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Nanocurcumin Encapsulation Enhances Alzheimer's Gene Expression in Neuroblastoma Cells Treated with Chemical Inducers

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Abstract

Introduction: Encapsulating of curcumin in calcium phosphate nanoparticles will boost its antioxidant potential while simultaneously lowering oxidative stress. Molecules having at least one oxygen atom and one or more unpaired electrons that are capable of independent living are known as reactive oxygen species. Free oxygen radicals such as singlet oxygen, hydroperoxyl radical, hydroxyl radical, superoxide anion radical, and free nitrogen radicals fall under this group. Aerobic respiration and the inflammatory response, which largely take place in hepatocytes and macrophages, produce trace amounts of reactive oxygen species (ROS).In a situation where antioxidants fail to counteract these charged species, patients with neurological disorders such as Parkinson's and Alzheimer's disease may develop. Free radicals and charged species have been demonstrated to be more prevalent in patients with neurological disorders. This is linked to neuronal cell oxidative damage. Thus, in helping with neuroprotection and lessen oxidative stress under these circumstances, antioxidants are frequently employed. Methodology: Five grams of turmeric were weighed and extracted using a Soxhlet apparatus. The extract was evaporated, and the sample was weighed for further calculation. Additionally, four different varieties of turmeric were sampled, weighing 10 gm of turmeric and extracting the extract in 500 millilitres of ethanol. 8 cycles for every sample. The Antioxidant Assay of Extracts (ABTS Assay) is also employed. Moreover, column chromatography was used to purify the extracts. that the fractions chosen for HPLC examination have the highest amount of curcumin.with s modifications aamorphous calcium phosphate nanoparticles using the co precipitation approach from (Xia et al. 2018). and the use of synthesized calcium phosphate nanoparticles to encapsulate curcumin. to treat SHSY-5Y cell line induce with glyceraldehyde and rotenone chemical inducers, Conclusions:These findings provide insights into potential avenues for developing treatments that target the genetic aspects of AD and Parkinson's disease. However, further mechanistic exploration is necessary to fully comprehend the underlying

molecular mechanisms and translate these findings into effective clinical strategies for these intricate neurological disorders.

Key words: Neuroblastoma, Chemical Inducers and Encapsulated Nano Cur Cumin

Introduction

Curcuma longa belongs to the Zingiberaceae family of herbaceous perennial plants, which also includes ginger. It has subterranean stems or tuberous rhizomes. *Curcuma longa L*, a plant of the Zingiberaceae family, is a popular spice across Asia, including India. The primary constituents are polyphenols, which have a bright yellow colour.Turmeric's pharmacological or biological properties can thus be advantageous for pharmaceutical drug research and innovative treatment development. Both in ancient and modern times, plant-based medicines have played a significant role in the healthcare systems of many societies. According to Verma et al. (2021) the composition of turmeric powder is around 60–70% carbs, 6–13% water, 6–8% protein, 5–10% fat, 3-7% dietary minerals, 3-7% essential oils, 2-7% dietary fibre, and 1-6% curcuminoids. Its most commonly used medicinal component, the root, contains a range of minerals and phytochemicals. Turmeric contains a variety of phytochemicals, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin, which belong to the family of curcuminoids known as diarylheptanoids. 34 essential oils are found in turmeric, the most important being zingiberene, atlantone, germacrone, and turmerone (Ahmad et al., 2020): (Verma et al., 2021). Supplements containing *curcuma longa L* exhibit several biological and pharmacological characteristics, such as antiviral, antibacterial, antiallergic, anticancer, and cardioprotective effects. Researchers are presently employing bio-nanotechnology as a contemporary option to undertake a variety of studies aimed at producing the required treatments for neurological illnesses.Numerous studies have employed nanoparticles as drug carriers for both in vitro study (Tukur and Karnawat 2021).

