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Molecular Docking Analysis of Phytochemicals from Tinospora Cordifolia as Potential Inhibitor against SARS CoV- 2

Amrita Sarkar[1], Shibnath Mukherjee[2], Debajyoti Sarkar[3], Shikha Thakur[4], Shouvik Kumar Nandy[5]
[1, 2, 3]*Department of Pharmacy, Burdwan Institute of Pharmacy, West Bengal, 713103*
[4, 5]*Department of Pharmacy, Shoolini University, Solan, HP, 173229*

Abstract: ***Since the beginning of time, the Indian system of medicine (ISM) and traditional Ayurvedic medicine have employed tinospora cordifolia, also known as giloy. In ayurveda, the plant is known as Rasayana and is highly regarded for boosting the body's defences against specific infectious microorganisms. Of the 40 species, only 4 are found in India. It is a perennial herbaceous vine that is a member of the Menispermaceae genus. It is frequently utilised as a distinctive component of several natural medicines and has been used traditionally for a wide range of illnesses, including fever, vomiting, diabetes, jaundice, anaemia, polyuria, and skin conditions. Instead of treating the disease's cause, plant-based medicine actually balances the body. Due to a lack of effective treatment options, the coronavirus strain (SAR-CoV-2) will become more dangerous. Ayurveda is a style of ancient medicine that offers a holistic approach to treating this illness. The only defence against the coronavirus illness, which is spreading like wildfire, is "immunity." The only way to keep healthy and safe while preparing for the impending epidemic is to build immunity. Good immunity protects us from disease progression and the spread of this dangerous virus in the current situation. Due to its immunomodulatory and antiviral properties, giloy herb gained popularity after the COVID-19 pandemic began. Keap1 keeps Nrf2 in check by securing it in its protein complex. Additionally, Keap1 aids in the ubiquitination-mediated degradation of Nrf2. Keap1 is a down-regulator of Nrf2, in other words. Keap1 must be suppressed and Nrf2 must be released in order to increase the production of biological antioxidants. Since freed Nrf2 is unbound, it moves to the nucleus to activate the antioxidant response element (ARE) found on the genes encoding for antioxidants. Keap1 is a 624 amino acid residue long protein that belongs to the BTB (bric-a-brac, tram-track, and broad-complex) Kelch family. Antioxidant production should therefore be increased in such a situation. We have summarised the function of the Keap1-Nrf2 system in the synthesis of antioxidants in this review article. We also suggest its possible therapeutic application in controlling COVID-19's cytokine storm. This article focuses on molecular docking of KEAP-1-Nrf2, NRF-2 proteins to inhibit COVID- 19 disease.***

Keywords: SARS CoV- 2, Tinospora cordifolia, molecular docking, phytochemicals, KEAP-1-Nrf2, NRF-2 proteins.

I. INTRODUCTION

A public health emergency developed as a result of the abrupt coronavirus outbreak that spread into a pandemic and caused significant socioeconomic and human losses. There isn't a single country left in the globe where the coronavirus hasn't expanded and encroached in just 3–4 months. Although it has been demonstrated that the recommended immunisations can lessen COVID-19 illness symptoms, it is unknown how exactly these vaccines contribute to the disease's spread. SARS-CoV-2 began to spread globally in December 2019 and eventually turned into a pandemic. The first case in Italy was reported in February 2020, and by May there were 211,938 cases, 29,079 fatalities, and potentially around 5,000,000 afflicted people [1]. There is growing evidence that COVID-19's immune response and disease development are related to anomalies in immune cells. Inflammatory markers and the cytokine storm are both implicated in the severity and prognosis of the disease. In COVID patients, severe cytokine storm, hyper inflammation, and multi-organ failure have also been reported. A cytokine storm and a number of adverse responses (ADRs) are also caused by an abundance of cytokines being produced in the body. Thus, it is essential to comprehend the mechanisms underlying cytokine storms [2]. The virus enters the host cells through membrane fusion or endocytosis and binds with the host receptors (ACE 2). (penetration). SARS-CoV-2 disassembles, proteins are eliminated, and genomic RNA is released in the cytoplasm once the virus has entered the cell. The ribosomes, part of the host cell machinery, convert the RNA strand into the proteins pp1a and pp1b, or viral polyproteins (biosynthesis). When these proteins join with genomic RNA, polymerase produces interrupted transcription, which releases subgenomic mRNAs.

