iJRASET
International Journal For Research in Applied Science and Engineering Technology



INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 8 **Issue:** V **Month of publication:** May 2020

DOI: http://doi.org/10.22214/ijraset.2020.5495

www.ijraset.com

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
Volume 8 Issue V May 2020- Available at www.ijraset.com

Computational Predictions and Comparative Structural Analysis for 4-Aminoquinoline/Umifenovir Drug Combinations towards Drug for Coronavirus Disease-19 (COVID-19)

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***Abstract:** As of 28 Mai 2020, more than 5 593 631 cases of confirmed COVID-19 have been documented globally with over 353 334 deaths. The COVID-19 patients have common presentations like the influenza patients include fever, dry cough, and difficulty of breath. Parallel evidence indicates that the risk of disease increases with critically chronic lung patients. No strong efficacy to use drugs on the market. We apply drug design computer techniques to find the expected drug for COVID-19 after knowing the repurposing the detailed of 3D-structures of its key proteins. The combination of the analyzed spectra of the antimalarial/antiviral drugs: Chloroquine (CQ)/Umifenovir, Hydroxychloroquine (HQ) /Umifenovir and Amodiaquine (ADQ)/Umifenovir have been discussed to give an additional information about the investigated set of complex drugs. The aim of this work is the bioinformatic study of COVID_19 inhibition by antimalarial/antiviral combined drugs.*
***Keywords:** Coronavirus, COVID-19, 4-Aminoquinoline derivatives, drug combination, Umifenovir.*

I. INTRODUCTION

As of 28 Mai 2020, more than 5 593 631 cases of confirmed COVID-19 have been documented globally with over 353 334 deaths. [1]. We reported previously a computational modeling drug design for a category of HIV drugs called non-nucleoside reverse transcriptase inhibitor (NNRTI), nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs), respectively [2&3]. Following these publications, Youssef *et al.* published recently other article describe the computational structural analysis and drug combination of a series of HIV drugs namely; Abacavir, Lamivudine and Zidovudine towards drug for coronavirus disease-19 (COVID-19) [4].

4-Aminoquinoline derivatives were famous drugs for the successful treatment of malaria. Among the candidates for 4-Aminoquinoline drugs are Chloroquine (CQ), Hydroxychloroquine (HQ) and Amodiaquine (ADQ). They have been approved previously by Food and Drug Administration (FDA). They used for treating malaria infection and therefore it has attracted the most attention during the past few months [5-7].

Nowadays, the antimalarial Chloroquine [8], Hydroxychloroquine [9-12] and Amodiaquine [13] have demonstrated antiviral activity against severe acute respiratory syndrome–coronavirus SARS-CoV and SARS-CoV-2 in addition coronavirus disease (COVID-19) in vitro and in small, poorly controlled or uncontrolled clinical studies with weak–moderate efficacy. They have limited and inconclusive data.

Umifenovir is a model of antiviral drug. It used for a variety of enveloped and non-enveloped RNA and DNA viruses. It can treat Flavivirus and Ebola virus. Its dual activity lead to an additional protection against viral resistance [14].

Umifenovir is currently investigated for COVID-19 as a potential treatment. It can be combined with investigational HIV therapies [15]. According to literature, Chloroquine, Hydroxychloroquine and Amodiaquine have serious side effects, especially if taken at high doses [16-18]. In this work we try to decrease their danger effects and risks by combination them with the safe Umifenovir drug 1:1ratio.

For this reason, we introduce for all researchers, pharmacies, clinicians, manufacturers, and governmental health agencies that interest with health care the proposed and expected drug to avoid the spread of the disease. The aim of this work is the bioinformatic study of COVID_19 inhibition by antimalarial/antiviral combined drugs.

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ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
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II. MATERIALS AND METHODS

A. *Materials*

Three models of 4-aminoquinoline drugs as anti-malarial drugs namely: Chloroquine (CQ) (sold under the brand name Aralen and others), Hydroxychloroquine (HQ) (sold under the brand name Plaquenil and others) and Amodiaquine (ADQ) (sold under the brand name Amobin and others). One model as anti-viral drug called: Umifenovir (sold under the brand name Arbidol).

B. *Computational Details*

Anti-malarial drugs geometry, electronic, and vibrational properties were studied using the program Gaussian 09. The 3D structural models viewed by GaussView 5.0.8 software [19].

