

Review

Nano-Formulating of Organic Shields for Hepatic Carcinoma Therapy

Shahrazad Ahmed khalaf ¹, 

¹ Department of Forensic sciences, College of Science, University of Diyala, Ba'quhba, Diyala, Iraq; Shahrazad.kh@uodiyala.edu.iq

Abstract: Oxidative stress is a crucial element in the pathogenic mechanisms that initiate numerous chronic liver illnesses and substantially aids in the progression of hepatocarcinogenesis. Natural antioxidants mitigate oxidative stress by neutralizing free radicals and are essential in the management of free-radical-induced hepatic disorders. Nonetheless, their effectiveness is often limited by inadequate bioavailability and metabolic stability. Recent advancements have concentrated on creating nano-drug delivery methods that safeguard against degradation and augment therapeutic efficacy to overcome these constraints. Among the many significant advantages, they demonstrated the capacity to enhance bioavailability and facilitate targeted distribution, thereby minimizing off-target effects by precisely directing the antioxidant to the hepatic tumor location. Furthermore, these nanosystems facilitated sustained release, extending the therapeutic impact over time. Several of them shown synergistic effects when used in conjunction with other therapeutic drugs, resulting in enhanced overall effectiveness. This study is to examine current scientific advancements in nano-formulations using natural antioxidant compounds, emphasizing their potential as viable therapeutic strategies for liver cancer therapy. This review's originality is rooted on its thorough examination of recent advancements in nano-formulations of natural antioxidants for liver cancer therapy.

Keywords: hepatic carcinoma; nanoformulations; pharmaceutical application; natural substances; hepatocellular carcinoma; oxidative stress; antioxidants

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1. Introduction

One of the most aggressive and constantly rising types of cancer worldwide, liver cancer poses a serious danger to life [1]. It is the sixth most frequent kind of cancer, according to recent data, and it affects more males (the fifth most common type) than women (the ninth most common type) [2]. The liver parenchyma or other liver structures, including the bile duct, blood vessels, and immune cells, are where primary liver cancer, often referred to as primary hepatic cancer or primary hepatic malignancy, begins and grows [3, 4]. On the other hand, the majority of liver cancers are secondary or metastatic, which means they start in another body area (such the breast, colon, or lungs) and then move to the liver. The most prevalent subtype of primary liver cancers is hepatocellular carcinoma (HCC), which develops from hepatocytes and accounts for 80–90% of cases [5]. Intrahepatic cholangiocarcinoma (~6%), angiosarcoma and hemangiosarcoma (0.1–2.0%), two uncommon and extremely aggressive forms of cancer that start from the endothelial layer of blood vessels and spread quickly, and hepatoblastoma (~1%), a type of cancer that develops in immature liver cells and mainly affects children under the age of 15 [6].

Cirrhosis brought on by long-term viral infections (like hepatitis B and hepatitis C) or excessive alcohol use, metabolic disorders (like nonalcoholic steatohepatitis, nonalcoholic fatty liver diseases, obesity, and diabetes), and inherited liver diseases are risk factors that raise the incidence of primary liver cancer [7]. (such Wilson's disease and hemochromatosis), aflatoxins, iron buildup [8], and certain biliary system conditions (like fascioliasis, a zoonotic infectious illness brought on by parasitic worms belonging to the *Fasciola* genus) [9].

The use of natural antioxidants has grown more and more significant in terms of both the prevention and therapeutic treatment of liver cancer, given the mounting evidence linking OS to the development of the disease and the liver's vital function as the body's main organ of detoxification and homeostasis regulator [10]. With its wealth of (poly)phenolic compounds, whose health benefits have been recognized since antiquity and whose usage as medicinal herbs is a component of traditional medicine in many nations, the plant kingdom provides the best resources in this area. Unfortunately, owing to their low oral bioavailability, which is mostly caused by their quick first-pass metabolism and poor solubility in water, the widespread use of these compounds as medications has not been particularly effective up to this point. Furthermore, it is necessary to take into account these compounds' inherent chemical instability, since they readily oxidize in light and air [11].

A rapidly developing yet under-researched area, the employment of nanotechnology and natural antioxidants in the treatment of liver cancer is the subject of this review. Furthermore, this assessment couldn't have come at a more critical time, what with the growing worldwide prevalence of liver cancer and the pressing want for better focused, less harmful treatments. Its originality comes from the fact that it analyzes in depth the nano-formulations developed over the last ten years with the express purpose of increasing the therapeutic efficacy of natural antioxidants; doing so sheds light on how these breakthroughs are starting to circumvent the shortcomings of conventional liver cancer therapies.

