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Bridges in Nano Pharmacology and Oncology – Engineering Guava Metabolites for Hepatobiliary Cancer

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Abstract

Hepatobiliary cancers, primarily hepatocellular carcinoma (HCC) and cholangiocarcinoma, are among the leading causes of cancer-related mortality worldwide. Current therapies, including surgical resection, liver transplantation, tyrosine kinase inhibitors, and immune checkpoint inhibitors, offer limited survival benefits due to late-stage diagnosis, therapeutic resistance, and systemic toxicities. In this context, ethanopharmacology provides a critical bridge for novel drug discovery by translating traditional knowledge into modern therapeutics. Guava (*Psidium guajava*), a widely used medicinal plant, is rich in bioactive metabolites such as quercetin, gallic acid, urosolic acid, and lycopene, which demonstrate antioxidant, anti-inflammatory, anti-proliferative, and pro-apoptotic effects. Mechanistic studies reveal their modulation of key signaling pathways—PI3K/AKT, NF-κB, Wnt/β-catenin, and JAK/STAT3—that drive Hepatobiliary carcinogenesis. Despite encouraging *in vitro* and *in vivo* evidence, poor solubility, low bioavailability, and pharmacokinetic variability hinder clinical translation. Emerging nano pharmacology approaches, including polymeric nanoparticles, liposomes, lipid carriers, and hydrogels, have shown promise in enhancing delivery, stability, and tumor-specific targeting of guava metabolites. This review synthesizes current evidence on the epidemiology, pharmacology, toxicology, and delivery strategies of guava metabolites in hepatobiliary cancer, while discussing translational challenges and future research directions. By integrating ethanopharmacology with nanotechnology, guava- derived therapeutics hold potential to advance oncology pipelines and improve outcomes in hepatobiliary malignancies.

Keywords: Guava metabolites, hepatobiliary cancer, nanopharmacology, ethanopharmacology, drug delivery, quercetin, ursolic acid.

1. Introduction

Hepatobiliary cancers, including hepatocellular carcinoma (HCC) and cholangiocarcinoma, are among the leading causes of cancer-related deaths worldwide, largely due to late diagnosis, tumor heterogeneity, multidrug resistance, and the limited efficacy of current systemic therapies. Conventional chemotherapeutic agents and molecularly targeted drugs often face challenges such as poor bioavailability, systemic toxicity, and rapid clearance, resulting in suboptimal therapeutic outcomes. This scenario highlights the need for innovative strategies that integrate natural bioactive compounds with advanced drug delivery platforms to improve treatment efficacy and safety [1].

Hepatobiliary cancers, comprising hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), represent a major global health challenge. According to the GLOBOCAN 2020 estimates, liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related mortality worldwide, with approximately 905,677 new cases and 830,180 deaths annually [2].

The management of hepatobiliary cancers, particularly hepatocellular carcinoma (HCC), relies on a combination of surgical, locoregional, and systemic therapies, tailored to the stage of disease and the underlying liver function. Curative options such as surgical resection and liver transplantation offer the best outcomes but are applicable only to a small subset of patients diagnosed at an early an advanced stage, where curative surgery is not feasible [3].

Locoregional therapies play a pivotal role in intermediate-stage disease. Trans arterial chemoembolization (TACE) is the most widely used modality, aimed at inducing ischemic necrosis while delivering high concentrations of chemotherapeutic agents directly to the tumor. Radiofrequency ablation (RFA) and microwave ablation are effective for small lesions, while Tran's arterial radio embolization (TARE) with Yttrium-90 has emerged as an alternative in selected patients [3 stage with preserved liver function and limited tumor burden. For the majority, diagnosis occurs at].

Ethanopharmacology, the scientific study of traditional medicines derived from plants, animals, and other natural sources, has played a pivotal role in modern drug discovery. By systematically documenting and validating the therapeutic practices of diverse cultures, ethanopharmacology provides a knowledge-driven approach to bioprospecting, guiding researchers toward bioactive compounds with therapeutic potential. Many landmark drugs—including artemisinin from *Artemisia annua* (antimalarial), paclitaxel from *Taxus brevifolia* (anticancer), and morphine from *Papaver somniferous* (analgesic)—were discovered through ethanopharmacological leads, underscoring the value of traditional medicine in shaping modern pharmacology [4].

