Clinical and Experimental Health Sciences

Neuroprotective effects of thymoquinone against ketamine -and MK-801-induced neurotoxicity in SH-SY5Y cells: From the perspective of glutamatergic dysfunction in schizophrenia

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ABSTRACT

Objective: Schizophrenia is a chronic disorder with approximately 1% prevalence and related to disrupted neurodevelopment process. It has been known that N-methyl D-Aspartate (NMDA) receptor antagonists such as ketamine and MK-801 mimic schizophrenia-like behaviors in rodents and cellular changes in cell culture. There are certain preliminary reports showing the beneficial effects of Nigella sativa L. extracts or its main active ingredient, thymoquinone, on psychiatric disorders. In our study, we aimed to investigate the neuroprotective effects of thymoquinone against ketamine – and MK-801 – induced neurotoxicites, which may be relevant to schizophrenia.

Methods: The neurotoxic concentrations of ketamine and MK-801, and non-toxic concentrations of thymoquinone were determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test at the 24th hour of administrations in SH-SY5Y cells. Seven different concentrations of thymoquinone (0.5 µM, 1 µM, 2.5 µM, 5 µM, 10 µM, 20 µM, 30 µM) were tested against two different concentrations of ketamine (250 µg/ml, 500 µg/ml) and one concentration of MK-801 (100 µM).

Results: Ketamine (250 µg/ml and 500 µg/ml) and MK-801 (100 µM) decreased ($P<0.05$) the cellular viabilities at the 24 hour of administrations. Thymoquinone pretreatment prevented ($P<0.05$) the decrease of cell viabilities against ketamine (250 µg/ml) and ketamine (500 µg/ml) at 1 uM, 2.5 µM, 5 µM, 10 µM, 20 µM, and 2.5 µM concentrations, respectively. Thymoquinone pretreatment also increased ($P<0.05$) cell viability compared to MK-801.

Conclusion: We suggested that thymoquinone had neuroprotective effects on the NMDA receptor antagonists induced neurotoxicity and encourage researchers for further in vivo studies for schizophrenia.

Keywords: Thymoquinone, ketamine, MK-801, SH-SY5Y cells, schizophrenia

1. INTRODUCTION

Schizophrenia is a severe psychiatric disorder with its complex symptoms. There are certain strong hypotheses about its neurobiology, even though the exact neuronal mechanisms are still unknown. According to the dopaminergic hypothesis, which is the oldest and well-accepted hypothesis, dopaminergic D2 receptor activity increased in the mesolimbic dopaminergic pathway while it decreased at the mesocortical pathway (1). One of the recognized complementary hypotheses, the glutamatergic N-methyl D-Aspartate (NMDA) receptor hypofunction hypothesis, emphasizes that the decrease in glutamatergic neurotransmission from cortical regions to brainstem cause a schizophrenia-related dopaminergic dysregulation. The fact that NMDA receptor antagonists such as ketamine and MK-801 lead to schizophrenia-like behaviors in humans and rodents is one of the reliable findings supporting this hypothesis (2). In addition, it has been shown that NMDA receptor antagonists mimic schizophrenia-like cellular and molecular alterations in cell culture (3). For these reasons, glutamatergic NMDA receptor antagonists are commonly used to set a schizophrenia model in rodents and cell culture.

There are also two essential hypotheses when the brain is considered structurally and functionally in schizophrenia. The first one is the neurodegenerative hypothesis, which was widely accepted by scientists until the 1990s. According to this hypothesis, individuals with normal brain functions and functions until young adulthood have degenerative damage that causes progressive impairment of neuronal functions in this period (4). In the neurodevelopmental hypothesis, which has become more accepted by the scientists in recent years, it is mentioned that a pathological condition that occurs during the development of the brain at early stages such as neuronal migration, neuronal survival, and plasticity causes disorders, and symptoms of schizophrenia occur in later periods (5). In both hypotheses, it has been seen that

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cell survival or cell death constitutes one of the main factors for the beginning of the disease. Therefore, cell viability has been accepted as an essential parameter in both *in vivo* and *in vitro* schizophrenia researches.

