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Phytomolecules as Sources of New Antimicrobials and Drug Resistance Modifying Agents

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Abstract: ***Plants contain a number of active compounds that are responsible for various biological activities and play an important role as constituents of medicine. It is also reported that phytochemicals, which are known as secondary metabolites from plants act in a synergistic manner along with other antibacterial agents. This makes phytochemical products and plant extracts as useful resistance-modifying agents. The therapeutic utility of these products, however, remains to be clinically proven. Antibiotics are very effective for treatment of number of infectious diseases. Traditional methods of antibiotic discovery have failed to keep pace with the evolution of antimicrobial resistance. Antimicrobial resistance (AMR) is the ability of a microorganism (like bacteria, viruses, and some parasites) to stop an antimicrobial (such as antibiotics, antiviral and anti malarials) agent from working against it. As a result, standard treatments become ineffective, infections persist and spread to others. Therefore, new strategies to control bacterial infections and to inhibit the resistance development are highly desirable. This strategy will provide away to accomplish the urgent need to find out some alternatives to overcome the problems of multidrug resistance. One approach is the use of combination of plant extracts with antibiotics. Many studies indicated that efficacy of antimicrobial agents can be improved by combining them with plant extracts. Interaction of plant extract with antibiotics leads to a novel strategy to treat infectious diseases.***
Keywords: Antimicrobial resistance, Phytomolecules, Resistance-modifying agents, infectious diseases.

I. INTRODUCTION

Human Infectious diseases caused by bacteria, fungiandvirus affect millions of people worldwide. Today, infectious diseases account for one-third of all deaths in the world. World Health Organization estimates that approximately 50,000 people die each day throughout the world from infectious diseases (WHO, 2002). Microbes are existing in earth since million years ago, being one of the oldest creatures in this planet. These microbes were already known since the time when humans are subjected to antibiotics produced from other microorganisms such as Penicilliumnotatum, as example. These microbes produce antibiotic resistant mechanisms, naturally (Opalet al, 2000). So, it is not surprising that the microbes have developed resistance in the modern era against our synthetic and semi-synthetic antibiotics. The discovery of antibiotics was an essential part in combating bacterial infections that once ravaged humankind. Different antibiotics exercise their inhibitory activity on different pathogenic organisms. The development and spread of resistance to currently available antibiotics is a worldwide concern. (Chanda&Rakholiya, 2011)The increasing phenomenon of acquisition of resistance among microorganisms to antimicrobial drugs is attributed to the indiscriminate and improper use of current antimicrobial drugs. Today, clinically important bacteria are characterized not only by single drug resistance but also by multiple antibiotic resistances, the legacy of past decades of antimicrobial use and misuse. Drug resistance presents an ever increasing global health threat that involves all major microbial pathogens and antimicrobial drugs. These resistant micro-organisms are difficult to treat and are responsible for a variety of infectious diseases. The rate of emergence of antibiotic resistant bacteria is not matched by the rate of development of new antibiotics to combat them. (Chanda&Rakholiya, 2011)Recently, the global problem of dramatic development of bacterial resistance to synthetic antibiotics has led researchers to consider the use of other natural products with antibiotic actions e.g. medicinal plants. Interestingly, traditional medicine (including herbal medicine) is currently considered as a rapidly growing health system worldwide, it remains widespread and increasing very fast in developed countries (WHO 2002). These medicinal plantscould be effective alternative source for many therapeutics, particularly after the recent dramatic failures of antibiotics against multi-drug resistant micro organisms. This review focus on new phytochemicals that can be combined with antibiotics in the treatment of drug resistant infections. This may prove to be an alternative for overcoming the problem of resistance in bacteria. Crude extracts of medicinal plants stand out as veritable sources of potential resistance modifying agents.

II. THEORY

A. *Development of antimicrobial resistance*

Antimicrobial resistance is an immense and serious global challenge and could endanger the lives of future generations. The phenomenon of antibiotic resistance was anticipated by Alexander Fleming since the discovery of penicillin in 1940s (Levy, 2002). Scientists know that when antibiotics are used incorrectly, the target bacteria will directly adapt and develop resistance. Then, with its rapid multiplication, bacteria pass resistant genes through plasmid exchange, leading to an increased prevalence of multi-drug resistant in factions. Many factors such as whether the antibiotic is a concentration or time-dependent killing agent, its effects against the population of bacteria and its duration of the serum concentration in patient may prove to be the effective treatment strategy for the resistant microbes (Coates *et al*, 2002).