In oncology, ethanopharmacology has been especially impactful, offering structurally diverse natural compounds capable of modulating apoptosis, angiogenesis, and immune pathways. Plant-derived metabolites such as flavonoids, alkaloids, terpenoids, and phenolic acids continue to serve as scaffolds for novel anticancer drugs. However, challenges such as poor bioavailability, pharmacokinetic limitations, and lack of standardization often hinder direct clinical application. Here, nano pharmacology emerges as a complementary strategy, enabling the formulation and delivery of ethanopharmacology-inspired metabolites with improved solubility, stability, and tumor-targeting properties.
Psidium guajava L. (guava), a plant widely used in traditional medicine across Asia, Africa, and Latin America, has attracted increasing scientific interest due to its rich phytochemical profile and broad pharmacological activities. Ethanopharmacological evidence highlights guava leaves, fruits, and bark as remedies for gastrointestinal, metabolic, and infectious disorders, many of which are linked to oxidative stress and chronic inflammation—pathological processes that also contribute to hepatocarcinogenesis [4].

Phytochemical investigations have identified flavonoids (quercetin, guaijaverin, and avicularin), phenolic acids (gallic acid and ellagic acid), and terpenoids as major secondary metabolites of guava. These compounds demonstrate multiple anticancer mechanisms, including modulation of apoptotic pathways, inhibition of NF-κB and PI3K/Akt/mTOR signaling, suppression of angiogenesis, and reduction of oxidative stress. In hepatocellular carcinoma (HCC) models, guava-derived flavonoids and phenolics have been shown to inhibit cell proliferation, induce apoptosis, and attenuate tumor-promoting inflammation.

The burden of hepatobiliary cancers, particularly hepatocellular carcinoma (HCC), continues to rise globally despite advances in surgical, locoregional, and systemic therapies. Limitations such as late-stage diagnosis, drug resistance, poor bioavailability of therapeutics, and systemic toxicities emphasize the urgent need for novel, integrative strategies. Natural products, guided by

ethanopharmacological knowledge, have historically contributed to oncology drug discovery, and *Psidium guajava* (guava) represents a promising candidate due to its diverse bioactive metabolites with documented antioxidant, anti-inflammatory, and anticancer properties [5].

2. Ethanopharmacological Background of Guava

Psidium guajava L. (family Myrtaceae), commonly known as guava, has been used for centuries in traditional medicine systems across Asia, Africa, and Latin America. In Ayurveda, guava leaves and fruits are prescribed for the management of gastrointestinal disturbances, wounds, and fevers. In traditional Chinese medicine, guava preparations have been employed to treat diabetes, inflammation, and liver disorders, while in African folk medicine, decoctions of the leaves are used for malaria, cough, and infections. These widespread uses highlight guava's ethanomedicinal versatility and cultural significance.

The pharmacological basis of these traditional applications lies in the plant's rich phytochemical profile, which includes flavonoids (quercetin, guaijaverin, and avicularin), phenolic acids (gallic acid, ellagic acid), tannins, and terpenoids. Ethnopharmacological reports link guava extracts to antimicrobial, anti-inflammatory, antioxidant, antidiabetic, and hepatoprotective effects, several of which overlap with mechanisms relevant to carcinogenesis and tumor progression. For example, guava's traditional use in liver-related ailments provides a rationale for exploring its metabolites as candidates for hepatoprotective and anticancer interventions [5].

2.1. Traditional Uses of Guava:

Psidium guajava L. has a long history of use in traditional medicine across different cultures. In Ayurveda and Siddha medicine, guava leaves, bark, and fruits have been employed to treat diarrhea, dysentery, wounds, ulcers, and diabetes. In traditional Chinese medicine (TCM), guava preparations are used for inflammation, cough, oral ulcers, and liver-related disorders. In many parts of Africa and Latin America, decoctions of guava leaves are commonly administered for malaria, gastrointestinal infections, toothache, and fever.

These ethanomedicinal practices are supported by the plant's rich phytochemical composition, including flavonoids (quercetin, guaijaverin, and avicularin), phenolic acids (gallic acid, ellagic acid), tannins, and terpenoids. The reported antimicrobial, antidiabetic, hepatoprotective, anti-inflammatory, and antioxidant properties form the pharmacological basis for many of its traditional uses. Importantly, guava's use in liver ailments and inflammatory conditions provides a rationale for its exploration in modern oncology research, particularly in hepatobiliary cancers where oxidative stress, inflammation, and metabolic dysregulation play critical roles in disease progression [5].

