



A REVIEW ON FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLET CONTAINING TURMERIC EXTRACT, GINGER EXTRACT AND BLACK PEPPER EXTRACT

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ABSTRACT

Orodispersible tablets (ODTs) have emerged as an advanced oral drug delivery system designed to enhance patient compliance and provide rapid onset of action, particularly in pediatric and geriatric populations. The present study focuses on the formulation and evaluation of ODTs containing turmeric extract (*Curcuma longa*), ginger extract (*Zingiber officinale*), and black pepper extract (*Piper nigrum*), which are well known for their diverse pharmacological activities. The formulation was developed using suitable excipients and superdisintegrants to achieve rapid disintegration and optimal drug release. The inclusion of piperine from black pepper plays a crucial role as a bioavailability enhancer, improving the absorption of curcumin and other phytoconstituents. The prepared tablets were evaluated for pre-compression and post-compression parameters such as flow properties, hardness, friability, weight variation, drug content, disintegration time, and in vitro dissolution. The results demonstrated that the formulated ODTs exhibited satisfactory physicochemical properties with rapid disintegration and improved dissolution profile. The combination of these herbal extracts showed a synergistic effect, enhancing therapeutic efficacy and overcoming limitations such as poor bioavailability. Thus, the developed orodispersible tablet formulation represents a promising, patient-friendly, and effective approach for herbal drug delivery.

KEYWORDS:

INTRODUCTION

Oral drug delivery systems are the most widely accepted and preferred route of drug administration due to their convenience, cost-effectiveness, and high patient compliance. Solid dosage forms such as tablets and capsules account for a major proportion of pharmaceutical formulations because of their stability, ease of manufacturing, and accurate dosing. However, conventional tablets present certain limitations, particularly in patients who experience difficulty in swallowing (dysphagia), including pediatric, geriatric, and bedridden individuals. Additionally, the requirement of water for administration and delayed onset of action due to gastrointestinal absorption may reduce patient compliance and therapeutic effectiveness.^[1]

To overcome these challenges, orodispersible tablets (ODTs) have been developed as an advanced drug

delivery system. These tablets rapidly disintegrate in the oral cavity within a short period, usually seconds to a minute, without the need for water. The drug is released in the saliva and can be absorbed through the oral mucosa as well as the gastrointestinal tract, resulting in faster onset of action and improved bioavailability. Due to these advantages, ODTs have gained significant importance in modern pharmaceuticals and are considered particularly beneficial for patients with swallowing difficulties.^[1]

In recent years, there has been increasing interest in the use of herbal drugs due to their wide therapeutic potential, safety, and minimal side effects compared to synthetic drugs. Herbal medicines have been traditionally used in various systems such as Ayurveda and continue to play an important role in healthcare. The incorporation of herbal extracts into novel drug delivery systems like

ODTs provides an opportunity to enhance their effectiveness, improve patient compliance, and overcome limitations associated with conventional herbal formulations.

The present study focuses on the formulation of orodispersible tablets containing turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), and black pepper (*Piper nigrum*), which are well-known medicinal plants with diverse pharmacological activities. Ginger is rich in bioactive compounds such as gingerols and shogaols and exhibits antioxidant, anti-inflammatory, antimicrobial, and antiemetic properties.^[3] Black pepper contains piperine, an important alkaloid responsible for various biological activities including antioxidant, anti-inflammatory, and immunomodulatory effects. Notably, piperine is widely recognized as a bioavailability enhancer that improves the absorption of drugs and phytoconstituents.^[4] Turmeric contains curcumin, a potent bioactive compound known for its anti-inflammatory, antioxidant, and anticancer properties; however, its clinical application is limited due to poor bioavailability. The combination of turmeric, ginger, and black pepper offers a synergistic therapeutic effect, where piperine enhances the bioavailability of curcumin and other phytoconstituents, while ginger contributes additional pharmacological benefits. Therefore, formulating these herbal extracts into orodispersible tablets can provide a novel, effective, and patient-friendly dosage form with improved therapeutic outcomes.

Historical Background

Evolution of Oral Drug Delivery Systems

The oral route of drug administration has been the most widely used and preferred method for delivering therapeutic agents since ancient times due to its simplicity, safety, and patient acceptability. In early medicinal practices, drugs were administered in the form of crude plant materials such as powders, decoctions, infusions, and tinctures. Traditional systems of medicine, including Ayurveda and Chinese medicine, extensively utilized natural products for oral administration, laying the foundation for modern pharmaceutical formulations.^[5] With the advancement of pharmaceutical sciences, the need for more accurate dosing, improved stability, and better patient compliance led to the development of solid dosage forms such as tablets and capsules. These dosage forms offered several advantages over traditional preparations, including ease of administration, portability, precise dosing, and enhanced shelf life. As a result, tablets became the most commonly used oral dosage form worldwide.^[1]

Despite these advantages, conventional oral dosage forms presented certain limitations, such as delayed onset of action, degradation of drugs in the gastrointestinal tract, and first-pass metabolism, which can reduce bioavailability. Additionally, swallowing difficulties in specific patient populations further

highlighted the need for alternative oral drug delivery systems.^[1] These challenges prompted continuous research and innovation in the field of oral drug delivery. Over time, various advanced oral drug delivery systems were developed to overcome these limitations, including controlled-release, sustained-release, and targeted drug delivery systems. These systems were designed to maintain optimal drug concentrations in the body over an extended period, reduce dosing frequency, and improve therapeutic outcomes.^[2] Furthermore, the incorporation of novel excipients and formulation techniques enabled the development of more patient-friendly dosage forms.

In recent decades, there has been a significant shift toward the development of innovative oral dosage forms such as fast dissolving tablets, orodispersible tablets, and buccal delivery systems. These formulations are designed to enhance drug dissolution, improve bioavailability, and provide rapid onset of action. The evolution of oral drug delivery systems reflects a continuous effort to improve patient compliance, therapeutic efficacy, and overall treatment outcomes, making it a dynamic and ever-advancing field in pharmaceutical sciences.^[1,2]

Development of Solid Dosage Forms (Tablets and Capsules)

The development of solid dosage forms marked a significant advancement in pharmaceutical technology, transforming drug administration from crude preparations to precise and standardized systems. Initially, medicinal substances were administered in the form of powders and granules, which often posed challenges in terms of dose accuracy, stability, and patient acceptability. To overcome these limitations, the concept of compressed tablets was introduced in the 19th century, providing a more convenient and reliable method of drug delivery.^[1]

Tablets quickly became the most popular solid dosage form due to their numerous advantages, including accurate dosing, ease of administration, cost-effectiveness, and large-scale manufacturing feasibility. The introduction of tablet compression machines further facilitated mass production and ensured uniformity in drug content. Over time, advancements in excipients, such as binders, disintegrants, lubricants, and fillers, improved the mechanical strength, disintegration, and dissolution properties of tablets, enhancing their overall performance.^[1,2]

Capsules were developed as an alternative to tablets to address issues related to taste masking and ease of swallowing. Gelatin capsules, introduced in the 19th century, allowed the encapsulation of powders, granules, and liquids, providing flexibility in formulation. Capsules offer advantages such as improved patient compliance, better bioavailability for certain drugs, and protection of sensitive ingredients from environmental factors like moisture and light. Hard gelatin capsules are

commonly used for solid drugs, while soft gelatin capsules are suitable for liquids and oils.^[2]

Despite their widespread use, solid dosage forms such as tablets and capsules have certain limitations. These include difficulty in swallowing for specific patient groups, delayed onset of action due to gastrointestinal disintegration and dissolution, and variability in drug absorption. Additionally, some drugs may undergo degradation in the gastrointestinal tract or experience extensive first-pass metabolism, reducing their therapeutic effectiveness.^[1] To address these challenges, continuous innovations have been made in the design and formulation of solid dosage forms. Modified-release tablets, coated tablets, chewable tablets, and dispersible tablets were developed to improve drug release profiles and patient acceptability. These advancements ultimately paved the way for the development of more sophisticated systems such as orodispersible tablets, which combine the advantages of solid dosage forms with rapid disintegration and improved patient compliance.^[1,2]

Emergence of Fast Dissolving and Orodispersible Drug Delivery Systems

The emergence of fast dissolving and orodispersible drug delivery systems represents a significant advancement in oral drug delivery technology, primarily aimed at improving patient compliance and therapeutic efficacy. Conventional tablets and capsules, although widely accepted, posed challenges such as difficulty in swallowing (dysphagia), delayed onset of action, and dependence on water for administration. These limitations were particularly evident in pediatric, geriatric, and bedridden patients, which led to the development of alternative dosage forms that could overcome these drawbacks.^[1,6]

The concept of fast dissolving tablets (FDTs), also known as orodispersible tablets (ODTs), was introduced in the late 20th century as a patient-friendly dosage form capable of disintegrating rapidly in the oral cavity without the need for water. Early formulations were initially developed to improve patient acceptability and compliance, particularly in special populations. These formulations later evolved into advanced pharmaceutical dosage forms with improved drug release characteristics and faster onset of action.^[1,7]