An excess of reactive species, such as oxygen and hydroxyl free radicals, can result in oxidative stress, which can also be produced by a deficiency in the antioxidant system. According to Priyanka et al. (2017), Sharifi-etal. 2020, Sies. 2020, Tanvir et al. 2017), and Xia et al. (2018), oxidative stress results from an imbalance between prooxidants (free radicals) and antioxidants. Both oxidants and free radicals can lead to oxidative stress. They therefore initiate the body's oxidation process. Because of the many effects it has, it contributes to the emergence of diseases. Moreover, DNA, lipids, and proteins are all harmed. The production of vital biological components and the oxidative phosphorylation process that supplies ATP to cells are two of the mitochondria's important roles. Reactive oxygen species (ROS) concentrations must be low for normal cellular signalling. The genesis of chronic illnesses as cancer, diabetes, neurological disorders, and cardiovascular diseases is significantly influenced by oxidative stress (OS) (Sharifi-et al., 2020); (Sies, 2020); (Tanvir, et al., 2017); (Xia et al., 2018).

According to Bhalani et al. (2022), curcumin, a hydrophobic polyphenol obtained from the dried rhizomes of Curcuma longa L., has great promise in the treatment of neurological conditions and brain tumours (Brain, &Delivery., 2021). The main barrier preventing curcumin from entering the brain is the blood-brain barrier (BBB). Because of this, curcumin has a number of drawbacks that make it difficult to utilise as a drug, such as a very low oral bioavailability. Curcumin's bioavailability will be improved through the recently developed drug encapsulation of Amorphous Calcium Phosphate (ACP) Nanoparticles. Because of its advantageous properties, including biocompatibility, biodegradability, and a significant affinity for binding to nucleic acids, (ACP) are hence efficient drug delivery materials. Askarizadeh, 2020; Brain & Delivery, 2021; Abrami, 2018. Using SH-SY-5Y neuroblastoma cells induced with Alzheimer's disease inducers such as glyceraldehyde and retenone,

among others, the research aims to present a current nanobiotechnological approach of curcumin encapsulation with (ACP) nanoparticles antioxidant potency that will be used for in vitro study in treatment of Alzheimer's age-related neurodegenerative diseases.

Materials and Methods

5 gm of turmeric were weighed, Soxhlet extracted, and the extract's evaporation process and sample weighing were all done for calculation. Additionally, four different varieties of turmeric were sampled, weighing 10 gm of turmeric and extracting the extract in 500 millilitres of ethanol. 8 cycles for every sample. The Antioxidant Assay of Extracts (ABTS Assay) is also employed. Moreover, column chromatography was used to purify the extracts. that the fractions chosen for HPLC examination have the highest amount of curcumin.with s modifications aamorphous calcium phosphate nanoparticles using the co precipitation approach from (Xia et al. 2018). and the use of synthesized calcium phosphate nanoparticles to encapsulate curcumin. to treat SHSY-5Y cell line induce with glyceraldehyde and rotenone chemical inducers,

Gene expression analysis

RNA isolation:

Total RNA was isolated and separated from DNA and protein after extraction with a solution called as Trizol (Sigma) according to manufacturer instruction. Briefly200 µL of cell culture sample were taken. 500 µL of Tizol solution was added vortexed vigorously for 30 second Kept on ice for 20 minutes. Centrifuged in refrigerated centrifuge at 10,000 RPM, at 4^0 C for 10 minutes. Collected the supernatant in fresh tube. Added 500 µL of chilled chloroform and 100 µL of Isoamyl alcohol. Vortexed thoroughly and kept in ice for 15 minutes. Centrifuged in refrigerated centrifuge at 10,000 RPM, at 4^0 C for 15 minutes. Collected aqueous phase in new eppendorf. Added equal volume of chilled Isopropyl alcohol and vortexed properly. Incubated at -20^0C for 30 - 35 minutes followed by centrifugation in refrigerated centrifuge at 10,000 RPM, at 4^0 C for 10 minutes. Supernatant discarded and pellet collected. Air dried the pellet. Added 50 µL of Nuclease free water and stored at -20^0C for 10 minutes. Qualitative and quantitative analysis of RNA was performed.

