# CURCUMIN- AND FISH OIL-LOADED SPONGOSOME AND CUBOSOME NANOPARTICLES: A PARADIGM SHIFT IN HERBAL DRUG DELIVERY SYSTEM

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**ABSTRACT**

*The aim of the present cram was to look at the potential for neuroprotective effects of sponges enriched with curcumin and fish oil. Curcumin is a holy grail molecule that can be utilized in a variety of diseases. As curcumin (CU) and other phytochemical antioxidant compounds are water-insoluble, delivery vehicles are necessary to improve their bioavailability for in vivo uses. When used in combination therapy, lipid nanoparticles (NPs) with internal self-assembled liquid crystalline structures show great promise as secure drug delivery vehicles. Apoptosis caused by oxidative stress is a prevalent factor in the death of neurons as neurodegenerative disorders advance. The improvement of drug delivery over traditional drug delivery, or the conventional strategy to provide target specificity and increase the bioavailability of phytochemicals, is the main emphasis of the current review. The development of tailored medicines for the treatment of neurological illnesses holds promise when using nanoscale delivery technologies. This development in herbal medicine delivery appears to be a feasible and promising carrier capable of giving a more effective therapeutic result.*

**KEYWORDS**: *Curcumin, Nanoparticles, Fish oil, Spongosomes, Neuroprotective*

**GLOSSARY OF ABBREVIATIONS:**

1. BDNF-Brain-derived neurotrophic factor
2. ROS- Reactive oxygen species
3. PUFA - Polyunsaturated fatty acids
4. SOD-superoxide dismutase
5. CAT -Catalase
6. GPx -glutathione peroxidase
7. SAXS -Synchrotron small-angle X-ray scattering
8. DDS-Drug delivery system
9. cryo-TEM-Cryogenic transmission electron microscopy

## INTRODUCTION:

Current treatments of neurodegenerative diseases are of limited efficacy and indicate the need of alternative approaches, accounting for the fact that neurodegenerative disorders involve multiple risk factors. According to WHO, there are 47.5 million individuals worldwide who have dementia, and 7.7 million new cases are reported

each year. Diseases of the central and peripheral nervous systems are referred to as neurological disorders. In other words, the muscles, the autonomic nervous system, the spinal cord, the cranial nerves, the peripheral nerves, and the nerve roots. These conditions include neurological illnesses brought on by malnutrition, epilepsy, Alzheimer's disease and other dementias, cerebrovascular diseases such as stroke, migraine, and other headache disorders, Parkinson's disease, multiple sclerosis, and neuroinfectious. Parkinson's disease, multiple sclerosis, neuro infections, and other headache conditions. Along with environmental factors and genetic mutations, other contributing factors include a lack of neurotrophic factor proteins like brain-derived neurotrophic factor (BDNF), an excess of reactive oxygen species (ROS) that results in DNA damage, mitochondrial dysfunction, and oxidative stress, a change in proteostasis, the formation of senile plaques and neurofibrillary tangles from misfolded proteins and pathological protein aggregates, and a change in lipid metabolism. [3,20,21] Endothelial damage brought on by homocysteine is well prevented by curcumin. Following a stroke, ischemia damage is a result of both free-radical damage and inflammation. This damage is lessened by prior and even postponed curcumin treatment [2, 3]. The brain consumes more oxygen than other organs, making it more susceptible to harm from reactive oxygen species (ROS). It contains a lot of membranes that are rich in oxidizable polyunsaturated fatty acids (PUFA) but has a weak antioxidant defense [4–7].

