An overview on various nano- formulations of resveratrol in combination with different drugs for the treatment of HCC

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Abstract— **Liver cancer remains a serious threat to global health, and its prevalence is increasing worldwide. Its causes include, among other factors, exposure to the C or B hepatitis viruses, alcohol use, smoking, obesity, nonalcoholic fatty liver disease, diabetes, and oxidative stress. There are other primary liver cancer types, but hepatocellular carcinoma will be our main focus (HCC). Naturally occurring bioactive food components such as polyphenolic compounds, for example, have demonstrated good antioxidant activity and show promise for use in the prevention of cancer. Since it has a broad spectrum of medicinal activities, including its anticancer, anti-inflammatory, and antioxidant properties, resveratrol, a natural polyphenol and phytoalexin, has received a lot of interest in the last 10 years. It has been shown that resveratrol suppressed HCC cell growth in a dose-dependent manner in both anchorage-dependent and independent conditions. However, its limited therapeutic value is due to its weak water solubility, poor chemical stability, and short biological half-life. Poor pharmacokinetics and low potency appear to be the two main bottlenecks of resveratrol among the many restrictions. To accelerate the transition of resveratrol from the laboratory to the bedside, new perspectives and tactics have been put forth. The most promising strategy in the meantime is to improve resveratrol bioavailability through novel formulations. As an alternative, stronger resveratrol analogues could be created to increase the substance's anticancer effectiveness. The physicochemical features of resveratrol, the therapeutic potential of resveratrol nano-formulations, and the anticancer efficacy of resveratrol encapsulated n nanoparticles on hepatocarcinoma and various malignancies are the key topics of this paper.**

Keywords— Resveratrol, Nanoparticle, HCC, Polyphenol, Anticancer.

I. INTRODUCTION

In terms of cancer-related mortality globally, liver cancer ranks fifth. The most prevalent and deadly kind of cancer is hepatocellular carcinoma (HCC). The prevalence of liver cancer has increased significantly in Japan, Western Europe, and the United States, even though the bulk of HCC occurrences still occurs in specific death and morbidity rate. (1) The substantial systemic toxicity of chemotherapeutic medicines makes treatment difficult and frequently results in treatment cessation (2).

Antioxidant resveratrol, which has a wide range of beneficial therapeutic effects, is one of the polyphenols that has received the most attention in the last 20 years. The Japanese scientist Takaoka discovered and extracted resveratrol from white hellebore in 1939. Resveratrol is found in both cis and trans isomeric forms and has two phenol rings (monophenol and diphenol) connected by a double styrene link. Compared to the cis form, the transform appears to be more stable. Lipid peroxidation and COX-2 are outmatched by it. Oxidative stress is caused by reactive oxygen species, which are continuously generated inside the body as a result of many biological activities.

These include anticancer, antiangiogenic, antioxidant, and cardioprotective actions. It also exhibits a variety of pharmacological properties. Due to its short biological half-life caused by hepatic metabolism and the existence of enterohepatic recirculation, resveratrol's therapeutic use is insufficient. Resveratrol concentrations in the blood and tissues are confirmed to be extremely low following oral ingestion due to metabolic pathways.

oral delivery, Nasal administration, and Intravenous injection are used for the delivery of resveratrol.

Increased plasma half-life, decreased immunogenicity, increased biopharmaceutical stability, improved low-molecular-weight drug solubility and bioavailability, and the potential for tailored drug delivery are all benefits of NDDS. They do, however, come with advantages and restrictions of their own(3).

II. PHARMACOKINETIC AND PHYSICOCHEMICAL PROPERTIES OF RESVERATROL

The melting point of resveratrol is 254°C, which has a molecular weight of 228.25 g/mol. It is a hydrophobic chemical with a log P O/W = 3.1,(4) and a poor aqueous solubility of 30 g/Ml (5). It is a creamy white powder. According to the Biopharmaceutical Classification System, resveratrol is classified as a "Class II" chemical since it exhibits a solubility-limited absorption across biological membranes. The resveratrol structure allows for the creation of both trans- and cis-isomers, with the trans-isomer being the most stable (6). This is made possible by a double bond connecting two phenolic rings. The trans and cis isomers may be identified clearly in nuclear magnetic resonance spectroscopy due to their chemical shifts, which are changes in the spectrophotometric UV absorption levels that allow for their identification. When exposed to UV radiation, trans-resveratrol, which is more physiologically active, transforms into the cis-isomeric form. (7). When shielded from light and maintained in a wide pH range, trans-resveratrol is stable for months. (8) Trans-resveratrol has pKa values of 8.99, 9.63, and 10.64 for the 1, 2, and 3 phenolic groups, respectively. (9) When the structure of resveratrol is not known, the substance is typically referred to as trans-resveratrol due to its stable nature and biological activity.

Despite having chemopreventive effects, the poor bioavailability and chemical instability of resveratrol provides several pharmacokinetic difficulties. Resveratrol is extensively absorbed (75%) by the intestinal epithelium after oral treatment thanks to passive diffusion. However, it undergoes substantial glucuronidation and sulfate conjugation in the liver and intestines, resulting in the metabolites trans-resveratrol-3-O-glucuronide and trans-resveratrol-3-sulfate, respectively(10). Only trace levels of free resveratrol remain in the systemic circulation since it can also be found as free resveratrol, which forms complexes with low-density lipoproteins and plasma proteins like albumin. t was discovered that glucuronides, sulfates, and free resveratrol are the three metabolites of resveratrol that are present in the systemic circulation in the order of abundance. (11) As a result, resveratrol has a relatively short plasma half-life of just 8 to 14 minutes and reaches its maximal plasma concentrations an hour (after intake) and six hours later (following enteric recirculation of resveratrol metabolites). The most important means of excretion are through urine or faeces. Sulfates are excreted in the urine at a faster rate (84%) than glucuronides and free resveratrol, which are only excreted in trace levels (17%). (12) Additionally, resveratrol and its metabolites are also discovered in faeces, although only a very small percentage of sulfates (1%) are passed through the faeces. The terminal elimination half-life of resveratrol after intravenous injection ranges between 7.8 and 35 minutes. (13)

III. MECHANISM OF ACTION

Resveratrol's modes of action can exhibit either cell death or cell protection; however, these actions are dependent on the state of the cells, the amount employed, and the length of the contract. (14) Resveratrol's chemical structure allows it to interact with many kinases and enzymes, which prevents cell damage or death brought on by oxidative stress, which can lead to a variety of disorders. (15)Additionally, resveratrol can block the phosphatidylinositol 3-kinase pathway, which normalizes cell variation, development, and a variety of other processes(16,17). Numerous resveratrol effects on the phosphatidylinositol 3-kinase pathway have been linked to numerous mechanisms, according to certain studies is transformed into prostaglandins by cyclooxygenases (COX), which are restrained by resveratrol(18).

