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Ferulic Acid Induces NURR1 Expression and Promotes Dopaminergic Differentiation in Neural Precursor Cells

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ABSTRACT

Degeneration of dopaminergic (DA) neurons in the substantia nigra is known as the main cause of Parkinson's disease (PD). Preventing the loss of DA neurons alongside the cell-replacement therapy have brought tremendous hope for the treatment of PD. For this purpose, various studies have been done to find the specific DA neuro-protective compounds or progressing DA-differentiation methods. Ferulic acid (FA) has strong neuro-protective effects, but at this point its role on protection and differentiation of DA neurons is not well-defined. Mouse neural stem cells (mNSCs) were treated with FA and expressions of TH (tyrosine hydroxylase) and NURR1 as the DA neuron specific markers were determined using real time qRT-PCR and immunostaining assays. Finally, efficacy of FA on DA differentiation was evaluated in comparison with other methods using fibroblast growth factor 8b (FGF8b) and sonic hedgehog (SHH). Treatment with FA could increase the *Th* and *Nurr1* gene expressions in mNSCs. Also, it enhanced *β-tubullin-III* expression and increased the neurite length in treated groups. Real time qRT-PCR and immunostaining assays showed that FA could increase DA differentiation in mNSCs effectively. Also, gene expression profile in some groups showed that FA can raise the differentiation rate of other neuronal subtypes such as cholinergic neurons. FA effectively induces the DA differentiation in neural precursor cells by its ability to increase the expression of the NURR1 transcription factor, which is a known transcription factor for differentiation of midbrain DA neurons.

Keywords: Dopaminergic, neural stem cell, Ferulic acid, differentiation, Nurr1, Tyrosine hydroxylase

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Introduction

Dopaminergic (DA) neurons of the midbrain are the main source of dopamine (DA) in the mammalian central nervous system (CNS) and they have different subtypes such as A9 group in the substantia nigra (SN) and the A10 group in the ventral tegmental area (VTA) (1, 2). Parkinson's disease (PD) is one of the most common progressive neuro-degenerative disorders in elderly people resulted from a loss of DA neurons in the SN pars compacta (SNpc) (3). Reducing the rate of neuronal death or replacing the lost neurons with fresh DA neurons are eventually the most hopeful therapeutic approaches for PD (4). Therefore, some studies have focused on neuro-protective roles of antioxidants to support DA neurons (5) and others on DA neurogenesis to replace them (4). The most ideal therapy could be a compound that can employ both of the neuro-protective and neuro-differentiating effects. Ferulic acid (FA) is one of the well-known natural compounds, which is found in seeds and leaves of plants like corn, brown rice, and oats (6, 7). FA has potential pharmacological features that benefit neuronal progenitor cell proliferation, anti-inflammatory reactions, anti-oxidative processes, and neuro-protective activities (8, 9). FA has efficient *in vitro* and *in vivo* effects in neurogenesis (10, 11). It has been shown that FA-treated PC12 and mouse neural stem cells (NSCs) exhibit neuronal differentiation and neurite outgrowth *in vitro* (12). FA also induces neuron-like differentiation in human mesenchymal stem cells (hMSCs) (13). It also effectively inhibits the gentamicin-induced hearing loss in animal models by stimulating the neuronal differentiation of NSCs in auditory nerve (14). Furthermore, some reports have suggested that FA can improve the symptoms of PD and increase the level of tyrosine hydroxylase (TH) protein in DA neurons (8). FA has also been shown to elevate dopamine synthesis and DA neuron proliferation in the limbic-system of brain in a mouse model of depression (15).

On the other hand, cell replacement therapies are requiring adequate number of DA neurons for the treatment of neurodegenerative disorders like PD, in which the production of DA neurons from stem cells using natural compounds could be a leading approach. However, there is no *in vitro* study in terms of inducing DA-differentiation using FA.DA neurons are classified into the category of catecholaminergic neurons that release dopamine, and tyrosine hydroxylase (TH) is their specific key enzyme converting phenylalanine into dopamine (16). Different transcription factors are responsible for the determination of the DA fate and the most important one is NURR1 (Nuclear receptor related 1), which is a critical factor for the development of midbrain DA neurons and regulation of their TH expression (17). Many studies have been conducted to investigate the DA-induction in NSCs and in the most successful reporting fibroblast growth factor 8 (FGF8b) and sonic hedgehog (SHH) were used to achieve a high percentage of DA neurons (18, 19). In this survey, the ability of FA on induction of NURR1 and TH expression as well as DA differentiation in mouse NSCs have been studied.