cDNA Synthesis:

mRNA (4ug) from tissue were used for first strand cDNA synthesis by reverse transcription using RevertAidTM First Strand cDNA Synthesis Kit (Fermentas) in a thermocycler (MWG Biotech). The RNA samples were incubated with 1 ul of oligo (dT) primers (100 µM, 0.2 µg/µl) and 12 µl of nuclease-free water at 65degreeC for 5 min. The reaction was cooled on ice to allow the primers to anneal to the RNA, then spin down and placed on ice again after which the following components were added to the reaction in order; 4ul of 5X Reaction Buffer, 1 ul of RibolockTMRNase inhibitor (20 U/ml), 2 ml of 10 mMdNTPs and 1.0 uL of RevertAidTM M-MuLV-Reverse Transcriptase (200 U/ul). The reagents were gently mixed and incubated for 1 hr at 42degreeC and then at 70degreeC for 5 min terminated the reaction and the synthesized cDNA was stored at –20 0 C for further use.

Gene expression analysis of Tau and αβ42 protein for Alzheimer's.

Briefly 5 ulcDNA, 15 ul of ddH2O incubated for 60 minutes at 45 Degree, followed by incubation at 95^0 for 5 min. Diluted with 30ml Nuclease free water. PCR reaction was set by adding 25 µl sybr green, 2 µl Primer F, 2 µl of Primer R, 5 µl of prepared cDNA and 16.0 µl of nuclease free water. 7 minutes at 95°C, then 40 cycles of 10 seconds at 95°C, 20 seconds at 60°C, and 20 seconds at 72°C were used for amplification. All of the tests were done in triplicate. The comparative cycle threshold approach was employed to assess the relative expression of target genes, with b-actin serving as a normalizer.

expression of target genes, with b-actin serving as a normalizer.

Samples	IC50 concentration(µg/ml)
Curcumin:	127.8305332
Calcium phosphate:	98.46698113
Encapsulated NP:	195.210122
Inducer for Alzheimer's disease	
Inducer1 (okadaic acid):	119.5099399
Inducer2 (AlCl3):	108.3870968
Inducer3 (Glyceraldehyde):	92.56163811
Inducers for Parkinson's disease	
Inducer 4 (Rotenone):	75.12713823

Table.1 Summarizing and exhibiting the IC50 Concentrations Graphs and Inducing Process

Cell Images under the Effect of Inducers and Inducer and Encapsulated (ACP) NaNOCurcumin

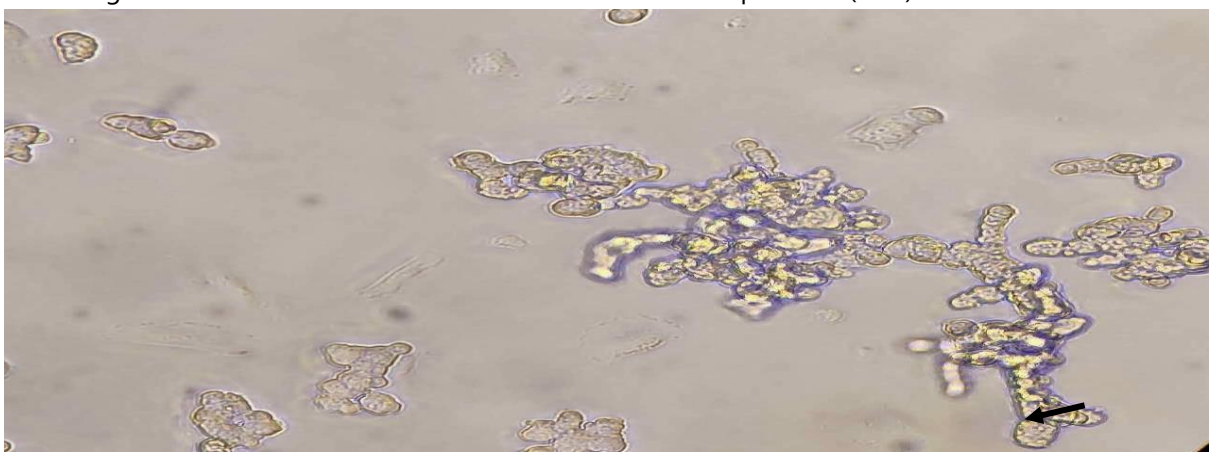

Figure. 1. SH-S5Y5 cell lines. Cells were in suspension and adhered also.

undifferentiatedneuroblastoma cells after 24 hrs. of incubation.

