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Review

RESVERATROL NANOFORMULATION FOR CANCER CHEMOPREVENTION AND THERAPY

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Abstract

Cancer remains one of the leading causes of morbidity and mortality worldwide, and conventional chemotherapy is often limited by non-specific targeting, systemic toxicity, and poor therapeutic efficacy. Recent advances in nanotechnology have introduced nanoformulation-based drug delivery systems as a promising strategy to overcome these limitations. Nanoparticles, typically below 100 nm in size, enhance drug stability, solubility, bioavailability, and selective accumulation in tumor tissues through passive and active targeting mechanisms such as the enhanced permeability and retention (EPR) effect. Various nanoformulations including nanocrystals, nanocapsules, nanospheres, nanosponges, solid lipid nanoparticles, polymeric nanoparticles, micelles, dendrimers, and vesicular systems have been explored for cancer therapy. Among chemopreventive agents, resveratrol—a natural polyphenolic compound—has gained significant attention due to its antioxidant, antiinflammatory, and anticancer properties. However, its clinical application is limited by poor solubility, low bioavailability, and rapid metabolism. Nano-encapsulation of resveratrol effectively addresses these challenges by improving its pharmacokinetic profile, enhancing cellular uptake, and enabling controlled and targeted delivery. Resveratrol-based nanoformulations have demonstrated improved anticancer efficacy against various cancers, including breast, lung, colon, and prostate cancers, by modulating key molecular pathways and inducing apoptosis while reducing systemic toxicity. Thus, nanoformulation-based delivery of resveratrol represents a promising approach for effective cancer prevention and therapy.

Keywords: Nanotechnology in Cancer Therapy, Resveratrol Nano-formulations, Targeted Drug Delivery Systems, Cancer Chemoprevention

INTRODUCTION

The incidence of cancer has significantly climbed globally, with over 10 million new cases emerging each year. The previous few decades, Cancer is a major source of morbidity and mortality in populations, and its treatment is difficult . Anticancer medications can be beneficial in treating cancer, but their effects and dosages are typically influenced by a number of variables. Chemotherapeutic medications and other conventional anti-cancer medicines non specifically target the body's normal and malignant cells. This phenomenon restricts the amount of medication administered to tumours, leading to less than ideal treatment efficacy. The unspecific targeting of cancer cells by conventional chemotherapeutic drugs has been addressed by targeted therapy .

Drugs should selectively target tumours by releasing their active forms in a controlled manner after they have reached the tumour cells. cells without affecting healthy tissue. By raising the intracellular concentration of medications and reducing dose-related toxicities, this phenomenon is essential for enhancing patient survival and quality of life. Nanoparticles appear to meet the specificity and efficiency requirements of cancer treatments as effective drug delivery vehicles . Researchers have worked to create novel cancer diagnosis techniques in recent years. In this sense, one of the most promising areas for cancer diagnosis and treatment is nanotechnology.

The study of creating materials and procedures at the molecular level is known as nanotechnology. In the medical field, The use of nanomaterials as drug-release vehicles is the result of extensive research on the subject. The majority of these nanocarriers are smaller than

100 nm, and they can transport and deliver the therapeutic substances to the targeted cells . Nanoparticles' penetrability and capacity to be stored and kept in tumour tissues determine how effective they are in treating cancer. As previously stated, intravenous infusion of toxic chemotherapeutic medicines limits their tolerated dosages since it offers a serious risk to healthy tissues. In summary, by utilising both passive and active targeting strategies, nanoparticles can enhance the intracellular absorption of medications by cancer cells and prevent toxicity to normal cells . Additionally, nanoparticles can enter cells as endosomes after attaching to certain receptors through endocytosis via receptors. By doing this, they can get around P-glycoprotein's function, which is one of the main ways that malignant cells resist drugs .[1]

TYPES OF NANO FORMULATION

NANOCRYSTAL:

Insoluble medications like paclitaxel have been administered using nanocrystals. Pegylation is a crucial concept that expands the prolongs the nanocarrier system's circulation and improves the therapeutic results of medications .

NANOCAPSULE:

This could improve the bioavailability and stability of medications. Nano capsules can shield peptides, hormones, proteins, enzymes, medications, metabolites, or reporter molecules from chemical and biological deterioration .

NANOSPHERES:

Anti-wrinkle, moisturising, and anti-acne nanoparticle creams all contain nanospheres. Active particles are transported by nanospheres. substances deeper into the skin, as well as to offer a controlled release or protect the active component from chemical or enzymatic degradation. This delivery method was proven to prolong active release in the case of fragrances

NANOSPONGES:

They can prolong the release and increase the bioavailability of medications by solubilising weakly water-soluble substances. Targeted drug delivery, which makes sure the medication reaches the intended cells in the body, such cancer cells, and enhanced drug delivery, which enables better physical properties of pharmaceuticals (like solubility), are the two main therapeutic uses for nanosponges.

