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# A Systematic Review on Neutraceutical

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***Abstract:*** ***Truly, nutraceuticals transformed the whole healthcare system with a view toward disease prevention and treatment as a whole. In this replete review, a multinational and complex world of nutraceuticals is brought stage-after-stage definition, historical progression, and categorization. It will deal with various nutraceuticals such as dietary supplements, functional foods, herbal extracts, probiotics with their underlying mechanisms of action and bioactive compounds. The wide-ranging benefits extended as health benefits by nutraceuticals-stating cardioprotective and anticancer properties along with neuroprotective and immunomodulatory benefits are highlighted by the review. The review also addresses some crucial issues concerning safety, efficacy, regulation, standardization, and quality control. It finally takes a look into the future in regard to newer and emerging trends and innovations, which include personalized nutrition, nanotechnology, and even synthetic biology. This review would be the first foundation stone for researchers, healthcare professionals, and industry experts who want to exploit the transformational potential of nutraceuticals.***

***Keywords: Nutraceuticals, Dietary supplements, Bioactive compounds, Probiotics, Prebiotics, Gut microbiota, Cardiovascular health, Cancer prevention, etc.***

## I. INTRODUCTION

A large part of the 21st century has completely been a paradigm shift from conventional medical practices, heralding nutraceuticals into an entirely new dawn [1]. Aware citizens have realized the importance of preventive healthcare and the awareness of demand for increasingly natural, as well as sustainable health options [2]. Consequently, rapid growth has been registered by the nutraceutical industry, and its global market size is expected to reach USD 722.49 billion by the year of 2027 [3].

The term Nutraceutical, coined by Dr. Stephen DeFelice in 1989, defines substances, which are able to give some medical or health benefits, including the prevention and treatment of diseases [4]. Such substances can fall into a wide category including dietary supplements, functional food, and beverages [5]. There is now more awareness about nutraceuticals as a result of their potential capacity to encourage health and well-being, prevention of chronic diseases, and healthy aging [6].

Nutraceuticals era has been characterized by various trends such as personal nutrition, which is getting more attention; increasing intrusion of digital technologies, which will increasingly provide health and wellness support; and rising sustainability and environmental responsibility in people's perspective [7]. On another front, the immediate fallout of the pandemic, COVID-19, has put in a fast lane the emergence speed of the nutraceutical industry, with more people going out of their way to buy more natural and sustainable nutraceuticals to improve health and immunity [8].

### *A. Definition*

Nutraceutical is a food or food product that imparts health benefits beyond basic nutrition. It usually refers to something that helps in the prevention and/or treatment of diseases or helps improve overall health, as well as improve particular bodily functions. Vitamins and minerals, herbs, amino acids, and other bioactive compounds, which are consumed either as supplements or included in foods and beverages, are some examples of nutraceuticals. The term brings together "nutrition" and "pharmaceutical" to signify its purported therapeutic effects.

### *B. History*

#### *1)* Ancient Civilization (3000-500)

The idea of being treated using food, herbs, and other natural substances started as early as in ancient civilizations such as Egypt, Greece, China, and India [9].

Ancient Egyptian society used spices and herbs for medical purposes while the Greeks relied on Hippocrates (460-370 BCE), who emphasized the role of food in health [10].

Herbs and other natural materials as medicine can be found in ancient China around 100 BCE in the Huangdi Neijing (Yellow Emperor's Inner Canon) [11].

 

*2)* Middle Ages (500-1500 CE)

The use of herbs and other natural substances for medicinal purposes continued into the Middle Ages, when many monasteries and convents kept gardens and apothecaries for the production of medicinal herbs [12].

That was a great period for the development of herbal medicine with works by Galen (129-216 CE) and Avicenna (980-1037 CE) [13].

*3)* Renaissance and Enlightenment (1500-1800 CE)

An interest in ancient learning and the writings of Greek and Roman physicians was renewed in the Renaissance and Enlightenment [14].

The growing numbers of botanical gardens and the publication of herbals such as John Gerard's Herball (1597) increased use of herbs as other natural materials for medicine [15].

