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Peptide-based functional foods and phytonanotechnology approaches in cancer prevention and therapy: A comprehensive review

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Abstract

Cancer remains one of the major global health challenges, demanding the development of safer, targeted, and sustainable therapeutic strategies. This review explores the role of peptide-based functional foods and phytonanotechnology approaches in cancer prevention and therapy, with emphasis on plant-derived bioactive peptides, phytochemicals, and green nanotechnology-mediated delivery systems. A comprehensive literature review was conducted using recent studies related to food-derived bioactive peptides, phytochemicals, medicinal plant-mediated nanoparticles, and nano-delivery systems for cancer therapy. Molecular mechanisms, therapeutic applications, pharmacokinetic properties, safety evaluation, and future perspectives were critically analysed. Plant-derived bioactive peptides and phytochemicals demonstrate significant anticancer activity through apoptosis induction, reactive oxygen species modulation, angiogenesis inhibition, and suppression of signaling pathways such as NF- κ B and PI3K/Akt. Green-synthesised nanoparticles and nanocarrier systems including liposomes, polymeric nanoparticles, and solid lipid nanoparticles improve stability, bioavailability, controlled release, and targeted delivery of therapeutic compounds. Phytonanotechnology provides an eco-friendly and biocompatible strategy for enhancing cancer treatment efficacy while minimizing systemic toxicity. Despite promising therapeutic outcomes, challenges such as peptide instability, limited bioavailability, toxicity concerns, large-scale production difficulties, and insufficient clinical trials restrict broader clinical translation. The integration of functional foods, bioactive peptides, phytochemicals, and nanotechnology may provide a novel platform for safer and more efficient cancer prevention and treatment. Dietary interventions based on peptide-rich functional foods and plant-derived therapeutics may contribute to improved public health and reduced cancer burden. This review comprehensively integrates peptide therapeutics, phytochemicals, and phytonanotechnology concepts in modern oncology and highlights their future clinical potential in targeted cancer therapy.

1. Introduction

Cancer is one of the leading causes of mortality worldwide and continues to impose a significant burden on healthcare systems and society. Conventional treatment strategies such as chemotherapy, radiotherapy, and surgical interventions are often associated with severe adverse effects, multidrug resistance, and poor selectivity toward cancer cells. Consequently, considerable attention has shifted toward the development of safer and more targeted therapeutic alternatives derived from natural products and food-based bioactive compounds (Huang *et al.*, 2021). Bioactive peptides are short sequences of amino acids released from food proteins during enzymatic hydrolysis, gastrointestinal digestion, fermentation, or food processing. These peptides possess multiple biological activities, including antioxidant, anti-inflammatory, antihypertensive, antimicrobial, immunomodulatory, and anticancer effects. Plant-derived peptides from soybeans, legumes, cereals, and medicinal

plants have gained particular importance because of their nutraceutical value and low toxicity profile (Korhonen and Pihlanto, 2006).

Phytochemicals such as flavonoids, alkaloids, polyphenols, terpenoids, and glycosides also play essential roles in cancer prevention and therapy. These compounds regulate oxidative stress, apoptosis, inflammation, angiogenesis, and cellular signaling pathways involved in carcinogenesis. However, poor solubility, instability, and limited bioavailability frequently reduce their therapeutic efficacy (Aggarwal and Shishodia, 2006). Recent advancements in phytonanotechnology have created innovative opportunities for improving the delivery and efficacy of plant-derived therapeutics. Green synthesis of nanoparticles using plant extracts provides environmentally sustainable, cost-effective, and biocompatible alternatives to conventional nanoparticle synthesis. Nanodelivery systems including liposomes, polymeric nanoparticles, solid lipid nanoparticles, and hybrid nanocarriers improve targeted drug delivery, controlled release, and therapeutic stability (Iravani, 2011).

This review focuses on peptide-based functional foods and phytonanotechnology approaches in cancer prevention and therapy. Particular emphasis is placed on plant-derived bioactive peptides, phytochemicals, molecular mechanisms of anticancer activity, nanoparticle synthesis, nanocarrier systems, pharmacokinetics, toxicity evaluation, and future clinical applications (Udenigwe and Aluko, 2012).

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2. Classification of peptides

Bioactive peptides can be classified according to chain length, structural characteristics, origin, and biological functions (Reddy *et al.*, 2004; Hartmann and Meisel, 2007; Hernandez-Ledesma *et al.*, 2009).

