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Advances in Nanotechnology-Enhanced Delivery Systems of Geraniol: A Promising Future in Cancer Therapeutics

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Abstract:- Geraniol, a naturally occurring monoterpenoid found in essential oils of several aromatic plants, exhibits numerous therapeutic properties, including anti-inflammatory, antimicrobial, and anticancer activities. However, its therapeutic potential is hindered by poor water solubility, limited bioavailability, and rapid metabolism. Nanotechnology-based delivery systems offer a promising solution to these challenges, by enhancing the solubility, stability, and bioavailability of geraniol through advanced delivery systems in cancer treatment. This review critically examines recent advances in nanotechnology-based delivery systems for geraniol, exploring various nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles. The review also highlights the mechanisms by which these nanocarriers improve geraniol's pharmacokinetic profile, its targeted delivery to cancer cells, and its impact on overcoming multidrug resistance. Future perspectives and potential clinical applications are discussed, emphasizing the need for further research to fully harness the potential of geraniol in cancer therapy.

Keywords:- *Geraniol, Anticancer, Drug-Delivary, Nanotechnology.*

I. INTRODUCTION

Cancer is a multifaceted disease characterized by uncontrolled cell growth and metastasis. Traditional treatments such as chemotherapy, radiation, and surgery, while effective, often come with significant side effects and limitations. Consequently, there is an urgent need for new, less toxic therapeutic agents. Natural compounds have gained attention for their potential anticancer properties. (1) Geraniol, a naturally occurring monoterpene alcohol, is found in essential oils of plants like lemongrass, rose, and citronella. Geraniol, a monoterpene alcohol, is a naturally occurring compound found in various essential oils, particularly in rose, geranium, and citronella. (2) Its history and development in scientific research have unveiled its diverse applications and potential benefits. Geraniol was first isolated in 1871 by Schimmel & Co. (3). Since then, it has been extensively studied for its aroma, medicinal properties, and potential industrial applications. Geraniol, with the chemical formula C10H18O, is a colorless to pale yellow oily liquid with a rose-like scent. It belongs to the family of monoterpenoids and is classified as a primary alcohol. Geraniol is *generally recognized as safe* (GRAS) when used in accordance with good manufacturing practices (4). However, high concentrations may cause skin irritation or allergic reactions in some individuals. Geraniol, a naturally occurring monoterpenoid alcohol, exhibits a broad spectrum of pharmacological activities, including anti-inflammatory, antimicrobial, and anticancer properties. (5) Despite its therapeutic potential, the clinical application of geraniol is limited by its poor aqueous solubility, volatility, and instability under physiological conditions. Nanotechnology-based delivery systems have emerged as a promising strategy to overcome these limitations, enhancing the bioavailability, stability, and controlled release of geraniol (6).This review comprehensively explores the recent advancements in the development of nanotechnology-based delivery systems for geraniol, including nanoparticles, liposomes, nano-emulsions, and polymeric micelles. The review also discusses the preparation methods, characterization techniques, in vitro and in vivo evaluations, and potential clinical applications of these nanocarriers.

II. CHALLENGES IN CANCER THERAPY

Geraniol exhibits a wide range of biological activities, including antioxidant, anti-inflammatory, and anticancer effects (7). Studies have shown that geraniol can modulate various signaling pathways involved in cancer progression, such as the PI3K/Akt, MAPK, and NF-κB pathways (8). Despite its promising anticancer properties, the therapeutic application of geraniol is hampered by several limitations: (9)

- **Poor Water Solubility:** Geraniol's hydrophobic nature results in low aqueous solubility, which limits its bioavailability when administered orally or intravenously.
- **Rapid Metabolism:** Geraniol is rapidly metabolized in the liver, leading to a short half-life and reduced therapeutic efficacy.

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- **Limited Targeting:** The non-specific distribution of geraniol in the body can lead to suboptimal concentrations at the tumor site and increased systemic toxicity.

III. PHARMACOLOGY AND MECHANISM OF ACTION OF GERANIOL

A. *Molecular Structure and Formulation of Geraniol:*

Geraniol is a naturally occurring compound found in various essential oils, particularly in rose oil, citronella oil, and palmarosa oil (10). It is a monoterpenoid alcohol with the chemical formula C10H18O and is classified as a fragrance compound due to its pleasant floral scent. Molecularly, geraniol consists of a linear hydrocarbon chain of ten carbon atoms with a hydroxyl group (-OH) attached to one of the carbon atoms, forming an alcohol functional group. Its structure can be represented as CH3(CH2)3CH=CHCH2CH=CH(CH2)2OH. In terms of formulation, geraniol can be synthesized or extracted from natural sources and then formulated into various products such as perfumes, cosmetics, insect repellents, and flavorings (11). Its formulation often involves blending it with other compounds to enhance its stability, efficacy, and aroma (12). Geraniol exhibits a range of biological activities, including antimicrobial, antioxidant, and insect repellent properties, which make it valuable for various applications (13). Its molecular structure contributes to these activities by enabling interactions with biological targets such as enzymes or cell membranes.