B. *Occurrence of multi-drug resistant microorganisms*

At present most clinical isolates of *S.* aureus, S. Pyogenes, *Mycobacterium tuberculosis* are considered as highly resistant to most commercially known antibiotics (Sbnda and Okoh, 2007).

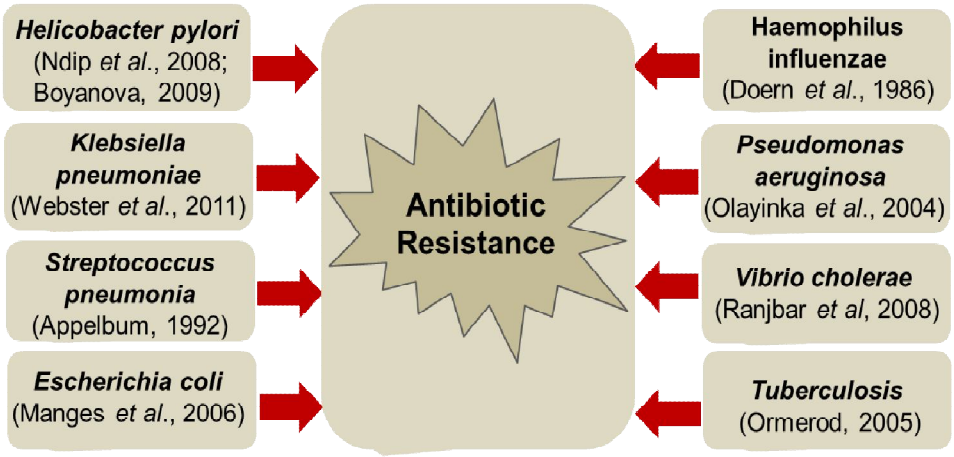

Figure 1: Antibiotic Resistant Microorganisms

In the last decades, prevalence and outbreaks of the multi-drug resistant bacterial strains have been increasingly documented throughout the world. The Figure 1 provides the information about the microbes that have developed antibiotic resistance till date. The use of antibiotics in veterinary practices and the growing presence of antibiotics in water, soil and food are contributed to the problem of antibiotic resistance (Moshirfar*et al.* 2006). Regretfully, quantitative data regarding the clinical implications of resistance are lacking for many common infections (Metlay and Singer, 2002).

C. *Phytomolecules As A Antimicrobial agents*

Medicinal plants are known to produce certain bioactive molecules which react with organisms in the environment, inhibiting bacterial or fungal growth and protect the human body against pathogens (Yano *et al.* 2006, Wojdylo*et al.* 2007).Antimicrobial properties in plants are attributed to the presence of active compounds e.g., quinones, phenols, alkaloids, flavonoids, terpenoids, essential oil, tannins, lignans, glucosinolates and some secondary metabolites (see Table 1 for example)(Lewis and Ausub*et al.*, 2006; Cowan, 1999; Twari 2004).

Table 1: Examples of some plant derived compounds with antimicrobial value.

S. No.	Name of Plants	Antimicrobials	Microbes treated	Refe.
1	Acacia nilotica	Terpenoids, flavanoid, Saponins, Tannins	S. viridians, S. aureus, E. coli, B. subtilis, Shigellasonnei, Multidrug ResistanceE. coli, C. albican, K. pneumoniae	Banso 2009,Riazet al. 2011,
2	Allium cepa	Flavanoid, Polyphenol	Multidrug Resistance Pseudomonas aeruginosa, S.	Adesinoet al. 2011.