Subsequent advancements in formulation technology led to the development of various manufacturing techniques such as lyophilization (freeze-drying), molding, sublimation, spray drying, and direct compression. These techniques significantly improved disintegration time, mechanical strength, and overall tablet performance. The incorporation of superdisintegrants such as croscarmellose sodium, sodium starch glycolate, and crospovidone played a crucial role in achieving rapid tablet disintegration, often within seconds.^[1,7]

Orodispersible tablets are characterized by their ability to disintegrate quickly in saliva, typically within a few seconds to a minute, allowing the drug to be released and absorbed through the oral mucosa and gastrointestinal tract. This results in a faster onset of action and may enhance bioavailability by reducing first-pass metabolism. Such properties make ODTs particularly suitable for drugs requiring rapid therapeutic action.^[1,2,7]

The pharmaceutical industry has further advanced ODT technology through the development of patented systems such as Zydis, Orasolv, Durasolv, WowTab, and FlashTab. These technologies have improved taste masking, mouthfeel, and tablet stability, thereby enhancing patient acceptance and commercial success. As a result, orodispersible tablets have emerged as a rapidly growing segment in modern drug delivery systems.^[7,8]

Overall, the emergence of fast dissolving and orodispersible drug delivery systems reflects a shift toward patient-centric formulations that prioritize ease of administration, rapid onset of action, and improved therapeutic outcomes. Continuous research and technological advancements are expected to further expand their applications in pharmaceutical sciences.^[2,8]

Technological Advancements in Orodispersible Tablets

The development of orodispersible tablets has been significantly influenced by continuous technological advancements aimed at improving their performance, stability, and patient acceptability. Initially, the major challenge in formulating ODTs was to achieve rapid disintegration while maintaining sufficient mechanical strength. To address this, various innovative formulation and manufacturing techniques have been introduced over time.^[1,7]

One of the earliest and most widely used technologies is **lyophilization (freeze-drying)**, which produces highly porous tablets that disintegrate almost instantly upon contact with saliva. This technique enhances rapid drug release and bioavailability; however, the resulting tablets are often fragile and require specialized packaging to protect them from moisture and mechanical damage.^[1,7] To overcome such limitations, alternative methods such as **tablet molding** and **sublimation** were developed. In sublimation, volatile substances are incorporated into the tablet matrix and later removed, leaving behind a porous structure that facilitates rapid disintegration.^[7]

The introduction of **direct compression techniques** marked a major breakthrough in ODT manufacturing. This method is simple, cost-effective, and suitable for large-scale production. The success of direct compression largely depends on the use of **superdisintegrants** such as crospovidone, croscarmellose sodium, and sodium starch glycolate, which promote rapid water uptake and tablet

disintegration within seconds.^[1,7] These excipients have become essential components in modern ODT formulations.

Another important advancement is the development of **spray drying and melt granulation techniques**, which improve the flow properties and compressibility of the powder blend while maintaining fast disintegration characteristics. Additionally, **nanonization and solid dispersion technologies** have been explored to enhance the solubility and dissolution rate of poorly water-soluble drugs, thereby improving their bioavailability in ODT formulations.^[7,8]

The pharmaceutical industry has also introduced several **patented technologies** to improve the quality and commercial viability of ODTs. Technologies such as Zydis, Orasolv, Durasolv, WowTab, and FlashTab have enabled the production of tablets with improved taste masking, mechanical strength, and mouthfeel. These systems utilize specialized excipients and processing techniques to achieve rapid disintegration along with acceptable hardness and stability.^[7,8]

In addition to formulation techniques, advancements in **taste masking technologies** such as microencapsulation, coating, and inclusion complexes have played a crucial role in improving patient compliance, especially for bitter drugs. Furthermore, innovations in **packaging systems**, such as blister packs with moisture protection, have enhanced the stability and shelf life of ODTs, which are often sensitive to environmental conditions.^[1]

Overall, technological advancements in orodispersible tablets have successfully addressed the challenges associated with their formulation, leading to the development of robust, effective, and patient-friendly dosage forms. Continuous research in excipient development, manufacturing processes, and drug delivery technologies is expected to further improve the performance and applicability of ODTs in modern therapeutics.^[2,7,8]

Historical Use of Herbal Medicines in Drug Therapy

The use of herbal medicines in drug therapy represents one of the oldest and most enduring practices in human history, with evidence dating back thousands of years across diverse civilizations. Since the dawn of mankind, plants have served as effective medicines for the treatment of illnesses, forming the foundation of traditional medical systems that continue to influence modern healthcare practices.^[1,5]

Traditional Medical Systems and Their Herbal Foundations

Three major traditional medical systems have significantly contributed to the global heritage of herbal medicine: Traditional Chinese Medicine (TCM), Ayurvedic Medicine from India, and Greco-Arabic (Unani) Medicine. These systems developed

independently yet share common principles regarding the therapeutic use of plants for health promotion and disease treatment.^[1,8]

Traditional Chinese Medicine has a history dating back several thousand years, with the earliest extant medical book, Huangdi Neijing (Canon of Internal Medicine), originating from 770–221 BCE. The first pharmacy monograph, Shennong Bencaojing (Shennong Materia Medica), was compiled between 25–220 CE and described 365 herbal drugs. The most influential pharmacy monograph in Chinese history is the Bencaojing (Compendium of Materia Medica), published between 1368–1644 CE, which documented 1,892 medicinal substances.^[10] Today, Traditional Chinese Medicine encompasses 11,146 different kinds of plants, 1,581 types of animal parts, and 80 kinds of mineral drugs, with more than 5,000 clinically validated herbal formulations.^[8]

Ayurvedic medicine, originating in India between 6,000 to 4,000 BCE, represents another ancient system of healthcare. The Vedas, particularly the Rig Veda (4500–1600 BCE) and Atharva Veda, contain the earliest references to medicinal plants. The Charaka Samhita and Sushruta Samhita, foundational texts of Ayurveda, describe hundreds of herbal drugs and their therapeutic applications.^[8] India possesses approximately 8% of the world's estimated biodiversity, with around 126,000 species, and approximately 25,000 plant-based formulations are used in traditional and folk medicines.^[1,8] Greco-Arabic medicine, which flourished from 632 to 1258 CE, adapted and improved upon ancient Hippocratic-Greek medical knowledge. During the Middle Ages, the Arabic world served as the center of scientific and medical knowledge, and European pharmacopoeias relied on Muslim writings until the late 19th century.^[8]

According to the World Health Organization, 75% of the world's population currently uses herbs for basic healthcare needs. The practice of herbal medicine now involves more than 53,000 plant species worldwide.^[1,5] Many conventional pharmaceutical drugs are derived directly from natural sources and traditional remedies, highlighting the enduring importance of herbal knowledge in modern drug discovery.^[8]

The Concept of Polyherbal Formulations

Traditional medical systems have long recognized that combining multiple herbs can produce enhanced therapeutic effects compared to single herbs. This principle of polyherbal formulations is exemplified by Trikatu, a classical Ayurvedic formulation consisting of three herbs in equal ratio: Shunthi (Zingiber officinale - ginger), Maricha (Piper nigrum - black pepper), and Pippali (Piper longum - long pepper).^[3,9] The term "Trikatu" first appears in the Agni Purana, detailing its applications in organ disorders, toxicology, and veterinary care. In the Samhita period, Trikatu is

classified under Mishraka Gana in the Sushruta Samhita, while numerous references appear throughout the Charaka Samhita and Ashtanga Hridaya. A thorough textual analysis reveals that the synonym "Vyosha" appears 81 times, "Tryushana" 30 times, and "Trikatu" itself is directly mentioned 9 times in the Charaka Samhita alone, collectively amounting to 121 instances.^[3] The therapeutic actions of Trikatu are well-documented in classical texts. The formulation is credited with Deepana (appetizing/digestive stimulant), Pachana (digestive), Krimighna (anthelmintic), and Kaphmedohara (reducing Kapha and fat) properties. It is indicated for conditions including Agnimandya (poor digestion), Ama (improperly metabolized food particles), Meha (diabetes), Kustha (skin diseases), and Gulma (abdominal tumors).^[3,9]

Spices in Phytomedicine

Spices have played a particularly important role in phytomedicine worldwide. Major spices including black pepper (*Piper nigrum*), ginger (*Zingiber officinale*), and turmeric (*Curcuma longa*) have been extensively used for their medicinal properties. These spices contain bioactive compounds such as piperine, gingerol, shogaol, and curcumin, which exhibit antioxidant, anti-inflammatory, antimicrobial, and immunomodulatory activities.^[2]

The historical significance of these spices extends beyond their culinary uses. In Ayurveda, they have been integral components of numerous formulations for treating digestive disorders, inflammatory conditions, respiratory diseases, and metabolic syndromes. Recent research has validated many of these traditional uses, demonstrating the scientific basis for their therapeutic applications.^[2,3]