B. *Target Receptors or Pathways:*

Geraniol, a natural monoterpene alcohol commonly found in essential oils of plants, has garnered significant interest in scientific research due to its diverse pharmacological properties (14). One area of interest is its interaction with various target receptors or pathways, elucidating its potential therapeutic applications (15). Here's a brief scientific overview:

➢ *TRPV3 Activation:*

Geraniol has been shown to activate the transient receptor potential vanilloid 3 (TRPV3) channel. TRPV3 is involved in various physiological processes such as skin barrier function and thermo sensation (16).

Activation of TRPV3 by geraniol may contribute to its analgesic and anti-inflammatory effects, making it a potential target for pain management and skin disorders (17).

➢ *Antioxidant Activity*:

Geraniol exhibits potent antioxidant properties, attributed to its ability to scavenge free radicals and inhibit lipid peroxidation (18). This antioxidant activity is mediated through multiple pathways, including the modulation of reactive oxygen species (ROS) production and the up regulation of endogenous antioxidant enzymes. By reducing oxidative stress, geraniol may offer protective effects against various oxidative stress-related diseases, including cardiovascular disorders and neurodegenerative diseases.

➢ *Anti-Inflammatory Effects*:

Geraniol has been reported to exert anti-inflammatory effects through inhibition of pro-inflammatory mediators such as cytokines and enzymes like cyclooxygenase (COX) and lipoxygenase (LOX) (19).These effects are mediated by the suppression of nuclear factor-kappa B (NF-κB) signaling pathway, a key regulator of inflammatory responses. By attenuating inflammation, geraniol may have therapeutic potential in managing inflammatory conditions such as arthritis and inflammatory bowel diseases (20, 21).

➢ *Anticancer Properties*:

Geraniol exhibits promising anticancer properties through various mechanisms, including induction of apoptosis, inhibition of cell proliferation, and suppression of angiogenesis and metastasis (22).Geraniol has been shown to modulate multiple signaling pathways involved in cancer progression, including PI3K/Akt, MAPK, and JAK/STAT pathways (23, 24). Additionally, geraniol enhances the efficacy of conventional chemotherapeutic agents and reduces their adverse effects, suggesting its potential as an adjuvant therapy for cancer treatment.

➢ *Neuroprotective Effects*:

Geraniol demonstrates neuroprotective effects against neuronal damage and neurodegenerative diseases by attenuating oxidative stress, inflammation, and apoptosis (25).It modulates various neurotransmitter systems and signaling pathways implicated in neuronal survival and synaptic plasticity, such as the Nrf2/ARE pathway and the BDNF/TrkB pathway. Geraniol'sneuroprotective properties hold promise for the treatment of neurodegenerative disorders like Alzheimer's and Parkinson's diseases (26, 27).

Overall, geraniol interacts with a diverse array of target receptors and pathways, exerting pharmacological effects that span across multiple therapeutic areas, including pain management, skin disorders, oxidative stress-related diseases, and inflammation, cancer, and neurodegenerative disorders (28).

IV. PHARMACOKINETICS AND DRUG INTERACTIONS

A. *Pharmacokinetics of Geraniol:*

Pharmacokinetics refers to the movement of drugs within the body, encompassing absorption, distribution, metabolism, and excretion (ADME). The ADME profile of geraniol, a naturally occurring monoterpenoid and alcohol found in the essential oils of various aromatic plants, provides insight into its pharmacokinetics and biological effects (29).

➢ *Absorption:*

Geraniol can be absorbed via multiple routes, including oral, dermal, and inhalation (30):

- *Oral Absorption:* Geraniol is readily absorbed in the gastrointestinal tract when ingested. Studies have shown that it has good oral bioavailability.

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- *Dermal Absorption:* Geraniol is also absorbed through the skin, which is relevant for its use in topical formulations and cosmetic products. The rate of dermal absorption can vary depending on the formulation and concentration.
- *Inhalation:* When inhaled, geraniol is absorbed through the respiratory tract, though this route is less commonly studied in comparison to oral and dermal absorption.

➢ *Distribution:*

Once absorbed, geraniol is distributed throughout the body. It is lipophilic (fat-loving), which means it can easily cross cell membranes and may accumulate in fatty tissues. It is also likely to bind to plasma proteins, affecting its distribution. It can also cross the blood-brain barrier, which may account for some of its central nervous system effects (31).

➢ *Metabolism:*

Geraniol undergoes extensive metabolism primarily in the liver.

- ***Phase I Metabolism*:** The major metabolic pathways include oxidation and conjugation. Enzymes such as cytochrome P450 (CYP450) may play a significant role in its metabolism, converting geraniol to various metabolites. Geraniol is primarily oxidized to its corresponding aldehyde (geranial) and subsequently to geranic acid (32).
- ***Phase II Metabolism*:** Conjugation reactions such as glucuronidation and sulfation further increase the solubility of geraniol metabolites, facilitating their excretion (33).

➢ *Excretion:*

The primary routes of excretion for geraniol and its metabolites are:

- *Renal Excretion*: Geraniol metabolites are mainly excreted via the urine. Glucuronides and sulfates of geraniol are commonly detected in urine (34).
- *Fecal Excretion*: A smaller portion of geraniol and its metabolites are excreted via the feces, especially unabsorbed geraniol or its conjugates secreted into the bile (35).

The exact half-life of geraniol can vary, but it is generally considered to have a relatively short half-life due to its rapid metabolism (36). The ADME profile of geraniol indicates that it is well-absorbed through various routes, distributed widely throughout the body, metabolized extensively by the liver, and primarily excreted through the kidneys (30). Understanding this profile helps in evaluating its efficacy and safety as a therapeutic agent or in other applications such as in perfumery and flavoring industries.