2. Materials and Methods

2.2 Oxidation in Nano Formula: Polyphenols

Extensive research is now being conducted in the realm of oncology regarding plant-derived polyphenols, which are well acknowledged as key OS effectors by the scientific community. Phenolic acids, stilbenes, flavonoids, coumarins, and lignans are the main categories into which these phytochemicals are grouped according to their chemical structure [12]. Of these, the stilbene-type aflatoxin resveratrol (RES) has garnered the most attention due to its extensive plant-based distribution (e.g., grapes, berries, legumes, peanuts, and different types of grasses) and, more significantly, its wide range of pharmacological activities, which encompass antioxidant, anti-inflammatory, anticarcinogenic, antiplatelet, cardioprotective, immunomodulatory, hyperlipidemic, neuroprotective, and vasorelaxant effects [13]. The trans-isomer of naturally occurring RES (3,5,4'-trihydroxystilbene; Figure 1) is more plentiful, stable, and therapeutically active than the cis-isomer. Resveratrol has pharmacokinetic and physicochemical instability, much as any polyphenol. Notwithstanding its high intestinal mucosal absorption rate (~75%), RES undergoes substantial metabolism in the intestines and liver, leading to the formation of inert 3-O-glucuronide and 3-O-sulfate molecules. Also, very little free RES is floating about in the bloodstream because it binds to plasma proteins and LDLs.



Figure 1: (A) Respirable elastin scaffold (RES) chemical structure; (B) FA-HSA conjugate synthesis; (C) FA-HSA-RES-NPs shown as a result of RES encapsulation inside FA-HSA by means of a high-pressure fluid nano-homogeneous emulsification technique; and (D) suggested mechanism of functional tumor targeting.

Using a similar high-pressure homogenization emulsification approach, the same scientists had previously created a composite nano-formulation, that encapsulated RES in a glycyrrhizic acid (GA)-HSA conjugate. Since GA accumulates on the surface of hepatocytes' cells and exerts its hepatoprotective and detoxifying activities toward GA receptors, GA was used as a targeted ligand instead of FA in this instance. Recent studies or reviews of the literature have focused on various nanoscale drug delivery devices that incorporate GA for the treatment of HCC. In a manner similar to what was previously said, the targeted ligand's free-COOH groups were used to conjugate with HSA in an alkaline environment. The resultant GA-HSA conjugates were then loaded with RES. The GAHSA-RES-NPs had an EE of 83.6% and DL of 11.5%, and they were around 108 nm in size, making them virtually spherical. The nanosystem gently and steadily emitted RES. The effect on the ability to block the growth of HepG2 cells was marginally better (1.5-fold) when contrasted with the prior nano-formulation, namely, GA-HSA-RES-NPs $\rightarrow$ IC₅₀ = 62.5 μ g/mL vs. RES $\rightarrow$ IC₅₀ = 95.5 μ g/mL. This nano-formulation was validated by in vivo body distribution experiments using a near-infrared fluorescence imaging approach in mice with H22 tumors, as well as by in vitro cell uptake tests [14].

Curcumin, a secondary metabolite found in the tuberous root (rhizome) of different species of turmeric, especially *Curcuma longa* L. [15], is a bright yellow-orange diarylethene-structured compound that has been the subject of extensive research due to its pharmacological importance and positive health effects. Another plant-derived polyphenolic derivative, RES, has received the greatest amount of attention. In terms of pharmacological activity and pharmacokinetic restrictions, CUR and RES have a spectrum that is quite similar.

Rather, by employing a high-pressure microfluidics approach, Zhao X. and colleagues aimed to create lipid NPs loaded with both CUR and Doxorubicin (Dox), a commonly used chemotherapeutic drug with limited efficacy in HCC management. This strategy would take advantage of CUR's synergistic effects with Dox.

Figure 2 shows that rutin (RU) is a common natural form of Q. It is also known as quercetin-3-O-rutinoside, rutoside, or sophorin, and it is simply Q with glucose and rhamnose replaced for the hydroxy group at position C-3. Q, like other flavonoids, is best used in nano-formulation preparations when it is in its glycoside form because it is more accessible and more soluble in water than when it is in its aglycone form. Researchers developed PLGA-based NPs loaded with RU using the double emulsion-solvent evaporation process. RU is a bioactive component.

In order to overcome these obstacles, Tang P. et al. [16] developed and manufactured a nanodrug delivery system that incorporates HK onto a polymer backbone called chitin (CH). This system is functionalized with a second bioactive component called epigallocatechin-3-gallate (EGCG; Figure 3). When it comes to the number of biopolymers found in nature, CH is second only to cellulose. It finds its way into the exoskeleton of arthropods, the cell walls of fungi, and the surface structures of a number of other invertebrates. Chemically, it is a polysaccharide that contains N-acetyl-glucosamine units.

