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Exotic Fruits and Their Signaling Pathways in Hepatocellular Carcinoma Prevention and Treatment: A Comprehensive Review

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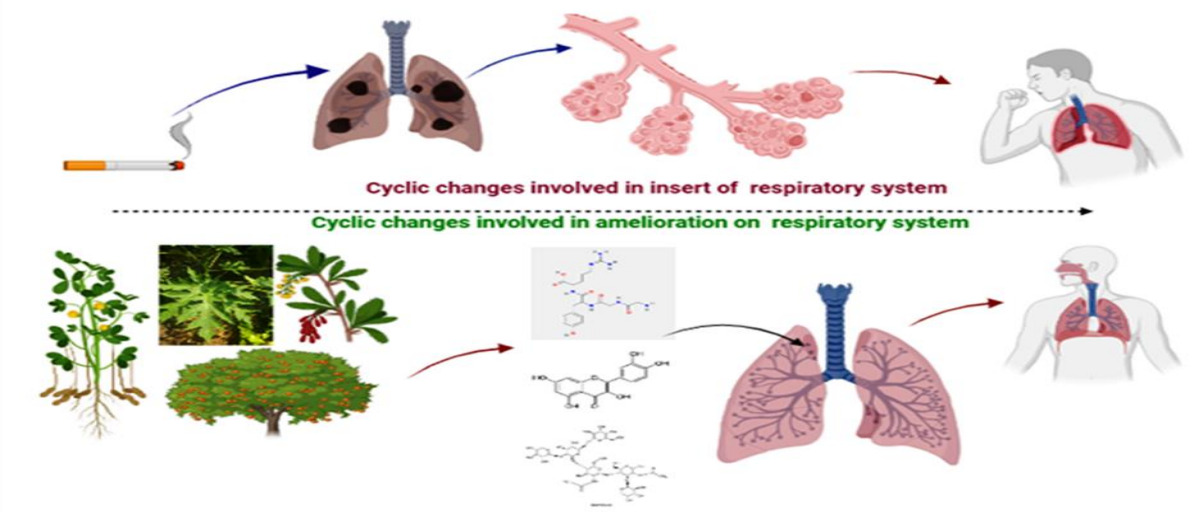
KEYWORDS

Hepatocellular carcinom,Signaling pathways, Exotic fruit, bioactive compoun, and treatment.

Abstract

Hepatocellular carcinoma (HCC) is a consideration malignancy of liver and a substantial global health issue. In worldwide, HCC secure the 5th and 3rd place in overall cancer burden and cancer related death are respectively. HCC is closely linked to chronic liver diseases, namely, Hepatitis virus, alcohol addiction, and non-alcoholic fatty liver disease. The pathophysiology of HCC involves complex molecular and genetic alterations that result in unorganized of diversify signaling pathways are PI3K/AKT/mTOR, Wnt/β-catenin, JAK/STAT, and MAPK/ERK pathways, which a vitalto both liver cancer progression. Exotic fruits embody a variety of bioactive substances, several of which have been found to have anti-cancer effects and to alter certain signaling pathways. Papaya, mango, guava, and pineapple, in particular, contain compounds such as papain, mangiferin, quercetin, and bromelain, respectively thatare currently studied for their efficacyin both the management and avoidance of HCC. These compounds have been documented to stop proliferation and survival pathways, initiatecell death, and modulate angiogenesis, inflammation, and immune response. Additional study is required to confirm the effectiveness and safety of these substances in people, explore their bioavailability and metabolism, and consider potential interactions with other medications. Overall, exotic fruits offer a promising natural approach to HCC prevention and treatment.