B. Drug Interactions of Geraniol:

Drug interactions occur when the presence of one drug affects the pharmacokinetics or pharmacodynamics of another. For geraniol, the potential for drug interactions can be influenced by its effects on metabolic enzymes and transporters (36).

➢ *Cytochrome P450 Enzyme Modulation:*

Geraniol can influence the activity of cytochrome P450 enzymes, which play a crucial role in the metabolism of many drugs (37).

- Inhibition: Geraniol has been shown to inhibit certain CYP enzymes (e.g., CYP3A4, CYP2B6, and CYP2C9) (38).This can lead to altered metabolism of drugs that are substrates for these enzymes, potentially increasing their plasma levels and the risk of adverse effects.
- Induction: Conversely, geraniol could also potentially induce certain CYP enzymes, leading to reduced efficacy of drugs metabolized by these enzymes due to accelerated breakdown (39).

➢ *P-glycoprotein (P-gp) Modulation:*

Geraniol might inhibit P-glycoprotein, a transporter protein that plays a role in drug excretion and absorption (40). Inhibition of P-gp can result in higher plasma concentrations of P-gp substrate drugs.

➢ *Herb-Drug Interactions:*

Given its presence in many herbal products, geraniol can interact with conventional drugs. For example, it might enhance the sedative effects of CNS depressants or alter the effectiveness of anticoagulants by affecting their metabolism (41).

➢ *Other Interactions:*

Geraniol may interact with other compounds in essential oils or herbal preparations, leading to synergistic or antagonistic effects on drug action or metabolism (42).

➢ Anticoagulants and Antiplatelet Drugs *Interactions*:

Geraniol has been reported to have antithrombotic and anticoagulant properties. Therefore, it might enhance the effects of drugs that prevent blood clotting, such as: Warfarin, Aspirin, Clopidogrel, Heparin, Nonsteroidal anti-inflammatory drugs (NSAIDs) (43).

➢ *Antihypertensive Drugs Interactions:*

Geraniol has shown potential hypotensive (blood pressure-lowering) effects in some studies (44). This might lead to additive hypotensive effects when used concurrently with antihypertensive medications, such as: Beta-blockers, ACE inhibitors, Calcium channel blockers, Diuretics.

➢ *CNS Depressants Interactions:*

Geraniol may possess mild sedative properties. When taken with other central nervous system depressants, such as: Benzodiazepines, Opioids, Alcohol, Antihistamines, and Sleep medications. The combined effect might lead to enhanced sedation and respiratory depression (45).

➢ *Herbal Supplements and Natural Products Interactions:*

Given its presence in many essential oils, geraniol might interact with other herbal supplements, potentially leading to synergistic or antagonistic effects. For example:

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St. John's Wort (which affects CYP enzymes), Ginkgo Biloba (which has anticoagulant properties), Garlic supplements (also having anticoagulant effects) (46).

- *Topical Medications and Skin Sensitization:*

When used in topical formulations, geraniol can cause skin sensitization and allergic reactions in some individuals. This could potentially interact with other topical medications or substances, exacerbating skin irritation or allergic responses (47).

Understanding the pharmacokinetics and potential drug interactions of geraniol is crucial for its safe and effective use, particularly when it is part of a complementary and alternative medicine regimen.