Materials and Methods

Cell culture

Mouse neural stem cells (mNSCs) were available as a cell line in Royan Institute (Isfahan, Iran) (20). NSCs were cultured in T25 flasks in complete NSC medium consisted of neurobasal medium, 1% N2

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supplement, 1% GlutaMAX, 1% NEAA, 20 ng/mL bFGF (Sigma) and 20ng/mL EGF (Sigma) to form neurospheres (20).

Because for the rest of the experiments, the neurospheres had to be single-celled, they were transferred into T15 tubes, centrifuged (110 g) and their supernatant was discarded and after two times wash with DPBS, they were incubated in 1 mL of 0.05% *Trypsin*-EDTA for 5 min. After adding equal volume of soybean trypsin inhibitor to stop the trypsin activity single cells were centrifuged (700g) and suspended in 1 mL of NSC medium.

To assess the effect of FA on *Th, β-tubulin III* and *Nurr1* expressions in mRNA level, cells were cultured for seven days on Poly-L-lysin (Sigma, P4707) coated 6-well plates (25×10^4 cell/well), in the basic NSC medium consisted of neurobasal medium supplemented with 1% N2 supplement, 1% GlutaMAX, 1% NEAA, and 200 mM L-Ascorbic acid (Sigma, A4544), in the presence of various concentrations (0, 50, 100, 200, 300 µg/mL) of FA (Sigma, 128708). Once every three days, half of the cell's culture media were refreshed. All of the cell culture media and reagents were purchased from Thermo Fisher Scientific, USA.

Differentiation induction

To evaluate the effect of FA on DA differentiation, according to the results from preliminary qRT-PCR assays (Figure 1), indicating that FA in the concentration of 100 µg/mL was the most effective dose for *Nurr1* expression, this concentration was used for complementary DA-differentiation induction assays. For this purpose, mNSCs were cultivated for seven days in three different treatment groups: 1) control (basic NSC medium), 2) FA-treated (basic NSC medium with FA (100 µg/mL)), and 3) DDF-treated (basic NSC medium in presence of DA differentiation factors (DDF), SHH 100 ng/mL (Sigma, S0191) and FGF8b 200 ng/mL (Sigma, F6926)) (21). Treatments were performed on mNSCs which were grown on Poly-L-lysin (Sigma, P4707)-coated 6-well plates (25×10^4/well for qRT-PCR) or 24-well plates (8000/well for immunostainings). Once every three days, half of the cell's culture media were refreshed.

Real-Time Quantitative Reverse Transcription PCR

Total RNA was extracted from mNSCs using Trizol and RNeasy Mini Kit (QIAGEN). Then, cDNA was synthesized from extracted RNA using MMLV reverse transcriptase and Oligo (dT) primer (AmpliSens). Quantitative real time-PCR was performed by SYBR-Green-based method. PCR was performed as follows: 35 cycles of denaturizing (94 °C, 30s), annealing (52 °C, 30s) and extension (72 °C, 30s). Real-time PCR SYBR Green Master Mix (LifeTechnologies, USA) was used for the amplification reactions. cDNA was prepared from 1 µg RNA in a reaction volume of 20 µL and then, 1 µL of cDNA was used for qPCR. The sequences of primers are listed in Table 1. The $2^{-\Delta\Delta CT}$ method was used to calculate the relative quantification of gene expressions. All experiments were repeated three times and each time was performed in triplicate.

Immunostaining

Double immunostainings were performed (22) to detect the presence of TH/Nurr1 and β-tubulin III/Nurr1 antigen pairs in cells. Initially, samples were fixed in 4% paraformaldehyde for 10 minutes at room temperature (RT). Next, permeabilization was performed by 10 min incubation with 0.1%Triton X-100. Then, nonspecific antibody binding was blocked through incubation with 10% heat inactivated normal goat serum (Merck G9023) for 30 minutes at 37 °C. To perform appropriate double staining, for TH/Nurr1

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Table 1. The list of primers used for real time qRT-PCR assay.