1. Introduction



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2. Hepatocellular carcinoma (HCC), a malignant tumor usually develops from hepatocytes and placed a 3rd most frequent cancer and5th most prevalentcancer in the worldwide. HCC has a poor prognosis despite advancements in diagnosis and therapy, the survival rate over a 5 year period at less than 20% [1]. Therefore, there is an urgency to investigate new tactics for the prevention and therapy for HCC. In current years, there has been anticipating interest in the potential effectiveness of natural compounds, particularly those found in exotic fruits, as chemo preventive and therapeutic agents against HCC. Exotic fruits are anabundantresource of phytocompounds, including polyphenols, carotenoids, vitamins, and minerals, which have demonstrated diverse biological process, such as antioxidant, anti-inflammatory, anti-proliferative, and pro-apoptotic activity [2]. The PI3K/AKT/mTOR, Wnt/β- Catenin, JAK/STAT, MAPK/ERK pathways are only a few of the various deregulated signaling pathways that these bioactive chemicals can target [3]. It would be helpful to comprehend the molecular mechanisms behind the effects of exotic fruit chemicals on HCC signaling pathways in order to develop innovative approaches for the prevention and treatment of HCC. With a focus on the underlying signaling pathways, the objective of this in-depth analysis is to provide a critical evaluation of the preclinical and clinical data on the effectiveness of exotic fruits and their bioactive compounds in HCC prevention and treatment.

The scope of this review includes an overview of HCC, its epidemiology, pathogenesis, as well as a discussion of the potential mechanisms of action of exotic fruit compounds on HCC signaling pathways, challenges and limitations of using exotic fruits in HCC prevention and treatment, and research's foreseeable future directions.

Epidemiology of Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is an unfortunate form of liver cancer that originating from hepatocytes, the liver's primary functional cells. Liver cancer will be the 6thmost often diagnosed malignancy in 2020, with about 906,000 new cases and 830,000 deaths attributedto it globally. In most locations, men experience greater rates of both incidence and mortality than women, and liver cancer stands as the second leading cause of death among men and secure the fifth rank among globally in terms of incidence. In 11 geographically distinct nations in Eastern Asia, South-East Asia, and Northern and Western Africa, the disease is an instance of cancer. Men's incidence rates are 2.4 times greater in switched countries, although these countries also have the highest rates overall [4].

HCC can develop due to various risk components, like as chronic viral hepatitis infections, exposure to aflatoxins, alcohol assault, non-alcoholic fatty liver disease (NAFLD), and metabolic disorders. The early stages of HCC often have no symptoms, making Early diagnosis and therapy are difficult. HCC can be aggressive and has a high mortality rate, making it a serious global public health issue [5].

Pathogenesis and molecular mechanisms of HCC

Hepatocellular carcinoma (HCC) is aninvolute disease with a multifactorial etiology, involving genetic, epigenetic, and surrounding factors. The aetiology of HCC is characterized by a cumulative accumulation of genetic and epigenetic abnormalities, which outcome in the dysregulation of important signaling pathways influence in cell growth, proliferation, survival, and angiogenesis.

PI3K/AKT/mTOR signaling axis:

PI3K/AKT/mTOR is an essential signaling system governs the cell multiple, and survival, as well as metabolism, angiogenesis, and autophagy [6]. Dysregulation of this pathway has convicted in multifaceted cancer, particularly hepatocellular carcinoma (HCC). In HCC, aberrant enhanced of the PI3K/AKT/mTOR pathway can promote tumor cell proliferation, inhibit apoptosis, and enhance angiogenesis, leading to tumor growth and progression [7].

The PI3K/AKT/mTOR pathway is triggered by various growth factors and cytokines, which bound to cell surface receptors and activate PI3K. Activated PI3K then phosphorylates and activates AKT, which in turn activates mTOR, a key regulator of protein synthesis and cell growth [8]. In HCC, various genetic and epigenetic changes can cause the activation of this pathway, including mutations in PI3KCA, amplification of AKT, lack of the tumor suppressor PTEN, and overexpression of growth factor receptors, including, EGFR and HER2 [9][10].

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Targeting the PI3K/AKT/mTOR pathway suggested as a possible therapeutic avenue in the therapy of HCC. Several drugs that inhibit various components of this pathway. For example, Everolimus, an mTOR inhibitor, inhibited proliferative activity in Hep3B and SNU398 HCC cells [11]. Everolimus hadillustrated to inhibit tumor progression and increase positive outcome in preclinical HCC models. Everolimus' effectiveness was examined in the phase III research on patients associated with advanced HCC. However, No noticeable distinction was evident between the control and treated group [12][13].