2.2 Historical Relevance of Guava in Disease Management:

The medicinal use of Psidium guajava L. dates back centuries and is deeply rooted in traditional healing systems across Asia, Africa, and Latin America. Historically, guava leaves, bark, and fruits were valued for their ability to manage infectious, metabolic, and inflammatory diseases. Ancient Ayurvedic texts describe guava preparations for treating diarrhea, dysentery, wounds, and ulcers, while traditional Chinese medicine recognized guava for managing cough, inflammation, and liver ailments. In African folk medicine, guava decoctions have long been prescribed for malaria, gastrointestinal infections, and fever.

Over time, these historical practices gained pharmacological validation as scientific studies revealed that guava is rich in bioactive metabolites such as flavonoids (quercetin, guayabera), phenolic acids (gallic acid, ellagic acid), tannins, and terpenoids. These compounds exhibit antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and hepatoprotective properties—mechanisms that align with guava's traditional use in managing diseases linked to oxidative stress and metabolic dysfunction [5].

2.3. Cultural and Clinical Anecdotes of Guava:

Guava (*Psidium guajava* L.) has been deeply embedded in the cultural and medicinal practices of many societies. In Indian traditional medicine (Ayurveda and Siddha), guava leaves and bark were boiled into decoctions to treat diarrhea, wounds, and liver disorders, and guava fruits were recommended for diabetes and digestive health. In Chinese folk medicine, guava tea was consumed to alleviate cough, inflammation, and fever, while in Latin American traditions, guava was widely prescribed for gastrointestinal infections, malaria, and toothache. These cultural anecdotes highlight guava's longstanding role as a "household medicine," trusted for its broad healing potential.

Clinically, anecdotal reports and small community-based studies have documented the use of guava leaf extracts in controlling diarrheal diseases and improving glycemic control in diabetic patients. Preparations such as guava leaf tea are still popularly consumed in Japan, Southeast Asia, and parts of Africa for managing blood sugar, hypertension, and liver health, reflecting both cultural continuity and a growing interest in plant-based preventive medicine. Although large-scale randomized clinical trials remain limited, these real-world practices provide an ethnopharmacological basis for modern pharmacological investigations into guavas anticancer and hepatoprotective properties [5].

3. Phytochemistry of Guava: Bioactive Metabolites

Guava (*Psidium guajava* L.) is rich in a diverse spectrum of secondary metabolites, which underlie its broad pharmacological activities. These compounds are distributed in various plant parts (leaves, fruits, bark, and roots), making guava a versatile source for drug discovery.

3.1. Flavonoids: Quercetin, quercetin glycosides (guayabera, avicularin, quercitrin), catechin, and epicatechin) Known for antioxidant, anti-inflammatory, hepatoprotective, and anticancer activities. Quercetin in particular has been extensively studied for its role in modulating signaling pathways such as PI3K/AKT, NF-κB, and MAPK, which are crucial in hepatobiliary cancer progression.

3.2. Phenolic Acids: (Gallic acid, ellagic acid, ferulic acid, caffeic acid, chlorogenic acid) these compounds contribute strong radical-scavenging and anti-inflammatory effects, protecting against oxidative liver damage and supporting chemopreventive potential.

3.3. Tannins: (Leucocyanidin, ellagitannins, Gallic tannins) Provide antimicrobial, astringent, and hepatoprotective benefits, aligning with guava's ethnomedicinal use in gastrointestinal and liver disorders.

3.4. Terpenoids & Essential Oils:(Oleanolic acid, ursolic acid, β-sitosterol, caryophyllene, limonene)

Exhibit anti-inflammatory, anticancer, and hepatoprotective properties. Ursolic acid, in particular, has shown activity in inducing apoptosis in cancer cells and inhibiting tumor growth.

Additionally, guava contains carotenoids (lycopene, β-carotene) and vitamin C, which synergize with polyphenols to enhance antioxidant defense mechanisms [5].

