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Hyaluronic Acid-Coated Nanoparticles Encapsulating Silymarin for Cancer Therapy

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ABSTRACT
Cancer remains the leading cause of mortality globally, underscoring the urgent need for innovative therapeutic strategies. Among these strategies, nanoparticle technology has emerged as a promising avenue for cancer treatment. Recent advancements have enabled the modification of nanoparticles to exhibit favourable pharmacological properties through the incorporation of chemical ligands that specifically bind to receptors on the surface of malignant cells. The application of hyaluronic acid as a targeted ligand for nanoparticle coating presents a compelling alternative for active targeting. This approach allows for the controlled release of drugs in response to pH changes, while the high affinity of hyaluronic acid for CD44 receptors facilitates enhanced accumulation of these nanoparticles within cells that overexpress these receptors, such as cancer cells. In this review, we examine the advantages and recent developments in the use of hyaluronic acid nanoparticles (HA-Np) for the treatment of various cancer types. The findings indicate that HA-Np can form a nanoparticle system characterized by favourable properties, efficacy, and effective targeting of diverse cancer cell types. Consequently, this system represents a promising candidate for targeted drug delivery in cancer therapy, with the potential for further development in various oncological applications.
Key Words: Nanoparticles, Hyaluronic acid.

I. INTRODUCTION

Cancer remains a formidable challenge within the realm of medical science, characterized by its complex nature and resistance to conventional therapeutic interventions, thereby underscoring the urgent necessity for enhanced treatment strategies. Recent years have witnessed a significant rise in the global incidence of cancer, establishing it as the second leading cause of mortality, following cardiovascular diseases. [1] In 2014 alone, approximately 1.7 million individuals were diagnosed with cancer in the United States, resulting in 586,000 deaths. Among males, lung and bronchus cancers were associated with the highest mortality rates, while breast cancer was the predominant form of cancer among females. [2] The impact of cancer is not uniformly distributed across populations, as evidenced by its disproportionate effect on Disability Adjusted Life Years (DALYs) worldwide. The World Health Organization (WHO) projects that cancer may emerge as the leading cause of death by the year 2030. [3] In 2018, there were 18 million new cancer cases reported, with lung, prostate, and breast cancers representing the majority of these diagnoses. [4] As advancements in screening and early detection technologies continue, contemporary approaches increasingly prioritize preventive measures, improved prognostic capabilities, and targeted treatment regimens. Historically, there has been a recognition of the exponentially increasing risk of cancer-related mortality among individuals aged 25 to 74, attributed to the understanding that a variety of DNA mutations significantly contribute to cancer pathogenesis. [5,6] The 'somatic cell theory' suggests that these mutations occur in oncogenes and tumor suppressor genes, leading to unregulated cell proliferation and ineffective execution of cell cycle arrest or apoptosis, respectively. [7] Additionally, it is important to acknowledge the pivotal role of tumor angiogenesis in facilitating tumor metastasis and invasiveness, which considerably diminishes the efficacy of standard chemotherapy agents and elevates Vascular Endothelial Growth Factor (VEGF) to a crucial position in tumor progression and survival. [8,9,10]

THE ROLE OF SILYBIN

silybin in cancer therapy is primarily attributed to their antioxidant, anti-inflammatory, and anti-proliferative properties. These compounds may play a significant role in cancer treatment through various modulatory mechanisms that influence cellular processes such as proliferation, survival, differentiation, and migration (Briguglio et al., 2020). While the application of polyphenols has shown promising outcomes in both the prevention and treatment of cancer, their low bioavailability presents a notable limitation.