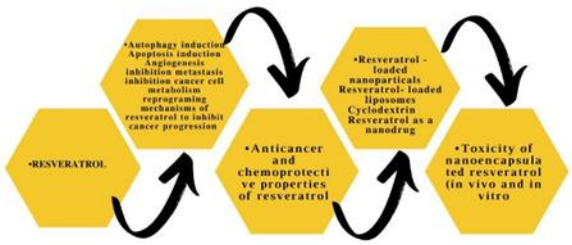

Fig 1. Mechanism of action of Resveratrol to inhibition of cancer cells [19]

IV. RESVRATROL NANOFORMULATION

Resveratrol is currently sold as a nutritional supplement that comes in the typical dose forms of pills, capsules, and powders. (20) The ability to increase the aqueous solubility and bioavailability of resveratrol, improve physicochemical stability, and enable targeted and controlled drug release are just a few advantages that novel drug delivery systems, such as polymeric nanoparticles, cyclodextrins, micelles, and liposomes, offer over traditional forms. Due to the enhanced penetration and retention (EPR) effect, in which these molecules aggregate preferentially in cancer tissues, nano-sized formulations are particularly favourable in cancer therapies. (21) were among the pioneers who postulated the EPR effect to explain the selective aggregation of nanocarriers around solids. Researchers have since then created a variety of medication delivery techniques to take advantage of this phenomenon. (22) Since the lymphatic system of the malignant tissues is also compromised, nanoparticles can easily diffuse out of the vasculature and concentrate in the interstitial fluid because the blood arteries surrounding the tumour cells are heavily fenestrated with pore widths ranging from 3380 nm to 780 nm. (23)

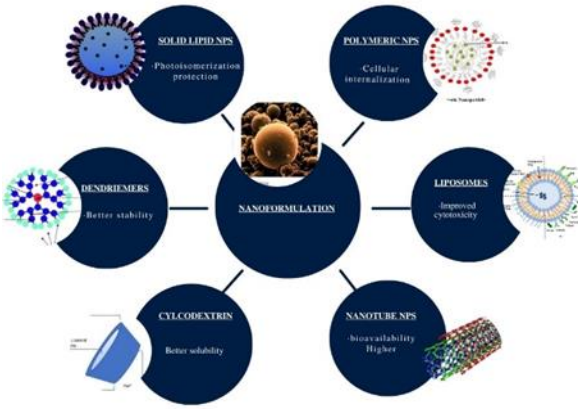

Fig 2. Types of various nanoformulation of Resveratrol for HCC treatment [24]

A. Liposome

Liposome-based nanoformulations were the first to enter clinical trials, and numerous studies in recent years have concentrated on the viability and effectiveness of resveratrol-loaded liposomes in pursuing cancer cells. investigated the efficiency of a dequalinium PEG distearoylphosphatidyl ethanolamine conjugate-modified mitochondrial targeting resveratrol in overcoming multidrug resistance. By reducing mitochondrial depolarization, releasing cytochrome c, and increasing the caspase-9 and -3 activities, the resveratrol-loaded liposomes were effective at inducing apoptosis in cancer cells that were both non-resistant and resistant to chemotherapy. Additionally, resveratrol-loaded liposomes had a remarkable anticancer effect by penetrating deeply into the coretumourumor spheroids and xenografted resistant A549/tumoursumors in nude mice. (25) Later, to reverse drug resistance in breast cancer cells, the produced liposomes were coloaded with paclitaxel and resveratrol. The liposome's average size was 50 nm, and its encapsulation efficiency was higher than 50%. The authors' key findings were that liposomes significantly improvetumouror retention and bioavailability in mice with drug-resistant tumours, as well as their pronounced cytotoxicity against drug-resistant MCF-7/ADR tumour cells. (26) Resveratrol and 5-FU were co-loaded in a single PEGylated liposome in a separate investigation to examine their synergistic effects on an NT8e head and neck squamous cancer cell line. Co-encapsulation with 5-FU significantly decreased the quantity of resveratrol needed to achieve 50% cell death (5.2 vs. 31 mM), (27) it was found. Similar to this, other researchers have investigated the defences against inflammatory/oxidative reactions linked to skin cancer of quercetin and resveratrol co-encapsulated in liposomes. In a mouse model of skin lesions, liposomes significantly reduced oedema and leukocyte infiltration while enhancing the anti-ROS activity in fibroblasts and improving tissue damage. (28) Using a Tf receptor, the serum glycoprotein transferrin (Tf) participates in the transfer of iron into developing cells (TfR). To address this increased need for iron, cancer cells express TfRs more than normal cells do. Because TfR is highly expressed in cancer cells and can internalize via clathrinid-mediated endocytosis, it is the perfect drug delivery target for malignant cells. (29) When compared to free resveratrol or resveratrol-PEGylated liposomes, Tf-targeted resveratrol-loaded liposomes (Tf-resveratrol-L) boosted cytotoxicity and generated higher levels of apoptosis with a corresponding rise in caspases 3/7 activation in glioblastoma (GBM) cells. Additionally, a xenograft mouse model of GBM showed Tf-resveratrol-L to be more efficient in reducing tumour growth and enhancing survival. (30)

