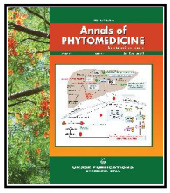
Annals of Phytomedicine 12(2): 21-28, 2023

DOI: http://dx.doi.org/10.54085/ap.2023.12.2.4

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Review Article : Open Access

An insight into the pathological pathways of hepatocellular carcinoma and the role of curcumin on the mediators of carcinoma

Mohd Yusuf, Badruddeen◆, Zeashan Hussain*, Juber Akhtar, Mohammad Irfan Khan and Mohammad Ahmad

Faculty of Pharmacy, Integral University, Lucknow-226026, Uttar Pradesh, India

**Mahatma Gandhi Institute of Pharmacy, Junabganj, Kanpur Road, Lucknow-226401, Uttar Pradesh, India*

Article Info

Article history

Received 18 August 2023

Revised 4 October 2023

Accepted 5 October 2023

Published Online 30 December 2023

Keywords

Carcinoma

Anti-inflammatory

Curcumin

Necrosis

Apoptosis

Immune suppression

Endoplasmic reticulum

Hepatocellular carcinoma

Abstract

Hepatocellular carcinoma (HCC) is a leading global cause of cancer-related deaths, primarily linked to inflammation. Hepatocytes can show varied inflammatory responses due to a wide range of causal factors. Inflammation can either decrease or continue based on the cause and contributing factors. The main factor contributing to immune suppression is chronic inflammation, along with tissue remodeling, genetic changes, and alterations in cellular signaling. Immune suppression causes a loss of the body's ability to combat tumors, leading to the advancement and growth of HCC. Tumor cell processes like DNA damage, necrosis, and ER stress influence immune-surveillance and inflammation, showing a mutual connection. In this article, we explore the present understanding of the initiation of chronic liver injury and inflammation, their association with HCC, and strategies for mitigating inflammation utilizing curcumin, the principal polyphenolic curcuminoid present in turmeric. The review article elucidates curcumin's role in hepato-carcinoma, detailing its antioxidant, apoptotic, and anti-inflammatory potential.

1. Introduction

Hepatocellular carcinoma (HCC) is a prevalent form of liver cancer and a major global cause of mortality. The occurrence of HCC is higher in males, with a male to female ratio of 2.4:1, and it is more prevalent in Eastern and Southern Asia, as well as Middle and Western Africa (Woo *et al.,* 2011). Oncogenic agents induce prolonged liver damage, ultimately resulting in cirrhosis. Hepatocellular carcinoma (HCC) is closely associated with alcohol consumption as well as infections caused by Hepatitis B (HBV) and Hepatitis C (HCV) viruses. Additional factors leading to hepatocyte destruction encompass iron and copper accumulation, non-alcoholic steatohepatitis, and primary biliary cirrhosis. Cirrhosis and persistent liver disease are recognized as primary factors contributing to the global onset of HCC. Heavy alcohol consumption is identified as the predominant risk factor for the development of hepatocellular carcinoma (Grivennikov *et al.,* 2010). Individuals with chronic medical conditions like diabetes mellitus and obesity have a higher prevalence of hepatocellular carcinoma. Due to its substantial role in glucose metabolism, the liver is promptly affected by diabetes mellitus. Persistently elevated blood glucose levels can lead to cirrhosis, fatty liver, chronic hepatitis, and ultimately progress to liver failure. The primary causes of HCC development are chronic hepatitis or cirrhosis, which cause hepatocyte damage, infiltration of inflammatory cells in the liver, and deposition of connective tissue. Prolonged inflammation is associated with an increased risk of various cancer types. Risk factors for hepatocellular carcinoma (HCC) encompass hepatitis B and C viruses, metabolic disorders, diabetes, obesity, excessive alcohol consumption, and other factors that trigger inflammation. These cellular alterations result in changes to the matrix and micro environment of hepatocytes (Greten *et al.,* 2015) (Figure 1).

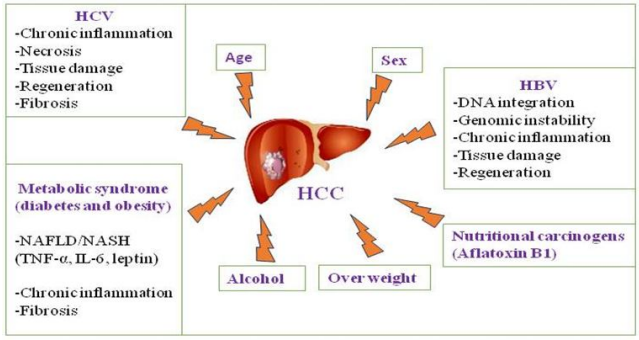


Figure 1: Different risk factors associated with hepatocellular carcinoma (HCC).

2. The microenvironmental factors in HCC

Chronic inflammation, genetic mutations, tissue remodeling, and alterations in cellular signaling are significant mechanisms implicated in the initiation and advancement of hepatocellular carcinoma (HCC). These processes are influenced by the hepatic microenvironment and its interconnected nature. Following a persistent HBV or HCV infection in humans, the progression of hepatocarcinogenesis can span over 30 years (Zucman-Rossi *et al.,* 2015). In some individuals

Corresponding author: Dr. Badruddeen

Professor, Faculty of Pharmacy, Integral University, Lucknow-226026, Uttar Pradesh, India

E-mail: badarmiracle@gmail.com

Tel.: +91-9918196188

with persistent HBV or HCV infections, cirrhosis and HCC may develop. Notably, livers affected by chronic hepatitis and cirrhosis show a higher incidence of HCC, particularly arising from dysplastic hepatocytes (McMahon, 2009).

