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3D food printing as an emerging platform for phytomedicine delivery: Integration of medicinal plant bioactives into personalized functional food systems

Samreen*◆, P. Srilatha and M. Prashanthi*****

** Department of Food Engineering, College of Food Science and Technology, PJT Agricultural University, Rudrur-503188, Telangana, India*
*** Department of Food Technology, College of Food Science and Technology, PJT Agricultural University, Rudrur-503188, Telangana, India*
**** Department of Food Quality Assurance, College of Food Science and Technology, PJT Agricultural University, Rudrur-503188, Telangana, India*

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Abstract

Three-dimensional (3D) food printing has emerged as a disruptive digital fabrication technology with expanding applications in functional foods and nutraceutical delivery. Beyond structural customization, this technology offers a novel platform for the precise incorporation, spatial distribution, and controlled release of plant-derived bioactive compounds. Medicinal plant phytochemicals, including polyphenols, flavonoids, alkaloids, terpenoids, carotenoids, and saponins, possess well-documented antioxidant, anti-inflammatory, antidiabetic, cardioprotective, and immunomodulatory activities. However, their incorporation into conventional food systems often results in instability, low bioavailability, and inflexibility in dosage.

This review critically examines the integration of phytochemicals into 3D printed food matrices, focusing on material formulation, rheological compatibility, encapsulation strategies, phytochemical stability during processing, and controlled gastrointestinal release. Applications in personalized phytomedicine, geriatric nutrition, metabolic disorder management, and immune-supportive functional foods are comprehensively discussed. Regulatory challenges, extract standardization issues, and sustainability considerations were also addressed. The convergence of additive manufacturing with phytomedicine represents a promising frontier in precision nutrition and plant-based therapeutic food systems.

1. Introduction

The global rise in non-communicable diseases (NCDs) such as diabetes mellitus, cardiovascular disorders, obesity, metabolic syndrome, neurodegenerative diseases, cancer, and chronic inflammatory conditions has intensified the search for preventive and therapeutic strategies beyond conventional pharmacotherapy. According to the World Health Organization, NCDs account for nearly 74% of global deaths (WHO, 2019), with a substantial proportion linked to modifiable dietary and lifestyle factors. Increasing evidence indicates that oxidative stress, chronic inflammation, insulin resistance, endothelial dysfunction, and mitochondrial impairment are central mechanisms underlying these disorders (Pandey and Rizvi, 2009). Consequently, dietary interventions enriched with bioactive compounds have gained prominence as sustainable, long-term approaches to disease prevention and health promotion.

Medicinal plants have historically constituted the foundation of traditional healthcare systems, including Ayurveda, Traditional Chinese Medicine, and various indigenous healing practices. In recent decades, phytochemical research has validated many traditional claims by isolating and characterizing plant-derived secondary metabolites with significant pharmacological potential (Ekor, 2014). These phytochemicals such as polyphenols, flavonoids, alkaloids, terpenoids, carotenoids, and saponins exert diverse biological activities including antioxidant, anti-inflammatory, antimicrobial, immuno-modulatory, hepatoprotective, cardioprotective, and neuroprotective effects.

Corresponding author: Dr. Samreen
Assistant Professor, College of Food Science and Technology, Rudrur, Nizamabad, Telangana
E-mail: samreen.sam26@gmail.com
Tel.: +91-7013128094

In recent years, there has been growing scientific interest in phytomedicine, the use of medicinal plant-derived bioactive compounds for disease prevention and therapeutic support. Phytomedicine integrates traditional herbal knowledge with modern pharmacological validation, emphasizing standardized plant extracts, bioactive phytochemicals, and evidence-based therapeutic applications. However, effective delivery of these plant-derived compounds remains a major challenge due to instability, poor bioavailability, and variability in dosage. Therefore, innovative delivery platforms that can integrate medicinal plant bioactives into daily dietary formats are increasingly being explored.

For example, curcumin derived from *Curcuma longa* L. modulates inflammatory signaling pathways such as NF-κB and down regulates pro-inflammatory cytokines (Anand *et al*., 2007). Catechins from *Camellia sinensis* L. enhance endothelial function and exhibit strong free-radical scavenging activity (Salehi *et al*., 2019). Resveratrol from grapes activates sirtuin pathways involved in metabolic regulation (Pandey and Rizvi, 2009). Berberine from Berberis species improves insulin sensitivity and glucose metabolism, while ginsenosides from *Panax ginseng* C.A. Meydemonstrate adaptogenic and neuroprotective effects (Imenshahidi and Hosseinzadeh, 2016; Attele *et al*., 1999). Collectively, these compounds represent promising candidates for managing metabolic, cardiovascular, inflammatory, and neurodegenerative disorders.

Despite their therapeutic potential, phytochemicals face significant translational limitations. Many plant bioactives exhibit poor aqueous solubility, low gastrointestinal absorption, rapid metabolic degradation, and limited systemic bioavailability (Anand *et al*., 2007). For instance, curcumin undergoes rapid hepatic conjugation, resulting in minimal circulating levels after oral administration. Polyphenols are susceptible to oxidation, photodegradation, and interaction with food macromolecules. Conventional phytomedicinal dosage forms capsules, tablets, syrups, decoctions often lack controlled release mechanisms and fail to provide individualized dosing aligned with patient-specific nutritional or therapeutic needs (Ekor, 2014). Additionally, high-dose supplementation may produce gastrointestinal discomfort or reduced compliance.

Functional foods enriched with medicinal plant bioactives have emerged as an attractive alternative delivery strategy. By incorporating phytochemicals into daily dietary matrices, therapeutic compounds can be consumed consistently at physiologically relevant doses, potentially enhancing long-term efficacy and adherence. However, conventional fortification methods present challenges, including uneven distribution of bioactives, degradation during thermal processing, undesirable sensory changes (bitterness, color alteration), and limited dose precision. Furthermore, traditional food manufacturing systems are designed for mass production rather than personalization, restricting their capacity to tailor formulations according to age, metabolic profile, disease condition, or genetic predisposition.