V. GERANIOL - A POTENT ANTICANCER AGENT WITH CHEMO-PREVENTIVE PROPERTIES

The research highlights the potential of geraniol, a naturally occurring compound found in essential oils, as a promising agent for cancer prevention and treatment. Studies conducted by various researchers have demonstrated that geraniol can inhibit the growth of cancer cells and tumors across different types of cancers, including pancreatic, colon, prostate, and skin cancers. Burke YD et al. 1997 (48) found that isoprenoids, including geraniol, significantly inhibited the growth of pancreatic tumor cells. In animal models, dietary geraniol completely prevented the growth of pancreatic tumors without affecting the animals' body weight or cholesterol levels. Carnesecchi S et al. 2001, 2002 (49, 50) showed that geraniol inhibited the growth of colon cancer cells by disrupting cell division and reducing key enzymes involved in cancer progression. Geraniol also made the cancer cells more sensitive to chemotherapy, enhancing the effectiveness of the treatment. Kim SH et al. 2011 (51) reported that geraniol induced cell cycle arrest and apoptosis in prostate cancer cells. It was also found to enhance the effectiveness of the chemotherapy drug docetaxel, leading to significant tumor growth suppression. Ahmad ST et al. 2011 (52) and Vinothkumar V et al. 2011, 2012 (53, 54) found that geraniol prevented the development of kidney and oral cancers in animal models by reducing oxidative stress and inflammation, and by modulating various molecular pathways involved in cancer progression. Studies by Polo MP et al. 2011 (55) and Chaudhary SC et al. 2013 (56) revealed that geraniol, especially when combined with other treatments like simvastatin, could inhibit the growth of liver cancer cells and reduce skin cancer development by interfering with critical signaling pathways in the cells. The study by Jin X et al. 2013 (57) explored the effect of geraniol, both alone and combined with gemcitabine, on the growth of BXPC-3 pancreatic cancer cells. They found that geraniol inhibited cell proliferation in a manner dependent on time and dose. When used together with gemcitabine, geraniol enhanced the drug's ability to induce cancer cell death, with the strongest effect seen when geraniol was administered before gemcitabine. Madankumar A et al. 2013 (58) studied how geraniol influenced enzymes involved in processing carcinogens in the body. Their research showed that geraniol could reduce the progression of chemically-induced oral cancer in animals by modulating these enzymes, which helps in detoxifying carcinogens and minimizing their harmful effects. Crespo R et al. 2013 (59) investigated how geraniol affects lipid metabolism in Hep-G2 liver cancer cells. They discovered that geraniol disrupts key metabolic pathways, inhibits cell growth, and increases apoptosis (programmed cell death). These findings suggest that geraniol could be a promising natural compound for treating cancer and cardiovascular diseases. Galle M et al. 2014 (60) focused on the impact of geraniol on lung cancer cells, both in laboratory culture and in mice. They found that geraniol inhibited cancer cell growth and tumor development by interfering with cholesterol metabolism and promoting apoptosis. Their results suggest that geraniol could be an effective anti-cancer agent without harming normal cells. Wittig C et al. 2015 (22) examined how geraniol affects the formation of blood vessels, which is essential for tumor growth. Their study found that geraniol reduced the migration and proliferation of endothelial cells, which are involved in forming new blood vessels. It also blocked key signaling pathways related to angiogenesis, leading to reduced tumor vascularization and growth. Soubh AA et al. 2015 (61) studied the effects of geraniol on colitis, a type of inflammatory bowel disease. They found that geraniol reduced inflammation and oxidative stress in the colon, thereby alleviating symptoms of colitis. Geraniol also inhibited several inflammatory signaling pathways, making it a potentially valuable treatment for colitis either alone or in combination with standard therapies. Hasan SK and Sultana S. 2015 (62) explored geraniol's protective effects against liver damage caused by the chemical 2-acetylaminofluorene (2-AAF) in rats. They found that geraniol reduced oxidative stress, inflammation, and tissue damage in the liver. It also helped restore normal liver architecture and reduced the expression of genes associated with cell proliferation and apoptosis. Liu W et al. 2015 (63) investigated the ability of different phosphatases to convert geranyldiphosphate (GPP) into geraniol. They discovered that an enzyme from Escherichia coli (PhoA) could effectively catalyze this reaction. This finding could pave the way for the industrial production of geraniol using engineered bacteria. Sawada S et al. 2016 (64) investigated geraniol's effects on liver cancer in rats and found that it significantly reduced liver weight and lowered harmful liver enzymes (AST and ALT) when compared to rats that were only exposed to a carcinogen. The study also showed that geraniol decreased the presence of proteins linked to cancer growth, suggesting its strong anti-cancer potential. Cho M et al. 2016 (65) reviewed the broader anti-cancer properties of geraniol, stating that it effectively targets various cancer types including breast, lung, colon, and prostate cancers. The study emphasized that geraniol can enhance the effects of conventional chemotherapy and interfere with cancer cell survival mechanisms, making it a promising multi-targeted cancer therapy. Lee S et al. 2016 (66) focused on prostate cancer, demonstrating that geraniol affects gene expression, particularly down regulating genes involved in the cell cycle. They identified E2F8, a key transcription factor, as a target of geraniol. Suppressing E2F8 was linked to halting cancer cell growth, indicating its potential as a therapeutic

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target in prostate cancer. Wang J et al. 2016 (67) explored geraniol's anti-inflammatory and antioxidant properties in spinal cord injury (SCI). The study showed that geraniol reduced inflammation, oxidative stress, and cell death in SCI, primarily through modulation of the NF-κB and p38 MAPK pathways, highlighting its protective role in traumatic injuries. Queiroz TB et al. 2017 (68) examined the safety of geraniol, finding that while it does not cause genetic damage in human cells, it can reduce cell viability, especially in liver cells. This suggests that while geraniol has therapeutic potential, its usage needs careful consideration to avoid toxicity. Pavan B et al. 2018 (36) investigated the pharmacokinetics of geraniol, finding that it has high bioavailability when taken orally, with minimal liver toxicity even at high doses. This study also confirmed that geraniol can cross into the cerebrospinal fluid, indicating its potential for treating central nervous system disorders. Qi F et al. 2018 (69) studied geraniol's effects on colon cancer, demonstrating its ability to inhibit cancer cell proliferation, induce apoptosis (programmed cell death), and cause DNA damage. The study suggested that geraniol, along with geranyl acetate, might be valuable in treating colon cancer due to these mechanisms. Overall, geraniol shows great potential as a chemo preventive agent due to its ability to inhibit cancer cell growth, enhance the effectiveness of existing chemotherapy drugs, and modulate various molecular pathways involved in cancer progression.

VI. NANOTECHNOLOGY-BASED DELIVERY SYSTEMS FOR GERANIOL

Nanotechnology offers innovative solutions to improve the delivery and efficacy of hydrophobic drugs like geraniol. Nanoparticles can enhance the solubility, stability, and bioavailability of geraniol, facilitating its controlled release and targeted delivery to cancer cells (70).The following sections describe various nanotechnology platforms used for geraniol delivery (**Fig. 1**).