2.1 Classification based on chain length

Peptides are categorised as dipeptides, tripeptides, oligopeptides, and polypeptides depending on the number of amino acid residues present in the chain. Dipeptides and tripeptides are smaller peptides with rapid absorption and high bioavailability, whereas oligopeptides and polypeptides possess more complex biological functions.

2.2 Classification based on structure

Structurally, peptides are classified as linear peptides and cyclic peptides. Linear peptides possess flexible conformations and participate in signaling functions, while cyclic peptides exhibit enhanced stability and resistance to enzymatic degradation.

2.3 Classification based on origin

Bioactive peptides may originate from plants, animals, microorganisms, or endogenous biological systems. Plant-derived peptides from soybeans, wheat, rice bran, legumes, and medicinal plants are particularly important in functional food applications.

2.4 Classification based on biological function

Based on biological activity, peptides are classified as antimicrobial peptides, hormonal peptides, immunomodulatory peptides, antioxidant peptides, anticancer peptides, and signaling peptides.

3. Plant-derived bioactive peptides

Plant-derived bioactive peptides have emerged as promising nutraceutical compounds due to their therapeutic potential and safety profile. These peptides are released from plant proteins during hydrolysis, fermentation, and digestion (de Mejia and Dia, 2009; Korhonen and Pihlanto, 2006; Pan and Ho, 2008).

3.1 Soy-derived peptides

Soybean proteins are rich sources of bioactive peptides such as lunasin and Bowman-Birk inhibitor peptides. Lunasin exhibits significant anticancer activity through apoptosis induction, suppression of histone acetylation, and inhibition of tumour cell proliferation. Soy peptides also demonstrate antioxidant and anti-inflammatory properties that contribute to cancer prevention.

3.2 Legume-derived peptides

Legumes including chickpeas, lentils, and peas contain peptides with antihypertensive, antioxidant, and anticancer activities. These peptides modulate immune responses and inhibit oxidative stress-related cellular damage.

3.3 Cereal and wheat peptides

Cereal-derived peptides from wheat germ, rice bran, and oats exhibit radical scavenging activity and contribute to modulation of inflammatory pathways. Wheat germ peptides have shown inhibitory effects against colon cancer cell proliferation.

3.4 Medicinal plant proteins

Proteins from medicinal plants generate peptides with strong pharmacological activities. These compounds exhibit cytotoxicity against tumour cells while maintaining lower toxicity toward healthy tissues.

3.5 Nutraceutical importance

The incorporation of plant-derived peptides into functional foods provides a preventive dietary strategy against chronic diseases including cancer. These peptides also support immune function, oxidative stress regulation, and metabolic homeostasis.

4. Phytochemicals in cancer prevention

Phytochemicals are naturally occurring secondary metabolites found in fruits, vegetables, herbs, and medicinal plants. They play important roles in preventing oxidative stress, inflammation, and carcinogenesis (Cragg and Newman, 2005; Ramos, 2008; Aggarwal and Shishodia, 2004).

4.1 Polyphenols

Polyphenols possess strong antioxidant activity and protect cells against reactive oxygen species-induced damage. They regulate signaling pathways involved in apoptosis and inflammation.

4.2 Flavonoids

Flavonoids, including quercetin, catechins, and kaempferol inhibit tumour growth by suppressing angiogenesis, metastasis, and inflammatory signaling pathways.

4.3 Alkaloids

Alkaloids such as berberine and vincristine interfere with DNA replication and microtubule formation, thereby inhibiting tumour proliferation.

4.4 Terpenoids

Terpenoids including paclitaxel exhibit anticancer activity by stabilising microtubules and preventing cancer cell division.

4.5 Glycosides

Cardiac glycosides have demonstrated emerging anticancer effects through modulation of Na⁺/K⁺-ATPase signaling and induction of apoptosis.

5. Molecular mechanisms of anticancer activity

Bioactive peptides and phytochemicals exert anticancer effects through multiple molecular mechanisms (Fresno *et al.*, 2004; Elmore, 2007; Ahmed *et al.*, 2016).

5.1 Apoptosis and caspase activation

Apoptosis is a programmed cell death mechanism essential for maintaining tissue homeostasis. Phytochemical-loaded nanoparticles activate intrinsic apoptotic pathways through mitochondrial membrane depolarisation and cytochrome C release. This process activates initiator caspase-9 and effector caspase-3, leading to DNA fragmentation and cancer cell death. Extrinsic apoptotic pathways involve activation of death receptors and caspase-8 signaling. Regulation of Bax and Bcl-2 proteins also contributes to mitochondrial-mediated apoptosis.

