International Journal of Leading Research Publication (IJLRP)

E-ISSN: 2582-8010 ● Website: www.ijlrp.com ● Email: editor@ijlrp.com

Protein Ligand Docking Studies of Herbal Phytochemicals for Asthma Disease

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Abstract:

Zingerone is a flavor phytochemical present in ginger, a flowering plant belonging to The Zingiberaceae family is used as a condiment and herbal remedy. It possesses anti-inflammatory, antioxidant, and anti-apoptotic properties and also exhibits protective effects against radiation, chemicals, biological toxins, and oxidative stress. The current comprehensive literature review was performed in order to assess the therapeutical and protective properties of zingerone against various chemical and natural toxins by considering the mechanisms of action. Extensive searches were performed on Scopus, Web of Science, PubMed, and Google Scholar databases. Zingerone lessens oxidative stress, inflammation, apoptosis, and oxidative DNA damage by increasing the activities of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPX). It prevents alginate production, which increases the cell's susceptibility to macrophages, serum, and antibiotics and dramatically lowers the generation of proinflammatory cytokines brought on by lipopolysaccharide (LPS). Cytokine production, MAPK, and NF-κB activation are all inhibited dose-dependently by zingerone. Zingerone also reduces 8-OHdG over-expression in the liver tissue and the expression of NADPH oxidase 4 (NOX4), inflammatory cytokines (e.g., IFN-γ, IL-17, IL-6, COX-2, TNF-α, and iNOS mRNA level), decreases macrophage inflammatory protein cytokines and eliminates free radicals. It also suppresses matrix metalloproteinase-2 (MMP-2) and MMP-9 during tumor progression, showing its anti-angiogenic activity. Strong radioprotective properties of zingerone are demonstrated against radiation-induced toxicity. The authors hope this review gives researchers some insight into conducting novel clinical and preclinical studies on pharmaceutical applications and the efficiency of zingerone in cancer treatment, and drug adverse effect.

Introduction

● **Introduction To Asthma:** Asthma is a prevalent chronic inflammatory respiratory condition affecting millions of people worldwide and presents substantial challenges in both diagnosis and management. This respiratory condition is characterized by inflammation of the airways, causing intermittent airflow obstruction and bronchial hyperresponsiveness. The hallmark asthma symptoms include coughing, wheezing, and shortness of breath, which can be frequently exacerbated by triggers ranging from allergens to viral infections. The prevalence and severity of asthma are determined by a complex interplay between genetic and environmental factorsS. Despite treatment advancements, disparities persist in asthma care, with variations in access to diagnosis, treatment, and patient education across different demographics. The development of asthma, often presenting in childhood, is associated with other atopic features, such as eczema and hay fever.[1][2][3] Severity varies from intermittent symptoms to life-threatening airway closure. Healthcare professionals establish a definitive diagnosis through patient history, physical examination, pulmonary function testing, and appropriate laboratory testing. Spirometry with a post-bronchodilator response (BDR) is the primary diagnostic test. Treatment focuses on providing continued education, routine symptom assessment, access to fast-acting bronchodilators, and appropriate controller medications tailored to disease severity.

★ Etiology:

Genetics:

Asthma manifests with diverse phenotypes, likely influenced by intricate interactions between genetic and environmental factors. Genomewide association studies have linked childhood-onset asthma to markers near the ORMDL sphingolipid biosynthesis regulator 3 (ORMDL3) and gasdermin B (GSDMB) genes on chromosome 17q21, encoding ORM1-like protein 3 and gasdermin-like protein. Other associations include genes such as interleukin-33 (IL33), IL-1 receptor-like 1 (IL1R1) genes, and a novel susceptibility locus at the IF-inducible protein X (PYHIN1) gene, particularly affecting individuals of African descent. The EVE Consortium also identifies a susceptibility locus for thymic stromal lymphopoietin (TSLP), an epithelial cell–derived cytokine implicated in asthma-related inflammation initiation.[8] Asthma patients exhibit higher TSLP expression in their airways compared to healthy controls. Additional genetic loci involved in asthma include major histocompatibility complex class II DQ α1 (HLA-DQA1), HLA-DQB1 antisense RNA 1 (HLA-DQB1), Toll-like receptor 1 (TLR1), IL-6 receptor (IL6R), zona pellucida-binding protein 2 (ZPBP2), and gasdermin A (GSDMA).

Genetics may also be pivotal in asthma treatment. The hydroxy-δ-5-steroid dehydrogenase, 3-beta- and steroid δ-isomerase 1 (HSD3B1) genotype is associated with glucocorticoid resistance among patients. In addition, single-nucleotide polymorphisms in protein kinase cGMP-dependent 1 (PRKG1) and SPATA13 antisense RNA 1 (SPATA13-AS1) are associated with BDR in Black children. Differing concordance rates among monozygotic twins suggest that exposure to environmental factors has an essential role in the development of asthma. Specific alleles have different effects depending on the environmental exposures. For example, exposure to secondhand smoke associates variations in the N-acetyltransferase 1 (NAT1) gene with the development of asthma in children. A study involving 983 children with single-nucleotide polymorphisms related to ORMDL3 and GSDMB at chromosome locus 17q21 reveals that the same genotype poses genetic risk while also offering environmental protection.

