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Systematic Review - Chemistry &Clinical Importance of Anticancer Drugs, Plus Recent Advances in Discovery

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Abstract: ***Cancer is a process of uncontrolled cell proliferation that leads to the development of an abnormally growing tumor, determining initially a local disease that might spread, impairing other organs or important processes.One of the most fatal diseases in recent times, cancer kills many lives each year.The effective management of this condition has been impacted by the variances in the disease across the globe, the impact of the medical facilities that are available, and other socioeconomic issues.The aim of this study was to summaries previously published articles regarding recent advances in anticancer drug discoveries.In this review, previously published literature regarding recent advances in anticancer drug discovery collected from journals through Pub Med Central, Google Scholar, and Science Direct from March 20 toMay 12 was identified well, and points that I assumed were important and recent (2017–2023) were included.Anticancer pharmacotherapy has evolved from broadly cytotoxic agents to precision medicines and biologics.This review summarizes the chemistry and clinical importance of major anticancer drug classes (alkylators, antimetabolites, plant alkaloids, topoisomerase inhibitors, kinase inhibitors, hormonal agents, monoclonal antibodies, antibody–drug conjugates (ADCs), immunotherapies and targeted protein degraders such as PROTACs). We highlight recent discovery advances — ADC design, targeted protein degradation (PROTACs/molecular glues), sophisticated kinase/RTK inhibitors, CAR-T and other cellular therapies, and regulatory trends — and outline remaining chemical and translational challenges.***

Keywords: Cancer, DrugdiscoveryDrugtargetsDrugrepurposing, cytotoxic.

I. INTRODUCTION

Cancer is a condition where cells grow uncontrollably, formingtumorsthatdevelopabnormallyandcanspread to other organs or vital systems, impairing their ability to function.[1] Several determinant agents, including genetic mutations, pollution, food contaminants, viruses, chemicals, andionizingradiation,interacttocausecancer,whichiswhyitisregardedasamultifactorialdisease.[2] Multiple evolutionarily conserved cell cycle control mechanisms tightly regulate cell division to guarantee the generation of two genetically identical cells.[3] One of the deadliest illnesses in recent memory, cancer claims many liveseachyear.

Thepropermanagementofthisdiseasehas beenimpactedbythevariationsinthediseaseacross the globe, the impact of the medical facilities that are available,andothersocioeconomicfactors.[4]According to the 2023 global cancer statistics, there will be 20million additional cases of cancer and 10 million deaths fromcancer.Overthefollowingtwodecades,therewill be a roughly 60% increase in the cancer burden, placingadditionalstrainoncommunities,individuals, and health systems.

AccordingtoresearchdoneinEthiopiabetween2000 and 2016, cancer was responsible for an estimated 50,913.5(95%)deathsamongpeopleofallagesand both genders (the majority of the patients were females), with a crude death rate of 49.7 per 100,000 and an age- standardized death rate of 93.5 per 100,000.