			Typhi, E. coli	
3	Allium sativum	Organosulphur compounds (Phenolic compounds), Allicin	Campylobacter jejuni, Multidrug ResistanceE. coli, C. albican, Entamoebahistolytica, Giardia lamblia	Luet al. 1999.Ankriet al. 1999
4	Angelica lucida L.	Coumarins	S. viridians, S. mutans	Widelski,et al. 2009
5	Chelidonianmajus	Glycoprotein	B. cereus, Staphylococcus spp.	Janovskaet al. 2003
6	Cinnamomum spp.	Cinnamaldehyde (essential oil)	Legionella pneumophila Multidrug ResistanceE. coli, C. albican, K. pneumoniae	Changet al. 2008
7	Cirsiumhypoleucum	Flavones	Multidrug ResistanceK. pneumoniae	Ozceliket al. 2008
8	Curcuma longa	Curcuminoid (A phenolic compound), turmerone, curlone, Essential oil, curcumins, turmeric oil	S. typhi, E. coli, S. aureus, B. cereus, B.subtilis, Ps. aeruginosa, B. coagulans, A. niger, P. digitatum, Antifungal and antiviral activity	Gul, P.; Bakht 2015
9	Cymbopogancitratus	Essential oil	C. albicals, Aspergillusflavus, A. parasiticus	Ragaso 2008
10	Galiumfissurense	Flavones	Multidrug ResistanceK. pneumoniae	Ozceliket al. 2008
11	Hypericumperforatum	Hypericin (anthraquinone)	Methicillin Resistant Staphylococcus aureusand Methicillin sensitive Staphylococcus	Dadgar et al 2006
12	Lawsoniainermis	Quinones	Multidrug ResistancePseudomonasaeruginosa	Habbalet al. 2011
13	Medicago sativa	Saponins, Canavanine	Enterococcus faecium, S. aureus, Antifungal	Aliahmadiet al. 2012
14	Menthalongifoilia	Essential oil	Multidrug ResistanceStaphylococcusaureus	Aliet al. 2015
15	Ocimumbasilicum	Essential oil	Multidrug ResistanceStaphylococcusaureus, S. Typhi, Aeromonashydrophila, Pseudomonas spp.	Wanet al. 1998
16	Onobrychis sativa	AMPs (antimicrobial peptides)	E. faecium, S. aureus	Aliahmadiet al. 2012
17	Origanumvulgare	Essential oil	B. subtilis, B. cereus, Multidrug ResistanceS. aureus	Falcoet al. 2013
18	Piper longum	Piperine, Saponin, alkaloid	Multidrug ResistanceB. subtilis, Shigellasonnei	Kumaret al. 2013

19	Raphanussativum	RsAFP2 (Antifungal peptide)	C. albicans	Aertset al. 2009
20	Rhazyastricta	Alkaloids and Non alkaloids	Multidrug ResistanceE. coli, K. pneumoniae (Extended Spectrum Beta Lactamase), E. faecium(Vancomycin Resistant Enterococci)	Khanet al. 2016
21	Rosmarinusofficinalis	Essential oil	Streptococcusmutans	Falcoet al. 2013
22	Sanguisorbaofficianalis	Alkaloids, antimicrobial peptides	Ps. aeruginosa, E. coli	Janovskaet al. 2003
23	Sorghum spp.	Tannins	S.aureus, S. typhimurium, A. niger, A. flavus, S. cerevisae	Moneimet al. 2007
24	. Stephaniaglabra	Alkaloids	S. aureus, S. mutans,Microsporumgypseum, M. canis and Trichophytonrubrum	Semwal, D.K.; Rawat 2009
25	Syzygiumaromaticum	Essential oil	Eugenol Streptococcus mutans, S. aureus, Lactobacillus acidophilus, Candida albicansandSaccharomyces cerevisiae, Multidrug ResistanceE. coli, K. pneumoniae	Kumaret al. 2013
26	Vetiveriaziznioides	Vetivone (vetiver oil)	Enterobacter spp.	Srivastavaet al. 2007
27	Viscum album	Flavones	Multidrug ResistanceK. pneumoniae	Ozceliket al. 2008
28	Zingiberofficinale	Gingerol	E. coli, Enterobacter spp., P. aeruginosa, Proteus spp., Klebsiella spp., S. aureus and Bacillus spp.	Adesino,et al. 2011, Karuppiahet al.2012