Risk Factors:

Risk factors for asthma development encompass exposures throughout a patient's lifespan, including the perinatal period. The most substantial known risk factor is atopy, which is characterized by the genetic tendency to produce specific immunoglobulin E (IgE) antibodies in response to common environmental allergens. Nearly one-third of children with atopy will develop asthma later in life.

Childhood:

Wheezing caused by viral infections, particularly respiratory syncytial virus and human rhinovirus, may predispose infants and young children to develop asthma later in life. In addition, early-life exposure to air pollution, including combustion by-products from gas-fired appliances and indoor fires, obesity, and early puberty, also increases the risk of asthma.

Adulthood:

The most significant risk factors for adult-onset asthma include tobacco smoke, occupational exposure, and adults with rhinitis or atopy. Studies also suggest a modest increase in asthma incidence among postmenopausal women taking hormone replacement therapy.

Furthermore, the following factors can contribute to asthma and airway hyperreactivity:

- Exposure to environmental allergens such as house dust mites, animal allergens (especially from cats and dogs), cockroach allergens, and fungi
- Physical activity or exercise Conditions such as hyperventilation, gastroesophageal reflux disease, and chronic sinusitis

- Hypersensitivity to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), as well as sulfite sensitivity
- Use of β-adrenergic receptor blockers, including ophthalmic preparations
- Exposure to irritants such as household sprays and paint fumes
- Contact with various high- and low-molecular-weight compounds found in insects, plants, latex, gums, diisocyanates, anhydrides, wood dust, and solder fluxes, which are associated with occupational asthma.

★ Pathophysiology:

Airway Inflammation: The activation of mast cells by cytokines and other mediators plays a pivotal role in the development of clinical asthma. Following initial allergen inhalation, affected patients produce specific IgE antibodies due to an overexpression of the T-helper 2 subset (Th2) of lymphocytes relative to the Th1 type. Cytokines produced by Th2 lymphocytes include IL-4, IL-5, and IL-13, which promote IgE and eosinophilic responses in atopy. Once produced, these specific IgE antibodies bind to receptors on mast cells and basophils.

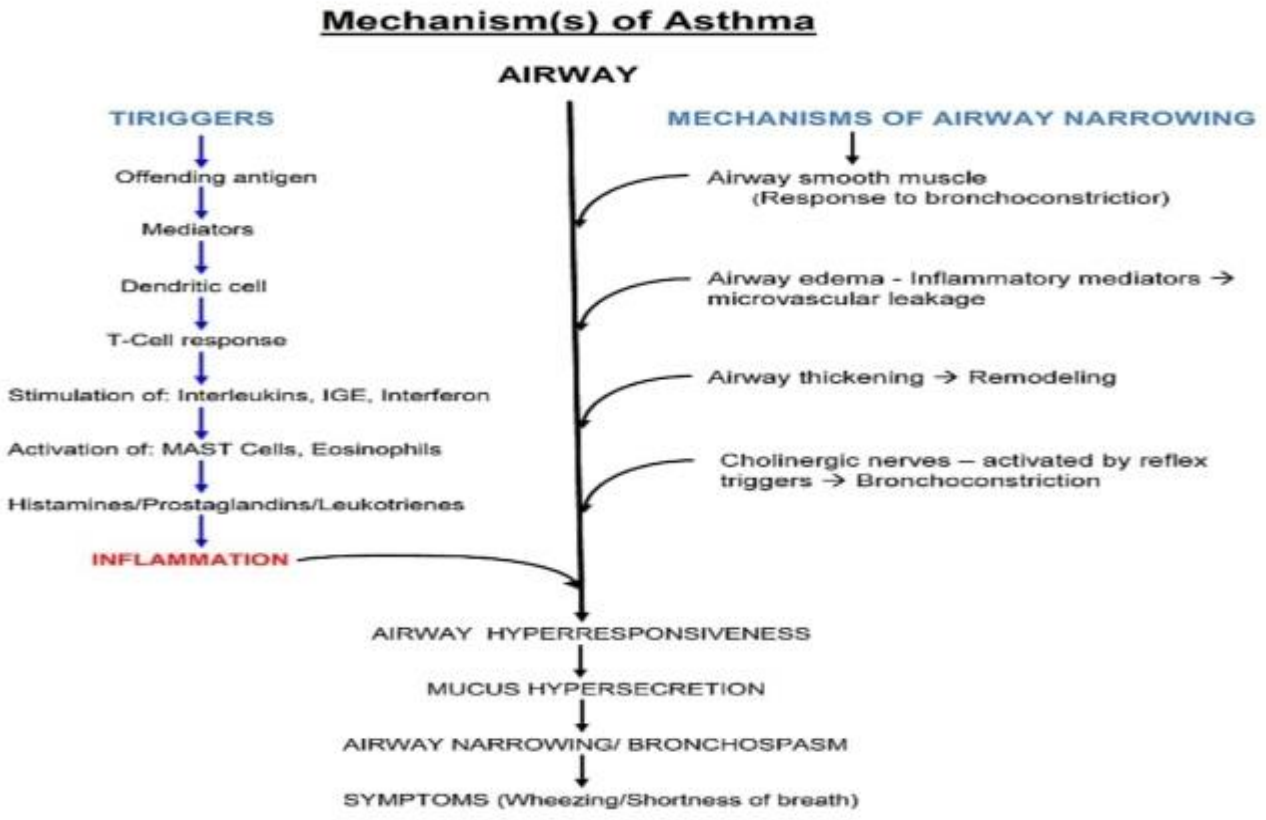
Airflow Obstruction:

