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Evaluation of Antioxidant, Antimicrobial and Anticancer Activity of *naringin* and *allyl sulphide* on Breast Cancer Cells

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Abstract: ***Cancer still continues to threaten the world as the second most prominent cause of deaths world over. Breast cancer is the common cancer diagnosed among women and its prevalence and severity is high in developing and underdeveloped countries. The present study was aimed to investigate the antioxidant, antimicrobial and anticancer activity of the natural compounds, Naringin and Allyl sulfide on breast cancer cell lines (MCF-7 cells). Naringin has showed high antioxidant activity than Allylsulfide, however, a combination of Naringin and Allyl sulfide has shown the highest antioxidant activity in terms of DPPH scavenging activity (75.15%) and NO scavenging activity (72.79 %). Antimicrobial studies revealed that, the combination of Naringin and Allyl sulfide showed considerable inhibitory activity in terms of zone of inhibition than individual compounds, when compared to standard drug (Azithromycin). In-Vitro cytotoxicity studies by MTT assay demonstrated the highest percent of cell death (55-60%) by combination of Naringin and Allyl sulfide after 24 hr than when they were treated individually. Together, our results demonstrate that Naringin and Allylsulfide (25+25µg/ml) possess potent antioxidant and anticancer activities and hence can be recommended for regular consumption as nutraceutical.***

Key words Allyl sulfide, Antioxidant, Antimicrobial, Cytotoxicity, MCF-7 cells, Naringin

I. INTRODUCTION

Cancer is a disease in which some of the bodys' cells grow uncontrollably and spread to other parts of the body (Hausman, 2019). Tumors can be cancerous or non cancerous (benign). Cancerous tumors spread into, or invade nearby tissues and/or can travel to distant places in the body (a process called metastasis) to form new tumors called malignant tumors. Benign tumors can sometimes be quite large, however, some can cause serious symptoms or be life threatening, such as benign tumors in the brain (Benvenuti et al., 2006). Anything that may cause a normal body cell to develop as abnormally potential and proliferative cell is said to be carcinogenic or causative agent (Zaorsky et al., 2017).The cancers of blood cell are called leukemia (Whiteley et al., 2021), cancers of lymph system are called lymphoma (Mugnaini and Ghosh, 2016), some are multiple myeloma melanomas and some are brain and spinal cord tumors (Vetrano et al., 2023). The incidence of cancer cases is estimated to increase by 12.8 per cent by 2025 as compared to 2020 (Sathishkumar et al., 2022). The continuous increase in cancer cases, failure of conventional chemotherapies to control cancer, and excessive toxicity of chemotherapies clearly demand an alternative approach. Plants and herbs from times immemorial are considered to possess immense therapeutic potential to treat several human ailments including cancer. A variety of phytochemicals (pharmaceuticals and nutraceuticals) present in plants-herbs are the active peinciples responsible for the potential beneficial effects of plants (Singh et al., 2017). A large number of dietary phytochemicals used in traditional medicine have been reported to have anti-proliferative, anti-metastatic, reactive oxygen species (ROS) inducing, anti-angiogenic and pro-apoptotic effects that may target cellular molecules and pathways implicated in malignancy regulation (Rastrelli et al., 2014). The first trial to show the benefit of chemoprevention was undertaken in breast cancer patients with the use of tamoxifen, which demonstrated a significant decrease in invasive breast cancer (Rodriguez-Otero et al., 2021). Dietary components such as capsaicin, cucurbitacin B, isoflavones, catechins, lycopenes, benzyl isothiocyanate, phenethyl isothiocyanate, and piper longumine have demonstrated to show inhibitory effects on cancer cells growth indicating that they may serve as chemo preventive agents. Interestingly, nutraceuticals/dietary phytochemicals can play a significant role in treating different cancers including breast cancer.

Breast cancer registers the highest prevalence in women and is the number-one cause of cancer mortality worldwide. Modifications in various cell signalling pathways promote tumour cell proliferation, progression, and survival. The PI3K/Akt/mTOR pathway is involved in cancer cells' growth, proliferation, motility, and immune response regulation.