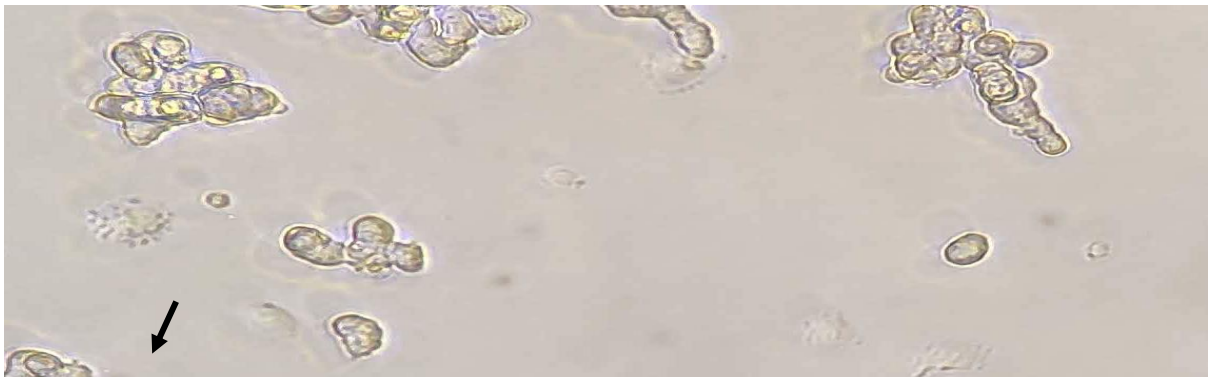

Figure. 2 Cell after induced with IC50 concentration of Glyceraldehyde.

Cell blebbing, indication of early apoptotic cells. Cells circularized and no initiation of differentiation of cells.

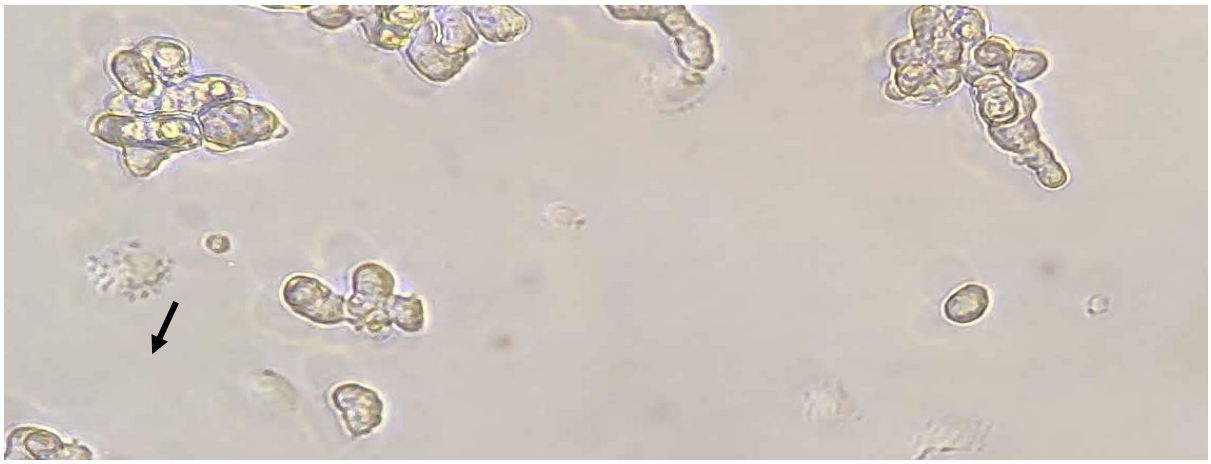

Figure. 3 Cell after induced with IC50 concentration of Glyceraldehyde.