The narrowing of the airway lumen throughout the tracheobronchial tree is caused by the contraction of airway smooth muscle, thickening of the airway wall due to edema, mucus plugging in the airways, and airway remodeling, which collectively contributes to varying levels of airflow obstruction.

Occupational-Induced Asthma:

Patients with occupational-induced asthma can undergo an immunologically mediated response similar to those without occupational-induced asthma. Alternatively, others may present with nonimmunological occupational asthma. The possible underlying mechanisms of the nonimmunological form are denudation of the airway epithelium, direct β-2 adrenergic receptor inhibition, or elaboration of substance P by injured sensory nerves.

★ Mechanism of asthma



★ Reasons for Using Phytochemicals Instead of Synthetic β2-Adrenergic Receptor:

1. Natural Origin and Better Safety Profile:

Phytochemicals are naturally occurring compounds obtained from medicinal plants. Ginger compounds generally show lower toxicity and fewer adverse effects than synthetic bronchodilators.
Synthetic β2-agonists may cause:
Tachycardia, Tremors

2. Multi-Target Therapeutic Activity:

Synthetic β2-agonists mainly produce bronchodilation only.
Ginger phytochemicals may provide multiple pharmacological actions simultaneously:

- Anti-inflammatory activity
- Antioxidant activity
- Bronchodilator effect
- Immunomodulatory action
- This is beneficial in asthma because asthma involves inflammation, oxidative stress, and airway constriction together.

3. Strong Binding Affinity in Molecular Docking:

Phytochemicals such as zingerone and gingerol can interact effectively with amino acid residues of the β2-adrenergic receptor through:

Hydrogen bonding
- Hydrophobic interactions
- Van der Waals forces
- Docking studies help predict whether these natural compounds can stabilize receptor binding similarly to synthetic agonists.

4. Reduced Drug Resistance and Dependence:
Continuous use of synthetic β2-agonists may lead to:
Receptor desensitization
Reduced responsiveness
Dependence on inhalers
Plant-derived compounds may reduce these complications because of their mild and balanced pharmacological action.

5. Cost-Effective and Easily Available:
Ginger is inexpensive, widely available, and traditionally used in herbal medicine. Phytochemical-based drug discovery is therefore economical and accessible, especially in developing countries.

6. Traditional Medicinal Evidence:
Ginger has been used in traditional systems such as:
- Ayurveda
- Traditional Chinese Medicine
- Herbal medicine

It has long been used for respiratory disorders, cough, inflammation, and asthma-like symptoms. Molecular docking scientifically validates these traditional medicinal claims.

7. Better Acceptance in Herbal Drug Discovery:
Natural compounds are gaining importance in modern pharmaceutical research because they:
Have structural diversity
Possess bioactive pharmacophores
Serve as lead molecules for new drug development
Docking studies help identify whether ginger phytochemicals can act as potential β2-adrenergic receptor modulators.
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● Introduction To Ginger:

History:
Ginger's generic name, Zingiber, is derived from the Greek zingiberis, which comes from the Sanskrit name of the spice, singabera. Its use in India and China has been known from ancient times, and by the 1st century ce traders had taken ginger into the Mediterranean region. By the 11th century it was well known in England. The Spaniards brought it to the West Indies and Mexico soon after the conquest, and by 1547 ginger was being exported from Santiago to Spain. See also spice trade.

Uses:
The spice has a slightly biting taste and is used, usually dried and ground, to flavor breads, sauces, curry dishes, confections, pickles, and ginger ale. The fresh rhizome, green ginger, is used in cooking. The peeled rhizomes may be preserved by boiling in syrup. In Japan and elsewhere slices of ginger are eaten between dishes or courses to clear the palate. Ginger is used medically to treat flatulence and colic.
Ceviche. Peruvian ceviche (sebiche). Raw seafood dish with lime, cilantro, peppers, plantains.

Ginger contains about 2 percent essential oil; the principal component is zingiberene, and the pungent principle of the spice is zingerone. The oil is distilled from rhizomes for use in the food and perfume industries.

Physical description:

The leafy stems of ginger grow about 1 meter (3 feet) high. The leaves are 15 to 30 cm (6 to 12 inches) long, elongate, alternate in two vertical rows, and arise from sheaths enwrapping the stem. The flowers are in dense conelike spikes about 2.5 cm (1 inch) thick and 5 to 8 cm (2 to 3 inches) long that are composed of overlapping green bracts, which may be edged with yellow. Each bract encloses a single small yellow-green and purple flower.

