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TRIPHALA: Insilico ADME and Toxicity Prediction by Comparison of Existing Software

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***Abstract:** Triphala is traditional indian medicine and it is made up of two words TRI+PHALA which means three fruits that are Indian gooseberry {Emblica officinalis} member of family Euphorbiaceae, Black myrobalan {Terminalia chebula} member of family combertaceae Haritaki {Terminalia chebulia] member of family combertaceae. It is a polyphenolic compounds under tannins category and its chemical constituents are Gallic acid, Ellagic acid, Chebulinic acid, Chebulagic acid, Terflavin-A, Corilagin. It balances and rejenuvates the 'Tridosha Rasayan ',i.e, Vatta,Pitta and kapaha.The pharmacological action of Triphala is to potentiate therpeutic and preventive illness including cancer, cardiovascular disease ,neurodegenerative disorderand in aging.*

There is folk in India as no Mother it means as long as you have Trifala do not worry it can take care of body internal organ just like a mother take care of her offspring. The purpose of the research is to involve prediction of ADMET [Absorption, Distribution, Metabolism and Toxicity] properties of triphala by SWISS ADME,ADME2.0 ,SCHODRINGER software and determine its drug-likeness using Lipinski Rule.

Keywords: Triphala, ADME, Insilico, toxicity, Lipinski Rule.

I. INTRODUCTION

Although serious adverse drug reactions (ADRs) with herbals drugs are very rare events, the occurrence of side-effects is not a rare phenomenon. Many studies during the last 2 decades have shown that 20-30% of patients experience unwanted effects of herbal drugs and it seems that in ambulant patients this incidence is even higher.(1) Though herbal medicines have been used since ancient times there is need of safety evaluation.

Proper clinical and phamacovigilance study of traditional medicines can ensure their safer use in the patient care. In-light of these observations we planned to evaluate clinically 'Triphala phytochemicals' by insilico method.(2) 'Triphala' is one of the well known powdered preparation (churna) in Indian system of medicine (ISM), being used in Ayurveda since ancient time. Triphala consists of equal parts of the Emblica officinalis Gaerth, Terminalia chebula Retzr. and Terminalia belerica Linn.(3) Triphala is traditionally been used as laxative in chronic constipation, colon cleansing, digestion problems and poor food assimilation. It has also been used in cardiovascular disease, high blood pressure disease, serum cholesterol reduction, poor liver function, large intestine inflammation, and ulcerative colitis.(4,5) Methanolic extract (70%) of Triphala has shown significant antioxidant activity in vitro. Oral administration of the extract reduced the blood sugar level in diabetic rats . Triphala has been found to have radio-protective effect in mice exposed to gamma radiation.

An ADMET study is the assessment of pharmacokinetics of a drug which stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. The prediction of the fate of a drug and the effects caused by a drug inside the body, such as how much drug is absorbed if administered orally and how much is absorbed in the gastrointestinal tract, is an indispensable part of drug discovery. In a similar way, if the absorption is poor, its distribution and metabolism would be affected, which can lead to causing neurotoxicity and nephrotoxicity.

Ultimately, the study is to understand the disposition of a drug molecule within an organism. Thus, ADMET study is one of the most essential parts of computational drug design. (6)