*4)* Modern Era (1800-1980 CE)

The modern era saw nutritional science as well as the discoveries of vitamins and minerals [16]. It was the works of scientists like Casimir Funk (1884-1967), who discovered vitamin B1, and Elmer McCollum (1879-1967) for vitamins A and D, that laid the grounds for what later became modern nutraceuticals[17].

*5)* Birth of the Term "Nutraceutical" (1980s):

The term nutraceutical owes its inception to Dr. Stephen DeFelice in 1989 [4]. - Nutraceuticals refer to food or part of food which provide medical or health benefit, including prevention and treatment of disease and it was defined by DeFelice who is a physician and researcher [1].

*6)* Growth and Development of the Nutraceutical Industry (1990-present):

The nutraceutical industry continues to grow and grow from the time of the 1990s, and by the year 2027, the global market size is meant to hit USD 722.49 billion [3]. The industry was propelled by the increase in the demands of the consumers on natural and sustainable, to the advancement of modern technology and scientific research [18].

C. *Importance and relevance of nutraceuticals in modern healthcare*

*1)* Preventing and Managing Chronic Illnesses

The major role of nutraceuticals in chronic conditions like heart disease, diabetes, cancer, among others, is prevention and mitigation [1]. Such substances become preventive because they contain micronutrients, antioxidants, and other useful minerals.

*2)* Personalized Diet and Treatment

Nutraceuticals can be personalized to specific individuals' needs so that they can provide a person's own customized version of nutrition and medicines [19]. The approach also includes optimizing health outcomes with minimal probability of contrary consequences.

*3)* Low-cost Affordable Sustainable Health Care

Cost-effective nutraceuticalism will prove to be a sustainable means of health care and will lower the use of expensive pharmaceuticals and medical procedures. It helps in the promotion of sustainable agriculture and food production practices [4].

*4)* New Holistic Health

The holistic approach to health is provided by nutraceuticals addressing the physical, emotional, and spiritual needs of individuals [9]. They bring overall well-being and better quality of life.

*5)* Rise in Demand for Natural and Organic Product

The growing demand with emerging buyers today for natural and organic products includes nutraceuticals as [3]. This is indeed consumer-driven because people are now growing concerned regarding the safety and efficacy of the use and, of course, about the realities of conventional medicines.

*6)* Technology Advancement and Research Progress

Technological and research advances have significantly bolstered knowledge about the benefits and risks associated with nutraceuticals [20]. In fact, they result in new products and far more effective quality control and regulatory regimes.

*7)* Integrate with Conventional Medicine

Nutraceuticals may complement conventional medicines in a complete, holistic approach toward health care [10]. In this way, health outcomes can be improved and adverse reactions minimized.

*8)* Prevention and Treatment of Disease

Nutraceuticals have a promise in the prevention and treatment of several diseases, chronic or not, including infectious diseases and mental disorders [13]. They will also play a role in ensuring healthy aging and reduction of age-related diseases.

## II. CLASSIFICATION OF NEUTRACEUTICALS

### *A. Dietary Supplements*

Dietary supplements are products that include nutrients such as vitamins or minerals, amino acids, or any other ingredient that is intended to supplement the diet. Thus, it is available in various forms, such as in tablets, capsules, powders, or liquids.

*1) Types of Dietary Supplements*

- Vitamin Supplements : Those vitamins which the body needs to work properly. Examples are vitamin C supplements, vitamin D supplements, and vitamin B12 supplements [21].
- Mineral Supplements: Mineral supplements are those which provide the essential minerals that the body needs to function properly. Some examples are calcium supplements, iron supplements, and zinc supplements [21].
- Amino Acid Supplements: Amino acid supplements are those which provide all the essential amino acids necessary for the proper functioning of the body to build and repair tissues. Some examples include protein powder and branched-chain amino acid (BCAA) supplements [23].
- Herbal Supplements: Having plant extracts or herbs which are thought to have health benefits; for example ginkgo biloba, St. John's wort, and echinacea supplements [24].
- Probiotic Supplements: Supplements containing live microorganisms intended to have health benefits in particular as beneficial for gut health [25].