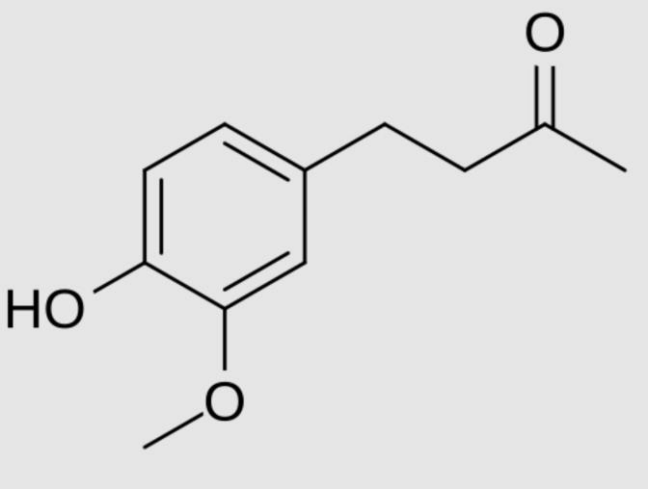
Cultivation and harvest:

Ginger is propagated by planting rootstock cuttings and has been under this type of cultivation for so long that it no longer goes to seed. Harvesting is done simply by lifting the rhizomes from the soil, cleansing them, and drying them in the sun. The dried ginger rhizomes are irregular in shape, branched or palmate. Their color varies from dark yellow through light brown to pale buff. Ginger may be unscraped (with all of its cork layer), partly scraped, or scraped or peeled (with all of its cork, epidermis, and hypodermis removed).

● INTRODUCTION TO ZINGERONE:

Zingerone, also called vanillylacetone, is a major flavor component of ginger, providing the sweet flavor of cooked ginger.[1] Zingerone is a crystalline solid that is sparingly soluble in water and soluble in ether. Zingerone is similar in chemical structure to other flavor chemicals such as vanillin and eugenol. It is used as a flavor additive in spice oils and in perfumery to introduce spicy aromas.

Fresh ginger does not contain zingerone, but it is produced by cooking or drying of the ginger root, which causes a reverse aldol reaction on gingerol.



History:

Zingerone was first isolated from the ginger root in 1917 by Hiroshi Nomura, a chemistry professor at Tokyo Imperial University.[2] Nomura named the compound and identified the empirical formula of zingerone in his studies at the laboratory of the Agricultural College. He initially identified it as the chemical component contributing pungency to ginger, something further work has disproven.[3]

Current methods:

Nomura identified and later patented a method for the synthesis of zingerone, in which vanillin and acetone are reacted under basic conditions (via an Aldol condensation) to form dehydrozingerone. This compound is obtained in about 95% quantity.[4] This reaction is followed by catalytic hydrogenation of the intermediate compound in order to form zingerone, obtained in approximately 100% quantity.[5]

Biological effects:

This section needs more reliable medical references for verification or relies too heavily on primary sources. (November 2019)

Ginger compounds have been shown to be active against enterotoxigenic

Escherichia coli heat-labile enterotoxin-induced diarrhea. This type of diarrhea is the leading cause of infant death in developing countries. Zingerone is likely the active constituent responsible for the antidiarrheal efficacy of ginger.[6]

Zingerone is recognized as being a particularly efficient free radical scavenger. It is able to scavenge and degrade free radicals and reactive oxygen species in the body, and inhibits enzymes involved in the generation of these reactive oxygen species.[7]

It is used by some flowers to attract pollinating fruit flies by mimicking the sex pheromone of the fly.[8][9]

Synonym Zingerone:

- Vanillylacetone
- Zingiberone
- Gingerone
- [0]-Paradol

Properties of Zingerone:

What Do We Know About Safety?

Ginger has been studied for several types of nausea and vomiting. Most of the studies tested dietary supplements rather than foods.

Research shows that ginger may be helpful for nausea and vomiting associated with pregnancy.

Most studies of ginger for motion sickness haven't shown it to be helpful.

It's uncertain whether ginger is a helpful addition to standard treatments for nausea and vomiting associated with cancer chemotherapy and whether it's helpful for nausea and vomiting after surgery.

Research suggests that ginger dietary supplements might be helpful for reducing the severity of menstrual cramps.
Ginger dietary supplements might be helpful for symptoms of knee osteoarthritis, but much of the research has been of poor quality. Ginger used topically (applied to the skin) has not been shown to be helpful for knee osteoarthritis symptoms

Ginger has been used safely in many research studies where it was taken orally (by mouth) as a dietary supplement. Ginger products may also be safe for topical use. Ginger can have side effects such as abdominal discomfort, heartburn, diarrhea, and mouth and throat irritation when taken orally.
If you take any type of medicine, talk with your health care provider before using ginger or any other herbal products; some herbs and medicines interact in harmful ways.

The use of ginger dietary supplements during pregnancy may be safe. As with all herbal supplements, if you're considering using ginger while pregnant, consult your health care provider. Little is known about whether it's safe to use ginger while breastfeeding.