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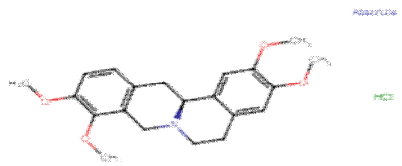
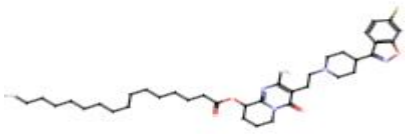
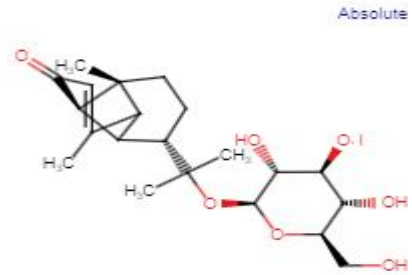
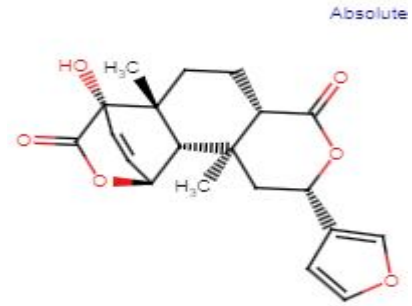
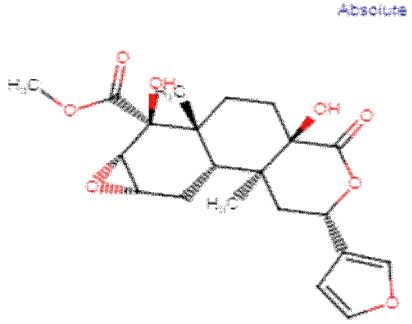
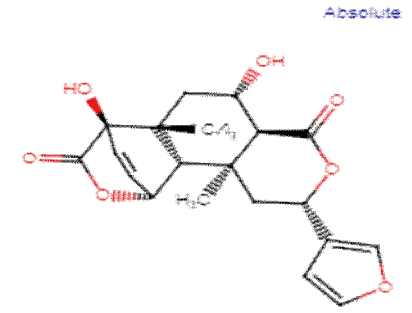
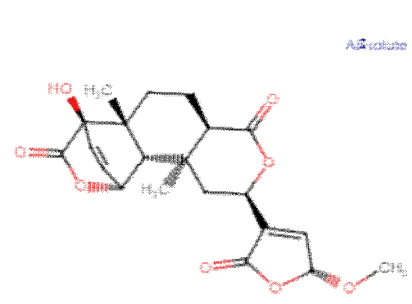
Viral proteins then carry out translation as a result (maturation). Viral proteins and genomic RNA come together to form virions in the Golgi apparatus and endoplasmic reticulum, which are then transported and released via vesicles. Although there is currently available medicinal care, there is no targeted therapy [3].