3. Genetic alteration during the preneoplastic and plastic phase

The uncontrolled generation of genetic abnormalities in cancer cells is influenced by several factors, including viral infections, exposure to carcinogens like aflatoxin B1, and deficiencies in DNA repair mechanisms. Throughout the extended preneoplastic phase preceding HCC, alterations in gene expression primarily manifest quantitatively due to epigenetic mechanisms, rather than structural changes to genes or chromosomes. Elevated expression of transforming growth factor (TGF) and insulin-like growth factor-2 (IGF-2) leads to increased hepatocyte proliferation (Coste *et al.,* 1998; Grisham, 2002). These shifts in TGF and IGF-2 expression signify a substantial upregulation of numerous genes during the preneoplastic stage driven by epigenetic mechanisms. The interplay of cytokines from infiltrating inflammatory cells causing hepatocyte damage, viral transactivation, and the liver's regenerative response to cell loss contributes to the heightened production of TGF and IGF-2 (Soni *et al.,* 1995; Schwienbacher *et al.,* 2000). The modified methylation and imprinting of the IGF-2 gene are associated with uncontrolled IGF-2 production (Theise *et al.,* 1996), leading to the inactivation of the P1 promoter, activation of the P3 promoter, and significant growth factor production. Commencing within the liver, the origin of chronic hepatitis and cirrhosis, abnormal methylation (either low or hypermethylation) disrupts the CpG islands of various genes and chromosomal segments (Toshikuni *et al.,* 1999). Changes in chromatin acetylation represent significant factors that can induce epigenetic alterations in DNA, although such modifications have not been observed in the livers of HCC patients. Ongoing inflammation and oxidative damage allow hepatocytes to continue accumulating genetic alterations (Chang *et al.,* 1993). Several studies suggest that HCV proteins may directly contribute to cancer by obstructing signaling pathways like the Wnt/β-catenin, TGF, NF-κB, or P53 pathways. Acetaldehyde and reactive oxygen species metabolites resulting from alcohol consumption can cause mutations through DNA attachment, lipid peroxidation, or the formation of DNA adducts. Moreover, persistent oxidative stress due to alcohol consumption and cytokine release is a leading cause of chronic inflammation, cirrhosis, and progression to HCC. Chen and colleagues (Kanai *et al.,* 1999) conducted an analysis of 1074 articles using bioinformatic methods, identifying approximately 560 human genes associated with HCC. These genes are involved in critical functions such as transcription, DNA methylation, protein catabolism, and gene expression. Through biological function enrichment analysis, the researchers discovered pathways linked to cellular processes like apoptosis, necro-apoptosis, and cell cycle, significantly relevant to hepatocarcinogenesis. These pathways can be categorized into three main modules: the first encompassing signaling, immunological suppression, cellular metabolism, and regulation of various hormonal variables; the second establishing a clear connection between HCC initiation and HBV and HCV viral infection; and the third comprising differentially expressed genes collaborating to influence the same biological activities across various malignancies. During their investigation, fourteen genes were identified as potential biomarkers for HCC diagnosis and treatment. CDK2 and CDK4 are particularly significant due to their cooperation with cyclin E and D, facilitating the cell cycle transition from phase G1 to phase S. Alterations in these genes directly impacts the control of the cell cycle in hepatocarcinogenesis. Notably, CDKN1A, a tumor suppressor and inhibitor of CDK2-4, is regulated by TP53. TP53 has a substantial impact on cancer growth by drastically reducing VEGFA expression, consequently influencing neo-angiogenesis. These genes play a crucial role in distinguishing cancer cells from normal cells (Nagai *et al.,* 1999).

4. Chronic inflammation

The major instigators of HCC and tumor growth likely involve invasion by macrophages and immature myeloid cells, uncontrolled production of cytokines, and persistent inflammation. In the early stages of carcinogenesis, when the chronic inflammatory pathway is activated, the production of reactive oxygen species (ROS) and nitric oxide synthase (NOS) takes place. Inflammatory cells produce numerous cytokines, growth factors, chemokines, proangiogenic factors, and various molecules (Balogh *et al.,* 2016) (Figure 2).

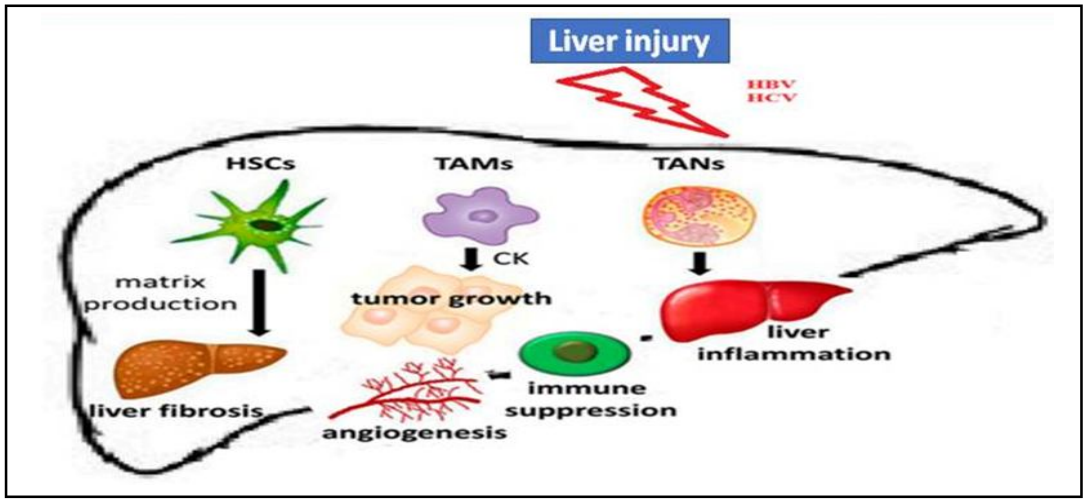


Figure 2: Role of stromal cells in creating a premalignant microenvironment and initiating HCC [HSCs (hepatic stellate cells), TAMs (tumor associated macrophages) and TANs (tumor associated neutrophils)].