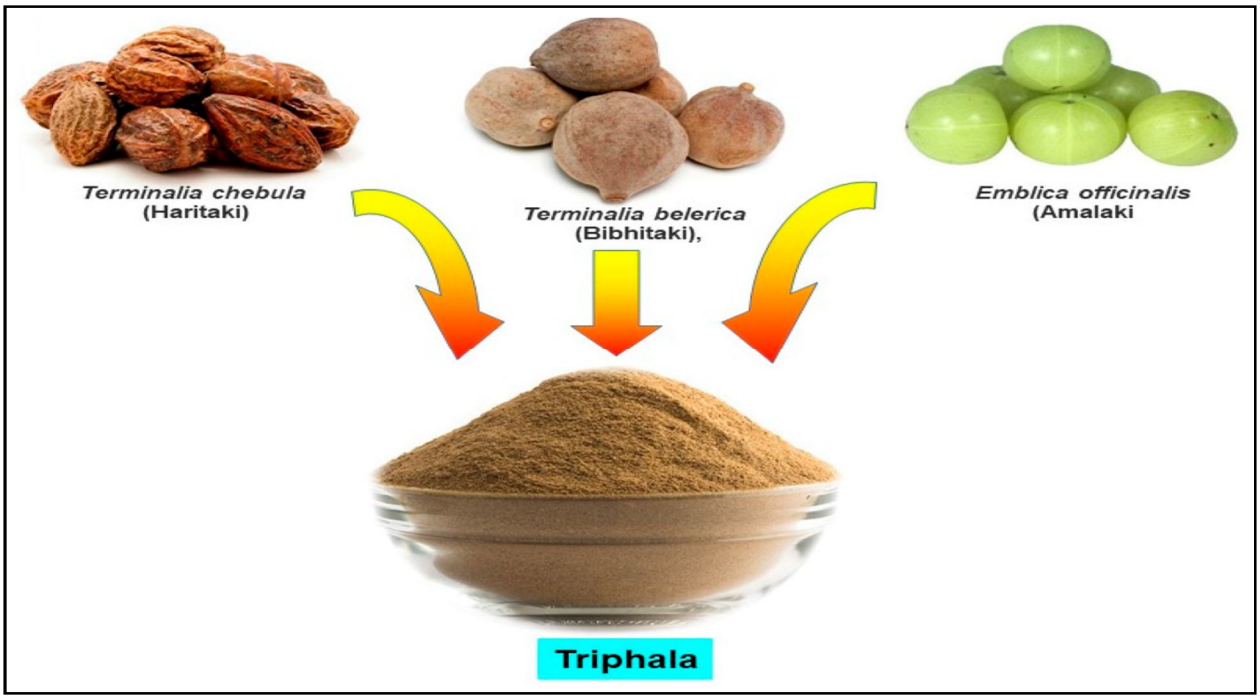

Figure No. 1- Constituent Of Triphala.

A compound can reach a tissue, if it is taken into the bloodstream. Usually, a drug is administered often through mucous surfaces such as the digestive tract, i.e., intestinal absorption before it is taken up by the target cells. Factors like poor compound solubility, intestinal transit time, gastric emptying time, inability to permeate the intestinal wall and chemical instability in the stomach are responsible for reducing the extent of drug absorption after oral administration. Critically, absorption determines the bioavailability of a compound.(7) VD is the theoretical volume required by a drug to be uniformly distributed in blood. The higher the VD is, the more of a drug is distributed in tissue rather than plasma. Cytochrome P450 is an important detoxification enzyme in the body. Many drugs are deactivated by the cytochrome P450 isoforms while some can be activated by it. Drug clearance occurs as a combination of hepatic clearance and renal clearance (excretion via the kidneys) which is related to bioavailability. AMES Toxicity s a widely employed methodology considered to check the mutagenic potential of a given drug using bacteria, thus indicating that when the results is positive, the studied compound will be mutagenic and could behave as a carcinogen. (8)

A. Lipinski Rule OF 5-

It is called as Pfizer Rule of 5 or Rule of 5 (RO5)as all the parameters are multiple of 5. It is a rule of thumb to evaluate drug likeliness or determine if a chemical compound with pharmacological or biological activity that would made orally active in humans. This rule describe the pharmacokinetic property of drug include absorption, distribution, metabolism, excretion{ADME}.
The rules states that

1) There should be not more than 5 hydrogen bond donor
2) There should be not more than 10 hydrogen bond acceptors.
3) Octanol water Partition coefficient log p not greater than 5.
4) A molecular mass should be less than 500da.

B. Partition Coefficient and LOG P-

LOG P or Octanol water partition coefficient system measures hydrophilic and hydrophobic nature of a molecule and also measure how easily a given molecule can partition between aqueous and organic phase. It helps to measure solubility and lipophilicity of a molecule.
It is given by formula –
LOG P=LOG [SOLUTE]unionised octanol/[SOLUTE]unionised water

C. Relationship Between LOG P ,LOG S, LOG D-

LOG P- It is defined as a measure of lipophilicity and important property which determines drug solubility, absorption, distribution, and tissue penetration.