B. Cationic solid lipid nanoparticle

In the current study, the creation and assessment of resveratrol (RV)-loaded cationic solid lipid nanoparticles (RV-c-SLNs) for the treatment of hepatocellular carcinoma are the main objectives (HCC). (31) Utilizing a factorial design, the formulation was optimized, and subsequent tests on drug release, cytotoxicity, biodistribution, in vivo preclinical use, and biochemical evaluation were conducted in vitro. (32) The ideal formulation had stable 12-week storage at 25°C/60% RH, homogeneous disparity, positive zeta potential, and uniform size. (33) The in vitro drug release and cytotoxicity investigation revealed that resveratrol-solid lipid nanoparticle (RV-SLN) had significantly higher cytotoxicity on the HepG2 cell line than RV solution, with 60% of the drug being released within the first six hours. (34) Additionally, a rat model of HCC used in the anticancer activity and biodistribution studies revealed increased accumulation of RV-c-SLN in the tumour tissue compared to RV solution and RV-SLN (P0.01). Additionally, the levels of pro-inflammatory cytokines were significantly reduced and antioxidant enzymes were balanced in the RV-c-SLN. (35) Hepatic nodules were less frequent, necrosis formed, inflammatory cells were infiltrated, blood vessels became inflamed, and cells swelled, according to histopathological analysis. Overall, the findings suggested that increased anticancer activity in RV-c-SLN was demonstrated by in vitro, in vivo, and biochemical tests. (36) Colloidal medication and/or gene carriers known as solid lipid nanoparticles (SLN) were created from solid lipids and surfactants and are thought to be safe. As positively charged particles may adhere to cellular surfaces and be ingested more easily than negatively charged SLN, cationic SLN, which is typically employed for manufacturing poorly water-soluble medicines and for gene delivery reasons, can also harm cells. (37) This work's major goal was to test a variety of cationic SLN and look into how they affected the activity of antioxidant enzymes, the number of reactive oxygen species (ROS), and potential oxidative damage to membrane lipids in HepG2 cells. After cells were exposed to SLN, a significant rise in ROS was detected by the Dichlorofluorescein assay. Superoxide dismutase and glutathione peroxidase activity were both boosted by exposure to SLN, however, glutathione reductase activity was lowered. Sulfhydryl groups decreased, but there was no discernible rise in thiobarbituric reactive species. These findings show that cationic SLN induced oxidative stress in HepG2 cells, but that the cells were able to reduce the stress under the exposure circumstances described, resulting in minimal damage to cellular components (38).

C.Nanomedicine

Nanoparticles eliminate the drawbacks of conventional chemotherapeutic medicines, such as their low tissue penetration, high systemic exposures, and concomitant damage to normal tissues. This review focuses on resveratrol's physicochemical properties, the therapeutic potential of resveratrol nanoformulations, and the anticancer activity of resveratrol-encapsulated nanoparticles on a variety of malignancies, including skin, breast, prostate, colon, liver, ovarian, and lung cancers (focusing on both in vitro and in vivo studies).

The solubility, oral bioavailability, stability, and controlled release of resveratrol have all been improved through the use of nanotechnology methods. Considered a possible technique to treat various tumours, the resveratrol nanoparticles have significantly improved their anticancer efficacy both in vitro and in vivo. (39)

D. Gold Nanoparticle:-

Gold nanoparticles (AuNPs) with antitumorigenic actions prevent the onset, growth, and spread of tumours by controlling some processes, including proliferation and apoptosis. The impact of AuNPs on the metastasis of breast cancer hasn't been thoroughly investigated, and it's unclear how they react when stimulated with 12-O-tetradecanoylphorbol-13-acetate (TPA). Therefore, utilizing green nanotechnology, we created resveratrol-capped gold nanoparticles (Rev-AuNPs) and looked into their potential anti-invasive capabilities in human breast cancer cells in response to TPA stimulation. The Rev-AuNPs generated spherical, 22.28±2.98 nm diameter nanoparticles. Next, we discovered that Rev-AuNPs dramatically reduced the ability of breast cancer cells to migrate and invade as a result of TPA at non-cytotoxic concentrations. Matrix metalloproteinase (MMP)-9 and cyclooxygenase-2 expression that was stimulated by TPA were inhibited by Rev-AuNPs (COX-2). Additionally, TPA-induced nuclear translocation and activator protein-1 (AP-1) and

nuclear transcription factor-B (NF-B) transcriptional activation were markedly reduced by Rev-AuNP administration (AP-1). In the TPA-stimulated breast cancer cells, Rev-AuNPs decreased the phosphorylation of phosphoinositide 3-kinase/Akt (PI3K/Akt) and extracellular signal-regulated kinase (ERK)1/2 signalling but did not affect the phosphorylation of Jun N-terminal kinase (JNK) or p38 MAPK. In particular, Rev-AuNPs demonstrated more effective anti-invasive efficacy than resveratrol without cytotoxicity. For the same doses, Rev-AuNPs had a larger inhibitory effect than resveratrol on the activation of MMP-9, COX-2, NF-B, AP-1, PI3K/Akt, and ERK. Additionally, we showed that the suppression of MMP-9 and COX-2 expression and MMP-9 enzymatic activity caused by Rev-AuNPs was reversed by siRNA knockdown of HO-1 expression. Our results demonstrated that the anti-invasive actions of Rev-AuNPs in response to TPA stimulation were mediated through the inhibition of MMP-9, COX-2, NF-B, AP-1, PI3K/Akt, and ERK and/or the activation of HO-1 signalling cascades. The pharmacological potential of Rev-AuNPs to treat breast cancer tumours is highlighted by this new result. (40)

