Colchicine as A Potential Therapy in Hepatocellular Carcinoma: A Review

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INTRODUCTION

Liver cancer is the seventh most common cancer and the fourth leading cause of cancer death worldwide [1]. Hepatocellular carcinoma (HCC) is the most prevalent malignancy of the liver (75%) [2]. HCC commonly occurs along with cirrhosis, and several risk factors have been identified, with chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatosis hepatic (NASH) as the most common causes. Various available treatments for HCC include liver resection, tumor ablation, trans-arterial chemoembolization (TACE), radioembolization, and chemotherapy such as sorafenib [3]. Despite the available therapies, the prognosis of HCC is poor. A study in China that analyzed 2278 patients diagnosed with HCC found the overall 5-year survival of HCC was 26.6% [4].

Colchicine is an anti-inflammatory medication that has been around for a long time. Colchicine is a low-cost drug with low negative effects. This is an old remedy that has not been printed in quite some time. Recent studies suggest that colchicine may have antitumor effects. A study of 186 hepatitis patients showed that the administration of colchicine prevented and delayed the development of HCC with an average time for the development of HCC in patients treated with colchicine of 222 ± 15 months and 150 ± 12 months in patients with no colchicine therapy. Studies using hepatic and gastric cell cancer also found that colchicine had antiproliferative activity on cancer cells, suggesting its potential as a chemotherapy drug [5,6]. HCC cells, cancer-associated fibroblasts, gastric cancer cells, and cholangiocarcinoma cells all demonstrated dose-dependent anti-cancer effects in previous in vitro and in vivo tests. Colchicine’s anti-cancer actions on HCC cells are due to both the well-known direct colchicine-tubulin interaction and colchicine-induced differential expression of many antiproliferative genes [7].

HCC diverges into 2 subtypes based on major molecular groups, proliferative and non-proliferative. Proliferative HCC is a phenotype of hepatitis B that has...
moderate to poor cellular differentiation, high \( \alpha \)-fetoprotein levels, frequent vascular invasion, significant tumor recurrence, and poor prognosis. Hepatocellular carcinoma non-proliferative is one type of HCC phenotype that is more benign and less aggressive when compared to the others, with well-to-moderately differentiated tumors on histologic examination, lower levels of \( \alpha \)-fetoprotein, and better outcome. Non-proliferative HCC is predominant in hepatitis C and alcohol-related HCC [8]. The phenotype of non-proliferative tumors is distinct. CTNNB1-mutated HCC is a homogeneous subtype within this molecular subgroup with cholestasis and architectural features that are micro trabecular and pseudoglandular. A non-proliferative subtype with a steatohepatitis characteristic has a gene expression pattern comparable to mature hepatocytes (G4). Proliferative HCC, on the other hand, is frequently misclassified and includes tumors with progenitor characteristics [9].

Colchicine anti-cancer actions on HCC cells are caused by the well-known direct colchicine-tubulin interaction as well as colchicine-induced differential expressions of multiple antiproliferative genes, such as AKAP12, TGFβ2, and MX1 [5,10]. Thus, colchicine may have a potential role in proliferative HCC. This study aimed to review the potential properties of colchicine as potential chemotherapy in HCC patients.

METHODS

Article searching was conducted with the three electronic databases, consisting of PubMed, ProQuest, and Cochran, to find journals that contain information regarding colchicine as chemotherapy in hepatocellular carcinoma. The search terms were managed with Boolean logic as seen in the following Table 1. The literature search was performed from June 4th to 26th, 2021. The journal articles were screened using PICO (P: hepatocellular carcinoma patients, I: colchicine, C: standard systemic therapy, and O: survival rate cancer). In the meantime, the exclusion criteria were contained in a journal that had discussed colchicine as a preventive therapy, not associated with hepatocellular carcinoma or hepatoma. All articles found were reviewed by four authors independently. Any disagreement among reviewers regarding study qualities was solved by further discussion. Studies found were critically appraised to determine their eligibility. Details regarding types of study, research subjects, intervention used in the study (e.g., the dose of colchicine), and outcomes were extracted.