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Consequently, the concurrent use of synthetic pharmaceuticals and plant-derived compounds may yield more favourable results (Heenatigala Palliyage, Singh, Ashby, Tiwari, & Chauhan, 2019). Numerous phytochemicals, including resveratrol, lycopene, and silybin, have demonstrated anti-tumor activity with relatively low toxicity to normal cells. Therefore, these compounds could be utilized in conjunction with chemical anti-tumor agents, potentially resulting in synergistic effects in cancer treatment (S. H. Kim et al., 2019). Recent years have seen an increase in both in vivo and in vitro studies investigating herbal medicine across various cancer types. In this review, a search of the PubMed database using the keywords "Silymarin" and "Cancer" yielded 782 relevant articles. Given the extensive research documenting the anticancer effects of natural polyphenols (Kausar et al., 2012; Koushik et al., 2018), this review aims to summarize recent findings regarding the anti-carcinogenic properties of silymarin and silybin, while also discussing the underlying mechanisms of action based on evidence from epidemiological studies, laboratory experiments, and clinical trials.

SILYMARIN AS A THERAPEUTIC AGENT IN CANCER TREATMENT

Review has demonstrated that silymarin possesses anti-tumor properties by modulating several key characteristics of cancer, including tumor cell proliferation, apoptosis, metastasis, angiogenesis, and autophagy within the tumor microenvironment (see Fig. 1). For example, Ramakrishnan et al. (2009)[11,12] reported that silymarin effectively inhibited the growth of the hepatocellular carcinoma cell line HepG2, induced apoptosis, and increased the population of cells in the sub-G0/G1 phase. The underlying mechanism of silymarin's action involved a reduction in mitochondrial transmembrane potential, which resulted in an elevation of cytosolic cytochrome c (Cyt c). This treatment also led to the downregulation of proliferation-associated proteins (such as PCNA, c-Myc, cyclin D1, and β-catenin) and anti-apoptotic proteins (including surviving and Bcl-2), while simultaneously upregulating pro-apoptotic proteins (such as caspase-3, Bax, APAF-1, and p53). In a separate investigation, Deep et al. (2006) compared the tumoricidal effects of silymarin and silybin on prostate cancer cells, finding that both compounds inhibited cell proliferation, promoted cell death, and induced cell cycle arrest at the G1 and G2-M phases. Their findings suggested that the primary inhibitory effect of silymarin on cell cycle progression is closely associated with silibinin. Furthermore, in human colorectal cancer cells, the tumoricidal effects of silymarin were linked to its ability to inhibit the downregulation of β-catenin, thereby suppressing Want signaling (Eo, Park, & Jeong, 2016). Additionally, silibinin has been shown to exert anti-tumor effects through the modulation of immune responses, including the downregulation of programmed death-ligand 1 (PD-L1) (Sellam et al., 2020). Table 1 provides a summary of the anti-tumor activities of silymarin and silibinin against various cancers, both in vitro and in vivo.

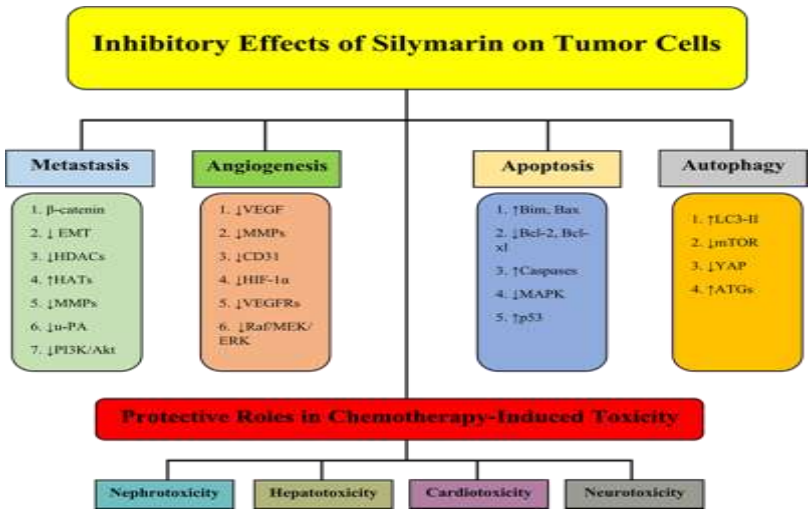

Figure 1.Illustrates the anti-tumor properties of silymarin, along with its molecular and signaling targets, as well as its protective functions against toxicity induced by chemotherapy.