It has been demonstrated that glutamatergic NMDA receptor antagonist decreased cellular viabilities in various studies. Xia et al. (6) have demonstrated that the NMDA receptor antagonist Phencyclidine, which behaviorally creates a well-validated schizophrenia model in rodents, significantly increases programmed cell death, apoptosis, in rat corticostriatal cell culture. Another study has also shown that MK-801 significantly reduces cell viability in rat prefrontal cortex neuron culture, and paliperidone, an antipsychotic drug, can reverse the effect of MK-801 (7). Lei et al. (8) have shown that administration of Phencyclidine triggers caspase-3, an apoptotic protein in rat embryonic forebrain cell culture, cause apoptosis in these cells. They also have shown that ketamine significantly decreased cell viability as a result of increased apoptosis triggered by the caspase-3 protein in cells (8). Our previous studies also indicated that MK-801 decreased the neuronal viability, and this effect was prevented by an antipsychotic drug in SH-SY5Y cells (3).

Nigella Sativa L. (Ranunculaceae) is a widely used medicinal plant for various diseases worldwide. It has been proved that thymoquinone is one of the main constituents of *N. sativa* and thought to be responsible for the beneficial effects of *N. sativa* in several studies. It has been demonstrated that thymoquinone has a therapeutical potential with its antiinflammatory, antioxidant, hepatoprotective, anticancer, neuroprotective properties. Besides, studies have indicated it has therapeutical potential for certain neurological and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, stroke, epilepsy, depression, and anxiety (9, 10). However, no study examined the effects of thymoquinone on schizophrenia related neurotoxicity in previous studies.

As a result of the knowledges presented above, it has been shown that neuronal survival is an important parameter for schizophrenia researches. Therefore, neuroprotective agents in cellular schizophrenia models promise hope for further studies. It has been repeatedly indicated that thymoquinine had neuroprotective effects against various neurotoxic agents in previous studies. However, there is no study that investigates the effects of thymoquinone in schizophrenia-related cellular and molecular deficits in rodents or cell culture. In this study, we aimed to investigate the neuroprotective potential of thymoquinone in ketamine –and MK-801–induced neurotoxicity, which represents certain cellular aspects of schizophrenia, in SH-SY5Y human neuroblastoma cell line.

2. METHODS

2.1. Cell culture and drugs

SH-SY5Y human neuroblastoma cells (ATCC®CRL-2266, VA, USA) were cultured with Dulbecco's Modified Eagle's Medium (DMEM), supplemented with 10% (v/v) heat-inactivated fetal bovine serum (FBS), 100U/ml penicillin, and 100µg/ml streptomycin. Cells were cultivated at 37 °C under humidified conditions with 5% CO2 and were routinely tested for any contamination. Thymoquinone was dissolved in dimethylsulfoxide (DMSO, Sigma Aldrich, Germany) and added to the incubation media, with the final concentrations of 0.5 – 100 µM in DMSO at 0.5% (v/v). (+)-MK-801 hydrogen maleate, (SigmaAldrich, Germany) dissolved in a trace amount (<0.01 w/v) of DMSO and diluted with media. Ketamine (Ketalar®, Pfizer Pharmaceuticals, USA) was directly diluted with an appropriate volume of media.

2.2. Experimental design

The neuronal viability was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) analyses. In order to investigate the neuroprotective effects of thymoquinone, it is aimed to determine the neurotoxic concentrations of ketamine and MK-801 and non-toxic concentrations of thymoquinone in SH-SY5Y cells. For these aims, ketamine and MK-801 were used at concentrations of 50, 100, 250, 500, 1000 µg/ml, and 25, 50, 100, 250, 500 µM, respectively. Thymoquinone was used at concentrations of 1, 3, 10, 30, 100 µM in concentration determination experiments. After the first experiments (concentration determination), non-toxic concentrations of thymoquinone were treated to media 1 hour before the administrations of selected toxic concentrations of ketamine (250 µg/ml and 500 µg/ml) and MK-801 (100 µM). Twenty four hours after the ketamine or MK-801 administrations, cellular viabilities of SH-SY5Y cells were evaluated by MTT test.

2.3. MTT test

SH-SY5Y cells were seeded at a density of 10.000 cells / 100 µl per well in 96-well plates. MTT test was conducted for evaluating the cell viability of SH-SY5Y neuroblastoma cells according to the prior studies (11). In sum, cells were allowed to adhere to wells for 24 hours. After that, the cells were exposed to 25 µl of thymoquinone, ketamine, or MK-801 administrations for 24 hours. Then, the medium carefully aspired from all wells with a syringe and incubated with 100 µl MTT solution (5 mg/ml in medium) at 37 °C for 4 hours. The medium aspired from wells with a syringe, and 50 µl DMSO was added per wells for dissolving MTT salts. The plate was shaken for 5 minutes in a plate shaker. The absorbances of each well were measured by a microplate reader at 560 nm (Biotek, Synergy HT, VT, USA). The relative viabilities of thymoquinone, ketamine, and MK-801 administered cells were calculated by the following formula: "Absorbance of treatments /Absorbance of medium x 100."