In this context, three-dimensional (3D) food printing has emerged as a transformative technology capable of addressing many of these limitations. Adapted from additive manufacturing principles, 3D food printing enables the layer-by-layer fabrication of edible materials using computer-aided digital designs (Sun *et al*., 2015; Godoi *et al*., 2016). This digitally controlled process allows precise spatial placement of ingredients, modulation of internal microstructure, customization of nutrient composition, and accurate portion control (Baiano, 2020). Unlike conventional processing methods, 3D printing provides unprecedented flexibility in designing structured food matrices with defined geometry, porosity, and multi-material layering.

From a phytomedicine delivery perspective, this structural precision offers several innovative advantages. First, phytochemicals can be encapsulated within protective hydrocolloid, protein, or lipid matrices during printing, enhancing stability against heat, light, and oxidative degradation. Second, multi-material printing permits the spatial separation of sensitive bioactives from reactive components, preserving functionality. Third, controlled internal architecture influences digestive behavior, potentially improving bioaccessibility and targeted release within specific regions of the gastrointestinal tract. The ability to design functional gradients or compartmentalized structures within a single food product introduces new possibilities for controlled phytochemical delivery.

Moreover, 3D food printing aligns closely with the emerging paradigm of personalized nutrition. Nutritional requirements vary widely based on age, sex, genetic background, metabolic health, disease status, and lifestyle factors. Digital integration of dietary algorithms with 3D printing platforms allows the formulation of individualized functional foods containing optimized levels of plant bioactives. For example, antioxidant-rich formulations may be designed for cardiovascular risk patients, polyphenol-enriched low-glycemic foods for diabetic individuals, or neuroprotective phytochemical blends for ageing populations. Such customization bridges the gap between preventive nutrition and therapeutic phytomedicine.

Another significant dimension is sustainability. Agro-industrial plant by-products such as fruit peels, grape pomace, vegetable residues, seed cakes, and herbal extraction remnants are often rich sources of phenolics, dietary fibers, and bioactive compounds. 3D food printing enables the valorization of these materials into structured functional foods, supporting circular bioeconomy models and reducing food waste. This integration strengthens the synergy between phytomedicine, sustainable processing, and innovative food engineering.

In addition to structural and nutritional advantages, 3D food printing facilitates precise dose standardization, a critical requirement for phytomedicinal efficacy. Digital control ensures reproducible distribution of bioactive compounds within each printed unit, enabling consistent therapeutic intake. This feature is particularly relevant for clinical nutrition, elderly care, pediatric populations, and patients requiring controlled dietary interventions.

Thus, 3D food printing represents an emerging interdisciplinary platform at the intersection of phytochemistry, food engineering, material science, and digital manufacturing. By enabling the structured incorporation of medicinal plant bioactives into customizable functional foods, this technology holds significant promise for enhancing stability, improving bioavailability, ensuring precise dosing, and advancing personalized preventive healthcare (Mantihal and Bhandari, 2021).

The present review aims to critically evaluate the integration of medicinal plant bioactives into 3D printed food matrices, discuss material formulation strategies, explore mechanisms enhancing phytochemical stability and bioaccessibility, examine disease-specific functional applications, and analyze regulatory and translational challenges associated with phytomedicine-oriented personalized food systems.

2. Phytochemicals and medicinal plant bioactives suitable for 3D printing

The successful integration of phytomedicinal compounds into 3D printed functional foods requires careful consideration of physicochemical properties, stability, therapeutic dose range, compatibility with printable matrices, and release behavior during digestion. Ideal candidates for 3D printing should demonstrate measurable health benefits at dietary concentrations, maintain structural stability under mild processing conditions, and be amenable to encapsulation or dispersion within semi-solid printable formulations.

Phytochemicals incorporated into printable matrices can be broadly classified into polyphenols, flavonoids, alkaloids, terpenoids, and saponins. Each class presents unique opportunities and formulation challenges in the context of additive food manufacturing.

2.1 Polyphenols

Polyphenols represent one of the most extensively studied classes of plant bioactives due to their potent antioxidant and anti-inflammatory properties. Structurally characterized by multiple phenolic hydroxyl groups, polyphenols scavenge reactive oxygen species (ROS), chelate transition metals, and modulate redox-sensitive signaling pathways such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK). These mechanisms underlie their protective roles against cardiovascular diseases, diabetes, cancer, and neurodegenerative disorders (Pandey and Rizvi, 2009).

2.1.1 Curcumin

Curcumin, derived from *C. longa*, is a hydrophobic polyphenolic compound with demonstrated anti-inflammatory, anticarcinogenic, hepatoprotective, and antidiabetic effects. It regulates inflammatory mediators, including COX-2, TNF-α, and interleukins, while influencing apoptotic pathways in cancer cells. However, its clinical translation is limited by poor aqueous solubility, rapid intestinal metabolism, and systemic elimination (Anand *et al*., 2007). 3D food printing provides a promising strategy to overcome these limitations. Curcumin can be incorporated into:

- Lipid-based printable emulsions
- Protein polysaccharide composite gels
- Hydrocolloid matrices (*e.g*., alginate, carrageenan, gelatin)
- Nanoencapsulated delivery systems embedded within printable pastes

Encapsulation within structured matrices enhances oxidative stability and may improve gastrointestinal bioaccessibility. Furthermore, internal geometric design such as controlled porosity or multilayer structures can modulate release kinetics during digestion, allowing sustained delivery of curcumin in functional food formats.

