

Neuroprotective Effects of Nebbiolo Red Wine Against Ethanol-induced Cognitive Dysfunction and Neurotoxicity

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ABSTRACT

Objective: Chronic alcohol consumption causes neurotoxicity, yet moderate red wine consumption is linked to health benefits, often attributed to its polyphenols. This study investigated whether Nebbiolo red wine (NRW), a variety with high polyphenol content, possesses sufficient neuroprotective capacity to counteract the concurrent neurotoxic effects of its own ethanol (EtOH) content.

Materials and Methods: Neuroprotective effects were evaluated in vitro (SH-SY5Y cells, WST-8 assay) and in vivo (mice, Y-maze test) following exposure to 14% EtOH or 14% NRW. Antioxidant capacity was determined by DPPH and ORAC assays.

Results: NRW demonstrated robust dose-dependent antioxidant activity. In vitro, NRW significantly protected SH-SY5Y cells from EtOH-induced cytotoxicity. In vivo, 14% EtOH administration severely impaired spatial memory (27.1% alternation vs. 67.5% Sham), an effect completely prevented by 14% NRW (65% alternation).

Conclusion: NRW mediates significant neuroprotection, effectively neutralizing ethanol-induced cytotoxicity in vitro and cognitive impairment in vivo. This suggests polyphenolic content is a critical determinant of alcohol's net neurological impact.

Keywords Nebbiolo red wine, Ethanol, Neuroprotection, Oxidative Stress, Cognitive Impairment, Y-maze

INTRODUCTION

Chronic and excessive alcohol consumption represents a major global health concern, contributing significantly to cognitive decline¹ and structural brain damage.² Long-term alcohol exposure is strongly associated with Alcohol Use Disorder (AUD), a condition characterized by progressive neurodegeneration, impaired memory function², and elevated dementia risk.^{3,4} The pathophysiology underlying alcohol-induced brain injury involves multiple overlapping mechanisms. Oxidative stress plays a central role, as ethanol metabolism generates substantial quantities of reactive oxygen species that

overwhelm endogenous antioxidant defenses.⁵⁻⁷ Additionally, chronic alcohol exposure triggers persistent neuroinflammatory responses^{8,9} and exerts direct toxic effects on neuronal populations,^{10,11} collectively driving progressive cognitive deterioration.

Despite ethanol's well-established neurotoxic properties, red wine consumption has been paradoxically associated with certain beneficial health outcomes in epidemiological studies.^{12,13} This apparent contradiction is typically attributed to the presence of bioactive polyphenolic compounds, including resveratrol, quercetin, and proanthocyanidins, which are abundant in red wine.^{12,13} These phytochemicals demonstrate robust antioxidant activity^{14,15} and can modulate inflammatory signaling pathways.¹⁶ Among red wine varieties, those produced from Nebbiolo grapes—the foundation of prestigious Italian wines such as Barolo and Barbaresco—are particularly notable for their exceptionally high polyphenol and tannin content.^{17,18}

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A critical unresolved question is whether the beneficial bioactive constituents present in red wine can meaningfully counteract the concurrent neurotoxic effects of the ethanol they contain. To address this gap, we investigated whether Nebbiolo red wine (NRW) possesses sufficient neuroprotective capacity to prevent or mitigate ethanol-induced cognitive impairment and cellular damage. We employed complementary experimental approaches: in vitro assessment of neuronal cell viability using the human SH-SY5Y neuroblastoma cell line, and in vivo evaluation of cognitive performance using the Y-maze spontaneous alternation test in mice. Additionally, we characterized the antioxidant properties of NRW through standard biochemical assays to establish a mechanistic foundation for any observed neuroprotective effects.