A. Lipid-Based Nanocarriers:

Lipid-based nanocarriers, such as liposomes and solid lipid nanoparticles (SLNs), are popular for their biocompatibility and ability to enhance the solubility of hydrophobic compounds. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are promising carriers for geraniol. These nanoparticles provide a stable matrix for encapsulating hydrophobic drugs and offer controlled release properties (71).

- *Liposomes:*

These are spherical vesicles composed of phospholipid bilayers, widely used as drug delivery systems due to their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic drugs like geraniol (72). Liposomal delivery systems enhance the solubility, stability, and bioavailability of geraniol while enabling controlled release and targeted delivery. Liposomes can be modified with surface ligands to target specific cancer cells, reducing off-target effects and enhancing therapeutic outcomes. Recent studies have demonstrated that liposomal encapsulation of geraniol significantly improves its anticancer activity by enhancing its solubility and stability. Liposomal geraniol has shown promising results in vitro and in vivo, particularly in targeting breast and liver cancer cells (73, 74).

- *Solid Lipid Nanoparticles (SLNs):*

Solid lipid nanoparticles (SLNs) are submicron-sized particles composed of solid lipids that can encapsulate hydrophobic drugs like geraniol (75). SLNs offer several advantages, including improved drug stability, controlled release, and enhanced bioavailability. Moreover, SLNs can be surface-modified to achieve targeted delivery to cancer cells, thereby minimizing systemic side effects. Geraniol-loaded SLNs have shown enhanced stability and bioavailability in vitro (76, 77).

- *Nanostructured Lipid Carriers (NLCs):*

NLCs combine features of SLNs and liposomes, offering improved drug loading capacity and stability. They can protect geraniol from degradation while providing a controlled release profile. NLCs are advantageous for oral, dermal, and transdermal delivery of geraniol, though formulation optimization remains a challenge (78).

B. Polymeric Nanoparticles:

Polymeric nanoparticles, made from biodegradable polymers like PLGA (poly(lactic-co-glycolic acid))and chitosanoffer precise control over drug release kinetics and improved targeting capabilities. Geraniol can be encapsulated within these nanoparticles, which protect the drug from degradation, prolong its circulation time, and allow for sustained release.Encapsulation of geraniol in PLGA nanoparticles has demonstrated improved stability and prolonged release, making them suitable for anticancer applications (73). Additionally, PNPs can be functionalized with targeting moieties to improve the selectivity of geraniol delivery to tumor cells. Geraniol-loaded PLGA nanoparticles have demonstrated enhanced cytotoxicity against prostate and colon cancer cells compared to free geraniol (79). The sustained release profile of polymeric nanoparticles ensures prolonged therapeutic effects, reducing the frequency of administration.

- *Nanoemulsions:*

Nanoemulsions are fine oil-in-water or water-in-oil emulsions with droplet sizes typically in the range of 20-200 nm. They enhance the solubility and absorption of hydrophobic drugs. Geraniol Nanoemulsions has shown promise in improving the bioavailability of geraniol and enhancing its antimicrobial and anticancer effects (80).

- *Cyclodextrin Complexes:*

Cyclodextrins (CDs) are cyclic oligosaccharides that can form inclusion complexes with hydrophobic molecules, enhancing their solubility and stability. Geraniol-CD Complexes have demonstrated enhanced solubility and stability, making them suitable for various therapeutic applications (81).

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➢ *Inorganic Nanoparticles:*

Metal and silica nanoparticles offer unique properties like enhanced imaging and hyperthermia potential (82).

➢ *Dendrimers:*

Dendrimers are highly branched, tree-like polymers with a well-defined structure and multiple functional groups on their surface. These features make dendrimers ideal for drug delivery, as they can encapsulate or conjugate geraniol molecules within their core or on their surface. Dendrimers can also be engineered to target specific cancer cells, enhancing the therapeutic index of geraniol (83).

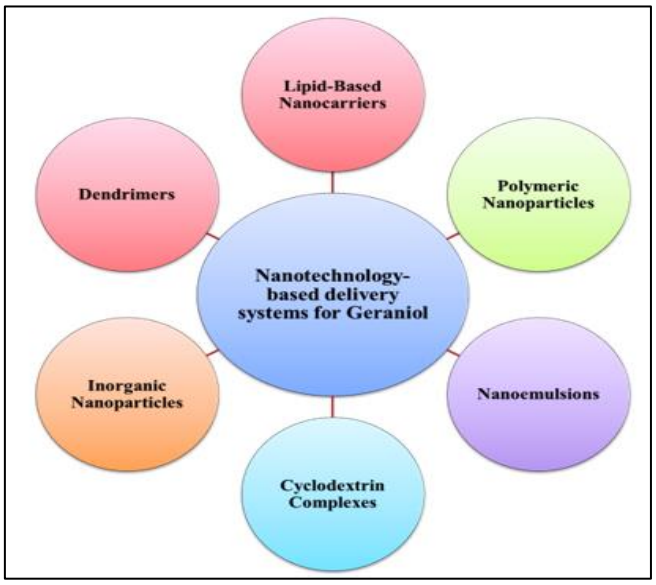

Fig 1 Nanotechnology-Based Delivery Systems for Geraniol

C. Mechanisms of Enhanced Delivery and Efficacy of geraniol:

The use of nanotechnology-based delivery systems significantly improves the pharmacokinetic and pharmacodynamic profiles of geraniol (84). Key mechanisms by which these systems enhance the delivery and efficacy of geraniol include:

➢ *Enhanced Solubility:*

Nano carriers increase the aqueous solubility of geraniol, improving its bioavailability.