Contribution to Modern Pharmacopoeias

The historical development of pharmacopoeias has been significantly influenced by traditional herbal knowledge. The domination of Eurasian herbal drugs in pharmacopoeias was conditioned by the geographical extension of Eurasia, which facilitated the interchange of materia medica and the creation of a consensus of use since ancient times.^[7] Many herbal drugs with historic importance in European and American pharmacopoeias have gained status as safe and efficacious through modern research, while continuing to be used in traditional medicine systems worldwide.^[1,7]

In recent years, there has been a significant resurgence of interest in herbal medicines, described as an herbal "renaissance" occurring all over the world. Increasing numbers of people are choosing herbal medicines or products to improve their health conditions, either alone or in combination with conventional drugs.^[1,5] However, this increased demand has led to concerns about the depletion of plant resources, with a number of medicinal species facing the threat of extinction due to overexploitation. This has prompted calls for

conservation efforts and sustainable harvesting practices.^[1,8]

Integration of Herbal Drugs into Novel Drug Delivery Systems

The integration of herbal drugs into novel drug delivery systems represents a significant paradigm shift in phytopharmaceutical research, addressing the longstanding challenges associated with traditional herbal formulations. Despite the well-documented therapeutic potential of plant-derived bioactives, their clinical utility has historically been limited by poor bioavailability, instability, and inconsistent therapeutic outcomes.^[11,15] Traditional herbal dosage forms, such as powders, decoctions, and crude extracts, present several inherent limitations. Many phytoconstituents exhibit poor aqueous solubility, with over 40% of plant-derived compounds demonstrating solubility characteristics that restrict gastrointestinal absorption and reduce systemic circulation levels.^[12] Additionally, once absorbed, numerous phytochemicals undergo rapid first-pass metabolism in the liver and intestines, leading to fast degradation and clearance from the body.^[11] Chemical instability poses another critical challenge. Phytochemicals such as curcumin and quercetin are sensitive to light, pH variations, and enzymatic oxidation, resulting in loss of bioactivity before reaching target tissues.^[12] Furthermore, poor membrane permeability and non-specific distribution limit accumulation at disease sites while increasing the risk of off-target effects. For instance, curcumin is infamous for its extremely low oral bioavailability, often cited as less than 1% due to poor absorption, rapid metabolism, and systemic elimination.^[11] Similarly, the oral bioavailability of resveratrol is considerably less than 1%, while that of free genistein is only 6.8%.^[11]

Nanotechnology-Enabled Herbal Drug Delivery

Nanotechnology has emerged as a transformative approach to overcoming these delivery challenges. By encapsulating phytochemicals in nanoscale carriers (typically 1-100 nm), researchers can significantly enhance solubility, protect compounds from degradation, and extend circulation time.^[12,15] Various nanocarrier systems have been developed for herbal drug delivery, including nanoparticles, liposomes, phytosomes, nanoemulsions, solid lipid nanoparticles (SLNs), and nanogels.^[15]

The application of these systems has yielded remarkable improvements in pharmacokinetic performance. Curcumin-loaded liposomes have demonstrated a ninefold increase in oral bioavailability compared to curcumin suspended in water.^[11] Piperine-loaded solid lipid nanoparticles exhibited a 2.5-fold increase in bioavailability over a piperine solution.^[11] A resveratrol-loaded nanoemulsion achieved a 3.2-fold higher relative bioavailability compared to unformulated resveratrol suspension.^[11] Encapsulating curcumin in

polymeric nanoparticles has been shown to improve its bioavailability by over 2000%.^[12]

Mechanisms of Enhanced Delivery

Nanocarriers improve herbal drug delivery through multiple mechanisms. They enhance solubility and dissolution rate of poorly water-soluble phytoconstituents, protect sensitive compounds from degradation in the harsh gastrointestinal environment, and enable controlled, sustained release that maintains therapeutic drug levels for prolonged periods.^[11,15] By improving solubility and enabling targeted delivery, nano-systems allow for lower effective doses, thereby reducing systemic toxicity.^[11] Furthermore, nanocarrier surfaces can be functionalized with ligands such as antibodies, peptides, or folic acid to ensure specific binding to target cells, improving therapeutic efficacy and reducing systemic toxicity.^[12] Stimuli-responsive carriers can trigger drug release in response to pH, temperature, or enzymatic activity at the disease site, enhancing precision medicine strategies.^[12] These advancements have enabled successful applications across diverse therapeutic areas, including antibacterial therapy, anticancer treatment, wound healing, and regenerative medicine.^[11]

Development of Orodispersible Herbal Formulations

The development of orodispersible formulations containing herbal extracts represents a convergence of two significant pharmaceutical advancements: patient-centric drug delivery systems and evidence-based phytotherapy. Orodispersible tablets (ODTs) and orodispersible films (ODFs) have emerged as promising platforms for delivering natural active compounds, offering advantages such as rapid disintegration, ease of administration without water, and enhanced patient compliance.^[13,14,16]

The incorporation of herbal extracts into orodispersible dosage forms addresses multiple limitations simultaneously. While conventional herbal tablets face challenges related to poor flowability, high hygroscopicity, and low compressibility of dried plant extracts, ODT formulations utilizing appropriate excipients can overcome these technological hurdles.^[17] Natural polymers, including locust bean gum, banana powder, mango peel pectin, and *Mangifera indica* gum, have been successfully employed as binders, diluents, and superdisintegrants in herbal ODT formulations, offering advantages such as accessibility, cost-effectiveness, non-toxicity, and chemical inertness.^[13]

The development of herbal ODTs requires careful consideration of several factors, including the dose of active compounds, size of dosage forms, standardization of extracts, handling of polyherbal mixtures, stability of active compounds, safety, efficacy, and pharmacokinetics.^[18] Various manufacturing techniques have been employed, including freeze-drying (lyophilization), spray drying, sublimation, and direct

compression.^[16] The use of superdisintegrants plays a crucial role in achieving rapid disintegration of herbal ODTs. Croscopovidone, croscarmellose sodium, and sodium starch glycolate promote rapid water uptake and tablet disintegration within seconds.^[13] Additionally, taste masking technologies such as microencapsulation, coating, and inclusion complexes are particularly important for herbal extracts, which often possess bitter or unpleasant tastes.^[17] Formulating tablets from dried plant extracts presents unique technological hurdles. Factors such as high hygroscopicity, low flowability, poor compressibility, and reduced bioavailability of the complex dried mixture obtained from plant materials pose challenges for tablet formulation.^[17] However, strategies including the use of excipients to improve flow, optimization of drying processes, granulation techniques, composite particles, solid dispersions, and liquid-solid systems have enabled successful development of various types of herbal tablets, including immediate-release, orodispersible, mucoadhesive, chewable, and extended-release formulations.^[17]

Global Adoption of Herbal FDDFs

Fast Dissolving/Disintegrating Dosage Forms (FDDFs) have gained significant acceptance in alternative medicine systems worldwide. Homeopathic systems and traditional Chinese medicine have embraced FDDFs for the delivery of active compounds, with most patents in this area originating from China or Chinese innovators. In Europe and the United States, FDDFs have been extensively studied for the delivery of natural active compounds.^[18] The field of herbal orodispersible formulations is witnessing rapid evolution, driven by technological innovations and increasing demand for patient-friendly phytopharmaceuticals. Several notable trends are shaping current research and development.

3D Printing Technology: Three-dimensional (3D) printing has emerged as a promising tool for manufacturing orodispersible dosage forms, enabling personalized dosage forms with improved functionality. Spritam (levetiracetam), the first orally dispersible tablet produced by 3D printing, received US FDA approval, opening avenues for personalized drug delivery tailored to individual patients.^[16,19] This technology holds particular promise for herbal formulations where dose customization may be required.

Nanocrystal-Based ODTs: The incorporation of drug nanocrystals into orodispersible tablets has been explored to improve the dissolution rate of poorly soluble drugs.^[16] This approach is directly applicable to herbal bioactives, which frequently exhibit poor solubility characteristics.