C. *Molecular Docking*

The PubChem and Protein Data Bank (PDB) used to extract the databases of COVID_19 protease. The Autodock 4.2 package used for all docking procedures [20].

III. RESULT AND DISCUSSION

In this work, we discuss the spectral analysis of 4-aminoquinoline drugs as fused-ring heterocyclic compounds through the variation of the aminoalkylamino chain. This variation lead to modification of the quinoline ring system with expected changing in the reactivity and chemical behavior of 4-aminoquinoline derivatives as illustrated in Figure1, and for umifenovir is an indole core with hydrophobic properties.

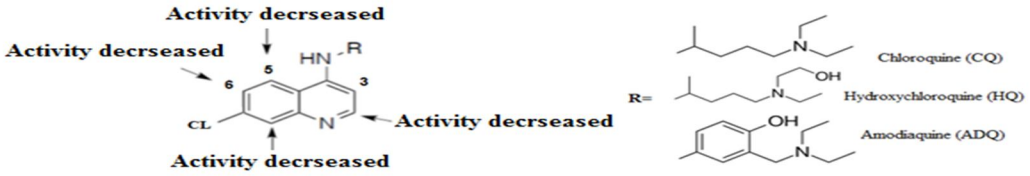


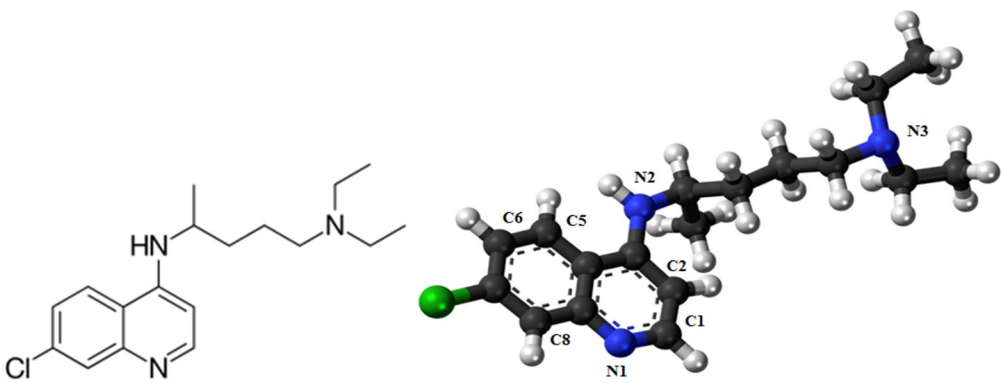
Figure 1: Chemical structures and ring substitution pattern of 4-aminoquinoline drugs analogs.

A. *Computational Details*

The chemical structure of 4-aminoquinoline drugs used in this study shown in Fig 1. The similarity in the spectral analysis can be observed in the vibrational frequencies between the Chloroquine, Hydroxychloroquine, Amodiaquine and Umifenovir. It demonstrates the isomeric conformations (a), (b), (c) and (d) in Figure 2. The amine stretching (NH) showed a strong peak in the regions of 1790 cm^{-1}, 1845 cm^{-1}, and 1860 cm^{-1} for CQ, HQ and ADQ, respectively. This peak was absent in Umifenovir, because it does not contain an NH group in its structure (Figure 2). The OH group showed a strong peak for HQ and ADQ in the region of 3793 cm^{-1} to 3863 cm^{-1}.

The theoretical ^{13}C NMR spectra of the CQ, HQ and ADQ show the peaks related to the CH groups (C2 – C8) at 35±39 ppm and C (C7) at 95 ppm, where the latter exhibits a Chloro atom. The resonance peaks at 122±129 ppm related to CH bonds in benzene ring were observed.