4. Engineered / Synthetic derivatives

While *Psidium guajava* is rich in bioactive phytochemicals, many of these natural metabolites face limitations such as poor solubility, low bioavailability, rapid metabolism, and limited tissue distribution. To overcome these barriers, researchers have developed synthetic derivatives and engineered analogs of guava-derived compounds, as well as novel formulation strategies that enhance their therapeutic value in oncology.

4.1. Flavonoid Derivatives (Quercetin-based analogs)

Quercetin, one of the most abundant guava flavonoids, has inspired the development of quercetin glycoside derivatives and semi-synthetic analogs with improved stability and water solubility.

Examples include quercetin-3-O-glucuronide and quercetin sulfates, which demonstrate enhanced plasma persistence and stronger anticancer potential compared to parent quercetin.

4.2. Triterpenoid Derivatives (Ursolic and Oleanolic Acid Analogs)

Ursolic acid, isolated from guava leaves, has been chemically modified to produce derivatives with increased potency and reduced hepatotoxicity.

Engineered forms such as C-28 ester/amide derivatives of ursolic acid show superior cytotoxicity against hepatocellular carcinoma (HCC) cells by promoting apoptosis and inhibiting angiogenesis.

Similarly, oleanolic acid derivatives have been explored for improved anticancer and hepatoprotective efficacy.

4.3. Nanostructured and Hybrid Derivatives

Instead of single-molecule modifications, guava metabolites have also been engineered into nanoformulations (liposomes, polymeric nanoparticles, and phytosomes).

For example, quercetin-loaded nanoparticles exhibit improved liver targeting, stability, and tumor suppression activity compared to free quercetin.

Hybrid formulations combining guava polyphenols with metal nanoparticles (e.g., silver, gold, and zinc oxide) have shown promising synergistic cytotoxic effects against cancer cells while reducing systemic toxicity. [5]

5. Mechanistic insights in hepatobiliary cancers

Hepatobiliary cancers, including hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), arise through a multifactorial process involving chronic liver injury, inflammation, genetic mutations, and dysregulated signaling cascades (Fig 2).

5.1. Chronic Injury and Inflammation

Persistent insults such as hepatitis B/C infection, alcohol abuse, NAFLD, aflatoxin exposure, or liver fluke infection lead to oxidative stress and DNA damage (Fig 1).

This creates a pro-tumorigenic environment characterized by fibrosis, cirrhosis, and altered extracellular matrix (ECM) dynamics.

5.2. Genetic and Epigenetic Alterations

TERT promoter mutations → telomerase reactivation. TP53 inactivation → impaired DNA repair and apoptosis. CTNNB1 mutations → constitutive Wnt/β-catenin activation.

5.3. Dysregulated Signaling Pathways

PI3K/AKT/mTOR → cell survival, metabolism, and angiogenesis. RAS/RAF/MEK/ERK (MAPK) → proliferation, differentiation, migration.

5.4. Tumor Microenvironment (TME)

Activated hepatic stellate cells promote fibrosis and angiogenesis. Immune suppression occurs via PD-L1 up regulation, regulatory T cells, and tumor-associated macrophages. [6]

