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Phytochemicals used in the Treatment of Hepatic Cancer or Cervical Cancer

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Abstract: ***The treatment of hepatic and cervical cancers has been a significant area of research due to their high morbidity and mortality rates worldwide. Phytochemicals, natural compounds derived from plants, have been explored for their anticancer properties due to their ability to modulate various molecular pathways involved in tumorigenesis. This review provides an overview of various phytochemicals, including flavonoids, terpenoids, alkaloids, and phenolic compounds, that have demonstrated potential in the treatment of hepatic and cervical cancers. The review also discusses the mechanisms of action, preclinical and clinical findings, and future prospects for phytochemical-based therapies in oncology.***
Keywords:-Curcumin , Silymarin , EGCG , Resveratrol.

I. INTRODUCTION

Background on hepatic cancer (liver cancer) and cervical cancer, their prevalence, and current treatment options.The growing interest in phytochemicals as alternative or adjunct therapies.Rationale for exploring plant-based treatments for cancer.

1) Phytochemicals in Hepatic Cancer Treatment:

Curcumin (from Curcuma longa): Known for its anti-inflammatory and antioxidant properties, curcumin has been shown to inhibit liver cancer cell proliferation and induce apoptosis. Its mechanisms of action include modulation of NF-κB, STAT3, and MAPK signaling pathways.Apigenin (from Apium graveolens): Apigenin has demonstrated potential as an anti-cervical cancer agent by reducing cancer cell viability, inducing cell cycle arrest at the G1 phase, and promoting apoptosis. It modulates various transcription factors like NF-κB and p53.Berberine (from Berberis species): An alkaloid with significant anti-cancer activity, berberine inhibits cervical cancer cell growth by inducing apoptosis and autophagy, and by modulating key signaling pathways such as AMPK/mTOR.Genistein (from Glycine max): A phytoestrogen that exhibits anti-cancer effects in cervical cancer by modulating estrogen receptors, inducing apoptosis, and inhibiting angiogenesis.

2) Mechanisms of Action:

Phytochemicals often exert their anticancer effects through several mechanisms:Induction of apoptosis via mitochondrial dysfunction, caspase activation, or death receptor signaling.Cell cycle arrest at key checkpoints (G1, S, G2/M).Inhibition of angiogenesis by reducing the expression of vascular endothelial growth factor (VEGF).Inhibition of metastasis by suppressing matrix metalloproteinases (MMPs) and enhancing the expression of tumor suppressor proteins like p53.Modulation of signaling pathways such as PI3K/Akt, MAPK, NF-κB, and Wnt/β-catenin.

3) Preclinical and Clinical Evidence:

Preclinical studies: Several in vitro and in vivo studies have demonstrated the efficacy of phytochemicals in inhibiting tumor growth and metastasis in both hepatic and cervical cancers.Clinical trials: While many phytochemicals show promise in preclinical settings, the results of clinical trials have been mixed. Clinical trials assessing curcumin, silymarin, and EGCG, among others, have provided insight into their safety profiles and potential as adjunct therapies.

4) Challenges and Limitations:

Bioavailability: Many phytochemicals suffer from poor bioavailability, which limits their clinical efficacy.Dosage and toxicity: Determining the appropriate dosage and understanding the potential toxicity of high doses remain significant challenges in translating phytochemicals into effective therapies.Interactions with conventional therapies: Phytochemicals may interact with chemotherapeutic agents, either enhancing their effects or causing adverse reactions, warranting further investigation

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5) Future Prospects:

Nanotechnology and formulation strategies to enhance the bioavailability of phytochemicals.Combining phytochemicals with conventional therapies (chemotherapy, radiotherapy, immunotherapy) to improve efficacy.Personalized medicine approaches to optimize treatment based on genetic and molecular profiling of tumors.

II. PHYTOCHEMICALS IN HEPATIC CANCER TREATMENT

1) Curcumin (from Curcuma longa):

- Exhibits anti-inflammatory and antioxidant properties.
- Inhibits liver cancer cell proliferation and induces apoptosis.
- Modulates pathways like NF-κB, STAT3, and MAPK.