E.Cyclodextrins

Cyclodextrins the impact of cyclodextrins that have been enhanced with resveratrol has also been studied by certain scientists. .(41) Using the 7,12-dimethylbenz[a]anthracene-induced hamster oral squamous cell carcinoma (OSCC) cell line (HCPC I) and an animal model, examined the effects of resveratrol complexed with two 2-hydroxypropyl—cyclodextrin formulations (cream and mouthwash). (42) In a dose- and time-dependent manner, formulations increased the antiproliferative activity. The formulations demonstrated increased efficacy in experimental settings where they reduced the emergence and growth of OSCC and oral pre-neoplastic lesions. (43) In another study, a resveratrol sulfonyl ether-ßcyclodextrin complex was prepared in a 1:1 ratio by freeze drying to assess its influence on drug aqueous solubility and anticancer efficacy against breast cancer cell line (MCF-7 cells). (45,46) This complex significantly increased resveratrol's aqueous solubility, increasing it from 0.03 to 1.1 mg/ml at 25°C and improving cancer The cytotoxicity of resveratrol/β-cyclodextrin (β-CD) and resveratrol /β-CD/2-hydroxypropyl-β-cyclodextrin complexes was examined in a different study using cancer cell lines (HeLa and Hep3B) and healthy cell lines (human umbilical vein endothelial cells [HUVEC]). (47) The complexes produced a significant level of cytotoxicity in both cancer cell lines, particularly Hep3B, and had no negative effects on normal cells, according to the major findings. (48)

F.Polymeric nanoparticle

FDA-approved polymeric particles or human because of being biodegradable, non-toxic, and biocompatible such as polyethylene glycol (PEG), poly(lactide-co-glycolide) (PLGA), and polycaprolactone (PCL) polymers. While polymeric NPs enhance drug penetration into cells and therefore enhance their bioavailability, erosion in the polymeric structure enables regulated release. On the other hand, drug loading into polymeric NPs can be accomplished either by conjugation with the polymer terminals or by dispersion within its matrix. (49) According to several studies, resveratrol polymeric NPs have different advantages than free resveratrol in terms of in vivo properties. For example, Singh and Pai found that when resveratrol was encapsulated into PLGA polymeric type NPs, the release time was prolonged to twelve days and the NPs remained stable for six months, but the absorption rate increased seven times and the area under the curve (AUC) was prolonged ten times more than the native compound. (50) The manufacturing of polymeric nanoparticles is generally expensive and time-consuming, and they have a very low drug-leading city in addition to not being stable in the bloodstream. As a result, scaling them up for mass production is challenging. (51)

V. RESVERATROL WITH VARIOUS HCC CHEMOPREVENTIVE DRUGS

Co-delivery drug combination	Liver disease	Important findings	REF
Resveratrol and Sulfasalazine	Liver cancer	The dual-targeted micelles displayed increased cytotoxicity and internalization, a decreased liver/body weight ratio, angiogenesis suppression, and accelerated apoptosis.	(52)

Resveratrol and Curcumine	Liver cancer	the enhanced permeability and retention (EPR) effect, improved bioavailability, Drug concentrations increased adjacent to the tumour, and a positive therapeutic impact was seen without any overt adverse effects.	(53)
Resveratrol – copper-based	Liver disease	These two components work well together to reduce NAFLD inflammation, and research suggests that liver-targeted, NAFLD-specific aptamer-mediated targeted ultrasonic nanobubbles may be a viable treatment option.	(54)
Resveratrol and poly (lactic-co-glycolic acid)	Fatty liver disease	These results demonstrated that RSV-PLGA-NPs offered excellent and steady drug delivery with tiny particle size, high capsulation efficiency, and well-controlled drug release, which significantly improved the stability, water solubility, and bioactivity.	(55)
Resveratrol and folate conjugated human serum albumin	Liver cancer	FA-HSA-RESNPs had a greater uptake rate than the original RES. The ability of FA-HSA-RESNP to target tumours was demonstrated by labelling in vivo activity with Cy5 fluorescent FA-HSA-RESNP utilizing near-infrared imaging. The bioavailability of FA-HSA-RESNPs following intravenous delivery was approximately 5.95 times greater than that of the original RES.	(56)
Resveratrol and Ethinylestradiol	Liver disease	Hepatic SOD and GPx both increased significantly as a result of the therapy. In comparison to EE-treated rats, RENE lowered serum TNF-, NO, MMP-2, MMP-9, and hepatic MDA. It also suppressed the serum ALP, ALT, and -GT activities. The findings unmistakably imply that RENE has a strong preventive effect on cholestasis brought on by EE.	(57)
Resveratrol-loaded glycyrrhizic acid-conjugated human serum albumin	Liver cancer	shown effective target orientation to liver tumours and sustained-release capability.	(58)
Resveratrol and polylactic-co-glycolic acid (PLGA)	Liver cancer	The XTT cytotoxicity study was used to assess the variations in the anticancer effects on cells after the synthesis of these nanoparticles, as well as the impacts of RES on cell viability.	(59)
Resveratrol and chitosan modified with biotin and avidin	Liver cancer	alteration of biotin inhibited NPs' capacity to target the liver. This was demonstrated in a liver cancer experiment. According to this study, A-B-CS-NPs may be a powerful drug	(60)

		delivery vector that is especially effective against hepatic cancer.	
RES-and chitosan TPP (sodium tripolyphosphate)	Liver Cancer	According to this study, drug-loaded CS-TPP nanoparticles could be used to administer bioactive Res for chemotherapy effectively.	(61)
Resveratrol and Nano-gold partical	Liver cancer	Res-GNPs significantly reduced vascular endothelial growth factor (VEGF) expression in tumour tissue, stimulated tumour apoptosis, and inhibited tumour development.	(62)
Resveratrol and glycogen modified using α-lipoic acid (α-LA)and lactobionic acid (Lac)	Liver cancer	The development of Gly-based nanocarriers for the encapsulation of Res in this study's method offers a promising means of effectively reducing the NAFLD process.	(63)
Hepatic-Targeted Nano-enzyme with Resveratrol	Liver cancer	This discovery demonstrated the possibility of the hepatic targeting and Res delivery nanoplatforms as a biosafety and effective technique for treating NASH and other liver diseases.	(64)

VI. FUTURE PROSPECTIVE

The chemical family of polyphenols may offer hope for the fight against cancer. Human epidemiological research confirms a link between consuming natural polyphenols and a lower risk of developing cancer. Several methods, such as resveratrol prodrugs and the creation of nanostructured delivery systems, have been used to increase the low systemic bioavailability and cellular uptake of resveratrol. (65)

The goal now is to create new medication formulations that will enable the medicine to reach the site of action, get through all the obstacles to resveratrol bioavailability, and function properly.