MATERIALS AND METHODS

Preparation of encapsulated Nebbiolo Red Wine Powder (NRWP)

The red wine used in this study was 'Barolo del Comune di Serralunga d'Alba' (14% alcohol), a 2020 Nebbiolo from Ettore Germano Winery in Serralunga d'Alba (Piedmont, Italy). To prepare the sample, EtOH was first evaporated from the red wine using a concentrator operated at 50°C for approximately 30 min, utilizing a -10°C "chiller". Following this, a wall material mixture of maltodextrin (419699, Sigma-Aldrich, USA) and gum Arabic (G9752, Sigma-Aldrich, USA) (65:35 ratio) was dissolved directly into the dealcoholized wine to achieve a 10% total weight concentration. This wine solution, containing the encapsulating agents, was then poured into an aluminum tray to a depth of 1 cm, frozen, and subsequently freeze-dried. The freeze-drying was conducted using a laboratory-scale ILShinBioBase freeze dryer (Model TFD8503, Republic of Korea), operating with the freezing plate and condenser at -70°C and a chamber pressure of 13 mTorr for 48 h, ensuring that the dry layer temperature did not exceed 25°C.

Measurement of the DPPH radical scavenging activity

The antioxidant capacity was assessed using the DPPH (D9132, Sigma-Aldrich, USA) radical scavenging assay. Briefly, 100 µL of serially diluted and filtered NRW samples were mixed with 100 µL of a 0.5 mM DPPH solution (prepared in 80% EtOH; 1.00983.1011, Supelco, USA) in a 96-well plate. Following a 20-min dark incubation at room temperature, the absorbance was measured at 540 nm using a Varioskan Lux Multimode microplate reader (Thermo Fisher Scientific, USA). Ascorbic acid (A92902, Sigma-Aldrich, USA) served as a positive control.

Assessment of Oxygen Radical Absorbance (ORAC) capacity through ORAC analysis

The ORAC capacity was evaluated using a commercial assay kit (ab233473, Abcam, Cambridge, USA) according to the manufacturer's instructions. Samples and Trolox standards were added in triplicate to a 96-well black-bottom microplate, followed by the fluorescein solution. The reaction was initiated

with AAPH solution, and the fluorescence decay was immediately monitored kinetically (Excitation: 480 nm; Emission: 520 nm) at 37°C for 90 min using a Varioskan Lux reader. The antioxidant capacity was determined by calculating the net area under the curve (AUC) relative to the blank and expressed as micromoles of Trolox Equivalents (TE) per milliliter of wine (µM TE/mL).

Cell culture

SH-SY5Y human neuroblastoma cells were maintained in high-glucose DMEM (SH30243.01, Hyclone, USA) supplemented with 10% fetal bovine serum (FBS, SH30919.03, Hyclone, USA) and 1% penicillin/streptomycin (SV30010, Hyclone, USA). Cells were cultured at 37°C in a humidified 5% CO₂ incubator.

WST-8 assay for Neuroprotection and cell viability

SH-SY5Y cells were seeded in 96-well plates at a density of 1.2×10^5 cells/mL and allowed to attach for 24 h. Following incubation, the culture medium was removed and replaced with serum-free medium (SFM) containing various concentrations of EtOH and/or NRWP. After a 24 h treatment period, cell viability was assessed using a WST-8 cell viability assay kit (QM1000, BIOMAX, Guri-si, Republic of Korea). The WST-8 reagent was added to each well, and the plates were incubated for 4 h at 37°C. The absorbance was then measured at 450 nm using a microplate reader to quantify cell viability.