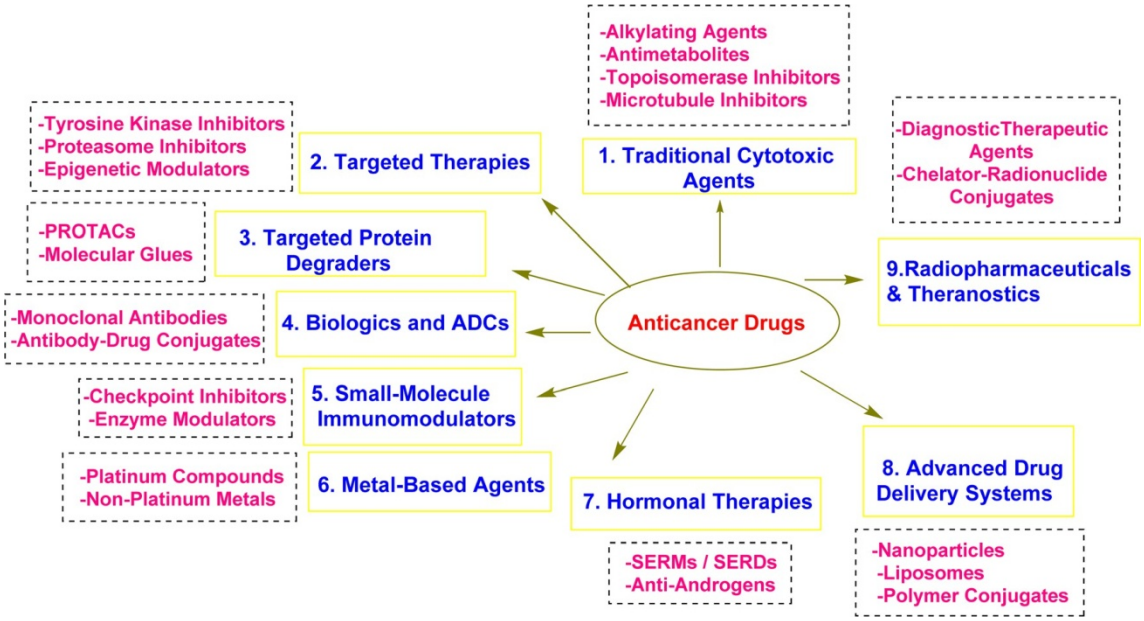
The numberofcancercaseshasincreasedtopreviouslyunheard-of levels as a result of longer life expectancies. As aresult, the pharmaceutical sector has invested a sizable amountofmoneyinthistherapeuticfield.Despitetheseefforts,thefieldofcancerdrug research continues to be remarkably difficult, and therapeutic advancements have not yetproducedthe anticipated clinical outcomes.[5] However, since the first half of the 20th century, drug manufacturers have continued to produce medicines despite their high cost-benefit ratio by taking into account the improved understanding of the disease's physiopathology.[6,7] Drug companieshavecreatedavarietyofanticancerdrugclasses,suchascytotoxicdrugs(alkylatingagents,antimetabolites,antibiotics,plantextracts,andothercytotoxicdrugs), hormones and hormone antagonists, and immunomodulators.[8,9]

However,thesechemotherapieshaveissueswithlackofspecificity,cytotoxicity,inductionofmulti-drugresistance,andstem likecell growth.[10] The identification of new molecular targets has raised hopesforcreatingbettertreatments.Themainobstacles in cancer drug discovery, improving drug selectivityandloweringsideeffects,havebeen addressedbymonoclonalantibodiesandantibody-small molecule conjugates.[5,10] Manufacturers and researchershavepublishedatonofliteratureon drug targets and new drug development strategies bytaking into account the difficulties of anticancer drugs, theirtoxicityprofiles,non-selectivitycharacteristics,andrelatedsideeffects.Thisreviewthereforeaims to compile and summarize a collection ofpublicationscenteredonnovelchemicalcompounds with cytotoxic activity on cancer cells in vitro, or both, in particular novel biomarkers and target proteins with potential therapeutic properties.

II. MATERIALS AND METHODS

In this review, the reviewer uses websites such as Google Scholar, PubMed Central, and Science Direct as searching tools via a personal computer and other accessories.

III. GENERALOVERVIEWOFANTICANCERDRUGDISCOVERY



Due to their intricate, pricey, time-consuming, anddifficulttasks,researchersanddrugmanufacturers have faced significant challenges in the design and discovery of anticancer drugs.[11] Aside from the complexity,first-handtreatmentsareextremelytoxic anddonottargetcancercellsspecifically.[12,13]This is true even though manufacturers are working on developinganticancerdrugs.Itisthereforeofgreatinterest to design and develop novel, selective small-molecule drugs, especially with the aid of in silico tools that have been developed in recent years.[14] But recently, artificial intelligence (AI) has emerged as a strong and promising technology for quicker, less expensive, and more efficient anti-cancer drug designs than the previously employed CADD.[11] The search for novel drug molecules and the synthesis of more appealing drug molecules can both be spedupbyartificialintelligence.Targetidentificationis the first step in the anti-cancer drug discovery process, and after that comes structure-based, ligand-based, and fragment-basedscreeningofsuccessfulcompounds,de novo anti-cancer drug design for large compounds,anti-cancerdrugrepurposing,andpreciseanti-cancer drug reaction prediction.[15,16] Anticancer medications advance as they are discovered fromnaturalproductsorsynthetically,takinginto accountthetoxicityandefficacyofmedicationsand using thisartificial intelligence-basedadvancedtechnology orpreviousCADDasatoolfordrugdesignanddiscovery. Asoflate,drugrepurposingbasedon promisingtargetshasalsobecomepopular.[17–19]However,therearedrawbackstocancerimmunotherapy,such as resistance, the ability of cancer cells to evade the immune response, and issues with delivery methods.[20] Nanoparticles using nanocarriers as vehicles have some issues that could solve these issues, according to recent advancements.[21]Becauseoftheirspecialqualities, such as biocompatibility, decreased toxicity, increased permeability, improved stability, precision targeting, and retentioneffect,[22]nanoparticlescanbeusedtotreatcancer.