The majority of research has been heavily invested in creating resveratrol controlled-release formulations with increased resveratrol stability and solubility, further increasing it's in vitro release capabilities.

To maximize resveratrol's pharmacological efficacy for HCC, efforts will be made to create nanoformulations of the compound with high loading capacities and colloidal stability.

To increase the bioavailability of these chemicals, many formulations have been developed, with canonization being one of the more famous methods. By expanding surface area and enhancing characteristics, a micronized resveratrol formulation was created to increase bioavailability. Since the Cmax of the micronized formulation was three times greater than that of a single dosage of non-micronized resveratrol, micronized formulations might be used to increase the bioavailability of resveratrol. (66)

Polyphenols have been shown to have anticancer and anticarcinogenic properties, making them a prospective therapeutic alternative with the potential to enhance the results of already-used treatments. Resveratrol is a naturally occurring polyphenolic chemical that may be combined with other chemopreventive compounds and is available in PLA, PEG, and PLGA formulations. These nanoformulations, either by themselves or in combination with other chemotherapeutic medicines, have demonstrated potential anticancer properties. (67)

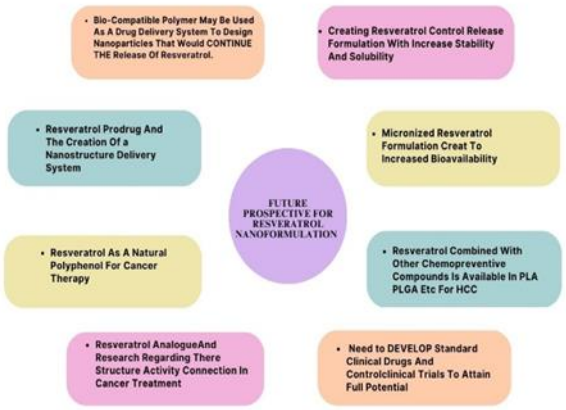

Fig: Future prospective for resveratrol nanoformulation

While being less effective than the trans-isomer, the cis-isomer is nevertheless an active form that is frequently disregarded. Although data on RSV metabolite activity is lacking, other conjugated polyphenols that share a strong structural similarity with RSV have been shown to exhibit biological activity and improved pharmacokinetics and pharmacodynamics. On the other hand, it's important to consider the deconjugation at specific sites leading to the parent aglycone (RSV) as well as the precise nature of the endogenous metabolite.

RSV has to be developed into a standard clinical drug, which calls for long-term epidemiologic research and controlled clinical trials to fully realize its potential. It is the perfect biomolecule for the treatment and prevention of chronic disorders, either alone or in conjunction with other medications, due to its long-term safety, affordability, and therapeutic potential. Hippocrates' dictum that "Let food be thy medicine and medicine be thy food" can be supported by the inclusion of RSV in reverse pharmacology. (68)

The future of resveratrol's use in cancer treatments and its translation into clinical applications has been brightened by its anti-tumour properties of resveratrol analogues and research regarding their structure-activity connection of them. (69)

To prevent anti-cancer drug resistance, combine anti-cancer medications with distinct modes of action and low cross-resistance; (II) employs anti-cancer medications with distinct toxicities so that each anti-cancer medication can be delivered at close to its maximum dose. (70)

According to the study, two biocompatible polymers may be used as a drug delivery system to create core-shell nanoparticles that would allow for the continuous release of the resveratrol that has been loaded into them. The core-shell nanoparticles created in this scientific effort might thus be utilized as a future medicine delivery system. (71)

VII. CONCLUSION

According to studies, liver cancer has a relatively high mortality and morbidity rate in men and is the fourth biggest cause of cancer-related deaths worldwide. The severe systemic toxicity of chemotherapy medicines makes treatment difficult and eventually resulted in treatment discontinuation. A variety of neoplasms have been studied to see if resveratrol, a well-known natural polyphenolic stilbenoid, could be used to treat them. Its wide availability and versatility have aided applications, making it appear as a promising agent for upcoming clinical use. Resveratrol therapy decreased cell viability, proliferation, invasion, and migration by inducing autophagy in HCC cells in a time- and dose-dependent manner in the investigation of the chemopreventive effect of resveratrol on hepatocarcinoma. Resveratrol, a naturally occurring anticancer compound, has the potential to be a potent chemopreventive drug because of its capacity to interact with some molecular targets involved in the metabolism of carcinogens, cell proliferation, apoptosis, etc. Also demonstrated the resveratrol ability to alter several signalling pathways. The low chemical stability, poor absorption and localized delivery, and limited bioavailability of resveratrol, however, have prevented its full potential from being investigated. Novel nanostructured delivery technologies were recently developed to successfully address these drawbacks, enhance resveratrol bioavailability, and increase cellular absorption. For resveratrol, advantageous effects in cancer chemoprevention as well as therapy, a variety of nanotechnology methods have been tried. The development of a library of nanomaterials with intelligent design and synthesis, perfect control over their physicochemical characteristics, and ease of surface functionalization to increase specificity is necessary for the effective development of cancer nanotherapeutics. These methods can reduce systemic toxicity at tumour sites by preventing harm to healthy cells. This review has explored and discussed the most current innovative nanotechnology methods utilized to deliver sustained amounts of resveratrol. This would serve as the drive for continued development of research on novel nanodevices able to consolidate the chemopreventive potential of resveratrol for hepatocarcinoma and other chemotherapeutics.

REFERENCE

[1] Jemal A, Bray F, Center M. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69–90.

[2] Sia D, Villanueva A, Friedman SL, Llovet JM. Liver cancer cell of origin, molecular class, and effects on patient prognosis. Gastroenterology. 2017;152:745–761.