NANOPRECIPITATION:

This method entails rapidly injecting a drug solution into an aqueous phase following its dissolution in an organic solvent that is water-miscible. Substances rapidly precipitate in aqueous solutions to create drug particles at the nanoscale. NANO

FORMULATION BASED ON EMULSIONS:

Solvent evaporation is the process of creating an oil-in-water or water-in-oil emulsion and then allowing the solvent to evaporate to create nanoparticles. Spray drying and phase inversion are two of its components .

ELECTROSPINNING:

Electrospinning is commonly used to create nanofibers, but with appropriate formulations, it can also make nanosized particles.

TECHNOLOGY FOR SUPERCRITICAL FLUIDS :

To precipitate nanoparticles from a solution, antisolvents such as carbon dioxide are employed at supercritical temperatures. Supercritical fluid extraction of emulsions: In order, to extract nanoparticles from an emulsion, supercritical fluids must first be generated.

NANOCARRIERS USED IN NANOFORMULATION :

Materials referred to as "nano carriers" are employed in nanoformulation to encapsulate and distribute pharmaceuticals, imaging agents, or other payloads in an exact and controlled manner. These carriers are essential to nanoformulations because they increase the stability, bioavailability, and solubility of medications and often allow for customised delivery . Here are some examples of common nano formulation.

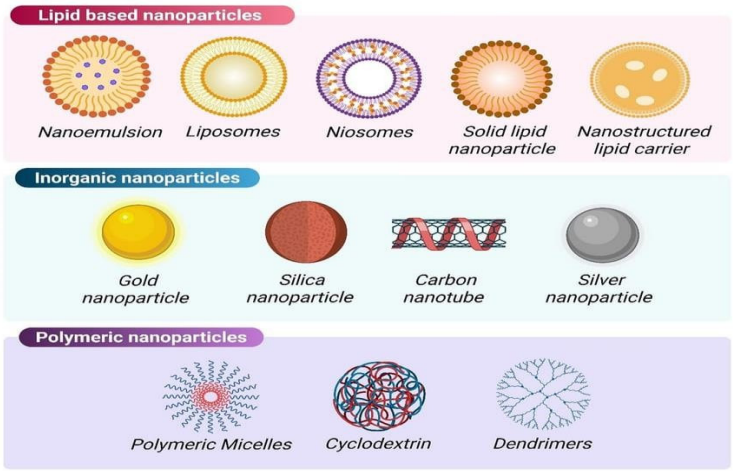


Figure :1

CARRIERS FOUND IN NANOFORMULATION

LIPOSOMES

Liposomes are spherical vesicles made of lipid bilayers. They may have hydrophilic or hydrophobic substances in their lipid bilayers or watery core drugs, in that order Because liposomes are biocompatible and versatile, they can be utilised for a range of drug delivery applications .

POLYMERIC NANOPARTICLES:

Polymeric nanoparticles are made from biocompatible and biodegradable polymers. They can be made to release drugs gradually or under close control. Two examples are poly (lactic-coglycolic acid) (plgA) nanoparticles and chitosan nanoparticles.

MICELLES:

Micelles are self-assembling structures composed of amphiphilic molecules. When the quantities of these molecules above their critical micelle concentration (cmc), they develop.

When hydrophobic drugs dissolve in the centre of micelles, drug distribution can be enhanced.

NANOCAPSULES:

These are nanoscale capsules with a core-shell structure. While proteins, polymers, or lipids are often found in the shell, drugs can be accommodated in the core. This architecture can be used to encapsulate both hydrophilic and hydrophobic compounds.

DENDRIMERS

Dendrimers are highly branched macromolecules with a unique structure. Their synthetic technique allows for exact control over their size and surface functioning. Dendrimers are often used to encapsulate drugs or imaging agents.

SOLID LIPID NANOPARTICLES:

SLNs are solid-state, room-temperature lipid-based nanoparticles. When compared to traditional liposomes, they offer improved stability and controlled release. The lipid matrix can protect drugs from degradation.

CARBON NANOTUBES:

These cylindrical structures with unique properties can transport therapeutic substances. A variety of payloads, including medications or imaging agents, can be delivered via functionalised carbon nanotubes .

METAL NANOPARTICLES:

Metal nanoparticles made of iron oxide, silver, or gold can be used as transporters. Their surfaces may have unique characteristics and can be functionalised for drug loading or targeting.

CYCLODEXTRINS :

Cyclodextrins are cyclic oligosaccharides that can form inclusion complexes that boost the solubility of hydrophobic drugs. of the former. They can be used as delivery systems for drugs, especially those that are poorly soluble in water .

PROTEIN-BASED NANOPARTICLES:

Proteins like albumin or gelatin can be used to create drug delivery nanoparticles. These protein-based carriers are biocompatible and can be designed to have specific targeting properties.[2]

NANOPARTICLE SIZE AND SURFACE PROPERTIES

Nanoparticles must be able to remain in the bloodstream for a long time without being eliminated in order for drug delivery to the targeted tumour tissue to be successful. Depending on their size and surface characteristics, conventional surface particles and non-modified nanoparticles are often captured in the

circulation by the reticuloendothelial system, which includes the liver and spleen . The fate of injected nanoparticles can be controlled by altering their size and surface characteristics.