2.1.2 Resveratrol

Resveratrol, a stilbene found in grapes and berries, exhibits cardioprotective and anti-aging effects through activation of sirtuin-1 (SIRT1) and modulation of mitochondrial biogenesis. Similar to curcumin, it suffers from rapid metabolism and limited oral bioavailability. Incorporation into lipid-rich or protein-stabilized printable matrices can enhance solubility and reduce degradation during processing. 3D printing allows spatially controlled placement of resveratrol within protected internal layers, minimizing exposure to oxygen and light.

2.1.3 Epigallocatechingallate (EGCG)

EGCG, the major catechin in green tea (*Camellia sinensis* L.), exerts antioxidant, anti-inflammatory, and antiobesity effects. It modulates lipid metabolism, inhibits adipogenesis, and enhances endothelial function. However, EGCG is highly sensitive to heat, pH variations, and oxidative degradation. Therefore, low-temperature extrusion printing and oxygen-limiting formulations are preferable. Incorporation into hydrocolloid-based matrices may improve stability and protect against premature degradation.

2.1.4 Quercetin

Quercetin, a flavonol widely distributed in onions, apples, and medicinal plants, demonstrates antiviral, anti-inflammatory, and cardioprotective properties. Its poor water solubility limits absorption. Nanodispersion or protein complexation strategies integrated into printable pastes may enhance their solubility and intestinal uptake. Overall, polyphenols are highly promising for 3D printed phytomedicinal foods, provided formulation strategies address solubility and stability challenges.

2.2 Flavonoids

Flavonoids are a subclass of polyphenols characterized by a C6-C3-C6 backbone structure. They include flavonols, flavan-3-ols, anthocyanins, flavones, and isoflavones. These compounds demonstrate strong cardioprotective, neuroprotective, antidiabetic, and anti-inflammatory effects (Salehi *et al*., 2019).

2.2.1 Catechins

Catechins, particularly those from, enhance nitric oxide bioavailability, reduce LDL oxidation, and improve endothelial function. Their incorporation into 3D printed food matrices can be particularly valuable for cardiovascular-targeted functional foods. However, catechins are prone to oxidation at elevated temperatures. Therefore, mild extrusion conditions and antioxidant stabilized formulations are recommended.

2.2.2 Anthocyanins

Anthocyanins, responsible for red, purple, and blue pigmentation in fruits and vegetables, exhibit antioxidant, antiobesity, and neuroprotective effects. Their pH-sensitive structural transformations present both challenges and opportunities in 3D printing. Controlled matrix pH and protective encapsulation are essential to maintain color stability and bioactivity. Interestingly, 3D printing may allow aesthetic-functional integration, where anthocyanin-rich layers provide both visual appeal and therapeutic benefit. Flavonoid incorporation into printable systems requires attention to:

- Thermal sensitivity
- Oxidative stability
- Interaction with proteins and carbohydrates
- Sensory impact (astringency, bitterness)

Microencapsulation, nanoemulsion formation, and protein-binding strategies can mitigate instability and improve bioavailability.

2.3 Alkaloids

Alkaloids are nitrogen-containing bioactive compounds with pronounced pharmacological effects. While potent, they require precise dosing due to narrow therapeutic windows in some cases.

2.3.1 Berberine

Berberine, derived from *Berberis* species, exhibits antidiabetic, lipid-lowering, antimicrobial, and anti-inflammatory properties. It activates AMP-activated protein kinase (AMPK), improving insulin sensitivity and glucose metabolism (Imenshahidi and Hosseinzadeh, 2016). However, high doses may cause gastrointestinal discomfort. 3D food printing offers a significant advantage in alkaloid delivery through:

- Accurate dose standardization
- Controlled spatial distribution
- Integration into low-glycemic matrices
- Personalized formulation based on metabolic profile

For diabetic patients, berberine-enriched low-carbohydrate printed snacks could provide therapeutic benefits alongside nutritional management. Given the pharmacological potency of alkaloids, regulatory considerations and safety assessments are particularly important when incorporating them into functional food systems.

2.4 Terpenoids and saponins

Terpenoids and saponins represent structurally diverse phytochemicals with adaptogenic, immunomodulatory, anti-inflammatory, and anticancer properties.

2.4.1 Ginsenosides

Ginsenosides from *P. ginseng* are triterpenoid saponins known for their neuroprotective, immunomodulatory, and anti-fatigue effects (Attele *et al*., 1999). They influence the hypothalamic pituitary adrenal axis and modulate inflammatory cytokines. However, ginsenosides may degrade under high heat or prolonged processing. Encapsulation within hydrogel-based printable matrices can:

- Protect ginsenosides from thermal degradation
- Modulate intestinal release kinetics
- Enhance gastrointestinal absorption

2.4.2 Other terpenoids

Terpenoids such as limonene, carotenoids, and essential oil constituents demonstrate antioxidant and antimicrobial activities. Lipophilic terpenoids are particularly suited for lipid-based printable emulsions. However, volatility and oxidation remain concerns; therefore, matrix protection and oxygen-limited processing are critical. Saponins also exhibit cholesterol-lowering and immune-enhancing properties. Their amphiphilic nature may influence the rheological properties of printable systems, requiring careful formulation optimization.

2.5 Key considerations for phytochemical selection in 3D printing

When selecting phytochemicals for incorporation into 3D printed personalized functional foods, the following criteria are critical:

- Demonstrated therapeutic efficacy at dietary concentrations
- Compatibility with printable rheological matrices
- Stability under mild extrusion or deposition conditions
- Controlled release potential within gastrointestinal environments
- Acceptable sensory impact
- Regulatory approval for food use

3D food printing enables multi-material deposition, microencapsulation integration, and geometric structuring, thereby addressing many traditional limitations associated with phytochemical fortification. Through digital precision, phytomedicinal compounds can be incorporated in spatially defined patterns that optimize both stability and bioavailability. Plant-derived bioactive compounds suitable for 3D printed functional foods are shown in Table 1.