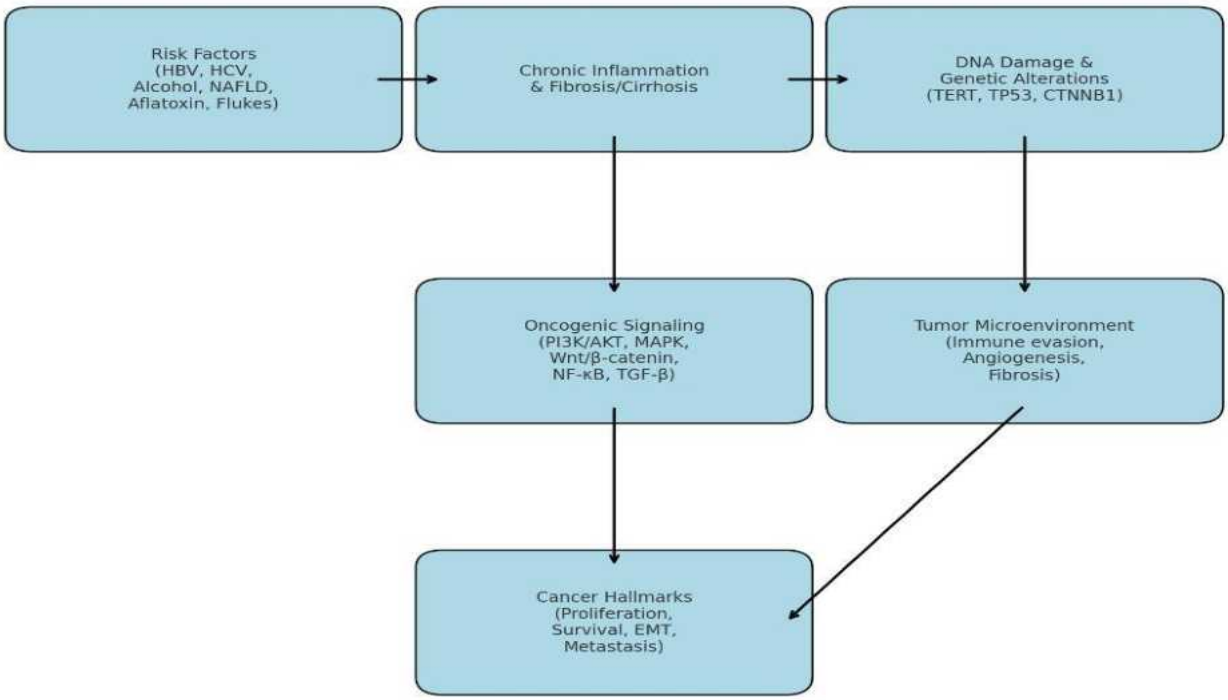

Fig 1: Pathway for risk factors lead to DNA damage, oncogenic signaling, and tumor progression in hepatobiliary cancer