RESULT

A total of 46 articles that discuss the impact of colchicine in hepatocellular carcinoma were identified using three databases including ProQuest, PubMed, and Cochrane Library. Published papers about colchicine as preventive therapy in hepatocellular carcinoma were identified, and 39 were excluded. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart can be seen in Figure 1. Seven articles were screened for titles and abstracts, and three articles were excluded owing to full-text unavailability. In conclusion, there were 3 articles reviewed. Furthermore, the information about the characteristics of the studies can be seen in Table 2. A critical appraisal based on the Centre of Evidence-Based Medicine Oxford University criteria was shown in Table 3.

DISCUSSION

Current Hepatocellular Carcinoma Therapy

Currently available treatments for HCC include liver resection, liver transplantation, trans-arterial chemoembolization (TACE), radioembolization, and chemotherapy. The therapy’s baseline of intact liver function is Child-Pugh A without ascites, which is regarded as an ideal condition for achieving the best results. Except in the case of transplantation, which is reserved for patients with decompensated or end-stage liver disease, this need applies to other therapeutic alternatives. A multiparametric evaluation was used to determine surgical candidacy, which includes compensated Child-Pugh class A liver function with a model for end-stage Liver disease (MELD) score of 10 that must be matched with the grade of portal hypertension, an acceptable amount of remaining parenchyma, and the ability to use a laparoscopic or minimally invasive approach. The above considerations should result in a perioperative mortality rate of 3% and a morbidity rate of 20% with a postsurgical severe liver failure rate of 5% [11].

Since 2017, sorafenib has been demonstrated to be effective as the first-line treatment while regorafenib is effective as the second-line treatment if sorafenib fails to work. In the first-line therapy, Lenvatinib has...
been proven to be non-inferior to sorafenib; however, no viable second-line therapy has been studied after Lenvatinib. Cabozantinib has been shown to improve OS from eight months (placebo) to 10.2 months in the second and third-line trials. Based on uncontrolled phase II data, the United States Food and Drug Administration (FDA) approved Nivolumab for second-line treatment, but not the European Medicines Agency (EMA) [11].

In patients with non-cirrhotic liver HCC, surgical resection is suggested as the treatment of choice. Indications for HCC resection in cirrhosis should be established on a multiparametric composite assessment of liver function, portal hypertension, hepatectomy extent, the estimated volume of future liver residual, performance status, and co-morbidities. When the hepatic function is preserved and sufficient remnant liver volume is maintained, liver resection (LR) is suggested for single HCC tumors of any size, but particularly for tumors > 2 cm. Within the Milan criteria, liver transplantation (LT) is suggested as the first-line treatment for HCC, but it is not suited for resection. The Milan criteria serve as a baseline for selecting

Figure 1. PRISMA Flowchart for studies of colchicine as preventive therapy in hepatocellular carcinoma

Representative data for the clinical question (PICO Criteria), Review article, clinical study, case control, case series with the full text available in English

Restricted discussion about colchicine as preventive therapy, yet not associating with hepatocellular carcinoma or hepatoma
Table 2. Characteristics of the studies

| Author, Years, country | Types of study | Subject | Intervention | Outcome | Result |
|------------------------|----------------|---------|--------------|---------|--------|
| Liu et al, 2005 China [25] | Experimental | HA22T/VGH Cells | Administration of colchicine at 0-8 ng/mL prior to irradiation at various dose (0, 1, 2, 4, 8 Gy). | Surviving cell fraction were measured. | Pre-treatment administration of colchicine enhanced the sensitivity for radiotherapy. |
| Lin et al, 2013 China [6] | Experimental Study | Two human HCC cell lines (HCC24/KMUH, HCC38/KMUH) and two human cancer associated-fibroblast (CAF) cell lines (F28/KMUH, F59/KMUH) Mice injected with cancer cells (HCC38/KMUH and F28/KMUH) | Each cells seeded in 96-well culture plate with serum containing medium for 24 hr then the medium replaced by serum free medium with various colchicine concentrations (0, 2, 6 ng/mL). Epirubicin were also administered in the same manner. Colchicine was also administered (0.07 mg/kgBB) to mice which developed tumor sized 4–5 mm. | Cells proliferation | The cell proliferation can inhibited on both HCC cell lines, similar effects with the dose in 1 μg/mL epirubicin. Colchicine dose 0.07 mg/Kg/day x 14 days can lowered the tumor volume ratios, slowing the tumor growth rates and large percentages of tumor necrotic areas than control mice (all P < 0.05). |
| Lin et al, 2021 China [10] | Cohort prospective | 13 patients received colchicine compared to sorafenib | Colchicine 1 mg orally three times per day after meal for 4 days and discontinuation in the following 3 days (one cycle). Cycle was repeated until participant was unable to take colchicine. | Adverse events | There was no huge contrast ence in mortality, median survival, and overall survival between two groups (all p > 0.2). Taking everything into account, the novel colchicine measurement plan is clinically achievable and can be applied in the palliative treatment of cutting-edge HCC particularly dependent on the expense adequacy thought. |