Activation of this pathway is one of the main causes of cancer cell resistance to antitumor therapies (Ersahin et al., 2015). This makes PI3K/Akt/mTOR signaling a crucial object of study for understanding the development and progression of this disease. Thus, this pathway may have a role as a potential therapeutic target, as well as prognostic and diagnostic value, in patients with breast cancer.

PI3K/Akt/mTOR is a cell signaling pathway involved in growth, proliferation, survival, motility, metabolism, and immune response regulation. This pathway is also reported to be associated with a number of diseases and syndromes, such as tuberous sclerosis, Parkinson's disease, and vascular diseases. Mutations in the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway are frequently found in breast cancers and associated with cellular transformation, tumorigenesis, cancer progression, and drug resistance. The dysregulation of this pathway has been related to a wide variety of cancer hallmarks, including uncontrolled proliferation, genomic instability, and metabolic reprogramming in tumor cells. In addition, PI3K/Akt/mTOR pathway activation is one of the main causes of cancer cell resistance to antitumour therapies. This makes the PI3K/Akt/mTOR pathway a crucial object of study for understanding the development and progression of this disease (Ersahin et al., 2015). The role of this pathway as a potential therapeutic target, and the prognostic and diagnostic value of this pathway in patients with breast cancer. Several drugs targeting PI3K/ATK/mTOR are currently in clinical trials, mainly in combination with endocrine therapy and anti-HER2 therapy (Guerrero-Zotano et al., 2016). The role of phytochemicals in regulating this path way is also an active field of cancer research.

Citrus fruits have been utilized as natural herbal treatments in traditional medicine. Citrus peel has been utilized in traditional Chinese medicine to enhance digestion, minimize gastric gas, bloating, and clear congestion. Clinical and epidemiologic research states that eating citrus fruits lowers the risk of lifestyle-related disorders like cancer, cardiovascular disease, diabetes (type-2), and osteoporosis. The primary source of naringin (NA) is citrus fruit, although the concentration is significantly different across different species. Naringin (NA) known as 4′,5,7-Trihydroxyflavanone 7-Rhamnoglucoside is a compound that falls under the classification of dihydroflavonoids. This complex compound comprises 4′,5,7-hydroxyflavone (saccharide ligand) conjoined with rhamnose-β-1,2-glucose. Naringin (NA), a natural flavanone glycoside, possesses a multitude of pharmacological properties, encompassing anti-inflammatory, sedative, antioxidant, anticancer, anti-osteoporosis, and lipid-lowering functions, and serves as a facilitator for the absorption of other drugs (Jiang et al., 2023). Solubilisation methodologies, including structural modification, the preparation of liposomes, inclusion complexes, nanoparticles, and solid dispersions could enhance the solubility and physiological efficacy of NA (Jiang et al., 2023). Some previous studies showed that, naringin works well in human cervical cancer treatment (Shilpa et al., 2023).

Garlic (*Allium sativum* L.) is one of the traditionally consumed plant for its dietary and medicinal values. Garlic possesses several pharmacological activities including antihypertensive, antithrombotic, antihyperlipidemic, antitumor and antimicrobial (Balaji et al, 2012) Garlic has been found to contain a large number of potent bioactive compounds with anticancer properties, largely Allyl sulfide derivatives. Allyl sulfide (AS) is an organosulfur compound with the chemical formula $CH_2=CHCH_2SCH_3$. It is a colourless liquid with a strong odour characteristic of alkyl sulfides. It is a metabolite of garlic, and "garlic breath" is attributed to its presence.

Chemical formula is C_4H_8S and has a Molecular mass of about 88.17 g.mol-1. AS is a leading compound of volatile garlic metabolites and found to exhibit antibacterial, antioxidant and anticancer properties (Fukao et al., 2004). Allicin derived products such as diallyl sulfide, diallyl disulfide, and diallyl trisulfide, constitute another source of redox modulatory molecules. Through these actions, signaling pathways driving antioxidant and cytoprotective mechanisms are triggered, conforming an integral protective response that can alleviate ulcers, inflammation and cancer (Powolny et al., 2008,. This antineoplastic effect is generally greater for lipid-soluble than water-soluble allyl sulphides and both can increase the antiproliferative effects of lipid and water-soluble allyl sulphides (Karmakar et al., 2011).