Cell blebbing, indication of early apoptotic cells. Cells circularized and no initiation of differentiation of cells.

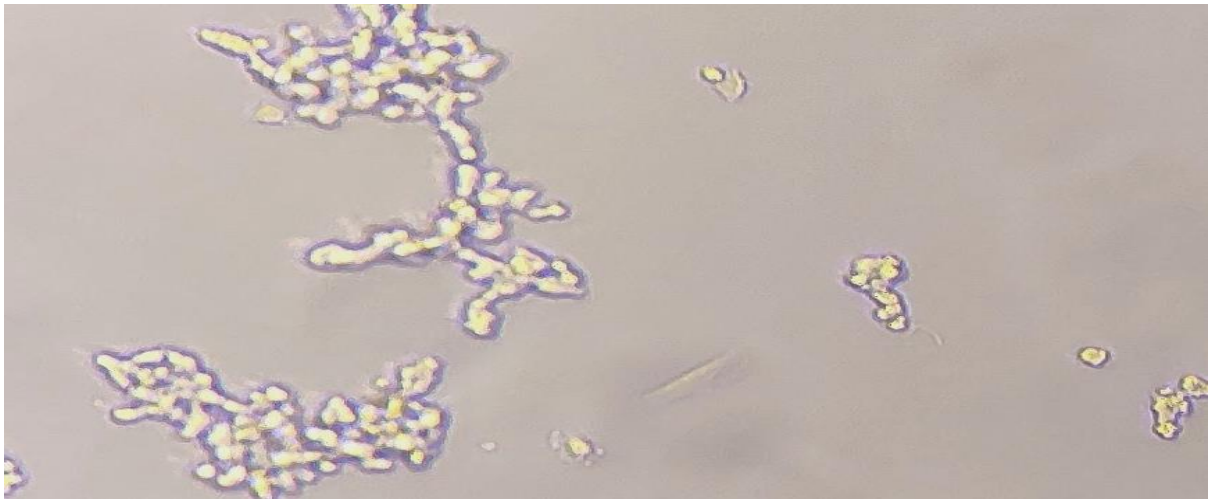

Figure. 4 Cell after treatment with IC50 concentrations of glyceraldehyde and Enapsulated (ACP) Nano Curcumin.

More differentiated cells after treatment of Enapsulated (ACP) Nano curcumin. Some early apoptotic cells observed.

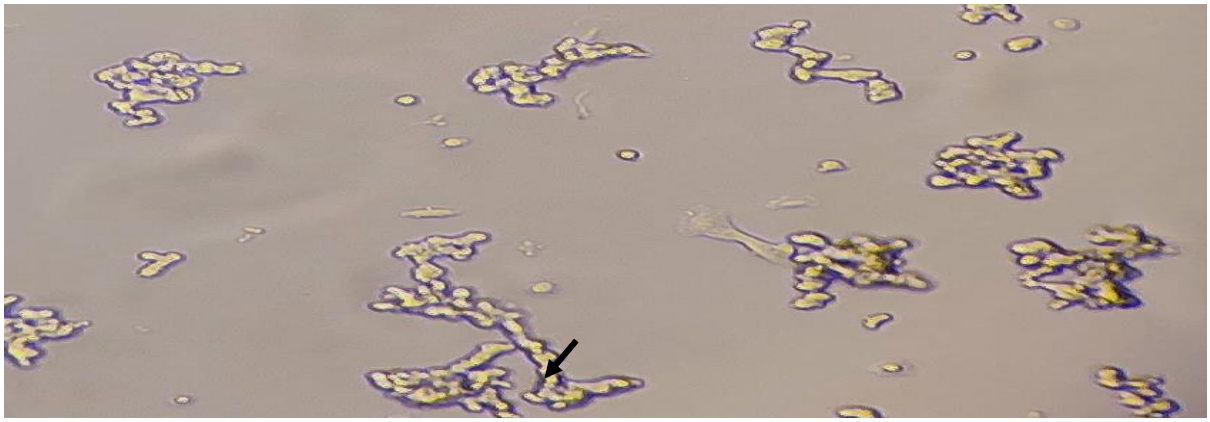

Figure. 5Cell after induced with IC50 concentration of rotenone.