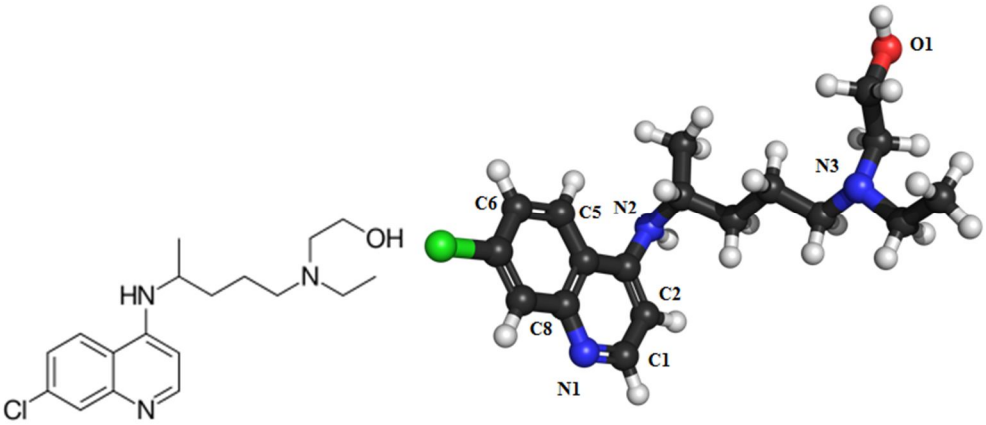
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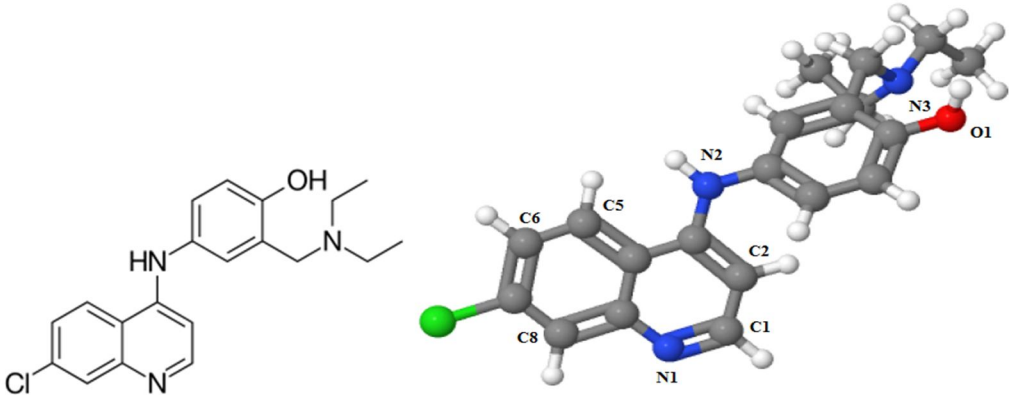
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B



C



D

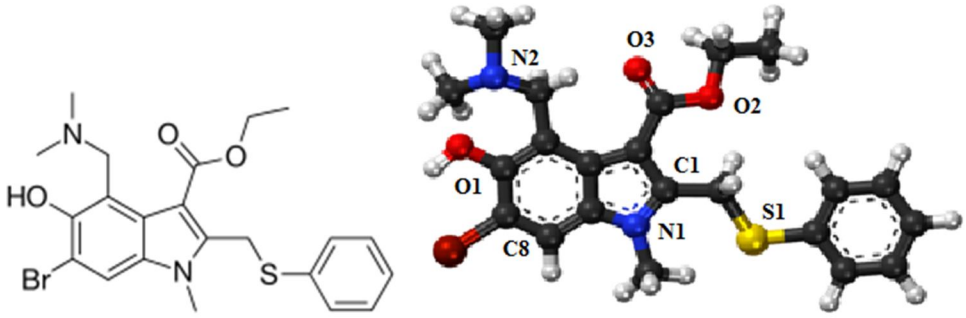


Figure 2: Optimized chemical 2D-Structures and 3D- Structures of 4-aminoquinoline drugs. a) Chloroquine, b) Hydroxychloroquine, c) Amodiaquine, and d) Umifenovir. Carbon, C: black; Hydrogen, H: white; Nitrogen, N: blue; Oxygen, O: red; Chlorine, Cl: green; Sulfur, S: Gold.

Electronic density in each molecule observed that the polar side of the drug is the more negative redder regions; this was observed in the pyridine ring (CQ, HQ and ADQ) and pyrrole ring (Umifenovir) by the N1 atom. The higher probability of chemical interactions represented with higher electronic density sites described in molecular docking.

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The three-dimensional observation of the linking between functional groups on the CQ, HQ, ADQ and umifenovir drugs and protease enzyme virus enabled by software as described in Table 1. All docking conditions for antimalarial/antiviral combined drugs, the interaction area, and the rate of docking still under consideration.

The molecular docking between antimalarial/antiviral combined drugs and protease showed the interaction between hydrogen-electrostatic in addition to van der Waals reactions in the active site of the enzyme.

Table 1: Docking results and binding affinity for CQ, HQ, ADQ and Umifenovir.