These inflammatory mediators play a vital role in creating an environment conducive to hepatocyte transformation, enhancing their survivability by activating antiapoptotic signaling pathways, and reducing immune surveillance. During an HBV infection, platelets, storing a range of inflammatory chemicals and immune mediators in their intracellular granules facilitate the accumulation of virus-specific $CD8^+$ T cells and nonspecific inflammatory cells within the liver parenchyma.

Activation of platelets, resulting in the release of various growth factors (GFs) that govern cellular proliferation and neo-angiogenesis, attracts inflammatory cells to the inflammation site. Platelets store a range of inflammatory substances and immune mediators within intracellular granules, aiding in the accumulation of virus-specific $CD8^+$ T cells and non-specific inflammatory cells in the liver parenchyma during an HBV infection (Figure 3). The pathways leading to HCC development from NASH are significantly influenced by chronic inflammation. Genetic variables and obesity exacerbate inherited disorders such as insulin resistance and steatosis. The altered metabolism of injured hepatocytes, regulated by Toll-like receptors, serves as the primary trigger for the inflammatory response (Yu *et al.,* 2018). By activating the inflammasome and simultaneously producing pro-inflammatory and pro-fibrogenic cytokines and ligands, hepatocytes effectively attract Kupffer cells and other components of the innate immune response, given their anti-inflammatory properties, these factors suggest the potential of anti-inflammatory medications in reducing the chronic risk of neoplastic development. Anti-inflammatory medications, by inhibiting the COX (Cyclooxygenase) enzyme pathway that induces inflammation, contribute to reducing cellular proliferation (Pancoska and Carr, 2014).

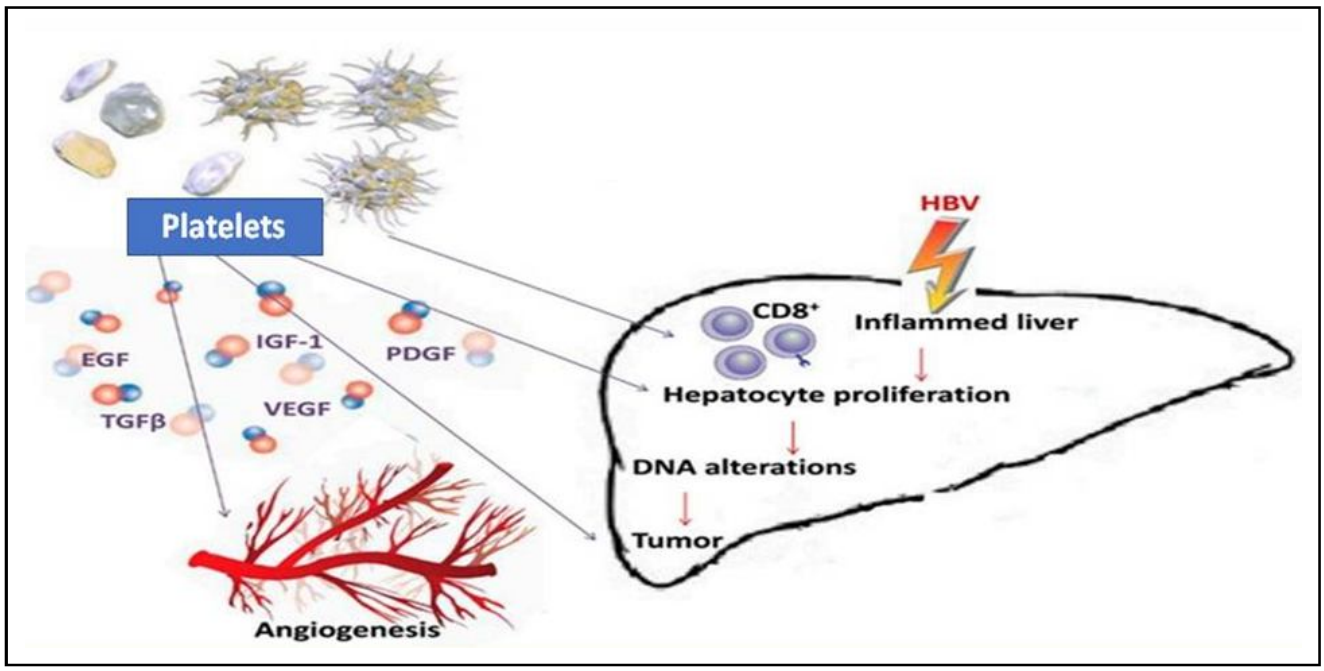


Figure 3: Platelet's role in accelerating liver damage through growth factor promotion.

5. Inflammation and its impact on tissue remodelling

Through the activation of platelet factors like VEGF (vascular endothelial growth factor) and EGF (epidermal growth factor), chronic inflammation can instigate tissue remodeling (Tao *et al.,* 2023). Stromal cells, such as fibroblasts and hematopoietic stem cells (HSCs), play a significant role in enhancing the formation of the extracellular matrix. Immune cells can influence ECM remodeling by activating stromal cells or generating MMPs (matrix metalloproteinases) that specifically break down ECM, altering the structure and functionality of the HCC microenvironment (Johansen, 2006).

Kupffer cells, macrophages, and platelets are attributed to the production and release of TGF-β, a growth stimulant for hematopoietic stem cells (Yu *et al.,* 2018). Tumor cells can induce the remodeling of stromal cells through altered signaling pathways. ECM degradation amplifies the release of growth factors (GFs), promoting tumor formation. Additionally, it may result in the production of cell surface receptors or bioactive cleavage products, acting as stimuli for cancer cell proliferation. The breakdown of ECM also disrupts growth-suppressing adhesion complexes, further encouraging cancer growth (Oishi *et al.,* 2014). These processes, including remodeling that alters blood flow and induces hypoxia, significantly contribute to tumor growth. Both tumor cells and non-tumor cells are prompted to express pro-angiogenic factors in hypoxic conditions. Studies have shown an upregulation of VEGF, promoting the formation of new blood vessels to balance oxygen levels (in hypoxic conditions) and provide the necessary nutrients for cancer growth (Forsythe *et al.,* 1996; Rakesh, 2005).