➢ *Prolonged Circulation Time:*

Encapsulation in nanoparticles protects geraniol from rapid metabolism and clearance, leading to a longer half-life in the bloodstream.

➢ *Targeted Delivery:*

Surface modifications of Nano carriers with ligands or antibodies allow for targeted delivery of geraniol to cancer cells, reducing off-target effects and improving therapeutic efficacy.

➢ *Overcoming Multidrug Resistance:*

Nano carriers can bypass efflux pumps in resistant cancer cells, increasing the intracellular concentration of geraniol and overcoming drug resistance.

D. Mechanisms Underlying Therapeutic Effects:

Geraniol, a natural compound found in various essential oils, has garnered attention for its potential therapeutic effects. Several mechanisms underlie its beneficial properties:

➢ *Antioxidant Activity:*

Geraniol exhibits potent antioxidant properties, scavenging free radicals and reducing oxidative stress (18). By neutralizing reactive oxygen species (ROS), it helps protect cells and tissues from damage associated with various diseases, including cancer and neurodegenerative disorders (85).

➢ *Anti-inflammatory Effects:*

Geraniol possesses anti-inflammatory properties, inhibiting pro-inflammatory mediators such as cytokines and enzymes like cyclooxygenase (COX) and lipoxygenase (LOX). By modulating the inflammatory response, it may alleviate symptoms of inflammatory conditions such as arthritis and colitis (19).

➢ *Antimicrobial Action:*

Geraniol demonstrates antimicrobial activity against a wide range of pathogens, including bacteria, fungi, and viruses. It disrupts microbial cell membranes, inhibits enzyme activity, and interferes with microbial metabolism, making it a promising agent for combating infections (86).

➢ *Anticancer Potential:*

Research suggests that geraniol exhibits anticancer properties by inducing apoptosis (programmed cell death) and inhibiting proliferation in various cancer cell lines (69). It may also modulate signaling pathways involved in tumor growth and metastasis, potentially complementing conventional cancer therapies (15).

➢ *Neuroprotective Effects:*

Geraniol has shown neuroprotective effects in preclinical studies, protecting neurons from oxidative stress, inflammation, and excitotoxicity. These properties hold promise for the management of neurodegenerative diseases such as Alzheimer's and Parkinson's (25).

➢ *Analgesic Properties:*

Geraniol exhibits analgesic effects, possibly through modulation of pain signaling pathways. It may alleviate pain associated with conditions like arthritis, neuropathy, and migraine (87).

➢ *Anxiolytic and Sedative Effects:*

Geraniol has been reported to possess anxiolytic (anxiety-reducing) and sedative properties, possibly mediated by its interaction with neurotransmitter systems in the brain. These effects may offer potential applications in the management of anxiety disorders and sleep disturbances (88).

Overall, the multifaceted therapeutic effects of geraniol make it a promising candidate for various health applications. However, further research, including clinical

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trials, is necessary to fully elucidate its mechanisms of action and evaluate its safety and efficacy in clinical settings.

VII. CELLULAR SIGNALING PATHWAYS

➢ *MAPK/ERK Pathway:*

Geraniol modulates the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway, (**Fig. 2**) which plays a crucial role in cell proliferation, differentiation, and survival by inhibiting the phosphorylation of ERK1/2, geraniol suppresses the downstream signaling events that lead to uncontrolled cell growth, particularly in cancer cells (89).

➢ *PI3K/Akt Pathway:*

The phosphatidylinositol 3-kinase (PI3K)/Akt pathway is another critical signaling pathway affected by geraniol (**Fig. 2**). This pathway is involved in regulating cell growth, survival, and metabolism. Geraniol inhibits the activation of PI3K and the subsequent phosphorylation of Akt, leading to reduced cell survival and increased apoptosis in cancer cells (90).