Natural Superdisintegrants: There is growing interest in utilizing natural polymers as superdisintegrants in ODT formulations. These natural alternatives offer advantages over synthetic counterparts, including

biodegradability, biocompatibility, and reduced toxicity.^[13]

Advanced Excipient Platforms: The excipient industry has developed ready-to-use platforms specifically designed for ODT formulation. Products such as PEARLITOL® Flash (mannitol-starch compound) offer the compactability, friability, and disintegration properties required for optimal ODTs while providing superior organoleptic properties.^[19]

Pharmacological Profile of Turmeric (*Curcuma longa*) Botanical Description and Traditional Significance

Turmeric, derived from the dried rhizome of *Curcuma longa* L., a perennial herb belonging to the Zingiberaceae family, has received widespread attention because of its extensive applications in pharmaceutical, food, cosmetic, and other industries. Traditionally, it has been widely used in Ayurvedic medicine and traditional Asian medicine systems such as Traditional Chinese Medicine for the treatment of digestive, respiratory, and circulatory diseases, as well as skin disorders.^[20] The plant primarily grows in tropical and subtropical regions, including Thailand, Indonesia, and Malaysia, and in China, approximately 20 varieties of *Curcuma Rhizoma* are cultivated, mainly in provinces such as Sichuan, Fujian, Zhejiang, and Guangxi.^[21]

Bioactive Phytoconstituents

The primary bioactive metabolites of *Curcuma longae* Rhizoma include curcuminoids and volatile oils. Curcuminoids consist of curcumin (approximately 77%), demethoxycurcumin, and bisdemethoxycurcumin, which together constitute the active pigments responsible for the yellow-orange color of turmeric.^[20] The volatile oil fraction contains important sesquiterpenes such as ar-turmerone, α -turmerone, and β -turmerone, which have demonstrated significant pharmacological activities.^[21] Chemically, curcumin is classified as a diarylheptanoid and exhibits tautomeric forms (enol and keto) that contribute to its reactivity and diverse biological effects.^[20] Recent studies have identified that the ratio of curcumin to other curcuminoids in various supplements consistently follows an 80%:18%:2% pattern for curcumin, demethoxycurcumin, and bisdemethoxycurcumin, respectively.^[22]

Anti-inflammatory Activity

The anti-inflammatory properties of *Curcuma longa* are largely attributed to its impact on crucial biochemical pathways that regulate inflammation in the human body. The primary mechanism involves the inhibition of the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway. Normally inactive in the cytoplasm and bound to the inhibitory protein I κ B, NF- κ B becomes active when I κ B degrades, facilitating its translocation to the nucleus where it promotes the expression of pro-inflammatory genes.^[21] Curcumin effectively blocks this process by preventing I κ B degradation, thereby reducing the expression of pro-

inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6).^[21]

Additionally, *Curcuma longa* modulates other significant inflammatory pathways including the Cyclooxygenase-2 (COX-2) and Lipoxygenase (LOX) enzymes that catalyze the production of major inflammatory mediators like prostaglandins and leukotrienes. By inhibiting these enzymes, the production of these mediators is decreased, contributing to reduced inflammation.^[21] *Curcuma longa* also influences the Mitogen-Activated Protein Kinases (MAPKs) and Phosphoinositide 3-kinases (PI3K)/Akt pathways, both known for their roles in cellular responses to inflammation.^[21,23] The key metabolites of turmeric, including curcuminoids and turmerones, engage with critical pathways such as NF- κ B, MAPK, JAK/STAT, and Nrf2, modulating cytokine production and both innate and adaptive immune activities.^[23]

Antioxidant Activity

Curcuma longa is highly regarded for its robust antioxidant properties, largely attributed to its active metabolite curcumin and other phytochemicals present in the rhizome. These metabolites are effective in neutralizing free radicals—unstable molecules that cause oxidative stress and cellular damage, contributing to aging and various chronic diseases, including cardiovascular disorders, diabetes, and neurodegenerative diseases.^[21] The antioxidant mechanisms of *Curcuma longa* are multifaceted. Primarily, curcumin directly scavenges different forms of free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS).^[21]

Beyond direct scavenging, *Curcuma longa* significantly enhances the body's antioxidant defenses. It upregulates the expression of key endogenous antioxidant enzymes, including glutathione peroxidase, superoxide dismutase (SOD), and catalase, which are crucial for the detoxification of harmful oxidants within the body.^[21] Additionally, *Curcuma longa* modulates the Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) pathway, which regulates the expression of detoxifying enzymes and antioxidant proteins. Curcumin promotes the dissociation of Nrf2 from its inhibitor Keap1, allowing Nrf2 to translocate to the nucleus where it enhances the transcription of genes encoding antioxidant proteins and phase II detoxification enzymes.^[21] In preclinical studies, curcumin has demonstrated the ability to inhibit NF- κ B, JAK/STAT, and MAPK signaling, reduce COX-2/5-LOX eicosanoids, activate Nrf2-driven antioxidant defenses, and preserve mitochondrial function.^[24]

Neuroprotective Activity

Curcuma longa is widely recognized for its neuroprotective effects, which are pivotal in combating neurodegenerative diseases. Many active metabolites of *Curcuma longa*, such as curcumin, modulate the NF- κ B pathway, significantly reducing neuroinflammation,

which directly impacts the progression of neurodegenerative diseases such as Alzheimer's and Parkinson's disease.^[21] By suppressing the production of inflammatory cytokines in the brain, Curcuma longa slows disease progression, helping manage symptoms and potentially altering disease trajectories.^[21]

In addition to its anti-inflammatory and antioxidant actions, Curcuma longa plays a crucial role in the regulation of neurotransmitter functions. It influences key neurotransmitter systems, including dopamine and serotonin, which are essential for maintaining cognitive function and emotional balance.^[21] Recent in silico studies have demonstrated that Curcuma longa-derived phytochemicals, particularly α -turmerone, β -turmerone, and bisdemethoxycurcumin, exhibit high binding affinities against the target neurotoxic enzyme monoamine oxidase B (MAO-B), with docking scores of -14.1001 kcal/mol and -13.2892 kcal/mol, respectively. These phytochemicals have shown favorable pharmacokinetic profiles, including blood-brain barrier permeability and high lipophilicity, suggesting significant potential as neuroprotective agents.^[25]

Anticancer Activity

Curcuma longa, particularly noted for its high content of bioactive metabolites like curcumin, demonstrates significant anticancer properties. The anticancer mechanisms of curcumin involve multiple pathways, including the inhibition of NF- κ B activation, downregulation of pro-inflammatory cytokines, suppression of angiogenesis, induction of apoptosis, and cell cycle arrest.^[21] Curcumin has been shown to interfere with various signaling pathways involved in cancer development and progression, including the PI3K/Akt, MAPK, and Wnt/ β -catenin pathways.^[21]

Immunomodulatory Activity

Curcuma longa exhibits significant immunomodulatory effects through its key metabolites, which engage with critical pathways including NF- κ B, MAPK, JAK/STAT, and Nrf2. This interaction modulates cytokine production, oxidative stress responses, and both innate and adaptive immune activities.^[23] Extensive preclinical evidence supports the immunomodulatory effects of Curcuma longa, although human evidence remains inconsistent, partly due to poor and variable oral bioavailability and substantial heterogeneity in extract composition.^[23]

Antidiabetic and Metabolic Effects

Curcuma longa has demonstrated beneficial effects in metabolic disorders, particularly diabetes. The hypoglycemic activity of curcumin and other curcuminoids is mediated through multiple mechanisms, including improved insulin sensitivity, reduced insulin resistance, suppression of hepatic gluconeogenesis, and enhanced glucose uptake in peripheral tissues.^[21] Additionally, curcumin has been shown to reduce lipid

accumulation, lower cholesterol levels, and protect pancreatic beta-cells from oxidative damage.^[21]

Hepatoprotective and Cardioprotective Activities

The hepatoprotective effects of Curcuma longa are attributed to its antioxidant and anti-inflammatory properties, which protect the liver from damage induced by various toxins and metabolic stressors.^[21] In the cardiovascular system, curcumin has been shown to reduce oxidative stress, inhibit platelet aggregation, lower cholesterol levels, and protect against ischemia-reperfusion injury.^[21]

Antimicrobial Activity

Curcuma longa exhibits broad-spectrum antimicrobial activity against various bacterial, viral, and fungal pathogens. The antimicrobial effects are mediated through disruption of microbial cell membranes, inhibition of biofilm formation, and interference with microbial metabolic processes.^[20]

Bioavailability Challenges

Despite its extensive pharmacological potential, the clinical efficacy of curcumin is severely limited by poor oral bioavailability. The major challenges include low aqueous solubility, rapid degradation in aqueous environments, rapid and extensive first-pass metabolism, and efflux by P-glycoprotein (P-gp).^[22,23] Studies have reported that the absolute oral bioavailability of curcumin in animal models ranges from only 0.6% to 3.1% depending on the formulation.^[26] In humans, plasma levels of unconjugated curcumin remain below 2 nM in most cases, even with high doses up to 2400 mg, and concentrations of unconjugated curcumin achieved in plasma are typically 100-fold lower than those used in vitro to demonstrate biological effects.^[22]

Bioavailability Enhancement Strategies

Recent technological strategies to improve curcumin bioavailability include the development of micelles, phytosomes, phospholipid complexes, nanoemulsions, polymeric nanoparticles, and liposomal systems.^[23] These advanced delivery systems have improved the solubility, stability, and systemic exposure of curcuminoids. A comparative bioavailability study demonstrated that a novel standardized extract containing 45% curcuminoids and 4.5% ar-turmerone achieved significantly higher bioavailability (C_{max} of 647.97 ng/mL) compared to standard curcumin-piperine combinations, with only a high dose of piperine (10%) being able to match its pharmacokinetic profile.^[27] The presence of ar-turmerone alongside curcuminoids suggests a synergistic effect, offering a simplified and effective alternative to piperine-based formulations.^[27]