T. cordifolia is also known as Guduchi/Amrita and by the Latin names Tinospora cordifolia (Wild) Hook. f. & Thomson, Tinospora Gulancha/Indian Tinospora, and Giloy. Its scientific name is Tinospora sinensis (Lour.) Merr. It can be found in Myanmar, Sri Lanka, and China and is a member of the Menispermaceae family [4]. The plant is frequently used in traditional ayurveda medicine and has a number of therapeutic benefits, including those for jaundice, rheumatism, urinary disorders, skin conditions, diabetes, anaemia, inflammation, allergic conditions, anti-periodic properties, and radioprotective qualities. To treat intestinal obstruction and as a powerful emetic, Giloy root is utilised. The starch from this plant reduces burning, boosts energy, and stimulates the appetite. It also works as a useful home cure for chronic fever [4, 5]. A variety of constituents have been isolated from different parts of T. cordifolia. They belong to different classes such as alkaloids, diterpenoid lactones, steroids, glycosides aliphatic compounds, polysaccharides. Some constituents have been isolated from plant mainly they are tinosporone, tinosporic acid, cordifolisides A to E, syringen, berberine, giloin, gilenin, crude giloininand, arabinogalactan polysaccharide, picrotene, bergenin, gilosterol, tinosporol, tinosporidine, sitosterol, cordifol, heptacosanol, octacosonal, tinosporide, columbin, chasmanthin, palmarin, palmatosides C and F,cordioside, tinosponone, ecdysterone, makisterone A, hydroxyecdysone, magnoflorine, tembetarine, syringine, glucan polysaccharide, syringine apiosylglycoside, isocolumbin, palmatine, tetrahydropalmaitine, jatrorrhizine respectively (table 1) [6, 7]. The purpose of this review study is to give thorough molecular docking on Keap-1 and the Neh2 domain of Nrf2 with T. cordifolia chemical compounds to prevent COVID-19.

Table 1- Chemical compounds with structures and pharmacological activity

Structure	Name of compound	Activities	References
	Tetrahydropalmatine	Anti-toxic	[4]
	Palmitate	Antidiabetic activity, anti cancer, anti-toxic	
	Magnoflorine	Anti-diabetic activity, anti-toxic	

	Tinocordiside	Anti-cancer	
	Isocolumbin	Anti-toxic	
	Tinosporin A	Anti-toxic	
	Tinosporin B	Anti-toxic	
	Tinosporin C	Anti-toxic	

II. OVERVIEW OF PATHOGENESIS OF COVID-19

A basic pathogenesis of COVID-19 and the immune response in SARSCoV-2 infection is crucial in the understanding of the role of inflammation in COVID 19 SARS-CoV-2 is an RNA virus. The SARS-CoV-2 virus has a positive sense, single-stranded RNA and a genome that is 29.9 kb in size [8]. The envelope that protects the virus' genetic material. The nucleocapsid (N) protein, envelope (E) protein, spike (S) protein, membrane (M) protein, and sixteen non-structural proteins are among the structural proteins linked to SARS-CoV-2. The SARS-CoV-2 virus has a positive sense, single-stranded RNA and a genome [9]. The envelope that protects the virus' genetic material. The nucleocapsid (N) protein, envelope (E) protein, spike (S) protein, membrane (M) protein, and sixteen non-structural proteins are among the structural proteins linked to SARS-CoV-2 [10]. The spike protein of SARS-CoV-2 is required for entrance into host cells. Human proteases are used by the virus to first connect its receptor binding domain (RBD) to the human angiotensin-converting enzyme 2 (hACE2) receptor. According to studies, the RBD of SARS-CoV-2 has a higher affinity for binding to hACE2 than that of SARS-CoV [11].

In illness states like diabetes, liver disease, and inflammatory bowel disease, NRF2 activity is typically dysregulated. Additionally, human lung disease susceptibility has been linked to single-nucleotide polymorphisms (SNPs) in the promoter region of NFE2L2, which codes for NRF2, further supporting NRF2 as a therapeutic target for pulmonary disorders. By suppressing proinflammatory genes like IL6 and IL1B, NRF2 also contributes to the development and resolution of inflammation [12]. This is especially evident in macrophage cells activated by lipopolysaccharide (LPS), as itaconate, an anti-inflammatory immunometabolite, accumulates during the metabolic reprogramming of these cells and activates NRF2. By increasing glutathione (GSH), NADPH, thioredoxin, thioredoxin reductase, and peroxiredoxin—all of which protect against oxidative stress and encourage alternative wound healing over traditional proinflammatory activation of macrophages—NRF2 activation restores redox balance [13].