6. Additional factors and their role in chronic inflammation

Chronic inflammation, often triggered by toxins, specific viral infections, excessive alcohol consumption, and non-alcoholic fatty liver disease (NAFLD/NASH), is the primary cause of hepatocellular carcinoma (HCC). These factors disrupt normal cellular processes, gradually leading to the development of liver cancer. Addressing inflammation is crucial in HCC prevention.

7. Role of curcumin on modulating different HCC mediators

Curcumin plays a significant role in suppressing and preventing the progression of the disease by regulating cellular processes and inhibiting inflammation. The inflammatory pathway comprises four components: inducers, receptors, mediators, and effectors, influencing various physiological and pathological processes that induce inflammation. Curcumin's anti-inflammatory effects involve modulating target tissues responses to inflammatory mediators, acting on receptors and signaling pathways, reversing the impact of the medium on the target tissue, generating anti-inflammatory mediators, and other actions (Raghavi *et al.,* 2023; Makwana *et al.,* 2021; Chandrakala and Vidyavathi, 2023). Through the control of inflammatory signaling pathways and prevention of inflammatory mediator generation, curcumin exhibits its anti-inflammatory effects (Rahmani *et al.,* 2016; Reddy *et al.,* 2023) (Figure 4). Curcumin effectively inhibits activator protein 1 (AP-1) activity and other signaling pathways by binding to Toll-like receptors (TLRs), influencing nuclear factor kappa-B (NF-κB), mitogen-activated protein kinases (MAPK), and related pathways (Zhang *et al.,* 2019; Rahimifard *et al.,* 2017). Additionally, curcumin can inhibit NF-κB by modulating the peroxisome proliferator-activated receptor-gamma (PPAR-β) receptor (Li *et al.,* 2019; Zhu *et al.,* 2019). Through modulation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) inflammatory signaling system, curcumin further exhibits anti-inflammatory effects (Ashrafizadeh *et al.,* 2020; Kahkhaie *et al.,* 2019). Human studies have demonstrated curcumin's ability to reduce various inflammatory and pro-inflammatory mediators, including interleukin-1 (IL-1), IL-6, IL-8, IL-17, IL-27, tumor necrosis factor-alpha (TNF-α), induced nitric oxide synthase (iNOS), NO, RANTES, G-CSF, and monocyte chemotactic protein-1 (MCP-1) (Dong *et al.,* 2018; Zeng *et al.,* 2012; Alizadeh *et al.,* 2017). The specific effects of curcumin on various inflammatory mediators are described in detail in the Table 1.

8. Role of curcumin in inhibiting proinflammatory cytokine production

Several *in vitro* and *in vivo* studies demonstrate the significant reduction of pro-inflammatory cytokines, including IL-1, IL-6, IL-8, and TNF-α, by curcumin and its analogues. Curcumin efficiently modulates inflammation through well-studied mechanisms, with a key pathway being NF-κB. The regulation of NF-κB signaling is multi-faceted, including inhibition of IKK activity as an initial step. In a head and neck cancer patient trial, curcumin administration led to decreased levels of IL-8, TNF, and IFN expression, along with reduced IKK activity in saliva samples (Zhou *et al.,* 2011). Furthermore, curcumin enhances the stability and expression of IγB, blocking cytokine-induced NF-κB activation and IγB phosphorylation at serine 32, consequently suppressing pro-inflammatory gene expression. Additionally, curcumin activates AMPK and disrupts the NF-κB pathway by acting on p65. During IAV (Influenza virus A) infection in macrophages, curcumin prevents NF-κB and p65 translocation to the nucleus, reducing pro-inflammatory cytokine gene transcription (Swatson *et al.,* 2017).