2) Silymarin (from Silybum marianum):

- A flavonoid complex known for hepatoprotective effects.
- Inhibits tumor growth and induces apoptosis in liver cancer cells.
- Modulates cell cycle regulators and apoptotic pathways.

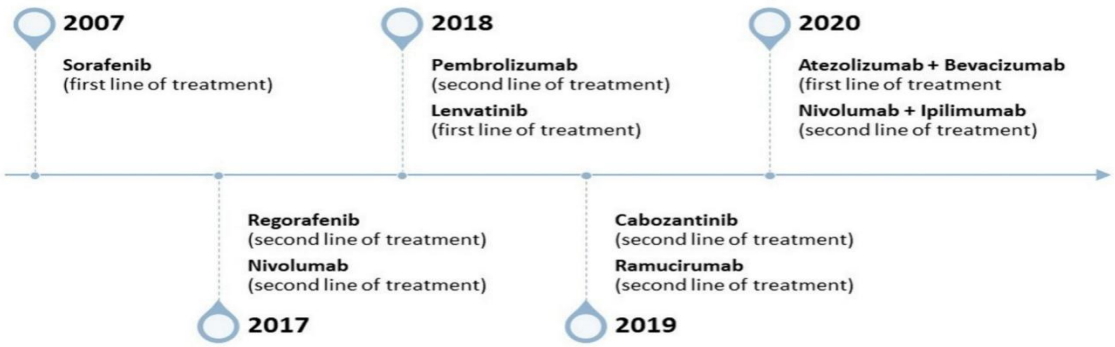
3) Epigallocatechin gallate (EGCG, from Camellia sinensis):

- Inhibits liver cancer cell growth and promotes apoptosis.
- Acts via PI3K/Akt/mTOR and Wnt/β-catenin signaling pathways.

4) Resveratrol (from Vitis vinifera):

- Polyphenol with antioxidant and anti-inflammatory properties.
- Reduces liver cancer cell proliferation, induces apoptosis, and suppresses metastasis.
- Modulates PI3K/Akt and JAK/STAT signaling.

Liver cancer is the third leading cause of cancer-related deaths worldwide and the most Widely occurring type of cancer in Asia [1]. Apart from cholangiocarcinoma, hepatocellular Carcinoma (HCC) is the major category of liver cancer; it accounts for 85% of liver cancer Cases globally, with high morbidity and mortality. There are significant differences in the Incidence of HCC across different genders, ethnicities, races, and geographical regions, with The incidence especially high across Asia and Africa [2]. HCC may be the terminal result Of chronic liver conditions, starting from liver fibrosis, cirrhosis, and finally malignancy.Approximately 80% of patients diagnosed HCC have poor prognosis [3]. While cirrhosis Is a major risk factor for liver cancer in humans, chronic hepatitis B and hepatitis C viral Infections are also among the established underlying causes of HCC. Although neonatal Hepatitis B vaccination has now been recommended in most countries as part of the global Strategy to alleviate HCC burden by 2030, the vaccine coverage in underdeveloped areas is Considerably poor, and complete prevention of viral infection is thereby not possible. Exposure to toxins, alcohol, and contaminated foods and the presence of metabolic diseases (such as non-alcoholic fatty liver) have also contributed to HCC development. At the Cellular level, the disease pathogenesis is, however, complex and involves several molecular Failures, such as cell cycle deregulation, chromosomal instability, immunomodulation,Epithelial-to-mesenchymal transition, microRNA dysregulation, and increases in HCC stem Cell populations.