5.2 Reactive oxygen species regulation

Reactive oxygen species play dual roles in cancer biology. Excessive ROS generation induces oxidative stress, mitochondrial dysfunction, DNA damage, and apoptosis. Bioactive phytochemicals modulate ROS production and enhance endogenous antioxidant defense mechanisms.

5.3 Angiogenesis inhibition

Tumour progression depends on angiogenesis and neovascularisation mediated by vascular endothelial growth factor. Bioactive peptides and phytochemicals inhibit VEGF expression and suppress endothelial cell proliferation.

5.4 NF- κ B signaling pathway

NF- κ B is a transcription factor associated with inflammation, cell proliferation, and antiapoptotic signalling. Inhibition of NF- κ B suppresses inflammatory cytokine production and enhances apoptosis in tumour cells.

5.5 PI3K/Akt signaling pathway

The PI3K/Akt pathway regulates cell survival and tumour growth. Phytochemicals and peptide-loaded nanoparticles suppress Akt

phosphorylation, inhibit downstream survival signals, and sensitise cancer cells to apoptosis.

5.6 Cell cycle arrest

Several phytochemicals induce cell cycle arrest at G0/G1 or G2/M phases, thereby preventing tumour progression and DNA replication.

6. Phytonanotechnology in cancer therapy

Phytonanotechnology combines plant-derived compounds with nanotechnology-based delivery systems to improve therapeutic efficacy (Iravani *et al.*, 2014; Anand *et al.*, 2007; Bozzuto and Molinari, 2015).

6.1 Green synthesis of nanoparticles

Green synthesis of nanoparticles utilises plant extracts containing flavonoids, phenolics, alkaloids, proteins, and terpenoids as reducing and stabilising agents. This eco-friendly approach reduces the use of hazardous chemicals and provides cost-effective nanoparticle production.

The synthesis process generally involves preparation of plant extract, reduction of metal salts, nucleation, nanoparticle stabilisation, and purification.