Ligand Drug	PubChem CID	MolDock Score (kcal/mol)	Rerank Score (kcal/mol)	Bond Interactions
Chloroquine	2719	-46.591	-37.825	Glu288 Lys5
Hydroxychloroquine	3652	-48.749	-39.499	Glu288 Lys5
Amodiaquine	2165	-110.32	-56.45	Glu288 Lys5
Umifenovir	131411	−7.9	-17.56	Glu288 Lys5

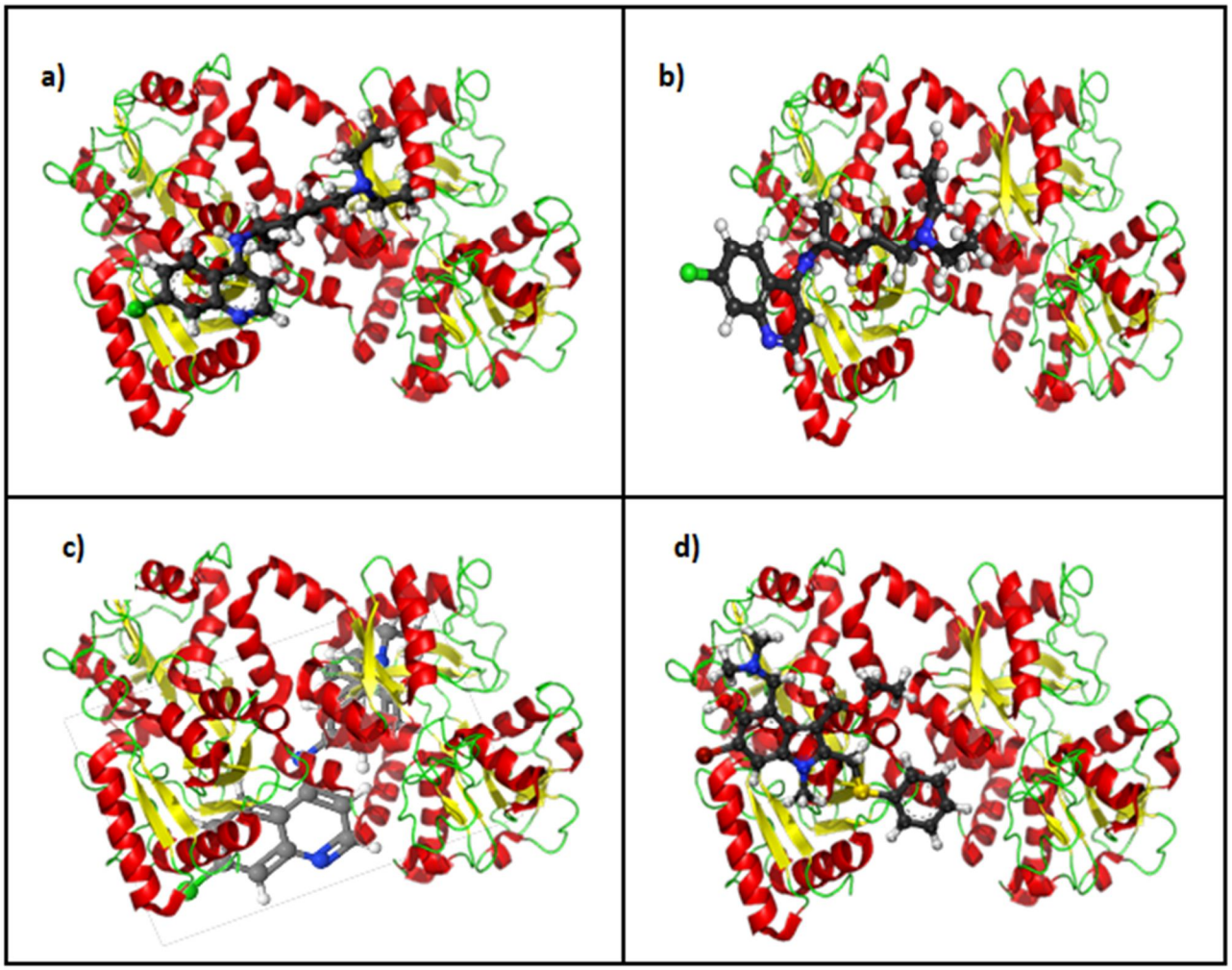


Figure 3: 3D-conformation of the active site of a) CQ, b) HQ, c) ADQ and d) Umifenovir drugs binding in forms of nonstructural proteins: Spike protein (S protein), Envelop small membrane protein (E protein), Membrane protein (M protein).

