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Introduction

Neurodegeneration is a process which includes the loss of neuronal structure and functions (Yadav, 2021). The 21st century has seen an increase in the prevalence of these disorders for which there is presently no known cure. The elderly population has a higher prevalence of neurodegenerative disorders. Due to a rise in the percentage of population that is elderly, these disorders are becoming more common worldwide. In elderly individuals, they develop systematically and ultimately result in mortality (Velmurugan *et al.,* 2018). The neuronal loss is due to different metabolic and toxic disorders in specific individuals. Nowadays, these diseases, which are associated with different multifactorial etiologies have created massive medical, social and financial problems (Hou *et al.,* 2019). The pathological signs of neurodegenerative disorders are ageing, disability and mortality. These include autism, learning disabilities, Huntington's disease, cerebral palsy, Schizophrenia, Alzheimer's disease, neuromuscular, Lateral sclerosis and Parkinson's disease (Baker *et al.,* 2018; Hussain *et al.,* 2018).

A number of lifestyles such as physical activity, diet, intellectual engagement and social interactions are associated with the risk of age-related neurodegenerative disorders (Kim *et al.,* 2019). Acetyl cholinesterase inhibitors are first-line medications for the treatment of neurodegenerative diseases and are associated with mild improvements in cognitive functions, behaviour and activities of daily living. However, the clinical relevance of these effects is unclear. The cholinergic theory hypothesizes that cholinergic system dysfunction contributes to cognitive decline. One of the biomarkers of neurodegenerative diseases is decreased acetylcholine concentration and function, which are associated with memory and learning (Marucci *et al.,* 2021). The world population is ageing and while people are living longer, neurological degeneration is becoming more prevalent (Vanni *et al.,* 2020). The World Health Organization predicts that the number of adults with dementia globally is roughly 55 million with nearly 10 million new cases each year (one every 3.2 seconds) and an expectancy of approximately 153 millions by 2050 (Napoli, 2023; Vardy, 2020).

Neuroprotection refers to the strategies and mechanisms that can fight neuronal damage caused by neuropsychiatric and neurodegenerative disorders. By the 2040s, neurodegenerative illnesses are predicted to rank as the second most common cause of mortality among the elderly Mukherjee *et al.,* (2020); Mensah-Kane and Sumien, (2023). Among the strategies for neuroprotection, phytochemicals may represent a valuable remedy in preventing neurodegenerative diseases. Herbal products generally contain various kinds of bioactive phytochemicals such as alkaloids, steroids, terpenoids, saponins, phenolics and flavonoids. It is also difficult to identify which parts of the herb such as the leaves, stems, roots, flowers, fruits and seeds are biologically active for specific functions. Researchers globally have been searching for phytochemicals with bioactive compounds that are present in herbs that could be employed as neuroprotectives in conventional medical systems such as traditional Chinese medicine, Indian Ayurvedic medicine, Korean medicine, Mediterranean medicine and so on (Kumar *et al.,* 2015).

Mammalian cells have free-radical scavengers that prevent or eliminate ROS before they cause harm to vital parts (Tewari *et al.,* 2014). The brain contains several kinds of antioxidants, including the thiol-containing molecules glutathione, a non-enzymatic antioxidant and the enzymatic antioxidant superoxide dismutase. The central nervous system is especially susceptible to peroxidation processes due to its high polyunsaturated fatty acid content. However, the central nervous system lacks specifically enhanced defenses against antioxidants. The human brain has substantial quantities of iron and ascorbate. In actuality, the brain has less antioxidant activity than other tissues. Thus, brain cells are more vulnerable to oxidative injury than cells in other tissues (Franco *et al.,* 2019; Mohebbati *et al.,* 2017). Increased levels of reactive oxygen species have been associated with ageing. Reactive oxygen species formation may not be necessary for ageing, but it can worsen age-related disorders due to oxidative damage and interactions with mitochondria (Tan *et al.,* 2018).