II. MATERIAL AND METHODS

A. Chemicals

Naringin, Allyl sulfide, DPPH (2,2-diphenyl-1-picrylhydrazyl), Methanol, Ascorbic acid, sodium nitroprusside, PBS (phosphate buffer saline), Griess reagent, Dulbecco's Modified Eagle Medium (DMEM), FBS (Fetal Bovine Serum), Anti- Anti, Insulin, Streptomycin and Penicillin were purchased from Gibco (St W Ste, US). MTT (3-(4,5-dimethylthiazol-2-yl)-2,5diphenyltetrazoliumbromide), IBMX were purchased form Sigma aldrich, Bangalore, and other chemicals used were of analytical grade and purchased from local manufacturers in India.

B. Antioxidant Assays

1) DPPH (2, 2-Diphenyl-1-picryl hydrazyl) activity

The DPPH radical scavenging potency of Naringin and Allyl sulfide was determined using the 2,2-diphenyl-2-picryl-hydrazyl assay according to the method (Cano-Lamadrid et al.2018). Briefly, 4mg of DPPH was prepared in 100 methanol. Stock solution was prepared by dissolving 10mg of compounds in 20ml of methanol. The working standard was prepared by using a diluted stock solution with methanol. Then, 4 mL of the DPPH standard solution was mixed with different concentrations of the compounds Naringin, Allyl sulphide, and in combination of both (dissolved in methanol) at different concentrations (25-150µg/mL). These solutions were mixed and incubated in the dark for 30 min at room temperature. The absorbance was measured at 517 nm against a blank lacking scavenger. Vitamin C was used as a standard. The antioxidant or free radical inhibitory activity was calculated according to the following formula.

% inhibition = (Ac – As) / Ac) x100

Where, Ac: Absorbance of control

As : Absorbance of Naringin and Allyl sulfide

The radical scavenging activity results were expressed as the half maximal inhibitory concentration (IC 50) compared to standard. All measurements were done in triplicate and values expressed as mean ± SD.

2) Nitric oxide (NO) free radical scavenging activity

Nitric oxide scavenging activity was measured by slightly modified method of Can et al., (2022). Nitric oxide radicals (NO) were generated from sodium nitroprusside. 1 ml of sodium nitroprusside (10 mM) and 1.5 ml of phosphate buffer saline (0.2 M, pH 7.4) were added to different concentrations (25, 50, 75, 100 and 150 µg/mL) of test compounds Naringin, Allyl sulfide, and in combination of both (dissolved in methanol) and incubated for 150 min at 25ºC and 1 ml of Griess reagent (1% sulfanilamide, 2% H3PO4 and 0.1% naphthyl ethylenediamine dihydrochloride) was added to the 1 ml of the reaction mixture. The standard antioxidant ascorbic acid was used as the positive control. The absorbance of the resulting reaction mixture was measured at 546 nm.

3) Antibacterial Activity

The antimicrobial activity was evaluated by slightly modified method of de Oliveira et al., (2022). The Naringin, Allyl sulfide and the combination of both compounds were evaluated for their in vitro antibacterial activity against the growth of four bacterial strains such as gram-positive bacterium *Bacillus megaterium*, *Bacillus subtilis* and gram-negative bacterium *Klebsiella pneumoniae* and E. Coli by using the agar well diffusion method. The antimicrobial activity wa calculated by measuring the diameter of inhibition zone. Azithromycin was used as a standard. The detailed procedure has been provided in the supporting information.

4) In-Vitro Cell Culture Experiments

MCF-7 Breast cancer cells were obtained from National Centre for Cell Science, Pune, India. They were maintained in DMEM (Dulbecco's modified Eagle's medium) supplemented with 10% Fetal Bovine Serum (FBS) and 10µg/mL streptomycin and penicillin, incubated at 37^{o}C in an incubator with 5% CO2.