Animals and habituation

Male Balb/c mice were acquired from DBL Co., Ltd. (Eumseong, Republic of Korea). Upon arrival, mice were given one week to acclimate to the vivarium conditions (group-housed, 3 mice/cage; 12 h light-dark cycle; ad libitum chow and water) before the initiation of EtOH exposure. All animal handling procedures and experimental protocols were approved by the JBK LAB Institutional Animal Care and Use Committee (IACUC) and conformed to the guidelines stipulated by the United States National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Following acclimation, seven-week-old male Balb/c mice (n = 6/group) were randomly assigned by cage to receive daily oral gavage (p.o.) of distilled water, 14% EtOH, or NRW. The wine dosage was determined using the Human Equivalent Dose (HED) calculation criterion from the U.S. Food and Drug Administration,¹⁹ which considers body surface area: [HED (mg/kg) = Animal dose (mg/kg) × (Animal weight/Human weight)^{0.33}]. This calculation method was also referenced by Wang and collaborators,²⁰ although their study delivered wine by diluting it into the drinking water to a final 6% EtOH concentration. For the present study, the dose was based on a human equivalent of one 200 mL glass of 14% (v/v) wine consumed by a 60 kg adult. Using this HED conversion, the equivalent dose for a 20 g mouse was calculated to be 94 µL. Therefore, mice were administered approximately 100 µL of their respective solutions daily (equivalent to 5 mL/kg/day). This

regimen was administered for 14 consecutive days, and on the 14th day mice were subjected to Y-maze testing as described in the experimental design (Fig. 3A).

Y-maze test

Spatial working memory was assessed via spontaneous alternation in a Y-maze. The apparatus consisted of three identical arms (35 cm long $\times$ 3 cm wide $\times$ 12 cm high, oriented at 120°) constructed from black Plexiglass. For each trial, a mouse was placed in the center and allowed 8 min of free exploration. The initial 2 min were considered a habituation period and excluded from analysis. During the subsequent 6 min test period, arm entries and alternations were recorded by an overhead video camera. An arm entry was defined as all four paws being within an arm, and a spontaneous alternation was defined as consecutive entries into three different arms (e.g., A, B, C). The maze was cleaned with 70% EtOH between trials. The percentage of alternation was calculated using the formula: [% Alternation = (Number of alternations / (Total arm entries – 2)) $\times$ 100].

Statistical Analysis

Data are presented as the mean $\pm$ standard deviation (SD). Statistical analyses were performed using Prism 8 software (GraphPad Software, San Diego, CA, USA). Differences between multiple groups were determined by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. A p-value < 0.05 was considered statistically significant. Significance levels are indicated as * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

RESULT

Antioxidant Activity of NRW

To evaluate the antioxidant capacity of NRW, which contains abundant polyphenols, we employed DPPH radical scavenging and Oxygen Radical Absorbance Capacity (ORAC) assays. Due to assay-specific considerations, different sample preparations were used. For DPPH measurements, the original liquid wine (containing 14% EtOH) was directly diluted in series, as ethanol does not interfere with this assay. However, for the ORAC assay, we utilized NRWP to avoid interference from the high ethanol content.

In the DPPH assay, NRW exhibited concentration-dependent free radical scavenging activity. Scavenging rates were $95.53 \pm 0.82\%$ for undiluted wine, $87.67 \pm 0.73\%$ (1:5 dilution), $84.25 \pm 0.63\%$ (1:10 dilution), $48.01 \pm 2.56\%$ (1:50 dilution), and $35.71 \pm 1.00\%$ (1:100 dilution) (Fig. 1A).

For ORAC analysis, NRWP was prepared at a maximum concentration of 1,000 $\mu\text{g/mL}$ and serially diluted. Concentrations of 1,000 and 500 $\mu\text{g/mL}$ exceeded the assay's upper quantification limit (data not shown). Within the detectable range, antioxidant activities expressed as Trolox equivalents were $45.59 \pm 0.15 \mu\text{M TE}$ (250 $\mu\text{g/mL}$), $29.40 \pm 1.63 \mu\text{M TE}$ (125 $\mu\text{g/mL}$), and $21.29 \pm 2.91 \mu\text{M TE}$ (62.5 $\mu\text{g/mL}$) (Fig. 1B).

These results confirm that NRW possesses substantial antioxidant capacity, showing dose-dependent increases in both assay systems, which indicates the presence of bioactive antioxidant compounds.