D. Phytomolecules AS resistance Modifying Agents

During 1990's, approximately 80% of all remedies were produced from roots barks and leaves of plants (McChesney*et al.*2007).Even after the antibiotic era and till now, many effective drugs traded globally were from plant origin such as Atropine, Ephedrine, Digoxin, Morphine, Reserpine and Tubocurarine (Gilani and Atta-ur-Rahman, 2005). Here, there is a correlation between the plant extract of antimicrobial activity and its major secondary metabolites. Accordingly, since times immemorial, plants have been resisting the continuous attacks of microorganisms (Parasites, fungi, Bacteria and Viruses) by producing endless secondary metabolites. On the other side, micro-organisms have continued trying to invade these plants by breaking down as many secondary metabolites as much as possible. According to this everlasting battle, plant kingdom develops a vast number of biochemical defense compounds. In a similar way, the conflict between humans and pathogenic microorganisms continues endlessly. As people develop new drugs to fight the disease, those microorganisms develops new ways to strengthen themselves and live longer. However, plants are able to develop new, faster and natural antimicrobials and then man-made remedies (Farnsworth *et al*. 1985). As antimicrobials are based onethno-botanical data, considerable number of studies have been conducted on the antimicrobial activity of medicinal plants and showed promising potency against multi-drug resistant microorganisms after the current antibiotics failed to eliminate them. Many studies have indicated that a broad range of plant extracts may act against bacterial resistance mechanisms(Schelzet al.2010).The majority of these have now been focused on combinations between plant extracts and antibiotics in order to screen for resistance modifying agents**(**Sibnda and Okoh, 2007). The following sections will

focus on combinatorial activities of plant extracts and products with antibiotics, mainly due to a resistance-modifying action. Table 2 shows some promising plants having antimicrobial activity against multidrug resistant strain.

Table 2: Synergism between phytochemical product and antibiotics due to resistance modifying activity.

S.No.	Phytochemical product	Plant source	Antibiotic potentiated	Mechanisms of action	Refe.
1	Carnosic acid	Rosmarinusofficinalis	Tetracycline Erythromycin	MDR efflux pumps inhibition	Oluwatuyiet al. 2004, Stavriet al. 2007, Gibbonset al. 2003.
2	Carnosol				
3	Reserpine	Rauwolfiaserpentina	Fluoroquinolones Tetracycline	MDR efflux pumps inhibition	Gibbons andUdo, 2000,Stavriet al. 2007, Gibbonset al. 2003, Marquez 2005, Markhamet al. 1999, Schmitz 1998.
4	Totarol	Chamaecyparisnootkatensis	Norfloxacin Tetracycline Erythromycin Methicillin	NorA inhibition Interference with PBP2a expression	Smithet al. 2007, Simoeset al. 2009, Nicolsonet al. 1999. Gibbons 2007.
5	Diterpene 416				
5	Berberine	Berberis spp.	Ampicillin Oxacillin	Intercalation into DNA; Increase membrane Permeability	Simoes et al 2009, Stermitz et al 2000, Lewis et al 2007, Yuet al.2005
7	5*-methoxy-hydnocarpin	Berberis spp.	Berberine Others (e.g. norfloxacin)	NorA inhibition	Guzet al. 2000,Stavriet al. 2007,Gibbons et al. 2003, Tegoset al. 2002.
8	pheophorbide a				
9	Ferruginol	Chamaecyparislawsoniana	Norfloxacin Erythromycin Oxacillin Tetracycline	EtBr efflux inhibition	SibandaandOkoh 2007, Smithet al. 2007.
10	5-Epipisiferol				
11	Catechingallate	Camellia sinensis	β-lactams Norfloxacin Carbapenems Tetracycline	b-lactamases inhibition; PBP2a synthesis inhibition; Reaction with peptidoglycan; EtBr efflux inhibition; TetK inhibition	Shibataet al. 2005, Marquez 2005, Zhaoet al. 2005, Yamet al. 1998, Hu et al. 2002, Roccaro and Enea 2004.
12	Epicatechingallate				
13	Epigallocatechingallate				