Wnt/β-catenin pathway axis:

The Wnt/β-catenin pathway is a crucial signaling pathway influence the regulation of several cellular processes notably, cell proliferation, differentiation, and survival [14]. The pathway's dysregulation wasinterlinked to the aetiology of HCC. The Wnt signaling pathway is triggered when Wnt ligands bounded to Frizzled receptors on the cell surface. This causes β -catenin to be stabilized and accumulated in the cytoplasm, where it shifts to the nucleus and communicate with TCF/LEF transcription factors to stimulate the encoding of specified genes participating in cell proliferation, survival, and migration [15][16].

In HCC, the Wnt/β-catenin pathway abnormal activation occurs often and can occur through various mechanisms, including abnormal in genes encoding pathway components, including β-catenin, Axin, and APC, or upstream regulators, such as RAS and EGFR (Jeong, et al., 2018)[17]. In addition to, epigenetic modifications, like DNA methylation and histone acetylation, can likewise exacerbate the HCC pathway dysfunction [18].

Wnt/β-catenin pathway activated in HCC is entangled with cell proliferation, invasion, and metastasis. A lot of downstream targets of the pathway was implicated in these processes like cyclin D1, c-Myc, and matrix metalloproteinases (MMPs) [19]. Focusing the Wnt/β-catenin pathway has thus emerged as aeffective therapy for HCC.Several agents that inhibit the Wnt/β-catenin pathway is currently under exploration for the management of HCC. These include small molecule inhibitors of β-catenin, namely PRI-724 [20] and BC2059 [21], which have shown promising results in preclinical studies. Additionally, Sulindac, a nonsteroidal anti-inflammatory medicine (NSAID), was found to suppress nuclear beta-catenin localization and beta-catenin/TCF-regulated transcription of target genes in vitro and animal model [22].

JAK/STAT pathway:

The Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) pathway is a critical signaling system that engaged an indispensable part in cell proliferation, differentiation, and immunological response [23]. Disorderly regulation of the JAK/STAT pathway has linked to the progression of numerous malignancies, including hepatocellular carcinoma (HCC) [24].

The JAK/STAT mechanisms can be switched on by cytokines or growth factors its attachment to their cell surface receptors. [25]. This binding activates JAK kinases, which subsequently phosphorylate STAT proteins. Following dimerization and nuclear translocation, the phosphorylated STAT proteins control the expression of target transcripts that influence cell growth, survival, and diversification [26].

In HCC, Inappropriate JAK/STAT pathway expression has been pertaining to tumor cell proliferation, survival, and invasion. Overexpression of the JAK/STAT pathway components, including JAK1, JAK2, STAT3, and STAT5, has been studied in HCC tissue samples. Moreover, dysregulated cytokine production in the tumor microenvironment, such as interleukin-6 (IL-6) and hepatocyte growth factor (HGF), can also activate the JAK/STAT pathway in HCC [27][28].

The JAK/STAT pathway emerged as a viable HCC remediation. In preclinical studies, inhibition of the JAK/STAT pathway using small molecule inhibitors or RNA interference has been portrayed to stifle HCC cell growth and induce apoptosis [29]. Clinical trials assessing the effectiveness of JAK inhibitors in HCC treatment are currently underway. Dysregulation of this pathway promotes tumor growth and survival, make appealing target for the therapy of HCC.

MAPK/ERK pathway:

Another signaling system that is crucial for the instigation and development of HCC is the

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MAPK/ERK pathway, which stands for mitogen-activated protein kinase/extracellular signal-regulated kinase [30]. This pathway is initiated by various extracellular stimuli, example growth factors, cytokines, and hormones, and control cellular processes, cell proliferation, survival, differentiation, and migration [31]. In HCC, aberrant activation of the MAPK/ERK pathway has been inculpate through multiple mechanisms, including overexpression or mutation of regulatory bodies upstream consisting of EGFR, Ras, and Raf, as well as downregulation of negative regulators such as Sprout and dual specificity phosphatases [32][33].

Furthermore, the MAPK/ERK pathway has been demonstrated to have a part in the resistance of HCC cells to chemotherapy and radiotherapy [34][35]. Thus, targeting this system has become a feasible strategy for HCC treatment, and various MAPK/ERK pathway inhibitors are now being developed for the therapeutic management of HCC in both clinical and preclinical studies. To achieve the best therapeutic results, combination therapy with additional targeted medicines may be required as these inhibitors' performance [36].