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In this scenario, we applied multiscale modified non-invasive computational modeling techniques to discover drugs that may be used for repurposing the target COVID-19 protease. We use drug combinations of three models of 4-aminoquinoline antimalarial drugs: Chloroquine (CQ), Hydroxychloroquine (HQ) and Amodiaquine (ADQ) with one model of anti-viral drug namely; Umifenovir as described in Table 2 [8,11&12].

Table 2: In vitro / in vivo efficacy of the CQ, HQ, ADQ and Umifenovir drugs selected for Combined Drug for COVID-19.

Approved FDA Drug	Drug Bank	Clinical studies On COVID-19	Combined Drug	Clinical studies On COVID-19
Chloroquine (CQ) Used as antimalarial& antiviral infection	DB00608	*Weak efficacy [8]*	CQ/ Umifenovir	Ongoing [Actual work]
Hydroxychloroquine (HQ) Used as antimalarial infection	DB01611	Moderate efficacy [8,11,12]	HQ/ Umifenovir	Ongoing [Actual work]
Amodiaquine (ADQ) Used as antimalarial infection	DB00613	Not studied	ADQ/ Umifenovir	Ongoing [Actual work]
Umifenovir Used as antiviral treatments for influenza	DB13609	Moderate efficacy [15]		

The core nucleus, 4-aminoquinoline is an essential for antimalarial activity; it can be consider for viral activity by modifying the side chain on the quinoline ring. The reason being that intact 4-aminoquinoline is required in hematin binding. According to literature it is evident that 7-chloro substituted 4-aminoquinoline derivatives are more active [21].

In order to extract the reliable information. We subject these data to the procedure of the optimal linear smoothing (POLS), in addition to 3-dimensional Multidimensional Scaling (MDS) methods [3]. Due to the importance of these three drugs for the medical treatment, we compare the cosine correlation through a 3×3 matrix of comparison of all drugs provide visualized information of the three 4-aminoquinoline/umifenovir combined drugs.

The results showed that the 4-aminoquinoline/umifenovir drugs can inhibit the virus protease. They were interacting with its key amino acids active site.

There are protected areas of the enzymatic flap identified by the software. The 4-aminoquinoline/umifenovir combined drugs studied have strong binding affinities with two enzymatic flaps. Therefore, due to the strong interaction, these combined drugs can be introduced as effective synthetic drugs to treat new coronavirus infections.

It should be noted that quantitative structure–activity relationships (QSAR) emerging from the use of an Al-driven analyzed data can facilitate rapid drug development, compared to the experimental methods; computer-modelling drug approaches are efficient in providing possible drugs for epidemic disease like COVID-19. However, using the drug combination of antiviral agents lowers the risk of resistant virus strains from emerging.

Based on our predictions, the described drug combinations of the following direct-acting antimalarial/antiviral drugs: Chloroquine (CQ)/Umifenovir, Hydroxychloroquine (HQ) /Umifenovir and Amodiaquine (ADQ)/Umifenovir could reduce viral replication, and the aberrant host inflammatory response and viral infectivity. Furthermore, the antimalarial/antiviral combined drugs have stronger affinity with COVID_19 protease.

IV. CONCLUSION

In this study, we use the crystal structure of COVID-19 protease. We try to decrease the danger effects and risks of 4-aminoquinoline drugs by combination them with the safe umifenovir drug 1:1ratio. The investigated antimalarial/antiviral combined drugs could combine with the amino acids in the enzymatic cavity of virus. They inhibit the protease enzyme virus.

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Our computational study can facilitate us to design novel inhibitors targeting COVID-19. We hope our research would be deemed hypothesis-generating at best and these combinations are considered extremely safe.

V. ACKNOWLEDGMENT

The author would like to thank National Research Center (NRC), Cairo, Egypt, for able guidance and support in completing his project and for providing him with all the facility that was required.