Table 1: Plant-derived bioactive compounds suitable for 3D printed functional foods

Class	Examples	Therapeutic activity
Polyphenols	Curcumin, resveratrol	Anti-inflammatory, antioxidant
Flavonoids	Quercetin, catechins	Cardioprotective
Alkaloids	Berberine	Antidiabetic
Carotenoids	Lycopene, β-carotene	Antioxidant
Saponins	Ginsenosides	Adaptogenic
Phenolic acids	Gallic acid	Antimicrobial

Many of these compounds are sensitive to heat, light, oxygen, and shear stress. Therefore, incorporation into 3D printed matrices requires careful optimization of printing conditions.

3. Material formulation and rheological considerations for phytomedicinal integration in 3D printed functional foods

The successful integration of medicinal plant bioactives into 3D printed food systems requires careful formulation strategies that preserve pharmacological activity while enabling precise, controlled delivery. From a phytomedicine perspective, the primary objective is not merely structural printability but the protection, stabilization, and targeted release of bioactive compounds within functional food matrices.

3.1 Preservation of phytochemical stability during processing

Many phytochemicals exhibit physicochemical instability under environmental stressors such as oxygen, light, heat, moisture, and pH variation. Polyphenols, flavonoids, and alkaloids are particularly prone to oxidative degradation and structural modification, which may compromise therapeutic efficacy.

For example

- Curcumin from *C. longa* is highly sensitive to alkaline pH and light exposure.
- Epigallocatechingallate (EGCG) from *C. sinensis* undergoes oxidation during thermal processing.
- Anthocyanins degrade under high pH and elevated temperature conditions.

Thus, the formulation of printable matrices must prioritize:

- Mild processing temperatures
- Controlled pH environments
- Oxygen-limiting conditions
- Protective carrier systems

Hydrocolloid-based systems, such as alginate and gelatin, can create microenvironments that shield sensitive phytoconstituents from degradation. The formation of gel networks around bioactives reduces diffusion of oxygen and protects against premature oxidation.

3.2 Role of hydrocolloids and plant biopolymers in phytomedicine delivery

Hydrocolloids are not merely rheology modifiers but functional carriers that influence release kinetics and gastrointestinal bioaccessibility of plant bioactives. Commonly employed phytocompatible polymers include:

- Alginate forms calcium-induced gel matrices enabling controlled release
- Xanthan gum stabilizes dispersions of herbal extracts
- Carrageenan supports gel strength and structural stability
- Gelatin enhances matrix cohesion and encapsulation efficiency

From a therapeutic perspective, these biopolymers serve to:

- Prevent rapid degradation in gastric conditions
- Facilitate sustained or delayed release
- Improve intestinal absorption
- Enhance mucosal adhesion and bioavailability

Plant protein isolates (soy, pea, lentil) further provide functional matrices that interact with phenolic compounds via hydrogen bonding and hydrophobic interactions. These interactions can improve stability and modulate release in the gastrointestinal tract.

3.3 Impact of phytochemicals on rheological behavior

Phytochemical incorporation can significantly alter the rheological characteristics of printable food inks due to:

- Interaction with polymer chains
- Modification of water-binding capacity
- Changes in viscosity and yield stress

Polyphenols may form cross-linking interactions with proteins and polysaccharides, affecting gel strength and extrusion behavior. While these interactions may complicate printability, they can enhance structural entrapment of bioactives, which is beneficial for sustained delivery.

Shear-thinning behavior remains essential to ensure smooth extrusion while maintaining post-print structural integrity. However, from a phytomedicinal standpoint, the rheological system must be optimized to prevent:

- Thermal degradation during extrusion
- Phase separation of active compounds
- Uneven dose distribution

Uniform dispersion of phytochemicals ensures reproducible therapeutic dosing - an essential consideration when functional foods are intended to deliver standardized bioactive quantities.

3.4 Encapsulation technologies for enhanced phytomedicinal performance

Encapsulation plays a pivotal role in improving the solubility, stability, and bioavailability of plant-derived compounds within 3D printed matrices. Key encapsulation approaches include:

Microencapsulation

Provides protective coating around sensitive bioactives, reducing oxidative degradation and masking bitter taste.

Nanoemulsions

Enhance the solubility of hydrophobic compounds such as curcumin and resveratrol, increasing intestinal absorption and systemic availability.

Liposomal carriers

Phospholipid vesicles encapsulate phytochemicals, improving membrane permeability and protecting against enzymatic degradation.

Biopolymeric nanoparticles

Enable targeted and sustained release profiles, particularly valuable for anti-inflammatory and antidiabetic phytocompounds. Encapsulation ensures:

- Controlled release in specific gastrointestinal regions
- Improved pharmacokinetic performance
- Reduced required dosage
- Enhanced therapeutic consistency

In phytomedicine-based 3D printed systems, encapsulation allows the development of functional foods that function as dose-controlled therapeutic carriers rather than simple nutraceutical fortifications.

3.5 Controlled release and personalized phytotherapy

One of the most significant advantages of 3D food printing in phytomedicine is spatial control over ingredient placement. Different phytochemicals can be layered or compartmentalized within a single printed structure to achieve:

- Sequential release profiles
- Synergistic multi-herb formulations
- Chrononutrition-based delivery
- Patient-specific dose adjustments

For example

- Antidiabetic phytochemicals may be localized in slow-release compartments.
- Adaptogenic compounds may be integrated into rapidly bioavailable layers.
- Polyherbal combinations can be precisely standardized per serving.

This spatial precision supports the evolution of personalized phytotherapy, where therapeutic doses are embedded within daily dietary formats tailored to age, metabolic profile, and disease condition.