Table 3. Critical appraisal

| Article | Validity | Relevance |
|---------|----------|-----------|
| Liu et al, 2005 [25] | + | - | - | - | + | + | + | 2b |
| Lin et al, 2021 [6] | + | - | - | - | + | + | + | 2b |
| Lin et al, 2021 [10] | + | - | - | - | + | + | + | 1b |

Note: (+) = signifies which a parameter mentioned in a significant exists in the literature; (-) = denotes that a parameter listed in the critical study is not present; 1b = evidence from at least one randomized clinical trial with control group; 2b = the evidence comes from at least one research result with a quasi-experimental design.
Anticancer Properties of Colchicine

Colchicine is an alkaloid derived from Colchicum autumnale. It is widely used as an anti-inflammatory agent in acute gout disease [12]. Colchicine also acts as a microtubule destabilizer that will bind to tubulin, interfering with the bond with microtubules [13–16]. Microtubule had been considered an anticancer drug target due to its role in mitosis and formation of dynamic spindle apparatus [17–21]. Microtubule binding in disrupted cells will affect the regulation of the mitotic spindle which will later disrupt the cell cycle in general and cause cell death [22]. Colchicine has also been shown to increase free tubulin in cells in mitochondrial metabolism in cancer cells through inhibition of voltage-dependent anion channels from the mitochondrial membrane [23]. Recently, colchicine is not also known as an anti-inflammatory agent, but it also has curative effects on several conditions such as severe hepatitis, post hepatic cirrhosis, biliary cirrhosis, and hepatic cirrhosis induced by alcohol. Furthermore, recent studies also found that colchicine has effects on malignancies, such as breast cancer, cervical, esophageal, lung, gastric, and chronic granulocytic leukemia [24]. In HCC cells, colchicine was found to sensitize human HCC cells to radiation [25].

The role of colchicine in cancer development may be through several mechanisms. A study by Lin et al. explains that colchicine has an anti-proliferative effect by increasing the regulation of the Dual-specificity phosphatase-1 (DUSP1) gene, which is important in the inactivation of mitogen-activated protein kinase (MAPK) that has a role in cell proliferation and apoptosis [5,26]. Zhang et al. [24] also found similar results that colchicine posed cytostatic and strong cytotoxic effects on gastric cell cancers. Colchicine could also increase the expression of cleaved caspase-3 and pro-apoptotic protein (Bax), decrease apoptosis-suppressed protein (Bcl-2), and upregulate cytochrome c release from mitochondria into the cytoplasm. Furthermore, colchicine could reduce the expression of p-P13K, Akt, and mTOR which play an important role in the regulation of cancer cell development. Colchicine induces caspase-3-dependent apoptosis by forcing the PI3K/Akt/mTOR signaling pathway. In addition, colchicine has also been shown to have an inhibitory effect on tumor volume on the average tumor weight in the gastric cell cancer cell model. Colchicine had also been shown to reduce the

Figure 2. Colchicine mechanism as an anticancer agent
risk of prostate cancer and colorectal cancer in patients with gout. It was possibly explained by the direct interaction between colchicine and tubulin which disrupted the dynamic bonds of microtubules [13,15,16]. The development of prostate adenocarcinoma cells could be inhibited by colchicine [27]. The induction of apoptosis is an important property of anticancer drugs to eliminate cancer cells [28,29]. Further information can be seen in Figure 2.

