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EDITORIAL

Therapeutic potential of kakkatin derivatives against hepatocellular carcinoma

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Abstract

In this article, we commented on the work done by Jiang *et al*, where they synthesized a kakkatin derivative, 6-(hept-6-yn-1-yloxy)-3-(4-hydroxyphenyl)-7-methoxy-4H-chromen-4-one (HK), and investigated its antitumor activities and mechanism in gastric cancer MGC803 and hepatocellular carcinoma (HCC) SMMC-7721 cells. HK was evaluated for its antitumor activity as compared to kakkatin and cisplatin. This article focused on various risk factors of HCC, the mechanism of HCC progression and molecular targets of the kakkatin derivative, and limitations of available treatment options. HCC is a predominant form of primary liver cancer characterized by the accumulation of multiple gene modifications, overexpression of protooncogenes, altered immune microenvironment, and infiltration by immune cells. Puerariae flos (PF) has been used in traditional medicine in China, Korea, and Japan for lung clearing, spleen awakening, and relieving alcohol hangovers. PF exerts antitumor activity by inhibiting cancer cell proliferation, invasion, and migration. PF induces apoptosis in alcoholic HCC *via* the estrogen-receptor 1-extracellular signal-regulated kinases 1/2 signaling pathway. Kakkatin isolated from PF is known as a hepatoprotective bioflavonoid. The kakkatin derivative, HK, exhibited anticancer activity against HCC cell lines by inhibiting cell proliferation and upregulating nuclear factor kappa B subunit 1 and phosphodiesterase 3B. However, further preclinical and clinical studies are required to establish its therapeutic potential against HCC.

Key Words: Hepatocellular carcinoma; Antitumor; Kakkatin; Protooncogenes; Cisplatin

Core Tip: The heterogeneity of tumor cells and their ability to migrate, invade, and metastasize distant tissue makes diagnosing and developing a cancer treatment difficult. Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths, and current therapies are either only effective at the early stage or have side effects. Puerariae flos-based treatment of HCC has shown a better potential to treat HCC than the known chemotherapeutic drug cisplatin. Kakkatin and its derivative 6-(hept-6-yn-1-yloxy)-3-(4-hydroxyphenyl)-7-methoxy-4H-chromen-4-one, derived from puerariae flos, were used as treatment against HCC and compared with cisplatin.

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INTRODUCTION

As the sixth most frequently diagnosed cancer worldwide, hepatocellular carcinoma (HCC) has the third highest mortality rate among all cancers[1]. It is a complex multistep chronic liver disease defined by the accumulation of multiple genomic and epigenomic changes that lead to loss of growth control, suggesting the role of several parallel pathways driving oncogenesis[2]. HCC constitutes more than 75% of total liver cancers.

It is estimated that low-income and middle-income nations, especially those in Eastern Asia and sub-Saharan Africa, account for about 85% of instances of HCC[3]. Age, sex, and geography are essential factors in the prevalence and severity of HCC. In Japan, North America, and European countries, the average age of HCC onset is 60 years and above [4]. In most parts of Asian and African countries, the age of onset is between 30 years and 60 years[5].

HBV and hepatitis C virus dominate the etiology of liver carcinoma worldwide, with 54% of cases attributed to HBV and another 31% to hepatitis C virus[2]. In addition, excessive abuse of alcohol, major metabolic disorders such as obesity, diabetes, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, and toxins are well-established etiological factors of HCC[6]. Nonalcoholic steatohepatitis has become an emerging risk factor for HCC. Following the onset of hepatic steatosis, additional factors, including obesity, insulin resistance, and genetic alterations, function as "second hits" or "multiple parallel hits" at the cellular level, ultimately resulting in hepatocarcinogenesis[7].

Conventional cancer therapies like surgery are effective at the early stage only. Moreover, surgical resection increases the risk of metastases by causing cancer cells to disseminate into the bloodstream and suppressing antitumor immunity. It also upregulates cell adhesion molecule expression in nearby organs and recruits immune cells that can ensnare cancer cells, inducing alterations in the target tissue and cancer cells and facilitating their migration and invasion to that organ [8]. Radiation can damage healthy neighbor cells, tissues, and organs, and cancer cells often develop resistance toward chemotherapy, making these treatment options futile[9]. A widely used HCC drug, sorafenib, is only effective in 35%-43% of cases and is known for side effects like diarrhea and skin reactions[10].