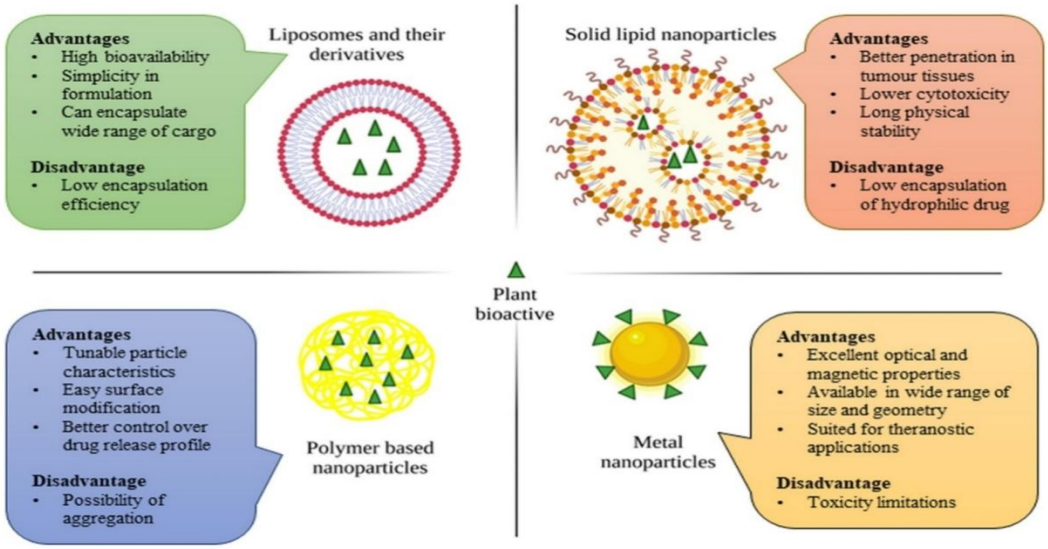
(Barcelona Clinic Liver Cancer (BCLC), Barcelona, Spain, stage A), when the tu-Mor or the lesion is less than 2 cm in size [9,10]. In fact, HCC can be cured with a good Long-term prognosis, if detected early. Despite several surveillance protocols and recom-Mendations, more than two-thirds of the patients are diagnosed during the advanced Stages (BCLC stage C), when curative treatments often fail. Destruction of cancer cells and Inhibition of their proliferation through chemotherapy are consequently the requisite Needs of most patients. A large number of clinical trials in recent years has led to the ap-Proval of multiple drugs by the Food and Drug Administration (FDA)

In 2007, The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) and Asian-Pacific trials were conducted with 602 and 226 participants, respectively. Sorafenib Was consequently approved as a first-line drug in inoperable HCC cases [11–13]. Sorafenib Is a dual aryl urea multi-kinase inhibitor, and it exhibits strong antitumor and antiangio-Genic activities. Between 2017 and 2019, the FDA permitted the use of other drugs, such As ramucirumab, cabozantinib, lenvatinib, and regorafenib, thus changing the scenario for The first line of treatment. Although there are several tyrosine kinase inhibitors now avail-Able, they only increase patient survival by two to three months [14]. More recently, the Use of immune checkpoint blockage therapy has been very successful in several condi-Tions, such as melanoma, non-small cell lung cancer, and colorectal cancer. This approach,

However, is in its infancy, and many phase I and phase II trials are currently investigating Different immune checkpoint blockers in combination with other agents or treatment Strategies in HCC [15]. Based on the results from the KEYNOTE and CheckMate trials in 2017–2018, the FDA approved the use of the antibodies pembrolizumab and nivolumab As advanced-stage second-line treatments for HCC patients with sorafenib failure [16]. While pembrolizumab can be used independently for HCC treatment.