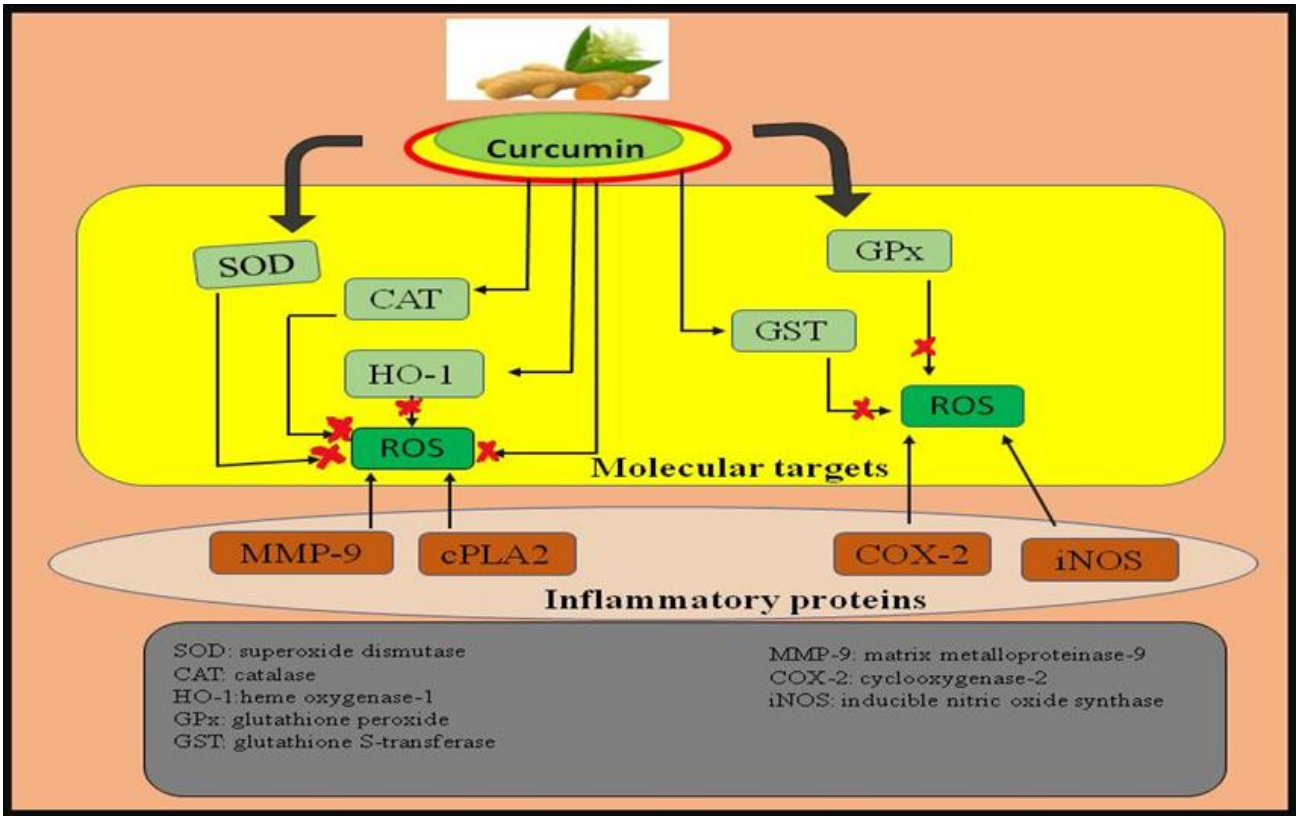


Figure 4: Molecular targets, anti-inflammatory and antioxidant mechanisms of curcumin.

9. Anti-inflammatory effect of curcumin *via* neutralizing reactive oxygen species

Oxidative stress and inflammatory responses are closely intertwined. The imbalance between reactive oxygen species (ROS) production and reduced antioxidant reactivity characterizes oxidative stress. ROS overproduction disrupts essential cellular functions and damages cell proteins, nucleic acids, and lipids at a structural and functional level. Accumulation of ROS leads to oxidative stress, amplifying inflammation by activating associated transcription factors. Curcumin, through its impact on NADPH oxidase and enhanced antioxidant enzyme activity, mitigates ROS generation and acts on the Nrf2-Keap1 pathway, resulting in its anti-inflammatory properties (Munevver and Akram 2016; Derochette *et al.,* 2013). Curcumin contains two active groups: the hydroxy hydrogen on the benzene ring, which exhibits antioxidative properties, and the diketone moiety. *In vitro* studies have demonstrated curcumin's effectiveness in scavenging superoxide anion radicals generated by riboflavin illumination and OH produced by the Fenton reaction, showcasing its potential in ROS removal and antioxidation (Srivastava *et al.,* 2016). Curcumin indirectly scavenges ROS through enzymatic regulation. For instance, it can activate the crucial enzyme superoxide dismutase (SOD), which converts O_2 to H_2O_2 and eventually to H_2O *via* the glutathione (GSH) redox system (Sies and Jones, 2020). In a study on rat liver injury, the folic acid antagonist Methotrexate was found to inhibit the GSH redox system, resulting in hepatic oxidative damage. Curcumin counteracts this effect, enhancing SOD's efficiency and maintaining the oxidant/antioxidant balance to prevent liver damage (Sharifi-Rad *et al.,* 2020). Additionally, curcumin inhibits thioredoxin interacting protein/NLR pyrin domain containing 3 (TXNIP/NLRP3), further attenuating the effect of ROS on the expression of pro-inflammatory cytokines like IL-1b and IL-18.

Table 1: Effect of curcumin on various inflammatory mediators

Role of curcumin on different transcription factors			
S. No.	**Transcription factors**	**Outcomes**	**References**
1.	Inflammatory cytokines	Excessive synthesis of pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6, significantly contributes to the onset of both localized and systemic inflammation in cases of severe infection or after major injuries. This heightened production can lead to severe pathophysiological disruptions and organ failure. Various studies have indicated that curcumin effectively modulates the production of diverse inflammatory cytokines, showcasing its potent anti-inflammatory properties.	Munford and Pugin, 2001; Abe, 1999
2.	Growth factor and protein kinase	The plasma membrane protein kinase EGFR (Epidermal Growth Factor Receptor) holds significant importance, as dysregulation in EGFR signaling is implicated in various cancers including breast, lung, colorectal, and head and neck cancers. The EGFR pathway plays a pivotal role in cancer cell growth, migration, survival, angiogenesis, and invasion. Curcumin effectively inhibits EGFR signaling by preventing EGFR tyrosine phosphorylation and suppressing EGFR gene expression, mediated by the activation of PPAR-γ. Additionally, curcumin down-regulates the expression of numerous pro-angiogenic growth factors such as VEGF and FGF, and it may directly impede angiogenesis.	Ahmed *et al*., 2006; Korutla and Kumar, 1994
3.	Enzymes	Curcumin has been found to modulate several enzymes closely associated with cancer and inflammation, including COX-2, iNOS, 5-LOX, and PLA2. It effectively reduces both COX-2 mRNA and activity in both *in vitro* and *in vivo* settings. Curcumin also strongly suppresses IMPDH (Inosine Monophosphate Dehydrogenase) activity, leading to a reduction in cellular GTP levels within HT-29 colon carcinoma cells. IMPDH is pivotal in the *de novo* biosynthetic reaction that converts inosine monophosphate into xanthosine monophosphate. Increased IMPDH enzyme expression or activity is linked to heightened cellular proliferation and a propensity for malignant transformation.	Chun *et al.,* 2003; Kunnumakkara *et al.,* 2007
4.	Apoptosis related enzymes	Disruption of apoptosis regulation can lead to inflammatory, degenerative, and cancerous ailments. Curcumin not only induces apoptosis in various human cancer cell types but also impedes tumor growth and promotion in animal models. Its mechanisms include the release of cytochrome c, activation of caspase-3, and downregulation of anti-apoptotic Bcl-XL and IAP proteins.	Zhou *et al.,* 2011; Jee *et al.,* 1998
5.	Other targets	The p53 gene plays a crucial role in cell cycle regulation, tumor suppression, and activation of apoptosis. Curcumin treatment has been found to lead to the overexpression of the p53 gene, consequently inducing apoptosis in diverse cell types.	Bae *et al.,* 2003; Michael *et al.,* 1995