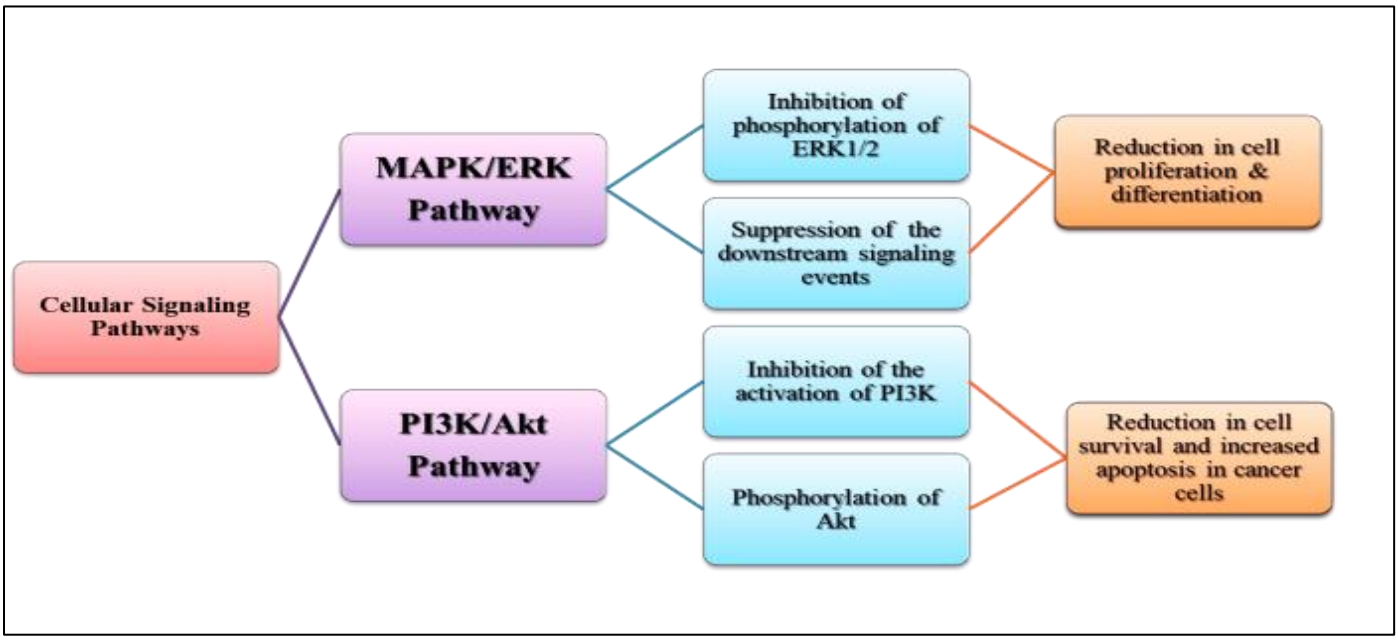

Fig 2 Cellular Signaling Pathways of Geraniol

VIII. IMPACT OF AGE, GENDER, AND CO-MORBIDITIES ON PHARMACOKINETICS

Geraniol is a naturally occurring monoterpenoid found in essential oils of various aromatic plants. Its pharmacokinetics, like that of many other compounds, can be influenced by several factors, including age, gender, and co-morbidities (46). Here is a detailed look at how these factors might impact the pharmacokinetics of geraniol:

➢ *Age:*

- *Absorption*: With aging, gastrointestinal motility and blood flow may decrease, potentially leading to slower absorption rates of geraniol. Additionally, age-related changes in gastric pH and enzymatic activity can affect the breakdown and absorption of orally administered geraniol (91).
- *Distribution*: Older adults often have increased body fat and decreased lean body mass, which can alter the distribution of lipophilic compounds like geraniol. Changes in plasma protein binding due to reduced albumin levels can also impact the distribution.
- *Metabolism*: Age-related declines in liver function, including reduced hepatic blood flow and enzymatic activity, can lead to slower metabolism of geraniol. The expression and activity of metabolic enzymes such as cytochrome P450 enzymes may decrease with age, affecting the biotransformation of geraniol (37).
- *Excretion*: Renal function typically declines with age, reducing the clearance of geraniol metabolites and potentially leading to higher systemic exposure over time.

➢ *Gender*

- *Absorption*: Gender differences in gastric emptying time and gastrointestinal transit can affect the rate and extent of geraniol absorption.
- *Distribution*: Differences in body composition between men and women, such as higher body fat percentage in women, can influence the distribution of lipophilic substances like geraniol.
- *Metabolism*: Gender-specific variations in liver enzyme activity can impact the metabolism of geraniol (92). For example, some cytochrome P450 enzymes exhibit sex differences in expression levels and activity, which can lead to variations in metabolic rates.

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- *Excretion*: Renal clearance rates can differ between men and women, potentially affecting the excretion of geraniol and its metabolites.

➢ *Co-Morbidities:*

- *Liver Diseases*: Conditions such as cirrhosis or hepatitis can impair hepatic metabolism of geraniol, leading to higher plasma concentrations and prolonged half-life (4).
- *Renal Impairments*: Chronic kidney disease can reduce the renal clearance of geraniol metabolites, increasing systemic exposure and potential toxicity (36).
- *Cardiovascular Diseases*: Conditions that affect blood flow, such as heart failure, can alter the distribution and clearance of geraniol (43).
- *Gastrointestinal Disorders*: Diseases that affect the gastrointestinal tract, such as Crohn's disease or irritable bowel syndrome, can influence the absorption of geraniol (4).

IX. GERANIOL INTERACTS WITH CELLULAR PATHWAYS INVOLVED IN CANCER PROGRESSION

Cancer remains one of the leading causes of mortality worldwide, necessitating continuous research into effective treatments. Natural compounds have been a rich source of therapeutic agents, and geraniol has emerged as a promising candidate due to its anti-inflammatory, antioxidant, and anti-cancer properties.

A. Anticancer Activity:

➢ *Apoptosis Induction:*

Geraniol has been shown to induce apoptosis in various cancer cell lines, including prostate, breast, and colon cancers. The primary mechanism involves the modulation of key apoptotic regulators such as Bcl-2 and Bax proteins. By down regulating Bcl-2 (an anti-apoptotic protein) and upregulating Bax (a pro-apoptotic protein), geraniol facilitates the release of cytochrome c from mitochondria, triggering the caspase cascade and leading to programmed cell death (15, 93).