Cancer cell metastasis and invasion of distant organs continue to be the primary causes of cancer-related deaths globally. Developing antimetastatic therapies is hampered by the difficulty in identifying the nature of tumor cells that have spread to and colonized distant sites. Therefore, it is crucial for cancer treatment to target the growth and metastasis of cancer cells[11].

For the last few decades, interest in the use of phytomedicine has increased. Plant-based medicines are preferred and used along with chemotherapy drugs since they are believed to have fewer side effects. One such herb, puerariae flos (PF), a flower-based medicine, is used to treat HCC. It is home to many metabolites and is used against alcoholism and cures alcoholic liver disease. Kakkatin is an isoflavonoid isolated from PF. Kakkatin and its derivative 6-(hept-6-yn-1-yloxy)-3-(4-hydroxyphenyl)-7-methoxy-4H-chromen-4-one (HK) show antitumor and inhibitory activity on HCC and gastric cancer cell lines, targeting the cyclic adenosine 3,5-monophosphate (cAMP) pathway (Figure 1)[12].

PATHOPHYSIOLOGY OF HCC

Transcriptomics and genomic characterization of HCC revealed its complex heterogeneity and dynamic molecular and clinical features. HCC is characterized by increasing dedifferentiation of hepatocytes, enlarged pleomorphic nuclei, increased nuclear-cytoplasm ratio, multinucleated hepatocytes, pseudoacini, irregular trabeculae, and unpaired visceral arteries[13]. Less than 1 mm dysplastic foci or ≥ 1 mm dysplastic nodules are precancerous stages further categorized into grades, *i.e.* low-grade and high-grade dysplastic nodules with potential malignancy. Initial stage HCC is characterized by the presence of indistinct nodules (< 2 cm) and stromal invasion. Well-differentiated HCC shows distinct nodules (< 2 cm or > 2 cm), vascular invasion, and metastases besides stromal invasion[14]. Early-stage HCC can be effectively treated by local ablation, surgical resection, or liver transplantation[15].

Growth factor signaling, cell differentiation, angiogenic factors, tumor microenvironment, and immunity disruption pathways are involved in neoplastic transformation and liver carcinogenesis. The elevated expression of immune repressing cytokines, for instance, interleukin (IL)-4, IL-5, IL-8, and IL-10, accompanied by decreased immune-inducing cytokines, namely, IL-6, tumor necrosis factor (TNF), and interferon gamma, promote tumor metastases and hinder