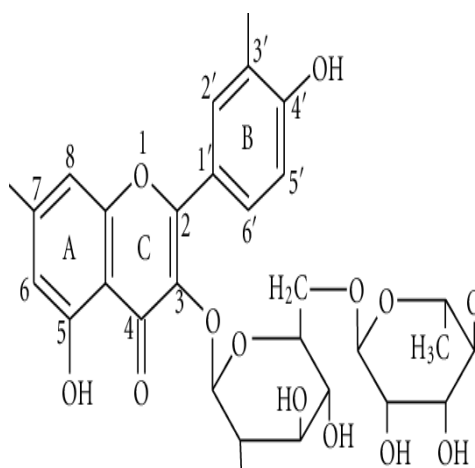


Figure 2. Chemical structure of rutin

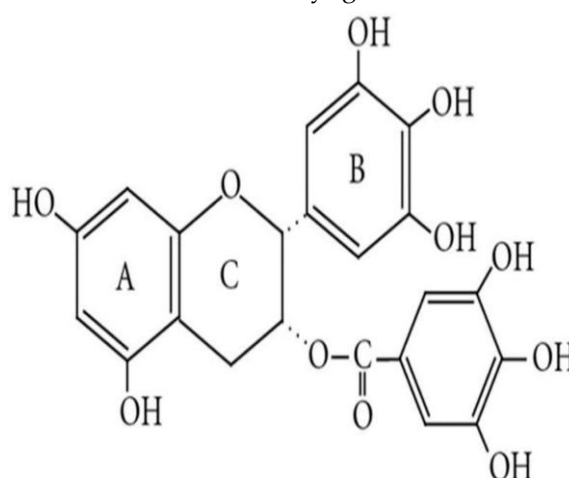


Figure 3. Hierarchy of the gallate of epigallocatechin crystals.

3. Functional Nanoparticles Rapeseed Oil-Based Antioxidants

Antioxidant, anti-inflammatory, immunomodulatory, and anticancer actions are only a few of the many pharmacological benefits enjoyed by terpenoids and other fascinating classes of naturally occurring chemicals. The majority of terpenoids are produced in chloroplasts by plants. They primarily function as a defense mechanism against heat and oxidative stress, and they are made from the lipophilic 5-carbon unit isoprene via the photosynthesis-dependent 2-C-methyl-D-erythritol-4-phosphate pathway. On the other hand, terpenoids aren't only a component of secondary and primary metabolism; they may also be produced by bacteria and yeasts. The isoprene unit, which has a C=C unsaturation, combines with ROS and quenches them, which is why these molecules work as antioxidants. One way to categorize terpenoids is by the number of isoprene units they contain. Monoterpenes have 2 units, sesquiterpenes have 3, diterpenes have 4, triterpenes have 6, tetraterpenes have 8, and polyterpenes have more than 8. Due to their ability to selectively kill liver cancer cells using a pleiotropic mode of action while sparing normal cells, these phytochemicals have recently gained attention as a potentially useful class of HCC chemopreventive and therapeutic agents [17].

Higher chemical stability and bioavailability compared to other poly(phenols) suggest it may have a significant overall impact on shielding cells against damage caused by OS [18], even if it is not as powerful as other natural antioxidants.

3. Obstacles and Ideas for the Future

All the big pharma firms are racing to be the first to market with nanomedicine and natural substances. When it comes to administering bioactive compounds, nanomedicine—the medical use of nanotechnology—holds tremendous promise, as it allows for the customization of dosage, site, and formulation to achieve maximum efficacy with minimal side effects. Various NP matrix properties, such as lipids in SLNPs, functionalizable organic polymers, or even real metals, allow for precise control over bioactive compound solubility and release timing, as well as the development of stimuli-responsive delivery platforms and the implementation of multiphase therapeutic treatments that involve the gradual release of a single active ingredient or the simultaneous administration of multiple active compounds with the ability to bind specific targets at different times and exert synergistic effects. These characteristics are particularly important in cancer, where selectivity of action is key, for both treatment and early detection by identifying tumor biomarkers. The use of natural substances aligns well with the future of medicine, which is focused on preventing and treating diseases through enhancing the body's defense systems and natural processes, as well as with the eco-sustainable methods of synthesizing bioactive compounds and the green approach to resource management. There are still a number of obstacles that need to be overcome before nano-formulations of natural antioxidants can be used to their full therapeutic potential in the treatment of liver cancer.

The need for substantial clinical studies is one of the key obstacles. There is a huge chasm between what works in the lab and what works in the clinic, even if preclinical research has been encouraging. To determine the effectiveness, safety, and long-term consequences of these nano-formulations in human patients with varying genetic variables, liver functioning, and disease stages, clinical studies are essential. During production, there is yet another major obstacle. Consistency, stability, and quality control from batch to batch are especially challenging in the large-scale manufacture of nano-formulations. Optimizing nano-formulation designs via continuous manufacturing processes allows for reproducible control over nanoparticle size, shape, and surface properties, which in turn improves targeted specificity and decreases the likelihood of side effects. Furthermore, it would be fascinating to see research into the use of nano-formulated antioxidants in conjunction with other therapeutic treatments to enhance the current standard of care for liver cancer, such as immunotherapy, chemotherapy, and radiation. Antioxidant nano-formulations show promise as a potential therapy for liver cancer, but more research is needed to confirm this. To sum up, there are still obstacles, but there's no denying the promise of nano-formulations of natural antioxidants in treating liver cancer. Improved outcomes for patients with liver cancer may be possible with the help of more focused, tailored, and effective treatments made possible by ongoing research and innovation.

Conflicts of Interest: Declare conflicts of interest or state “The authors declare no conflict of interest.”

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