3.6 Clinical and regulatory implications

For phytomedicine-oriented 3D printed systems to gain clinical acceptance, the following considerations are critical:

- Standardization of phytochemical concentration
- Reproducibility of dose per serving
- Stability during storage
- *In vitro* and *in vivo* bioavailability studies
- Toxicological and safety evaluation

Standardized quantification methods (HPLC, LC-MS) must confirm phytochemical retention post-printing. Additionally, regulatory frameworks governing functional foods and botanical therapeutics must be carefully considered. From a phytomedicine standpoint, material formulation in 3D food printing is not merely a structural challenge but a therapeutic design strategy. By combining hydrocolloid systems, plant-based polymers, and advanced encapsulation technologies, it is possible to develop structured functional foods capable of delivering standardized, stable, and bioavailable medicinal plant compounds. Thus, 3D food printing offers a transformative platform for translating traditional herbal therapeutics into scientifically standardized, personalized, and diet-integrated phytomedicinal delivery systems.

4. Stability of phytochemicals during 3D printing

The therapeutic efficacy of medicinal plant bioactives is intrinsically dependent on their chemical stability during processing, storage, and gastrointestinal transit. While 3D food printing offers unparalleled precision in formulation and dosing, the printing process itself may expose phytochemicals to physicochemical stressors capable of reducing biological activity. Therefore, understanding stability dynamics during 3D printing is fundamental to developing clinically meaningful phytomedicinal functional foods.

4.1 Thermal stress during extrusion

Extrusion-based 3D food printing systems may involve mild to moderate temperature exposure depending on the material matrix. Although, many printable formulations operate at relatively low temperatures compared to conventional food extrusion, certain bioactives remain thermolabile even under mild thermal conditions. Temperature-induced degradation mechanisms include:

- Structural isomerization
- Oxidative decomposition
- Hydrolytic breakdown
- Loss of volatile phytoconstituents

For example

- Curcumin undergoes rapid degradation under prolonged heat exposure.
- Epigallocatechingallate (EGCG) from green tea exhibits thermal instability at elevated temperatures.
- Anthocyanins degrade through cleavage of glycosidic bonds under heat stress.

However, studies have demonstrated that extrusion-based printing under carefully controlled temperature regimes can preserve antioxidant capacity in polyphenol-enriched systems. Controlled processing conditions such as maintaining temperatures below critical degradation thresholds and minimizing residence time are crucial in preserving phytochemical integrity. From a phytomedicine perspective, mild-temperature extrusion provides a significant advantage over conventional high-temperature food processing techniques.

4.2 Shear induced oxidative degradation

During extrusion, bioactive compounds are subjected to shear forces that may promote oxidative reactions, particularly in the presence of dissolved oxygen. Shear can enhance molecular mobility and increase exposure of reactive functional groups, facilitating oxidation of phenolic hydroxyl groups. Polyphenols are especially vulnerable to:

- Auto-oxidation
- Radical-mediated degradation
- Enzymatic browning reactions

Oxidative degradation leads not only to loss of antioxidant activity but also to potential formation of inactive or unstable derivatives. To mitigate shear-induced oxidation, formulation strategies include:

- Incorporation of natural antioxidants (ascorbic acid, tocopherols)
- Reduction of dissolved oxygen in inks
- Use of inert gas flushing systems
- Encapsulation within protective matrices

By stabilizing phenolic structures within polymer networks or lipid carriers, oxidative reactions can be significantly minimized.

4.3 Oxygen exposure and environmental factors

Oxygen exposure during mixing, extrusion, and post-print handling remains one of the major threats to phytochemical stability. Many plant-derived bioactives contain conjugated double-bond systems and phenolic structures that are highly susceptible to oxidative degradation. Key environmental destabilizers include:

- Oxygen
- Light (especially UV exposure)
- Moisture
- pH fluctuations

For example

- Resveratrol undergoes photo-isomerization and oxidative degradation.
- Anthocyanins exhibit pH-dependent structural transformations.
- Alkaloids may degrade under alkaline conditions.

Protective strategies during 3D printing involve:

- Oxygen-reduced printing environments
- Light-protective packaging
- Controlled humidity storage
- Optimization of matrix pH

Hydrocolloid networks act as diffusion barriers, limiting oxygen penetration and protecting encapsulated phytochemicals from environmental degradation.

4.4 Impact of post-processing treatments

Certain 3D printed foods may undergo post-processing treatments such as:

- Mild drying
- Surface setting
- UV curing
- Refrigerated storage

Each of these treatments may influence phytochemical stability. Drying can concentrate reactive oxygen species, while UV exposure may degrade photosensitive compounds. Even refrigeration can affect matrix hydration and alter release kinetics. From a phytomedicinal standpoint, post-processing conditions must be validated through:

- Quantitative phytochemical analysis (HPLC, LC-MS)
- Antioxidant activity assays (DPPH, FRAP, ABTS)
- Stability studies under accelerated storage conditions

These analyses confirm whether therapeutic potency is retained throughout product shelf-life.

4.5 Protective role of encapsulation technologies

Encapsulation represents one of the most effective strategies for preserving phytochemical stability during and after 3D printing. Protective mechanisms include:

- Physical barrier formation
- Reduction of oxygen diffusion
- Prevention of direct exposure to heat
- Controlled release in gastrointestinal environments

Microencapsulation and nanoemulsion systems have demonstrated significant improvement in retention of curcumin, catechins, and other phenolic compounds during processing. Liposomal encapsulation enhances membrane stability and prevents enzymatic degradation. Encapsulation also reduces undesirable sensory attributes such as bitterness or astringency, thereby improving consumer acceptability of phytomedicinal functional foods.

4.6 Spatial separation of incompatible bioactives

A unique advantage of 3D food printing is its capacity for layer-by-layer spatial control. Many phytochemicals may exhibit antagonistic interactions when co-formulated. For example:

- Certain polyphenols may chelate metal ions, affecting the stability of other compounds.
- Alkaloids may interact with acidic phenolics.
- Oxidizable compounds may accelerate the degradation of neighboring bioactives.