Colchicine as Antitumor Agent in HCC

Colchicine has its special place on HCC. Colchicine is proven to have an anticancer in the HCC cell model [6]. The administration of colchicine can inhibit the development of a tumor and destroy the tumor-free survival from malignant cells of the tumor [24]. The HCC has a 5-year survival rate of about 8.37%. This rate is based on the clinical symptoms, including the number of involved lymph nodes, metastasis, type of treatment, tumor size, and hepatitis as the main prognostic factors in the survival rate of HCC patients [30]. Nonetheless, the 5-year survival rate related to colchicine has not yet been identified further. A retrospective study with 186 patients as samples found that there was a long-term effect of colchicine on patients with viral hepatitis correlated with cirrhosis incidents that could be prevented, and its development could be pressed to develop HCC. A study from Kuo et al. found that the effect of colchicine prescription on gout patients could decrease the risk of cancer (HR = 0.85, 95% CI, 0.77–0.94; P = 0.001) [31].

As an anticancer agent, colchicine was comparable with another chemotherapy agent as the nonresectable hepatocellular carcinoma standard of care, which was sorafenib. The colchicine group had a higher incidence of biliary tract obstruction (p = 0.0184) than the sorafenib group when it came to serious adverse events. When comparing the incidence of grade 1 or 2 adverse events between the two groups, the colchicine group had a greater incidence of diarrhea (p = 0) while the sorafenib group had a greater incidence of palmar-plantar erythrodysesthesia syndrome (p = 0.0045). Mortality, median survival, and total survival were not significantly different between the two groups (p > 0.2). Colchicine could also be used along with radiation therapy because an in-vitro study suggested that colchicine was able to sensitize HCC cells to radiation in a lower dose (1 and 2 ng/mL). Cell cycle arrest at the G2/M phase was also found at a higher dose of colchicine treatment (8 and 16 ng/mL) [25]. Finally, based on cost-effectiveness, our proposed colchicine dose schedule is clinically practical and has the potential to be used in the treatment of HCC [32].

Colchicine can induce cytotoxic effects as its anticancer function without inhibiting angiogenesis. Antiproliferative effects from colchicine are obtained at 6 ng/mL dosage on HCC cells or equal to 1 ug/mL dosage [6]. Colchicine can also cause different expressions of several genes that have roles in HCC: upregulation of AKAP12, MX1, and TGFβ2. Signaling dysregulation of the TGF-β pathway is known to cause inflammation, fibrogenesis, and immunomodulation in the HCC microenvironment. TGFβ-2 was upregulated in CAFs as well but not in a dose-dependent manner. The increasing regulation of TGFβ-2 contributes to the anticancer effect of colchicine on HCC cells. TGFβ-2 is one of the transforming growth factors from the beta cytokines family. TGFβ-2 can inhibit the growth of portal fibroblast [33]. Furthermore, it can suppress the progress of cancer cell cycles in the G1 phase and induce replicative senescence on HCC cells [34].

On the other hand, colchicine can induce downregulation of C4BPA, HSD11B2, and SEPP1. AKAP12 gene is a member of the A-kinase anchor proteins group linked with kinase A and C protein and phosphatase and has the function to construct protein on viral transduction that controls the activity of developing actin-cytoskeleton in a spatiotemporal manner. The downregulation of AKAP12 on HCC cells can induce the existence of hypermethylation [35]. This gene, later, is going to work as a tumor suppressor that will regulate the cell cycles and decelerate Src-mediated oncogenic signaling and cytoskeletal pathways [35–38]. Colchicine also caused dose-dependent up-regulation from AKAP12 on HCC cells which can hinder cell proliferation. This process is encoded by the MX1 gene, which is a type of GTP-binding protein induced by interferon which has been known to increase cell mortality through caspase-dependent and independent mechanisms [39,40]. Lin et al. [6] argued that the intensity of MX1 regulation on colchicine as the anticancer effect was found in 6 ng/mL dosage. Nevertheless, it was also found that this effect led to tumor mortality inhibition and invasion of the tumor cell [41].