TNF-α: Tumour necrosis factor alpha, IL-1β: Interleukin 1 beta, EDGRG; Epidermal growth factor receptor PPAR-γ: Peroxisome proliferator-activated gamma receptor, VEGF: Vascular endothelial growth factor, FGF: fibroblast growth factor COX 2: Cyclooxygenase 2, iNOS: Inducible nitric oxide synthase NF-κB: LOX: Lipooxygenase, PLA2: Phospholipases A2, IMPDH: Inosine monophosphate dehydrogenase, GTP: Guanosine, triphosphate, IAP: Inhibitor of apoptosis protein.

10. Conclusion

We have extensively explored various aspects concerning the genetic alterations in hepatocyte cells and their relationship with the hepatic microenvironment in the context of HCC development. It is imperative to comprehensively characterize these components within the liver microenvironment to pave the way for effective novel therapies targeting both the tumor and its microenvironment. This approach is vital to mitigate the reciprocal influence they exert on each other and to forestall the phenomena of recurrence and resistance commonly associated with current HCC treatments. Remarkably, several inflammatory variables in the microenvironment have been identified, presenting promising targets for potential therapeutic interventions. In this regard, numerous immunomodulatory drugs are presently undergoing clinical testing for HCC, either as standalone treatments or in combination with existing therapies. Our findings underscore that the inflammatory response is an actively dynamic process, intricately involved in carcinogenic events and responsive to them. Moreover, it stands as a promising and viable target for novel treatments, furthering our quest for effective HCC management and improved patient outcomes.

Acknowledgements

We are thankful to the Faculty of Pharmacy Integral University Lucknow for providing suitable facilities and support for the successful completion of this study (IU/R&D/2023-MCN0001894).

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Abe, Y.; Hashimoto, S.H.U. and Horie, T. (1999). Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. Pharmacological Research, **39**(1):41-47.

Ahmed, K. M.; Cao, N. and Li, J.J. (2006). HER-2 and NF-κB as the targets for therapy-resistant breast cancer. Anticancer Research, **26**(6B):4235-4243.

Alizadeh, F.; Javadi, M.; Karami, A. A.; Gholaminejad, F.; Kavianpour, M. and Haghighian, H. K. (2018). Curcumin nanomicelle improves semen parameters, oxidative stress, inflammatory biomarkers, and reproductive hormones in infertile men: A randomized clinical trial. Phytotherapy Research, **32**(3):514-521.

Ashrafizadeh, M.; Rafiei, H.; Mohammadinejad, R.; Afshar, E.G.; Farkhondeh, T. and Samarghandian, S. (2020). Potential therapeutic effects of curcumin mediated by JAK/STAT signaling pathway: A review. Phytotherapy Research, **34**(8):1745-1760.

Bae, J.H.; Park, J.W. and Kwon, T.K. (2003). Ruthenium red, inhibitor of mitochondrial Ca^{2+} uniporter, inhibits curcumin-induced apoptosis *via* the prevention of intracellular Ca^{2+} depletion and cytochrome c release. Biochemical and Biophysical Research Communications, **303**(4):1073-1079.

Balogh, J.; Victor III; D., Asham; E.H.; Burroughs, S.G.; Boktour, M.; Saharia, A. and Monsour Jr, H.P. (2016). Hepatocellular carcinoma: a review. Journal of Hepatocellular Carcinoma, 41-53.

Carr, B.I.; Lin, C.Y. and Lu, S.N. (2014). Platelet-related phenotypic patterns in hepatocellular carcinoma patients. In: Seminars in Oncology, **41**(3):415-421.

Chandrakala, B. and Vidyavathi, M. (2023). Simultaneous estimation using UV spectrophotometry of curcumin and silymarin in crude form and in prepared topical sunscreen cream. Ann. Phytomed., **12**(1):743-748.

Chen, G.; Liu, S.; Pan, R.; Li, G.; Tang, H.; Jiang, M. and Dong, J. (2018). Curcumin attenuates gp120-induced microglial inflammation by inhibiting autophagy via the PI3K pathway. Cellular and Molecular Neurobiology, **38**:1465-1477.

Chen, T.C.; Hsieh, L.L.; Kuo, T.T.; Ng, K.F.; YH, W.C.; Jeng, L.B. and Chen, M.F. (2000). p16INK4 gene mutation and allelic loss of chromosome 9p21-22 in Taiwanese hepatocellular carcinoma. Anticancer Research, **20**(3A):1621-1626.

Chun, K.S.; Keum, Y.S. and Han, S.S. (2003). Curcumin inhibits phorbol ester-induced expression of cyclooxygenase-2 in mouse skin through suppression of extracellular signal-regulated kinase activity and NF-êB activation. Carcinogenesis, **24**:1515-24.