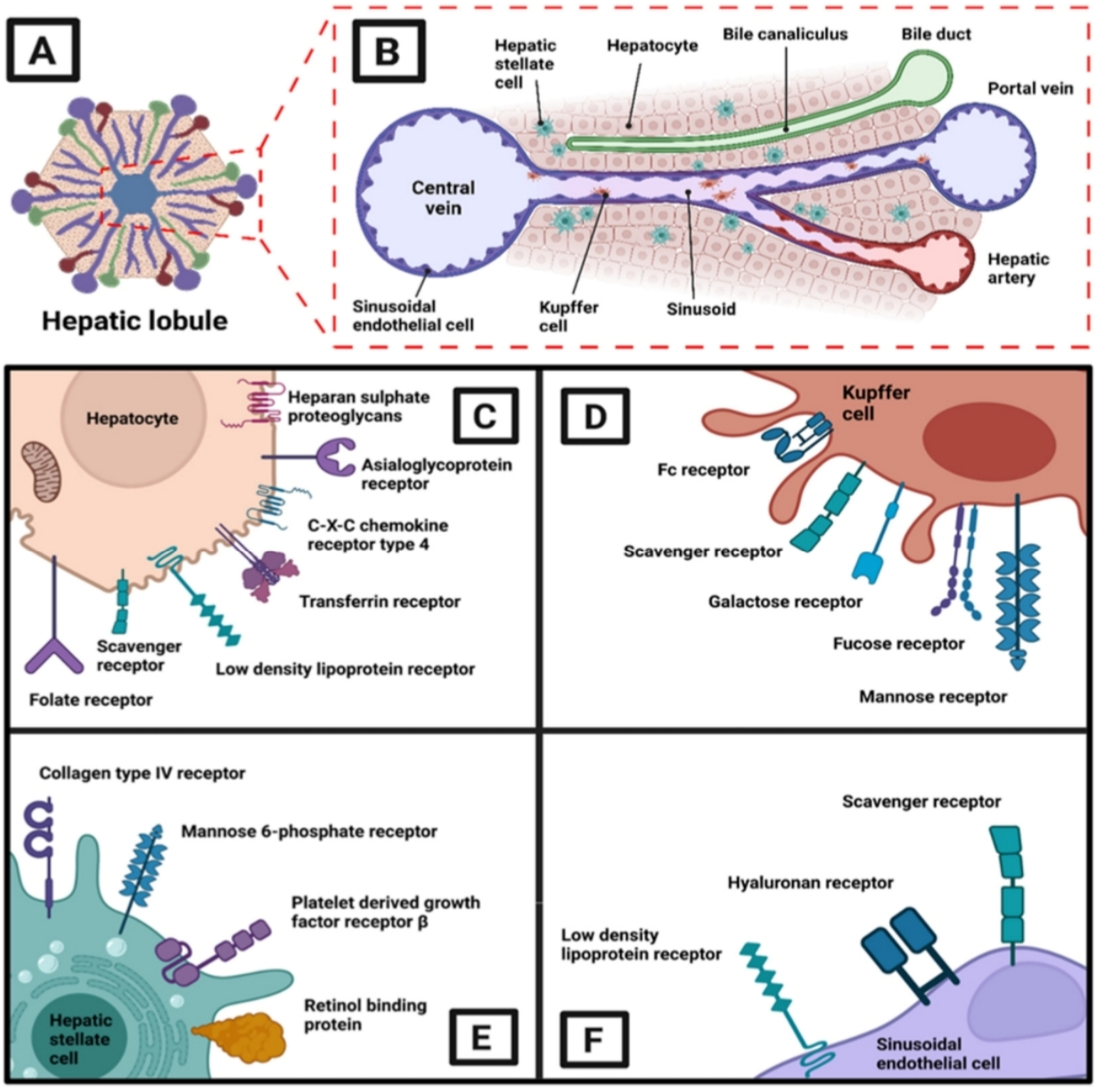
Sorafenib has an overall survival benefit of three months, while the second line Of treatment, using regorafenib and carbozantinib, has managed to prolong survival to Approximately 10 months [18,19]. Incidences of tumor recurrence and poor survival rates Strongly persist despite the various lines of treatments and ongoing clinical trials, as Well as the variations in morphological and molecular patterns in the disease render the Clinical trials more challenging [20]. In fact, sorafenib is associated with mild to severe Adverse reactions, including diarrhea, elevated blood pressure, and skin rashes [12]. The