14	Methyl-1a-acetoxy-7a-14a-dihydroxy-8,15-isopimaradien-18-oate	Lycopuseuropaeus Piper nigrum	Tetracycline Erythromycin	MDR efflux pumps inhibition	Gibbonset al. 2003.
15	Methyl-1a,14a-diacetoxy-7a-hydroxy-8,15-isopimaradien-18-oate				
16	Piperine	Piper longum	Ciprofloxacin	EtBr efflux inhibition	Jinet al. 2011,Khanet al. 2006.
17	Thymol	Thymus vulgaris	Several	Increase membrane permeability	Helanderet al. 1998, Simoeset al. 2009, Lambertet al. 2001, Zhanget al.2011, Palaniappan and Holley2010.
18	Carvacrol				
19	Baicalein	Scutellaria species	Tetracycline b-lactams Gentamicin Ciprofloxacin	Inhibition of PBP2a; Reaction with the peptidoglycan; NorA inhibition	Chanet al. 2011, Wagner and Ulrich-Merzenich 2009, Fujitaet al. 2005.
20	2,6-dimethyl-4-phenyl-pyridine-3,5-dicarboxylic acid diethyl ester	Jatrophaelliptica	Ciprofloxacin Norfloxacin	NorA inhibition	SibandaandOkoh 2007, Marquezet al. 2005.
21	Ethyl gallate	Caesalpiniaspinosa	β-lactams	Restriction of substrate diffusion for PBPs	Shibataet al. 2005.
22	Cinnamaldehyde	Cinnamomumzeylanicum	Clindamycin	CdeA inhibition	Shahverdiet al. 2007
23	Gallic acid	Berry extracts	Tetracycline	Increase membrane permeability	Jayaramanet al. 2010, Nohyneket al. 2006, Saavedraet al. 2010.
24	Xanthohumol	Humuluslupulus	Polymyxin B sulphate Tobramycin Ciprofloxacin	Increase membrane permeability	Zahinet al. 2010,Natarajanet al.2008.
25	Lupulon				

26	Tellimagrandin I	Rosa canina L.	β-lactams	Inactivation of PBPs, particularly PBP2a	Shiotaet al. 2002, Shiota, et al. 2004.
27	Rugosin B				
28	Corilagin	Arctostaphylosuva -ursi	β-lactams Cefmetazole	Inhibition of PBP2a activity or Production	Shimizuet al. 2001, Shiotaet al. 2004.
29	Myricetin	Widespread among plants including tea, berries, fruits, vegetables and medicinal herbs	Cefmetazole Amoxicillin/ clavulanate Ampicillin/ sublactam Cefoxitin	DNA B helicase inhibition	Hemaiswaryaetal. 2008, Linet al. 2005.
30	Allicin	Allium sativum	Cefazolin	RNA synthesis inhibition; Interaction with important thiolcontaining Enzymes	Hemaiswaryaet al. 2008, Caiet al. 2007, Abascal and E. Yarnell 2002, Ankri and D. Mirelman 1999.
31	Silybin	Silybummarianum	Ampicillin Oxacillin	MDR efflux pumps inhibition	Stermitzet al. 2000, Kanget al. 2011.
32	The polyacylated	Geranium caespitosum	Berberine Ciprofloxacin Norfloxacin Rhein	MDR efflux pumps inhibition	Stavriet al. 2007, Tegoset al. 2002, Stermitzet al. 2003.
33	Neohesperidoses				
34	Chrysosplenol D	Artemisia annua	Artemisinin Berberine Norfloxacin	MDR efflux pump inhibition	Stavriet al. 2007.
35	Chrysoplenetin				
36	Chalcone	Daleaversicolor	Berberine Erythromycin Tetracycline	NorA inhibition	Zdzis 2007, Belofskyet al. 2004.
37	4',5'-O-dicaffeoylquinic acid	Artemisia absinthium	Berberine	MFS family efflux systems inhibition	Fiamegoset al. 2011.
38	Genistein	Lupinusargenteus	Fluroquinolones Berberine Norfloxacin	MDR efflux pump inhibition	Morelet al. 2003.
39	Orobol				
40	Biochanin A				

III. CONCLUSION

The quest for solutions to the global problem of antibiotic resistance in pathogenic bacteria has often focused on the isolation and characterization of new antimicrobial compounds from a variety of sources including medicinal plants. Continuous efforts are being made to explore the plant kingdom in order to find wonder drugs that could save human life from harmful microbial and viral infections. Medicinal plants are very effective in the treatment of many infectious diseases. The mechanisms of bacterial resistance have exposed that active efflux plays a significant role in the development of bacterial acquired and intrinsic resistance. Overcoming efflux has therefore been seen as an attractive alternative to avoiding the problem. Bacterial efflux pump inhibitors(phytochemicals) have since been isolated from some plants. The combination of such MDR inhibitors (phytochemicals) with antibiotics *in vitro* has shown that the activities of some antibiotics can be dramatically increased even against antibiotic resistant strains of bacteria. The large varieties of compounds produced by plants have proved to have therapeutic potentials as antimicrobials and as resistance modifiers.The Indian biosphere that is gifted with the highest biodiversity of plant species promises to be a potential source of therapeutically useful compounds especially from the perspective of their potentials in combination with antimicrobial chemotherapy which should form the subject of further extensive study.