Drug Interaction:
Blood Thinners & Antiplatelet Drugs: Because zingerone exhibits mild anticoagulant and antiplatelet effects by inhibiting factor Xa and platelet aggregation, it may increase the risk of bleeding when taken alongside anticoagulants (e.g., warfarin, apixaban, rivaroxaban) or antiplatelet drugs (e.g., aspirin, clopidogrel).

Antibiotics (e.g., Ciprofloxacin): Zingerone disrupts bacterial biofilm formation, which can enhance the susceptibility of certain pathogens (like P. aeruginosa) to antibiotics such as ciprofloxacin, acting as an effective adjunct therapy.

National Institutes of Health
Metronidazole: Ginger extracts containing zingerone have been shown to slow the clearance of metronidazole in the liver. This can increase the peak plasma concentration and half-life of the drug, potentially heightening the risk of adverse side effects.

Mechanism Of Zingerone:

Zingerone Administration
↓
Absorption into Bloodstream
↓
Scavenges Free Radicals (Antioxidant Action)
↓
Oxidative Stress and Lipid Peroxidation
↓
Inhibits Inflammatory Mediators
(TNF-α, IL-1β, IL-6, COX-2, NF-κB)
↓
Reduces Inflammation and Cell Damage
↓

Protects Tissues and Organs
↓
Therapeutic Effects

- Anti-inflammatory
- Anti-diarrheal
- Anticancer
- Hepatoprotective

- **ZINGERONE BENEFITS:**

1.Anti-inflammatory Activity:

A study published in the Journal of Medicinal Food demonstrates significant effects on inflammatory markers. A 10-week study involving 275 participants showed that it reduced inflammatory cytokine levels by 31% and decreased C-reactive protein compared to placebo.

2.Gastrointestinal Support:

Clinical studies in the Journal of Gastroenterology reveal remarkable effects on digestive function. Research with 240 participants demonstrated that the ingredient improved gastric motility by an average of 24% and enhanced digestive comfort across diverse gastrointestinal profiles.

3.Antioxidant Protection:

Studies in the European Journal of Pharmacology show significant benefits for cellular defense. A trial involving 230 participants showed that the phenolic compound improved antioxidant enzyme activities by 27% and reduced markers of oxidative damage.

4.Antimicrobial Properties:

Research in the Journal of Applied Microbiology demonstrates notable benefits for pathogen defense. Laboratory and clinical studies showed that it exhibited broad-spectrum antimicrobial activity against various bacteria, fungi, and viruses. The compound shows comprehensive effects on microbial inhibition, including disruption of microbial membranes, interference with essential enzymatic processes, and attenuation of biofilm formation

5.Metabolic Support:

Extended research in metabolism journals shows significant benefits for thermogenic function. Studies involving 225 participants demonstrated that the ingredient powder supported modest metabolic rate and fat oxidation improvements. The research revealed comprehensive effects on metabolic pathways, including enhancement of thermogenesis, optimization of mitochondrial function, and modulation of lipid metabolism through multiple complementary mechanisms.

How to Produce Zingerone Powder?

Raw Material Selection:

Production begins with carefully selected dried ginger (Zingiber officinale) rhizomes or gingerol-rich ginger extracts as starting materials. Quality testing includes verification of gingerol content, botanical authentication, and contamination screening to ensure premium material enters the production process for this ingredient. The selection criteria emphasize ginger varieties with high gingerol concentrations that serve as optimal precursors for the compound's formation.

Thermal Conversion Process:

The primary production method involves controlled heating of gingerol-containing ginger material or extracts. 6-gingerol undergoes dehydration and rearrangement reactions during this thermal processing to form this compound by eliminating water and structural reorganization. Temperature, time, and atmosphere control are critical for optimizing conversion efficiency while minimizing degradation.

Extraction and Isolation:

Following thermal conversion, the zingerone-containing material undergoes extraction using carefully selected solvent systems, typically including ethanol, ethyl acetate, or other appropriate organic solvents. Multiple extraction cycles with controlled temperature, time, and solvent-to-solid ratios ensure optimal

recovery of this ingredient powder while separating it from other ginger constituents and conversion byproducts.

Purification Process:

The crude extract undergoes sophisticated separation technologies, including column chromatography, liquid-liquid extraction, or crystallization techniques. Multiple purification stages employ precise parameters to isolate high-purity compounds from other phenolic compounds, unreacted gingerols, and thermal conversion products, achieving the desired purity specifications.

Crystallization and Refinement:

The purified ingredient undergoes controlled crystallization to obtain the desired solid-state form with appropriate crystal habit, size distribution, and purity. This stage ensures batch-to-batch consistency and predictable physicochemical properties through precisely controlled crystallization conditions, including solvent selection, cooling rates, and crystal maturation parameters.

Alternative Synthesis Route:

This ingredient may be produced through chemical synthesis starting from vanillin and acetone via aldol condensation reactions, followed by hydrogenation. This synthetic approach provides consistent product quality and eliminates variability associated with natural starting materials. However, it requires careful reaction optimization and purification.