STORM trial, conducted on 1114 participants, showed that sorafenib failed to mitigate the Recurrence after curative treatment [21]. Alternatively, new immune-modulatory therapies Using immune-checkpoint inhibitors are prone to unbalance the immune system and cause Adverse reactions that occasionally may be fatal [22]. Thus, there is an urgent need for the Development of new therapeutic strategies based on a thorough understanding of tumor Biology, mechanisms of anticancer molecules, and their delivery options.Several molecules originating from medicinal and dietary plants have been reported To be effective against different types of cancer by prohibiting the activation of onco-Genic pathways at cellular levels. Molecules such as quercetin, curcumin, resveratrol,Epigallocatechin-3-gallate, and many others have been studied extensively due to their High potency, minimum toxicity, and ability to overcome drug resistance [23,24]. Specific Bioactives, such as Guttiferone K (isolated from Garcinia yunnanensis) and safranal (isolated)From Crocus sativus), have shown cytotoxicity against quiescent cancer cells. These cellsbReside in the G0/G1 phase and are usually resistant to conventional chemotherapy [25].



However, the effects have been mostly limited in vitro, especially due to the poor bioavail- Ability and low biological half-lives of the plant bioactive compounds. The body treats These molecules as xenobiotics, and they are rapidly cleared by the reticuloendothelial System (RES). The required therapeutic levels are, therefore, difficult to achieve and re-Salt in high inter- and intrasubject variability, as well as a lack of dose proportionality.Furthermore, the compounds vary in their molecular structures, resulting in differences In their physical states, solubilities, partitioning, and chemical stability.

Low aqueous Solubility, poor gastrointestinal absorption, and clearance prevent pharmacological con-Centrations from being achieved in the target tumor and restrict the use of the majority of These phytochemicals in clinics [26]. Nanotechnology-based approaches or nanomedicines Can provide avenues to circumvent plant bioactive-related limitations and help to increase Bioavailability, improve cellular uptake through site-specific targeting, and accomplish Steady-state concentrations of bioactives throughout the therapeutic regimen [27]. The Present review initially describes the various molecular pathways of plant bioactives against HCC and highlights the recent advancements in plant-based nanoparticle formulations For HCC treatment. We further present the challenges in the design and development of Plant bioactive-based nanomedicines for HCC treatment and reveal possible strategies to Facilitate clinical translation.