It has been suggested that the KEAP-1-Nrf2 ARE signalling pathway controls the transcription of a number of cytoprotective proteins in a number of illnesses, including cancer, neurological disorders, cardiovascular disease, and ageing [14]. The role of this route in controlling oxidative, electrophilic, or other forms of stress has made it a prime candidate for anti-inflammatory pharmacological responses. Research has been done extensively to determine how it relates to COVID-19 pathogenesis [15]. The cytoplasmic Nrf-2 interacting protein Keap-1 controls the activity of Nrf2 negatively. With the help of its BTBdomain, Keap1 joins with Nrf2's Neh2 domain to form a homodimer. There are two binding motifs in the Nrf2 Neh2 domain called ETGE and DLG that have differing binding affinities to the Keap1 DC domain (figure 1) [16].

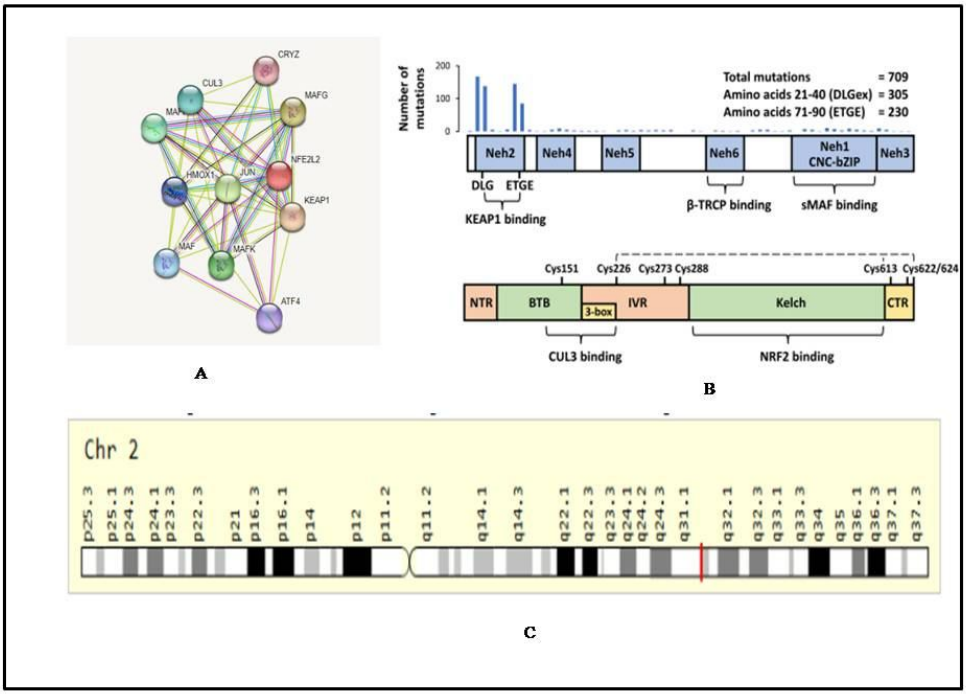


Figure 1:- A- Network analysis showing interaction of different Proteins with KEAP-1, B- Structural components of KEAP-1, C- Nrf2 transcription factor activation downregulates ACE2 expression. The Nrf2 is encoded by NFE2L2 gene.

Diseases associated with NFE2L2 include Immunodeficiency, Developmental Delay, And Hypohomocysteinemia and Lung Squamous Cell Carcinoma. Among its related pathways are KEAP1-NFE2L2 pathway and Cellular responses to stimuli [17]. There are four distinct and interlinked components associated with molecular activation and cytoprotective action of KEAP-1 NRF2 pathways. These components include chemical inducers of NRF2activity, (ii) KEAP1, the protein sensor of these inducers, (iii) the transcription factorNRF2, which modulates the transcriptional response to inducers and oxidativestress, and (iv) the target genes which provide the cytoprotective output of thepathway [18].