FEATURES OF NANO PARTICLES :

The lifespan and fate of nanoparticles during circulation in relation to macrophage absorption are largely determined by their surface characteristics. In order to prevent being taken up by macrophages, nanoparticles should preferably have a hydrophilic surface . There are two ways to do this: Initially, applying a hydrophilic polymer to the surface of nanoparticles, like such as PEG, and then resist plasma proteins to prevent opsonisation; alternatively, block copolymers having hydrophilic and hydrophobic domains can be used to create nanoparticles.

SIZE:

In addition to their surface characteristics, nanoparticles also have the benefit of being able to alter their size. When used in drug delivery systems, nanoparticles should be both large enough to prevent rapid leakage and small enough to evade capture by fixed macrophages trapped in the reticuloendothelial system, such as those present in the liver and spleen into capillaries of blood. The gap junction between endothelial cells of the leaky tumour vasculature can vary in size from 100 to 600 nm , while the sinusoid in the spleen and the fenestra of Kuffer cells in the liver range in size from 150 to 200 nm . For nanoparticles to enter tumour tissues through these two circulatory routes, they must be up to 100 nm in size .

EXAMPLES OF MARKET AVAILABLE DRUGS

SYSTEM\TYPE	CHARACTERISTICS	EXAMPLES OF COMPOUNDS
Polymeric nanoparticles	(a)Water-soluble, nontoxic, (b)Biodegradable Surface modification (pegylation) (c)Selective accumulation and retention in tumour tissue(EPR effect) (d)Specific targeting of cancer cells while sparing normal cells–receptormediated targeting with a ligand	Albumin-Taxol(Abraxane) PGA-Taxol(Xyotax) PGA-Camptothecin(CT 2106) HPMA-DOX(PK1) HPMA-DOX galactosamine(PK2)
Liposome	(a)Amphiphilic, biocompatible (b)Ease of modification (c)Targeting potential	Pegylated liposomal DOX(Doxil) Non-pegylated liposomal DOX(Myocet) Liposomal daunorubicin (DaunoXome)
Polymeric micelles	(a)Suitable carrier for water-insoluble drug (b)Biocompatible, self-assembling, biodegradable (c)Ease of functional modification (d)Targeting potential	PEG-pluronic-DOX PEG PAA-DOX(NK911) PEG-PLA-Taxol(Genexol PM)
Viral nanoparticles	(a)Surface modification by mutagenesis or bioconjugation – multivalency	HSP-DOX CPMV-DOX

	(b)Specific tumour targeting, multi functionality (c)Defined geometry and remarkable uniformity (d)Biological compatibility and inert nature	
Carbon nanotubes	a)Water-soluble and biocompatible through chemical modification (organic functionalization) (b)Multifunctionality	CNT-MTX CNT-amphotericin B
dendrimers	(a)Biodistribution and PK can be tuned (b)High structural and chemical homogeneity (c)Ease of functionalization, high ligand density (d)Controlled degradation (e)Multifunctionality	PAMAM-MTX PAMAM-platinate

IMPORTANT PRINCIPLES IN CANCER NANOPARTICLE DRUG DELIVERY

There are some important ideas to keep in mind while delivering medications using nanoparticles. These include the EPR effect, the mononuclear phagocyte system's (MPS) removal of nanoparticles, and the desired characteristics of nanoparticles for cancer applications .

INCREASED PERMEABILITY AND PERMEATION :

Tumours usually have aberrant vasculature with asymmetric branching and permeable walls. This leakiness is brought on by the rapid proliferation of endothelial cells and the absence of pericytes. These features cause the tumour vasculature to have large pores that range in diameter from 100 nm to several hundred nanometres, unlike normal vascular 5–10 nm connections . Macromolecules like nanoparticles can pass through tumours with large holes because they increase vascular permeability and hydraulic conductivity . Macromolecules are eliminated from healthy tissue by the lymphatic system. Conversely, impaired lymphatics are often associated with solid tumours . Proliferating tumour cells, particularly in the centre of tumours, compress and collapse lymphatic vessels. The EPR effect is brought on by both increased tumour vascular permeability and a weakened lymphatic system. Similar to other macromolecules, nanoparticles stay longer in tumours than in plasma or other organs. leading to higher concentrations. Nanoparticles are capable of passive tumour targeting due to the EPR effect.

THE MONONUCLEAR PHAGOCYTE SYSTEM CLEARS NANOPARTICLES

To fully profit from the EPR effect, nanoparticles must be in circulation long enough for tumour buildup. Conversely, the mononuclear phagocyte system, also referred to as the reticuloendothelial system, can eliminate nanoparticles. The immune system's MPS is responsible for eliminating macromolecules. from circulation. Immunotoxin therapy for cancer. The MPS is composed of tissue macrophages, blood monocytes, and bone marrow progenitors. It also includes the macrophages in the spleen and the Kupffer cells in the liver, which are responsible for removing macromolecules from the blood. When nanoparticles interact with MPS cells, they have the ability to opsonise them. A lot of effort has gone into creating "stealth" nanoparticles since early removal from circulation keeps them from building up in tumours contacts. The most common method is grafting PEG or other macromolecules, like polysaccharides, onto the surface of nanoparticles. Steric stability is made possible by the addition of PEG or other substances, which inhibits particle interactions, protein adsorption, and immunological cell contacts.[3]