*2) Benefits of Dietary Supplements*

- Nutritional gaps can be filled Dietary supplements ensure the uptake of nutrients needed by the body in sufficient amounts [26].
- It can facilitate the prevention of deficiencies of important vitamins and minerals [21].
- Supplementation encourages an overall well-being for individuals in need of some health restriction [27].
- Certain supplements, such as protein powder and BCAA supplements, will enhance an athlete's performance and contribute to muscle growth and recovery [23].

*3) Regulation on Dietary Supplements*

- FDA Regulation: Food indeed, not drugs, are the categories under which the FDA considers dietary supplements [28].
- GMP: Good Manufacturing Practice also applies to all dietary ingredient as implemented by an employer on dietary supplements [29].
- Labelling Information: The labels of dietary supplements must have some required information, for example, the name and quantity of each ingredient as well as some warnings or cautions [28].

*4) Safety and Efficacy of Dietary Supplements*

- Quality Control: There is a lot of variation regarding the quality of dietary supplements because of the manufacturer and type of dietary supplement [30].
- Adverse Events: Eating dietary supplements can cause adverse events and in most cases with overdose and other medication [31].

- Efficacy: Efficacy of dietary supplements is often varying with products and with individuals taking them [24].

### *B. Functional Foods*

Functional foods are defined as those foods that contain some beneficial effect beyond basic nutrition. In addition to that, functional foods contain bioactive compounds that function in the prevention or management of some diseases.

#### *1) The types of Functional foods*

- Probiotic food: this is food with live microorganisms which can be used to maintain gut health, for example: yogurt, kefir, and fermented vegetables [25].
- Prebiotic Food: Food with indigestible fibers which could feed the beneficial gut microorganisms such as asparagus, bananas, and onions [32].
- Omega-3 Rich Foods: Foods rich in omega-3 fatty acids as it helps decrease inflammatory activity and improve heart health, and some examples are salmon, walnuts, and chia seeds [33].
- Antioxidant Foods: Foods that are high in antioxidants that can serve to protect cells against damage and therefore reduce the risk of certain diseases. Some examples include berries, leafy greens, and all other fruits and vegetables [34].

#### *2) Benefits of Functional Foods*

- Promotes gut health: By utilizing an adequate level of functional foods in the daily dietary intake, maintain the gut microbiome, thereby maintaining immune functioning and overall health [35].
- Limit inflammation: Functional foods are known to limit inflammatory conditions attached to several chronic diseases [36].
- Better heart health: Functional foods reduced low-density lipoprotein (LDL) levels, blood pressure, and risk of heart disease [37].
- Cancer Prevention: Some of the functional foods proved to be capable of producing an anti-cancer effect [38].

#### *3) Examples of Functional foods*

- Kefir: Fermented milk drink containing probiotics; it helps maintain gut health [39].
- Salmon: Fatty fish having omega-3 fatty acids used for the reduction of inflammatory processes [33].
- Yogurt: A fermented dairy product containing probiotics that help maintain gut health [25].
- Green Tea: A beverage full of antioxidants that help guard against cell damage [40].

### *C. Herbal And Botanical Extracts*

Herbal and botanical extracts are agents containing active constituents derived from plants for health care promotion.

#### *1) Types of Herbal and Botanical Extracts*

- Leaves

Herbal extracts from leaves, e.g., peppermint, chamomile, and lemon balm, have calming and digestive benefits [41].

- Roots

Herbal extracts from roots, e.g., ginseng, turmeric, and ginger, are well-known for their anti-inflammatory and antioxidant benefits [42].

- Flowers

Herbal extract flowers include rose, lavender, and hibiscus, which help reduce nervous tension and inflammation [43].

- Bark

Herbal extracts of bark such as willow bark and slippery elm have anti-inflammatory and digestive properties [44].

#### *2) Advantages of Herbal and Botanical Extracts*

- Antioxidant Activity

Herbal and botanical extracts can be believed to be antioxidants because they defend cells against oxidative damage and can prevent chronic diseases [34].

- Anti-Inflammatory Properties

Herbal and botanical extracts anti-inflammatory properties may reduce the inflammation and symptoms of chronic disease [45].