Notch signaling:

The Notch signaling system is imperative in determining cell death, development, and differentiation. Dysregulation of Notch signaling has been tied to anailment, including cancer [37]. In HCC, aberrant activation of the Notch signaling pathway has been noticed in numerous investigations, indicating its crucial role in HCC pathogenesis. Notch signaling is intermediate by the adhere to Notch receptors (Notch1-4) with their ligands (Jagged and Delta-like), leads to the Notch intracellular domain (NICD) were breakdown and its translocation to the nucleus [38]. In the nucleus, NICD communicate with transcription factors like as CSL to activate the expression of downstream target genes participate in cell proliferation, survival, and angiogenesis [39]. Studies have conveyed that overexpression of Notch receptors and ligands is linked with poor prognosis and aggressiveness of HCC [40]. Notch signaling pathway inhibitors (PF-03084014 & Xanthohumol) have been demonstrate to stop HCC cell proliferation and trigger apoptosis, making them to open new avenue in therapeutic aspects for HCC treatment [41][42].

Crosstalk and interactions of signaling pathways in HCC:

HCC advancement and growth involve the activation of multiple signaling pathways that crosstalk and interact with each other. The cross-regulation and feedback mechanisms between these pathways contribute to the heterogeneity and complexity of HCC. The PI3K/AKT/mTOR, Wnt/β-catenin, JAK/STAT, and MAPK/ERK pathways are interconnected and can influence each other's activity in Hepatocellular carcinoma [43].

As an illustration, the Wnt/-catenin pathway can be increased by the switch on the PI3K/AKT/mTOR pathway, which in turn enhanced HCC cell proliferation and survival [44]. The JAK/STAT pathway can also activate the Wnt/β-catenin pathway by inducing the expression of Wnt ligands or downregulating negative regulators of the pathway [45]. Furthermore, by phosphorylating and activating their downstream effectors, the MAPK/ERK pathway can influence the activation of other signaling pathways like as PI3K/AKT/mTOR and JAK/STAT [46]. The Notch and Hedgehog pathways are also involved in crosstalk with other signaling pathways in HCC [47].

Therefore, understanding the crosstalk and interactions among signaling pathways in HCC is essential for developing targeted therapies that can simultaneously block multiple pathways and overcome drug resistance. Combination therapy that targets several pathways has demonstrated merit in preclinical research and clinical trials and may represent a promising aspect for HCC treatment in the future [48].

Exotic fruits and their bioactive compounds

Exotic fruits are defined as fruits that are not commonly consumed or cultivated in a particular region or country, and are typically grown in tropical or subtropical climates. Examples of exotic fruits include mango, papaya, guava, pineapple, kiwi, dragon fruit, and passion fruit, among others.These fruits are known to have unique flavors, textures, and nutritional profiles compared to more common fruits such as apples or oranges [49]. Exotic fruits consist of a diversity of bioactivesubstance that are referred to for their beneficial effects on health. Bioactive substances

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areknown as non-nutritive components of food ingredients which possess the potential to improve human health. These compounds include vitamins, minerals, fiber, and phytochemicals, including, polyphenols, carotenoids, and flavonoids (Table 1). Exotic fruits are rich sources of these compounds are believed to provide various health benefits, such as reducing inflammation, preventing chronic diseases, and improving overall well-being [50].

Polyphenols are a class of bioactive compounds that are found abundantly in exotic fruits such as papaya, mango, and guava. These substances have anti-inflammatory and antioxidant effects that aid to lessen oxidative stress in the body [51]. Evidence have conveyed that polyphenols may hinder the proliferation of cancer cells and led to apoptosis, which is programmed cell death, in cancer cells [52][53].