Normally, small levels of reactive oxygen species are normally not hazardous, but excessive amounts can cause oxidative stress, which is the major cause of neurodegenerative disorders. Antioxidants can limit the generation of reactive oxygen species, tissue damage and increase cell survival. A free radical is defined as any chemical species that contains unpaired electrons which produce highly reactive free radicals that react with singlet oxygen in the biological system and produce reactive oxygen species and reactive nitrogen species.

Oxidative stress and nitrogen stress occur when there is an imbalance between the production of reactive oxygen species and antioxidant molecules in the body. However, the excess production of reactive oxygen species can damage or inhibit the normal functions of lipids, proteins and DNA (Sisein, 2014). Thus, the "redox hypothesis" has replaced the original free radical theory, which states that oxidative stress is caused by the breakdown of thiol redox circuits. This is critical in cell signaling and physiological regulation without causing macromolecular damage. In fact, proteins' thiols can serve as transducing elements between chemical (reactive oxygen species) and biological structure (Checa and Aran, 2020). These reactive oxygen species trigger the production of pro-inflammatory cytokinins and chemokinin mediators (Mzindle, 2017; Jomova *et al.*, 2023).

Phytochemicals are naturally found and they are shown to have protective action against oxidative stress and neuroinflammation, which are major hallmarks of neurodegenerative diseases common phytochemicals which we come across in our daily lives are curcumin, quercetin, diallyl trisulfide, flavonoids and epigallocatechin-3-galate. Phytochemicals induce the immune system, decrease platelet aggregation and regulate hormone metabolism (Velmurugan *et al.*, 2018; Limanaqi *et al.*, 2020; Dash *et al.*, 2021). Phytochemical substances in plants contain phenolic and flavonoid groups, which have potential health benefits such as cell protection against oxidative damage, neurodegenerative disease prevention and many types of cancers. Plants (fruits, vegetables, or medicinal plants) may contain a wide range of chemical compounds such as flavonoids that are rich in antioxidant activity (Junsathian *et al.*, 2018; Shivapriya *et al*., 2015; Singh *et al.*, 2019). In herbal medicine, plant parts including leaves, stems, roots, flowers, fruits and seeds are used for alternative and complementary therapy. Some derived compounds in herbs include resveratrol, curcumin, ginsenoside, polyphenols and triptolide which have neuroprotective characteristics. Herbal products contain complex active components or phytochemicals like flavonoids, alkaloids and isoprenoids. Therefore, it is frequently difficult to determine which component(s) of the herb(s) have more biological activity (Khazdair *et al.*, 2019). Phytochemicals are produced as a wide range of secondary metabolites and are well known sources of many novel drugs. These phytochemical compounds have significant physiological and therapeutic effects on the metabolism of biological systems (Radha *et al.*, 2021).

Numerous natural products, but primarily plant extracts, have been reported to be used in traditional medicine for neuroprotection, memory enhancing and anti-ageing purposes. Examples of such plants include *Ginkgo biloba* (Maidenhair tree), *Panax ginseng* (Asian ginseng), *Curcuma longa* (Turmeric), *Bacopa monnieri* (Water hyssop) and *Salvia officinalis* (Common garden sage) (Rehman *et al.,* 2020).

Tea, from the plant of *Camellia sinensis* is consumed in different parts such as green tea (unoxidized tea), oolong tea (half-oxidized tea) and as black tea (full-oxidized tea) in worldwide. Tea is the world's oldest and most popular caffeine containing beverage. Tea has well established nutritional and medicinal properties, attractive aroma and pleasant taste due to many of the characteristic secondary metabolites present in tea leaves. The chemical composition of green tea consists of phenolic compounds, alkaloids, proteins and carbohydrates (Maslov *et al.,* 2021). Phenolic compounds are the major components of green tea, which are present as flavonols, flavandiols, flavonone and phenolic acids. Most of the flavonoids are present as catechins, which have serveral beneficial effects on human health. The proportions of chemical components have been major parts for the flavor of tea (Vishnoi *et al.,* 2018; Han *et al.,* 2016). Many researchers have reported that green tea contains catechins which possess significant antioxidant activity (Musial *et al.,* 2020).