CHEMOPREVENTION

The definition of cancer chemoprevention, which was initially used by Sporn and colleagues in 1976, is "the use of medicines, vitamins, or other agents to lower the risk of cancer or delay its development or recurrence. It is crucial to remember that chemoprevention is not the same as consolidated cancer chemotherapy. Nonetheless, there is some overlap between these two strategies, and the term "chemoprevention" can be broadened to encompass the prevention or suppression of new tumour recurrence in high-risk people. For the majority of solid cancers, chemoprevention can be defined as delaying the carcinogenesis process.

Chemoprevention is expected to reduce cancer development and outcome at the clinical level, regulate proliferation and differentiation at the cellular level, and reverse premalignant lesions at the tissue level. Additionally, because chemoprevention is the most popular and affordable alternative to chemotherapy, it is receiving special attention in light of the social effects. In reality, there is a lot of interest in preventing or lowering the risk of cancer by avoiding biological, chemical, and physical factors that cause cancer as well as by regularly consuming diets high in antioxidants, including chemopreventive agents. A number of natural Compounds are thought to be safe because to their availability, inclusion in the diet, and tolerability, as well

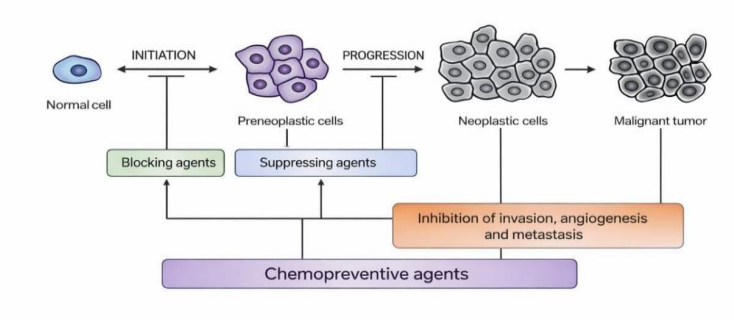


Figure : 2

As epidemiological research indicating that food high in fruits, vegetables, and certain spices may lessen the incidence of several human cancers. Based on the traditional classification Initially put out by Lee Wattenberg, these There are two categories of chemopreventive drugs. primary classifications: suppressing and blocking agents. Blocking agents stop the development of cancer from arriving at the intended locations, from going through metabolic activity, or by contact with Nucleic acids and other cellular macromolecules as well as cellular signalling proteins. They can function by actively deactivating or metabolising carcinogens, acting as scavengers of free radicals or altering activity of antioxidative enzymes, as well as initiating DNA repair mechanisms.

Conversely, suppressive drugs prevent started cells from undergoing malignant transformation, which may have an impact on later phases of carcinogenesis, either in the progression or promotion stages (Fig. 2). Through the downregulation of many signal transduction pathways, they impede the growth of cancer cells. Additionally, by encouraging apoptosis and blocking angiogenesis, invasion, and dissemination mechanisms, suppressing medicines may lessen or postpone the capacity of cancer cells to develop metastatic characteristics.

Numerous cellular substances and events that could be potential targets of chemopreventive drugs have been identified thanks to recent advancements in our understanding of the carcinogenesis process.

Regarding the potential chemopreventive agents' mode of action, the capacity of any one phytochemical bioactive substance to stop the growth of tumours should be understood as the result of several different sets of intricate intracellular actions rather than a single biological reaction.

CLASSIFICATION AND OCCURRENCE OF DIETARY POLYPHENOLS

The polyphenolic group of chemicals is one class of bioactive food ingredients that has drawn a lot of interest in recent clinical research as well as in cancer experimental models. Fruits, vegetables, and other plants contain polyphenols, which make up one of the biggest and most common classes of phytochemicals. Twenty It has been discovered that a number of polyphenols exhibit differential cell cytotoxicity, with cancer cells being more susceptible to their antiproliferative actions than normal cells.

The most prevalent antioxidants in human diets are polyphenols, of which flavonoids and phenolic acids are the most prevalent. Emerging data from retrospective analysis indicates that consumption of specific nutrients, particularly diets high in polyphenols, may be linked to a lower incidence of cancer in some populations.

As a result, a thorough analysis of polyphenolic chemicals' chemopreventive potential in recent years has shown their health advantages, including their ability to prevent cancer. Depending on the quantity of phenol rings they have, the structural components that hold these rings together, and the existence of other functional groups, they can be categorised into many general categories.

RESVERATROL FOR CANCER CHEMOPREVENTION AND THERAPY

A nonflavonoid polyphenolic compound, resveratrol can be found in a variety of plants and foods that are typically taken as part of a human diet, including peanuts, grapes, mulberries, blueberries, cranberries, and red wine. Resveratrol's chemopreventive effects in preventing multistage carcinogenesis were first shown by Jang et al. This polyphenolic compound has since been shown to inhibit the proliferation of a wide range of human tumour cells in vitro, which has prompted numerous preclinical animal studies.