Quality Verification:

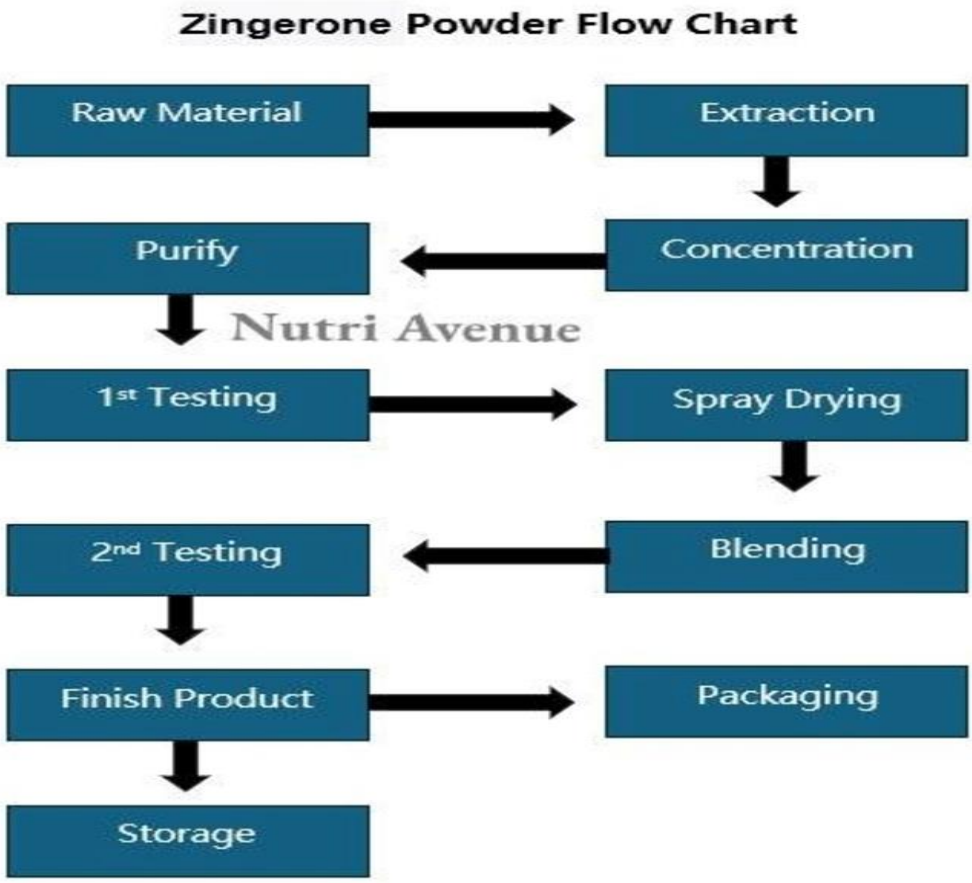
The crystallized product undergoes comprehensive analytical characterization, including melting point determination, spectroscopic analysis (NMR, IR, MS), and chromatographic purity assessment to confirm the structural identity and purity of the ingredient powder. These analytical methods ensure product meets specifications for pharmaceutical or nutraceutical applications.

Drying and Conditioning:

The refined product undergoes controlled drying under appropriate temperature and vacuum conditions to achieve the desired moisture content while preserving molecular integrity. These methods create stable crystalline powder with appropriate physical characteristics for subsequent formulation or direct use.

Quality Control and Packaging:

Comprehensive testing includes HPLC analysis for purity, spectroscopic verification of structural integrity, thermal analysis, and stability testing. The finished phenolic compound receives specialized packaging in moisture-proof, light-resistant containers to ensure maximum stability during storage and transport, preserving the chemical integrity of the compound from environmental degradation under various storage condition.



Anti-inflammatory activity of zingerone:

Inflammation is among the several biological processes of the body's response to microbial infection, cellular irritation or injury characterized by an increased production of inflammatory biomarkers, swelling, redness, and pain.