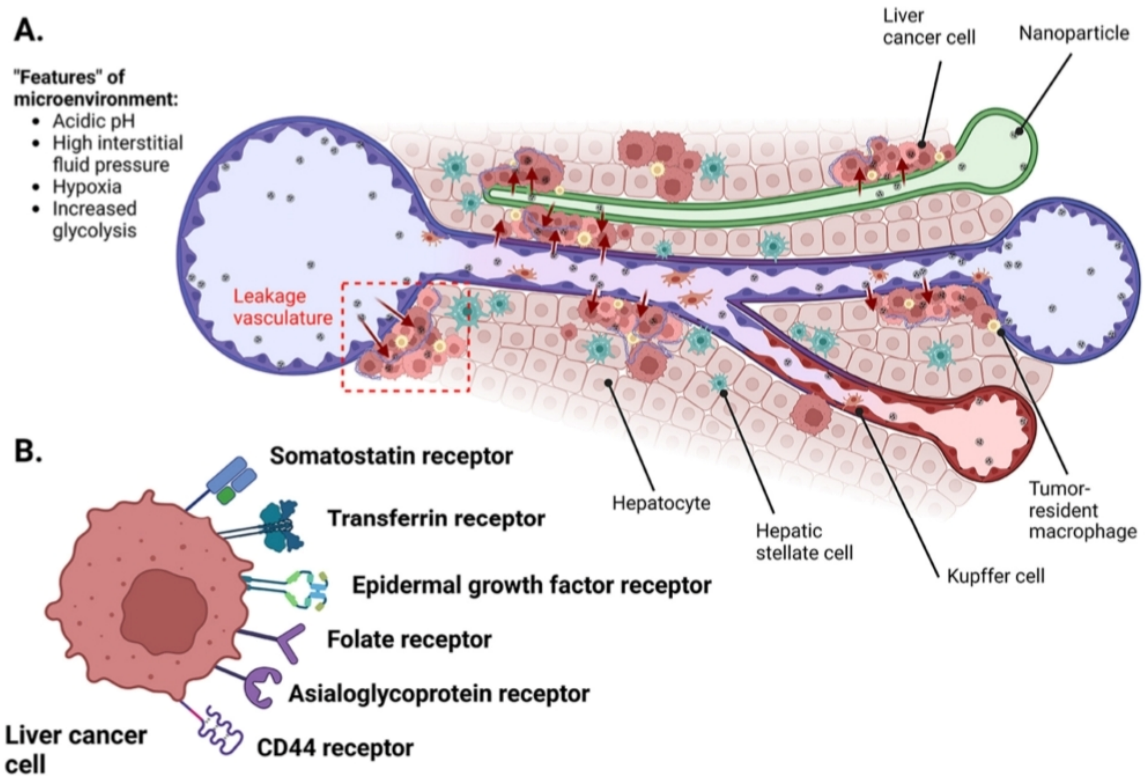


III. TUMOR BIOLOGY: HCC AND CURRENT LIMITATIONS OF DRUG DELIVERY DESIGN

The liver is the largest abdominal organ, receiving its blood supply from two promi-Nent sources: the hepatic artery and hepatic portal vein (Figure 2A,B). These blood vessels Divide into finer capillaries and the liver sinusoids, ultimately leading to the lobules. The Hepatocytes are a major cell population in the liver (~85%), providing primary sites for Protein synthesis, metabolism, and detoxification [28]. Other important cell-types include Hepatic stellate cells (HSCs), liver sinusoidal endothelial cells, and Kupffer cells, all of Which contribute to the maintenance of liver homeostasis. In case of chronic injury to

The liver, these cells commence a crosstalk, leading to production of fibrous collagen and Extracellular matrix (ECM) remodeling factors. Consequently, liver diseases, such as HCC,Typically initiate from underlying inflammation and cause significant changes in the liver's Extra- and intracellular pathophysiology, thus perturbing drug delivery. While normal liver Tissues receive 80% of the blood supply from the hepatic portal vein, HCC is characterized By high perfusion from the hepatic artery. Therefore, low blood influx through the portal Vein in HCC patients causes low nanoparticle penetration into the liver after systemic Administration [29]. While the sinusoidal fenestrates are decreased, the nanoparticles must Penetrate the endothelial barrier, the extracellular matrix (ECM), and the tumor stromal Barriers to reach the HCC cells [30]. Understanding the biological barrier of the tumor Is critical for the judicious selection of plant bioactive compounds and designing a new Generation of nanomedicines for HCC therapy. Recent advancements in molecular biology Techniques, including microarrays and high-throughput screening, have greatly improved our knowledge about the tumor characteristics and molecular mechanisms of HCC [31,32].

The tumor microenvironment consists of tumoral and non-tumoral cells, such as hepatic Stellate cells, immune cells, fibroblasts, cytotoxic T-cells, and tumor-associated macrophages.These cells play significant roles in tumor progression by inhibiting antitumor responses,Stimulating the development of new blood vessels (angiogenesis), and supporting the Proliferation of cancer cells [33,34].



Recent emerging clinical trial data have suggested That sorafenib significantly affects neither the stages of angiogenesis nor proliferation in Tumor progression; therefore, it is necessary to discover new drug candidates that can fill In this gap and hinder the disease at the molecular level [35]. There are also extracellular Components, including different collagens, glycoproteins, proteoglycans, proteolytic en-Zymes (matrix metalloproteinases), cytokines, and exosomes, that usually maintain the Tumor integrity and are sometimes involved in the development of drug resistance [36].One of the proteoglycans, chondroitin sulfate, has shown abnormally high expression Levels in HCC cells and is now widely exploited to develop targeted therapies against HCC [37,38].