Gene name	Primer sequences	Gene ID
Gapdh	F: TGCCGCCTGGAGAAACC R: TGAAGTCGCAGGAGACAACC	NM_008084.2
Th	F: TGCCAGAGAGGACAAGGTTC R: ATACGCCTGGTCAGAGAAGC	NM_009377.2
Nurr1	F: TGGCTATGGTCACAGAGA R: GTAGTTGGGTCGGTTCAA	NM_019328.3
β-tubulin 3	F: GCCTCCTCTCACAAGTATG R: CCTCCGTATAGTGCCCTT	NM_023279.2
Chat	F: GTGAACTCCCTGCTCCCAGA R: CTCAGTGCCAGAGATGGTTGT	NM_009891.2
Gad1	F: TGATACTTGGTGTGGCGTAG R: ACTCTTCTCTTCCAGGCTATTG	NM_008077.5

pair, at first samples were incubated for an overnight at 4 °C with primary mouse anti-TH antibody (Merck, T1299, 1:200). And for β-tub III/Nurr1 pair, incubation with primary mouse anti-β-tub III antibody (Merck, T8578, 1:250) was the first one. Then, they were incubated for two hours with suitable goat anti mouse secondary antibodies (Chemicon, AP124F, FITC conjugated (1:100), and Merck, T7782, TRITC conjugated (1:125), respectively). Next, samples were incubated with the second round of primary and secondary antibodies, first with rabbit anti-Nurr1 primary antibody (sc-5568, 1:200) for an overnight, and then with goat anti rabbit secondary antibodies (Chemicon, AP132C, Cy3 conjugated, and AP132F, FITC conjugated, both 1:100) for two hours. Finally, their nuclei were counterstained using DAPI (3 µM for 15 minutes). Before and after of each one of the above explained incubations samples were washed for three times in PBS, 5 min for each wash. Ten images were captured from each sample at 40x magnification (Nikon DS-Fi1 Digital Sight 5MP Camera) and the ratio of the Nurr1 and TH stained cells was determined in each image by counting the stained cells. All of the staining steps were done in the dark room.

Statistical analysis

One-way analysis of variance (one-way ANOVA) with post-hoc Tukey test was used to compare the differences in the means. P-values less than 0.05 were considered statistically significant. Data were represented as Mean ± SEM.

Results

Effect of different concentrations of FA on Th and Nurr1 expression in mNSCs

To confirm the effect of FA on Nurr1 and Th expression in mNSCs, cells were treated with different concentrations of FA (0-300 µg/mL) and our results revealed a concentration -dependent enhancement in neurite outgrowth in the FA-treated groups (Figure 1A-E). Furthermore, FA increased the expression of *β-tubulin III* in the treated cells, which is an essential structural protein for axonal growth. Also, FA in 100 µg/mL concentration had the highest impact on expression of *Th*, which is a critical marker for DA neurons ($P < 0.0001$, compared to the control, Figure 1F).