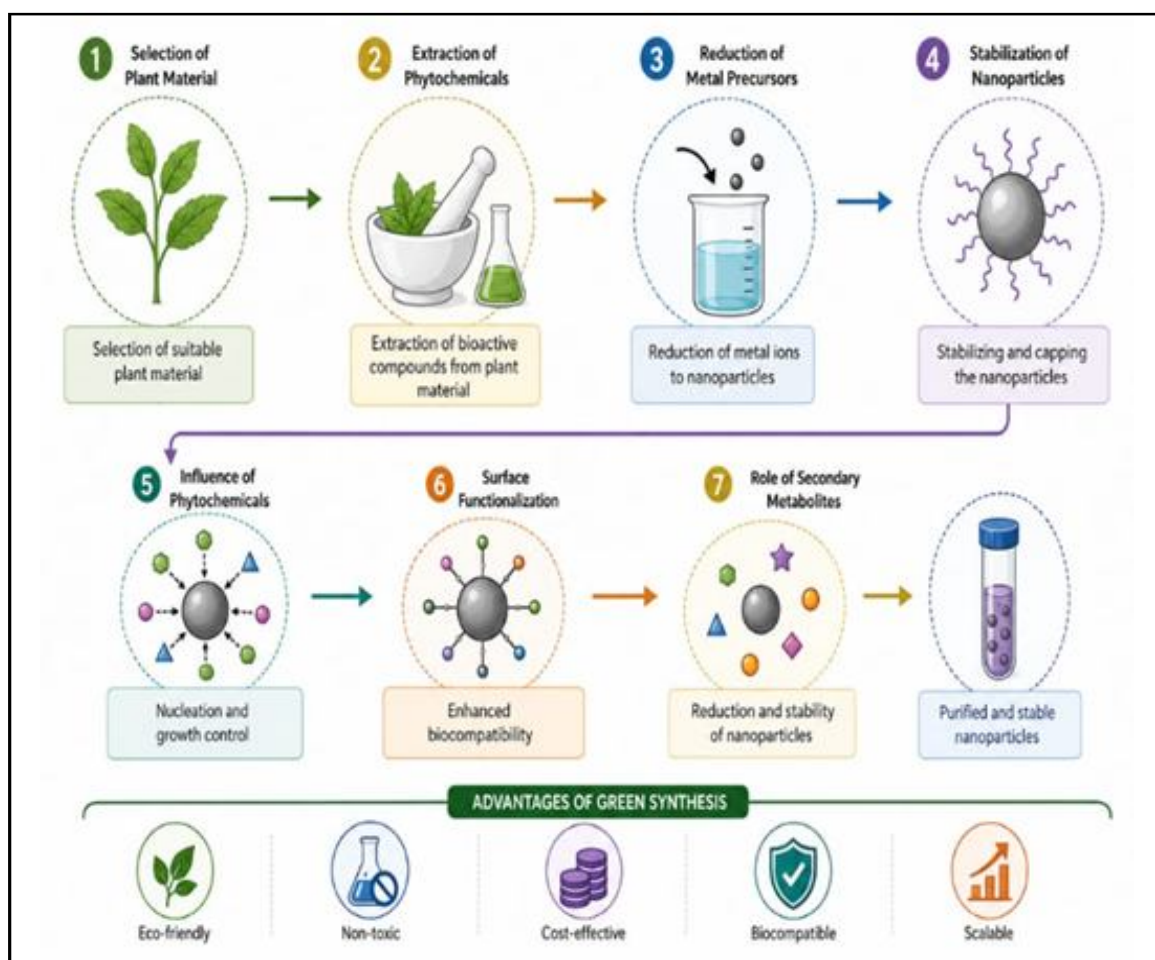


Figure 1: Green synthesis of nanoparticles using plant-mediated phytochemicals.

6.2 Advantages of green synthesis

Plant-mediated nanoparticle synthesis offers several advantages, including environmental sustainability, reduced toxicity, biocompatibility, low energy consumption, and scalability.

6.3 Medicinal plant-mediated nanoparticles

- ***Aloe vera*-mediated silver nanoparticles:** Exhibit strong anticancer activity against breast and lung cancer cell lines through ROS generation and apoptosis induction.
- ***Moringa oleifera*-mediated nanoparticles:** Demonstrate selective cytotoxicity toward cancer cells and improve therapeutic biocompatibility.
- ***Azadirachta indica*-mediated nanoparticles:** Neem-mediated nanoparticles induce oxidative stress and DNA fragmentation in tumour cells.

- ***Curcuma longa*-mediated nanoparticles:** Suppress NF-kappa B signaling pathways and improve anticancer efficacy.

7. Nanocarrier systems for phytochemical delivery

Nanocarrier systems improve the delivery, stability, and therapeutic efficiency of phytochemicals and peptides (Danhier *et al.*, 2012; Torchilin, 2009; Korhonen and Pihlanto, 2006).

7.1 Liposomes

Liposomes are phospholipid vesicles capable of encapsulating hydrophilic and hydrophobic compounds. They improve drug stability, circulation time, and tumour targeting.

7.2 Solid lipid nanoparticles

Solid lipid nanoparticles provide controlled release, improved stability, and enhanced bioavailability of poorly soluble phytochemicals.