Colchicine’s anticancer effect on HCC is not only through the increasing regulation of MX1. The decreasing of regulation C4BPA, HSD11B2, and SEPP1 is not supported for the development of HCC cells. The protein coded by the C4BPA gene delays the activation from complement cascade through a classic route that is inducted by apoptosis and necrotic cells [42,43]. The binding process of this protein with S protein can delay the ability of S protein to induct phagocytosis activity and apoptosis cells by macrophage [36]. The protein coded by HSD11B2 gen is a type of isozyme II from corticosteroid 11-beta-dehydrogenase that triggers catalyzation activity from cortisone. This protein prevents the activity of mineralocorticoid receptors in the system and protects cells from the development or pro-apoptotic effects of cortisol in the system without the expression of mineralocorticoid [38]. The existence of SEPP1 is a code from glycoprotein extracellular with its
function as protein supply and antioxidant [44]. The decreasing activity of regulation from a gene can increase the possibility of a cell undergoing oxidative stress [6].

Colchicine is found to downregulate DUSP9 expression in HCC cells [6]. DUSP9 has a critical role in the pathogenesis of HCC, particularly in the early stages. MAPK phosphatases (MKPs) regulate MAPKs by dephosphorylating phosphorytrosine and phosphoserine/phosphothreonine residues on extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase, and p38 [45]. It is becoming clear that DUSPs have a role in a variety of cellular functions [46,47]. While dysregulated MAPK signaling is a driver of HCC that is being targeted with treatments, the involvement of DUSPs is unknown.

The only DUSP with elevated expression was DUSP9, which was joined by additional genes such as the HCC markers AFP and glypican 3 (GPC3). The connection between increased expression of DUSP9 and increased expression of both AFP and GPC3 was further verified using TCGA gene expression data. When comparing tumors to neighboring liver tissue and healthy human liver controls, the qPCR assay indicated considerably higher DUSP9 expression in malignancies. DUSP9 was found in four different human HCC cell lines (HepG2, Hep3B, PP5, and Huh7), as well as the human hepatic progenitor cell line HepaRG, but not in the normal human liver cell line THLE-2 [48].

Human HCC patients had higher DUSP9 expression, which is linked to shorter disease-free life and a higher likelihood of disease recurrence after liver resection. RNA sequencing indicated that DUSP9 regulates a variety of activities in HCC cells, including protein kinase activity, apoptosis, and cytoskeleton and extracellular matrix modulation (ECM). HCC recurrence after resection was linked to higher DUSP9 expression. A higher level of DUSP9 was likewise linked to a shorter disease-free survival (DFS) following surgery. Overall survival (OS) was not found to have a significant connection with DUSP9 expression. Higher levels of DUSP9 expression were linked to more advanced HCC characteristics [48].

E26 transformation specific (ETS) and ETS transcription factors are transcriptionally controlled by DUSP9 (TFs). Because ETS TFs are MAPK downstream effectors, this data supports the notion that DUSPs are transcriptionally regulated by MAPK signaling and that they work as part of a negative feedback loop controlling MAPK activity [77,78]. Increased DUSP9 expression in HCC could potentially be a result of abnormal ETS TF activity as seen in many solid tumors [49].

Moreover, colchicine can cause upregulation of GDF15 and IL32 as well as decrease the regulation of APOH in HCC cells. An exaggerated expression of the GDF15 gene can increase DNA synthesis and promote cell proliferation and increase the invasive level of HCC cells [50]. IL32 was overexpressed in HCC cells and suppression from this gene can cause the blockage of

![Figure 3: Summary of the role of colchicine in hepatocellular carcinoma](image)
cell growth and induce apoptosis intrinsically [43]. The protein coded by APOH gen has an anti-angiogenic effect [51]. The different expressions from this gen can affect the enhancement of progression of HCC cells [6]. The mechanism action of colchicine especially in hepatocellular carcinoma is shown in Figure 3.