[3] Zahra Ahmadi, Reza Mohammadinejad, Milad Ashrafizadeh, Drug delivery systems for resveratrol, a non-flavonoid polyphenol: Emerging evidence in last decades, Journal of Drug Delivery Science and Technology, 2019, (51), Pages 591-604,

[4] Robinson K, Mock C, Liang D. Pre-formulation studies of resveratrol. Drug Dev Ind Pharm. 2015;41(9):1464-1469.

[5] Amri A, Chaumeil JC, Sfar S, Charrueau C. Administration of resveratrol: what formulation solutions to bioavailability limitations? J Control Release. 2012;158(2):182-193.

[6] Perrone D, Fuggetta MP, Ardito F, et al. Resveratrol (3,5,4'-trihydroxystilbene) and its properties in oral diseases. *Exp Ther Med*. 2017;14(1):3-9.

[7] Trela BC, Waterhouse AL. Resveratrol: isomeric molar absorptivities and stability. J Agric Food Chem. 1996;44(5):1253-1257.

[8] Deak M, Falk H. On the chemistry of the resveratrol diastereomers. Monatsh Chem. 2003;134(6):883-888. 23. Walle T. Bioavailability of resveratrol. Ann N Y Acad Sci. 2011;1215 (1):9-15.

[9] Albuquerque B, Costa MS, Peca IN, Cardoso MM. Production of double-walled nanoparticles containing meloxicam. Polym Eng Sci. 2013;53(1):146-152.

[10] Sergides C, Chirila M, Silvestro L, Pitta D, Pittas A. Bioavailability and safety study of resveratrol 500 mg tablets in healthy male and female volunteers. Exp Ther Med. 2016;11(1):164-170.

[11] Singh G, Pai RS. Optimized PLGA nanoparticle platform for orally dosed trans-resveratrol with enhanced bioavailability potential. Expert Opin Drug Deliv. 2014;11(5):647-659.

[12] Wenzel E, Somoza V. Metabolism and bioavailability of trans-resveratrol. Mol Nutr Food Res. 2005;49(5):472-481.

[13] Walle T, Hsieh F, DeLegge MH, Oatis JE, Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. Drug Metab Dispos. 2004;32(12):1377-1382.

[14] Vijayakumar MR, Kumari L, Patel KK, et al. Intravenous administration of trans-resveratrol-loaded TPGS-coated solid lipid nanoparticles for prolonged systemic circulation, passive brain targeting and improved in vitro cytotoxicity against C6 glioma cell lines. RSC Adv. 2016;6(55):50336–50348

[15] Williams CB, Hughes MC, Edgett BA, et al. An examination of resveratrol's mechanisms of action in human tissue: impact of a single dose in vivo and dose responses in skeletal muscle ex vivo. *PLoS One*. 2014;9(7):e102406.

[16] Berman AY, Motechin RA, Wiesenfeld MY, Holz MK. The therapeutic potential of resveratrol: a review of clinical trials. NPJ Precis. (2017)(1), 35 .

[17] Parekh P, Motiwale L, Naik N, Rao KV. Downregulation of cyclin D1 is associated with decreased levels of p38 MAP kinases, Akt/PKB and Pak1 during the chemopreventive effects of resveratrol in liver cancer cells. Exp. Toxicol. Pathol. (2011) 63(1–2), 167–173.

[18] Kundu JK, Shin YK, Kim SH, Surh YJ. Resveratrol inhibits phorbol ester-induced expression of COX-2 and activation of NF-kappaB in mouse skin by blocking IkappaB kinase activity. Carcinogenesis (2006) 27(7), 1465–1474.

[19] Higdon J. Resveratrol: nanocarrier-based delivery systems to enhance its therapeutic potential 16 Nov 2020 VOL 15, ISSUE 28

[20] Sharifi-Rad J, Quispe C, Mukazhanova Z, et al. Resveratrol-Based Nanoformulations as an Emerging Therapeutic Strategy for Cancer. *Front Mol Biosci*. 2021;8:649395. Published 2021 Sep 1.

[21] Rossi D, Guerrini A, Bruni R, et al. trans-Resveratrol in nutraceuticals: issues in retail quality and effectiveness. *Molecules*. 2012;17(10):12393-12405.

[22] Rotches-Ribalta M, Andres-Lacueva C, Estruch R, Escribano E, Urpi-Sarda M. Pharmacokinetics of resveratrol metabolic profile in healthy humans after moderate consumption of red wine and grape extract tablets. *Pharmacol Res*. 2012;66(5):375-382.

[23] Fang J, Sawa T, Maeda H. Factors and mechanism of "EPR" effect and the enhanced antitumor effects of macromolecular drugs including SMANCS. *Adv Exp Med Biol*. 2003;519:29-49.

[24] Hobbs SK, Monsky WL, Yuan F, et al. Regulation of transport pathways in tumour vessels: role of

tumour type and microenvironment. *Proc Natl Acad Sci U S A*. 1998;95(8):4607-4612.

[25] Fang J, Nakamura H, Maeda H. The EPR effect: Unique features of tumour blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Adv Drug Deliv Rev*. 2011;63(3):136-151.

[26] Wang, X. X., Li, Y. B., Yao, H. J., Ju, R. J., Zhang, Y., Li, R. J., et al. The use of mitochondrial targeting resveratrol liposomes modified with a dequalinium polyethylene glycol-distearoylphosphatidyl ethanolamine conjugate to induce apoptosis in resistant lung cancer cells. Biomaterials (2011)32, 5673–5687. 04.029

[27] Meng J, Guo F, Xu H, Liang W, Wang C, Yang XD. Combination Therapy using Co-encapsulated Resveratrol and Paclitaxel in Liposomes for Drug Resistance Reversal in Breast Cancer Cells in vivo. *Sci Rep*. 2016;6:22390.

[28] Mohan, A., Narayanan, S., Sethuraman, S., and Krishnan, U. M. Novel resveratrol and 5-fluorouracil encapsulated in PEGylated nanoliposomes improve chemotherapeutic efficacy of combination against head and neck squamous cell carcinoma. BioMed. Res. Int. 2014:424239.