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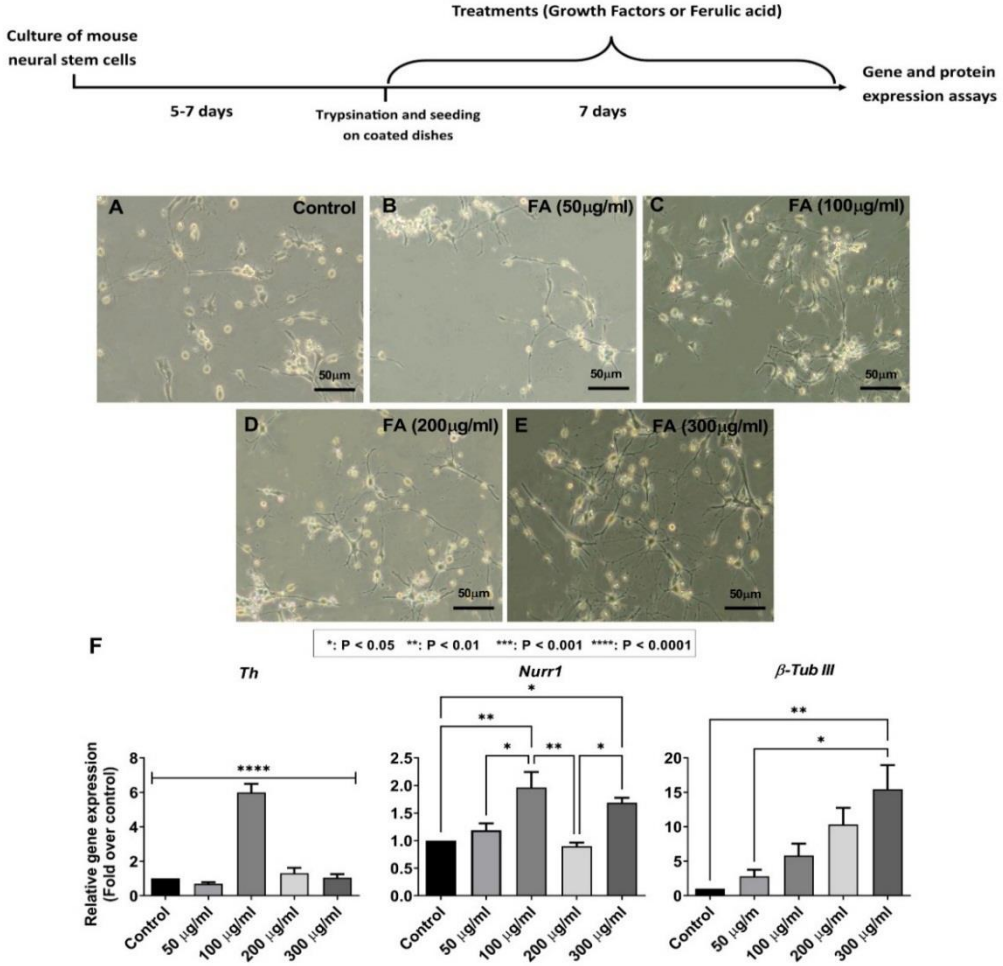

Fig 1. Effect of different concentrations of FA on expressions of *Th*, *Nurr1* and *β-tubulin 3* genes in mNSCs. As represented in schematic timeline, cells were treated for 7 days with 0, 50, 100, 200 and 300 µg/mL of FA (A-E). Real time qPCR results for *Th*, *Nurr1* and *β-Tub* III gene expressions shows that FA 100 µg/mL had the most potent effect on expressions of *Th* and *Nurr1* (F). Scale bars represent 50 µm (A-E). Data is presented as mean ± S.E.M.

FA at 100 µg/mL concentration showed the strongest effect on *Nurr1* expression compared to all other groups. Also, FA at 300 µg/mL concentration significantly increased the expression of *Nurr1* compared with the control group but at 200 µg/mL FA could not increase the expression of *Nurr1* ($P<0.05$, Figure 1F).

Effect of FA treatment on DA differentiation rate compared to FGF8 and SHH

Since the gene expression level, it was found that FA has the ability to increase the expression of *Nurr1* and *Th* in mNSCs, its effect on induction of DA differentiation in mNSCs was investigated in more detail, and ultimately the concentration of 100 µg/mL was chosen as the best FA concentration for complement studies. In the terms of differentiation induction influence, the ability of FA was compared with the well-known DA induction factors SHH and FGF8b. The results of these experiments showed that treatment with FA increases the expression of *Th* gene almost 4 folds over that in the control group ($P < 0.01$), while in the

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SHH+FGF8b treatment group it was 6 folds over the control group (P < 0.001). Thus, compared with other groups, the SHH+FGF8b group had the greatest effect on increasing the *Th* expression as compared to FA group (P <0.05, respectively, Figure 2D).

