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Chapter 11

Molecular Insights Into Herbal Therapeutics For Hepatocellular Carcinoma: Targeting Oxidative Stress, Inflammation, And Apoptotic Pathways.

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Abstract: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, driven by chronic liver diseases such as viral hepatitis, non-alcoholic fatty liver disease (NAFLD), and prolonged toxin exposure. Conventional treatment strategies, including surgical resection, liver transplantation, and chemotherapy, face challenges such as drug resistance, limited efficacy, and high recurrence rates. Herbal medicine has emerged as a promising complementary approach in HCC management, offering bioactive compounds with hepatoprotective, antioxidant, anti-inflammatory, and anticancer properties. This chapter explores the molecular mechanisms by which herbal compounds such as Silymarin (Milk Thistle), Curcumin (Turmeric), Withania somnifera (Ashwagandha), and Green Tea Extract (EGCG) exert their therapeutic effects. These botanicals regulate key pathways involved in oxidative stress, inflammation, apoptosis, and tumor proliferation, contributing to the inhibition of hepatic carcinogenesis. Additional herbal extracts, such as Scutellaria baicalensis and Artemisia annua, demonstrate potential in modulating cell signaling, inhibiting metastasis, and promoting liver health. Integrating herbal medicine into oncological treatment protocols may offer a holistic and effective strategy for improving HCC outcomes while minimizing adverse effects.

Keywords: Hepatocellular carcinoma, herbal medicine, oxidative stress, inflammation, apoptosis, Silymarin, Curcumin, Withania somnifera, Green Tea Extract, Scutellaria baicalensis, Artemisia annua, liver cancer therapy, phytochemicals, integrative oncology.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies worldwide and a leading cause of cancer-related mortality. Its incidence is rising due to a combination of viral, environmental, and metabolic risk factors. Historically, HCC has been strongly linked to chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as prolonged exposure to aflatoxins and excessive alcohol consumption [1]. However, in recent years, metabolic disorders such as obesity, type II diabetes, and non-alcoholic fatty liver disease (NAFLD) have emerged as significant contributors to liver carcinogenesis. These metabolic conditions promote chronic inflammation, oxidative stress, and hepatic fibrosis, ultimately increasing the likelihood of malignant transformation [2]. Despite advances in medical and surgical interventions, HCC remains challenging to treat due to its aggressive nature and high recurrence rates. Early detection is critical for effective management, yet most cases are diagnosed at an advanced stage when treatment options are limited. Surgical resection, radiofrequency ablation, and liver transplantation are viable curative approaches for early-stage HCC. However, the availability of suitable organ donors is restricted, and post-transplant recurrence remains a concern. Additionally, resistance to conventional chemotherapy and targeted therapies further complicates disease management. Therefore, there is an urgent need to explore novel treatment strategies that can improve patient outcomes while minimizing adverse effects [3].

In response to these challenges, researchers and clinicians are increasingly turning to natural products as potential therapeutic agents for HCC. Herbal medicine has been an integral part of traditional healing systems for centuries, offering a rich source of bioactive compounds with diverse pharmacological properties. Many plant-derived compounds, including flavonoids, alkaloids, terpenoids, and saponins, have demonstrated hepatoprotective, anti-inflammatory, antioxidant, and anticancer activities. These bioactive molecules exert their effects by modulating key cellular pathways involved in carcinogenesis, including oxidative stress regulation, apoptosis induction, immune modulation, and inhibition of tumor angiogenesis and metastasis [4]. The exploration of plant-derived natural products and their role in liver cancer therapy has led to the identification of promising candidates for both chemoprevention and chemotherapy. Several herbal extracts, either as single agents or in combination therapies, have shown significant potential in reducing tumor progression and enhancing the efficacy of conventional treatments. This chapter delves into the therapeutic mechanisms and pharmacological benefits of key herbal extracts commonly studied for HCC treatment. Specifically, it highlights the anticancer and hepatoprotective properties of compounds such as Silymarin (Milk Thistle), Curcumin (Turmeric), Withania somnifera (Ashwagandha), and Green Tea Extract (EGCG). Each of these natural agents has been extensively studied for their ability to mitigate oxidative damage, suppress inflammatory signaling, and regulate cell proliferation and apoptosis in liver cancer models[5]. By understanding the molecular targets and pharmacokinetics of these plant-derived compounds, researchers can develop more effective therapeutic strategies that integrate natural medicine with modern oncological treatments. Given the limitations of current HCC therapies, the integration of herbal extracts as complementary or alternative medicine holds promise for improving treatment efficacy and patient survival while reducing toxicity and side effects. Thus, this chapter provides a comprehensive review of the potential applications of herbal medicine in liver cancer management, with a focus on its mechanisms of action, preclinical and clinical evidence, and future prospects for drug development.