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HYALURONIC ACID COATED NANOPARTICLES

Hyaluronic acid is a biodegradable, biocompatible, and non-toxic natural polysaccharide that is extensively utilized in the formulation of nanoparticles. It is classified as a non-sulfated glycosaminoglycan, characterized by its high hydrophilicity and composed of disaccharide units of glucuronic acid and N-acetyl-D-glucosamine. This polysaccharide is synthesized endogenously within the human body. Hyaluronic acid has the capacity to facilitate cellular communication by binding to CD44 receptors, which are distributed throughout various tissues, with a notable prevalence in cancerous cells. Consequently, hyaluronic acid functions as a ligand within targeted drug delivery systems by specifically interacting with CD44 receptors. This interaction is crucial as it modulates the release of BCL-2 within the cell, thereby inhibiting apoptosis, promoting cell proliferation, and enhancing cellular motility. The engagement of CD44 receptors by hyaluronic acid ligands is strategically employed to effectively target therapeutic agents, particularly in the context of cancer treatment.[45,46,47]

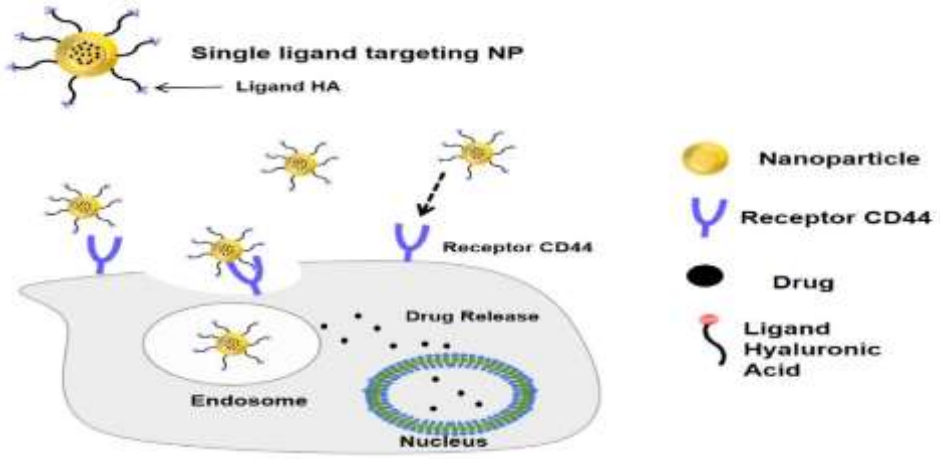

Figure 2Illustrates the internalization of HA-Np within cancer cells via the CD44 receptor.

THE BENEFITS OF HYALURONIC ACID-COATED NANOPARTICLES:

Targeted Delivery: Hyaluronic acid (HA) exhibits the ability to bind to receptors that are overexpressed on cancer cells, such as CD44, thereby enabling the selective delivery of therapeutic agents to tumor locations.

Enhanced Permeability and Retention (EPR) Effect: Nanoparticles, particularly those of smaller size, can take advantage of the EPR effect, which allows for their accumulation in tumor tissues due to heightened vascular permeability and inadequate lymphatic drainage.

Biocompatibility and Biodegradability: HA is a naturally occurring polymer characterized by its exceptional biocompatibility, biodegradability, and non-toxic properties, rendering it an appropriate candidate for drug delivery applications.

Improved Drug Stability and Solubility: The encapsulation of drugs within nanoparticles serves to shield them from degradation while simultaneously enhancing their solubility in aqueous environments.

Controlled Release: The structural design of nanoparticles can be tailored to facilitate the controlled release of encapsulated drugs, thereby optimizing therapeutic effectiveness and reducing adverse side effects.