To assess the ability of FA to induce differentiation into other neuronal categories, *Chat* expression for cholinergic neurons and *Gad1* expression for GABAergic neurons were measured, and it was found that FA is able to increase *Chat* expression by 1.5 times (P < 0.05, compared to the control group). However, in this respect, the SHH+FGF8b group was able to increase the expression of the *Chat* gene more effectively than the other groups (P < 0.001, P < 0.01 compared to the control, and FA, groups respectively). Examination of the *Gad1* expression level, on the other hand, revealed that there was no significant difference in the expression of this gene among different groups (Figure 2D).

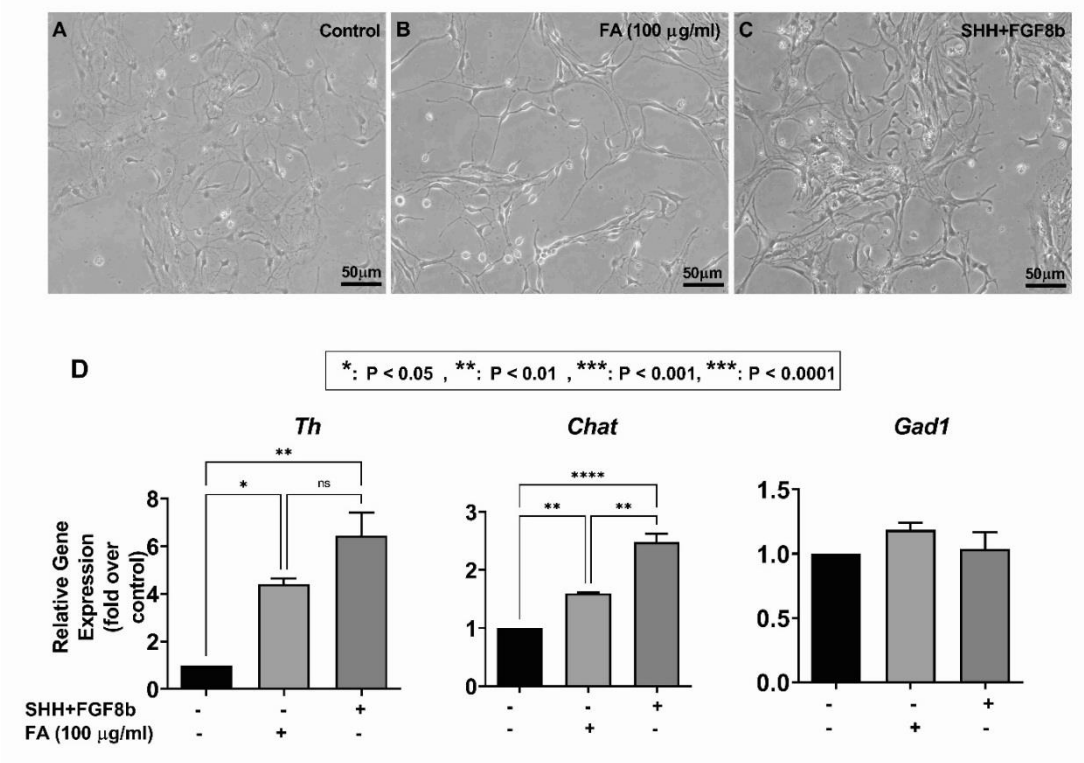

Fig. 2. Expression of *Th*, *Chat* and *Gad1* genes in FA-terated group and its comparison with cells treated with DA induction factors (SHH and FGF8b) and control. NSCs were treated based on different groups: 1) no treatment or control, 2) FA 100 µg/mL, and 3) SHH+FGF8b (A-C), for seven days, and later the expressions of *Th*, *Chat* and *Gad1* genes were evaluated (D). Scale bars are representing 50 µm (A-C). Data is presented as mean ± S.E.M.

Immuno-staining for proteins TH and NURR1 was used to confirm the effect of FA on the differentiation of DA neurons, and the findings confirmed that the percentages of Th-positive cells in FA and SHH+FGF8b treated groups were significantly higher than the control group (P < 0.001, P < 0.0001, respectively).

Also, in comparison between FA group with the SHH+FGF8b group, it was detected that the mean number of TH-positive neurons was higher in the SHH+FGF8b group, but the difference was not statistically significant (Figure 3G).