- Immune System Maintenance

Herbal and botanical extracts can help in the immunity system fortifying and diminishing the risk of illness or infection [46].

*3) Some Examples of Herbal and Botanical Extracts:*

- Turmeric

Turmeric extracts with curcumin show anti-inflammatory and antioxidant properties [47].

- Ginger

Ginger extract is an anti-inflammatory agent and nausea as well as digestive distress relief [48].

- Ginkgo Biloba

Extraction from Ginkgo Biloba has antioxidant action and is also reported to improve the brain function and memory [49].

*D. Probiotics and prebiotics*

Usually by enhancing the gut flora or restoring that, probiotics are live microorganisms that give rise to health benefits on consumption [41].

*1) Probiotics:*

- Lactobacillus: Found in fermented foods such as yogurt and sauerkraut, these probiotics are useful in digestion and for the immune system [25].
- Bifidobacterium: Mostly found in some kinds of fermented dairy products; they help in digestion and for the immune system [32].
- Saccharomyces: It is a type of yeast probiotic; it is often associated as helpful to digestive health [50].

*2) Benefits of Probiotics*

- Enhanced Digestion: Probiotics can be beneficial for intestinal symptoms related to irritable bowel syndrome, for example, distension and abdominal pain [51].
- Strengthening the Immune System: One of the most important functions is how probiotics improve or enhance your immune system and decrease the risk of illness or infection [52].
- Gain Mental Health Benefits: Probiotics will be helpful in the area of mental health, reducing some of the signs and symptoms of anxiety and depression [53].

*3) Prebiotics*

A group of compounds referred to as prebiotics are non-digestible fibers that serve as feeding sources for the beneficial microorganisms residing in the intestine and ensure a healthy gut microbiome.

*4) Types of prebiotics*

- Inulin: is a fructan, this can be found in chicory root and in artichokes [54].
- Oligofructose: this is also categorized as fructan and is most commonly used as a pectin supplement [32].
- Galacto-oligosaccharides: These are also called prebiotics usually found in legumes and beans [55].

*5) Benefits of prebiotics*

- Gut Health Development: Prebiotics promote the healthy gut microbiomes for proper digestion and immune functionality [56].
- Increased Absorption of Calcium: Prebiotics can cause an increase in the absorption of calcium and as a result, reduce the chances of getting osteoporosis [57].
- Improved Mental Health: It is already known that prebiotics have a positive effect on mental health by reducing symptoms typical of anxiety and depression [53].

*E. Other Types of Nutraceuticals*

*1) Polyphenols*

Polyphenols are basically plant-based bioactive molecules that are famous for their antioxidant and anti-inflammatory properties.
Types of Polyphenols:

- Flavonoids: They are widely distributed in fruits, vegetables, and tea, and have proved effective in antioxidant and anti-inflammatory effects [58].
- Phenolic Acids: Whole grains fruits and vegetables are good sources of phenolic acids which are reported to display antioxidant and anti-inflammatory effects [59].
- Stilbenes: Found in grapes, berries, and peanuts, stilbenes have been demonstrated to have antioxidant and anti-inflammatory activities [60].

*2) Carotenoids*

Carotenoids are a class of bioactive compounds found in plant-based foods, which are known for their antioxidant and anti-inflammatory properties.
Classifications of Carotenoids:

- Beta-Carotene: This has been shown to be antioxidant and anti-inflammatory in sweet potatoes, carrots, and dark leafy greens [61].
- Lycopene: Tomato, watermelon, and pink grapefruit can be mentioned as something lycopene can be extracted from. It has been known to possess antioxidant and anti-inflammatory properties [63].

## III. MECHANISMS OF ACTION AND BIOACTIVE COMPOUNDS

*A. Antioxidant and Anti-Inflammatory Effects*

These essential effects include antioxidant and anti-inflammatory effects, which are the action mechanisms of several bioactive compounds. Components of action in these effects include the following:

*1)* Scavenging of free radicals: Reactive oxygen species are neutralized by bioactive compounds to prevent oxidative stress and inflammation [34].
*2)* Modulating enzyme activities: Different bioactive compounds modulate the enzyme activities responsible for inflammation such as cyclooxygenase (COX) and lipoxygenase (LOX) [64].
*3)* Anti-inflammatory signaling: The bioactive compounds also inhibit the pro-inflammatory signaling such as NF-κB and MAPK [65].