A. Hepatic Cancer

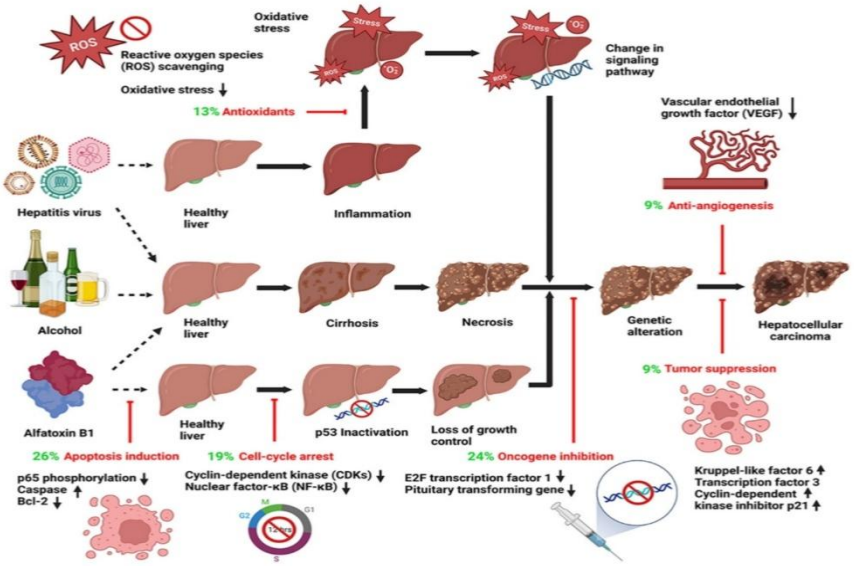
- *Quercetin*: A flavonoid found in various plants, quercetin has been shown to inhibit the growth of hepatic cancer cells and induce apoptosis.[1]
- *Curcumin*: A polyphenol extracted from turmeric, curcumin has potent anti-inflammatory and antioxidant properties, which can help prevent the development of hepatic cancer.
- *Resveratrol*: A polyphenol found in grapes, berries, and peanuts, resveratrol has been shown to inhibit the growth of hepatic cancer cells and induce apoptosis.

B. Cervical Cancer

- - *Epigallocatechin-3-gallate (EGCG)*: A polyphenol found in green tea, EGCG has been shown to inhibit the growth of cervical cancer cells and induce apoptosis.
- - *Lycopene*: A carotenoid found in tomatoes, lycopene has been shown to have anti-proliferative effects on cervical cancer cells.
- - *Silymarin*: A flavonoid extracted from milk thistle, silymarin has been shown to have anti-cancer properties and inhibit the growth of cervical cancer cells.

Plant-Based Nanoparticle Formulations

Research has also focused on developing plant-based nanoparticle formulations to improve the delivery and efficacy of phytochemicals in cancer treatment. These formulations can help overcome the limitations of phytochemicals, such as poor solubility and bioavailability.



Progression of hepatocellular carcinoma and molecular mechanisms of plant bioactives Against various oncogenic pathways. The frequencies of compounds targeting in each pathway have Been highlighted in green. The percentage was calculated from data in , and the Apoptosis, or programmed cell death, is an essential cell-death mechanism to maintain

Cellular homeostasis, and it can be induced either through surface death receptors or via Mitochondria-mediated pathways. Cancer cells experience genetic mutations to evade Apoptosis and survive under pathological stimuli. Alterations of B-cell lymphoma 2 (Bcl-2)Proteins, apoptosis protein inhibitors, death receptors, and executioner caspases are certain Features of cancer cells.