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Staining against Nurr1 showed that treatment with FA has improved the number of Nurr1-positive cells ($P < 0.001$, compared to the control). Also, in the SHH+FGF8b treated group, as it was expected, there was a significant increase in the number of Nurr1-positive cells compared to the control group ($P < 0.0001$) (Figure 3H).

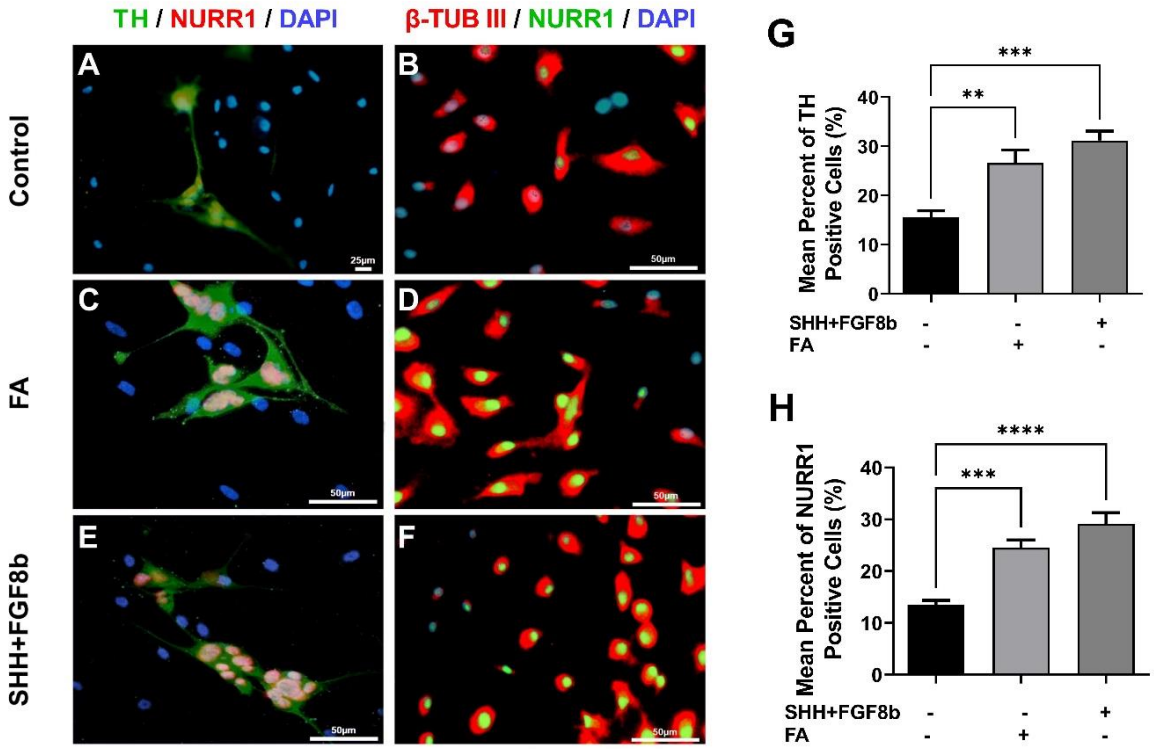

Fig. 3. Effect of FA on DA differentiation in comparison with conventional DA induction factors (SHH and FGF8b). To determine the DA differentiation in neurons, NSCs were treated with defined factors and then stained against TH, NURR1 and β-TUB III proteins (A-F). G & H are representing the percentage of TH- and NURR1-positive neurons respectively. Scale bars represent 25 µm (A) and 50 µm (B-F). Data is presented as mean ± S.E.M (***: $P < 0.001$ and ****: $P < 0.0001$).

Discussion

The most important finding of the present study revealed that FA is able to increase TH and NURR1 expression in both gene and protein levels in neural stem cells. This ability of FA for induction of DA differentiation was relatively close to the effect of conventional DA-inducing factors FGF8b and SHH.

Previous reports have shown that FA has anti-apoptotic and differentiation-inducing effects (12), and the results of present study revealed that FA can induce DA differentiation in neural stem cells probably by its NURR1 inducing effect. Our findings also revealed that FA at a concentration of 100 µg/mL has the most potent effect on both TH and NURR1 expressions in mNSCs. Also, it could increase the expression of β-tubulin III in neuron dose dependently.