Nanotechnology is one of the modern in research area, which is centered on the use of nanoscale materials (such as nanoparticles, nanotubes, nano-membranes, nanowires, nanofibers and so on) in a variety of practical applications. Among the many benefits of nanomaterials are their great stability, target selectivity and malleability (Anjum *et al.,* 2021; Shahcheraghi *et al.,* 2022). Currently, nanotechnology is regarded as a validated cutting-edge technology with multiple applications in industrial domains like the chemical, pharmaceutical, mechanical and food processing sectors. In the fields of computing, power generation, optics, drug delivery and environmental sciences, nanotechnology also has an intriguing role to play. According to Faisal *et* al., (2021), several nanoscale devices have been created via a number of techniques, including physical, chemical and green approaches since the advent of nanotechnology. Unfortunately, nanoparticles which are synthesized from coal, silica, gold, silver, materials, asbestos and anthropogenic sources bypass the blood brain barrier and testicular blood barrier due to their smaller sizes (less than 100 nm in diameter) to elicit neurotoxicity and male reproductive disorders, respectively (Akintunde *et al.,* 2021).

In contrast to hazardous chemicals and physical methods, the green synthesis of metal nanoparticles using biological material as the reducing and stabilizing agents has garnered significant attention and consideration in the pharmaceutical and biomedical sectors. This is because eco-friendly, safe and non-toxic reagents are used during the biosynthesis process (Bhuyan *et al.,* 2015). On the other hand, there are a number of disadvantages to using chemical and physical methods for synthesis of nanoparticles, such as the need for hazardous substances, lengthy processing times, expensive costs and difficult steps. These constraints have led to a focus of most pertinent research on rapid and environmentally friendly synthesis procedures for nanoparticle manufacturing. The establishment of environmentally friendly processes for creating nanoscale materials has drawn a lot of attention from material scientists lately. In this regard, the green synthesis of nanoparticles particularly through the use of extracts derived from various plants is a developing field in green chemistry that is regarded as easy, affordable and safe (Faisal *et al.,* 2021).

The benefits of zinc oxide nanoparticles over other metals is the reason for the increased popularity of nanoparticles in the fields of agriculture and medicine is their exceptional applicability, vast surface area, high catalytic activity, reduced cost and white appearance. Zinc oxide nanoparticles exhibit remarkable potential as antimicrobial agents due to their potent antibacterial action against spores that are resistant to high temperatures and pressure. In addition to protecting food and wood products, cosmetics, innovative nanomedicines, wound dressings and disinfectants, it is thought that the antimicrobial activity of zinc oxide nanoparticles may be caused by the production of hydrogen peroxide or by the electrostatic binding of the particles on the microbial surface (Moghaddas *et al.,* 2020). For this reason, the current research is focused on green synthesis of zinc oxide nanoparticles using *Camellia sinensis* leaf extract, which possesses many phytochemicals especially polyphenols as reducing and capping agent for nanoparticle synthesis.

Work has already been carried out with green tea on the role of phytochemicals in neuroprotection, neurorescueing and neurodegenerative disease. Also, the role of zinc oxide nanoparticles in various types of neuronal cell lines have been well researched. But still there is no proper treatment available for several neurodegenerative diseases. Several studies are available on the role of zinc oxide nanoparticles in neuroprotection. However, there is no information available on synthesized zinc oxide nanoparticle-capped catechin in

Camellia sinensis. Studies have shown that polyphenols help in several neurodegenerative diseases and hence it was decided to exploit green tea rich in polyphenols to study its neuroprotective activity and employ zinc oxide nanoparticle-capped catechin from green tea to study neuroprotection.

Therefore the present study entitled '**Neuroprotective effect of synthesized zinc oxide nanoparticle-capped catechin'** was carried with the following objectives:

- To evaluate active compounds against neuroprotective target proteins using molecular docking studies
- To identify active constituents and study the antioxidant activity of *Camellia sinensis*
- To synthesize and characterize zinc oxide nanoparticles from *Camellia sinensis*
- To characterize and study the *in vitro* neuroprotective activity of synthesized zinc oxide nanoparticle-capped catechin to neuro 2a cells

A collection of background information available in the literature relevant to the current study is reviewed in the following chapter.