NRWP protects SH-SY5Y cells from EtOH-induced neurotoxicity

Before assessing neuroprotective properties, we determined the cytotoxicity profile of NRWP on SH-SY5Y neuroblastoma cells. Cells were exposed to NRWP at concentrations ranging from a 500 $\mu\text{g/mL}$ stock solution through serial dilutions. WST-8 assay analysis revealed no significant cytotoxicity at concentrations up to 500 $\mu\text{g/mL}$ (Fig. 2A), thereby establishing this range as

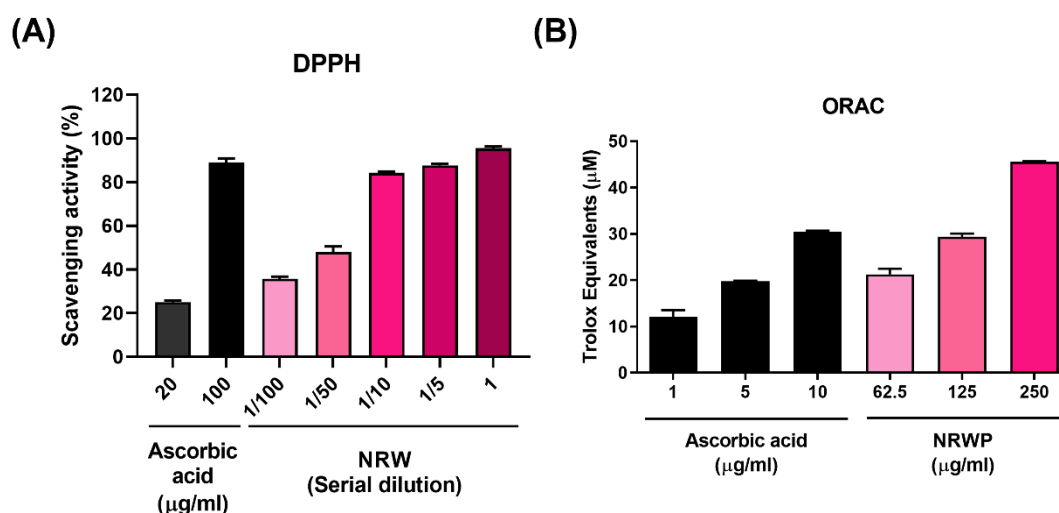


Fig. 1. Antioxidant capacity of NRW and its powder (NRWP). (A) DPPH radical scavenging activity of serially diluted NRW (original, 1:5, 1:10, 1:50, 1:100). Ascorbic acid was used as positive control. (B) ORAC activity of NRWP (62.5–250 $\mu\text{g/mL}$) expressed as μM Trolox equivalents. Both assays demonstrated a dose-dependent antioxidant capacity. Data represent mean $\pm$ SD from three independent experiments.

appropriate for subsequent neuroprotection studies.

To examine the protective potential of NRWP against ethanol-induced cellular damage, we conducted WST-8 viability assays in SH-SY5Y cells. Ethanol treatment alone decreased cell viability to approximately 80% relative to vehicle-treated controls. Co-treatment with NRWP significantly attenuated this cytotoxicity in a concentration-dependent manner, with 250 $\mu\text{g/mL}$ restoring viability to 92% and 500 $\mu\text{g/mL}$ achieving complete restoration to 100% (Fig. 2B).

These findings demonstrate that the non-alcoholic constituents of the wine confer direct cytoprotective effects at the cellular level.

NRW prevents EtOH-induced cognitive impairment in Y-maze test

Having established both the antioxidant properties of NRW and its capacity to mitigate ethanol-induced neurotoxicity in vitro, we next investigated whether these effects translate to cognitive protection in vivo. Following two weeks of treatment, cognitive function was assessed using the Y-maze spontaneous alternation test in mice (Fig. 3A).

Animals in the Sham group (distilled water) demonstrated normal working memory and spatial exploration behavior, with a spontaneous alternation rate of approximately 67.5%. The Control group (14% EtOH) exhibited marked cognitive impairment, with alternation rates declining to approximately 27.1%, confirming ethanol-induced cognitive dysfunction (Fig. 3B).