Ideal value-<5

LOG D-It is a distribution constant and measures lipophilicity of ionizable compound

For non-ionizable compounds-

LOG P=LOG D

Ideal value-0 to 3

LOG S- It measures water solubility of a drug and predict solubility in the decimal logarithm of the molar solubility in water.

Ideal value -0 to -2 are soluble

-2 to -4 are slightly soluble

Greater than -4 are insoluble

D. QED Score

It is quantitative estimate of drug likeliness[QED]is an integrative score to evaluate compounds favourably to become 'HIT'. This value is generated by combination of MW,LOG P,HBAs,HBDs.

II. MATERIAL AND METHODS

A. Database Screening For Compound Selection

1. SWISS ADME-It is a free web tool which is used to determine pharmacokinetics,drug likeness,medicinal chemistry of molecules. It is a simple and accurate method to understand admADME properties.
2. ADME2.0 – It is the enhanced version of ADMET and involves evaluation and batch screening which allow calculation of 88 ADMET-related including 17 physicochemical properties,13 medicinal chemistry properties.
3. SCHODRINGER-This software has highest number of applications for a variety modeling,analysis and computational tasks. It is the best software among all software. (7)

B. Ligand Generation

PUBCHEM is a database of chemical molecules and dataset of 6 ligands of triphala were selected and its 2D structure is retreived from the pubchem database and its online canonical smiles were obtained.

These smiles were put in SWISS ADME and ADME 2.0 Software and ADMET studies were done. (8)

C. Admet Prediction

1) Absorption

Absorption is a process by which a drug molecules reaches to its site of administration.Bioavailability is defined as the fraction of drug administered reaching to systemic circulation.As per the SWISS ADME Data; The gastrointestinal absorption of chebullinic acid, chebulagic acid, coraligin, terflavin A is low whereas the ellagic acid,gallic acid has high GI Absorption.Due to high absorption their bioavailability score is also highest i.e;0.55 and 0.56. As per the ADME2.O data; chebullinic acid, chebulagic acid, coraligin, terflavin A don't follow Lipinski rule hence they are less lipophilic and have least absorption and Bioavailability.

But ellagic acid, gallic acid follow lipinski rule they are having high lipophilicity and Bioavailability. (9)

2) Distribution

Distribution is a process by which a drug molecule gets transfer from one compartment to another.Lower the LOG P higher is the lipophilicity.As per the SWISS ADME Data; the LOG P of gallic acid is 0.21 which means it is highly lipophilic nature and it has least LOG P value and its permeability to reach target tissue is highest compare to chebullinic acid,chebulagic acid,coraligin,terflavin A, ellagic acid.

The order of lipophilicity is-

Gallic acid>chebulagic acid>ellagic acid>chebullinic acid>terflavin A>coraligin

Skin permeation [logKp] of gallic acid is highest compare to other compounds due to high perfusion and lipophilicity. Higher the LOG P more is the solubility[LOG S];hence Gallic acid has highest solubility compare to other compounds.

The order of solubility is as follows-
Gallic acid> ellagic acid > coraligin> chebulagic acid >chebullinic acid>terflavin A
As per the ADME2.O data; The BBB Penetration of gallic acid is 0.053 highest compare to other compounds. (10)

Number of hydrogen bond donors	Number of hydrogen bond accceptors	LOGP	LOGS	GI absorption	Lipinski rule	Bioavailability score	Skin permeation (log kp)
13	27	0.42	-5.92	Low	No	0.11	-11.87
17	30	0.98	-7.71	Low	No	0.17	-11.48
11	18	2.03	-3.92	Low	No	0.17	-10.12
4	8	0.79	-2.94	High	Yes	0.55	-7.36
4	5	0.21	-1.64	High	Yes	0.56	-6.84
17	30	0.98	-7.71	Low	No	0.17	-11.48

Table 1- Data Analysis By Swiss Adme Software.

3) Metabolism

According to SWISS ADME 2.0; ellagic acid is CYP1A2 inhibitor.