The domain architechture of KEAP-1 and NRF-2 proteins provided the frequency of mutations and location of stress sensors. Nrf2 activity is amplified by exogenous and/or endogenous stressors. Under primary conditions, Nrf2 ubiquitination is mediated by keap-1 and subsequent proteasomal degradation through acting as an adaptor molecule for CUL-E3 ligase [19]. When xenobiotics and/or ROS, which are external and/or endogenous stressors, are present, Nrf2 is translocated into the nucleus, where it binds to the ARE and activates cytoprotective molecules such as antioxidant and detoxifying enzymes. Superoxide dismutase (SOD) mediates the dismutation of superoxide radicals (O2-), which results in the creation of hydrogen peroxide (H2O2). Through the use of catalase and glutathione peroxidase, H2O2 is degraded (GPx). By catalysing the breakdown of heme into biliverdin and bilirubin, HO-1, which may act as antioxidants, is involved [20]. CO: carbonmonoxide Benefits of pharmacological activation of NRF2 in the context of SARS-Cov-2 infection will be threefold: (i) increasing fitness and providing protection to the host cell;(ii) promoting the anti-inflammatory phenotype during macrophage activation, thus preventinguncontrolled production of proinflammatory cytokines and pyroptosis; and (iii) inhibiting viralpropagation. Notably, unlike direct antioxidants such as vitamin C, that are short-lived(minutes to hours) and are consumed in the process of ROS scavenging, the antioxidantand cytoprotective effects of NRF2 activation are long-lasting and persist for several days after induction elimination (figure 2) [21].

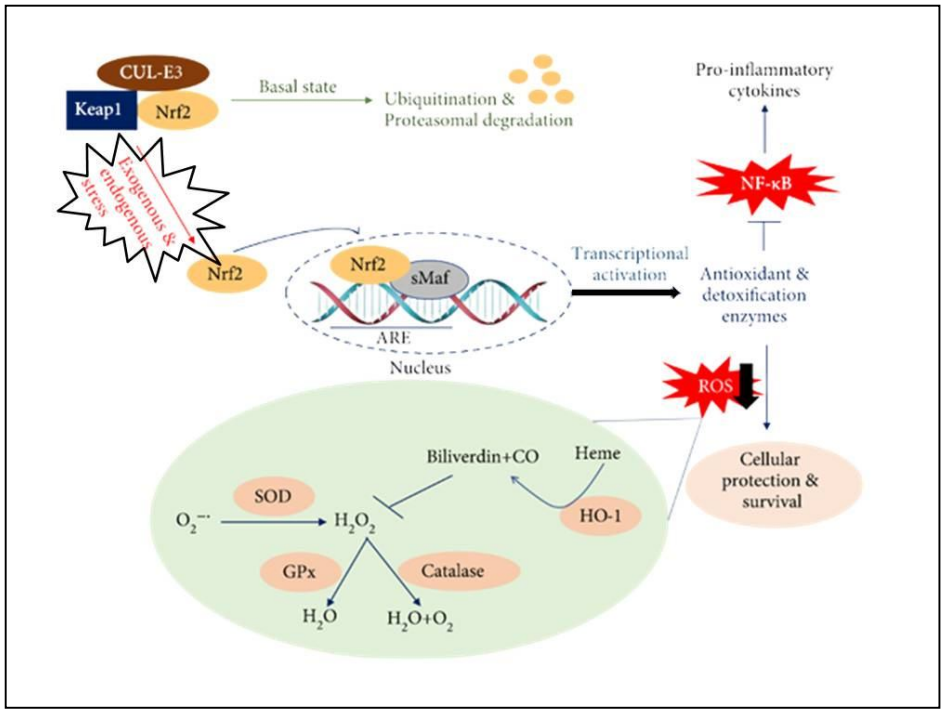


Figure 2- Nrf2 activity is augmented by exogenous and/or endogenous stressors. Keap1 functions as an adapter molecule for CUL-E3 ligase to mediate Nrf2 ubiquitination and subsequent proteasomal destruction under normal circumstances. When xenobiotics and/or ROS, which are external and/or endogenous stressors, are present, Nrf2 moves into the nucleus and binds to the ARE, activating cytoprotective molecules such as antioxidant and detoxifying enzymes. The generation of hydrogen peroxide is mediated by superoxide dismutase (SOD), which breaks down superoxide radicals (O2) (H2O2). The breakdown of H2O2 is catalysed by the enzymes catalase and glutathione peroxidase (GPx). The potential antioxidants biliverdin and bilirubin are produced when heme is degraded by HO [21, 22].