Coste, A.D.L.; Romagnolo, B.; Billuart, P.; Renard, C.A.; Buendia, M.A.; Soubrane, O. and Perret, C. (1998). Somatic mutations of the β-catenin gene are frequent in mouse and human hepatocellular carcinomas. Proceedings of the National Academy of Sciences, **95**(15):8847-8851.

Derochette, S.; Franck, T.; Mouithys-Mickalad, A.; Ceusters, J.; Deby-Dupont, G.; Lejeune, J.P.; Neven, P. and Serteyn, D. (2013). Curcumin and resveratrol act by different ways on NADPH oxidase activity and reactive oxygen species produced by equine neutrophils. Chem. Biol. Interact., **206**(2):186-93.

Forsythe, J.A.; Jiang, B.H.; Iyer, N.V.; Agani, F.; Leung, S.W.; Koos, R.D. and Semenza, G.L. (1996). Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. Molecular and Cellular Biology, **16**(9):4604-4613.

Greten, T.F.; Wang, X.W. and Korangy, F. (2015). Current concepts of immune based treatments for patients with HCC: From basic science to novel treatment approaches. Gut, **64**(5):842-848.

Grisham, J.W. (2002). Molecular genetic alterations in primary hepatocellular neoplasms: hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma. The Molecular Basis of Human Cancer, 269-346.

Grivennikov, S.I.; Greten, F.R. and Karin, M. (2010). Immunity, inflammation, and cancer. Cell, **140**(6):883-899.

Jain, R.K. (2005). Normalization of tumor vasculature: An emerging concept in antiangiogenic therapy. Science, **307**(5706):58-62.

Jee, S.H.; Shen, S.C.; Kuo, M.L.; Tseng, C.R. and Chiu, H.C. (1998). Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells. Journal of Investigative Dermatology, **111**(4):656-661.

Johansen, J.S. (2006). Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodelling, fibroses and cancer. Dan Med Bull., **53**(2):172-209.

Kahkhaie, K.R.; Mirhosseini, A.; Aliabadi, A.; Mohammadi, A.; Mousavi, M.J.; Haftcheshmeh, S.M. and Sahebkar, A. (2019). Curcumin: A modulator of inflammatory signaling pathways in the immune system. Inflammopharmacology, **27**:885-900.

Kanai, Y.; Hui, A. M.; Sun, L.; Ushijima, S.; Sakamoto, M.; Tsuda, H. and Hirohashi, S. (1999). DNA hypermethylation at the D17S5 locus and reduced HIC 1mRNA expression are associated with hepatocarcinogenesis. Hepatology, **29**(3):703-709.

Kastan, M.B.; Canman, C.E. and Leonard, C.J. (1995). P53, cell cycle control and apoptosis: implications for cancer. Cancer and Metastasis Reviews, **14**:3-15.

Korutla, L. and Kumar, R. (1994). Inhibitory effect of curcumin on epidermal growth factor receptor kinase activity in A431 cells. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, **1224**(3):597-600.

Kunnumakkara, A.B.; Guha, S. and Krishnan, S. (2007). Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-kappa B-regulated gene products. Cancer Research, **67**:3853-3861.

Leslie, Mitch. (2010). "Beyond clotting: the powers of platelets". Science, 562-564.

Li, Q.; Sun, J.; Mohammadtursun, N.; Wu, J.; Dong, J. and Li, L. (2019). Curcumin inhibits cigarette smoke-induced inflammation *via* modulating the PPARγ-NF-κB signaling pathway. Food and Function, **10**(12):7983-7994.

Liu, Y.W.; Chang, K.J. and Liu, Y.C. (1993). DNA hypomethylation of proliferating cell nuclear antigen gene in human hepatocellular carcinoma is not due to cell proliferation. Cancer Letters, **70**(3):189-196.

Loprieno, N. (1975). International Agency for Research on Cancer (IARC) monographs on the evaluation of carcinogenic risk of chemicals to man: Relevance of data on mutagenicity. Mutation Research, **31**(3):210.

Makwana, C.N.; Patel, U.D.; Rao, S.S.; Ladumor, V.C.; Modi, C.M. and Patel, H.B. (2021). Protective effect of quercetin and curcumin against cadmium-induced alterations in brain cortex and heart of rats. Ann. Phytomed., **10**(2):367-375.

McMahon, B.J. (2009). The natural history of chronic hepatitis B virus infection. Hepatology, **49**(S5):S45-S55.

Munford, R.S. and Pugin, J. (2001). Normal responses to injury prevent systemic inflammation and can be immunosuppressive. American Journal of Respiratory and Critical Care Medicine, **163**(2):316-321.

Nagai, H.; Kim, Y.S.; Yasuda, T.; Ohmachi, Y.; Yokouchi, H.; Monden, M. and Matsubara, K. (1999). A novel sperm-specific hypomethylation sequence is a demethylation hotspot in human hepatocellular carcinomas. Gene, **237**(1):15-20.

Oishi, N.; Yamashita, T. and Kaneko, S. (2014). Molecular biology of liver cancer stem cells. Liver Cancer, **3**(2):71-84.

Ott, J.J.; Stevens, G.A.; Groeger, J. and Wiersma, S.T. (2012). Global epidemiology of hepatitis B virus infection: New estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine, **30**(12):2212-2219.

Pancoska, P. and Carr, B.I. (2014). Macro-and micro-environmental factors in clinical hepatocellular cancer. In: Seminars in Oncology, **41**(2):185-194.

Puche, J.E.; Saiman, Y. and Friedman, S.L. (2013). Hepatic stellate cells and liver fibrosis. Compr Physiol., **3**(4):1473-1492.

Raghavi, R.; Aanandhi, M.V. and Sumithra, M. (2023). Analysis of phytoconstituents and its phytoformulation of curcumin chewable tablet as per ICH guidelines. Ann. Phytomed., **12**(1):601-605.