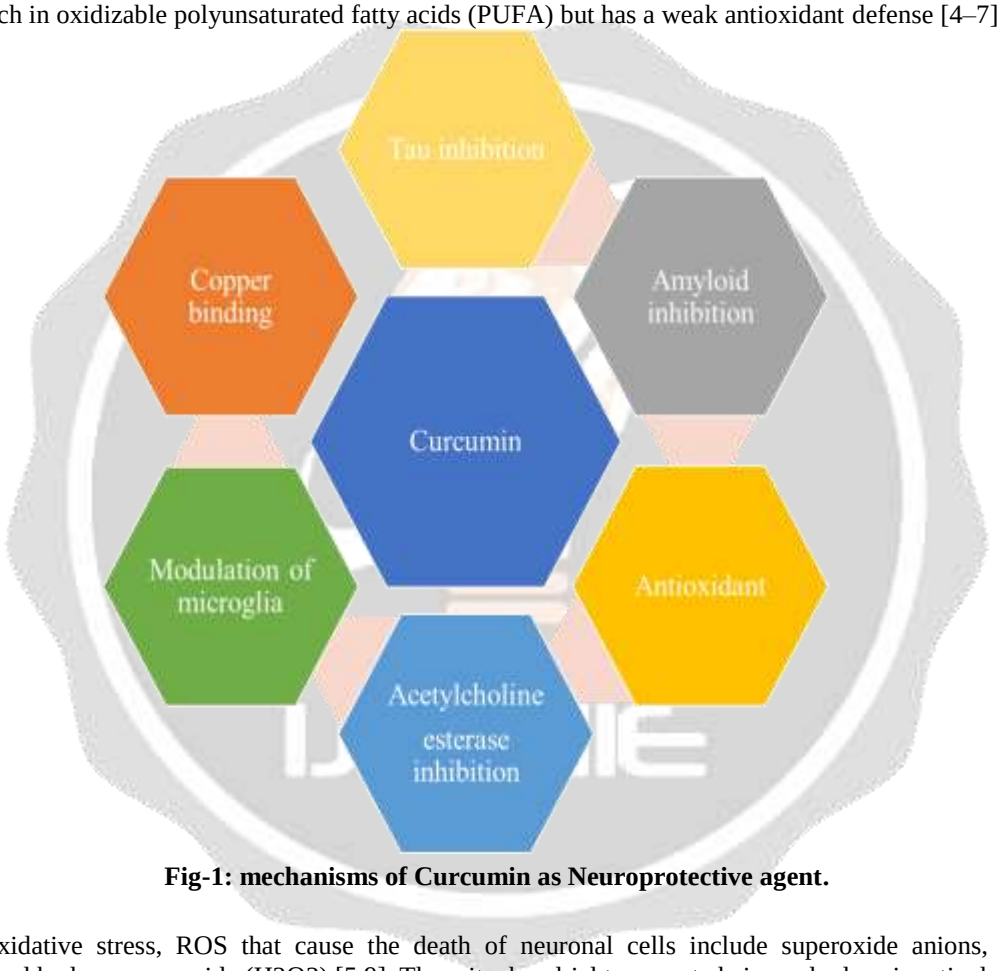


**Fig-1: mechanisms of Curcumin as Neuroprotective agent.**

During oxidative stress, ROS that cause the death of neuronal cells include superoxide anions, hydroxyl radicals, and hydrogen peroxide (H2O2) [5,9]. The mitochondrial transport chain, endoplasmic reticulum, Krebs cycle, and plasma membrane are the primary sources of ROS production. (3,7) When the production of ROS outweighs the cells' built-in antioxidant defenses, oxidative stress results. Antioxidant enzymes [superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)] and nonenzymatic processes are part of the defense mechanism against the harmful effects of ROS. The accumulating free radicals damage the biomolecules that have a lot of electrons, such as proteins, nucleic acids, and lipids. The functions of the neuronal cells are hampered as a result [9,10,11]. H2O2 can quickly produce neurotoxicity among the different ROS because it can damage cellular integrity via mitochondrial DNA mutations, disruption of the calcium (Ca2+) homeostasis, activation of the mitochondrial permeability transition pore, and modification of the intracellular bioenergetics, ROS mediate mitochondrial dysfunction [8−14]. As a result, a vicious cycle develops, which intensifies the malfunctioning of neuronal cells and leads to neurodegeneration [7,8].