[29] Caddeo, C., Nacher, A., Vassallo, A., Armentano, M. F., Pons, R., FernàndezBusquets, X., et al. (2016). Effect of quercetin and resveratrol co-incorporated in liposomes against inflammatory/oxidative response associated with skin cancer. Int. J. Pharm. 513, 153–163.ijpharm.2016.09.014

[30] Daniels, T. R., Delgado, T., Rodriguez, J. A., Helguera, G., and Penichet, M. L.The transferrin receptor part I: biology and targeting with cytotoxic antibodies for the treatment of cancer. Clin. Immunol.(2006). 121, 144–158.

[31] Jhaveri, A., Deshpande, P., Pattni, B., and Torchilin, V. Transferrintargeted, resveratrol-loaded liposomes for the treatment of glioblastoma. J. Control. Release (2018). 277, 89–101.

[32] Rahman M, Almalki WH, Afzal O, Alfawaz Altamimi AS, Kazmi I, Al-Abbasi FA, Choudhry H, Alenezi SK, Barkat MA, Beg S, Kumar V, Alhalmi A. Cationic Solid Lipid Nanoparticles of Resveratrol for Hepatocellular Carcinoma Treatment: Systematic Optimization, in vitro Characterization and Preclinical Investigation. Int J Nanomedicine. 2020 Nov 23;15:9283-9299.

[33] El-Serag HB. Hepatocellular carcinoma. *N Engl J Med*. 2011;365(12):1118–1127.

[34] Kumar V, Bhatt PC, Rahman M, Al-Abbasi FA, Anwar F, Verma A. Umbelliferon-α- d - glucopyranosyl-(2 I → 1 II)-α-Dglucopyranoside ameliorates Diethylnitrosamine induced precancerous lesion development in the liver via regulation of inflammation, hyperproliferation and antioxidant at the pre-clinical stage. *Biomed Pharmacother*. 2017;94:834–842

[35] . Liu Z, Peng Q, Li Y, Gao Y. Resveratrol enhances cisplatin-induced apoptosis in human hepatoma cells via glutamine metabolism inhibition. *BMB Rep*. 2018;51(9):474–479.

[36] Rahman M, Beg S, Alharbi KS, et al. QbD-driven development of nano-antioxidant therapy containing solid lipid nanoparticles of ganoderic acid for the treatment of hepatocellular carcinoma. *J Pharm Innov*. 2020.

[37] Doktorovová S, Santos DL, Costa I, et al. Cationic solid lipid nanoparticles interfere with the activity of antioxidant enzymes in hepatocellular carcinoma cells. *Int J Pharm*. 2014;471(1–2):18–27.

[38] Tolba R, Kraus T, Liedtke C, Schwarz M, Weiskirchen R. Diethylnitrosamine (DEN)-induced carcinogenic liver injury in mice. *Lab Anim*. 2015;49(1_suppl):59–69.

[39] Bhatt H, Rompicharla SVK, Komanduri N, et al. Development of curcumin-loaded solid lipid nanoparticles utilizing glyceryl monostearate as single lipid using QbD approach: characterization and evaluation of anticancer activity against human breast cancer cell line. *Curr Drug Deliv*. 2018;15(9):1271–1283.

[40] Annaji M, Poudel I, Boddu SHS, Arnold RD, Tiwari AK, Babu RJ. Resveratrol-loaded nanomedicines for cancer applications. *Cancer Rep (Hoboken)*. 2021;4(3):e1353.

[41] PARK, S. Y., CHAE, S. Y., PARK, J. O., LEE, K. J., & PARK, G. Gold-conjugated resveratrol nanoparticles attenuate the invasion and MMP-9 and COX-2 expression in breast cancer cells. Oncology Reports, (2016). 35(6), 3248–3256.

[42] Gregoriadis G, Florence AT. Liposomes in drug delivery. Clinical, diagnostic and ophthalmic

potential. *Drugs*. 1993;45(1):15-28. doi:10.2165/00003495-199345010-00003

[43] Peters, S., Physiologically-based Pharmacokinetic (PBPK) Modeling and Simulations: Principles, Methods, and Applications in the Pharmaceutical 868 Industry. John Wiley & Sons, Sweden. 2013 Jul; 2(7): e55.

[44] Szejtli, J., Past, present, and future of cyclodextrin research. Pure Appl. Chem. 2004 76, 1825–1845.

[45] Silva, Figueiras, A., Gallardo, E., Nerin, C., Domingues, F.C.,. Strategies to 910 improve the solubility and stability of stilbene antioxidants: a comparative study between cyclodextrins and bile acids. Food Chem. 2014145, 115–125.

[46] Ansari, K.A., Vavia, P.R., Trotta, F., Cavalli, R.,. Cyclodextrin-based nanosponges for delivery of resveratrol: in vitro characterisation, stability, cytotoxicity and permeation study. AAPS PharmSciTech 2011 12, 279–286.

[47] Venuti, V., Cannava, C., Cristiano, M.C., Fresta, M., Majolino, D., Paolino, D., Stancanelli, R., Tommasini, S., Ventura, C.A., A characterization study of resveratrol/sulfonyl ether-beta-cyclodextrin inclusion complex and in vitro anticancer activity. Colloids Surf. B Biointerfaces 2014. 115, 22–28

[48] Parveen S, Sahoo SK. Polymeric nanoparticles for cancer therapy. *J Drug Target*. 2008;16(2):108-123.

[49] SINGH, G an RS PAI. Optimized PLGA nanoparticle platform for orally dosed trans-resveratrol with enhanced bioavailability potential. Expert Opinion on Drug Delivery. 2014, 5(11), 647–659.

[50] O'Reilly, RK, CJ HAWKER a KL WOOLEY. Cross-linked block copolymer micelles: 1075 functional nanostructures of great potential and versatility. Chemical Society Reviews. 2006, 11(35), 1068–1083

[51] Lactobionic/Folate Dual-Targeted Amphiphilic Maltodextrin-Based Micelles for Targeted Codelivery of Sulfasalazine and Resveratrol to Hepatocellular Carcinoma Doaa M. Anwar, Sherine N. Khattab, Maged W. Helmy, Mohamed K. Kamal, Adnan A. Bekhit, Kadria A. Elkhodairy, and Ahmed O. Elzoghby *Bioconjugate Chemistry* 2018 *29* (9), 3026-3041

[52] Zheng Y, Jia R, Li J, Tian X, Qian Y. Curcumin- and resveratrol-co-loaded nanoparticles in the synergistic treatment of hepatocellular carcinoma. J Nanobiotechnology. 2022 Jul 20;20(1):339.