Resveratrol activates many intracellular pathways that converge with NF-B and AP1 activation (Fig. 3). Following repeated UVB radiation exposures, resveratrol has been

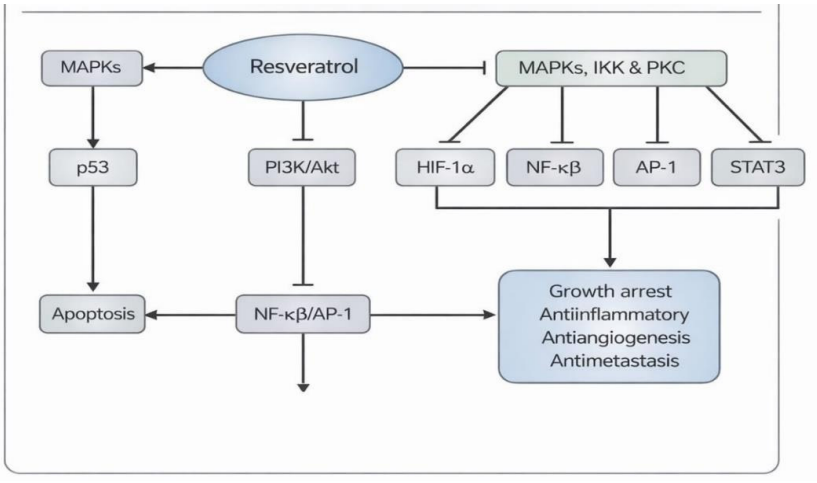


Figure : 3

implicated in the regulation of the cell cycle in the skin of SKH-1 hairless mice. Resveratrol in the diet significantly decreased the incidence and multiplicity of carcinogenesis-induced mammary tumours in mice while simultaneously prolonging the latency period, although having no effect on tumour incidence.

Once more, resveratrol reduced angiogenesis, enhanced apoptosis, and prevented the growth of oestrogen receptor (ER)— and ER-+ tumour explants in a xenograft animal model. Thirty In HER2/neu transgenic mice, resveratrol supplementation slowed the growth and decreased the ability of spontaneous mammary tumours to spread. This was linked to the downregulation of HER2/neu expression, which caused tumour cells to undergo apoptosis. Additionally, in the transgenic cancer mouse and rat prostate models, dietary resveratrol dramatically decreased the incidence of prostatic adenocarcinoma.

In rats, oral resveratrol reduced the quantity and multiplicity of lung, esophageal, and colon cancer. Additionally, it has been discovered that in mice with highly metastatic Lewis lung cancer, resveratrol dramatically decreased tumour volume, tumour weight, and lung metastasis. The effectiveness of resveratrol and resveratrol-rich products for the prevention and treatment of colorectal cancer has been the subject of numerous clinical trials.

Resveratrol supplementation for cancer prevention and cancer risk factors in healthy persons has been the topic of other clinical studies.34. Results from a number of additional completed and continuing clinical trials examining resveratrol and cancer have not yet been released. All of these studies either target patients with colorectal cancer or evaluate resveratrol's potential to prevent cancer in healthy individuals.[4]

SOURCE

Resveratrol was first isolated from the roots of Veratrum grandiflorum and later from the roots of Polygonum cuspidatum . From P. cuspidatum, an important traditional medicine in China, the content of resveratrol has been reported to be 1.8 mg/g. The compound has been isolated from more 70 plant species, including grapes and red wine.

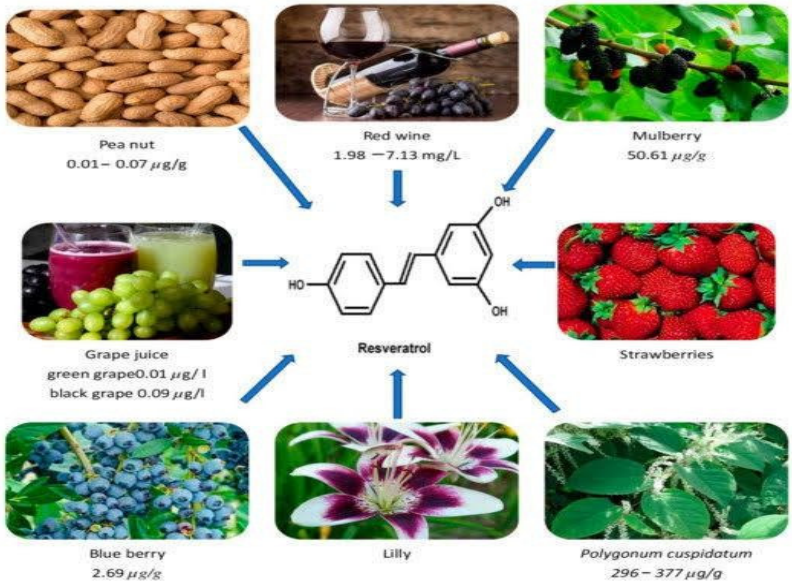
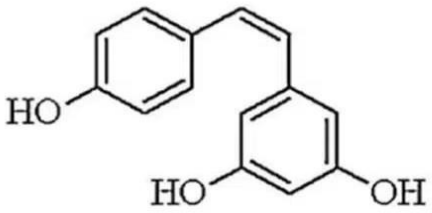