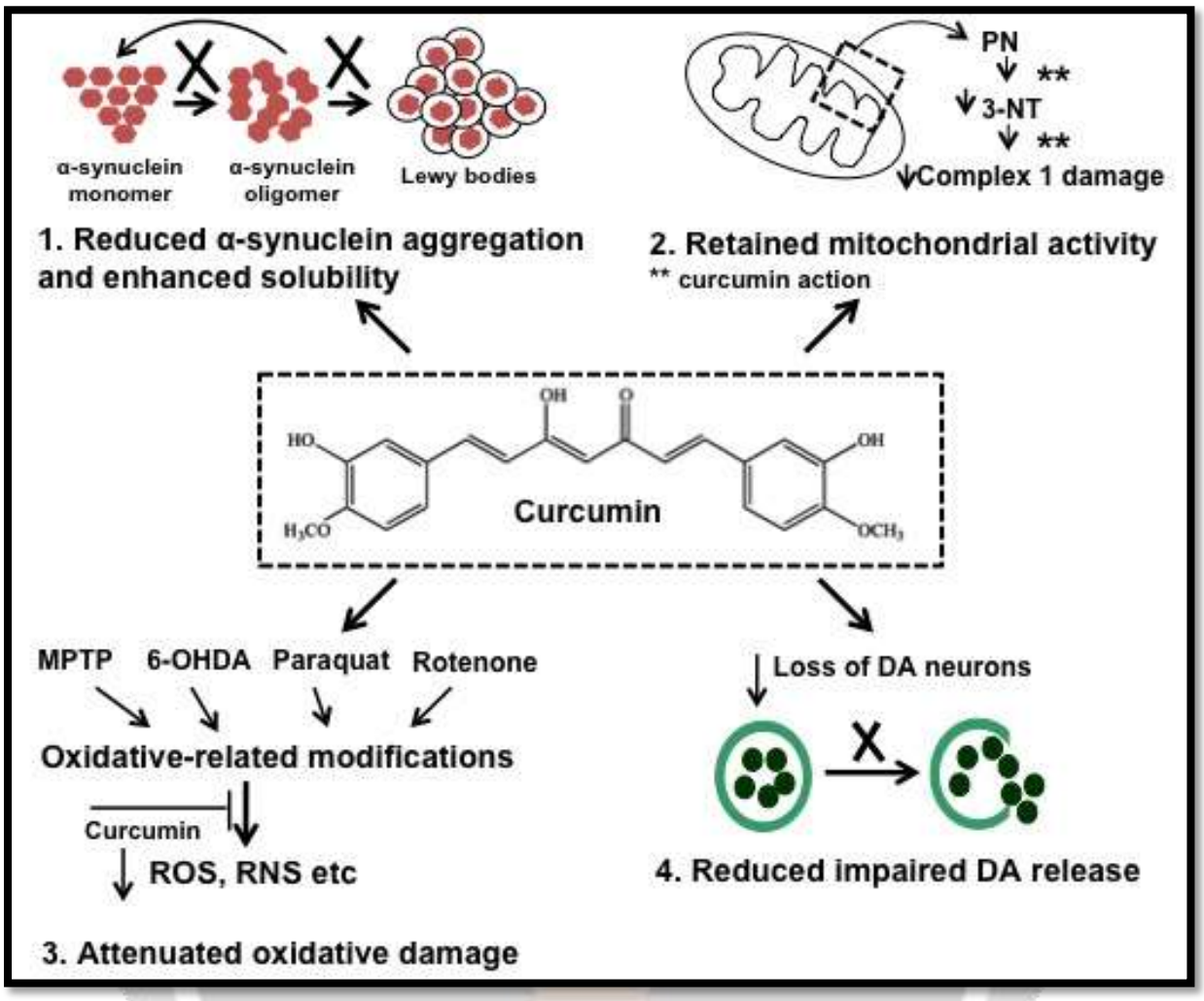


**Fig- 2: Role of curcumin in preventing neurodegeneration [24].**

The many compartments and structural benefits of the liquid crystalline nanocarriers (such as the structuring of the nanochannel network, for example) allow for a higher encapsulation efficacy for visitor molecules. The persistent release of encapsulated compounds, such as medicinal macromolecules, is supported by them [15,16,17]. Nanocarriers offer the ability to combine different active pharmacological components, which might be either hydrophilic or lipophilic molecules appealing for drug delivery applications. Such nanocarriers can increase the bioavailability of encapsulated biomolecules and guarantee their safety. They frequently use naturally occurring types of lipids that may have a propensity for fusing to biological membranes. The self-assembled lipid-based nanocarriers appear to be biodegradable and have minimal toxicity for in vivo applications, in addition to increasing the drug's bioavailability. The central nervous system (CNS) has recently been the target of liquid crystalline nanoparticles of the cubosome type [22,23]. So, it is possible to think of the control of ER stress by drug-loaded liquid crystalline lipid nanoparticles as a therapeutic potential for neuroprotection and the avoidance of neurodegeneration.