*B. Modulation of Gene Expression and Epigenetics*

The bioactive compounds are capable of modulating gene expression and epigenetics. It also has an influence on the underlying processes in the cell and its prevention from diseases:

*1)* Modulation of transcription factors: The bioactive compounds can modulate the activity of some of the transcription factors such as NRF2 and PPARγ participating in gene expression [66].
*2)* Epigenetic modification: The bioactive compounds can be responsible for the epigenetic modulation of DNA methylation and histone modification that lead to the regulation of gene expression [67].
*3)* MicroRNA modulation: Bioactive compounds may also be responsible for the modulation of the expression of microRNAs, which allow manipulation of gene expression and cellular processes [68].

*C. Interaction with Gut Microbiota and Immune System*

Bioactive compounds can also interact with the gut microbiota and immunological system of the body, eventually influencing the immune functioning and prevention of disease. The ways this may happen through are:

*1)* Prebiotic effects: bioactive compounds can actually act as prebiotics, thus feeding beneficial gut microbial and supportive healthy gut microbiome [32].
*2)* Immune system modulation: bioactive compounds can modulate the immune system by possibly altering the activity of immune cells or cytokines associated with the immune response [69].

3) Modulation of gut associated lymphoid tissue (GAL): bioactive compounds can modulate GA LT and thereby influencing immune function and tolerance [70].

*D. Bioactive Compounds and Their Mechanisms of Action*

For example, in addition to the multitude of bioactive substances identified, it is interesting to note that each of them has quite different mechanisms of action:

1) Polyphenols: Some polyphenols that modulate several functions of inflammation, oxidative stress and immune function include quercetin and resveratrol [71].
2) Carotenoids: Some carotenoids, such as lycopene and beta-carotene, modulate functions involving oxidative stress, inflammatory response, and immune function [62].
3) Omega-3 fatty acids: Some omega-3 fatty acids, such as EPA and DHA, modulate inflammation, oxidative stress, and immune function [33].
4) Probiotics: Probiotics, including Lactobacillus and Bifidobacterium, can modulate the gut microbiota, immune function, and disease prevention [25].

## IV. HEALTH BENEFITS AND DISEASE PREVENTION

*A. Enhancing and Preventing Cardiovascular Disease*

1) Better lipid profiles: Bioactive compounds such as plant sterols and omega-3 fatty acids could lower levels of LDL cholesterol and triglycerides [72].
2) Blood pressure regulation: Potassium and calcium can have an important moderating effect, both generally and individually, on blood pressure levels [73].
3) Anti-inflammatory effects: These are biological entities such as polyphenols and omega-3 fatty acids, which lower the inflammation associated with cardiovascular disease [74].
4) Endothelial function improvement: Bioactive compounds like L-arginine and omega-3 fatty acids could improve endothelial function, thus reducing the risk of cardiovascular disease [75].

*B. Cancer Prevention and Treatment*

1) Antioxidant: Oxirapic compounds like polyphenols and carotenoids cause free radical neutralization, attenuating oxidative stress and reducing cancer risk [76].
2) Anti-inflammatory: Bioactive factors like omega-3 fatty acids, polyphenols, reduce inflammation, linked to cancer development [77].
3) Cell Cycle Regulation: Bioactive compounds such as isothiocyanates and indoles can regulate cell cycle progression arrest and cancer cell growth inhibition [78].
4) Inducing Apoptosis: Apoptosis in cancer cells can be termed cytotoxic cell death due to bioactive compounds such as polyphenols and terpenes [79].

*C. Neuroprotection And Cognitive Function*

1) Antioxidation: This form of bioactive compound includes polyphenols and omega-3 fatty acids, which might reduce oxidative stress and inflammation in the brain [80].
2) Neurotransmitter regulation: These bioactive compounds include omega-3 fatty acids and Ginkgo biloba and can improve cognitive function by regulating neurotransmitter activity [81].
3) Neuroinflammation has connected with neurodegenerative diseases, and bioactive chemicals like curcumin and resveratrol can reduce the impact caused by neuro-inflammation [82].