5) Cell viability by Microscopic Assay

The MCF-7 cells were cultured in T-25 flasks until reach 75% confluence, then 1.5 x 104 MCF-7 cells were cultured in each well of 6-well plate containing DMEM media with 10% FBS, 1% antibiotic. The cells were treated with Naringin and Allyl sulfide to each well and incubated for 24 h. The viable cells were observed under the fluorescent microscope.

6) MTT Assay for Cytotoxicity

The cytotoxic effect of Naringin and Allyl sulfide was determined by 3-[4,5-dimethylthiazole-2-yl] 2,5-di-phenyl-tetrazoliumbromide (MTT) assay. Briefly, 100µL of MCF-7 cells were aliquoted, placed into two separate 96-well plates at a density of 1.5 x 10 4cells/well and left to attain 70-80% of cell confluency for 24 h. Then, the cells were treated with various concentrations of Naringin and Allyl sulfide (25+25 µg/mL) and incubated for 24 h. After the treatment, 0.8 mg/mL of MTT solution was added to each well of the cells and after 4 h incubation, the supernatant was removed, then 100µL of DMSO was added into each well to dissolve the formazan crystals, and the plates were incubated on a shaker and the absorption was read at 570 nm using a micro-plate reader (Bio-Rad). All experiments were performed in triplicate. The relative cytotoxicity was compared using untreated control cells as the baseline (Alessandria et al. 2014, Venkataswamy et al., 2023).

7) Statistical Analysis

All the experiments were carried out in triplicate. Data were loaded to Microsoft Excel, Prism 8.0 and one-way ANOVA Programme was used to analyze the data. All the data were presented as mean ± SD. Statistically, the significance between control and treated groups were indicated with different superscripts.

III. RESULTS AND DISCUSSION

A. Antioxidant Assays

1) DPPH Radicals Scavenging Activity

The DPPH free radical scavenging assays were performed to determine the antioxidant activity of Naringin (NA) and Allyl sulfide (AS). The results of DPPH showed that, among all the NA, AS and NA+AS combinations, NA+AS at 125 µg/mL had the strongest free radical scavenging activity (84.84±3.7) followed by NA and AS. The IC50 value of NA+AS was 46.96 µg/mL, where the ascorbic acid exhibits IC50 of 24.99 µg/mL. The antioxidant activities are shown in Table 1.

Analysis of antioxidant assay by DPPH method						
Compounds	25µg	50µg	75µg	100µg	125µg	IC_{50}
Naringin	38.42±1.2	49.74±1.8	58.13±2.2	68.41±2.6	78.2±3.4	50.26±1.2
Allyl sulfide	26.11±1.1	36.23±1.9	47.14±2.3	55.4±2.5	66.71±3.2	79.55±0.8
Naringin + Allyl sulfide	45.14±2.4	54.31±2.5	65.34±2.7	75.15±3.3	84.84±3.7	46.96±0.9
Ascorbic acid(std)	50.01±2.1	60.34±2.6	71.1±3.4	80.47±3.8	92.11±4.3	24.99±1.1

Table 1: DPPH radicals scavening activity of Naringin (NA) and Allyl sulphide (AS)

2) Nitric Oxide Radicals Scavenging Activity

The Nitric oxide free radical scavenging assays were performed to determine the antioxidant activity of Naringin (NA) and Allyl sulfide (AS). The results of NO showed that, among all the NA, AS and NA+AS combinations, NA+AS at 125 µg/mL had the strongest free radical scavenging activity (83.54) followed by NA and AS. The IC50value of NA+AS was 46.27 µg/mL, where the ascorbic acid exhibits IC50 of 26.93 µg/mL. The antioxidant activities are shown in Table 2.