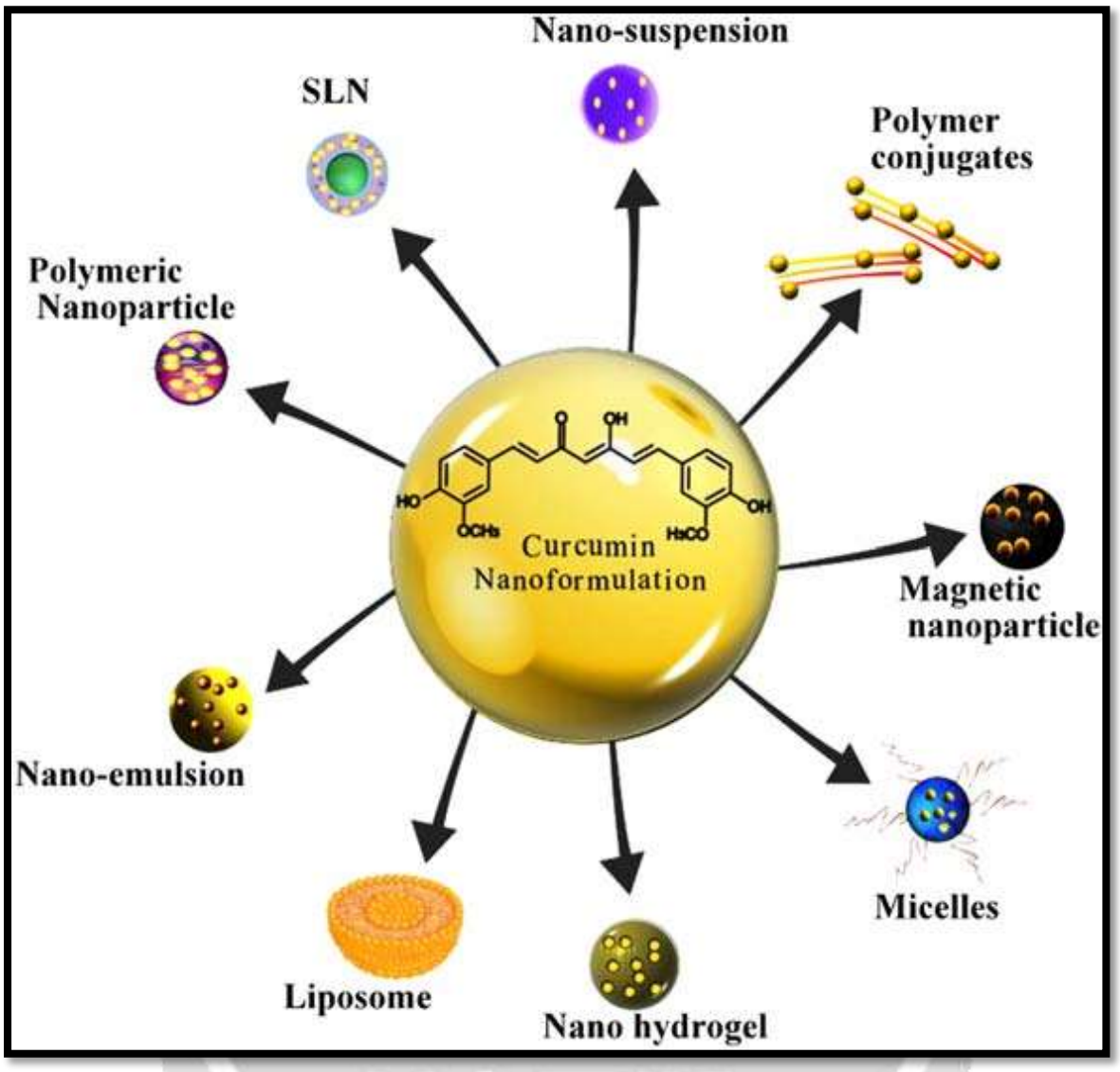


**Fig- 3: Nanformulations of Curcumin [18].**

## METHODOLOGY:

Self-assembly is the process through which disorganized molecules spontaneously organize themselves into ordered structures. Synthetic molecules including amino acids, oligo- and polypeptides, polymers, dendrimers, and conjugated chemicals are used to construct nanostructures like nanotubes, nanofibers, micelles, and vesicles. These molecules are crucial for the development and preservation of life. Nanostructures are constructed using synthetic molecules including amino acids, oligo- and polypeptides, polymers, dendrimers, and conjugated substances.

Living materials including lipid bio membranes, protein aggregates, folded proteins, structured nucleic acids, and molecular machineries all depend on self-assembly. It facilitates the acquisition of materials with regular structures, such as molecular crystals, liquid crystals, semicrystalline materials, and phase-separated polymers. It also occurs in huge molecules, which has created new opportunities for their application in delivery and material sciences. The exchange of theories and techniques between various domains, it has also given people the chance to create new substances and elements of life.