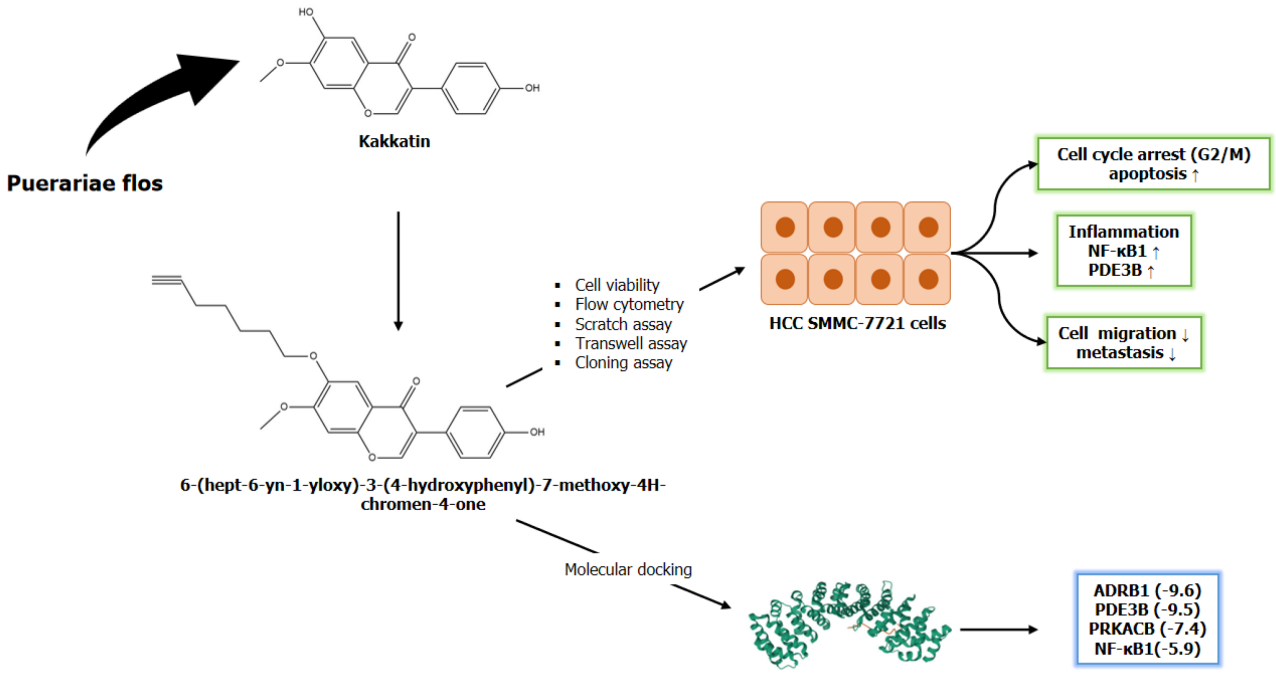

Figure 1 Intervention of 6-(hept-6-yn-1-yloxy)-3-(4-hydroxyphenyl)-7-methoxy-4H-chromen-4-one, a kakkatin derivative, induces the activation of the apoptotic pathway and inhibition of cell proliferation, migration, invasion, and metastasis in the hepatocellular carcinoma cell line SMMC-7221. A kakkatin derivative formed by the introduction of a competing group, hept-6-yn-1-yl ethane sulphonate, to the phenolic hydroxyl group of the kakkatin structure was explored for its antitumor activity in hepatocellular carcinoma (HCC) SMMC-7221 cells. Binding energy (kcal/mol) of 6-(hept-6-yn-1-yloxy)-3-(4-hydroxyphenyl)-7-methoxy-4H-chromen-4-one with phosphodiesterase 3B (PDE3B), adrenoceptor beta 1 (ADRB1), protein kinase cyclic adenosine 3,5-monophosphate-activated catalytic subunit beta (PRKACB), and nuclear factor kappa B subunit 1 (NF-κB1) was checked by molecular docking. Real-time reverse transcriptase-PCR was performed to validate upregulation of NF-κB1 and PDE3B expression, which in turn inhibit cancer cell invasion, migration, and HCC progression.

diagnosis[16].

Regardless of diverse risk factors, one common mechanism driving HCC comprises a vicious cycle of uncontrolled liver cell death compensated with increased cell division and proliferation, eventually stacking up to genomic instability and carcinogenesis[17]. In most HCC cases, the gene promoter of telomerase reverse transcriptase, tumor suppressor p53, and catenin beta-1 are the dominantly mutated genes[18,19]. cAMP is a second messenger in numerous signaling pathways that regulate cell proliferation. An increase in the intracellular levels of cAMP is directly proportional to the proliferation of cells, but in transformed hepatocytes, elevated cAMP results in halted proliferation and downregulation of liver cancer cells[20]. Phosphodiesterases (PDE) are intracellular enzymes that are known regulators of cAMP and cyclic guanosine 3′,5′-monophosphate. PDE3 is an intracellular myocardial and vascular tissue enzyme. The PDE3 family is further classified into two subfamilies, PDE3A and PDE3B. Similar but distinct genes encode both and have specific functions, but their expression pattern coincides in different tissues and cells[21]. Isoforms of PDE3B are comparably more expressive than PDE3A in energy homeostasis-regulating tissues such as adipose, liver, and pancreas[22].

Nuclear factor kappa B (NF-κB) a key transcription factor responsible for the expression of proinflammatory makers such as cytokines and chemokine. The canonical and noncanonical (or alternative) signaling pathways are the two main mechanisms that activate NF-κB. While the noncanonical NF-κB pathway appears to have evolved as an additional signaling axis that collaborates with the canonical NF-κB route to regulate functions of the adaptive immune system, canonical NF-κB is functionally involved in almost every aspect of immune responses[23].

Liver cancer develops in the backdrop of inflammation, proving that HCC is not connected to random probability but a series of accumulated microenvironmental factors. Thus, the research should focus on specific factors responsible for negative alterations in the hepatic microenvironment, producing an adverse carcinogenic field effect and increasing the likelihood of malignancy[24].

The NF-κB pathway is involved in the crosstalk between precancerous/cancerous and immune cells in this inflammation-cancer axis. NF-κB is directly and indirectly involved in the progression of liver carcinogenesis and is a potential treatment target[25]. Activation of NF-κB regulates inflammation by activating transcription of various genes such as IL-1, IL-2, IL-8, TNF-α, anti-apoptotic factors such as Fas, B-cell lymphoma 2, caspases, and survivin, angiogenic factors, and cell-adhesion molecules[26], thus promoting cell survival, proliferation, angiogenesis, adhesion, invasion, and migration. A study on mice showed that conditional deletion of NF-κB essential modulator/IkappaB kinase gamma, which usually activates NF-κB subunit 1 (NF-κB1), promotes cancer development[27]. The inhibition of NF-κB increased the risk of hepatocarcinogenesis by sensitizing hepatocytes to spontaneous apoptosis[27].