Figure : 4

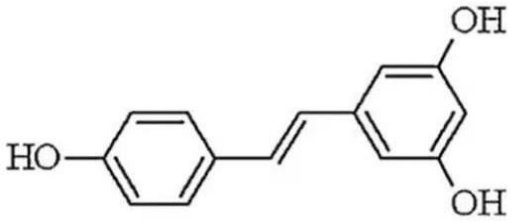
Red grapes and red wine, as shown in Figure 5, are the main dietary sources of resveratrol. Red grapes contain mainly of piceid (1.5−7.3 μg/g), while red wine is rich in resveratrol (1.0−18 μg/ml). From the skin of grapes, the content of resveratrol ranged from2.48 to 6.47 μg/g. The concentration of trans-resveratrol in red wine is six times higher than in white wine, which contains high levels of cis-resveratrol. A possible explanation is that red wine is produced without removing the skin of grapes, whereas white wine is fermented after the removal of the skin. Pterostilbene was first isolated from Pterocarpus santalinus (sandalwood) in 1940, and later identified in Vitis vinifera (grape vine), Pterocarpus marsupium (Indian kino), Vaccinium berries, and Arachis hypogaea (peanut).

CHEMISTRY

Resveratrol or trans-3,4′,5-trihydroxystilbene is a monomer stilbene with a molecular formula of C14 H12 O3 and a molecular weight of 228.25 g/mol. The molecule has two aromatic rings, linked by an ethylene bridge with an ethene double bond. Ring A has two hydroxyl (−OH) groups at C3 and C5, and ring B has one −OH group at C4′. Resveratrol has a 6−2−6 carbon skeleton with m-hydroquinone and 4′-hydroxystyryl moieties involving rings A and B, respectively. In food products, resveratrol commonly occurs in the trans form rather than in the cis form. When resveratrol is exposed to ultraviolet and visible light, trans to cis isomerization occurs. The rarer cis-resveratrol is less stable and is not commercially available. Red wine is rich in trans-resveratrol, and its moderate consumption has health benefits of lower rates of prostate cancer. Against PC-3 prostate cancer cells, trans-resveratrol was reported to be a more effective anti-cancer agent than cis-resveratrol and dihydro-resveratrol. Earlier, transresveratrol has been reported to be 10 times more potent in inducing apoptosis of HL60 leukemia cells as compared to cis-resveratrol. [5]



cis-Resveratrol



trans-Resveratrol

RESVERATROL : biopharmaceutical challenges associated with different routes of administration

RSV distribution via several pathways is fraught with difficulties. RSV is not suitable for oral and topical treatments alone due to its limited solubility in an aqueous media and nearly nil bioavailability profile. Innovative medicine delivery methods are crucial in this situation. Despite being an ideal antioxidant, Insolubility, low skin penetration, poor photostability, and bioavailability are issues with chemoprotective and anti-inflammatory agents . Oral route: RSV has a number of benefits, as previously mentioned, but it also has difficult issues, such as low solubility (0.05 mg/mL in water) and metabolism. Because RSV is lipophilic (Log P/Ko/w = 3.10), it rapidly absorbs into the portal veins almost 75% of the time.

However, the liver actively breaks it down through phase 2 metabolism and the production of glucuronidated, methylated, and sulfated complexes. RSV's bioavailability is limited by sulphate complexes containing phenolic groups. A few of these complexes return to the gastrointestinal tract (GIT) in order to trigger metabolism. The fact that RSV raises its own metabolism is intriguing. The majority of medications form complexes with albumin and lipoprotein, although much less of them enter the systemic circulation unaltered. Additionally, it made temperature-mediated diffusion and passive diffusion possible. However, the majority of medications are transported and distributed to different compartments for cellular absorption when they are coupled with albumin complexes. Additionally, the RSV active metabolite possesses anti-cancer properties. According to the study, oral dosages of 25 mg exhibit approximately 70% absorption, a peak plasma level of 491 ± 90 ng/mL, and a half-life of 9.2 ± 0.6 hours. Liquid chromatography-mass spectrometry (LC-MS) finds the majority of the dosages in the urine. Epithelial cells readily absorb RSV. As a result, these cells have a high drug concentration.

TOPICAL ROUTE:

Excellent apparent permeability across the skin and minimal skin irritation are necessary for a noticeable topical therapy. RSV's low permeability and poor skin retention limit its topical application. As a result, less medication reaches the target site and the concentration of API needed for effectiveness decreases. RSV cannot pass through the stratum corneum due to its high partition coefficient and molecular weight of more than 500 Da. Additionally, erythema and moderate allergic reactions are linked to RSV, which results in low patient compliance. Therefore, the primary causes of RSV's low therapeutic efficacy are ineffective administration and unwanted skin interactions.

