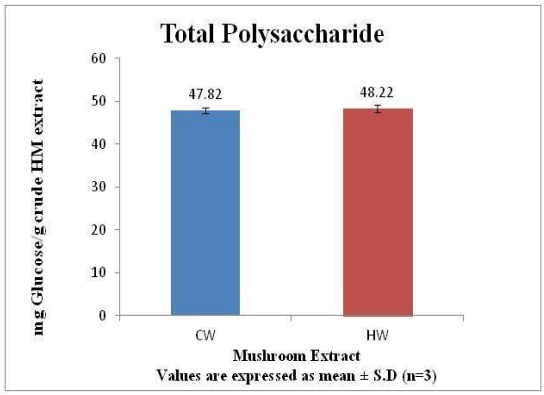
Antioxidant Compounds

The analysis of antioxidant compounds in the crude *Hypsizygus marmoreus* (HM) extracts showed variations influenced by the extraction method.

1. **Total Phenolic Content (TPC):** The highest content was recorded in **Cold Water Extraction (CWE)** (23.53 ±SD mg GAE/g crude HM), significantly higher than Hot Water Extraction (HWE) (19.49 ±SD mg GAE/g crude HM) (P < 0.05$). This result suggests that CWE is more effective in preserving phenolic compounds, which are often susceptible to degradation during high-temperature treatments, aligning with reports that phenolic compounds are best extracted at low or moderate temperatures.
2. **Total Flavonoid Content (TFC):** No significant difference was observed between CWE (0.64 ± SD mg QE/g crude HM) and HWE (0.62 ± SD mg QE/g crude HM) (P < 0.05$). This similarity may be due to the low concentrations and limited water solubility of flavonoids in HM, as organic solvents are generally more effective for their extraction.
3. **Total Water-Soluble Polysaccharide Content:** Both extraction methods showed nearly identical and high yields. HWE yielded 48.22 ± SD mg glucose/g crude HM, slightly higher but not statistically significant compared to CWE (47.82 ±SD mg glucose/g crude HM) (P <0.05). This suggests that both methods are effective for polysaccharide recovery in HM, although higher temperatures can be more efficient for extracting certain fractions like β glucans.







Antioxidant Activities

Scavenging Activity on DPPH Radicals

Both CWE and HWE demonstrated strong, concentration-dependent scavenging activity on DPPH radicals.

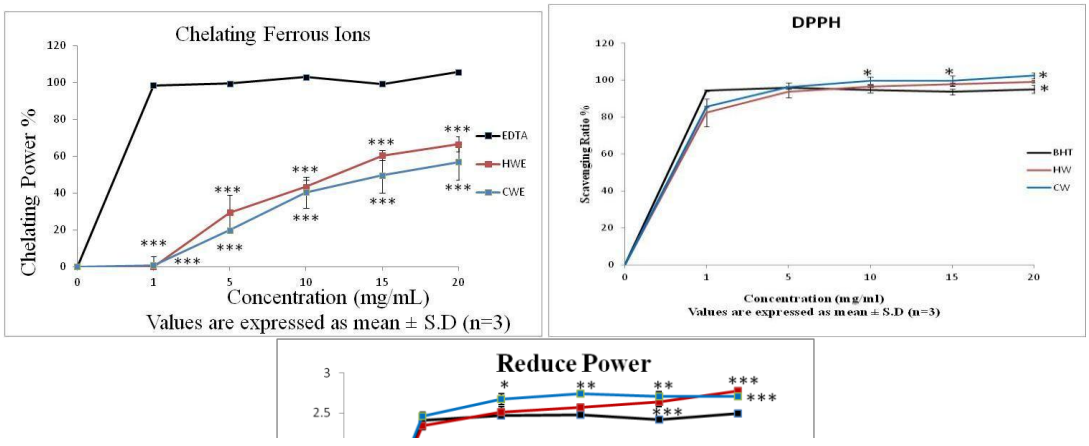
The EC_{50} values for CWE (1.37 mg/mL) and HWE (1.40 mg/mL) were very close to the BHT standard (1.30 mg/mL). At 20 mg/mL, CWE achieved the highest scavenging effect (102.35 ± 1.45%), which was comparable to the synthetic antioxidant BHT (99.3%). This indicates that while the HM extracts are effective antioxidants, they require higher concentrations to match the potency of BHT at lower doses.