SILYMARIN (MILK THISTLE) AND ITS HEPATOPROTECTIVE AND ANTICANCER EFFECTS.

Silybum Marianum, or Milk thistle is a species of thistle. This an annual or biennial plant with red to purple flowers and shiny pale green leaves with white vein. It is a polyphenolic flavonoid which is known to show antioxidative, immunomodulatory, hepatoprotective, anti-lipidemic, anti-diabetic, antihypertensive and anti-cancer activity. [,6,7,8,9]. The primary bioactive components are; flavonolignans: silybin, silydianin, silychristin and isosilybin, along with minor flavonoids like taxifolin. Silybin is the most abundant and biologically active compound. These compounds exhibit potent free radical scavenging abilities, membrane stabilization effects, and enzyme-modulating properties, which contribute to their therapeutic benefits in liver diseases and cancer. [10] Silymarin's Pharmacokinetic activities can be understood by absorption, metabolism, distribution and elimination. Silymarin has poor oral bioavailability due to low water solubility and high first-pass metabolism. Hence Silymarin when taken with fatty meals improves absorption. Silymarin is metabolized in liver through both Phase 1 and Phase 2. [11] It undergoes glucuronidation and sulfation to enhance excretion. It can cross Blood Brain Barrier as it binds to plasma proteins and distributes to liver, kidney, lungs and prostate. It is eliminated in bile and urine. [12]

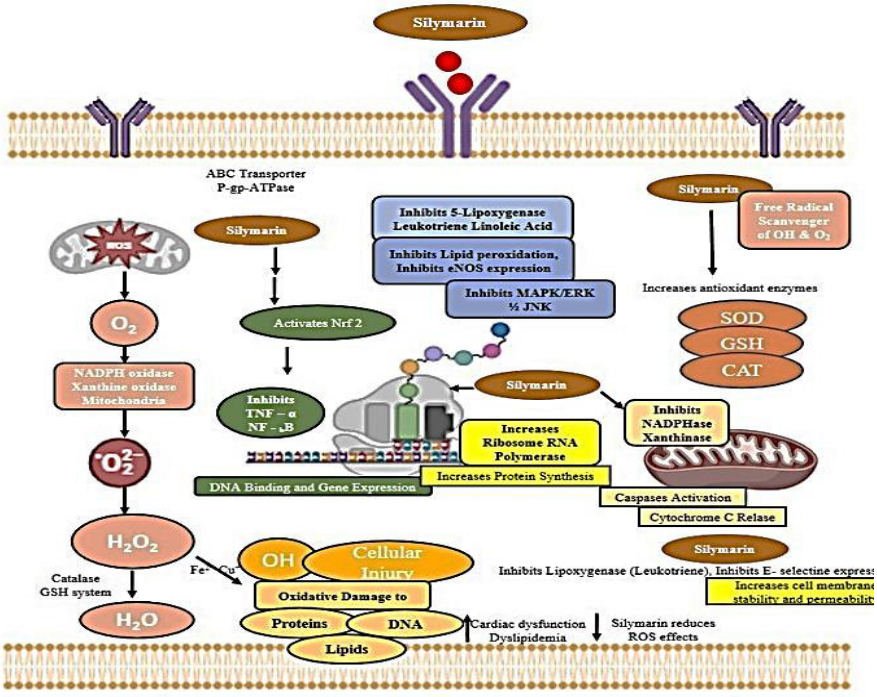

Fig 1. The antioxidant action of silymarin in a cell membrane. [13].

Silymarin boosts key antioxidants like glutathione (GSH) and superoxide dismutase (SOD), crucial for neutralizing ROS and maintaining liver cell integrity Fig 1.[13] It also activates the Nrf2 pathway, leading to increased expression of antioxidant enzymes such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1), further enhancing cellular defense. Similarly, silymarin inhibits NF-κB signaling, reducing inflammation and preventing liver fibrosis. This dual antioxidant and anti-inflammatory action protects hepatocytes from chronic damage and supports liver function. Clinical studies have shown that silymarin improves liver enzyme levels and reduces oxidative markers in patients with liver disease. [14] .