NURR1 is one of the most important transcription factors playing important roles in regulation of genes involved in the development of DA neurons and DA transmission in the CNS (23). Nurr1 acts through targeting the CREB-induced survival proteins and modulating the signaling function of neurotrophic factor receptors. For example, NURR1 supports the survival and maintenance of DA neurons by regulating its

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downstream target Ret (canonical receptor of GDNF). In addition, NURR1 affects the expression of several genes contributing in synthesis, neurotransmission and metabolism of DA, including TH, VMAT2, and DAT (17).

In addition, other studies have reported that following the induction of NURR1 overexpression in NSCs, they start to differentiate toward DA neurons (23), and other reports confirmed that these NURR1-overexpressing cells have close similarities with developing VM (ventral midbrain) neurons (24). These findings suggest that DA neurons can be obtained by inducing NURR1 expression in neuronal progenitor cells, a feature that could be important for therapeutic applications.

Other studies have shown that FA can stimulate mitochondrial dynamics through modulation of PGC1α expression (25). Also, it has been reported that Nurr1 can modify the expression of several nuclear mitochondrial genes such as SOD1, TSFM, and COX5β, which are important markers for stable respiratory functions of mitochondria (17). Accordingly, FA can contribute to the respiratory function of cells and therefore plays an important supportive role in the reduction of mitochondrial damage in DA neurons. In addition, there are some *in vivo* studies confirming the effectiveness of FA for PD. As it was reported that FA could increase the concentration of TH in the striatum of Parkinsonian animal models (26), and in another study FA therapy could elevate dopamine synthesis in the brain and consequently reduces depressive behaviors in animal models (15). These findings reflect the undeniable effects of FA in the treatment of PD by increasing Nurr1 expression, improving mitochondrial activity, and exerting neuroprotective properties.

Regarding the potency of FA on NURR1 induction, a 7-day *in vitro* treatment was used in this study to differentiate mNSCs toward DA neurons. Various other methods have been proposed by other scientists to achieve DA neurons, such as induction by growth factors or by co-culture with stromal cells (SDIA) (27), and using genetic manipulations (28). Interestingly, the required time to achieve DA neurons by these methods lasts approximately 14-20 days. This suggests that the use of FA can effectively reduce the required time for production of DA neurons *in vitro*.

The FA method enabled us to induce the expression of the Th marker in about 30% of the cells, which was relatively close to the number counted in the FGF8b + SHH method. In a similar study, Barberi *et al*., reported that by using SHH and FGF8b factors, they were able to obtain 50% of positive Th cells (18). Also, Tan *et al*., have reported that they have achieved to 25% of mesencephalic DA subtype by culturing neural progenitor cells on an engineered cell culture surface in the presence of SHH and FGF8b factors (19). Therefore, according to these reports, our study showed that treatment with FA can be as effective as other methods in the induction of DA differentiation.

In assessing the ability of FA to induce the genes of other neuronal types, such as cholinergic and GABAergic, our results showed that FA can induce *Chat* expression. In agreement with our results, it has been reported that FA elevates the expression of *Chat* gene in TMT-induced memory impaired mice (29). Also, in another study, T6FA (Tacrine-6-Ferulic Acid) was able to increase Chat activity and reduces AChE activity in AD mice (30).

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On the other hand, FA did not increase the expression of *Gad1*, which is related to GABAergic neurons. Nonetheless, Kim et al. have reported that the combination of rice extract and FA might increase the expression of *Gad1* in rats (31).

This study showed that FA, by increasing the expression of *Nurr1*, can increase the DA differentiation in NSCs, however, it did not define the exact subtype of these DA neurons. Since Nurr1 is specifically involved in the development of DA neurons in the midbrain, it is possible that FA may have produced midbrain specific DA neurons. Therefore, further studies are needed to determine the role of FA in subtype specification of DA neurons.

In conclusion, our findings showed that FA could increase the differentiation of DA neurons by inducing NURR1 expression thereby helps to improve the function of the brain's DA system.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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