2.4. Statistical analyses

GraphPad Prism 8 was used to perform the statistical analyses of this study. One-way analysis of variance (ANOVA) was used for statistical analysis. Multiple comparisons of groups were

made by Dunnett's post hoc test. The data were shown as mean ± standard error of the mean (SEM), and *P*<0.05 was accepted for the value of significance.

3. RESULTS

The cellular viabilities were measured by MTT test at 24th hours of administration to determine non-toxic concentrations of thymoquinone in a range of 1 uM – 100 µM. In parallel with this, cellular viabilities were investigated 24th hour after ketamine and MK-801 administrations to find toxic concentrations in a range of 50 µg/ml – 1000 µg/ml and 25 µM – 100 µM, respectively. After the determination of non-toxic concentrations of thymoquinone and toxic concentrations of ketamine and MK-801, the potential neuroprotective effects of thymoquinone were evaluated against ketamine and MK-801 induced neurotoxicity in SH-SY5Y cells.

Thymoquinone treatments (1 µM and 3 µM) increased (*P*<0.05) the cellular viability compared to medium at the 24th hour of administration in SH-SY5Y cells. Thymoquinone (100 uM) decreased (*P*<0.001) the cell viability, while 10 uM and 30 uM concentrations of its did not alter the viability compared to medium treated cells (Figure 1).

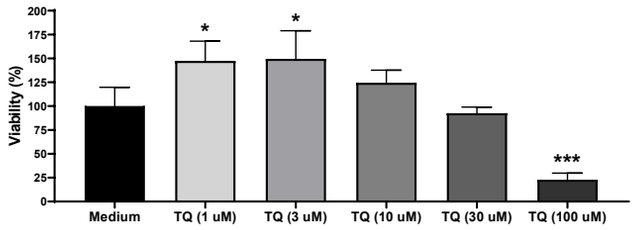

Figure 1. *The effects of thymoquinone on cellular viabilities in SH-SY5Y cells. Data were presented as mean ± SEM, and statistical analyses were done with one way ANOVA followed by Dunnett's post hoc test. * P<0.05, *** P<0.001 compared to medium treated cells. (TQ: Thymoquinone)*

Ketamine at the concentrations of 50 µg/ml and 100 µg/ml did not alter the cell viabilities compared to medium at the 24th hour of administrations in SH-SY5Y cells. However, ketamine concentration-dependently decreased the cell viabilities at the 250 µg/ml, 500 µg/ml, and 1000 µg/ml concentrations compared to medium treated cells (Figure 2).

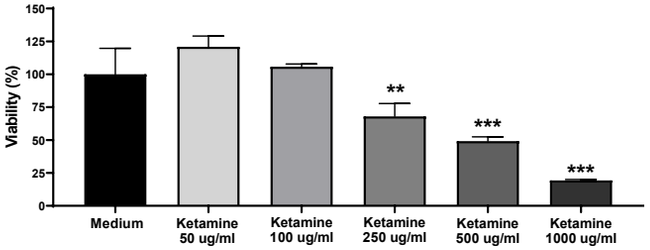

Figure 2. *The effects of ketamine on cellular viabilities in SH-SY5Y cells. Data were presented as mean ± SEM, and statistical analyses were done with one way ANOVA followed by Dunnett's post hoc test. ** P<0.01, *** P<0.001 compared to medium treated cells.*

MK-801 administrations did not alter the cell viabilities at the concentrations of 25 µM and 50 µM compared to medium treated cells. MK-801 markedly decreased (*P*<0.001) the viabilities at the concentrations of 100 µM, 250 µM, and 500 µM (Figure 3).

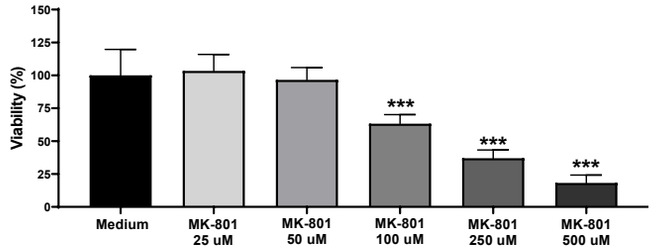

Figure 3. *The effects of MK-801 on cellular viabilities in SH-SY5Y cells. Data were presented as mean ± SEM, and statistical analyses were done with one way ANOVA followed by Dunnett's post hoc test. *** P<0.001 compared to medium treated cells. (TQ: Thymoquinone)*

Ketamine (250 µg/ml) administration significantly decreased (*P*<0.001) cell viability compared to medium in SH-SY5Y cells. Thymoquinone pretreatments at the concentrations of 1 µM (*P*<0.01), 2.5 µM (*P*<0.001), 5 µM (*P*<0.001), 10 µM (*P*<0.001), 20 µM (*P*<0.01) markedly increased viability compared to ketamine (250 µg/ml) administrated cells. However, there is no significant difference between ketamine and thymoquinone pretreated cells (Figure 4).