Cell blebbing indicating late apoptotic cells, more circularized cells indicating more cells in suspension and lost properties of adhering.

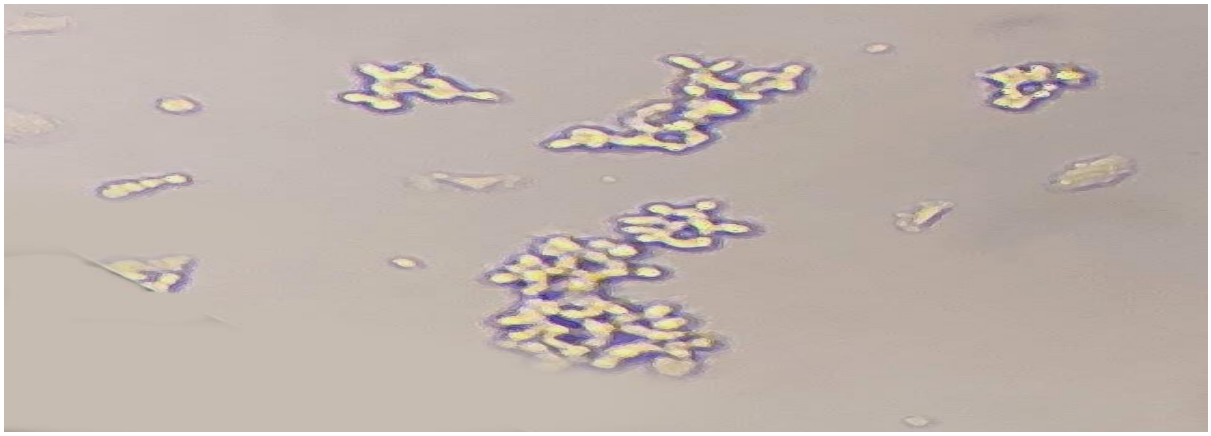

Figure. 6 Cell after treatment with IC50 concentrations of rotenone and Enapsulated (ACP) Nano Curcumin.

Increased circularization of cells implies a greater presence of cells in a suspended state, resulting in a loss of their adhesive characteristics. The impact of Enapsulated (ACP) Nano Curcumin. curcumin on rotenone induced morphological changes in cells were found to be relatively insignificant.

Gene Expression Analysis of APP, MAPT and MAP2 Genes of Alzheimer's
Amplification plot