Rahimifard, M.; Maqbool, F.; Moeini-Nodeh, S.; Niaz, K.; Abdollahi, M.; Braidy, N. and Nabavi, S.F. (2017). Targeting the TLR4 signaling pathway by polyphenols: A novel therapeutic strategy for neuroinflammation. Ageing Research Reviews, **36**:11-19.

Rahmani, A.H.; Alsahli, M.A.; Aly, S.M.; Khan, M.A. and Aldebasi, Y.H. (2018). Role of curcumin in disease prevention and treatment. Advanced Biomedical Research, **7**(1):38.

Reddy T, P.K.; Kondle, R.; Challa, P.K. and Wani, A.W. (2023). A review on nutritional, phytochemical, and medicinal properties of under exploited fruit crops. Ann. Phytomed., **12**(1):132-147.

Schwienbacher, C.; Gramantieri, L.; Scelfo, R.; Veronese, A.; Calin, G. A.; Bolondi, L. and Negrini, M. (2000). Gain of imprinting at chromosome 11p15: A pathogenetic mechanism identified in human hepatocarcinomas. Proceedings of the National Academy of Sciences, **97**(10):5445-5449.

Sharifi-Rad, M.; Anil Kumar, N.V.; Zucca, P.; Varoni, E.M.; Dini, L.; Panzarini, E. and Sharifi-Rad, J. (2020). Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases. Frontiers in Physiology, **11**:694.

Shen, L.A.; Fang, J.I.; Qiu, D.E.; Zhang, T.E.; Yang, J.I.; Chen, S.H. and Xiao, S.H. (1998). Correlation between DNA methylation and pathological changes in human *hepatocellular carcinoma*. Hepato-gastroenterology, **45**(23):1753-1759.

Sies, H. and Jones, D.P. (2020). Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nature Reviews Molecular Cell Biology, **21**(7):363-383.

Soini, Y.; Virkajarvi, N.; Lehto, V. P. and Paakko, P. (1996). Hepatocellular carcinomas with a high proliferation index and a low degree of apoptosis and necrosis are associated with a shortened survival. British Journal of Cancer, **73**(9):1025-1030.

Sokmen, M. and Akram, K.M. (2016). The antioxidant activity of some curcuminoids and chalcones. Inflammopharmacology, (**24**):81-86.

Srivastava, S.; Saksena, A. K.; Khattri, S.; Kumar, S. and Dagur, R.S. (2016). Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: A four-month, double-blind, randomized, placebo-controlled trial. Inflammopharmacology, **24**:377-388.

Swatson, W. S.; Katoh-Kurasawa, M.; Shaulsky, G. and Alexander, S. (2017). Curcumin affects gene expression and reactive oxygen species *via* a PKA dependent mechanism in Dictyosteliumdiscoideum. PLoS One, **12**(11):e0187562.

Tao, Y.; Li, Y.; Liu, X.; Deng, Q.; Yu, Y. and Yang, Z. (2018). Nonsteroidal anti-inflammatory drugs, especially aspirin, are linked to lower risk and better survival of hepatocellular carcinoma: A meta-analysis. Cancer Management and Research, 2695-2709.

Theise, N. D.; Marcelin, K.; Goldfischer, M.; Hytiroglou, P.; Ferrell, L. and Thung, S. N. (1996). Low proliferative activity in macroregenerative nodules: evidence for an alternate hypothesis concerning human hepatocarcinogenesis. Liver, **16**(2):134-139.

Toshikuni, N.; Nouso, K.; Higashi, T.; Nakatsukasa, H.; Onishi, T.; Kaneyoshi, T. and Tsuji, T. (2000). Expression of telomerase-associated protein 1 and telomerase reverse transcriptase in hepatocellular carcinoma. British Journal of Cancer, **82**(4):833-837.

Woo, H.G; Park E.S; Thorgeirsson, S.S. and Kim, Y.J. (2011). Exploring genomic profiles of hepatocellular carcinoma. Molecular Carcinogenesis, **50**(4):235-43.

Yu, L.X.; Ling, Y. and Wang, H.Y. (2018). Role of nonresolving inflammation in hepatocellular carcinoma development and progression. NPJ Precision Oncology, **2**(1):6.

Zeng, Z.; Zhan, L.; Liao, H.; Chen, L. and Lv, X. (2013). Curcumin improves TNBS-induced colitis in rats by inhibiting IL-27 expression via the TLR4/NF-κB signaling pathway. Planta Medica, **29**(02):102-109.

Zhang, J.; Zheng, Y.; Luo, Y.; Du, Y.; Zhang, X. and Fu, J. (2019). Curcumin inhibits LPS-induced neuro inflammation by promoting microglial M2 polarization *via* TREM2/TLR4/NF-κB pathways in BV2 cells. Molecular Immunology, **116**:29-37.

Zhou, H.; Beevers C. and Huang, S. (2011). The targets of curcumin. Current Drug Targets, **12**(3):332-347.

Zhu, T.; Chen, Z.; Chen, G.; Wang, D.; Tang, S.; Deng, H. and Li, C. (2019). Curcumin attenuates asthmatic airway inflammation and mucus hypersecretion involving a PPARγ-dependent NF-κB signaling pathway *in vivo* and *in vitro*. Mediators of Inflammation, **2019**:1-15.

Zucman-Rossi, J.; Villanueva, A.; Nault, J.C. and Llovet, J.M. (2015). Genetic landscape and biomarkers of hepatocellular carcinoma. Gastroenterology, **149**(5):1226-1239.

Citation **Mohd Yusuf, Badruddeen, Zeashan Hussain, Juber Akhtar, Mohammad Irfan Khan and Mohammad Ahmad (2023). An insight into the pathological pathways of hepatocellular carcinoma and the role of curcumin on the mediators of carcinoma. Ann. Phytomed., 12(2):21-28. http://dx.doi.org/10.54085/ap.2023.12.2.4.**