Table 1: List of Exotic Fruit and their bioactive compounds

Sl. No	Exotic Fruit	Scientific Name	Bioactive Compounds	Reference
1	Papaya	*Carica papaya*	Papain, Carpain, chymopapain, lycopene, β-Carotene, and polyphenols	[54]
2	Mango	*Mangifera indica*	Mangiferin, Gallotannins, Quercetin, Kaempferol, and β-Carotene	[55]
3	Guava	*Psidium guajava*	Quercetin, Lycopene, β-Carotene, and gallic acid	[56]
4	Pineapple	*Ananas comosus*	Bromelain, Ananas Comosus Protease, and Phenolic compounds	[57]
5	Pomegranate	*Punica granatum*	Ellagic acid, Punicalagin, anthocyanins, and flavonoids	[58]
6	Kiwi	*Actinidia arguta*	Actinidin, Quercetin, and Vitamin C	[59]
7	Dragon fruit	*Selenicereusundatus*	Betalains, Hydroxycinnamates, and flavonoids	[60]
8	Acai berry	*Euterpe oleracea*	Anthocyanins, flavonoids and fatty acids	[61]
9	Goji berry	*Lyceum barbarum*	Polysaccharides, Zeaxanthin, and betaine	[62]
10	Acerola cherry	*Malpighiaemarginata DC*	Vitamin C, anthocyanins and carotenoids	[63]

Sed enim ut sem viverra. Donec ultrices tincidunt arcu Carotenoids are another group of bioactive compounds found in exotic fruits, which give these fruits their distinctive bright colors. Beta-carotene, for example, is found in high amounts in papaya and mango, and is converted in the body into vitamin A [64]. This vitamin is important for maintaining healthy skin and vision, as well as supporting immune function. Lycopene, another carotenoid found in exotic fruits such as watermelon, has been connectwithsuppress risk of certain class of cancer [65].

Flavonoids, which are abundant in fruits such as kiwi and blueberries, have been scientifically demonstrated to possess anti-inflammatory and antioxidant properties [66]. Quercetin, a flavonoid proven in enormous amounts in guava, has been suggest that have anticancer effect by stop cell proliferation and inducing apoptosis [67].

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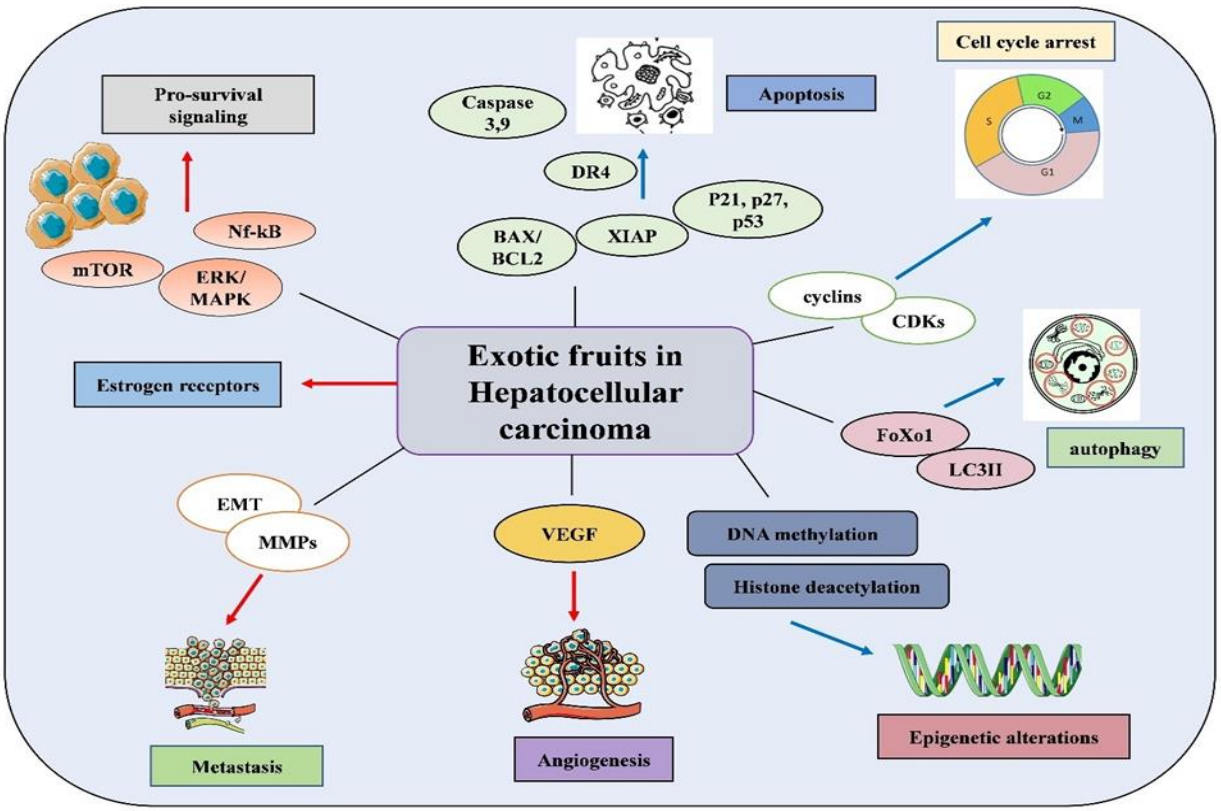
In addition to these bioactive compounds, Exotic fruits are also abundant in vitamin and mineral content, which are essential for maintaining optimal health. For example, pineapple is a promising source of vitamin C, that is crucial for immune function and collagen synthesis [68], while mango is abundant source in vitamin E, which has antioxidant properties and helps to protect cells from damage [69].