4) Excretion

According to ADME 2.0;

COMPOUND	CLEARANCE	T1/2
CHEBULLAGIC ACID	4.962	0.978
CHEBULLINIC ACID	7.858	0.983
GALLIC ACID	10.108	0.947
ELLAGIC ACID	2.346	0.863
CORALIGIN	6.728	0.956
TERFLAVIN-A	1.247	0.945

Table no. 3- clearance and t1/2 value for triphala phytochemicals

THE IDEAL VALUE OF CLEARANCE IS
High: >15 mL/min/kg
Moderate: 5-15 mL/min/kg
Low:<5ml/min/kg (11)

Compound	LOG P	LOG S	LOG D	QED	SA score	Lipinski rule	Pfizer rule	GSK rule	BBB penetration	AMES toxicity
Chebullagic acid	0.921	-3.62	0.816	0.051	7.315	Rejected	Accepted	Rejected	0	0.075
Chebullinic acid	1.113	-3.303	0.481	0.042	6.853	Rejected	Accepted	Rejected	0.005	0.077
Coraligin	0.911	-2.809	0.262	0.098	5.836	Rejected	Accepted	Rejected	0.007	0.199
Ellagic acid	1.117	-4.446	0.794	0.356	3.683	Accepted	Accepted	Accepted	0.011	0.38
Gallic acid	0.645	-1.22	0.343	0.46	2.905	Accepted	Accepted	Accepted	0.099	0.053
Terflavin-A	1.138	-7.136	0.196	0.02	6.612	Rejected	Accepted	Rejected	0	0.06

Table 3- Admet Data Analysis By Adme2.0 Software

5) Toxicity

The AMES test[salmonella typhimurium reverse mutation assay] is the test to identify revert mutation which are present in strains by testing its capacity to revert mutation present in a mutant bacteria and restore its ability to synthesize an essential amino acid required for growth. If the test is positive it indicates that the given chemical is mutagenic.If it is category 1 then AMES positive and Category 0 than AMES negative (12)

According to ADME 2.0;

COMPOUND	AMES TEST
CHEBULLAGIC ACID	0.075
CHEBULLINIC ACID	0.077
GALLIC ACID	0.053
ELLAGIC ACID	0.38
CORALIGIN	0.199
TERFLAVIN-A	0.06

Table No.4- Toxicity Ames Test Value For Tripahala Phytochemicals

The other toxicities are as follows-

According to ADMETlab 2.0

Compound	Acute toxicity rule	Skin sensitization rule	Aquatic Toxicity Rule	Non-Biodegradable Rule
CHEBULLAGIC ACID	+	+	+	-
CHEBULLINIC ACID	+	+	+	-
GALLIC ACID	+	-	-	-
ELLAGIC ACID	-	-	-	-
CORALIGIN	+	+	+	+
TERFLAVIN-A	+	-	-	+

Table No.5- Toxicity Value For Tripahala Phytochemicals

The gallic acid and ellagic acid show negative skin sensitization,aquatic and non-biodegradable rule and chebulagic acid and chebullinic acid shows positive test.

III. CONCLUSION AND RESULT

Triphala is a used to deliver novel drugs. This ADME tox study shows that among all compounds Gallic acid & Ellagic acid has greater activity and its QED score is highest. These plant has major 5 constituents which are having anticancer properties. This in-silico study helps to screen every compound and lead to development against various disease.