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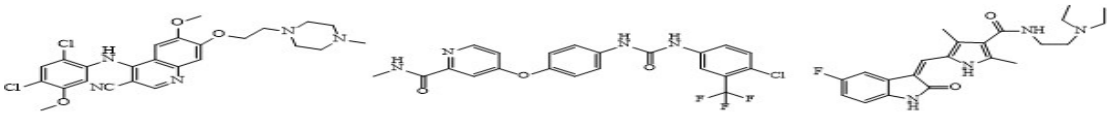
IV. RECENT ADVANCE SINANTIC ANCER DRUG TARGETSAND BIOMARKERS

Targetedtherapyholdsthekeytoraisingoverall survival rates while lowering the unfavorable side effects ofcancertreatment.Comparedtopatientswhodid notreceivematchedtargetedtherapies,patientswho did both overall survival and progression-freesurvival significantly improved.[23] For the purpose of treating cancer, numerous drug targets have been found. Due to efficacy or toxicity issues, the majority of molecularly targeted agents were ineffective. Researchers are being challenged to concentrate on the drug targetsthat can aid in the complete eradication of the disease by recent work in the field of molecular biology and a better understanding of the molecular pathology of cancer.[24]

A. Kinasesastargets

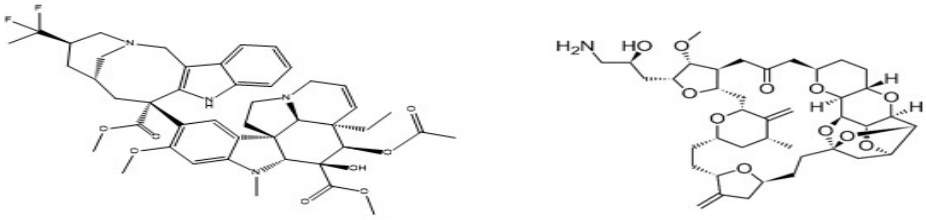
A group of anti-cancer medications known as kinase inhibitorsdirectlyinteractwiththeactivesiteofthe targetenzymetopreventkinaseactivity.According to estimates, the human genome contains about 2000 kinases that are either serine/threonine- or tyrosine- specificandconnectedtooneanother.[24]Clinical oncologywasfirstintroducedtoimatinib,thento bosutinib, sorafenib, and sunitinib. Despite having the samemodeofaction—competitiveATPinhibitionatthe tyrosine kinase catalytic binding site—they are distinct from one another in terms of the range of targeted kinases, theirpharmacokinetics,andthenegativeeffectsthatare substance-specific.[25]