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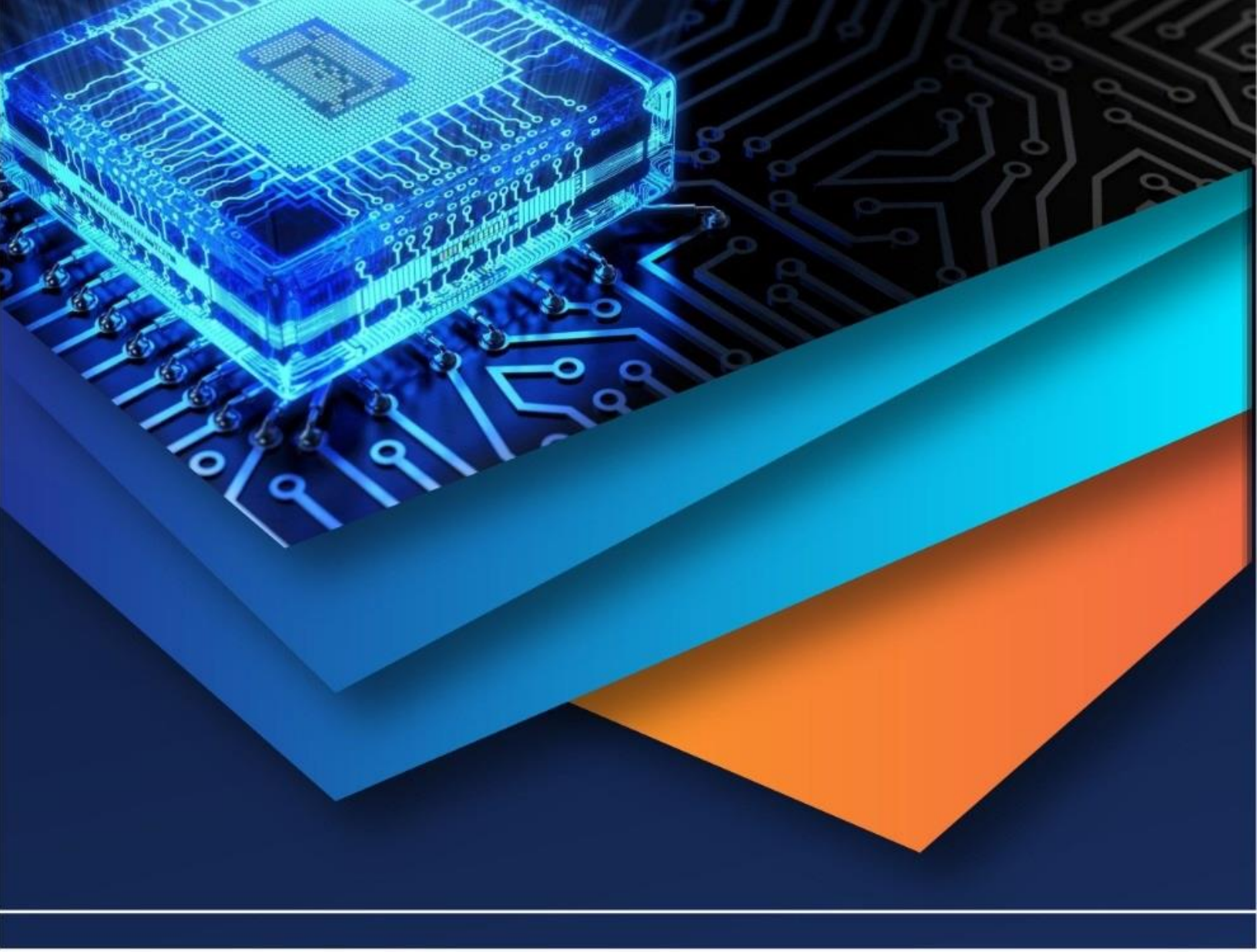

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