In order for anything to self-assemble, three forces must be balanced: an appealing driving force, a repellent opposing force, and a directing force. While directional force can be added to the other forces to generate directional self-assembled aggregates, colloidal and micellar systems fit in the non-hierarchical kind of self-assembly [35,36,37].

Surfactant systems and other amphiphilic block copolymers are being studied using the theory of amphiphile self-assemblies. Drugs that are both hydrophobic and hydrophilic are simultaneously trapped in vesicles. For the purposes of drug delivery, recent publications emphasize the manipulation of vesicles' size, shape, physical characteristics, and biodistribution.

Hydrogels are 3-D continuous interpenetrated networks of phases, where the solid phase is made up of nanofibers assembled by molecular self-assembly and the liquid phase is water. The outside section of the nanofibers, where the hydrophilic component of the molecule is situated, forms hydrogen bonds with the nearby water molecules. As compared to native biomolecules, these supramolecular structures interact with the target molecules or locations more effectively, improving their bioactivity. Hydrogel materials were created with the intention of encasing and delivering medicinal compounds that are soluble in water. The true mechanical strength of hydrogels is determined by non-covalent crosslinking, which holds them together. Hydrogels can be classified according to their source, origin, degradability or non-degradability, networking, and network type.

In order to solve issues with medicine and healthcare, therapeutic delivery is a crucial topic. By preventing degradation, enhancing absorption, preserving the therapeutic dosage, and lowering toxicity, controlled drug administration has demonstrated improved bioavailability of medicines. Because of their favorable properties, nanoparticles have been shown to be potential DDS. Delivery mediated by nanoparticles has a number of advantages [38].

**1)Synchrotron small-angle X-ray scattering (SAXS)**

The SAXS investigation was conducted. A two-dimensional Eiger X 4 M detector was used to capture the patterns at 12 keV, allowing measurements in the q-range of 0.00426 to 0.37 1. Å−1. The exposure period was 500 milliseconds and the wavelength of the synchrotron radiation was 1.033. Silver behenate was used as the reference sample for the q-range calibration. Each sample received an average of five spectra. The FOXTROT program processed the data of the captured 2D pictures [25,26,27].

**2)Cryogenic transmission electron microscopy (cryo-TEM)**

The cryo-TEM study's approach was the same as that of the earlier research. A sample droplet of 2 μL was placed on a copper grid coated in lacey carbon film and hydrophilized there for the 30s by glow discharge. Blotting paper was then used to absorb the majority of the liquid, leaving a thin film that was stretched over the lace holes. The specimen was rapidly submerged in liquid ethane and then chilled to about 90 K using liquid nitrogen in a temperature- and humidity-controlled freezing machine. The specimen was put into a Zeiss EM922 Omega energy-filtered TEM (EFTEM) equipment using a cryo-transfer holder. Exams were performed at about 90 K in temperature and the TEM apparatus was used with a 200 kV acceleration voltage. Low dosage settings (100–1000 e/nm2) were used to capture pictures with zero loss. Digital imaging processing systems were used to merge and process the pictures. No deformations were noticed since the diameters of the studied nanoparticles were within or below the range of the film thickness. The in-column filter of used Zeiss EM922 Omega can enhance contrast, the photographs were captured extremely close to focus or just slightly out of focus (a few nanometers). The deep under focused pictures are completely avoidable with EFTEMs [28,29,30].

**3)Cellular viability determined by MTT assays**

The tetrazolium salt test (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide, MTT) was used to assess the viability of SH-SY5Y cells following treatment with retinoic acid (RA), tunicamycin (TUN), and researched nanoparticles. The mitochondrial succinate dehydrogenase enzyme in the live cells converted the MTT reagent to formazan. The RA-differentiated cells were stressed for 24 hours by being denied access to FBS or by being incubated with an ER stress inducer (1μM TUN) following five days of treatment with 10μM retinoic acid. At lipid concentrations of 2.5μM and 5 ng/ml BDNF, blank (not loaded) or BDNF-laden nanoparticles were cultured with the cells for 24 hours at 37 °C. MTT was applied to the wells at a concentration of 5 mg/mL at 37 °C, using untreated cells as the control. The media was withdrawn after 1 hour of incubation, and the cells were then dissolved in 100% DMSO. A multiwell scanning plate reader was used to evaluate the samples' optical density at 570 nm. A minimum of six wells' worth of data were averaged to do the quantification [31,32,33]

**4) Statistical analysis**

The Tukey test was used to examine the findings of three separate studies, and the probability values p 0.05 across treatment groups were considered statistically significant [34].