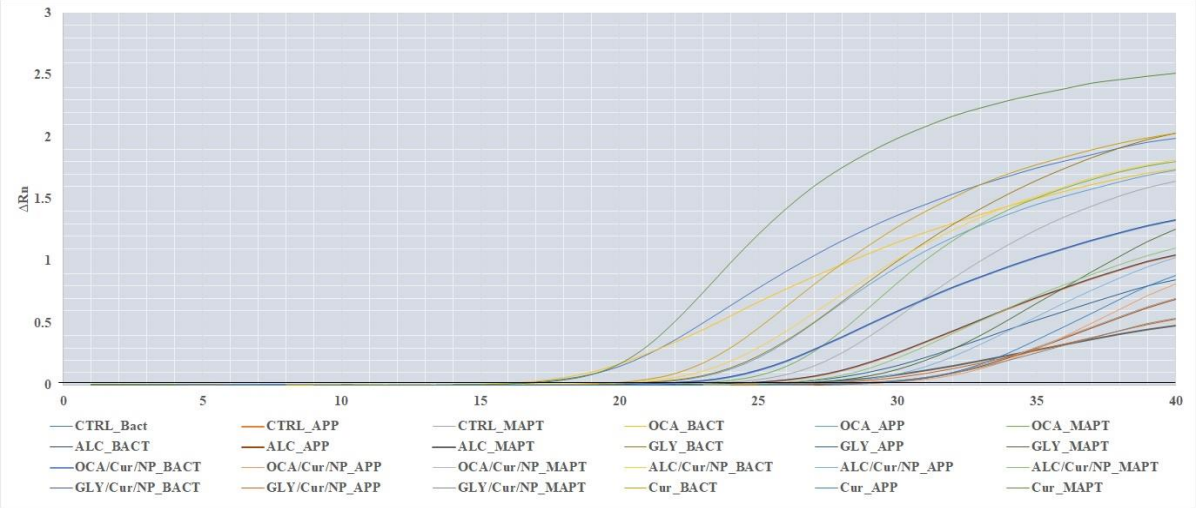

Figure7: Amplification plot of genes. Florescence (ΔRn) on Y axis and Number of cycles on x axis.

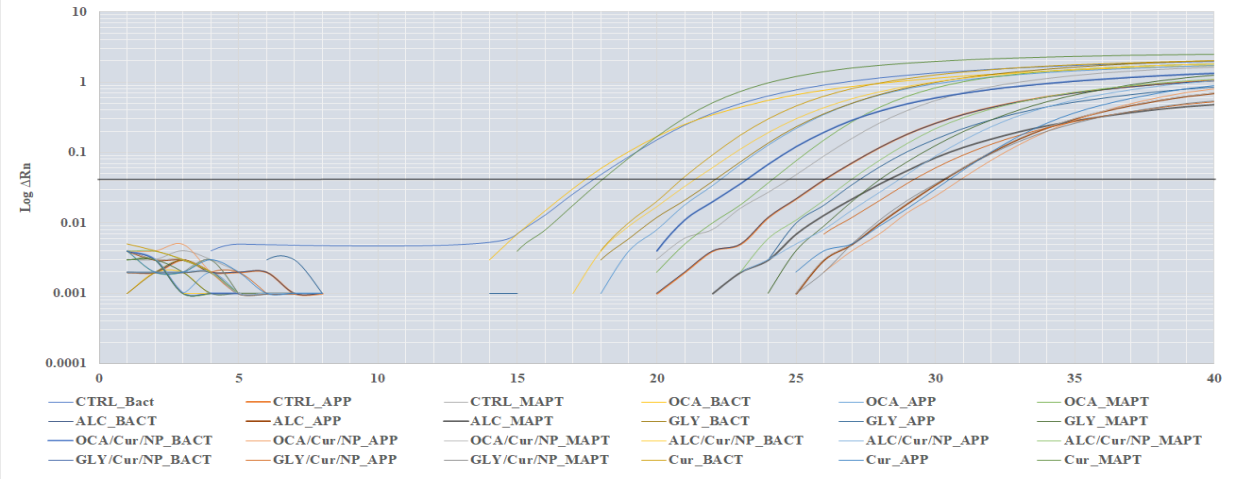

Figure8: Amplification plot of genes. Log of Florescence (Log ΔRn) on Y axis and Number of cycles on x axis.

Fold change calculation:

Sample	Ct	delta ct	delta delta Ct	negative delta deltact	fold change
CTRL_Bact	18.350				
CTRL_APP	26.610	8.261			
CTRL_MAPT	25.344	6.995			
OCA_BACT	18.069				
OCA_APP	22.854	4.785	-3.476	3.476	11.126
OCA_MAPT	24.704	6.635	-0.360	0.360	1.2833
ALC_BACT	26.610				
ALC_APP	30.919	4.308	-3.953	3.953	15.483
ALC_MAPT	28.860	2.250	-4.745	4.745	26.814
GLY_BACT	22.633				
GLY_APP	27.916	5.283	-2.978	2.978	7.8768
GLY_MAPT	28.649	6.016	-0.979	0.979	1.9708
OCA/Cur/NP_BACT	23.755				
OCA/Cur/NP_APP	31.445	7.690	-0.571	0.571	1.4858
OCA/Cur/NP_MAPT	30.919	7.163	0.169	-0.169	0.8897
ALC/Cur/NP_BACT	21.955				
ALC/Cur/NP_APP	29.322	7.366	-0.895	0.895	1.8590
ALC/Cur/NP_MAPT	27.617	5.661	-1.333	1.333	2.5199
GLY/Cur/NP_BACT	23.755				
GLY/Cur/NP_APP	29.777	6.021	-2.240	2.240	4.7228
GLY/Cur/NP_MAPT	30.868	7.112	0.118	-0.118	0.9217
Cur_BACT	21.580				
Cur_APP	31.013	9.433	1.172	-1.172	0.4436
Cur_MAPT	18.601	-2.979	-9.973	9.973	0.0009