Papaya and papain in HCC prevention and treatment

Papaya (*Carica papaya*) is a tropical fruit, widely consumed for its sweet taste and nutritional benefits. Together with its wonderful flavor, papaya contains a variety of bioactive compounds, including papain, chymopapain, carpain, and flavonoids, that have been evident to possess anti-cancer capability [70]. Papain, a proteolytic enzyme found in papaya, has been studied extensively for its potential anti-cancer effects, particularly in HCC [71]. A study has demonstrated that papain (1000µg/ml) has 85% cytotoxicity against Hepatocellular carcinoma [72]. In addition, Natural killer (NK) cells and T cells can be stimulated to promote more interferon-gamma (IFN-) and interleukin-2 (IL-2) when papain from papaya is consumed [73] to reduce tumor growth [74].

Papain can stop HCC cells from multiplying and growing by initiate apoptosis, evidenced by several experiments. Papain determined that block the angiogenic factor VEGF, which reduces the manifestation of tumor metastasis [75]. Additionally, papaya leaf extracts triggers apoptosis by augmenting pro-apoptotic proteins and restricting anti-apoptotic protein [76]. Rahmat et al.'s 2002 research team also looked at the antiproliferative effects of papaya and watermelon extracts as well as their juice on human breast and liver cancer cell lines. They claimed that the Hep G2 cell line (Hepatocellular carcinoma) was destroyed thorough papaya juice and raw lycopene at half maximum inhibitory concentrations (IC50) of 20 mg/mL and 22.8 g/mL, respectively [77]. The anti-cancer effect of papaya and its bioactive compound papain make it a potential candidate for HCC prevention and treatment.



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Mango and mangiferin in HCC prevention and treatment

Mango (*Mangifera indica*) is a popular tropical fruit all over the world. It is also rich in bioactive compounds, especially mangiferin, a xanthone glucoside. Numerous pharmacological activities of mangiferin have been documented discovered, including anti-inflammatory, antioxidant, and anticancer actions [78].

Several works have suggested the anticancer ability of mangiferin in several cancers. One study found that mangiferin inhibited A549 lung cancer cell cycle and activate apoptosis (programmed cell death) in vitro by decreasing the expression of anti-apoptotic genes and arising pro-apoptotic genes [79]. In animal model experiments have also revealed the anti-cancer effects of mangiferin against HCC. For example, a study on rats with induced liver cancer showed that mangiferin administration significantly reduced tumor growth and improved liver function markers [80].

The mechanisms behind mangiferin's anti-cancer actions in HCC are thought to involve influence ofdifferent signaling pathways, Wnt/β-catenin pathways [81]. Inhibiting the initiation of these pathways, mangiferin has been reported to engender cell cycle inhibition and death in HCC cells. According to these outcomes, mangiferin may someday be developed as a natural anti-cancer agent for the HCC management.

Guava and quercetin in HCC prevention and treatment

Guava*(Psidium guajava)*is another exotic fruit that has been investigated for its capability in treating HCC. Quercetin, a flavonoid having antioxidant, anti-inflammatory, and anticancer effects, is present in guava in significant concentrations [82].