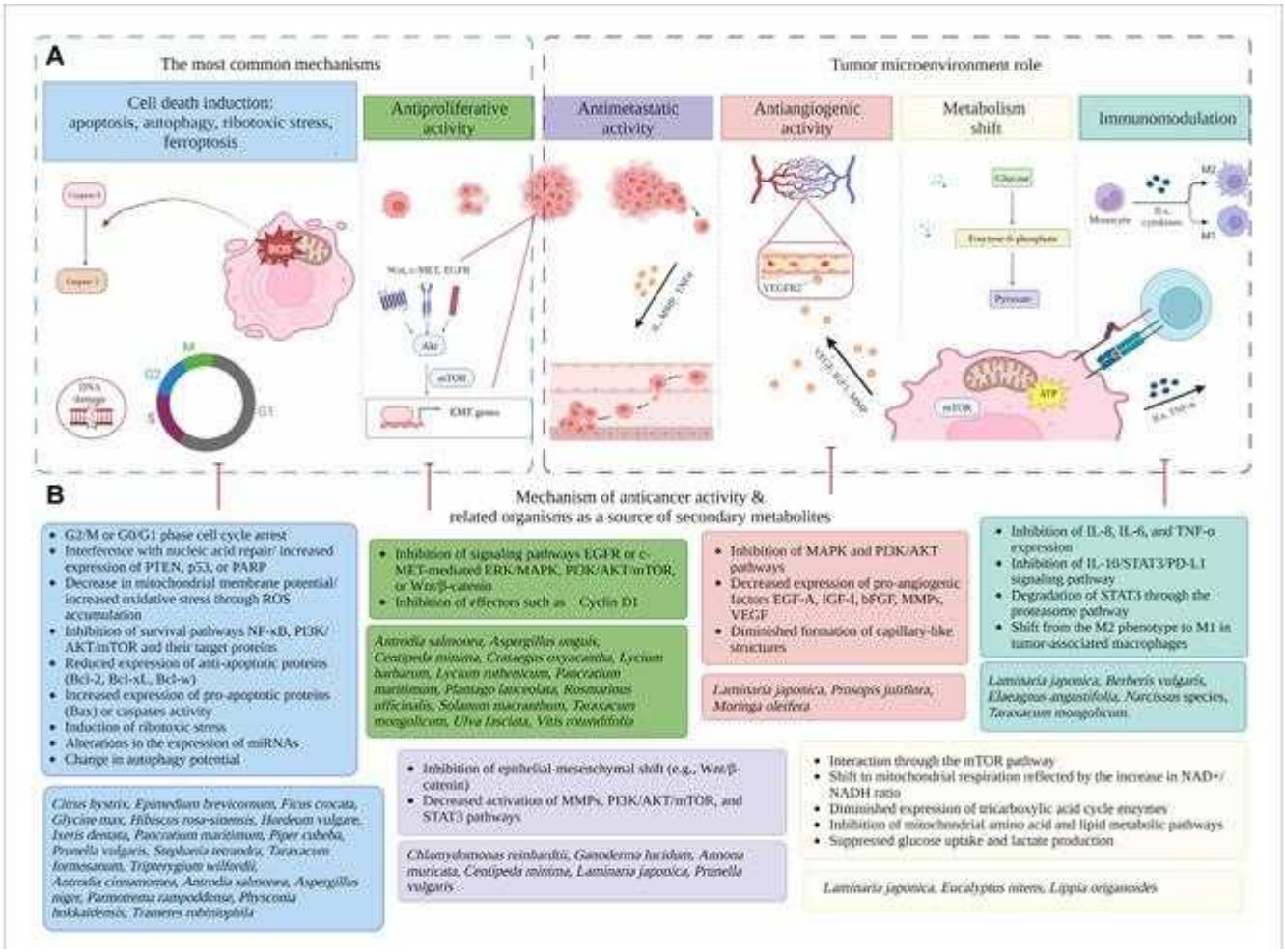

Fig 2: An overview of mechanistic effects of natural metabolites in endocrine-independent HER - 2negative breast cancer. (A). each mechanism of anticancer activity is described in details and recently studied organisms a source of secondary metabolites are presented (full species names including authorities and family are presented.

6. Toxicology

6.1. *In vitro* toxicology

6.1.1 Quercetin

In cancer cell lines (including HepG2 and other hepatoma lines) quercetin exhibits cytotoxicity and apoptosis induction at micro molar concentrations typically reported in the low-to-mid tens of μM (study-dependent). Effects measured include capsize activation, mitochondrial depolarization, cell-cycle arrest and down regulation of survival pathways (PI3K/AKT, NF-κB). These are pharmacodynamics effects (desirable in cancer cells) rather than generalized cytotoxicity—non-malignant hepatocytes are often less sensitive at the same concentrations, but sensitivity depends on exposure time and metabolic capacity.

6.1.2 Gallic acid

Shows antioxidant and pro-apoptotic activity in vitro. At higher micromolar concentrations it can induce apoptosis in hepatoma cells, but in non-transformed hepatocytes the responses are usually protective/antioxidant at lower doses. Cytotoxic concentrations vary across studies.

6.2. *In vivo* toxicology

6.2.1 Ursolic/Oleanolic acids

Generally cause low acute toxicity in animals but have limited oral bioavailability. Some long-term high-dose studies report liver enzyme perturbations or GI effects at supraphysiological doses—these are formulation- and dose-dependent. Nano- or co-formulations that increase exposure may require fresh toxicology evaluation.

6.2.2 Nano carrier-related *in vivo* toxicity

Nanoformulations can change bio distribution and toxicity profiles. For example:
Lipid nanoparticles and polymeric NPs often show acceptable tolerability but may accumulate in liver/spleen (desired liver targeting can increase local exposure and therefore local toxicity if payload or carrier is harmful at high concentration). [7]

7. Delivery Strategies for Guava Metabolites

Despite their strong pharmacological promise, guava-derived metabolites (quercetin, ursolic acid, gallic acid, lycopene) face poor aqueous solubility, low oral bioavailability, and rapid metabolism. These limitations restrict systemic exposure and therapeutic efficacy. To overcome these barriers, advanced delivery systems are being explored:

7.1. Nanoparticle-Based Delivery

Polymeric nanoparticles (PLGA, chitosan, PEGylated NPs): Improve stability, control release, and enhance hepatocyte uptake.
Solid lipid nanoparticles (SLNs) & nanostructured lipid carriers (NLCs): Effective for lipophilic metabolites (e.g., ursolic acid, quercetin).
Example: Chitosan-coated ursolic acid noisome improved liver targeting and protected against chemically induced hepatotoxicity in vivo.

7.2. Liposomes and Niosomes

Biocompatible lipid bilayers encapsulate hydrophobic guava metabolites, enhancing solubility and circulation time.

Suitable for co-delivery with chemotherapeutics (e.g., sorafenib) to achieve synergistic effects in hepatocellular carcinoma.