IV. CONCLUSION

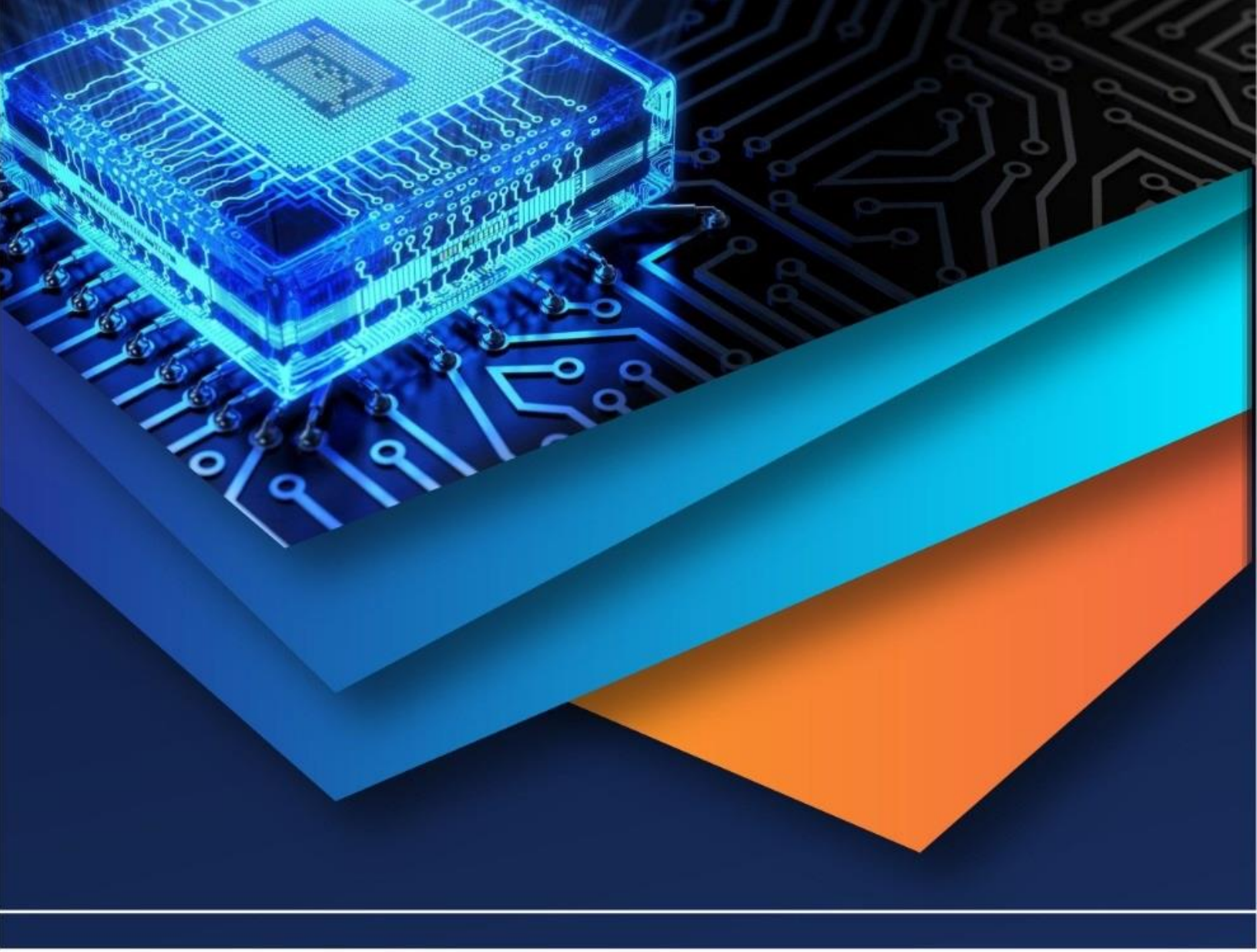
Phytochemicals, derived from natural plant sources, hold significant promise as therapeutic agents for the treatment of hepatic and cervical cancers. These compounds, including flavonoids, terpenoids, alkaloids, and phenolic compounds, have demonstrated potential in inhibiting tumor growth, inducing apoptosis, and modulating key molecular signaling pathways involved in cancer progression.

While preclinical studies provide compelling evidence of their efficacy, the clinical translation of these phytochemicals faces challenges such as bioavailability, optimal dosing, and potential interactions with conventional therapies. Nevertheless, the clinical translation of these phytochemicals faces challenges such as bioavailability, optimal dosing, and potential interactions with conventional therapies. Nevertheless, the growing body of research suggests that phytochemicals could be integrated into future cancer treatment regimens, either as standalone therapies or as adjuncts to traditional treatments. Further clinical trials and advancements in drug delivery technologies will be crucial in fully realizing the potential of phytochemicals in cancer therapy.

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