Table 1: Summary of Major Pathways Targeted by Silymarin in Hepatoprotective and Anti-Cancer Effects

PATHWAY	EFFECT OF SILYMARIN
Nrf2/ARE	Enhances antioxidant response [14]
NF-κB	Reduces inflammation [14]
JAK/STAT	Suppresses immune overactivation, cancer growth [15]
p53/p21	Induces apoptosis, cell cycle arrest [16]
PI3K/Akt/mTOR	Inhibits survival and proliferation [15]
MAPK (ERK, JNK, p38)	Promotes apoptosis, inhibits growth [17]
VEGF	Suppresses tumor angiogenesis [17]
MMP-2, MMP-9	Reduces metastasis [17]

Silymarin exhibits potent hepatoprotective and anticancer properties through its antioxidant, anti-inflammatory, and cell-regulating mechanisms.

CURCUMIN (TURMERIC) IN HEPATIC CANCER TREATMENT

Curcuminoids are phenolic compounds present in the roots of Turmeric also *Curcuma longa*, a perennial plant which belongs to the Zingiberaceae family. These compounds give turmeric its distinctive yellow to orange color. This plant is originally native to India, but now it is widely cultivated in tropical regions of Asia, including Indonesia and China, where the climate is warm and humid. Traditionally, turmeric has been used both as a spice to enhance flavor and as a natural yellow pigment in various cuisines. Due to its constituents, curcumin has a wide range of bioactivities including antioxidant, anti-inflammatory, anticancer, antimicrobial, neuroprotective, and hepatoprotective properties. [18] Curcuminoids contains bioactive components like; curcumin, demethoxycurcumin, bisdemethoxycurcumin. Along with these compounds curcumin also contains essential oils like; turmerone, zingiberene, elemene. It also contains saponins, tannins, sugars, resins and proteins. [19] Curcumin has poor bioavailability, less absorption, rapid metabolism and fast excretion making it pharmacokinetically challenging. Hence there has been many studies to overcome this for example; Liposomal and nanoparticle formulations and Curcumin-phytosome technology. [20] Hepatocellular carcinoma is malignant disease which arises from uncontrolled division of liver cells or hepatocytes. Curcumin acts in many ways on hepatic cells they are;

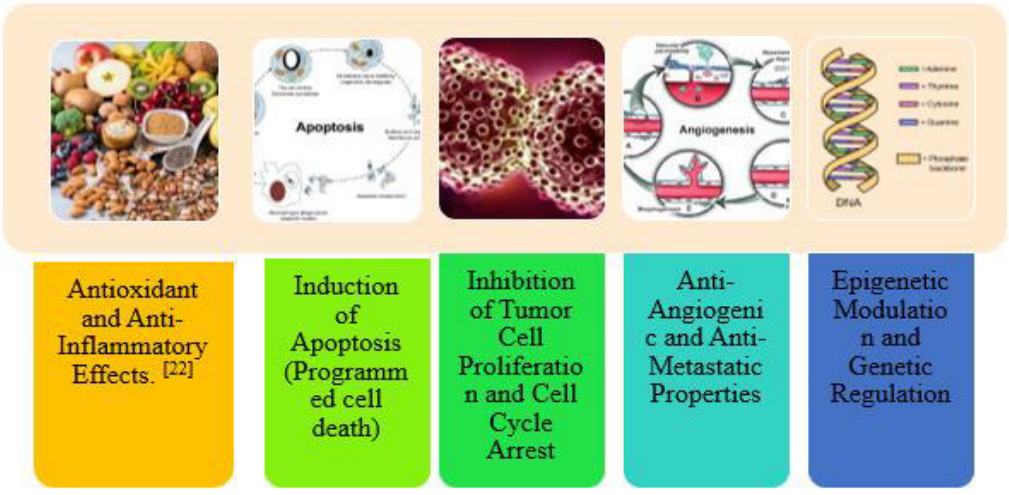

Figure 2: Diverse Pharmacological action of curcumin against hepatocellular malignancy.

THE ANTIOXIDANT ACTIVITY OF CURCUMIN IN LIVER CELLS

- Reduction of Reactive Oxygen Species (ROS):- Curcumin decreases the levels of ROS, which are harmful molecules that cause oxidative stress and cellular damage. It enhances the expression of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and thioredoxin (Trx1/NOX1), which neutralize free radicals and reduce oxidative damage.
- Modulation of Stress and Inflammatory Pathways: - It inhibits key inflammatory pathways such as STAT3, NF-κB, and p38, preventing excessive inflammation and cellular damage.
- Regulation of Apoptotic Proteins: - Curcumin modulates Bcl-1 and Bax proteins, which control cell survival and apoptosis, preventing liver cell death.
- Stabilization of Lysosomes: - Curcumin helps maintain lysosomal stability, which is crucial for cellular detoxification and waste clearance. [22].