Several investigations have shown that quercetin may stop HCC cells from multiplying and growing. One study found that quercetin decrease cell viability and prompt apoptosis in HCC cells by the incite of caspase-3 and caspase-9 pathways [83]. Another evidence that quercetin suppress the metastasis of HCC cells via suppressing the activity of matrix metalloproteinases (MMPs) [84].As well its direct target on HCC cells, quercetin has also been demonstrated to modify a numerous of signaling pathways regulate in the initiation and development of HCC. For example, quercetin has been demonstrated to prohibit the PI3K/Akt/mTOR signaling pathway, which is commonly dysregulated in HCC and performs a vital part in tumor growth and survival [85]. Further, quercetin has been shown to regulate the Wnt/β-catenin signaling axis, is also regularly triggered in HCC and promotes cell proliferation and survival. By inhibiting this pathway, quercetin can effectively suppress HCC growth and metastasis [86]. Furthermore, the *Vijayakumar, K et al., 2019* revealed the ethanolicextract of guava leaf and their isolated compounds has quercetin has good potential to decrease the cytotoxicity induce by CCl-4 in HEPG2 cell line [87]. The guava extract induces apoptosis via mitochondria disfunction in HCC [88]. Quercetin from guava has also been shown to enhance the activity of NK cells and T cells, as well as escalate the production of cytokines involved in the immune response against HCC [89]. These results imply that quercetin and guava extract consist the ability to be improve as a natural anti-cancer agent for HCC prevention and treatment.

Pineapple and bromelain in HCC prevention and treatment

It has been noted that the proteolytic enzyme bromelain, which is contained in the stem and fruit of pineapple, has anti-inflammatory, immunomodulatory, and anticancer properties [90]. In colorectal cancer, bromelain have inhibition properties against tumor growth by generate ROS and autophagy [91]. For instance, in a study on Hep G2 cell line, bromelain treatment trigger caspase-dependent apoptosis and cell cycle arrest, while also reducing cell migration and invasion [92]. Pineapple bromelain has been found to induce autophagy throughout the incitement of the AMPK pathway in liver [93]. Bromelain has also been discovered to improve the antitumor effects of chemotherapy drugs, such as 5-fluorouracil, by making cancer cells more responsive to the therapy [94].

Pineapple also contains other bioactive compounds with potential anticancer properties, such as quercetin and kaempferol [95]. Moreover, Kaempferol, another flavonoid found in pineapple, has also been divulged to have anticancer effects in HCC, including the enhanced of apoptosis and suppress of cell proliferation and

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invasion [96][97]. While the evidence on the use of pineapple, Kaempferol and bromelain in HCC prevention and treatment is limited, these exotic fruits and their bioactive compounds hold promise as potential adjuvant therapies for HCC. Further preclinical and clinical work are integral to evaluate their effectiveness and assurance in HCC patients, as well as to explore their potential interactions with other medications.

Overall, the modulation of angiogenesis, inflammation, and immune response by exotic fruits and their bioactive compounds may contribute to their potential in HCC prevention and treatment. To completely understand the processes underlying these benefits and to investigate their potential in clinical applications, additional research is required.

Clinical evidence on the efficacy of exotic fruits in HCC prevention and treatment

Clinical evidence also encourages ability of exotic fruits in HCC Prevention as well as care. In a clinical trial, the administration of a papaya leaf extract supplement to HCC patients was found to improve liver function and decrease tumor marker levels [98][99]. Further clinical research reported that the imbibed of a mango pulp extract supplement was linked with reduced liver damage and oxidative stress in liver disease are experience by patient [100]. Similarly, in individuals with liver illness, guava leaf extract supplementation substantially lowered liver enzymes and signs of oxidative stress, according to a research of *Sharma et al., 2022* [101].

Extensive research efforts are essential to ascertain the efficacy and assurance of exotic fruits and their bioactive compounds in HCC prevention and therapy, despite the encouraging data. To establish their practical clinical effectiveness, large -scale clinical trials with extended durations are imperative [102]. Moreover, standardized and quality-controlled extracts or supplements of exotic fruits should be developed to ensure consistency in bioactive compound content and dosages [103]. Finally, potential interactions with other medications should be thoroughly evaluated to ensure the safety of using exotic fruits as a complementary or alternative therapy for HCC

Challenges and limitations of using exotic fruits in HCC prevention and treatment

While exotic fruits show potential as a bioactive compound for HCC management, to overcome these issues and show their therapeutic utility, additional study is required.