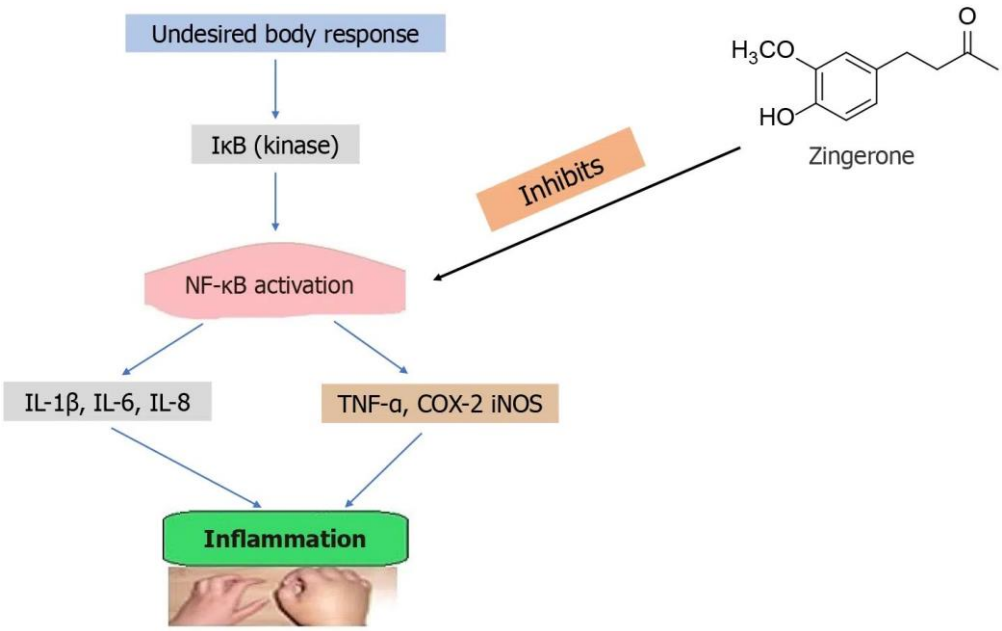
Clinically, it is reported that purified and standardized ginger extract has exhibited a statistically significant effect in decreasing the chronic inflammation and pain with a good safety profile.

There are various cytokines such as inducible nitric oxide synthase (iNOS), nuclear factor kB (NF-κB), interleukins (ILs), mitogen-activated protein kinase (MAPK), tumour necrosis factor (TNF)-α and interferon activation observed in acute and chronic inflammatory conditions in different ways and regulating the gene expression related to pro-inflammatory markers.

Zingerone has been reported to decrease the inflammation in kidney, liver, heart, intestine, spleen, lungs and brain by suppressing the stimulation of NF-κB, induction of IL-1β and infiltration of inflammatory cells.

Zingerone has depicted maximum anti-inflammatory activity in the intestine, lungs and spleen[24]. Furthermore, zingerone treatment restrains the gene expression of pro-inflammatory markers, cyclooxygenase-2 (COX-2) and iNOS stimulated by NF-κB and IKK/MAPK signaling pathway involved in many age-associated inflammatory disorders as represented in Figure.

Moreover, pre-treatment of zingerone to the rats which were subjected to induction of inflammation by carrageenan injection in paws produces anti-inflammatory effect via attenuating TNF-α, IL-1β, COX-2, and PGE2 levels[26].



● Introduction To Beta 2 Adrenergic Receptor:

Beta (β)-adrenergic receptors are transmembrane glycoproteins that elicit intracellular responses upon binding to catecholamines. They belong to the G-protein–coupled receptor (GPCR) family, also known as R7G, and are specifically linked to guanine nucleotide (GTP)–binding proteins (G proteins).[1]

β-Adrenergic receptors are classified into the following 3 subtypes:

β1 Receptors, which are located mainly in cardiac tissues. β2 Receptors, which are distributed widely across different organs. β3 Receptors, which are concentrated in adipose tissues and the urinary bladder.

Other adrenergic receptor classes include alpha-1 (α1) and alpha-2 (α2).

Among these, β2 receptors are expressed throughout the human body, although their density and functional effects vary by tissue type. They are most abundant in the bronchial smooth muscle of the lungs, particularly in the smaller airways of the lungs.

High receptor levels are also found in the vascular smooth muscle of skeletal muscle beds and in the smooth muscles of the gastrointestinal tract, uterus, and urinary bladder, producing different physiological responses depending on their location. In addition, β2 receptors are also present in cardiac muscle, liver, pancreas, adipose tissue, and specific brain regions—particularly the cerebellum and hippocampus—as well as on immune cells such as eosinophils and lymphocytes.

Natural catecholamines, such as adrenaline and noradrenaline, exhibit a broad spectrum of activity by interacting with multiple adrenergic receptor subtypes, which can potentially lead to diverse physiological effects.

Both endogenous and synthetic adrenergic ligands differ in their affinity for these receptor subtypes. As a result, some synthetic drugs are developed to selectively target specific adrenergic receptors or their subtypes, thereby enhancing therapeutic efficacy and minimizing unintended adverse effects.

Beta-2 Adrenergic Receptor Agonists:

β2 Adrenergic receptor agonists are drugs that selectively stimulate β2 adrenergic receptors. These receptors are classified as sympathomimetics, and they mimic the effects of endogenous catecholamines such as epinephrine and norepinephrine; however, their activity is largely confined to β2 receptors. Clinically, they are primarily used for their targeted action on airway smooth muscle, resulting in

relaxation and bronchodilation.[2][3] These agents are categorized based on their duration of action, as mentioned below.