PARENTERAL ROUTE:

For safe medicine delivery, transition points—where pharmaceutical errors are more likely to happen—need special care. Parenteral administration is preferred over alternative drug delivery techniques in situations like anaphylactic shock and cardiac arrest . This mode of administration provides numerous advantages, such as constant dosage, enhanced bioavailability, and avoidance of first-pass metabolism. Parenteral delivery produces more predictable pharmacodynamic and pharmacokinetic properties than oral treatment since it is better controlled in terms of dose and tempo. Many parenteral medications are classified as high-alert medications due to the grave risk that could arise from incorrect use. However, administering RSV parenterally results in serious side effects such as moderate inflammation, muscle spasms, and anaphylactic shock. Steady-state concentrations cannot be maintained throughout repeated doses, which results in poor patient compliance.

HOW RSV BENEFICIAL FOR CANCER PATIENTS

RSV affects several routes, receptors, and other modulators to demonstrate its impact. Although the exact causes of cancer are still unknown, some theories include aberrant cells, cytoplasmic cell division, and gene theory. RSV stimulates SIRT1 , an enzyme found in the cell nucleus that is in charge of the deacetylation of transcription factors and other histone and non-histone proteins. Additionally, it is necessary to control the several pathways that impact endothelial function, inflammation, immunological response, metabolism, cell survival, circadian rhythms, and stress tolerance. SIRT1 controls inflammation, cell cycle abnormalities, and aberrant metabolic regulation in cancer. Additionally, it controls problems including obesity, neurological diseases, and cardiovascular diseases. In human

articular chondrocytes, RSV inhibits the proteasome, which controls the protein in charge of apoptosis and cell cycle progression, thereby modulating the nuclear factor-κB (NF-κB) pathway. The antiapoptotic gene is regulated by NF-κB.

RESVERATOL NANO-FORMULATIONS

SOLID LIPID NANOPARTICLE

Solid lipid matrices including surfactants provide the best physico-chemical stability, extended drug release, and in vivo tolerability. Micrometer-sized particles make up solid lipid particles. Solid lipid nanoparticles (SLNs) loaded with RSV have superior capacity to impede or reduce the growth of MDA-MB-231 human breast cancer cells compared to free RSV. They have been characterised as lipidic drug carrier systems for topical applications that can take the place of polymers and allow for large-scale production at a comparatively lower cost when compared to liposomes. Although they have received less scientific interest than SLNs for skin applications, solid lipid microparticles (SLMs) for RSV offer the potential for oral delivery to improve their solubility and bioavailability. SLMs can be produced using a number of methods, including as solvent evaporation, melt dispersion, hot and cold homogenisation, spray drying, and spray congealing . When RSV was administered intravenously to Charles Foster rats, the D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) coated SLNs formulation demonstrated a 9.37-fold increase in plasma half-life, enhanced circulation time, and better passive brain delivery.

MICROEMULSIONS

Microemulsions (MEs) are transparent, colloidal, isotropic, and thermodynamically stable liquid dispersions of water and oil because of their cutaneous tolerance and balanced hydrophilic-lipophilic nature. Water, oil, a surfactant, and a cosurfactant, such as alcohol, comprise a multiphase system that mainly provides as a co-solvent and exhibits transparency by providing globule sizes smaller than 140 nm was the first to be called a ME by Schulman in 1959. According to a study, MEs gel-loaded RSV for sustained release in vitro and ex vivo show 71.11 ± 0.47 and 68.15 ± 0.12, respectively, throughout a 24-hour period when evaluated for B16F10 melanoma cell lines. For topical distribution, MEs offer a number of advantages, including as the ability to efficiently dissolve lipophilic drugs, increased skin permeability, and a prolonged release of both lipophilic and hydrophilic drugs. Oleic acid (OA) MEs are reported to have a higher concentration of drug retention in the skin and a stronger ability to solubilise RSV. MEs can pass through the stratum corneum barrier and partition the medication into the epidermis due to their high capacity for drug loading and high capacity for drug solubilisation. According to a study, MEs shield RSV from ultraviolet B (UVB) radiation for up to an hour and postpone photodegradation, which aids in RSV absorption in the skin.

VESICULAR DRUG DELIVERY SYSTEM

Vesicular drug delivery devices are highly ordered assemblages made up of one or more concentric bilayers. When amphiphilic construction materials self-assemble in the presence of water, they are produced. These methods are useful for targeted drug delivery because they can localise the medication to the site of action, lowering the drug's concentration in other parts of the body. In contrast to other of the well researched non-vesicularized dosage forms, this one aids in improving skin permeability and retention. Vesicular systems for topical distribution include liposomes, transferosomes, ethosomes, and niosomes.[6]