However, it is important to note that despite these bioavailability enhancement strategies, unconjugated curcumin plasma levels remain minimal, and some researchers argue that bioavailability claims should be based on unconjugated curcumin rather than its poorly

membrane-permeable conjugates.^[22] Interestingly, despite low plasma concentrations of parent curcumin, oral curcumin formulations have demonstrated pharmacodynamic responses in the induction of Nrf2-mediated antioxidant genes, suggesting that the overall health benefits of oral curcumin may be mediated through mechanisms other than systemic availability of the parent compound.^[26]

Pharmacological Profile of Ginger (*Zingiber officinale*)

Botanical Description and Traditional Significance

Ginger, derived from the rhizome of *Zingiber officinale* Roscoe, is a perennial herb belonging to the Zingiberaceae family, which comprises approximately 52 genera and more than 1300 species distributed throughout tropical Africa, Asia, and the Americas.^[28] The plant has been widely used both as a spice and as a traditional herbal remedy for centuries, with its rhizome commonly employed to alleviate ailments such as headaches, colds, nausea, and emesis.^[28,29] In traditional medicine systems including Ayurveda and Traditional Chinese Medicine, ginger has been valued for its therapeutic properties and continues to play an important role in modern phytotherapy.^[28]

Bioactive Phytoconstituents

The rhizome of ginger is characterized by a complex phytochemical composition, including phenolic compounds, terpenoids, alkaloids, and essential oils, which collectively underpin a wide spectrum of biological activities.^[28] The primary bioactive constituents responsible for ginger's pharmacological effects are the phenolic compounds, particularly gingerols, shogaols, and paradols.^[29] Among these, 6-gingerol, 8-gingerol, and 10-gingerol are the most abundant in fresh ginger, while during processing or heating, 6-gingerol undergoes dehydration to form 6-shogaol, which exhibits enhanced bioactivity.^[29] Further metabolic conversion produces paradols, compounds with improved bioavailability and biological activity.^[29] Zingerone, another important flavor phytochemical present in ginger, possesses anti-inflammatory, antioxidant, and anti-apoptotic properties.^[30] The essential oils obtained from ginger contain volatile terpenoids such as zingiberene and α -curcumene, known for their antimicrobial and gastroprotective benefits.^[29]

Different extraction techniques yield ginger extracts with varying chemical compositions and therapeutic profiles. Aqueous extracts are rich in hydrophilic compounds such as flavonoids and polysaccharides that show antioxidant and immunomodulatory effects, while ethanolic extracts contain high levels of gingerols and shogaols, exhibiting significant anti-inflammatory and anticancer activity. Supercritical CO₂ extraction results in lipophilic concentrates with enhanced bioavailability and stability of bioactive molecules.^[29]

Anti-inflammatory Activity

The anti-inflammatory properties of ginger are well-documented and primarily attributed to its ability to modulate multiple inflammatory pathways. Gingerols and shogaols exert their effects by inhibiting pro-inflammatory cytokines and disrupting NF- κ B signaling pathways.^[29,31] Studies have demonstrated that these compounds effectively reduce the production of inflammatory mediators such as tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and cyclooxygenase-2 (COX-2).^[29,31]

Zingerone, another bioactive constituent, has been shown to inhibit cytokine production and suppress MAPK and NF- κ B activation in a dose-dependent manner. It also reduces the expression of inflammatory cytokines including IFN- γ , IL-17, IL-6, COX-2, TNF- α , and iNOS mRNA levels, while decreasing macrophage inflammatory protein cytokines and eliminating free radicals.^[30] The anti-inflammatory effects of ginger have been validated in numerous clinical studies, with meta-analyses confirming significant reductions in inflammatory biomarkers following ginger supplementation.^[31,32] In patients with active rheumatoid arthritis, ginger supplementation has been shown to modulate the gene expression of IL2, TNF α , and IL1 β cytokines.^[32]

Antioxidant Activity

Ginger exhibits potent antioxidant properties through multiple mechanisms. The phenolic compounds in ginger effectively scavenge free radicals and mitigate oxidative stress within the body.^[29] This antioxidant activity is essential for safeguarding cells from damage and has been linked to the prevention of various chronic diseases.^[29] Gingerols and shogaols have been shown to upregulate the Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) pathway, which regulates the expression of detoxifying enzymes and antioxidant proteins.^[33]

Zingerone lessens oxidative stress and oxidative DNA damage by increasing the activities of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPX).^[30] It also reduces 8-OHdG over-expression in liver tissue and the expression of NADPH oxidase 4 (NOX4), demonstrating its protective effects against oxidative damage.^[30] The antioxidant properties of ginger have been demonstrated to reduce oxidative stress markers and improve overall cellular redox balance in both preclinical and clinical studies.^[29,33]

Antiemetic and Anti-nausea Activity

Ginger has been extensively studied for its antiemetic properties, particularly in the context of pregnancy-related nausea, postoperative nausea and vomiting, and motion sickness. Scientific studies suggest that ginger is effective for pregnancy-related nausea and postoperative nausea and vomiting, although it may not be as effective for chemotherapy-induced nausea.^[34,35] The mechanisms

underlying ginger's antiemetic effects involve its action on serotonin receptors and its ability to enhance gastric emptying.^[29]

Clinical evidence from randomized controlled trials supports the use of ginger for nausea and vomiting during pregnancy, with several studies demonstrating significant reductions in symptoms compared to placebo.^[35] The safety profile of ginger during pregnancy has been evaluated in multiple studies; while some animal studies have suggested potential reproductive toxicity at high doses, human studies have not provided convincing evidence of such effects, and ginger is generally considered safe for use during pregnancy when taken at recommended doses.^[35,36]

Antidiabetic and Metabolic Effects

Ginger has demonstrated significant antidiabetic potential through multiple mechanisms. Key compounds, including gingerols and shogaols, support glucose homeostasis by enhancing insulin sensitivity, promoting Glucose Transporter Type 4 (GLUT4)-mediated glucose uptake, improving β -cell function, and modulating metabolic signaling pathways such as PI3K/Akt, AMPK, PPAR γ , and NF- κ B [28]. The potent antioxidant and anti-inflammatory activities of ginger further reduce oxidative stress and chronic low-grade inflammation, both central to the progression of type 2 diabetes and its complications.^[28]

Emerging evidence from clinical studies has shown that ginger supplementation produces a slight but significant decrease in HbA1c, a form of hemoglobin that indicates average blood sugar levels, suggesting potential benefits for glycemic control in patients with type 2 diabetes.^[34,37] A systematic review and meta-analysis of randomized controlled trials confirmed the beneficial effects of ginger supplementation on biomarkers of inflammation and oxidative stress in adults, further supporting its role in metabolic health.^[31]

Anticancer Activity

Ginger exhibits promising anticancer properties through multiple mechanisms. The active constituents, particularly 6-gingerol and 6-shogaol, have been shown to induce apoptosis, suppress tumor proliferation, and inhibit angiogenesis and metastasis.^[29,38] Studies have demonstrated that 6-shogaol inhibits the cell motility of prostate cancer cells by suppressing the PI3K/AKT/mTOR and Ras/Raf/MAPK pathways, with effects comparable to paclitaxel treatment.^[38] Zingerone has been shown to obstruct cell cycle G2/M progression and initiate apoptosis in human colorectal cancer cells.^[39]

The anticancer effects of ginger constituents have been particularly documented in gastrointestinal and breast cancers, with evidence suggesting that ginger extracts can attenuate angiogenesis and metastasis via PI3K/Akt blockade.^[33,38] The synergistic interaction between gingerols and shogaols enhances their anticancer

potential, with network pharmacology studies revealing synergy hubs where shogaols amplify gingerols' actions on multiple cancer-related pathways.^[33]

Neuroprotective Activity

Ginger has demonstrated significant neuroprotective effects, making it a promising candidate for the management of neurodegenerative disorders. The phenolic compounds in ginger, particularly 6-gingerol and 6-shogaol, have been shown to reduce reactive oxygen species (ROS) and protect against neuronal damage.^[33] The anti-inflammatory and antioxidant properties of ginger contribute to its neuroprotective effects by reducing neuroinflammation and oxidative stress in the brain.^[29,33]

The combination of gingerols and shogaols has shown particular promise for neuroprotective applications, with studies indicating their potential in Alzheimer's and Parkinson's diseases through the reduction of ROS and α -synuclein aggregation.^[33] Pharmacokinetic profiling has confirmed excellent oral bioavailability and blood-brain barrier permeability for these compounds, making them suitable candidates for neuroprotective interventions.^[33]

Cardiovascular Protective Activity

Ginger exhibits cardiovascular protective properties through multiple mechanisms. The antioxidant and anti-inflammatory actions of ginger constituents help reduce oxidative stress and inflammation in the cardiovascular system.^[29,37] Studies have suggested that ginger may help reduce blood pressure and improve lipid profiles, contributing to overall cardiovascular health.^[37] The anti-platelet aggregation activity of ginger has been documented; however, this property may increase the risk of bleeding when combined with anticoagulant medications, necessitating careful monitoring in patients taking such drugs.^[36]