III. RESULTS AND DISCUSSION

Discovery of novel coronavirus main protease (SARS CoV-2 M pro) played a crucialrole during the disease propagation, and hence SARS-CoV-2 Mpro represents as a drug target forthe drug discovery. Herein, we bioinformatics approach is applied for screening of chemicalcompounds from Indian spices as potent inhibitors of SARS-CoV-2 main protease (PDBID: 6Y84) (figure 4).
The structure files of Indian spices chemical compounds were taken from PubChem database and screened by molecular docking, by using PyRx.

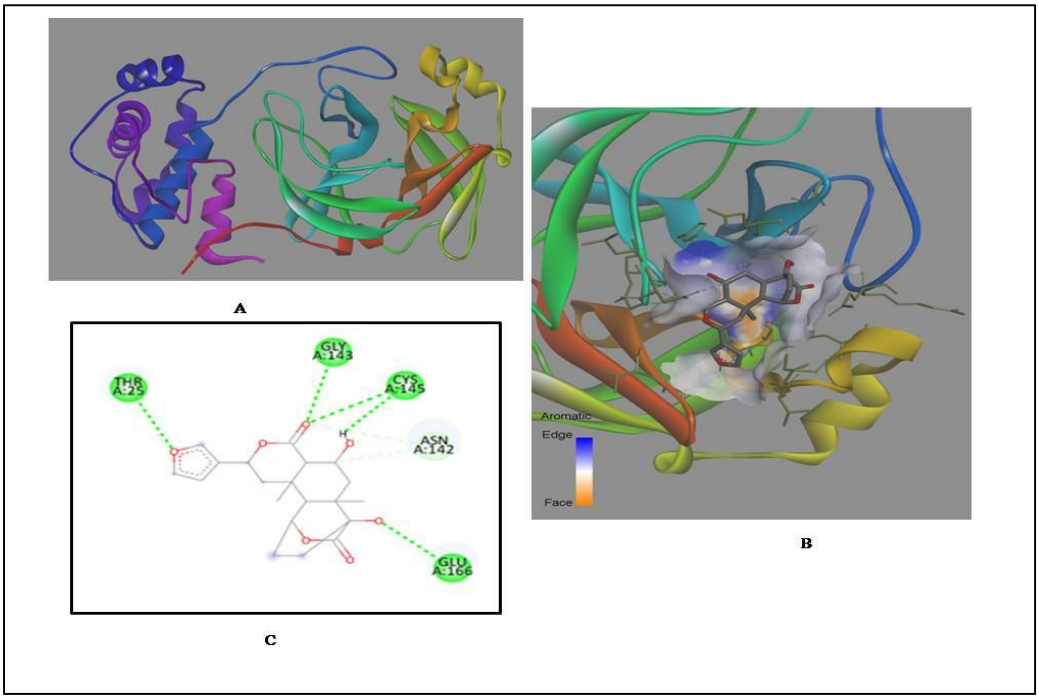


Figure 4- A- SARS CoV-2 main protease, B- SARS CoV-2 main protease docked with, C- Among various drug targets that have been explored by researchers around the globe, structural proteins, non-structural proteins and human targets are involved. For the KEAP1-NRF2 ARE pathway, BTB domains of Kelch-like associated protein-1(KEAP-1) and Nuclear receptor factor erythroid-p45 (NRF2) have been extensively investigated using computer aided-drug designing (CADD) softwares like PyRx, UCSF Chimera X.

The Molecular Dynamic simulation is carried out using myPresto for the BTB domain of Keap-1 (PDB:4CXT) for inhibitor docking pocket of the protein using tinosporinone as ligand. The energy minimization was calculated using steepest decent method,500 steps, no position constraints, no generalized Born Method (Figure 5).