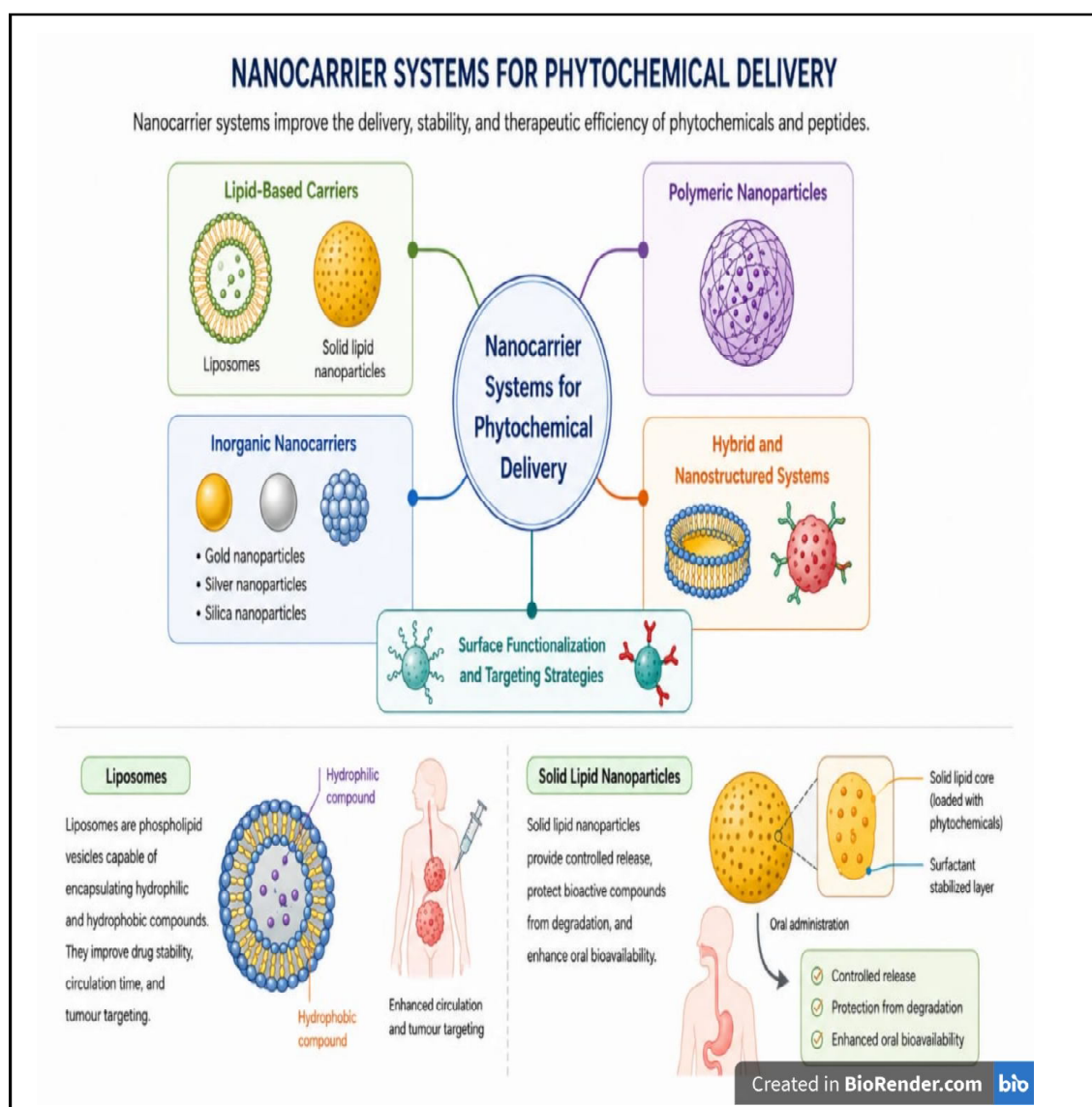


Figure 2: Nanocarrier systems for phytochemical delivery.

7.3 Polymeric nanoparticles

Polymeric nanoparticles prepared from biodegradable polymers such as PLGA provide sustained drug release and targeted delivery.

7.4 Hybrid nanocarriers

Hybrid lipid-polymer nanoparticles combine the advantages of both lipid and polymeric systems, improving circulation stability and therapeutic performance.

7.5 Stimuli-responsive nanocarriers

Stimuli-responsive nanoparticles release therapeutic agents selectively in response to pH, temperature, enzymes, or redox conditions present in tumour microenvironments.

7.6 Surface functionalisation

PEGylation, antibody conjugation, peptide targeting, and biomimetic coatings enhance tumour-specific uptake and minimise immune clearance.

8. Production of bioactive peptides

8.1 Enzymatic hydrolysis

Enzymatic hydrolysis is widely used for the rapid production of bioactive peptides using proteolytic enzymes under controlled conditions (Merrifield, 1963; Nongonierma and FitzGerald, 2017; Veronese and Pasut, 2005).

8.2 Simulated gastrointestinal digestion

Simulated gastrointestinal digestion reproduces peptide release during human digestion and helps evaluate biological activity.

8.3 Fermentation

Fermentation using probiotic microorganisms generates peptides with antioxidant and anticancer activities.

8.4 Chemical synthesis

Solid-phase peptide synthesis enables precise sequence control and high-purity peptide production.

8.5 Recombinant production

Recombinant DNA technology supports large-scale peptide production with improved efficiency.

8.6 Purification and characterisation

Chromatographic methods and mass spectrometry are commonly used for peptide purification and structural characterisation.

9. Peptide instability and protection strategies

Despite therapeutic potential, peptides are susceptible to hydrolysis, oxidation, aggregation, and enzymatic degradation (Manning *et al.*, 2010; Torchilin, 2014; Nel *et al.*, 2006).

9.1 Hydrolytic degradation

Hydrolysis occurs under acidic or alkaline conditions and results in peptide cleavage and deamidation.

9.2 Oxidative degradation

Oxidation mediated by reactive oxygen species affects methionine, cysteine, and aromatic amino acid residues.

9.3 Aggregation and dimerisation

Physical stress such as heating and freezing promotes peptide aggregation and precipitation.