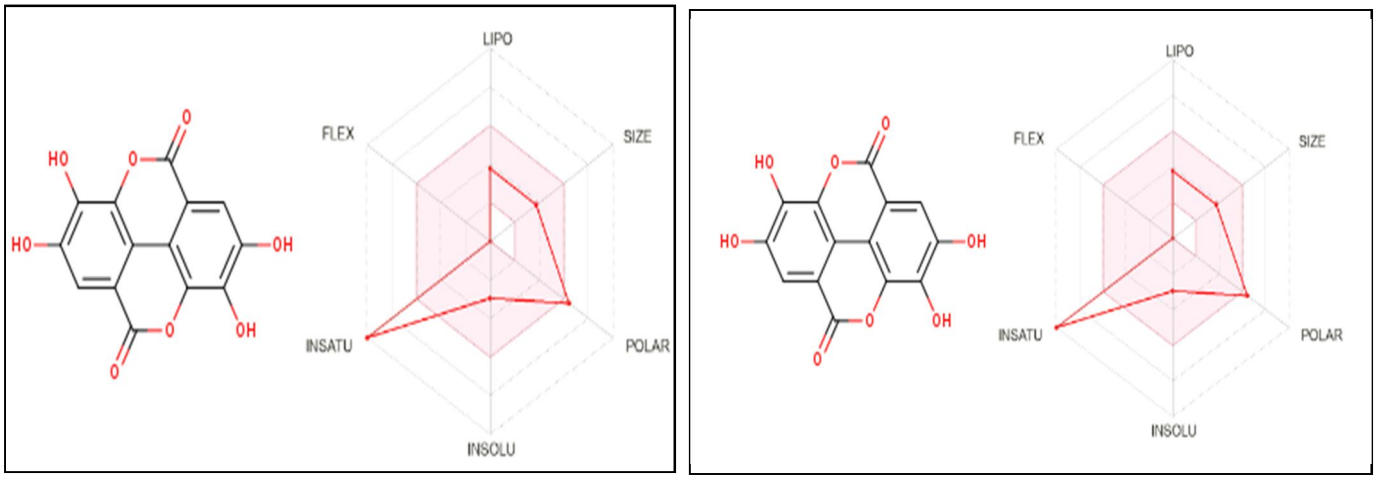

Figure No. 2- Ellagic acid, Gallic acid follow Lipinski Rule they are having high lipophilicity and Bioavailability

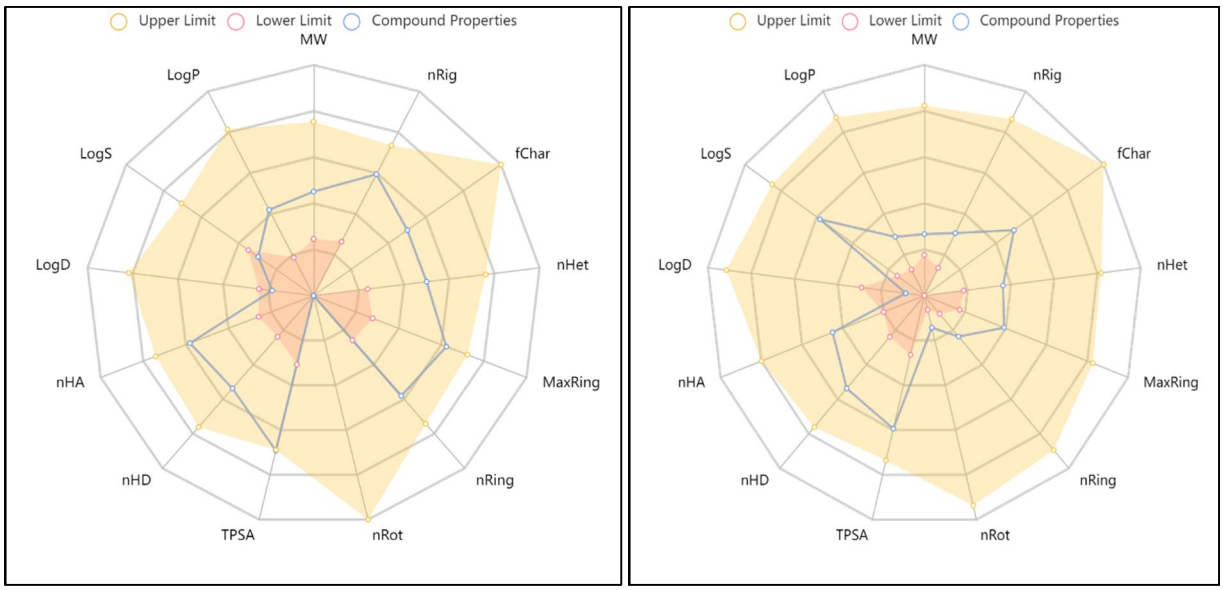

Figure No. 3- Ellagic acid, Gallic acid follow Lipinski Rule they are having high lipophilicity and Bioavailability by SWISS ADME