Analysis of antioxidant activity by NO scavenging method						
Compounds	25µg	50µg	75µg	100µg	125µg	IC50
Naringin	33.12±1.2	43.41±2.6	52.92±2.5	62.61±2.7	73.01±3.4	71±0.7
Allyl sulfide	21.31±0.8	32.11±1.7	44.3±2.1	53.52±2.9	61.22±3.7	93.42±1.1
Naringin + Allyl sufide	43.11±2.5	54.02±2.7	62.31±3.1	72.79±3.2	83.54±4.2	46.27±0.9
Ascorbic acid(std)	46.44±2.6	56.31±2.6	64.79±3.3	75.13±3.5	86.01±4.4	26.93±1.2

Table 2: Nitric oxide radicals scavenging activity of Naringin (NA) and Allyl sulfide (AS)

3) Antimicrobial Activity

The Naringin (NA) and Allyl sulphide (AS) compounds were screened for the antibacterial activity against Gram positive and Gram negative bacterial strains by using the disc diffusion method. Azithromycin was used as a standard. The compounds AS, NA, NA+AS showed antibacterial activity against all the tested pathogens. Among all, NA+AS exhibits potent antimicrobial activity compared to the standard drug. The zones of inhibition of all the title compounds were presented in Table 3.

Zone of Inhibition of naringin, Allyl sulphide				
Compounds	*Gram positive*		*Gram negative*	
	B. subtilis	*B. megaterium*	*E. coli*	*K. pneumoniae*
Naringin	0.8±0.02	0.8±0.02	0.6±0.02	1.2±0.07
Allyl sulfide	0.9±0.02	0.7±0.02	0.4±0.01	0.9±0.03
Naringin + Allyl sulfide	1.3±0.04	1.2±0.03	1.1±0.02	1.4±0.06
Azithromycin (std)	2.7±0.07	2.8±0.07	2.9±0.08	3.2±0.08

Table 3: Analysis of antibacterial activity of Naringin (NA) and Allyl sulfide (AS)

4) Cell viability by Fluorescent Microscope

The fluorescent microscopic images were observed to find the cytotoxicity of Naringin (NA) and Allyl sulphide (AS) on MCF-7 cells. Figure 1 demonstrated moderate inhibition of cell viability when treated with NA or AS. However, high level inhibition of cell viability was noted with combination of NA+AS and the results were compared with doxorubecin treated cells (Fig 1).

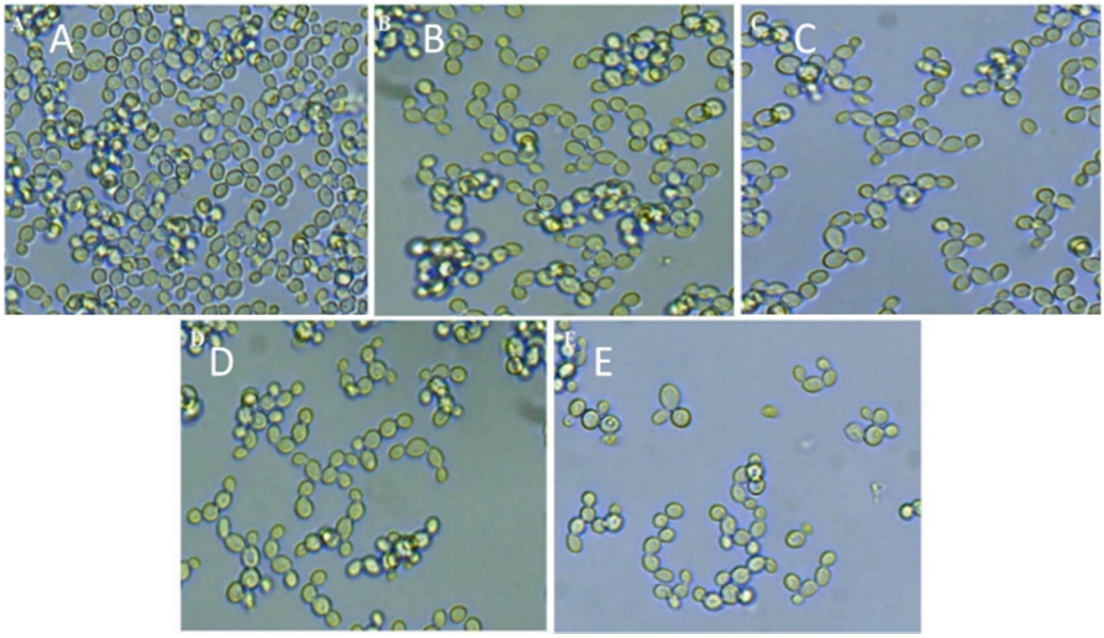

Fig 1: Microscopic observation of MCF-7 cells' viability (A) Control (untreated cells) (B) Allyl sulfide -treated cells (C) Naringin-treated cells (D) Naringin + Allyl sulfide-treated cells (E) Doxorubicin treated cells.