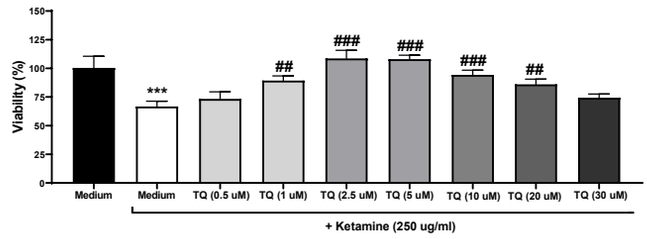

Figure 4. *The effects of thymoquinone pretreatments on ketamine-induced cellular death in SH-SY5Y cells. Data were presented as mean ± SEM, and statistical analyses were done with one way ANOVA followed by Dunnett's post hoc test. *** P<0.001 compared to medium, ## P<0.01 and ### P<0.001 compared to ketamine (250 ug/ml) treated cells. (TQ: Thymoquinone)*

It has been found that ketamine (500 µg/ml) administration markedly decreased (*P*<0.001) the number of living cells compared to medium treated ones. Thymoquinone pretreatment at the 2.5 µM concentrations increased the cell viability compared to ketamine (500 µg/ml) administered cells while did not alter the cell viabilities at the other concentrations in SH-SH5Y cells (Figure 5).

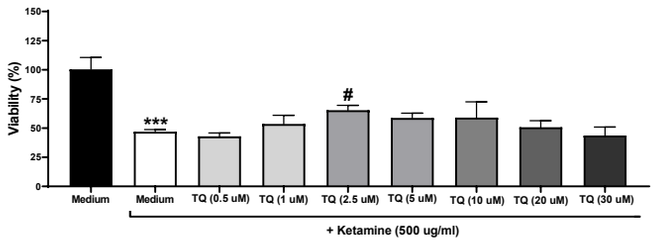

Figure 5. *The effects of thymoquinone pretreatments on ketamine (500 ug/ml) induced cellular death in SH-SY5Y cells. Data were presented as mean ± SEM, and statistical analyses were done with one way ANOVA followed by Dunnett's post hoc test. *** P<0.001 compared to medium, ### P<0.001 compared to ketamine (500 µg/ml) treated cells. (TQ: Thymoquinone)*

It has been seen that MK-801 (100 µM) administration markedly (*P*<0.001) decreased the cellular viabilities in SH-SY5Y cells. Thymoquinone pretreatment significantly increased the survival at the concentrations of 1 (*P*<0.01), 2.5 (*P*<0.001), 5 (*P*<0.01), 10 (*P*<0.001) µM whereas it is ineffective at the concentrations of 0.5, 20 and 30 µM against MK-801 induced cell death in SH-SY5Y cells (Figure 6).

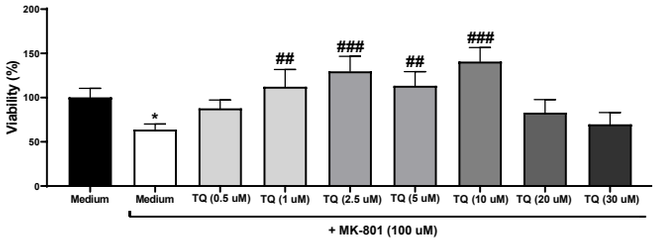

Figure 6. *The effects of thymoquinone pretreatments on MK-801 induced cellular death in SH-SY5Y cells. Data were presented as mean ± SEM, and statistical analyses were done with one way ANOVA followed by Dunnett's post hoc test. * P<0.05 compared to medium, ## P<0.01, ### P<0.001 compared to MK-801 treated cells. (TQ: Thymoquinone)*