ANTI CANCER EFFECTS OF RESVERATROL IN LUNG AND PROSTATE CANCER

INHIBITION OF LUNG CANCER

The WHO report states that LC is the most prevalent cancer kind globally. This cancer is the second most common cause of death for women, while it is the top cause for males. Notably, despite medical and technological advancements, the total 5-year survival rate is less than 16%, with 1.76 million deaths globally attributed to LC in 2018. These findings make it clear that new medications and treatments for LC are required. Because the levels needed for cell senescence are smaller than those needed for apoptosis, some scientists have discussed resveratrol's capacity to cause cell senescence. The major results showed that resveratrol increased the expression of p53, p51, and β-galactosidase (associated with senescence) in human NSCLC at a low level (10 50μM). Therefore, an increase in ROS generation and DNA double-strand breaks has been linked to the processes by which resveratrol may cause premature senescence. Similar to this, another study examined the impact of resveratrol on the generation of ROS in human NSCLC cells (H129 cells) and a breast cancer cell line (MCF-7 cells). The primary results showed that both cell lines showed a dose-dependent decrease in TIGAR protein 48 hours after resveratrol treatment due to the downregulation of mTOR signalling and an increase in Poly(ADP-ribose) polymerase (PARP) cleavage, which is thought to be the hallmark of an increase in cell death and apoptosis.

PROSTATE CANCER

The second most prevalent type of cancer in male participants is prostate cancer (PC). Although it is typically curable in its early stages, over 2,50,000 people die from clinically advanced cases worldwide. Instances PC is linked to DNA changes that cause dysregulation in genes implicated in PC development, according to genetic research. Recurrent variations in PC include mutations in forkhead box A (FOXA)1, speckle type POZ protein (SPOP), and TP53, as well as copy number changes in MYC, PTEN, and retinoblastoma (RB)1. Resveratrol has so been suggested as an effective treatment approach for PC. Numerous studies have examined resveratrol's impact on PC by looking at its impacts on EMT, a mechanism linked to the disease's advancement . The authors' primary conclusions were that cell proliferation decreased when resveratrol was present.

Furthermore, compared to control cells (which did not include resveratrol), the mesenchymal cell phenotype was less noticeable. Therefore, it was proposed that resveratrol's anticancer effects might be connected to its capacity to prevent EMT, most likely through the deactivation of a hedgehog signalling pathway. A critical downregulation of metastasis-associated protein (MTA1), which is closely linked to the repressive chromatin involved in cancer progression and metastasis in three PC cell lines, was also observed when the effect of resveratrol in PC was investigated to clarify the mode of action of this compound. Additionally, overexpression and amplification of the carcinogenic miR-17–92 and miR-106b–25 clusters are among the changes in miRNA expression in PC. Furthermore, it has been discovered that the tumour suppressor gene PTEN, which is frequently impacted in PC, is targeting some of these clusters.[7]

APPLICATIONS

- ✓ TARGETED CANCER DRUG DELIVERY:

Nanoformulations enhance selective accumulation of resveratrol in tumor tissues via the

Enhanced permeability and retention (EPR) effect, improving therapeutic efficacy.

- ✓ MPROVED BIOAVAILABILITY:

Encapsulation of resveratrol in nanoparticles overcomes poor solubility and rapid

metabolism, resulting in increased systemic circulation time.

- ✓ ENHANCED ANTICANCER ACTIVITY:

  Resveratrol nanoformulations effectively inhibit cancer cell proliferation and induce apoptosis in breast, lung, colon, prostate, and liver cancers.

- ✓ MODULATION OF SIGNALING PATHWAYS:

  Nano-resveratrol regulates key molecular pathways such as NF-κB, PI3K/Akt, STAT3, and p53 involved in cancer progression.

- ✓ CHEMOSENSITIZATION:

  Nano-encapsulated resveratrol enhances the efficacy of conventional chemotherapeutic agents and helps overcome multidrug resistance.

- ✓ REDUCED SYSTEMIC TOXICITY:

  Targeted delivery minimizes off-target effects and protects normal cells, improving safety profiles.

- ✓ ANTI-ANGIOGENIC EFFECTS:

  Resveratrol nanoformulations suppress tumor angiogenesis by down-regulating VEGF and related pathways.

- ✓ CONTROLLED AND SUSTAINED RELEASE:

  Nanocarriers provide prolonged drug release, maintaining effective intracellular concentrations.[8-11]

CONCULUSION

Nanotechnology-based drug delivery systems have emerged as a powerful approach to overcome the limitations of conventional cancer therapy. Nanoformulations enhance drug solubility, stability, bioavailability, and targeted delivery, thereby improving therapeutic efficacy while minimizing systemic toxicity. Resveratrol, a natural polyphenolic compound with proven chemopreventive and anticancer potential, faces challenges such as poor bioavailability and rapid metabolism. Encapsulation of resveratrol into various nanocarriers effectively addresses these issues by enabling controlled release, improved cellular uptake, and selective tumor targeting. Overall, resveratrol-based nanoformulations represent a promising and innovative strategy for cancer prevention and treatment, offering improved safety, efficacy, and patient outcomes.

DISCUSSION

Nanoformulation-based drug delivery systems play a crucial role in enhancing the anticancer efficacy of resveratrol by improving its solubility, stability, and bioavailability. Targeted nanocarriers enable selective tumor accumulation through the EPR effect and controlled drug release. These advantages lead to improved cellular uptake, modulation of critical signaling pathways, reduced systemic toxicity, and better therapeutic outcomes compared to conventional formulations.

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