HYALURONIC ACID-COATED NANOPARTICLES FOR SILYMARIN DELIVERY:

Enhanced Solubility and Stability:

The encapsulation of silymarin within hyaluronic acid (HA)-coated nanoparticles has been demonstrated to enhance its solubility and stability in biological fluids.

Controlled Release Mechanism:

These nanoparticles can be engineered to facilitate the controlled release of silymarin, thereby optimizing its therapeutic efficacy.

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Mitigation of Systemic Toxicity:

By specifically targeting cancer cells, HA-coated nanoparticles can diminish the systemic toxicity associated with silymarin, thereby reducing potential side effects.

Augmented Anticancer Efficacy:

Research indicates that HA-coated nanoparticles containing silymarin can significantly enhance its anticancer activity, as evidenced by both in vitro and in vivo studies.

STRATEGIES FOR FORMULATING SILYMARIN TO ENHANCE ITS BIOAVAILABILITY

The subsequent subsections will provide a comprehensive review of various methodologies specifically developed for the delivery of silymarin. These approaches will be systematically categorized in the concluding Table 1, which will also include relevant cross-references cited within the text. Additionally, Figure 2 presents the different formulations that have been created to enhance the solubility and bioavailability of silymarin, the majority of which are primarily intended for oral administration.[13 ,20]

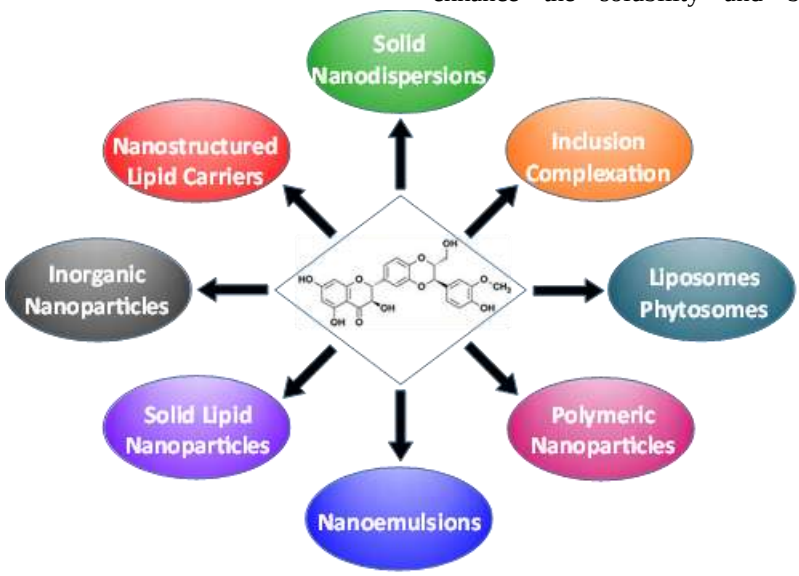

Figure 3 Current formulation strategies aimed at enhancing the bioavailability of silymarin.

EXAMPLES OF SILYMARIN-LOADED NANOPARTICLES AND THEIR EFFECTS

Silymarin-loaded zein nanoparticles (SLNPs):
These nanoparticles, stabilized by beta-cyclodextrin, have shown enhanced bioavailability and cytotoxicity against breast cancer cells (MCF-7).

Silymarin-loaded silver nanoparticles (AgNPs):
These nanoparticles exhibit improved anticancer activity in breast cancer cell lines (MCF-7 and MDA-231).

Silymarin-loaded tin(IV) nanoparticles:
These nanoparticles exhibit enhanced bioavailability and antiproliferative effects on colorectal cancer cells.

Silymarin-functionalized selenium nanoparticles (Si-SeNPs):
These nanoparticles have been shown to induce apoptosis and autophagy in gastric cancer cells (AGS).

Silymarin-loaded iron oxide nanoparticles (IONPs):
These nanoparticles have shown excellent anticancer activity against lung and liver cancer cells.