5) Cytotoxicity by MTT assay

The cytotoxicity of Naringin (NA) and Allyl sulfide (AS) compounds against MCF-7 breast cancer cells at different dosages (25+25 µg/mL) during 24 h treatment was tested using the MTT assay. The results are presented in Fig. 2. On MCF-7 cells, Naringin (NA) and Allyl sulfide (AS) compounds exhibited potent cytotoxicity (55%). In comparison to the reference medication Doxorubicin, the NA+AS demonstrated considerable anti-proliferation efficacy against breast cancer cells.

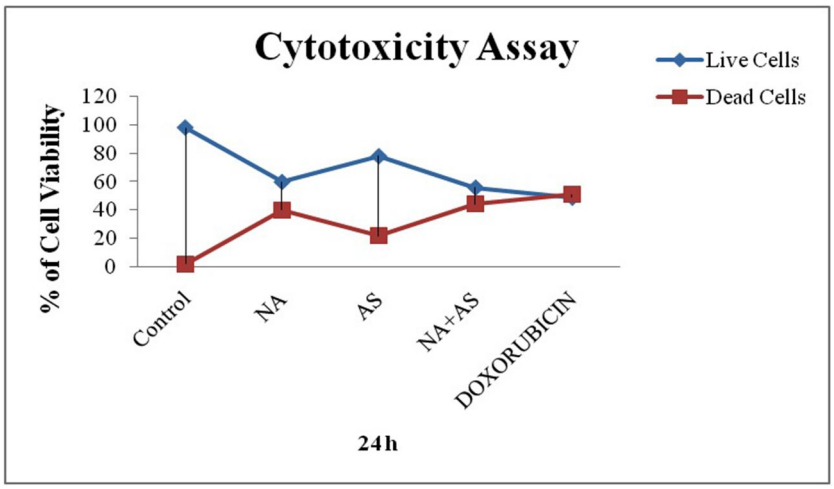

Fig. 2: MTT assay showing the effect of NA and AS on MCF-7 breast Cancer cells

IV. DISCUSSION

Plants and herbs have played an important role in providing foods as well as in the treatment of several human ailments and are the immense and abundant sources for drug development. Garlic has been used from ancient times as a curative food-based plant for the treatment of several diseases due to its rich phyto-constituents. In the present study Allyl suflide inhibited cell viability and caused cytotoxicity of MCF-7 cells. This inhibition of cell growth and proliferation and anticancer activity might be due to its ability to suppress cellular proliferation by blocking cells in the G2/M phase and by the induction of apoptosis. This increase in the G2/M and apoptotic cell populations correlates with depressed p34cdc2 kinase activity, increased histone acetylation, increased intracellular calcium and elevated cellular peroxide production (Knowles et al., 2000). Previous studies showed that apoptosis is stimulated by garlic. Suppression of angiogenesis and experimental metastasis by Allium constituents has also been reported.

Naringin is well reported for its antioxidant activity and to mitigate oxidative-stress induced pathophysiologies. In the present study Naringin might scavenge the oxygen and nitrogen free radicals which otherwise might trigger signaling path ways that promote cancer progression) Shilpa et al., 2023). AS and NA together were found to be more effective than when they were treated alone to inhibit MCF-7 cells growth and proliferation as well as to inhibit microbial growth.

V. SUMMARY

Naringin (NA) and Allyl sulfide (AS) were found to have potent antioxidant activity as evident from DPPH and NO free radical scavenging activity, however, the combination of NA and AS showed more potent antioxidant activity than when they were used alone. Similarly, the combination of NA and AS have demonstrated reasonable antimicrobial activity than when they were used singly against selected gram positive and gram negative bacteria. The MTT assay demonstrated the potent cytotoxic effect of NA and AS, however a combination of both NA and AS were found to be more efficacious against breast cancer cells than when they were used separately.