[53] Guo, Xinmin, Huang, Zhihui, ChnJialin, He, Kun, Lin, Jianru, Zhang, Hui, Zeng, Synergistic delivery of resveratrol and ultrasmall copper-based nanoparticles by aptamer-functionalized ultrasound nanobubbles for the treatment of nonalcoholic fatty liver disease, Frontiers in Physiology, 2022 Vol13,

[54] Wan, Shuqian et al. "Resveratrol-loaded PLGA nanoparticles: enhanced stability, solubility and bioactivity of resveratrol for non-alcoholic fatty liver disease therapy." Royal Society open science. 14 Nov. 2018, vol. 5,11 181457

[55] Lian, Bolin; Wu, Mingfang; Feng, Ziqi; Deng, Yiping; Zhong, Chen; Zhao, Xiuhua, Folate-conjugated human serum albumin-encapsulated resveratrol nanoparticles: preparation, characterization, bioavailability and targeting of liver tumours. Taylor & Francis.2022

[56] Hussein MA, Kasser AK, Mohamed AT, Eraqy TH, Asaad A Resveratrol Nanoemulsion: A Promising Protector Against Ethinylestradiol-Induced Hepatic Cholestasis in Female Rats. J Biomol Res

[57] Wu M, Lian B, Deng Y, Feng Z, Zhong C, Wu W, Huang Y, Wang L, Zu C, Zhao X. Resveratrol-loaded glycyrrhizic acid-conjugated human serum albumin nanoparticles wrapping resveratrol nanoparticles: Preparation, characterization, and targeting effect on liver tumours. J Biomater Appl. 2017 Aug;32(2):191-205.

[58] DOĞAN M, ZİŞAN GÜRGAH F. Preparation of resveratrol containing poly (lactic-co-glycolic acid) nanoparticles and investigation of its cytotoxic effect in C6 glioma cells. J.Res.Pharm. 2022; 26(4): 911-919

[59] Le Bu, Liang-Chun Gan, Xiao-Qiang Guo, Feng-Zheng Chen, Qin Song, Qi-Zhao, Xiao-Jun Gou, Shi-Xiang Hou, Qian Yao, Trans-resveratrol loaded chitosan nanoparticles modified with biotin and avidin to target hepatic carcinoma, International Journal of Pharmaceutics, Vol 452,355-3622013,

[60] Jie Wu, Yaping Wang, Hao Yang, Xiangyu Liu, Zhong Lu, Preparation and biological activity studies of resveratrol loaded ionically cross-linked chitosan-TPP nanoparticles, Carbohydrate Polymers, 2017, Volume 175, Pages 170-177,

[61] Zhang D, Zhang J, Zeng J, Li Z, Zuo H, Huang C, Zhao X. Nano-Gold Loaded with Resveratrol Enhance the Anti-Hepatoma Effect of Resveratrol In Vitro and In Vivo. J Biomed Nanotechnol. 2019 Feb 1;15(2):288-300.

[62] Xiang Li, Xian-Xin Chen, Yu Xu, Xian-Bing Xu, Wen-Fei Wu, Qi Zhao, and Jiang-Ning Hu*Construction of Glycogen-Based Nanoparticles Loaded with Resveratrol for the Alleviation of High-Fat Diet-Induced Nonalcoholic Fatty Liver Disease, Biomacromolecules (2022) 23, 1, 409–423,

[63] Teng, Wendi & Zhao, Liyun & Yang, Songtao & Zhang, Chengying & Liu, Meiyu & Luo, Jie & Jin, Junhua & Zhang, Ming & Bao, Chen & Li, Dan & Xiong, Wei & li, Yuan & Ren, Fazheng, The hepatic-targeted, resveratrol loaded nanoparticles for relief of high fat diet-induced nonalcoholic fatty liver disease. Journal of Controlled 2019 307,

[64] Siddiqui, Imtiaz & Sanna, Vanna & Ahmad, Nihal & Sechi, Mario & Mukhtar, Hasan. Resveratrol nanoformulation for cancer prevention and therapy. Annals of the New York Academy of Sciences. (2015). 1348. 10.1111/nyas.12811.

[65] D.J. Boocock, G.E.S. Faust, K.R. Patel, A.M. Schinas, V.A. Brown, M.P. Ducharme, T.D. Booth, J.A. Crowell, M. Perloff, A.J. Gescher, et al., Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent, Cancer Epidemiol. Biomark. Prev. 16 (2007) 1246–1252,

[66] Davatgaran-Taghipour Y, Masoomzadeh S, Farzaei MH, Bahramsoltani R, Karimi-Soureh Z, Rahimi R, Abdollahi M. Polyphenol nanoformulations for cancer therapy: experimental evidence and clinical perspective. *Int J Nanomedicine*. 2017;12:2689-2702

[67] Guohua Han, Jufeng Xia, Jianjun Gao, Yoshinori Inagaki, Wei Tang, Norihiro Kokudo, Anti-tumor effects and cellular mechanisms of resveratrol, Drug Discoveries & Therapeutics, 2015, Volume 9, Issue 1, Pages 1-12

[68] Najat Binothman, Phytochemical Based Nano Design for Cancer: A Recent Update, Department of Chemistry, College of Science and Arts, King Abdulaziz University, Rabigh, SAUDI ARABIa, Int. J. Pharm. Investigation, 2022; 12(2) : 151-159

[69] Sarma S, Agarwal S, Bhuyan P, Hazarika J, Ganguly M. Resveratrol-loaded chitosan-pectin core-shell nanoparticles as novel drug delivery vehicle for sustained release and improved antioxidant activities. *R Soc Open Sci*. 2022;9(2):210784. Published 2022 Feb 2.