INDUCTION OF APOPTOSIS (PROGRAMMED CELL DEATH)

- Intrinsic Pathway: Curcumin affects mitochondrial-mediated apoptosis by regulating Bcl-2 family proteins, leading to cytochrome c release and activation of caspases (Caspase-3, -9).
- Extrinsic Pathway: It can enhance death receptor-mediated apoptosis via activation of Fas/FasL and TNF-related pathways.
- Oxidative Stress: Curcumin reduces reactive oxygen species (ROS), preventing oxidative damage and promoting apoptosis in cancerous liver cells while protecting normal hepatocytes.
- Inflammation Modulation: It inhibits NF-κB, a key regulator of inflammation and apoptosis resistance in liver diseases.

INHIBITION OF TUMOR CELL PROLIFERATION, CELL CYCLE ARREST AND EPIGENETIC MODIFICATION.

- Curcumin triggers apoptosis in HepG2 cells through both intrinsic and extrinsic pathways.
- Curcumin down regulates cyclin D1 and CDK4, leading to G1-phase cell cycle arrest, preventing HepG2 cell division.
- It also reduces β-catenin signaling, which is involved in cancer cell survival. [22]
- Curcumin downregulates VEGF (vascular endothelial growth factor), reducing tumor blood supply. [23]
- Curcumin exerts DNA methylation, histone modificaions and non-coding RNAs on cancer cells. [24] Curcumin exhibits anticancer activity by the above mechanism of action in liver cells.

***WITHANIA SOMNIFERA* (ASHWAGANDHA) AND ITS ROLE IN CANCER CHEMOPREVENTION.**

This is an evergreen shrub which is grown in India, Nepal, China, Yemen and South Africa. It is commonly known as ashwagandha. It belongs to the family Solanaceae. It is used as a traditional Indian medicine. It is used as anti-Inflammatory, anti-cancer, anti-aging and immunomodulatory agent. Its main use is to normalize cortisol levels, which reduces the stress responses. [25] Major constituents are Withaferin A, Withanolide A, Withanolide B, Withanolide C, Withanolide D, Withanoside IV, Withanoside V and Withanone. [26] Withaferin A (WA) and Withanolides (W) have different types of actions as WA acts as Chemoprevention whereas W act in treatment of cancer. Hence Withania somnifera has both Chemopreventive and therapeutic action.

As we are discussing in this chapter Chemoprevention, Let's understand the underlying mechanism:

A. **Cysteine-Reacting Nature**: The α, β-unsaturated carbonyl group in WA interacts with cysteine residues in proteins, enabling WA to bind directly to proteins such as Vimentin, GFAP, IKKβ, and β-Tubulin. This interaction may alter the function of these proteins, potentially disrupting cellular processes, affecting cell structure, signaling pathways, and the integrity of the cytoskeleton.
B. **Modulation of Cellular Signaling**: WA influences several vital cellular pathways, including:
    - Autophagy: WA has been shown to modulate autophagy, a process that helps degrade and remove dysfunctional cellular components. This regulation plays a role in eliminating damaged cells, contributing to cancer prevention.
    - Proteasomal Degradation: WA affects the proteasomal degradation pathway, which is responsible for eliminating damaged or unnecessary proteins. Disruptions in this pathway can result in the buildup of toxic proteins, aiding in cancer chemoprevention.
    - Heat Shock Response: WA activates the heat shock response, a cellular mechanism that helps cells cope with stress. This response can protect cells from damage and supports cancer prevention by preserving cellular balance.
C. **Minimizing Cytotoxicity While Enhancing Cytoprotective Activity**: Studies indicate that modifying WA's structure can reduce its cytotoxicity while boosting its ability to protect cells, a critical factor in enhancing its potential use as a therapeutic agent for cancer chemoprevention. [27]

- Given the significant role of *Withania somnifera* in Ayurveda and its promising effects in modern cancer research, it holds potential to be developed as a cancer chemopreventive nutraceutical.