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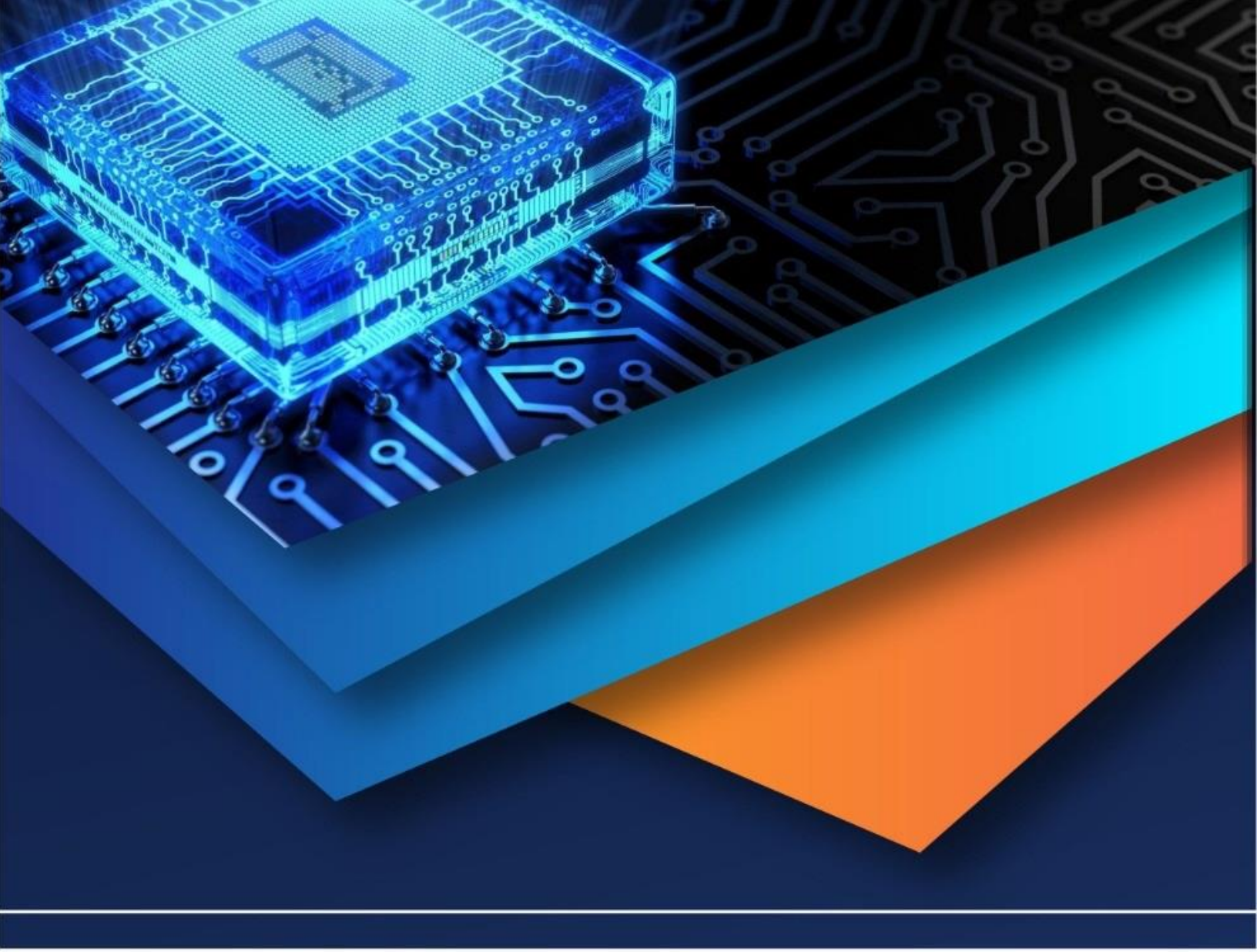

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