Bosutinib Sorafenib Sunitinib

B. Tubulin/microtubuleastarget

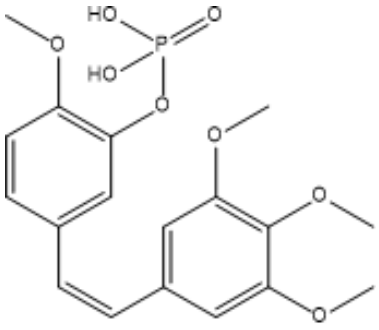
A major component of the eukaryotic cytoskeleton, microtubulesareformedbythepolymerizationof theglobularproteintubulin,whichhasamolecular weight of 52 KD. Through each stage of the cell cycle, microtubules continuously lengthen and shorten.Comparedtonormalcells,cancercellsrapidlydivide and expand. The development of microtubule-targeting agents for the treatment of cancer is being investigated becausetheyareessentialforcelldivisionandgrowth. As a result, the development of anti-cancer medications nowincludestubulinasoneoftheirkeytargets.Tofindand develop safer and more effective drug candidates, a number of tubulin-targeting agents have been synthesized, andstructure-activityrelationshipstudieshavebeencarried out.[24,26]



Vinflunine Eribulin

C. Vasculartargetingagents

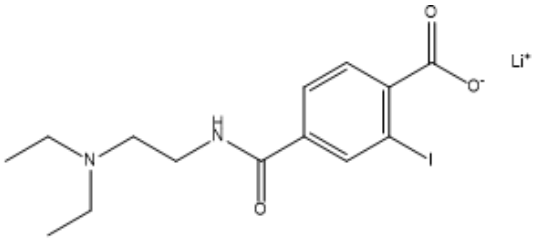
Vascular targeting agents (VTAs) are primarily cancer therapiesthatarecreatedspecificallytotargetthe tumor's vasculature and, as a result, prevent the growthanddevelopmentoftumors.Giventheavailabilityofblood- bornemedications,itbecomesasuccessfulstrategyin the treatment of cancer. A steady flow of oxygen and nutrients is necessary because tumor cells divide rapidly. Therefore,thegrowthofbloodvesselnetworksisnecessary for the development, progression, and metastasis oftumors. Vascular disrupting agents (VDAs) can stop blood flow to tumors.[27,28]



Fosbretabulin

D. Angiogenesisinhibitors

A brand-new class of medicines called angiogenesis inhibitors is intended to prevent tumor vascularization. VEGF-A is overexpressed in tumor growth, invasion, and metastases. Targeting VEGF-A at the moment are VEGF-AandVEGFR2inhibitors[28].Non-small-celllungcancer.
(NSCLC) is treated with angiogenesis inhibitors, such as bevacizumab and ramucirumab. These medicines aim to block VEGFs.[29]



Bevacizumab

E. Monoclonalantibodies

To stop tumor vascularization, a new class of drugs called angiogenesis inhibitors is being developed. Tumor growth, invasion,andmetastasesallexhibitoverexpressed VEGF-A. VEGF-A and VEGFR2 inhibitors currently target VEGF-A.[28] Angiogenesis inhibitors (AIs), like bevacizumabandramucirumab,areusedtotreatnon-small-celllungcancer(NSCLC).Thesedrugstry to stop VEGFs.[29]

Recent Advance sin Drug Repurposing for the Discovery of New Anticancer Drugs
Drug repositioning, another name for drug repurposing, isa tactic that looks at additional diseases besides the one for which a drug has already received approval.[30–32]

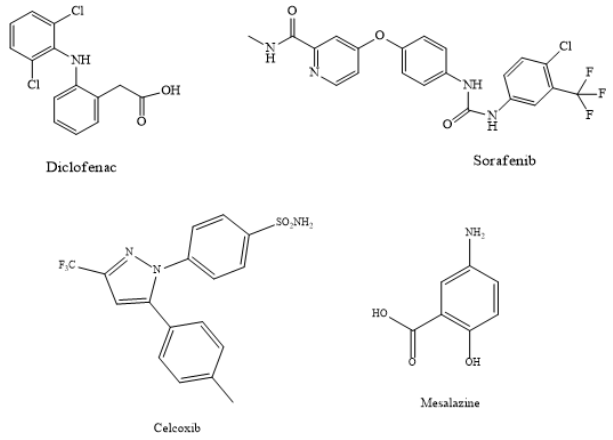
1) Antiplatelet Agents

Althoughaspirin'sclinicaluseasananticancermedication hasbeenexpandedandregularuseofthe medication is associated with a lower risk of breast cancer, aspirin is primarily used as an antiplatelet medication for cardiovascular diseases. Henry et al. suggests that aspirin andPI3Kinhibitorsmaybeusedincombinationtherapyto treat breast cancer.[33]