Ferric Reducing Antioxidant Power (FRAP)

The reducing power of the HM extracts increased with concentration, reflecting a strong electron-donating ability. The EC_{50} values for CWE (0.58 mg/mL) and HWE (0.585 mg/mL) were almost identical to the BHT standard (0.57 mg/mL). At the highest concentration of 20 mg/mL, HWE (2.74 ± 0.04) surpassed both CWE (2.70 ± 0.03) and the BHT standard (2.50 ± 0.05), indicating that both extracts possess strong reducing ability, with HWE showing the greatest effect at maximum concentration. The strong reducing activity is consistent with other edible mushrooms and is attributed to their phenolic compounds and polysaccharides.

Ferrous Ions Chelating Capacity

The extracts showed a dose-dependent increase in chelating power, a critical mechanism for preventing Fe^{+2} catalyzed Fenton reactions that generate harmful hydroxyl radicals. While the reference standard EDTA achieved near complete chelation at very low concentrations, HWE reached the strongest activity at 20 mg/mL (64.21 ± 3.15%), followed by CWE (55.87 ± 2.84%). The EC_{50} values were 4.50 mg/mL for CWE and 5.15 mg/mL for HWE. This suggests that heat treatment may enhance the release of bound polysaccharides and phenolics responsible for metal sequestration, highlighting *H. marmoreus* as a potential source of natural chelating agents.

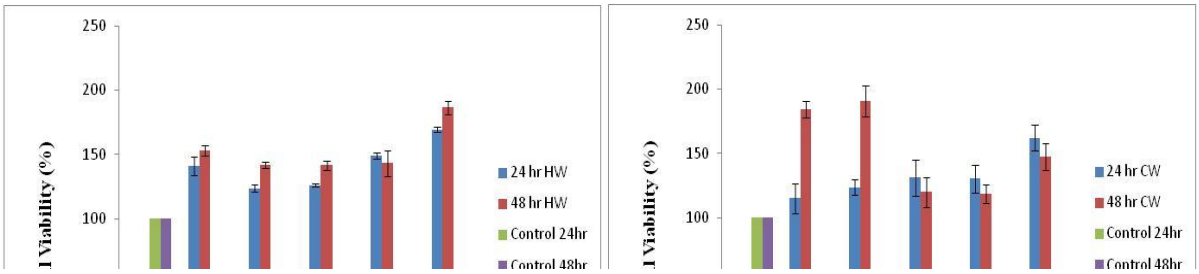


Effect of HM Extracts on NIH/3T3 Cell Viability

The evaluation of the cytotoxicity and proliferation profiles in NIH/3T3 fibroblast cells is crucial for determining the safety and biological effects of the extracts.The results showed that both CWE and HWE did not exhibit cytotoxic activity at any tested concentration (0.5 to 8 mg/mL), as cell viability consistently remained above 100%. In fact, both extracts promoted cell proliferation in a concentration- and time-dependent manner.

1. **CWE Treatment (CW):** Showed the most pronounced proliferative effect at lower concentrations (0.5 and 1 mg/mL), reaching nearly 200% viability at 48 hours compared to the control. At higher concentrations (2–8 mg/mL), proliferation plateaued, suggesting a possible saturation effect or nutrient limitation in dense cultures.
2. **HWE Treatment (HW):** Induced a steady and concentration-dependent increase in proliferation, with the highest proliferation recorded at 8 mg/mL after 48 hours, exceeding 190% viability.

These findings align with previous research on other edible mushrooms, where polysaccharides were reported to enhance fibroblast proliferation and support the role of mushroom-derived compounds in stimulating cell growth and protection against oxidative damage. The observed lack of cytotoxicity and the proliferative effect suggest that both CW and HW extracts of *H. marmoreus* are biocompatible and may have potential applications in formulations aimed at supporting tissue repair and cellular health.



CONCLUSION

The aqueous crude extracts of *Hypsizygus marmoreus*, obtained through both cold and hot water extraction methods, are rich in bioactive compounds, particularly total phenolics and water- soluble polysaccharides, and possess strong antioxidant activities comparable to the synthetic standard BHT. Specifically, the Cold-Water Extract showed higher phenolic content and the most pronounced cell proliferation effect in NIH/3T3 fibroblasts, reaching nearly 200% viability, while neither extract exhibited cytotoxicity. The potent radical-scavenging, reducing power, and ferrous ion chelating capacity, combined with the safety and proliferative effects on dermal cells, highlight *H. marmoreus* as a promising natural source for developing anti-photoaging and skin health formulations. Further research should focus on isolating the specific bioactive compounds responsible for the anti-photoaging effects in vivo.

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Declaration of Interest Statement

The authors declare that they have no conflict of interests.

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