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Table 1. Anti-cancer activities of silybin

Cancer	Model	Dose	Anti-tumor activity	Ref
Ovarian	*in vitro*	50 and 100 µg/ ml	↓Cell proliferation, Cell cycle arrest, ↑Apoptosiss	(Fan, Ma, Liu, Zheng, & Huang, 2014)
Cervical	*in vitro*	40–100 µM	↓Cell viability, ↑Apoptosis, ↓Invasion, ↓Migration	(Yu et al., 2012)
Oral	*in vitro in vivo*	40–80 µg/ ml 200 mg/ kg/day	↓Cell proliferation, ↑Apoptosis, ↓Tumor growth	(Won et al., 2018)
Colon	*in vitro*	25 µM	↓Cell viability, ↑Apoptosis, ↑Necrosis, ↑Autophagy	(Khorsandi, Saki, Bavarsad, & Mombeini, 2017)
Skin	*in vivo*	0.5 %, w/ w in diet	↓Tumor growth, Tumor regression, ↑Apoptosis	(Singh, Tyagi, Zhao, & Agarwal, 2002)
Gastric*	*in vitro*	50–200 µM	↓Cell viability, ↑Apoptosis, Cell cycle arrest	(Wang, Cai, Jiang, Zhou, & Wu, 2014)
Lung	*in vivo*	25 and 50 mg/kg	↓Tumor growth, ↑Apoptosis, ↑$CD8^+$ *T*- cells, ↓MDSCs, ↓IL-10, ↑IL-2 and IFN-γ	(Wu, Liu, Guo, & Zhu, 2016)
Melanoma	*in vitro in vivo*	10–60 µg/ ml 500 mg/ kg/2 × a week	↓Cell viability, Cell cycle arrest, ↑Apoptosis, ↓Tumor growth, ↓Angiogenesis	(Vaid, Singh, Prasad, & Katiyar, 2015)
Glioma*	*in vitro in vivo*	30 µM 200 mg/ kg/day	↓Cell proliferation, ↑Apoptosis, ↓Metastasis, ↓Tumor volume	(K. W. Kim et al., 2009)
RCC	*in vitro*	35 µg/mL	↓PGE2-induced cell migration	(Woo, Min, Chae, Chun, & Kwo 2015)
Breast*	*in vitro*	60–90 µM	↓Cell proliferation, ↓Invasion, ↓Migration, ↓EMT, ↓Inflammasome activation	(Si et al., 2020)
Prostate*	*in vivo*	0.5 %, w/ w in diet	↓Tumorgrowth,↓Tumor progression, ↑Apoptosis, ↓Angiogenesis, ↓Metastasis	(Singh, Raina, Sharma, & Agarwal, 2008)
Pancreatic*	*in vitro in vivo*	25–100 µM 0.5 %, w/ w in diet	↓Cell proliferation, Cell cycle arrest, ↑Apoptosis, ↓Tumor growth, ↓Angiogenesis	(Nambiar, Prajapati Agarwal, & Singh, 2013)

Reference

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II. CONCLUSIONS

Natural products and their derivatives are emerging as promising therapeutic candidates for the treatment of various malignancies. Silymarin, known for its multi-targeting properties, has been extensively utilized in both in vitro and in vivo research to modulate cancer hallmarks and mitigate the toxicities associated with chemotherapy. The development of nano-delivery systems aims not only to protect silymarin from degradation but also to enhance its bioavailability, solubility, stability, and targeted, controlled delivery to specific sites. Additionally, nano formulations facilitate a sustained release of silymarin at the injection site, which presents a significant advantage by reducing the risk of side effects compared to silymarin in its unformulated state. However, the therapeutic efficacy of silymarin-loaded nanoparticles is contingent upon various factors, including the methods of preparation, particle size and charge, mechanisms of cellular uptake, intracellular metabolism, distribution, and the materials employed. Despite the potential of nano formulated silymarin or its unformulated counterpart as viable candidates for cancer treatment, several limitations and challenges persist.

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