Through compartmentalized deposition, incompatible phytochemicals can be spatially separated within a single printed structure. This prevents adverse chemical interactions while allowing synergistic therapeutic action upon ingestion. Such structural precision enables:

- Sequential release profiles
- Targeted intestinal delivery
- Chronotherapeutic design
- Standardized multi-herb formulations

This approach aligns strongly with traditional polyherbal therapeutic strategies while introducing modern precision and dose reproducibility.

4.7 Implications for therapeutic efficacy

The clinical relevance of phytomedicinal 3D printed systems depends on:

- Retention of active compound concentration
- Preservation of antioxidant capacity
- Stability during storage
- Predictable release kinetics
- Bioaccessibility and bioavailability

Without stability assurance, therapeutic claims cannot be substantiated. Therefore, a comprehensive stability assessment must accompany product development, including *in vitro* digestion models and *in vivo* validation studies. Stability of phytochemicals during 3D printing is a critical determinant of therapeutic functionality. Although exposure to heat, shear, oxygen, and post-processing treatments presents potential risks, optimized formulation strategies-particularly encapsulation and spatial structuring can effectively preserve bioactive integrity. By integrating protective matrix systems with controlled processing parameters, 3D food printing emerges as a scientifically robust platform for delivering stable, standardized, and clinically relevant phytomedicinal compounds within personalized functional food systems.

5. Controlled release and bioavailability enhancement in 3D printed phytomedicinal functional foods

One of the most significant challenges in phytomedicine is the limited oral bioavailability of plant-derived bioactive compounds. Many phytochemicals exhibit poor aqueous solubility, rapid metabolism, low intestinal permeability, and instability in gastric conditions. Consequently, even compounds with strong *in vitro* pharmacological activity may demonstrate reduced *in vivo* efficacy.

Three-dimensional (3D) food printing offers a transformative approach by enabling precise microstructural design of food matrices that influence digestion kinetics, phytochemical release profiles, and intestinal absorption. From a phytomedicinal standpoint, the ability to engineer release behavior represents a critical advancement toward functional foods that deliver standardized therapeutic effects.

5.1 Influence of microstructure on digestion kinetics

The internal architecture of 3D printed foods such as porosity, layer thickness, infill density, and matrix composition directly affects enzymatic accessibility and nutrient diffusion during gastrointestinal digestion.

Structured matrices can:

- Reduce rapid starch hydrolysis
- Slow glucose diffusion
- Prolong gastric retention time
- Modify intestinal transit

By altering microstructure, it is possible to delay starch digestion and moderate postprandial glycemic response. This is particularly relevant for functional foods targeting metabolic disorders such as diabetes mellitus and obesity. Phytochemicals such as polyphenols further interact with digestive enzymes (*e.g.*, α-amylase, α-glucosidase), and when embedded within structured matrices, their inhibitory effects may be prolonged. The combination of matrix engineering and enzyme inhibition can synergistically contribute to glycemic modulation. Thus, 3D printing does not merely incorporate phytochemicals into food, it enables metabolic regulation through structural design.

5.2 Modulation of glycemic response

Controlled microstructural design allows the development of low-glycemic phytomedicinal foods. By reducing starch digestibility and controlling carbohydrate availability, 3D printed systems can support:

- Improved insulin sensitivity
- Reduced postprandial glucose spikes
- Sustained energy release

When combined with antidiabetic phytochemicals such as berberine, curcumin, or catechins, these structured systems provide dual mechanisms:

- Structural glycemic control
- Phytochemical-mediated metabolic regulation

This integrated approach aligns strongly with preventive phytotherapy strategies for managing non-communicable diseases.

5.3 Colon-targeted delivery of phytochemicals

Many plant bioactives exhibit enhanced activity in the lower gastrointestinal tract, particularly in modulating gut microbiota and reducing intestinal inflammation. However, premature release in the stomach can lead to degradation or reduced efficacy. 3D printing allows incorporation of protective matrix systems that resist gastric digestion and enable colon-targeted delivery. Advantages of colon-targeted phytochemical delivery include:

- Local anti-inflammatory action
- Modulation of gut microbiota
- Enhanced microbial biotransformation into active metabolites
- Reduced systemic degradation

For example

- Polyphenols may undergo microbial metabolism to produce bioactive phenolic acids.
- Certain alkaloids and flavonoids demonstrate enhanced activity after colonic fermentation.

By designing multi-layer or encapsulated systems resistant to gastric pH but degradable in colonic conditions, therapeutic efficacy can be significantly improved.

5.4 pH-sensitive biopolymers for targeted intestinal release

pH-responsive polymers are particularly valuable in phytomedicinal delivery systems. These polymers remain stable in acidic gastric conditions (pH 1.5-3.5) but swell or dissolve in the near-neutral intestinal environment (pH 6-7.5). Examples of pH-sensitive biopolymers include:

- Alginate (calcium-crosslinked)
- Chitosan-based systems
- Modified cellulose derivatives
- Certain plant-derived polysaccharides

These polymers enable:

- Protection of acid-sensitive phytochemicals
- Prevention of early degradation
- Controlled release in the small intestine
- Improved absorption across the intestinal epithelium

For compounds such as curcumin and resveratrol, protection from gastric degradation significantly enhances systemic bioavailability. From a phytomedicine perspective, this targeted release strategy ensures that active compounds reach their optimal absorption site in pharmacologically effective concentrations.

5.5 Multi-material printing and core-shell structures

A unique advantage of advanced 3D printing systems is multi-material deposition, allowing fabrication of core-shell architectures. In such structures:

- The core contains the active phytochemical
- The outer shell provides mechanical protection and controlled release

Core-shell designs offer several phytomedicinal advantages:

- Protection of heat-sensitive or oxidation-prone compounds
- Separation of incompatible bioactives
- Sequential release profiles
- Sustained delivery over extended digestion periods

For example

- A hydrophobic phytochemical can be encapsulated in a lipid-rich core.
- The outer shell may consist of a hydrocolloid matrix controlling diffusion.