Remarkably, animals receiving 14% NRW maintained cognitive performance with an alternation rate of approximately 65%, which was statistically comparable to the Sham group and

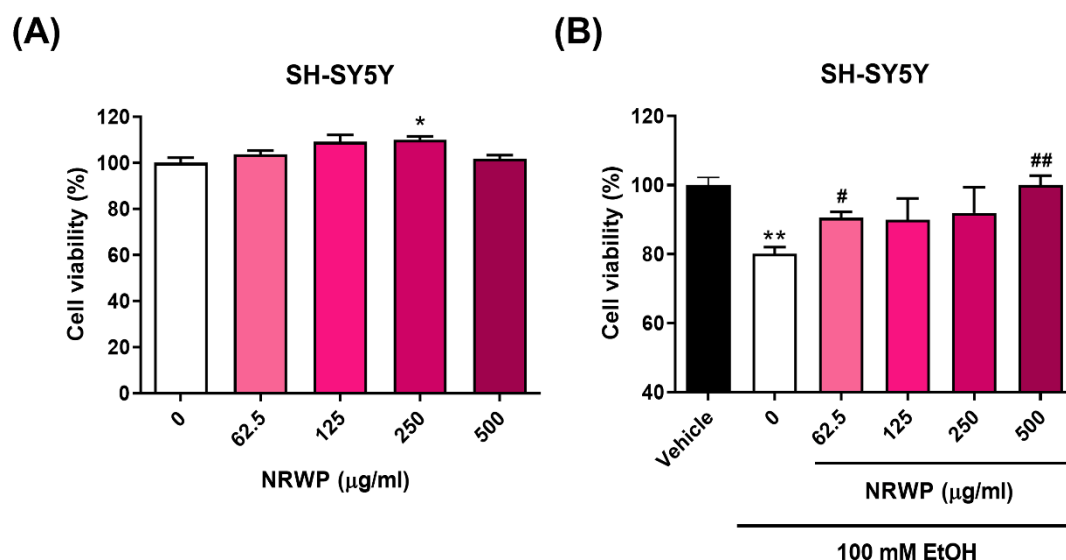


Fig. 2. Neuroprotective effect of NRWP against EtOH-induced cytotoxicity in SH-SY5Y cells. (A) Cell viability following 24 h treatment with NRWP (0–1000 $\mu\text{g/mL}$). NRWP showed no cytotoxicity up to 500 $\mu\text{g/mL}$. (B) Protective effect of NRWP against 100 mM EtOH-induced cytotoxicity. NRWP dose-dependently protected cells from EtOH-induced cell death. Data are mean $\pm$ SD from three independent experiments. ### p < 0.001 vs. Vehicle; * p < 0.05, ** p < 0.01, *** p < 0.001 vs. EtOH (one-way ANOVA with Tukey's test).