GREEN TEA EXTRACT (EGCG) AND ITS APPLICATION IN LIVER CANCER

Green tea is composed of a complex mixture of compounds, including flavonols or polyphenols (GTPs). Flavonols, commonly referred to as catechins, are present in higher concentrations in green tea compared to black or oolong tea. Green tea contains four primary catechins: epicatechin, epigallocatechin, epicatechin-3-gallate, and epigallocatechin-3-gallate. These catechins have demonstrated various anticancer properties by modulating multiple cancer-related pathways. The major component of polyphenols found in green tea extract is Epigallocatechin-3-gallate (EGCG). [28,29]

Reduction of Oxidative Stress

Oxidative stress occurs due to an imbalance between free radicals (reactive oxygen species, ROS) and the body's antioxidant defenses. Excessive ROS can cause DNA damage, mutations, and promote cancer development. EGCG combats oxidative stress by:

- Scavenging free radicals: EGCG neutralizes ROS, preventing cellular damage.
- Enhancing antioxidant enzymes: It increases levels of enzymes like superoxide dismutase (SOD) and catalase, which help detoxify harmful oxidants.
- Protecting DNA from damage: By reducing oxidative DNA damage, EGCG helps prevent mutations that could lead to liver cancer. [30]

Anti-inflammatory Effects

Chronic inflammation is a major factor in liver cancer progression, often resulting from conditions like hepatitis, liver fibrosis, or cirrhosis. EGCG helps control inflammation by:

- Inhibiting pro-inflammatory cytokines: It reduces the production of cytokines such as TNF-α, IL-6, and IL-1β, which promote cancer growth.
- Suppressing NF-κB signaling: EGCG blocks NF-κB, a key regulator of inflammation and cancer cell survival, thereby reducing tumor-promoting inflammation.
- Reducing COX-2 and iNOS expression: These enzymes contribute to inflammation and tumor progression, and EGCG helps downregulate them. [31]

Green Tea Extract EGCG was found to help in Liver cancer by antioxidant and anti-inflammatory activity.

OTHER HERBAL EXTRACTS: SCUTELLARIA BAICALENSIS, ARTEMISIA ANNUA AGAINST HEPATIC CARCINOMA

Scutellaria baicalensis

Scutellaria baicalensis is Chinese plant primarily used in Chinese medicine. It belongs to the Lamiaceae family. It is cultivated in China, Japan, Korea, Mongolia, Siberia and Russia. It is commonly known as Chinese Skullcap and it contains baicalin, baicalein, flavonoids, alkaloids and terpenoids. [32]

Table 2: Major cell signaling pathways regulate the anti cancer potential of *Scutellaria baicalensis.*

PATHWAY	EFFECT OF SCUTELLARIA BAICALENSIS
Bax/Bcl-2	Inhibits apoptosis
LC3-1, LC3-II, ATG5	Autophagy Regulation
CX26/CX43	Inhibition of Invasion and Metastasis
ATF6	Endoplasmic Recticulum Stress Activation
PI3K/Akt/mTOR	Inhibits survival and proliferation

Artemisia annua

It is commonly known as Sweet wormwood or annual wormwood. It is native to Asia. This plant is grown in Vietnam, China, Nigeria, India and some American countries. It contains artemisinin, dihydroartemisinin, artesunate, polyphenols, coumarins, flavones and phenolic acids. Most common use of Artemisinin is to treat malaria. [33]

Table 3: Molecular effect of *Artemisia annua* against hepatic carcinoma.

PATHWAY	EFFECT OF ARTEMISIA ANNUA
D-GalN	Hepatoprotective effect
ROS,SOD	Oxidative stress
TNF, IL-6, IL-1B, TLR	Anti Inflammatory Action

CONCLUSION

Hepatocellular carcinoma remains a major global health challenge due to its aggressive nature, limited treatment options, and high recurrence rates. Conventional therapies, while effective in early stages, are often insufficient in advanced cases, necessitating the exploration of alternative approaches. Herbal medicine, with its long history of therapeutic applications, has emerged as a promising avenue for HCC treatment and prevention. This chapter highlights the potential of several plant-derived compounds, including Silymarin, Curcumin, *Withania somnifera*, and Green tea extract, in targeting key molecular pathways involved in liver cancer progression. These bioactive

constituents exhibit hepatoprotective, antioxidant, anti-inflammatory, and anticancer properties, offering a multifaceted approach to disease management. Additionally, other herbal extracts such as *Scutellaria baicalensis* and *Artemisia annua* have demonstrated significant therapeutic potential through mechanisms that inhibit tumor growth, prevent metastasis, and enhance cellular defense systems.

While preclinical and clinical studies support the efficacy of these natural compounds, further research is required to optimize their bioavailability, standardize dosages, and explore synergistic effects with existing treatments. Advancements in formulation technologies, such as nanoparticles and phytosome-based delivery systems, could enhance the therapeutic potential of these herbal agents. In conclusion, integrating herbal medicine into modern oncological strategies may provide a complementary approach to conventional therapies, potentially improving treatment outcomes with fewer side effects. Future research and well-designed clinical trials will be crucial in validating these natural compounds as viable options for HCC management, ultimately bridging the gap between traditional knowledge and modern medical applications.

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