VI. CONCLUSION

In conclusion our results demonstrate that Naringin and Allyl sulfide possess potent antioxidant and anticancer activities and their combination is more efficacious and hence can be recommended for regular consumption as Nutraceuticals.

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B. Conflict of Interest

The authors state that they have no conflict of interests.

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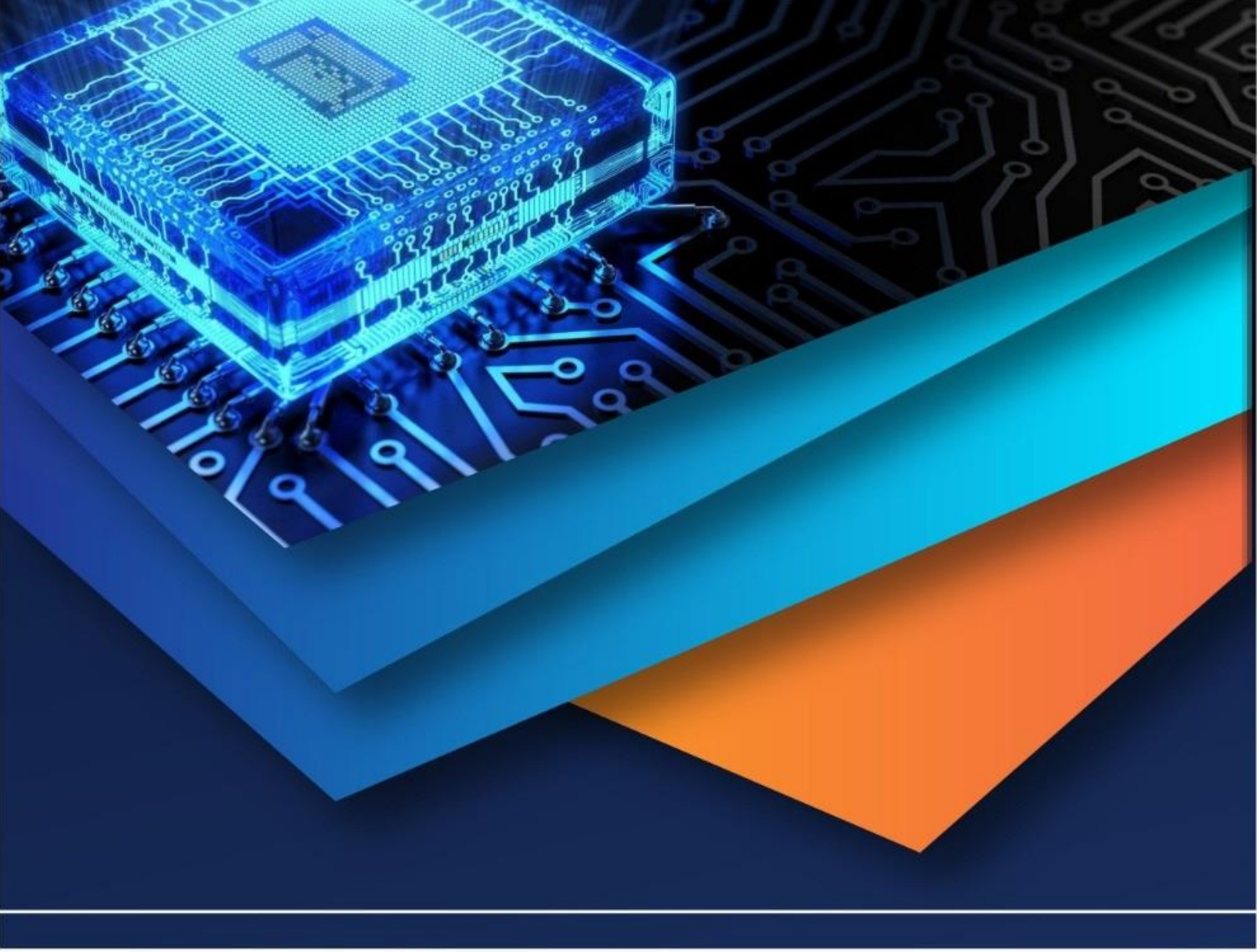

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