7.3. Self-Emulsifying Drug Delivery Systems (SEDDS)

Oil-based carriers that spontaneously form Nan emulsions in GI fluids. Enhance dissolution and absorption of poorly soluble guava flavonoids like quercetin.

7.4. Hydrogel and Hybrid Systems

Biodegradable hydrogels can release guava metabolites in a controlled manner. Hybrid Nano-hydrogel formulations of quercetin have shown improved tumor accumulation and sustained drug release in preclinical cancer models.

7.5. Targeted Delivery Approaches

Ligand-modified Nano carriers (e.g., galactose, glycyrrhizin, or folate) selectively bind receptors overexpressed on hepatocytes or tumor cells, increasing specificity.

Magnetic nanoparticles are also being tested for site-specific delivery under external magnetic guidance.

7.6. Combination & Co-Delivery Systems

Loading guava metabolites together with tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitors can help overcome resistance in hepatobiliary cancer.

Synergistic nano carriers allow simultaneous delivery of antioxidant phytochemicals + chemotherapeutic agents, enhancing efficacy while reducing toxicity. [7]

8. Challenges and Future Directions

8.1. Challenges

8.1.1 Poor Pharmacokinetics

Major guava-derived compounds (e.g., quercetin, ursolic acid, gallic acid) exhibit poor aqueous solubility, low oral bioavailability, and rapid metabolism, which limit systemic exposure and therapeutic potential.

8.1.2 Variability in Plant Extracts

Guava metabolite content depends on plant part, growth conditions, harvest time, and extraction method, creating difficulties in ensuring consistent quality and dosing for clinical applications.

8.1.3 Lack of Clinical Translation

While extensive in vitro and in vivo studies show anticancer activity, human trials are scarce, making it difficult to validate safety, efficacy, and dosing strategies in hepatobiliary cancers.

8.1.4 Toxicity and Drug Interactions

Although generally safe at dietary levels, high-dose use or Nano-formulation strategies may alter toxicological profiles or interact with liver enzymes and transporters, leading to unpredictable pharmacokinetics.

8.2. Future Directions

8.2.1 Advanced Delivery Systems

Development of nanoparticles, lipid carriers, hydrogels, and ligand-modified systems to enhance liver-specific delivery, bioavailability, and co-delivery with conventional therapeutics.

8.2.2 Systems Biology & Omics Integration

Transcriptomics, proteomics, and metabolomics can help elucidate precise molecular targets of guava metabolites, enabling personalized therapy strategies in oncology.

8.2.3 Combination Therapies

Exploring guava metabolites as adjuvants with TKIs, immune checkpoint inhibitors, and chemotherapy to overcome resistance and enhance efficacy in hepatobiliary cancer.

8.2.4 Standardization & Regulatory Framework

Establishing standardized extraction methods, pharmacopoeial profiles, and quality-control guidelines for guava-derived products to facilitate clinical translation. [7]

9. Conclusion

Hepatobiliary cancers remain a formidable global health challenge due to late-stage diagnosis, therapeutic resistance, and poor patient survival. Conventional treatment strategies, though advancing, are constrained by systemic toxicity, limited efficacy, and the inability to address tumor heterogeneity and the complex tumor microenvironment. In this context, ethanopharmacology-driven drug discovery provides a valuable bridge between traditional medicine and modern oncology.

Guava (*Psidium guajava*) metabolites—notably quercetin, gallic acid, ursolic acid, and lycopene—exhibit multifaceted bioactivities including antioxidant, anti-inflammatory, and pro-apoptotic effects, which are mechanistically relevant to hepatobiliary carcinogenesis. Preclinical studies consistently demonstrate their anticancer potential, but challenges remain regarding bioavailability, pharmacokinetics, standardization, and clinical validation. Nanopharmacology offers promising solutions through advanced delivery systems—nanoparticles, liposomes, hydrogels, and ligand-modified carriers—that can enhance solubility, target specificity, and therapeutic efficacy.

Moving forward, the integration of systems biology approaches, advanced drug delivery, and well-designed clinical trials will be pivotal in translating guava metabolites from bench to bedside. Establishing standardized extraction methods, safety profiles, and regulatory frameworks will further accelerate their transition into the oncology pipeline.

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