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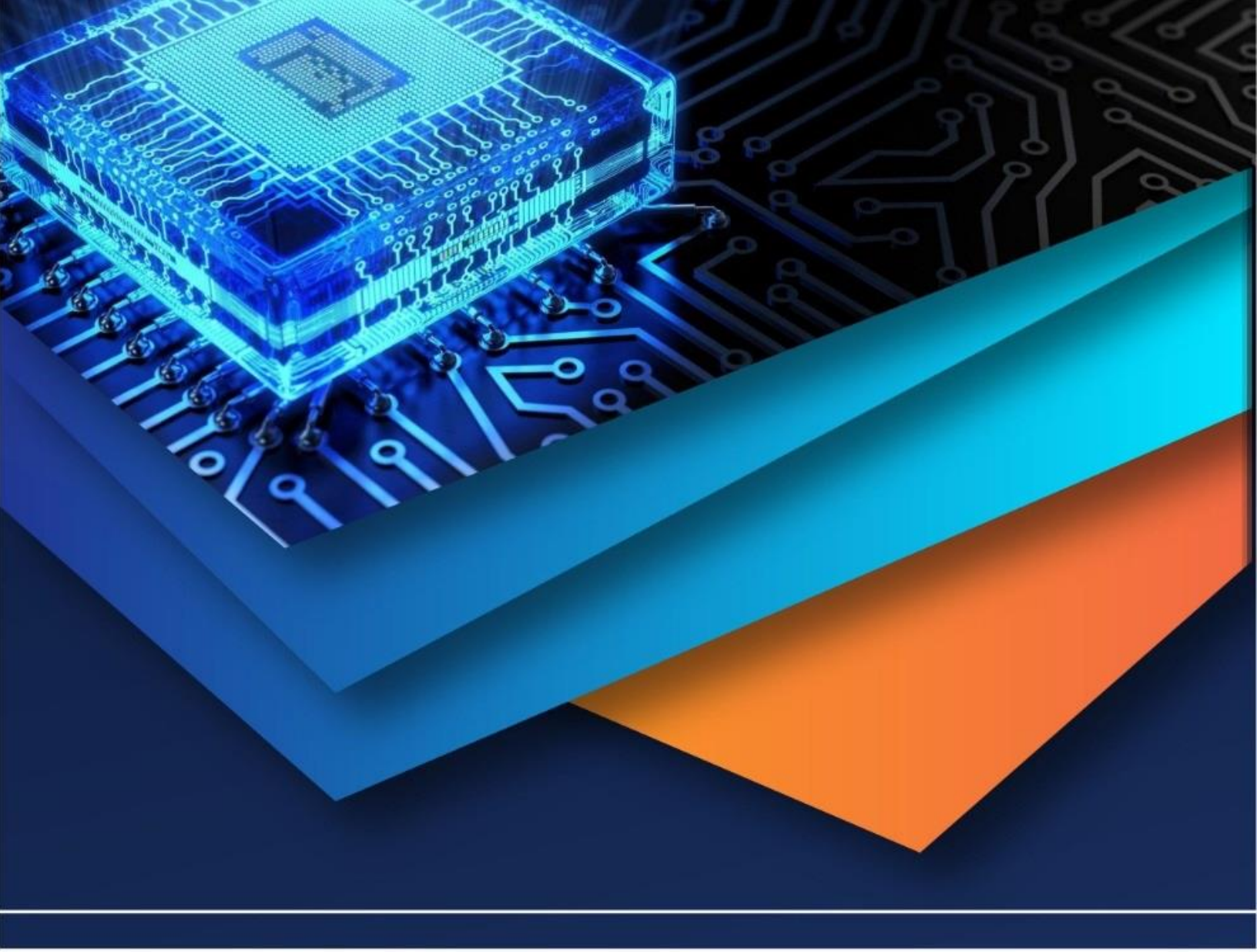
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Professor Tamer Ezzat received the Ph.D. degree in materials science from Eberhard Karls University of Tübingen, Germany in 2004. He worked at Leibniz Universität Hannover, Germany as a visiting assistant professor in 2007-2011, at the King Abdulaziz University (KAU) through attracting distinguished academics track till became a full professor in 2017, and then at Imam Abdulrahman Bin Faisal University (IAU), kingdom of Saudi Arabia in 2017 as a chair professor and as a director of Renewable and Sustainable Energy Unit of the Basic and Applied Scientific Research Centre from year 2018. He received numerous prestigious scientific research publishing awards, particularly in 2011 award conferred by the National Research Centre, 2013, 2014 and 2019 awards of KAU& IAU, kingdom of Saudi Arabia. In addition to his home field in Chemical Industries Research Division.

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