4. DISCUSSION

In our study, the potential neuroprotective effects of thymoquinone on ketamine and MK-801, which are widely used to create an experimental models of schizophrenia and cell culture, induced neurotoxicity was investigated in SH-SY5Y cells. Prior to this, it has been examined whether single thymoquinone administration has neuroprotective or neurotoxic effects on SH-SY5Y cells and determined the toxic and non-toxic concentrations of it. After that, toxic concentrations of ketamine and MK-801 were also determined in SH-SY5Y cells. Our results showed that thymoquinone has a neuroprotective effect at the low concentrations (1 µM and 3 µM) and neurotoxic effect at the high concentration (100 µM) in SH-SY5Y cells. It has also been found that NMDA receptor antagonism caused toxicity at the higher concentrations than 250 µg/ml, and 100 µM for ketamine and MK-801, respectively. When the neuroprotective potential of thymoquinone was investigated, it has been seen that thymoquinone prevented the neurotoxicity induced by both NMDA receptor antagonists in SH-SY5Y cells.

The studies which aim to enlighten the neurobiology of schizophrenia have revealed that the hypofunction of glutamatergic NMDA receptors plays a critical role in the neurobiology of disease. The fact that NMDA receptor antagonists, such as ketamine, caused schizophrenia-like manifestions in healthy volunteers and mimick schizophrenia-like behaviors and neurobiological findings in preclinical studies supports this hypothesis (12, 13). In recent years, some parts of the psychiatry researches shifted to *in vitro* studies because of its certain advantages such as low cost, time-effective, and lack of ethical approval compared to *in vitro* or clinical studies. In these studies, neuronal survival and intracellular signaling pathways are commonly investigated in certain neuronal cell lines. Zhao et al. (14) showed that ketamine (5 mM) administration caused neurotoxicity in embryonic stem cell-derived neuron culture. In another study, it has been indicated that ketamine (300 µM and 1000 µM) increased cell death at the 24th hour of administrations in rat hippocampal cells (15). It has also been demonstrated that ketamine (100 µM) administration induced apoptosis and decreased neuronal survival in rat cortical neuron culture (16). When our results were investigated from this aspect, it has been shown that ketamine administrations at the 250 µg/ml (900 µM) and 500 ug/ml (1,8 mM) had neurotoxic effects on SH-SY5Y neuroblastoma in accordance with the previous researches. For MK-801, our previous study also showed the neurotoxic effects of 100 uM MK-801 at the 6th, 12th, and 24th hours of administrations in SH-SY5Y cells (3). Besides, it has been shown that MK-801 caused neuronal death in prefrontal cortical neurons, and this effect was reversed by atypical antipsychotic drugs (17). In accordance with these studies, MK-801 caused neurotoxicity at the 24th hour of administrations in SH-SY5Y cells in our study.

There are limited number of studies about the effects of thymoquinone on schizophrenia. It has been indicated that thymoquinone treatment decreased certain schizophrenia-related behaviors in mice (18). In addition to this, our previous studies showed that the hydroalcoholic extract of *N. sativa* reversed schizophrenia-like behaviors in acute ketamine models of schizophrenia in rats (19). Besides, certain studies may indirectly contribute to the investigation of the effects of thymoquinone on schizophrenia. It has been known that neurodegeneration and related inflammatory alterations play a role in schizophrenia pathophysiology (20). Certain studies showed that thymoquinone had an antiinflammatory effect in microglial cell culture besides of its neuroprotective effect against some neurotoxic agents (21). In these studies, it has been demonstrated that the usage of thymoquinone at the concentrations of 0.1 – 1000 µM protected neurons from neurotoxicity induced by 1-methyl-4-phenylpyridinium (MPP) and amioid beta, which present Parkinson and Alzheimer like neuronal conditions (21). At this point, we first reported that thymoquinone had neuroprotective effects on ketamine and MK-801 induced neuronal toxicities. Our results provide a confirmation for neuroprotective effects of thymoquinone

against different neurotoxic agents. Moreover, our results suggest a therapeutical potential of thymoquinone on schizophrenia, even though our study provides a preliminary perspective to schizophrenia pathophysiology and does not mimic the complete alterations of schizophrenia.

In conclusion, we showed that ketamine and MK-801 caused a neuronal injury in parallel with its schizophrenia-like effects in clinical and preclinical studies. We have firstly demonstrated that thymoquinone may have beneficial effects on ketamine and MK-801 induced cellular models of schizophrenia. We suggest that our study will provide a basis for the studies that will investigate the beneficial effects of thymoquinone in further studies and will give a promising prospect for effective treatment of schizophrenia. Also, investigating the potential beneficial effects of thymoquinone with all aspects such as behavior and *ex vivo* analyses will be valuable for further studies.

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