Bioavailability and metabolism of exotic fruit compounds

The amount of an active ingredient that is ingested or administered that makes it into the bloodstream and eventually reaches the intended tissues is referred to as bioavailability [104]. The structure and composition of the chemicals, the form and dosage of the fruit, the individual's gut flora, and genetic make-up all have an impact on the bioavailability of bioactive compounds in exotic fruits [105].

Emergingevidence suggest that low bioavailability of certain exotic fruit compounds, such as mangiferin and curcumin, due to their poor solubility and stability in the gastrointestinal tract. Research have to explored various strategies, to increase the bioavailability of active compounds, with the help of nanotechnology, emulsion and encapsulations [106][107].

Exotic fruit component’s effectiveness in avoiding or alleviating HCC is significantly impacted by how well they are metabolized. The liver serves as the main location for metabolism, where enzymes such cytochrome P450 and UDP-glucuronosyltransferases catalyze the biotransformation of substances into more excretable and water-soluble metabolites [108]. According on their concentration and length of exposure, reactive intermediates produced by the metabolism of exotic fruit chemicals may have either positive or negative effects on liver cells [109]. Additionally, interactions of exotic fruit compounds with other medicines or food ingredients may affect their metabolism and bioavailability. For instance, it is well -known that grape fruit increase the bioavailability and toxicity of a number of drugs by boosting thte activity of cytochromeP450 enzymes [110]. The absorption and metabolism of exotic fruit components must therefore be better understood in order to maximize their application in HCC prevention and treatment. Additionally, studies should look into possible drug interactions and negative consequences

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of using exotic fruits with other prescription drug s or nutritional supplements [111].

Standardization and quality control of exotic fruit extracts and supplements

The use of exotic fruit extracts and supplements for HCC prevention and treatment faces significant challenges with regard to standardization and quality control. Exotic fruit cultivars, growing environments, and bioactive compounds content and composition of the fruit [112]. As a result, it's critical to check that the extracts and supplements utilized in research or clinical trials have reliable and effective concentrations of the necessary bioactive substance.

The development of standardized extraction and purification techniques for certain bioactive compounds is one approach to overcoming this difficulty. This can help minimize the presence of potentially dangerous pollutants and maintain constant quantities of the desired compounds in the extracts or supplements [113][114].

Maintaining quality control is equal vital in guaranteeing the safety and effectiveness of exotic fruit extracts and supplements. This entails verifying the identifications and purity of the compounds, as well as conducting tests to detect the presence of contaminants such as heavy metals, pesticides and microorganisms [115][116].

Additionally, there may be hazards associated with using supplements and extracts from exotic fruits with other treatments due to possible drug interactions. To ensure the effectiveness and safety of these combinations, it is essential to carry out both preclinical and clinical investigations [117].

Finally, the lack of regulatory oversight in the production and marketing of exotic fruit supplements can be a limitation in their applicationin HCC prevention and treatment. The absence of standardized regulations can lead to inconsistencies in product quality and efficacy, Along with the possibility of incorrect or misleading assertions [118][119].

Conclusion and future directions

In summary, exotic fruits contain high levels of secondary metabolites that hold promise in preventing and treating HCC. These compounds functions by inhibiting pathways that promote cell proliferation and survival, triggering apoptosis and autophagy, and influencing processes like angiogenesis, inflammation, and the immune response. Both preclinical and clinical studies have offered evidence supporting the potential of exotic fruits in HCC prevention and treatment. Nonetheless, several challenges and limitations remain, including understanding the bioavailability and metabolism of these compound, potential interactions with other medications and ensuring the quality and standardization of exotic fruit extracts and supplements.

Future research should prioritize addressing these challenges and limitations while delving deeper into the mechanisms of action of exotic fruit compounds. Additionally, to establish the safety and efficacy of exotic fruits as complementary or alternative treatments for HCC, large -scale randomized controlled trials are essential. It is also crucial to explore the possibility of synergistic effects when combining exotic fruits with traditional therapeutic approaches.

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