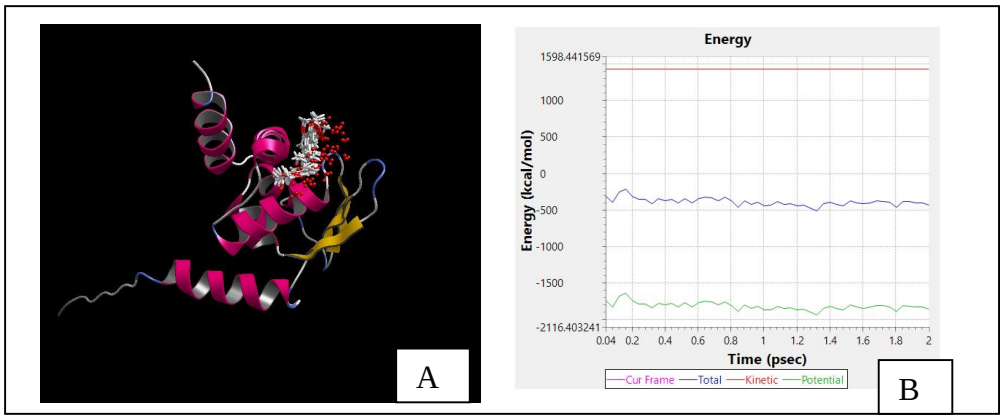


Figure 5- A- BTB domain of Keap-1 with various docking pose of tinosporinone, B- Energy Graph

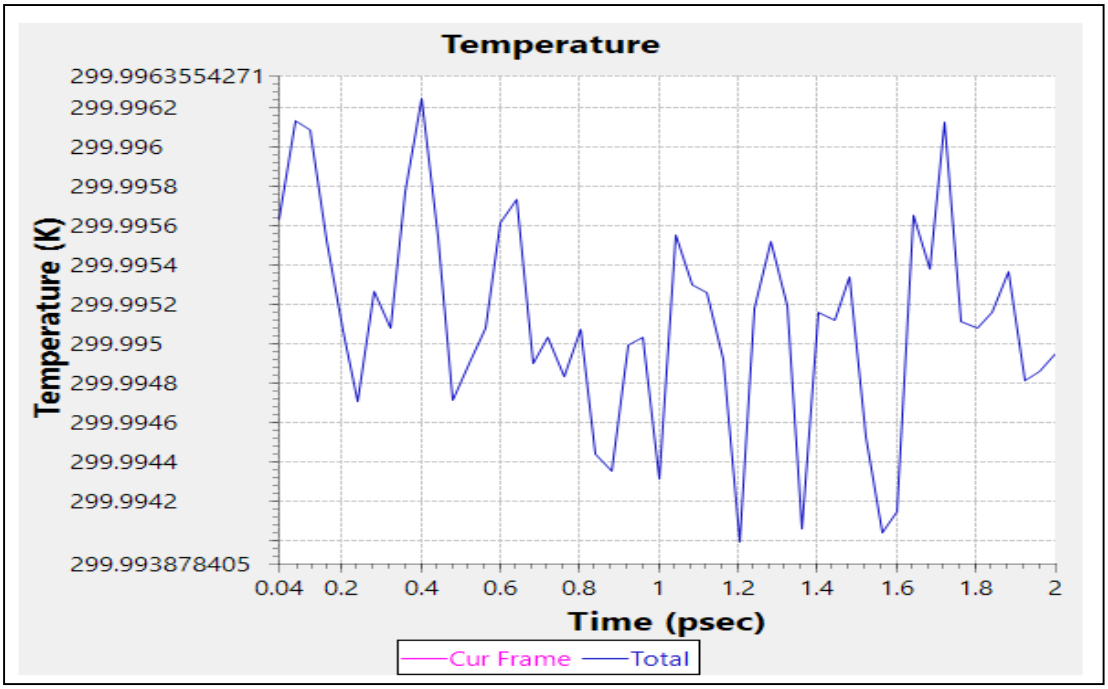


Figure 6- The Temperature graph is calculated with 200MD steps with NVT ensemble with initial temperature 300K with cut off radius 14.0Å with FMM method that calculates long distance Coulomb forces.