2) Anti-inflammatorydrugs

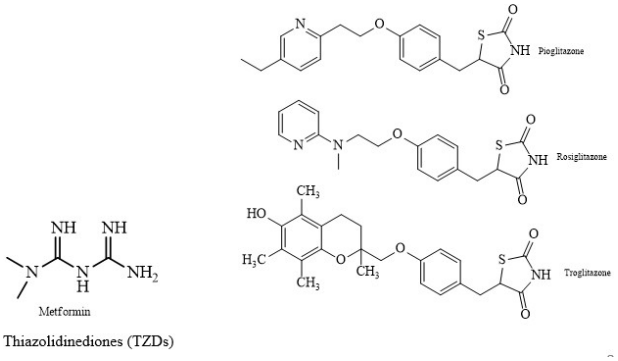
Accordingtorecentinvivodata,diclofenacsuccessfullyslowsthegrowthofpancreatictumorsinmice.Diclofenactherapyresultedinarisein apoptosisandafallinangiogenesis,accordingto analysis of the tumor tissue removed during surgery. Additionally, melanoma cells were used to test the effectiveness of a diclofenac and sorafenib (a kinase inhibitor)combination,andtheresultswerepositiveforall cancercells.[34]Furthermore,ininvivoratmodels,theselective COX-2 inhibitor celecoxib inhibited the growthof breast cancer cells and decreased tumor development.

It was discovered that the level of COX-2 expression andthe invasiveness of the tumor cells were required for growth inhibition.[35]Mesalazine has also been mentioned as having anti-cancer potential in a variety of cancers, including colorectal cancer, gastric cancer, breast cancer, and colon cancer.[36]



3) Antidiabetic agents

Thefirstlineoftreatmentfortype2diabetesmellitus ismetformin,anoralmedication.Numerouscancer types,includingpancreatic, endometrial,breast,lung, and prostrate, have shown it to have anti-neoplastic activity.[37] Through numerous preclinical and clinical studies, thiazolidinediones (TZDs) have been identified as apotentleadinthetreatmentofbreastandprostatecancer. Troglitazone, rosiglitazone, and pioglitazone are the three key components of this medication.[38]



V. CONCLUSION

The global impact of cancer is extremely negative. Beginningwiththefirstnitrogenmustards,researchersand pharmaceuticalcompaniestriedtheirbesttofind cures.Thelackofselectivity,effectiveness,sideeffects,andmetastaticnatureofthediseases make effective treatment challenging, despite the availabilityofawiderangeoftreatmentoptions asalternatives.Recentadvancesinthefieldof molecularbiologyandadeepercomprehensionofthe molecular pathology of cancer have pushed researchers toconcentrateonthedrugtargetsthatcanaidin the total eradication of the disease.

The discovery of anticancer drugs is outlined in this review's recent highlights. Researchers are now betterabletoidentifyspecifictreatmentswithlowertoxicity and better tolerability thanks to recent advances in drug target and discovery. Numerous drug targets have been found for the treatment of cancer based on a variety of articles written by academics, in order to improve their efficacy and decrease their toxicity. The most effective cancertreatmentfocusesarekinase,microtubulin,vascular targeting, angiogenesis, and monoclonal antibodies. Researcherslookintoalternativeusesofadrugthathas already been approved for one condition for other diseases in addition to its original indication in order to significantly reduce the cost, labor, and research time.

Antiplatelet,antidiabetic,anti-inflammatory,antimicrobial, and antipsychotic agents are among the repurposed medications that are mentioned.

Apopularmethodforfindingnewclassesofanticanceragentsaswellastheirinventivemodesofactionisthroughthediscoveryofphytochemicals. Quercetin,ginseng,artemisinin,andcurcumin allhavethepotentialtofightcancer.Ontheother hand, natural products are recognized as superior andmore potent chemotherapeutic agents. A significantamountofanticanceractivityisexhibited bynewlydevelopedmechanismsthataredesigning novelheterometalliccomplexeswithmetalcenters andheterocyclicandbis-heterocyclicsubstances like thiazolidin-4-ones, 1,3,4-thiadiazoles, and thiazoles to overcome the toxicity of chemotherapies.