MEDICINAL POTENTIAL OF KAKKATIN SOURCE, PUERARIA LOBATE

PF, also known as 'kudzu flower', is a traditional Chinese medicine extracted from dried-up flowers of Pueraria lobate. It is used for clearing lungs, spleen awakening, and relieving alcohol hangover. In China, PF is extensively used for the management of alcohol-driven HCC[28]. In addition, recent pharmacological studies divulged their biological significance as hepatoprotective, antitumorigenic, antidiabetic, anti-inflammatory, and antioxidative, explaining traditional use[29]. PF is home to many metabolites, such as flavones, isoflavones, saponins, and one phenolic acid identified *in vivo* [30].

According to cellular experiments, alcohol-treated HepG2 cells were shown to be less likely to increase and migrate when exposed to serum containing PF. This suggests that PF may influence alcohol-related HCC. PF induces apoptosis in alcoholic HCC, targeting the estrogen-receptor 1-extracellular signal-regulated kinases 1/2 signaling pathway. The extracellular signal-regulated kinases 1/2 pathway regulates cell proliferation, differentiation, survival, and apoptosis. Hence, this pathway plays a significant role in cancer progression[31]. By upregulating estrogen-receptor 1, PF is known to negatively regulate the proliferation and migration of cells in alcoholic HCC attributing to its numerous components, including genistein, tectorigenin, daidzein, glycitein, 2-propenoic acid, 3-(3,4,5-trimethoxyphenyl), butylated hydroxytoluene, 6-methoxy-4-methylcoumarin, 1-(4-chlorophenyl) isoquinoline, 9-hydroxyoctadeca-10,12-dienoic acid, and 2-cyclopentene-1-tridecanoic acid[32]. Assessed PF metabolites against liver injury in rodents due to alcohol abuse and the hepatoprotective properties of PF may be attributed to the effective forms of phase II conjugated metabolites of isoflavonoids[33].

One such isoflavone, kakkatin (molecular formula: 7-methoxy-6,4'-dihydroxyisoflavone), a polyphenolic compound isolated from PF, *Fusarium spp.*, Wisteria brachybotrys, fungi, and actinomycetes, is a known hepatoprotective bioflavonoid. Flavonoids have various physiological processes like antioxidant, anti-inflammatory, antimicrobial, hypoglycemic, and antitumor properties in addition to being hepatoprotective. Flavonoids enhance anti-inflammatory mechanisms by inhibiting the NF-κB and TNF-α activity or activation of adenosine monophosphate-activated protein kinase. One example is kaempferol, which sustains anti-inflammatory effects by negatively regulating NF-κB and TNF-α[34]. Hence, the metabolites found in PF are known to be protective against various diseases.

ANTITUMOR ACTIVITY OF HK (KAKKATIN DERIVATIVE) OVER KAKKATIN

Metabolites from PF are well known to have hepatoprotective effects. Kakkatin, isolated from dried PF, is a polyphenolic compound. Like other polyphenolic compounds, adding a different substituent on the parent nucleus may improve its functional properties. Its antitumor efficacy against HCC and gastric cancer remains unexplored. Jiang *et al*[12] confined their study to liver cancer and gastric cancer. Liver and gastric cancers have similar risk factors, such as alcohol consumption, that are responsible for the progression of these cancers. They chose these two cancer cell lines for *in vitro* validation of the kakkatin derivative, HK. HK is produced by adding the competing group hept-6-yn-1-yl ethane sulphonate to the phenolic hydroxyl group of the kakkatin structure.

Jiang *et al*[12] investigated HK for its antitumor efficacy and probable mode of action on HCC and gastric cancer cells [12]. Liquid chromatography-mass spectrometry and 1H nuclear magnetic resonance spectroscopy characterization confirmed the molecular structure of HK. Various *in vitro* experiments were conducted to compare the anticancer effects of HK, which were studied in HCC SMMC-7721 cells and gastric cancer MGC803 cells. The SMMC-7221 cell line used by Jiang *et al*[12] is a human HCC cell line known to be highly invasive when compared with other liver cancer cell lines, such as HepG2, which is less invasive[35].