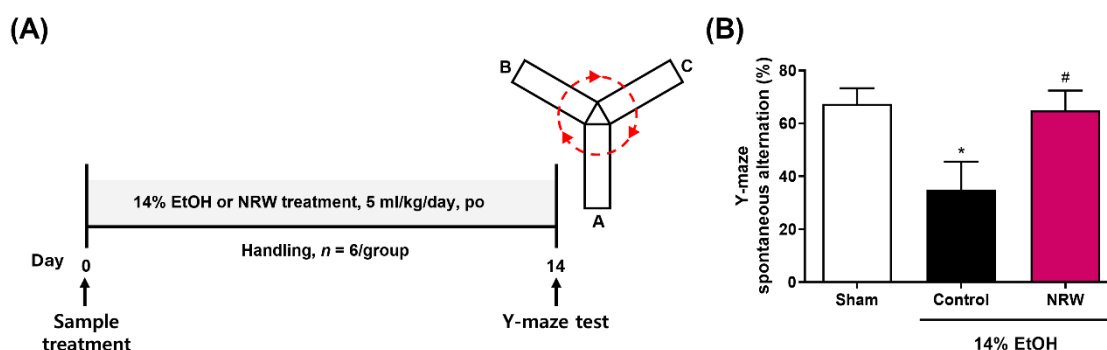


Fig. 3. Protective effect of NRW on EtOH-induced cognitive impairment in mice. (A) Schematic diagram of the experimental schedule. Mice received daily oral administration (Sham, EtOH Control, or NRW) for 14 consecutive days, followed by the Y-maze test. Groups: Sham (water), EtOH (14% EtOH), and NRW (14% NRW). NRW completely prevented EtOH-induced cognitive impairment. Data are presented as mean $\pm$ SD (n = 6/group). ### p < 0.001 vs. Sham; *** p < 0.001 vs. EtOH (one-way ANOVA with Tukey's test).

significantly higher than the Control group. This preservation of cognitive function suggests that NRW possesses robust neuroprotective properties capable of preventing ethanol-induced cognitive deficits *in vivo*.

DISCUSSION

This study demonstrates that Nebbiolo red wine effectively counteracts ethanol-induced neurotoxicity. While 14% ethanol solution produced marked cognitive deficits in the Y-maze test (approximately 27.1% alternation vs. 67.5% in controls), 14% NRW containing equivalent ethanol concentration completely preserved cognitive function (approximately 65% alternation). This striking difference indicates that NRW's phytochemical constituents exert potent neuroprotective effects.

The primary mechanism appears to be antioxidant-mediated ROS neutralization. Ethanol metabolism generates substantial reactive oxygen species in neural tissue,⁶ triggering oxidative damage that compromises neuronal function.⁷ Our demonstration of NRW's robust, dose-dependent antioxidant capacity in both DPPH and ORAC assays supports ROS scavenging as a key protective pathway.^{14,21} This is reinforced by our *in vitro* findings showing NRW directly protected SH-SY5Y cells from ethanol-induced cytotoxicity.²² The polyphenolic compounds in NRW are likely to cross the blood-brain barrier²³ and intercept ROS generated during ethanol metabolism, thereby preserving neural circuits underlying spatial working memory.

These findings underscore that alcoholic beverages should be viewed as complex mixtures rather than simply ethanol solutions. The rich polyphenolic profile of Nebbiolo grapes creates a protective effect that substantially offsets ethanol neurotoxicity, aligning with previous research on wine-derived antioxidants like resveratrol²⁴ and the general neuroprotective potential of wine polyphenols.^{12,25}

While these findings are compelling, several limitations warrant acknowledgment and suggest directions for future research. We did not quantify specific polyphenolic constituents in our NRW preparation, which would enable identification of the most protective compounds. Additionally, we did not measure molecular biomarkers such as BDNF,²⁶ neuroinflammation markers,⁸ or oxidative stress indicators that would elucidate underlying mechanisms. Finally, cognitive assessment was limited to the Y-maze test; a comprehensive behavioral battery would provide a fuller picture of NRW's neuroprotective scope.

Despite these limitations, our findings clearly demonstrate that NRW's antioxidant capacity translates into meaningful neuroprotection at both cellular and behavioral levels. These results suggest that beverage polyphenolic content may critically determine the net neurological impact of alcohol consumption,¹²

and highlight the need for greater attention to phytochemical composition in both research and public health contexts.

CONCLUSION

This study demonstrates that Nebbiolo red wine possesses significant neuroprotective properties mediated by its antioxidant polyphenolic compounds. NRW effectively prevented ethanol-induced cognitive impairment in mice and protected neuronal cells from ethanol-induced cytotoxicity *in vitro*, strongly supporting that wine's non-alcoholic constituents can counteract ethanol neurotoxicity. These findings suggest that polyphenolic composition may be a critical determinant of alcoholic beverages' net neurological impact, opening avenues for exploring wine-derived compounds as potential interventions to mitigate alcohol-related neurodegeneration.

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CONFLICT OF INTEREST

The authors state that there is no conflict of interest.

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