Gastroprotective Activity

Ginger has long been valued for its beneficial effects on the digestive system. Ginger extracts provide gastroprotective benefits by enhancing mucosal defence and modulating gut microbiota, which can significantly improve conditions such as peptic ulcers and inflammatory bowel diseases.^[29] The therapeutic effect of ginger on gastritis involves regulation of STAT3/MAPK signaling pathways and gastrointestinal hormone balance.^[40] Additionally, ginger has been shown to improve digestion, reduce bloating, and alleviate functional dyspepsia symptoms.^[29]

Bioavailability Challenges and Enhancement Strategies

Despite the extensive pharmacological potential of ginger, the clinical application of its bioactive constituents is limited by poor solubility, rapid metabolism, and low bioavailability.^[29,41] The solubility of main active compounds such as 6-gingerol and 8-

gingerol is approximately 100 μM in various buffer solutions, which significantly restricts their absorption in the gastrointestinal tract.^[29] To overcome these barriers, innovative drug delivery systems have been developed to improve the absorption and therapeutic efficacy of ginger bioactives.^[29,41]

Recent advances in delivery systems include lipid-based nanocarriers such as liposomes, transfersomes, transethosomes, phytosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs); niosomes; emulsion-based systems including nanoemulsions and microemulsions; self-emulsified drug delivery systems; polymeric systems such as polymeric nanoparticles and micelles; metallic nanoparticles; nanofibers; hydrogels; and cyclodextrin inclusion complexes.^[29,41]

The application of these delivery systems has resulted in significant improvements in biological effects. Nanoencapsulation of ginger constituents has been shown to enhance selective cytotoxicity against cancer cell lines, improve anti-inflammatory and anti-bacterial activities, and increase overall bioavailability.^[29,41] Nanocarriers have been demonstrated to increase the bioavailability of gingerols by up to 3.2-fold, with tumor-targeting delivery efficiency reaching 68%.^[42] Liposomal delivery systems have shown a 50% improvement in blood-brain barrier penetration efficiency, enhancing the neuroprotective potential of ginger constituents.^[42] Nanocapsulated gingerenone A has demonstrated improved efficacy in suppressing obesity and adipose tissue inflammation.^[42] These technological advances position ginger as an increasingly viable candidate for evidence-based therapeutic applications.^[28,29,41]

Safety Considerations and Drug Interactions

Ginger is generally well-tolerated, with few documented adverse effects. However, some individuals may experience mild side effects such as a burning sensation, digestive discomfort, or a disagreeable taste in the mouth.^[34] Ginger may increase the risk of bleeding, particularly when taken in high doses or in combination with anticoagulant medications.^[34,36] Studies have shown that ginger can inhibit CYP3A4, CYP2C9, and P-glycoprotein activities in vitro, which may lead to potential herb-drug interactions.^[36] Case reports have documented possible over-anticoagulation resulting from ginger-phenprocoumon interactions, and patients taking ginger alongside blood-thinning medications should be monitored for signs of bleeding or altered anticoagulation status.^[36] Despite these considerations, ginger is relatively safe and may be effective for various conditions when used appropriately at recommended doses.^[34]

Pharmacological Profile of Black Pepper (*Piper nigrum*)

Botanical Description and Traditional Significance

Black pepper, derived from the dried unripe fruits of *Piper nigrum* L., a perennial climbing vine belonging to the Piperaceae family, is one of the most widely used spices globally and has been extensively utilized in traditional medicine systems for thousands of years.^[43] The Piperaceae family comprises approximately 52 genera and more than 1300 species distributed throughout tropical regions of Africa, Asia, and the Americas. *Piper nigrum* has been deemed the "king of spices" and has been used in ancient Ayurvedic medicine for its numerous health-promoting properties.^[43,44] The plant produces small drupes that are harvested at different stages of maturity to produce black, white, and green pepper, each with distinct flavor profiles and chemical compositions.^[44]

Bioactive Phytoconstituents

The primary bioactive compound responsible for the characteristic pungent flavor and numerous pharmacological effects of black pepper is piperine, an alkaloid belonging to the amide class.^[43,45] The piperine content in black pepper typically ranges from 2% to 7.4%, varying significantly depending on the plant variety, growing conditions, and processing methods. Some studies have reported piperine content up to 9% in certain black pepper cultivars.^[45,46] In addition to piperine, black pepper contains several other important phytochemicals including piperettine, pipernonaline, myristicin, sesamin, lupenone, and various essential oils such as β -caryophyllene, limonene, and sabinene.^[44,47] These compounds contribute synergistically to the overall pharmacological profile of black pepper.^[47]

Recent phytochemical investigations of *Piper nigrum* leaves have identified additional bioactive molecules including pentanamide N,N-didecyl, curcumin, and several other alkaloids, expanding the understanding of the plant's medicinal potential beyond the traditionally studied fruit.^[44,47] The presence of these diverse phytochemicals underpins the wide spectrum of biological activities exhibited by black pepper extracts.^[44,47]

Bioenhancer Activity and Mechanisms of Absorption Enhancement

The most remarkable and well-documented pharmacological property of piperine is its ability to enhance the bioavailability of various drugs and nutrients, a characteristic that has positioned it as a natural bioenhancer in pharmaceutical science.^[43,46] The oral bioavailability of many therapeutic agents is often limited by metabolic barriers, including enzymatic degradation and active efflux processes in the gastrointestinal tract. Piperine addresses these limitations through multiple interconnected mechanisms.^[43]

The primary mechanism of bioavailability enhancement involves the inhibition of cytochrome P450 (CYP) enzymes, particularly CYP3A4, which is responsible for the first-pass metabolism of numerous drugs. Piperine also inhibits other CYP isozymes including CYP2C9 and CYP2E1, thereby reducing the presystemic metabolism of coadministered therapeutic agents.^[43,45,46] A systematic review and meta-analysis of randomized controlled trials concluded that piperine significantly increases the bioavailability of CYP substrates, with pooled analyses showing significant increases in peak plasma concentration (C_{max}), area under the curve (AUC_{0-∞} and AUC_{0-t}), and half-life (T_{1/2}) of conventional drugs when coadministered with piperine.^[46]

Additionally, piperine inhibits efflux transporters such as P-glycoprotein (P-gp) and multidrug resistance-associated protein 1 (MRP-1), which are responsible for pumping drugs out of intestinal cells back into the lumen, thereby reducing absorption. By inhibiting these efflux pumps, piperine allows greater intracellular accumulation and enhanced absorption of drug molecules.^[43,48] Furthermore, piperine modulates intestinal permeability by altering the dynamics of membrane lipids and increasing the paracellular transport of compounds, contributing to its overall bioenhancing effects.^[43,48]

Anti-inflammatory Activity

Piperine exhibits significant anti-inflammatory properties through multiple molecular pathways. Studies have demonstrated that piperine suppresses the production of pro-inflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6).^[44,49] The anti-inflammatory effects are mediated through the inhibition of nuclear factor kappa B (NF- κ B) activation, a master regulator of inflammatory responses. Piperine has also been shown to inhibit the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), reducing the production of inflammatory mediators such as prostaglandins and nitric oxide.^[44]

In animal studies, treatment with piperine resulted in reduced joint swelling and decreased blood markers of inflammation in arthritic models. Piperine has also demonstrated efficacy in suppressing inflammation in airways caused by asthma and allergic conditions in preclinical studies.^[44,49] The leaf extract of *Piper nigrum* has shown anti-inflammatory activity through inhibition of phagocytosis and reduction of cytokine levels, further supporting the anti-inflammatory potential of this plant.^[44,47]

Antioxidant Activity

Black pepper and its active constituent piperine possess potent antioxidant properties that contribute to their overall health-promoting effects. Piperine has been shown to effectively scavenge free radicals, including reactive oxygen species (ROS) and reactive nitrogen

species (RNS), thereby reducing oxidative stress and cellular damage.^[43,44] The antioxidant mechanisms involve both direct radical scavenging and the upregulation of endogenous antioxidant defense systems.^[44]

Studies have demonstrated that piperine treatment reduces markers of free radical damage in cells and tissues. In rodent studies, animals fed a high-fat diet supplemented with black pepper or black pepper extract exhibited significantly fewer markers of free radical damage compared to control animals.^[44] The leaf extract of *Piper nigrum* has also demonstrated significant antioxidant activity through neutralization of free radicals and inhibition of intracellular ROS generation.^[44,47]

Anticancer and Chemosensitizing Activity

Piperine has emerged as a promising anticancer agent with the ability to modulate multiple cellular signaling pathways involved in cancer development and progression.^[48,50] The antineoplastic properties of piperine are mediated through the regulation of key cellular signaling pathways and the modulation of various biological processes including apoptosis induction, cell cycle arrest, inhibition of angiogenesis, and suppression of metastasis.^[48,50] A particularly significant aspect of piperine's anticancer potential is its ability to overcome multidrug resistance (MDR) in cancer cells, a major obstacle in effective chemotherapy. Piperine reverses drug resistance by inhibiting P-glycoprotein (P-gp) and multidrug resistance-associated protein 1 (MRP-1), which are often overexpressed in drug-resistant cancer cells and are responsible for efflux of chemotherapeutic agents.^[48,50] By inhibiting these efflux transporters, piperine resensitizes cancer cells to conventional chemotherapeutic agents, enhancing their therapeutic efficacy.^[48,50]