➢ *The Induction of Apoptosis by Geraniol Involves Both Intrinsic and Extrinsic Pathways:*

- *Intrinsic Pathway*: Geraniol upregulates pro-apoptotic proteins such as Bax and downregulates anti-apoptotic proteins like Bcl-2, leading to mitochondrial membrane potential loss and cytochrome c release.
- *Extrinsic Pathway*: Geraniol increases the expression of death receptors such as Fas and FasL, activating caspase-8 and caspase-3, which are critical for the execution phase of apoptosis.

➢ *Cell Cycle Arrest:*

Geraniol induces cell cycle arrest at the G1 phase by modulating the expression of cyclins and cyclin-dependent kinases (CDKs). Specifically, it downregulates Cyclin D1 and CDK4, which are crucial for G1 to S phase transition, thereby inhibiting cell proliferation (94).Geraniol has been reported to cause cell cycle arrest in the G0/G1 and G2/M phases in several cancer cell lines. This is achieved by modulating the expression of key regulatory proteins:

- *Cyclins and Cyclin-Dependent Kinases (CDKs):* Geraniol decreases the levels of cyclins D1 and E and their associated CDKs, CDK4, and CDK2, thereby inhibiting the progression of the cell cycle.
- *CDK Inhibitors:* Geraniol upregulates CDK inhibitors such as p21 and p27, which further suppress CDK activity and halt cell cycle progression**.**

B. Anti-inflammatory Activity:

Geraniol exerts significant anti-inflammatory effects by inhibiting key inflammatory mediators and pathways. It downregulates the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (8). Additionally, geraniol inhibits the NF-κB signaling pathway, a critical regulator of inflammation. By preventing the phosphorylation and degradation of IκBα, geraniol blocks the nuclear translocation of NF-κB, reducing the transcription of inflammatory genes (95).

C. Inhibition of Metastasis:

Metastasis is a hallmark of cancer progression that significantly reduces the chances of successful treatment (65).Geraniol interferes with several pathways critical for metastasis:

- *Matrix Metalloproteinases (MMPs):* Geraniol downregulates MMP-2 and MMP-9, enzymes that degrade extracellular matrix components, thus impeding cancer cell invasion and migration.
- *Epithelial-Mesenchymal Transition (EMT):* Geraniol inhibits EMT by reducing the expression of mesenchymal markers (e.g., N-cadherin, vimentin) and increasing the expression of epithelial markers (e.g., E-cadherin).

D. Anti-Angiogenic Effects:

Angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis (22). Geraniol exerts anti-angiogenic effects through several mechanisms:

- *Vascular Endothelial Growth Factor (VEGF):* Geraniol decreases the expression of VEGF, a key mediator of angiogenesis.
- *VEGF Receptors and Signaling Pathways:* Geraniol inhibits VEGF receptor activation and downstream signaling pathways such as PI3K/Akt and MAPK/ERK, which are crucial for angiogenesis and endothelial cell proliferation.

E. Modulation of Oxidative Stress:

Oxidative stress is implicated in cancer development and progression (5, 93). Geraniol has potent antioxidant properties that help modulate oxidative stress:

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- *Reactive Oxygen Species (ROS):* Geraniol reduces intracellular ROS levels, thereby preventing DNA damage and mutation.
- *Antioxidant Enzymes:* Geraniol upregulates the expression of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, enhancing the cellular defense against oxidative stress.

X. FUTURE PERSPECTIVES

Future research directions in the field of geraniol should focus on elucidating its pharmacokinetic properties, exploring novel delivery systems to enhance its bioavailability and tissue specificity, and conducting well-designed clinical trials to evaluate its safety and efficacy in humans. Furthermore, investigations into the synergistic interactions of geraniol with other bioactive compounds and conventional therapeutics could uncover new avenues for combination therapies with enhanced efficacy and reduced adverse effects. Overall, the multifaceted pharmacological properties of geraniol offer exciting prospects for its translation into clinical practice, paving the way for the development of innovative therapeutic interventions to improve human health and well-being.

XI. CONCLUSION

Geraniol holds significant promise as a natural anticancer agent due to its multifaceted mechanisms of action and broad-spectrum efficacy against various cancer types. Nanoparticle-based delivery systems have significantly advanced the therapeutic potential of geraniol in cancer treatment. The enhanced solubility, stability, and targeted delivery of geraniol nanoparticles offer promising outcomes in preclinical studies. Nanotechnology-based delivery systems offer significant potential for improving the therapeutic efficacy and application of geraniol. While there are challenges to address, ongoing research and technological advancements hold promise for overcoming these barriers and harnessing the full potential of geraniol in various therapeutic contexts. Recent studies have demonstrated the potential of nanotechnology-based delivery systems to enhance the anticancer activity of geraniol. For example, liposomal formulations of geraniol have shown increased cytotoxicity against breast cancer cells in vitro, while polymeric nanoparticles have demonstrated improved bioavailability and tumor targeting in animal models of colorectal cancer. Nanotechnology-based delivery systems hold great promise for enhancing the therapeutic potential of geraniol in cancer therapy. By improving the solubility, stability, and targeted delivery of geraniol, nanocarriers can overcome the limitations associated with its clinical use. Continued research in this field is essential to fully realize the potential of geraniol as a novel anticancer agent and to translate these advances into clinical practice.

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