**Drug Interaction and Potential Adverse Effect**

Colchicine has some interaction possibilities with some drugs and side effects that can appear within daily usage. Colchicine metabolites are absorbed and metabolized by the liver in the cytochrome P450 CYP3A4 and subsequently through the glomerular filtration process together with drugs from the CYP3A4 inhibitor class, such as clarithromycin, anti-HIV drugs, azole groups, calcium channel blockers, and antifungals, or class P-GP group inhibitors (cyclosporine, ranolazine). One of the effects that can be seen is the accumulation of metabolite colchicine results that can affect toxicity in the short or long term [52–58].

A potential cause of the interaction among drugs is also worth noticing, including the interaction between colchicine and drugs from the statin group that has a substrate for CYP3A4 in the liver [59,60]. The interaction between colchicine and drugs from the statin group becomes more complex because both drugs can cause muscle toxicity. It is important to minimize colchicine dosage for those with renal damage such as patients with a history of chronic renal disease or patients who do hemodialysis regularly, even when there is proof of liver damage that can be an important note for this drug prescription [61].

Elderly patients also need to be observed since there is renal insufficiency that can emerge with the age [62]. In addition, in patients with renal insufficiency, colchicine therapy has been reported to have serious problems with certain doses, especially when it is administered with drugs from the CYP3A4 inhibitor group [63,64]. The interaction between colchicine and chemotherapy drugs, such as etoposide, vincristine, and doxorubicin, can also happen due to the substrates from CYP3A4. The decrease in clearance of these drugs will decrease along with the administration of colchicine, and then side effects can also appear. The drug clearance process may be dropped by those drugs which will cause damage. Colchicine and vincristine in the kidney also cause toxicity when the drugs are given at the same time [14].

The existence of side effects from colchicine administration can also emerge in the digestive tract including diarrhea, nausea, and vomiting. Gastrointestinal toxicity can also happen even though it can be done by increasing the dosage of colchicine. Other rare side effects like myopathy, rhabdomyolysis and myelosuppression also need to be noticed [65]. Neuromyopathy can also happen, especially in patients with colchicine usage history and patients with renal damage consuming colchicine [66]. Side effects in form of gastrointestinal and a long suppression from bone marrow are also reported [67]. This is due to CYP3A4-mediated disturbances caused by concomitant administration of colchicine and several chemotherapy drugs. It depends on the availability of metabolites and their inhibitory effect on tubulin structure [18]. Toxicity symptoms that emerge on colchicine administration will experience resolution around 1 week until several months, depending on the discontinuation of drugs and tapering off [68].

The use of colchicine as a preventive therapy, specifically for HCC, needs to be considered because of its potential. Colchicine can be easily bought from the market at a reasonable price, and it is available in many healthcare centers. Anticancer effects on colchicine are also proven by an in-vivo study. The mechanism of colchicine is known to inhibit cancer cells through an inhibitory mechanism on microtubules [13,69,70]. Effects of colchicine on some anticancer drugs are anti-mitotic targeting to work specifically on microtubules which later can block the polymerization and depolymerization of cells so that the usage of cancer drugs begins to be observed and studied further. Drugs with anti-mitotic nature, such as vinblastine, vinorelbine, and vincristine, also target microtubules [66]. Therefore, the use of colchicine and chemotherapy drugs at the same time needs to be observed since they can cause damage from competitive inhibition. Many studies had been done using a modification of colchicine components as cancer cell therapy [16,71].

**CONCLUSIONS**

Colchicine can affect HCC, especially in preventive therapy. The use of colchicine has been shown to affect several in vitro assays on cancer cells with different models. The potential of colchicine as preventive therapy for HCC needs to be studied further and done by some additional tests especially in-vivo tests. Studies on a bigger population also need to be done to see the safety, usage, as well as appropriateness of colchicine on HCC. Further study needs to be done on the interaction between colchicine and other chemotherapy drugs on the cancer cell. The further study aimed to acknowledge direct results on colchicine for HCC cells, especially with an anti-mitotic effect which is on cancer cell drugs needs to be considered since there is a new development and update on cancer these days.

**DECLARATIONS**

**Competing of Interest**
The author(s) declare no competing interest in this study
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