Such spatial precision significantly improves stability and bioavailability compared to conventional blending approaches.

5.6 Enhancement of bioavailability

Bioavailability of phytochemicals depends on:

- Solubility
- Stability in gastrointestinal fluids
- Permeability across the intestinal epithelium
- Resistance to first-pass metabolism

3D printed functional foods can enhance these parameters through:

- Particle size reduction (*via* nanoemulsion systems)
- Lipid-based incorporation for hydrophobic compounds
- Encapsulation to prevent enzymatic degradation
- Controlled release to maintain a sustained plasma concentration

Improved bioavailability translates directly into enhanced therapeutic outcomes and reduced dosage requirements.

For example

- Nanoemulsifiedcurcumin shows improved intestinal absorption.
- Liposomal resveratrol demonstrates enhanced stability and systemic availability.

Embedding such delivery systems within printable matrices allows simultaneous structural precision and pharmacological optimization.

5.7 Personalized phytomedicine through controlled release design

Personalized nutrition and phytotherapy require dose customization based on:

- Age
- Metabolic condition
- Disease severity
- Genetic predisposition

3D printing enables precise control over:

- Quantity of phytochemicals per serving
- Distribution within the matrix
- Release rate
- A combination of multiple herbal bioactives

This precision transforms phytomedicine from traditional empirical dosing into standardized, individualized therapeutic nutrition.

6. Applications in personalized phytomedicine

Three-dimensional (3D) food printing represents a paradigm shift in phytomedicine by enabling individualized therapeutic nutrition. Unlike conventional herbal dosage forms that offer fixed-dose preparations, 3D printing permits precise modulation of phytochemical concentration, spatial distribution, and release kinetics tailored to individual metabolic needs, disease conditions, and age-related requirements. This convergence of medicinal plant science and digital fabrication supports the development of personalized functional foods that function as therapeutic dietary interventions.

6.1 Antidiabetic functional foods

The global burden of type 2 diabetes mellitus necessitates innovative dietary strategies that combine glycemic modulation with plant-derived therapeutic agents. Several medicinal plant bioactives have demonstrated hypoglycemic and insulin-sensitizing effects. Key phytomedicinal candidates include:

- **Berberine** from *Berberis* species improves insulin sensitivity and modulates AMP-activated protein kinase (AMPK) pathways.
- **Cinnamon polyphenols** from *Cinnamomum verum* enhance glucose uptake and improve insulin receptor signaling.
- **Fenugreek (*Trigonella foenum-graecum*) extracts** contain 4-hydroxyisoleucine and soluble fibers that reduce postprandial glucose levels.

Through 3D printing, these phytochemicals can be incorporated into controlled carbohydrate matrices designed to:

- Slow starch digestion
- Reduce glycemic index
- Provide sustained release of active compounds
- Deliver standardized therapeutic doses per serving

This dual-action approach - structural glycemic control combined with phytochemical-mediated metabolic regulation - supports integrative management of diabetes within daily dietary patterns.

6.2 Anti-inflammatory phytomedicinal formulations

Chronic low-grade inflammation is implicated in numerous disorders, including cardiovascular diseases, metabolic syndrome, neurodegeneration, and autoimmune conditions. Plant-derived anti-inflammatory compounds offer safer long-term alternatives to synthetic anti-inflammatory drugs. Prominent bioactives include:

- **Curcumin** from *C. Longa* modulates NF-κB signaling and reduces pro-inflammatory cytokines.
- **Gingerol and shogaol** from *Z. officinale* inhibit cyclooxygenase and lipoxygenase pathways.

3D printed protein or hydrocolloid gels enriched with these bioactives can provide:

- Sustained release in the intestinal tract
- Enhanced bioavailability *via* lipid-based incorporation
- Improved palatability through flavor masking
- Personalized dosage adjustment

Spatial layering allows the combination of complementary anti-inflammatory phytochemicals while preventing instability or antagonistic interactions. Such structured phytomedicinal foods may serve as supportive dietary therapies for inflammatory bowel disease, arthritis, and metabolic inflammation.

6.3 Immune supportive functional foods

The role of medicinal plants in immune modulation is well documented in traditional systems of medicine. In the context of modern preventive healthcare, immune-supportive phytomedicinal foods can enhance resilience against infections and oxidative stress.Notable examples include:

- **Moringa (*Moringa oleifera*) leaf powder** - rich in polyphenols, vitamins, and essential amino acids with immunomodulatory properties.
- **Tulsi (*Ocimum sanctum*) extracts** exhibit adaptogenic, antimicrobial, and antioxidant activities.

Through 3D printing, these bioactives can be integrated into:

- Personalized snack bars
- Nutrient-dense therapeutic bites
- Fortified protein-based structures

Dose customization is particularly beneficial for vulnerable populations such as children, elderly individuals, and immunocompromised patients. By embedding immune-enhancing phytochemicals within appealing food formats, compliance and long-term consumption can be significantly improved.

6.4 Geriatric and clinical nutrition

Elderly individuals often experience dysphagia, reduced appetite, impaired nutrient absorption, and polypharmacyrelated complications. Conventional herbal supplements may be difficult to swallow or poorly tolerated. 3D food printing enables fabrication of texture-modified, easy-to-swallow phytomedicinal foods that:

- Improve palatability
- Enhance swallowing safety
- Deliver controlled therapeutic doses
- Maintain nutrient density

Soft, gel-based, or semi-solid matrices enriched with anti-inflammatory, antioxidant, and adaptogenic phytochemicals can address age-related oxidative stress, sarcopenia, and cognitive decline. In clinical settings, such personalized phytotherapeutic foods may support recovery, reduce inflammation, and improve overall quality of life.