Research across various cancer types has demonstrated piperine's role in chemosensitization, with studies showing enhanced therapeutic effects when piperine is used in conjunction with other chemotherapeutic agents or natural compounds.^[48,50] The leaf extract of *Piper nigrum* has shown anti-proliferative activity against human breast cancer cells (MDA-MB-231), rat mammary tumor cells (LA7), and mouse melanoma cells (B16-F10), with the highest activity observed against MDA-MB-231 cells. The extract did not inhibit normal human kidney cells (HEK-293), indicating selective toxicity toward cancer cells.^[44,47] Fluorescence staining techniques confirmed induction of apoptosis in cancer cells following treatment with *Piper nigrum* leaf extract.^[44,47]

Neuroprotective Activity

Piperine has demonstrated significant neuroprotective effects in preclinical studies, making it a promising candidate for the management of neurodegenerative disorders such as Alzheimer's and Parkinson's

diseases.^[43,44] Studies in animal models of Alzheimer's disease have shown that piperine improves memory and cognitive function. In one rodent study, piperine administration enabled rats to navigate a maze more efficiently compared to control animals.^[44]

The neuroprotective mechanisms of piperine involve reduction of oxidative stress, suppression of neuroinflammation, inhibition of amyloid plaque formation, and modulation of neurotransmitter systems. Piperine has been shown to decrease the formation of amyloid plaques, which are dense clumps of damaging protein fragments in the brain that are characteristic of Alzheimer's disease pathology.^[44] Additionally, piperine has demonstrated the ability to inhibit monoamine oxidase B (MAO-B), an enzyme involved in the metabolism of dopamine, suggesting potential benefits in Parkinson's disease management.^[43]

Antidiabetic and Metabolic Effects

Piperine has shown promising effects in regulating glucose homeostasis and improving metabolic health.^[51] Studies have demonstrated that piperine treatment results in improved insulin sensitivity, reduced insulin resistance, and better glycemic control. In animal studies, rats fed black pepper extract exhibited smaller spikes in blood sugar levels after glucose consumption compared to control animals.^[44,51]

The antidiabetic mechanisms of piperine involve multiple pathways including enhanced glucose uptake in peripheral tissues, inhibition of hepatic gluconeogenesis, protection of pancreatic beta-cells from oxidative damage, and modulation of AMP-activated protein kinase (AMPK) signaling.^[44,51] Clinical studies in overweight individuals taking supplements containing piperine have shown significant improvements in insulin sensitivity, suggesting potential benefits for metabolic syndrome and type 2 diabetes management.^[44,51]

Cardioprotective and Cholesterol-Lowering Activity

Black pepper and piperine have demonstrated beneficial effects on cardiovascular health, particularly in relation to cholesterol metabolism. Animal studies have shown that rats fed a high-fat diet supplemented with black pepper extract exhibited decreased blood cholesterol levels, including reduced LDL (bad) cholesterol, compared to control animals.^[44] Additionally, piperine has been shown to increase HDL (good) cholesterol levels and reduce triglyceride accumulation.^[44]

The cholesterol-lowering effects of piperine are mediated through multiple mechanisms including inhibition of intestinal cholesterol absorption, enhancement of bile acid excretion, and modulation of lipid metabolism enzymes.^[44] Furthermore, piperine has been shown to enhance the absorption of other cholesterol-lowering compounds, such as curcumin from turmeric, by up to 2000%, demonstrating its potential as an adjunct in cardiovascular health management.^[44]

Antimicrobial Activity

Piper nigrum extracts exhibit broad-spectrum antimicrobial activity against various bacterial, fungal, and parasitic pathogens. Studies have demonstrated that Piper nigrum leaf extract shows significant antibacterial activity, with higher activity against Gram-positive bacteria, particularly *Staphylococcus aureus*.^[44,47] The antimicrobial effects are attributed to the presence of multiple bioactive compounds including piperine, piperettine, and other alkaloids that disrupt microbial cell membranes and interfere with essential metabolic processes.^[44]

Gastroprotective and Digestive Effects

Black pepper has been traditionally used to improve digestion and alleviate gastrointestinal disorders. Piperine has been shown to stimulate digestive enzymes, enhance gastric emptying, and improve gut health.^[44] Research suggests that piperine may increase the population of beneficial gut bacteria, contributing to improved immune function, mood regulation, and overall health.^[44] The gastroprotective effects of piperine also involve reduction of gastric acid secretion and enhancement of gastric mucosal defense mechanisms.^[44]

Safety Considerations and Drug Interactions

Despite its numerous health benefits, piperine is not without safety concerns. Piperine exhibits limitations including poor water solubility, dose-dependent toxicity, and potential for significant drug-drug interactions.^[43,45] The bioenhancing effects of piperine, while therapeutically beneficial in many contexts, can lead to increased plasma concentrations of coadministered drugs, potentially resulting in toxicity if not properly managed.^[43,45,46]

Piperine has been shown to inhibit multiple CYP450 enzymes and P-glycoprotein, which can alter the pharmacokinetics of numerous conventional medications including phenytoin, propranolol, theophylline, carbamazepine, fexofenadine, and midazolam.^[45,46] Patients taking anticoagulant medications should exercise caution, as piperine may increase the risk of bleeding.^[45] Additionally, case reports have documented drug-induced liver injury associated with consumption of turmeric and piperine supplements, highlighting the need for awareness of potential hepatotoxicity, particularly with enhanced bioavailability formulations.^[52] Reproductive and hepatic concerns have been reported at higher doses, emphasizing the importance of appropriate dosing and medical supervision when using piperine-containing supplements.^[43,45]

Bioavailability Challenges and Enhancement Strategies for Piperine Itself

Paradoxically, despite its role as a bioavailability enhancer for other compounds, piperine itself suffers from poor water solubility, which limits its own absorption and therapeutic efficacy.^[43,45] To overcome this limitation, recent developments in nanotechnology

have led to innovative formulation strategies including nanoemulsions, liposomes, phytosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and self-emulsifying drug delivery systems.^[43,45] These advanced delivery systems enhance piperine's solubility, stability, and bioavailability, thereby improving its therapeutic potential.^[43,45]

Future Outlook

Nanotechnology Integration: The convergence of nanotechnology and orodispersible drug delivery represents a frontier for herbal formulation research. Nano-encapsulation of herbal bioactives prior to incorporation into ODTs could further enhance bioavailability while maintaining rapid disintegration characteristics.^[11,12] The development of nano-enhanced ODTs combining the benefits of both technologies is an active area of investigation.

Artificial Intelligence in Formulation: Artificial intelligence (AI) is increasingly being integrated into pharmaceutical formulation design. AI-guided formulation development can optimize excipient selection, predict stability profiles, and accelerate the development of herbal ODTs.^[15] Machine learning algorithms can analyze complex interactions between herbal extracts and excipients to predict optimal formulation compositions.

Personalized Herbal Medicine: The combination of 3D printing technology with herbal ODTs could enable personalized phytotherapy, where formulations are tailored to individual patient needs based on genetic profiles, disease status, or preferences.^[16,19] This approach aligns with the traditional Ayurvedic principle of individualized treatment.

Sustainable Manufacturing: Green synthesis approaches using plant extracts in nanoparticle preparation provide eco-friendly and cost-effective routes to phytochemical stabilization.^[12] Sustainable manufacturing practices, including continuous manufacturing processes, are expected to gain prominence in herbal ODT production.^[17]

Smart Delivery Systems: Stimuli-responsive nanocarriers that trigger drug release in response to pH, temperature, or enzymatic activity at disease sites represent an advanced frontier in herbal drug delivery.^[12] Incorporating such systems into orodispersible formulations could enable site-specific delivery of herbal bioactives.

Clinical Translation and Regulatory Frameworks: As herbal ODTs advance toward clinical applications, the establishment of appropriate regulatory frameworks for nano-phytopharmaceuticals becomes increasingly important.^[15] Future efforts must address safety considerations, including nanotoxicity assessment, and develop standardized protocols for efficacy evaluation.

DISCUSSION

The formulation of orodispersible tablets containing turmeric, ginger, and black pepper extracts represents a rational approach to developing a patient-friendly phytopharmaceutical dosage form with enhanced therapeutic potential. The selection of these three herbal extracts is grounded in both traditional knowledge and modern scientific evidence, as each component contributes unique pharmacological properties while exhibiting synergistic interactions when combined.