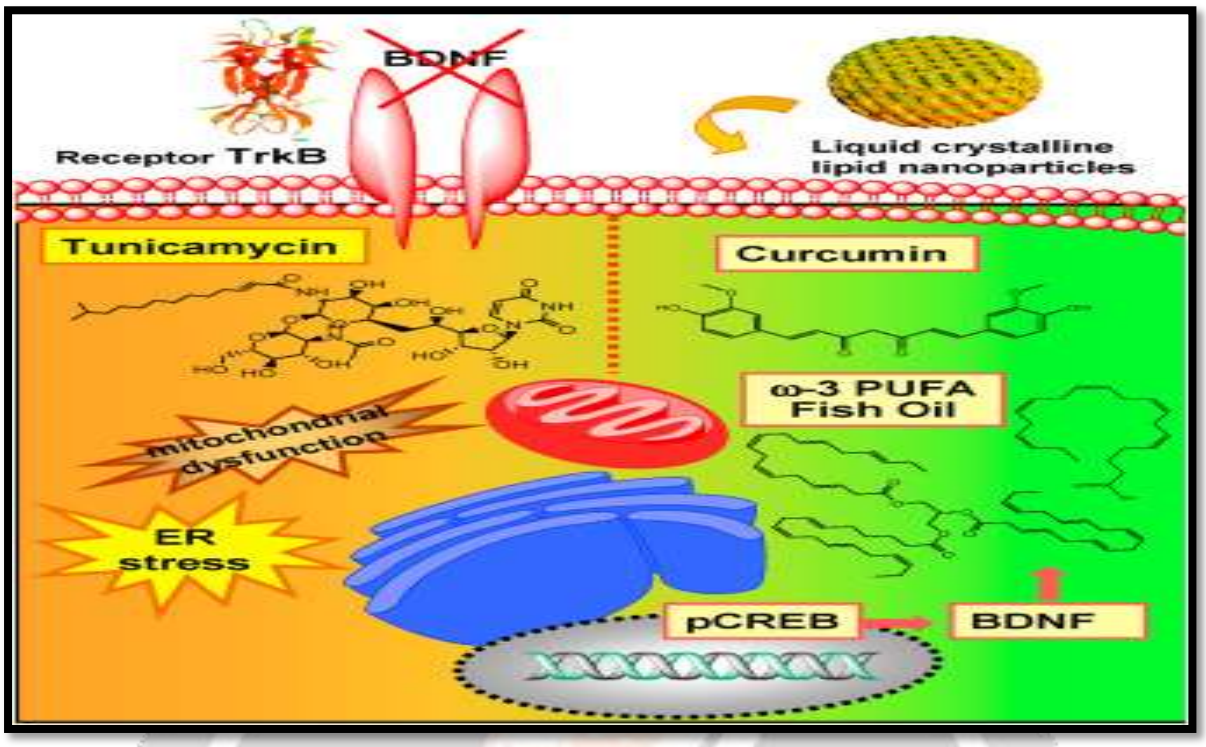


**Fig-4: Effect of loaded nanoparticles on Endoplasmic Reticulum stress [19].**

## CONCLUSION:

In the current study, an advantage of the potential for co-encapsulating lipophilic drugs with liquid crystalline nanostructures to achieve neuroprotection in combination therapy was observed. Nanocarrier-based DDSs have drawn interest as a potential new drug transporter in recent years because of the benefits the active components offer. The review that is offered in this manuscript shows how science and technology have advanced for the best possible neuroprotective activity. When compared to the Curcumin and Fish oil-aqueous suspension, cubosomes and spongosomes loaded with these compounds significantly reduced the ROS accumulation in the neuronally derived cells. According to the findings of the current study, the formation of spongosomes and cubosomes may result in a paradigm shift in the approach to treating disorders associated with neurodegenerative diseases.

## FUTURE SCOPE:

Multiple bioactive molecules can be enclosed within nano sponges, cubosomes, ethosomes or various nanocarriers for a potentiated pharmacological effect. The synergistic action of 2 or more phytochemicals can be utilized for this nano delivery systems.

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