7. Regulatory and safety considerations

Despite promising therapeutic potential, the regulatory classification of 3D printed phytomedicinal foods remains ambiguous. These products may fall under functional foods, nutraceuticals, botanical supplements, or medical nutrition therapy, depending on jurisdiction. Key regulatory challenges include:

- Standardization of plant extracts
- Batch-to-batch variability in phytochemical concentration
- Accurate labeling of active constituents
- Maximum permissible intake levels
- Stability validation during storage

Variability in medicinal plant composition due to cultivation conditions, harvest timing, and extraction methods necessitates rigorous quality control. Analytical validation using chromatographic techniques is essential to ensure dose consistency in each printed serving. Additionally, safety evaluation must consider:

- Potential herb drug interactions
- Toxicological thresholds
- Allergenicity
- Long-term consumption effects

Establishing internationally harmonized guidelines for phytochemical incorporation levels and stability testing is essential for safe commercialization.

8. Sustainability and plant-based innovation

The integration of medicinal plant bioactives into 3D printed food systems aligns strongly with sustainability and circular bioeconomy principles. Sustainable opportunities include:

- Utilization of plant protein isolates as structural matrices
- Valorization of herbal processing residues
- Incorporation of agro-by-products rich in bioactives
- Reduction of food waste through on-demand production

However, sustainability benefits must be evaluated holistically. Energy consumption during printing, sourcing of raw materials, and lifecycle environmental impacts should be carefully assessed. Responsible sourcing of medicinal plants is critical to prevent overharvesting and biodiversity loss. Cultivation-based supply chains and standardized extract production are preferable to wild collection practices.

9. Future perspectives

The future of 3D printed phytomedicinal functional foods lies at the intersection of biotechnology, digital health, and precision nutrition.

9.1 Nanoencapsulationof phytochemicals

Advanced nanoencapsulation systems can significantly improve solubility, permeability, and systemic availability of hydrophobic compounds. Integration of nano-delivery systems within printable matrices may optimize therapeutic performance.

9.2 AI-assisted personalized herbal formulation

Artificial intelligence algorithms can analyze individual health data, dietary patterns, metabolic markers, and disease risk to recommend customized phytochemical formulations. When integrated with 3D printing platforms, AI can enable real-time personalization of therapeutic foods.

9.3 Clinical validation studies

To establish credibility within phytomedicine, robust clinical trials are required to evaluate:

- Bioavailability enhancement
- Glycemic modulation
- Anti-inflammatory efficacy
- Immune response outcomes

Evidence-based validation will support regulatory approval and medical acceptance.

9.4 Integration with digital health platforms

Digital health monitoring systems can track biomarkers such as glucose levels, inflammatory markers, and metabolic indicators. These data can guide dynamic adjustment of phytochemical doses in personalized printed foods.

9.5 Smart 4D phytomedicinal food systems

Emerging 4D printing technologies incorporate stimuli-responsive materials that change structure in response to environmental triggers such as pH, temperature, or enzymatic activity. Such systems could enable:

- Time-controlled phytochemical release
- Site-specific activation
- Chronotherapeutic dietary interventions

9.6 Nutrigenomics and precision phytotherapy

Integration of nutrigenomic data with 3D printing platforms offers the possibility of tailoring phytochemical combinations to individual genetic profiles. Variations in genes affecting metabolism, inflammation, and antioxidant capacity could inform personalized phytomedicinal nutrition strategies. This convergence of genomics, phytochemistry, and digital fabrication may redefine preventive healthcare by transforming medicinal plants into precisely dosed, genetically tailored functional foods.

10. Conclusion

Three-dimensional (3D) food printing represents a transformative convergence of digital fabrication technologies and phytomedicine, offering a scientifically advanced platform for the development of structured, dose-controlled, and personalized therapeutic foods. Unlike conventional functional food fortification strategies, which often involve simple blending of plant extracts into food matrices, 3D printing enables precise spatial incorporation of medicinal plant bioactives within architecturally designed edible systems. This structural precision facilitates the protection of labile phytochemicals from environmental degradation, modulation of gastrointestinal release kinetics, and optimization of bioavailability.

By integrating controlled microstructural design with encapsulation technologies and pH-responsive biopolymers, 3D printed phytomedicinal foods can overcome long-standing limitations associated with plant-based therapeutics, including poor solubility, low systemic absorption, rapid metabolic degradation, and inconsistent dosing. Furthermore, the capacity for individualized formulation allows customization of phytochemical profiles based on metabolic status, age, disease condition, and nutritional requirements. Such personalization aligns strongly with contemporary preventive healthcare paradigms that emphasize diet-based interventions for the management of non-communicable diseases.

Importantly, the therapeutic credibility of 3D printed phytomedicinal systems depends on rigorous interdisciplinary collaboration. Advances in phytochemistry are required to ensure standardized extract preparation, stability profiling, and quantification of active constituents. Material science contributes to the development of biopolymeric matrices capable of protecting bioactives while enabling targeted release. Simultaneously, clinical validation studies are essential to establish *in vivo* efficacy, pharmacokinetic improvements, safety parameters, and long-term health outcomes.

The integration of digital health technologies, nutrigenomics, and artificial intelligence further expands the potential of 3D printed phytomedicine toward precision phytotherapy. By coupling individualized health data with controlled fabrication, it becomes feasible to design therapeutic foods that are not only nutritionally optimized but also pharmacologically targeted.

In the context of modern preventive healthcare systems, 3D printed phytomedicinal foods have the potential to function as adjunctive or supportive therapeutic modalities, bridging traditional herbal knowledge with contemporary biomedical innovation. However, their successful translation into clinical and commercial practice will require robust regulatory frameworks, quality standardization protocols, and evidence-based validation.

Collectively, 3D food printing emerges not merely as a technological innovation but as a strategic platform capable of redefining the delivery of medicinal plant bioactives through personalized, structured, and scientifically standardized dietary systems.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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