The primary challenge in formulating herbal orodispersible tablets lies in the inherent physicochemical limitations of dried plant extracts. As documented in the literature, dried plant materials typically exhibit high hygroscopicity, poor flowability, low compressibility, and reduced bioavailability of active constituents.^[17] These characteristics pose significant hurdles for direct compression, which is the preferred manufacturing method for ODTs due to its simplicity and cost-effectiveness.^[1] The present formulation addresses these challenges through the strategic selection of excipients, including superdisintegrants such as croscopovidone or croscarmellose sodium, which promote rapid water uptake and tablet disintegration within seconds.^[1,7] The use of direct compression as the manufacturing technique offers advantages in terms of scalability and economic viability while maintaining the integrity of heat-sensitive herbal constituents.^[17]

The incorporation of piperine from black pepper as a bioavailability enhancer is a particularly significant aspect of this formulation. Piperine has been extensively documented as a natural bioenhancer that inhibits cytochrome P450 enzymes, particularly CYP3A4, and P-glycoprotein efflux transporters, thereby increasing the systemic absorption of coadministered drugs and phytoconstituents.^[43,45,46] A systematic review and meta-analysis confirmed that piperine significantly increases the peak plasma concentration, area under the curve, and half-life of conventional drugs when coadministered.^[46] In the context of the present formulation, piperine is expected to enhance the bioavailability of curcumin from turmeric and gingerols from ginger, both of which suffer from poor oral absorption due to extensive first-pass metabolism and rapid systemic elimination.^[11,22,23] The oral bioavailability of curcumin in its native form is less than 1%, primarily due to poor aqueous solubility, rapid degradation in the gastrointestinal tract, and extensive conjugation in the liver and intestines.^[22,26] The presence of piperine addresses this limitation by inhibiting the metabolic enzymes responsible for curcumin conjugation and reducing its efflux from intestinal cells.^[43]

The synergistic anti-inflammatory effects of the three herbal extracts warrant particular attention. Curcumin from turmeric inhibits the NF- κ B pathway, reducing the expression of pro-inflammatory cytokines including TNF- α , IL-1 β , and IL-6.^[21] Gingerols and shogaols from ginger similarly suppress inflammatory mediators

through inhibition of COX-2 and modulation of MAPK signaling pathways.^[29,31] Piperine complements these actions through its own anti-inflammatory mechanisms while simultaneously enhancing the bioavailability of both curcumin and gingerols.^[43,44] This polyherbal approach aligns with the traditional Ayurvedic principle of Trikatu, which combines ginger, black pepper, and long pepper to enhance digestion and absorption of nutrients and drugs.^[3,9] The clinical relevance of this synergistic combination has been demonstrated in a randomized, double-blind controlled trial where a herbal formulation containing turmeric extract, black pepper, and ginger produced reductions in prostaglandin E2 levels in patients with chronic knee osteoarthritis comparable to the NSAID Naproxen over a four-week treatment period.^[2] This finding suggests that the combination may offer comparable anti-inflammatory efficacy to conventional medications while potentially avoiding the gastrointestinal adverse effects associated with long-term NSAID use.

The antioxidant properties of the three herbal extracts provide additional therapeutic benefits. Curcumin, gingerols, and piperine each exhibit potent free radical scavenging activity and upregulate endogenous antioxidant defense mechanisms including the Nrf2 pathway, which regulates the expression of detoxifying enzymes and antioxidant proteins.^[21,33,44] A systematic review and meta-analysis of randomized controlled trials examining curcuminoid plus piperine co-supplementation found significant reductions in AST levels and IL-6 levels, supporting the anti-inflammatory and hepatoprotective potential of this combination.^[3] The reduction in IL-6, a key pro-inflammatory cytokine involved in the pathogenesis of numerous chronic inflammatory conditions, is particularly noteworthy as it suggests systemic anti-inflammatory effects beyond the gastrointestinal tract.^[3]

From a formulation development perspective, the evaluation parameters employed in this study are consistent with established quality standards for orodispersible tablets. Pre-compression parameters including angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio are essential for assessing powder flow and compressibility, which directly influence tablet weight uniformity and mechanical strength.^[1] Post-compression parameters including hardness, friability, weight variation, drug content uniformity, disintegration time, wetting time, and in-vitro dissolution provide comprehensive characterization of tablet quality and performance.^[1,4,7] The disintegration time is a critical quality attribute for ODTs, with acceptable limits typically requiring disintegration within three minutes according to pharmacopoeial standards.^[4] The use of superdisintegrants facilitates rapid water uptake and tablet breakup, while the porous structure of the tablet matrix contributes to fast disintegration.^[1,7]

The clinical significance of formulating these herbal extracts into orodispersible tablets extends beyond the pharmacological benefits of the individual components. The ODT dosage form offers practical advantages for patient populations that may have difficulty swallowing conventional tablets, including pediatric, geriatric, and bedridden patients.^[1,6] Additionally, the rapid disintegration and pregastric absorption characteristics of ODTs may further enhance the bioavailability of herbal constituents by bypassing first-pass metabolism to some extent.^[1] This is particularly relevant for curcumin and gingerols, which are extensively metabolized in the liver.^[11,22] The potential for absorption through the oral mucosa may provide a direct route to systemic circulation, although the extent of buccal absorption for these specific phytoconstituents requires further investigation.^[1]

However, several limitations of the current formulation approach must be acknowledged. The variability in the chemical composition of herbal extracts due to differences in plant source, growing conditions, harvesting time, and extraction methods presents challenges for batch-to-batch consistency and quality control.^[17,28] Standardization of extracts to specific marker compounds such as curcuminoids, gingerols, and piperine is essential to ensure reproducible pharmacological activity and regulatory compliance.^[17] Additionally, the hygroscopic nature of many herbal extracts may affect the stability of the final dosage form, necessitating appropriate packaging and storage conditions.^[17] The potential for herb-drug interactions, particularly through piperine-mediated inhibition of CYP450 enzymes and P-glycoprotein, requires careful consideration when the formulation is coadministered with conventional medications.^[45,46]

The present findings align with the growing body of evidence supporting the integration of herbal medicines into modern drug delivery systems. The development of orodispersible tablets containing turmeric, ginger, and black pepper extracts represents a successful example of this integration, combining traditional knowledge with contemporary pharmaceutical technology.^[17] The polyherbal approach leverages the synergistic interactions among the three extracts to achieve enhanced therapeutic effects while potentially reducing the required dose of individual components.^[2,3] Future research directions should include pharmacokinetic studies to quantify the bioavailability enhancement provided by piperine within this specific formulation, pharmacodynamic studies to establish dose-response relationships, and long-term stability studies to determine shelf life under various storage conditions.^[17,22] Clinical trials comparing the efficacy of the ODT formulation to conventional herbal extracts and standard pharmacological treatments would provide valuable evidence for regulatory approval and clinical adoption.^[2]

In conclusion, the formulation of orodispersible tablets containing turmeric, ginger, and black pepper extracts successfully addresses the limitations of conventional herbal dosage forms by providing a patient-friendly, rapidly disintegrating delivery system with enhanced bioavailability through piperine-mediated bioenhancement. The synergistic pharmacological activities of the three extracts, particularly their anti-inflammatory and antioxidant effects, support the therapeutic potential of this formulation for conditions such as osteoarthritis, metabolic syndrome, and other chronic inflammatory diseases.^[2,3,21,29,44] The application of quality-by-design principles in formulation development and evaluation ensures that the final product meets established quality standards for orodispersible tablets.^[1,4,17] Continued research and development in this area will further advance the field of phytopharmaceuticals and contribute to the evidence base for herbal medicines in modern healthcare.

CONCLUSION

The formulation of orodispersible tablets containing turmeric, ginger, and black pepper extracts represents a significant advancement in phytopharmaceutical drug delivery, successfully integrating traditional herbal knowledge with modern pharmaceutical technology. The review has established that each of the three herbal extracts possesses well-documented pharmacological activities, including anti-inflammatory, antioxidant, neuroprotective, antidiabetic, and anticancer properties, which collectively support the therapeutic potential of the polyherbal combination. The inclusion of piperine from black pepper as a natural bioavailability enhancer addresses the critical limitation of poor oral absorption associated with curcumin and gingerols, thereby improving the overall therapeutic efficacy of the formulation. Furthermore, the orodispersible tablet dosage form overcomes the swallowing difficulties associated with conventional tablets, offering rapid disintegration, ease of administration without water, and potential for pregastric absorption, making it particularly suitable for pediatric, geriatric, and bedridden patient populations.

The development of this herbal ODT formulation requires careful attention to formulation strategies, including the selection of appropriate superdisintegrants, binders, fillers, and lubricants, as well as optimization of manufacturing techniques such as direct compression. Comprehensive evaluation through pre-compression and post-compression parameters ensures that the final product meets established quality standards for orodispersible tablets. While challenges related to extract standardization, batch-to-batch consistency, stability, and potential herb-drug interactions remain, these can be addressed through rigorous quality control measures and further research. The synergistic therapeutic effects of the three herbs, combined with the patient-friendly characteristics of the ODT platform, position this formulation as a promising candidate for the

management of chronic inflammatory conditions, metabolic disorders, and other diseases where oxidative stress and inflammation play a central role. Future clinical studies and pharmacokinetic investigations will be essential to fully validate the therapeutic potential and safety profile of this innovative herbal orodispersible tablet formulation.

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