*D. Immune System Modulation and Infection Prevention*

1) Immune Activation: Bioactive Compounds such as Beta-glucans and polyphenols activate immune cells, enhancing the immune system [83].
2) Anti-inflammation: Bioactive Compounds such as Omega-3 Fatty Acids and polyphenols are quite anti-inflammatory that is associated with infections and diseases [84].

3) Antimicrobials: Bioactive compounds such as polyphenols and terpenes have antimicrobial actions and help to prevent infections [85].
4) Immunomodulation: bioactive compounds such as probiotics and prebiotics modulate the immune system making the immune system more efficient and disease protected [86].

*E. Other Health Benefits*

1) Digestive System: Bioactive compounds such as prebiotics and probiotics offer a healthy gut microbiome for improved digestive health [32].
2) Bone health: bioactive compounds such as calcium and vitamin D promote bone health and reduce the risk for osteoporosis [87].
3) Skin health: Bioactive compounds such as polyphenols and carotenoids may protect the skin from damage and promote healthy aging [88].
4) Eye health: Bioactive compounds such as lutein and zeaxanthin can protect the eyes from damage and promote healthy vision [89].

## V. SAFETY, EFFICACY, AND REGULATORY FRAMEWORK

*A. Safety Issues and Side Effects*

Bioactive compounds have proven to be those that may have probable safety concerns and adverse effects, especially in cases of excess consumption and in vulnerable populations. Some of the most common safety concerns include the following:

1) Allergic reactions: There are cases where some bioactive compounds, such as polyphenols, could lead to allergic reactions in sensitive individuals [90].
2) Drug interactions: Bioactive compounds could interact with drug actions, particularly blood thinners, to reduce their efficacy [91].
3) Gastrointestinal Effects: High doses of these bioactive compounds, e.g., fiber, can cause gastrointestinal side effects like bloating and gas [92].

*B. Efficacy and Clinical Trials*

Efficacy and clinical trials will be most useful in establishing the health advantages of bioactive compounds. Such points include:

1) Randomized controlled trials (RCTs): There is an RCT that serves as the gold standard among clinical trials, providing high-quality evidence of efficacy [93].
2) Dose-response relationships: Understanding dose-response relationships between bioactive compounds and health outcomes is critical for efficacy establishment [87].
3) Synergism: Bioactive compounds have synergetic effects when combined, thus enhancing efficacy [94].

*C. Regulatory Framework and Guidelines*

1) Food and Drug Administration (FDA): By FDA dietary supplements, bioactive compounds are regulated to comply with Good Manufacturing Practices (GMPs) [95].
2) European Food Safety Authority (EFSA): EFSA is responsible for the scientific advice on the safety and efficacy of bioactive compounds in the EU [96].
3) GRAS (Generally Recognized as Safe) Status: Bioactive compounds could achieve GRAS status, meaning they are recognized as safe for consumption [97].

*D. Quality Control and Standardization*

Quality control and standardization are also very essential in consistency and potency in bioactive compounds. Some key points include:

1) Standardization of Extracts: Standardization extracts to specific bioactive compound concentration guarantees consistency and efficacy [98].
2) Quality Control Measures: Implementing quality control measures such as testing for heavy metals and pesticides ensures the bioactive safety [99].

*3)* Third-party Certification: Third-party certification, NSF International or National Science Foundation approval guarantees following all quality and safety standards [100].

## VI. FUTURE DIRECTIONS

*1)* Personalized Nutrition and Genomics [101]
*2)* Emerging Ingredients and Technologies [102]
*3)* Sustainability and Environmental Focus [103]
*4)* Digital Health and Wellness [104]
*5)* Regulatory Frameworks and Standards [105]
*6)* Emerging Markets and Trends [106]
*7)* Plant-based Proteins [107]

## VII. CONCLUSION

Nutraceuticals are a burgeoning avenue in modern healthcare, with numerous applications ranging from health benefits to disease prevention. The classification and types of nutraceuticals are myriad, ranging from dietary supplements, functional foods, soothing herbal extracts, and probiotics. The research on the modes of action and bioactive compounds that form the basis of nutraceuticals is extensive; antioxidant and anti-inflammatory effects have even been reported from immunomodulation.