The IC50 value of HK and kakkatin on gastric cancer cells were not significantly different from one another. However, the IC50 value of HK on HCC cancer cells was shown to be up to 30 times lower than the IC50 value of kakkatin and less than that of the positive drug cisplatin, a known chemotherapy drug with cancer cell inhibitory function[12,36]. The experiments demonstrated that HK attenuated colony formation in HCC SMMC-7221 cells exponentially with an increase in HK dose concentration by inhibiting cell proliferation, migration, and invasion. It showed a greater effect than cisplatin in a time-dependent and dose-dependent manner. Treatment with HK resulted in an increase in apoptotic and necrotic cells in a concentration-dependent and time-dependent manner. The count of early and late apoptotic and necrotic cells increased when HK concentration increased over time relative to the control.

The result of the examination of cell cycle stages indicated that following a 24-h treatment, HK-induced cell cycle arrest was dose-dependently produced in SMMC-7221 cells, as evidenced by an elevation in the proportion of cells in the G2/M phase and an enhanced G0/G1 distribution of cells. The G2/M phase is a checkpoint in the cell cycle; its arrest signifies downregulation of cell proliferation and induction of apoptosis[37].

To comprehend the mechanism and possible targets of HK in SMMC-7221 cells that are primarily responsible for inducing apoptosis, network pharmacology analysis was performed. This suggests a relationship between HK and the cAMP signaling pathway and the generation of neutrophil extracellular traps (NETs). NETs show cytotoxic effects against the cancer cells by releasing various components that can kill and inhibit the growth of cancer cells[38]. NETs can destroy endothelial cells, thus hampering blood supply to tumor cells. In contrast, studies have shown the metastasis-promoting nature of NETs[39].

NF-κB1, one of the major targets associated with cAMP along with adrenoceptor beta 1, PDE3B (PDE family), and protein kinase cAMP-activated catalytic subunit beta (protein kinase A family) downstream of the cAMP pathway, were used for further validation of the inhibitory effects of HK on cancer cells. Molecular docking using AutoDock Tools software followed by real-time reverse transcriptase-PCR verification were performed to understand the relationship

between HK and protein targets. In silico results showed good binding activity of these four genes used as receptor molecules with the ligand molecule HK. Low binding energy indicated good binding affinity of HK with target proteins with stable configuration. Real-time reverse transcriptase-PCR results showed elevated mRNA expression of *NF-κB1* (p105/p50), one of the five subunits of NF-κB, and *PDE3B*, both responsible for the decrease in cancer migration and invasion, pointing towards tumor suppressive properties of HK[40]. Increased NF-κB1 and PDE3B inhibit carcinogenesis and metastasis, respectively.

CONCLUSION

Kakkatin derivative HK shows better antitumor activity in SMMC-7721 cells, a human HCC cell line, over gastric cancer MGC803 cells. HK was shown to interact with key targets related to the cAMP signaling pathway, including PDE3B, adrenoceptor beta 1, NF-κB1, and protein kinase cAMP-activated catalytic subunit beta. These targets are known to regulate crucial cellular processes such as apoptosis, migration, and invasion, reinforcing the multifaceted mode of action of HK in inhibiting HCC progression. This illustrates the specificity of HK to HCC and the considerable suppression of SMMC-7721 proliferation, migration, invasion, and metastasis that it exerts by stimulating cell cycle arrest and apoptosis. The known involvement of PF metabolites in treating liver-related anomalies might be the reason for the specificity of HK against HCC.

The liver and gastric tumor biomarker testing may further reveal the presence of drug targets in both cancers. The tumor inhibition effect of HK was seen to be superior to that of kakkatin and cisplatin. The effect was due to the upregulated expression of PDE3B and NF-κB1 target proteins in the cAMP pathway. Further, RNA sequencing to compare and identify the entire gene expression profile of HCC and gastric cancer lines in response to HK can be done to get a more detailed insight into which genes, signaling pathways, and molecular markers, HK influences in each cancer type. Proteome profiling of treated cells to understand protein expression and post-translational modification in response to treatment could help identify critical proteins involved in the mechanism of action of HK and potential resistance mechanisms in gastric cancer cells.

In the future, other liver cancer cell lines such as Huh 7, Huh 7.5, HepG2, Hep 3B, and MHCC97-H should also be explored for the antitumor activity of kakkatin and its derivative HK. Rodent models could be incorporated to further validate the biomarkers identified in *in vitro* human cell lines and improve clinical translation efficiency.

FOOTNOTES

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