9.4 PEGylation

PEGylation improves peptide stability, solubility, circulation time, and shelf-life.

9.5 Buffer systems and chelating agents

Buffer optimisation and metal ion chelators reduce oxidation and stabilise peptide formulations.

9.6 Hydrophobic ion pairing

Hydrophobic ion pairing enhances membrane permeability and peptide stability.

10. Pharmacokinetics and pharmacodynamics

Nanotechnology-based delivery systems improve pharmacokinetic properties by enhancing bioavailability, prolonging circulation time, and improving tumour targeting. Controlled release mechanisms maintain therapeutic drug concentrations while reducing adverse effects. Pharmacodynamic improvements include enhanced receptor binding, improved intracellular uptake, selective toxicity toward tumour cells, and synergistic therapeutic effects (Nel *et al.*, 2006).

11. Toxicity and safety evaluation

Plant-mediated nanoparticles generally exhibit lower toxicity compared to chemically synthesised nanoparticles. However, dose-dependent toxicity, oxidative stress, inflammatory responses, and organ accumulation remain important concerns. Comprehensive toxicity studies including cytotoxicity assays, animal models, pharmacovigilance, and long-term safety evaluations are necessary before clinical application (Udenigwe and Aluko, 2012).

12. Therapeutic applications

Bioactive peptides exhibit diverse therapeutic applications including anticancer, antioxidant, antimicrobial, antihypertensive, immunomodulatory, and antidiabetic effects. Soy-derived lunasin suppresses tumour growth through apoptosis induction, while glutathione-like peptides protect cells from oxidative damage. Lactoferricin demonstrates antimicrobial and anticancer activities through membrane disruption (Leader *et al.*, 2008).

13. Diagnostic applications

Peptides and peptide-conjugated nanoparticles are increasingly used in diagnostic imaging and theranostic applications. Peptide ligands improve tumour-specific imaging, biomarker detection, and targeted radiotherapy. Marine-derived peptides such as dolastatin and plitidepsin exhibit significant diagnostic and therapeutic potential in oncology (Shi *et al.*, 2017).

14. Clinical applications and future perspectives

Advancements in targeted therapy, personalised medicine, and artificial intelligence are transforming cancer treatment strategies. Nanotechnology-based systems provide improved tumour targeting, reduced systemic toxicity, and enhanced therapeutic outcomes.

Future research should focus on large-scale clinical trials, toxicity standardisation, precision oncology, and development of multifunctional nanocarrier systems. Artificial intelligence-assisted formulation design may accelerate discovery and optimisation of novel anticancer therapeutics.

Phytonanotechnology offers significant promise for future oncology applications by integrating natural products, nanomedicine, and molecular targeting approaches (ICH, 2009).

15. Regulatory guidelines

Regulatory agencies, including the International Council for Harmonisation and the European Medicines Agency, provide guidelines for peptide therapeutics, pharmaceutical development, quality management, and safety evaluation.

16. Conclusion

Peptide-based functional foods and phytonanotechnology have emerged as promising multidisciplinary approaches in modern cancer prevention and therapy. Plant-derived bioactive peptides and phytochemicals demonstrate significant therapeutic activities through modulation of apoptosis, oxidative stress, angiogenesis, and intracellular signaling pathways, including NF- κ B and PI3K/Akt. Green-synthesised nanoparticles and advanced nano-delivery systems improve the stability, bioavailability, and targeted delivery of these bioactive compounds while reducing systemic toxicity. The integration of nutraceutical science, phytomedicine, and nanotechnology offers sustainable and biocompatible therapeutic strategies for future oncology applications. Despite significant progress, further clinical investigations, toxicity assessments, and manufacturing standardisation are required to support successful clinical translation. Future advancements in personalised medicine, artificial intelligence-assisted drug development, and targeted nanoformulations may further enhance the therapeutic potential of peptide-based anticancer systems.

Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

Dubbaka Manasa: Contributed to writing the original draft, literature review, data collection, methodology, and manuscript editing. **E. Mounika:** Contributed to data curation, investigation, methodology, validation, and manuscript review. **Katroth Akhil:** Contributed to software handling, formal analysis, visualization, data interpretation, and manuscript editing. **Chithakari Akshaya:** Contributed to investigation, literature review, data validation, methodology, and manuscript review. **M.P. Kusuma:** Contributed to conceptualization, supervision, project administration, methodology, validation, reviewing and editing the manuscript, and overall guidance of the study.

Consent for publication

All authors gave their full consent for publication and submission to this journal.

Conflict of interest

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