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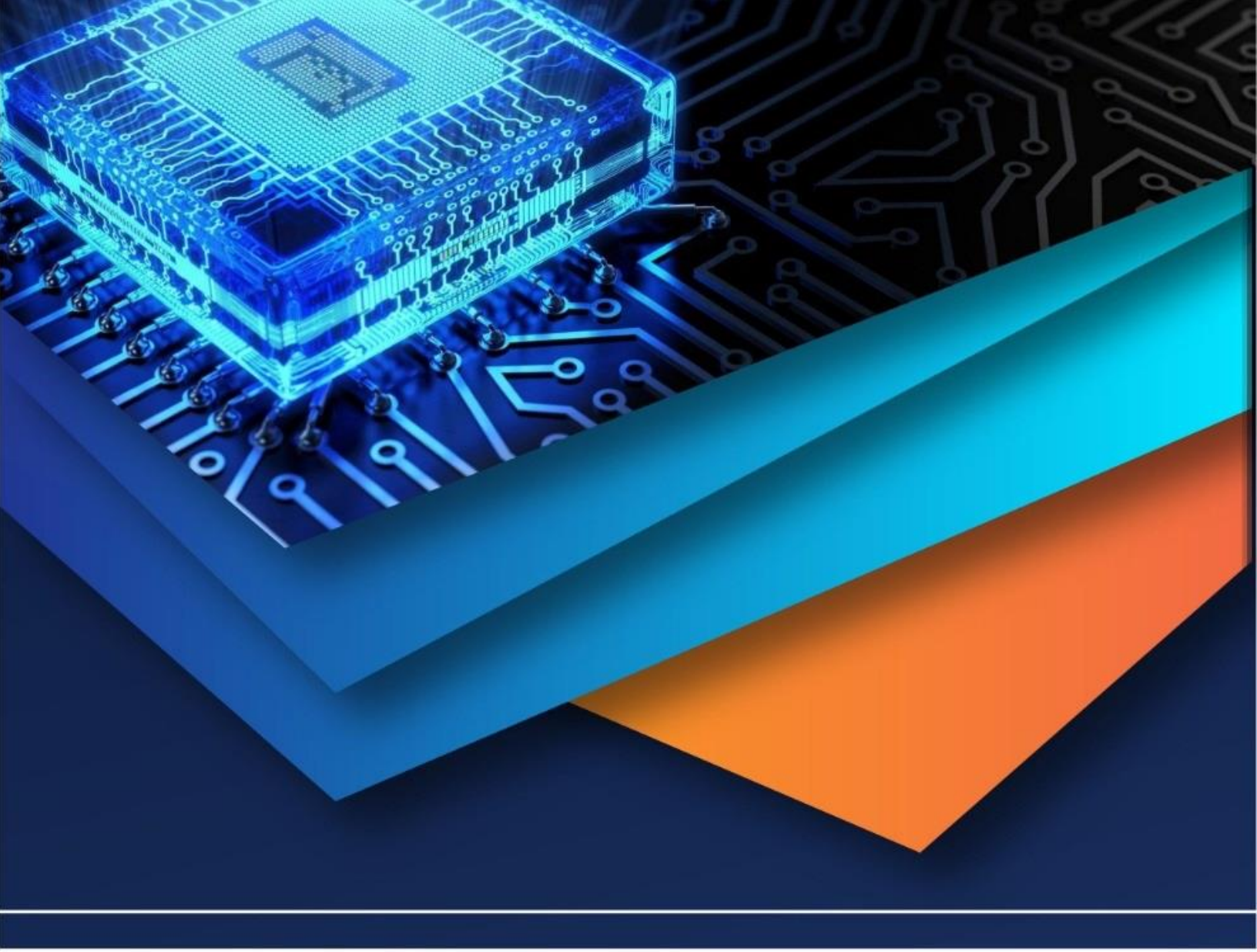

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