Table2 Gene Expression Analysis of APP, MAPT And MAP2 Genes of Alzheimer's. Disease.

Sample	Fold change (2^-ΔΔCt)
CTRL	1
Oca/APP	11.13
Oca/MAPT	1.28
AlCl3/APP	15.48
AlCl3/MAPT	26.81
Gly/APP	7.87
Gly/MAPT	1.97
Oca/Cur/APP	1.48
Oca/Cur/MAPT	0.88
AlCl3/Cur/APP	1.85
AlCl3/Cur/MAPT	2.51
Gly/Cur/APP	4.72
Gly/Cur/MAPT	0.92
Cur/APP	0.44
Cur/MAPT	0.0009

Table3. Gene Expression Analysis of APP, MAPT And MAP2 Genes of Alzheimer's. Disease.

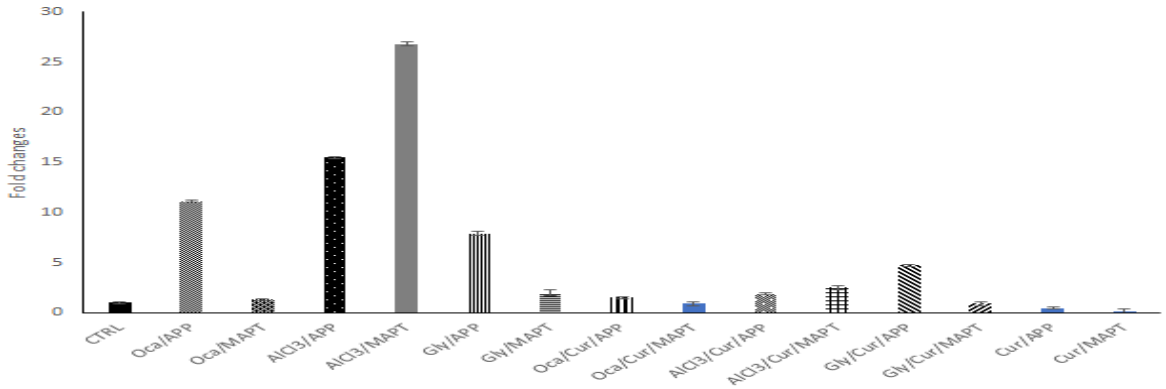

Figure10: Fold change or 2-ΔΔCt of APP and MAPT genes in SH-SY5Y cells incubated with inducers and inducer/Curcumin.TheqRT-PCR slope should be between -3.6 and -3.2; if the slope is -3.32, the PCR efficiency is said to be 100%. The PCR efficiency should be between 90 and 110 percent, but 100 percent is ideal. In the present study the efficiency of the target and selected controls were compared to see if they were nearly equal, which is a requirement for using the Ct method for quantification. The present study shows the over expression of APP and MAPT for all inducers treated SH-SY5Y cells while their expression is greatly reduced after the treatment of 128 µg/ml (IC50) concentration of curcumin. Only curcumin treated cells showed under-expressed APP and MAPT.

Conclusions: These findings provide insights into potential avenues for developing treatments that target the genetic aspects of AD and Parkinson's disease. However, further mechanistic exploration is

necessary to fully comprehend the underlying molecular mechanisms and translate these findings into effective clinical strategies for these intricate neurological disorders.

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