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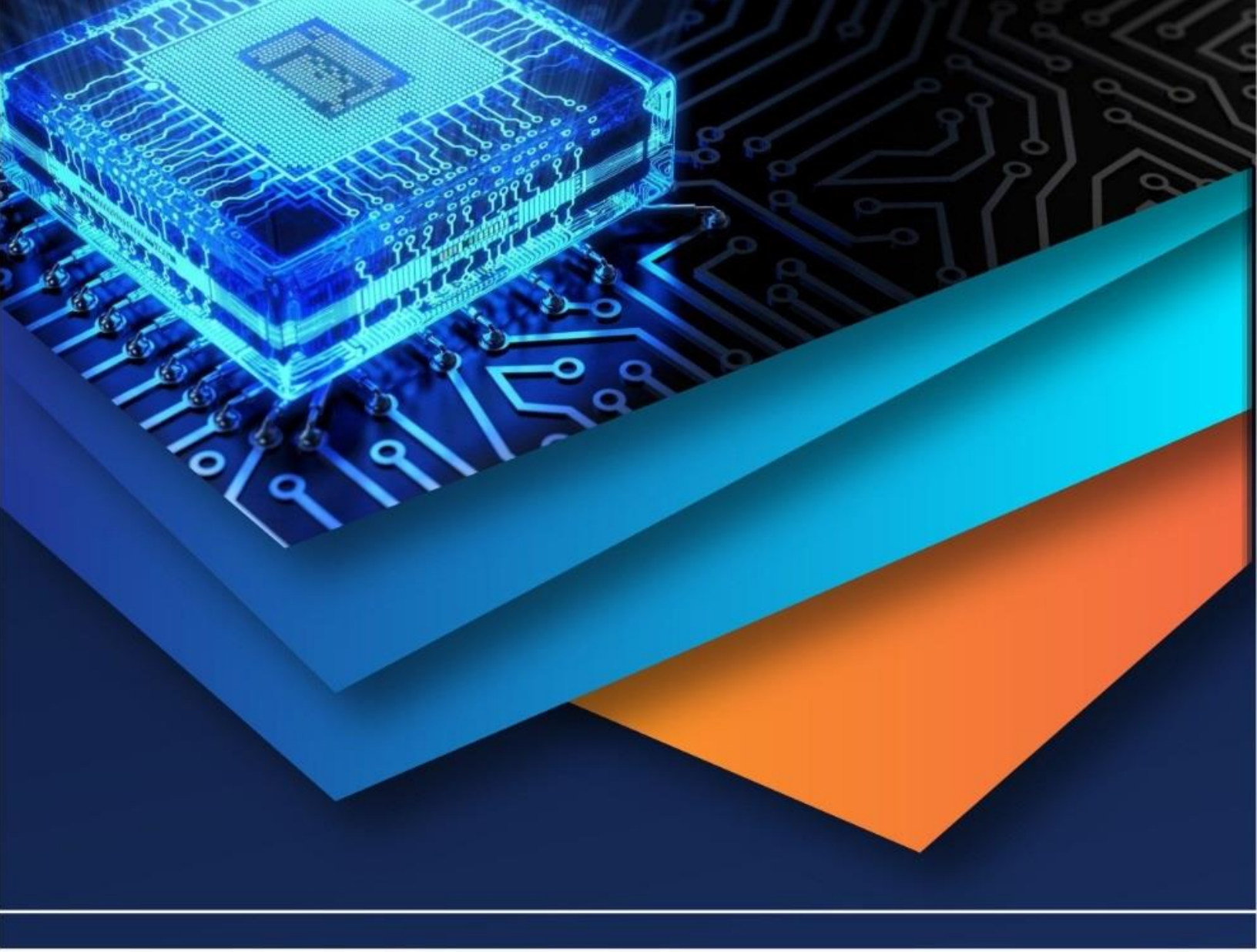

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