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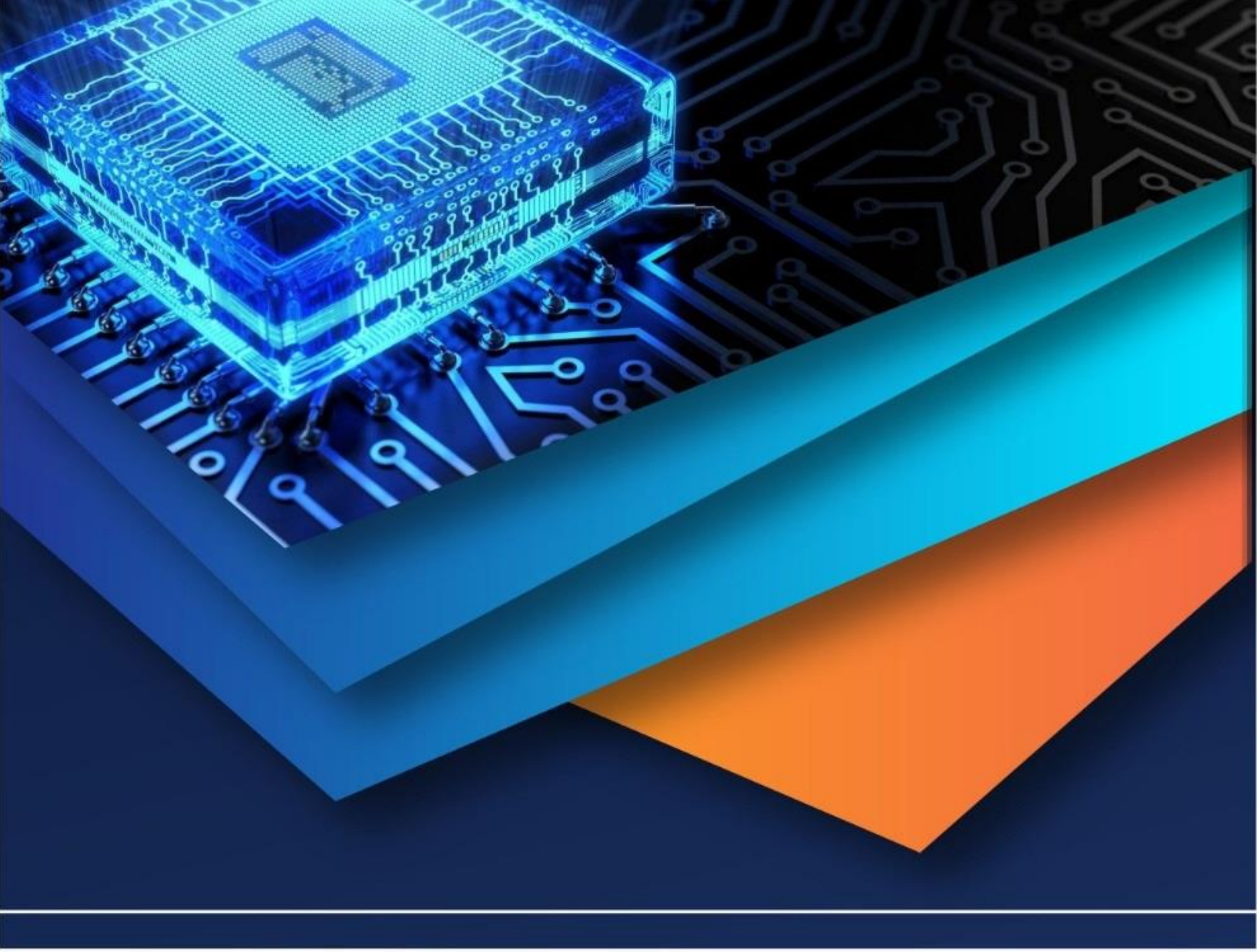

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