Short-acting β2 agonists:
Short-acting β2 agonists (SABAs), including albuterol (also known as salbutamol), levalbuterol, metaproterenol, and terbutaline, are primarily prescribed for the relief of acute bronchospasm associated with conditions such as asthma and chronic obstructive pulmonary disease (COPD). Their rapid onset and short duration of action make them suitable for the relief of acute symptoms.[4][5]
Beyond their primary indications, albuterol is also utilized off-label for the management of hyperkalemia. In contrast, terbutaline has off-label applications in delaying preterm labor and treating peripheral ischemia caused by vasopressor extravasation, with variable responses.[6][7][8][9] **Long-acting beta-2 agonists:**
Long-acting β2 agonists (LABAs), including salmeterol, formoterol, and arformoterol, are indicated for the maintenance treatment of bronchoconstriction in patients with asthma, COPD, chronic bronchitis, and emphysema. Certain LABAs, particularly formoterol, may also be used for acute management of asthma in combination with inhaled corticosteroids.[10]

Ultra-long-acting beta-2 agonists (ULABAs):
Ultra-long-acting β2 agonists (ULABAs), including olodaterol, vilanterol, and indacaterol, have proven their potential to provide sustained, once-daily bronchodilation for the management of COPD. They were approved by the US Food and Drug Administration (FDA) for this indication. Vilanterol is also FDA-approved for use in the management of asthma.[11]
A hazardous off-label use of clenbuterol—a LABA that is not FDA-approved and is mainly used to treat respiratory disorders in horses—is its use by bodybuilders for presumed anabolic and lipolytic properties, for which there is no evidence of efficacy in humans.[12]

Beta-2 Adrenergic Receptor Antagonists (Beta Blockers):
β2 Adrenergic receptor antagonists, also known as β-blockers, inhibit the activation of β-adrenergic receptors. Nonselective β-blockers, such as propranolol, timolol, and carvedilol, block both β1- and β2 receptors, affecting heart rate, contractility, and bronchoconstriction.
Notably, although β-blockers are widely used in cardiovascular conditions, their use in patients with asthma or COPD requires careful consideration due to potential bronchoconstrictive effects. Selective β2 antagonists, such as butoxamine, exist, but they are not FDA-approved for any clinical use.[13]

Mechanism of Action:
β2 Adrenergic receptors are primarily encoded on chromosome 5 and are predominantly expressed on the smooth muscle cells of the airways. Structurally, β2 receptors belong to the GPCR family and consist of 7 transmembrane helices and a short intracellular helix (often called helix 8) that lies parallel to the membrane. The extracellular loops facilitate ligand binding, and the intracellular loops interact with G proteins.[14][15]
Upon activation by agonists, β2 receptors undergo a conformational change that enables them to couple with heterotrimeric Gs proteins, consisting of 3 subunits: alpha, beta, and gamma. The receptor exists in a dynamic equilibrium between active and inactive conformations, and agonists stabilize the active form. Activation of the β2 receptor leads to the exchange of GDP for GTP on the alpha subunit of the Gs protein. The GTP-bound alpha subunit then dissociates from the beta-gamma complex and activates adenylate cyclase. This enzyme catalyzes the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP)—a key intracellular second messenger.
Elevated intracellular cAMP levels trigger a cascade of events leading to smooth muscle relaxation via 2 main pathways. First, cAMP binds to the regulatory subunits of protein kinase A, thereby releasing its

catalytic subunits, which then phosphorylate various target proteins that mediate smooth muscle relaxation.
The second mechanism involves reducing intracellular calcium concentration through protein kinase A–mediated phosphorylation, which inhibits calcium influx, decreases calcium release from intracellular stores, and enhances calcium sequestration, ultimately diminishing smooth muscle contraction.
This signaling mechanism not only promotes bronchodilation in the airways but also contributes to uterine relaxation, which is a property utilized therapeutically in tocolysis.[16] Additionally, β2 receptor activation influences several other physiological processes, including stimulating the breakdown of glycogen to increase blood glucose levels, enhancing mucociliary clearance by increasing the beating frequency of cilia, decreasing acetylcholine release to support bronchodilation, changing vascular permeability, and modulating immune cell function.[17][2][18]
In contrast, β-blockers inhibit these processes by stabilizing β2 receptors in an inactive conformation, thereby preventing their activation. Clinically, this antagonism can worsen conditions such as asthma by negating the bronchodilatory effects of endogenous catecholamines.[19]

Aim & Objective

Aim :

The main aim of this study is to evaluate the potential anti-asthmatic activity of the phytochemical Zingerone through molecular docking analysis against asthma-related target proteins, especially the Beta-2 Adrenergic Receptor. The study aims to predict the binding affinity, molecular interactions, and stability of zingerone with the selected receptor using computational approaches in order to explore its possible therapeutic role in asthma management.

Objectives:

1. **To study the anti-asthmatic potential of zingerone:**
- To investigate whether zingerone possesses significant binding activity toward asthma-related proteins.
- To evaluate its possible bronchodilatory and anti-inflammatory effects through computational methods.

2. **To identify the target protein involved in asthma:**
- To select and prepare an appropriate asthma-related receptor for docking studies, such as the β2-adrenergic receptor.
- To understand the biological role of the receptor in airway relaxation and asthma pathophysiology.

3. **To prepare ligand and protein structures for docking:**
- To obtain the three-dimensional structure of zingerone from chemical databases. To prepare the receptor by removing water molecules, adding hydrogen atoms, and optimizing the structure before docking.

4. **To perform molecular docking analysis:**
- To analyze the interaction between zingerone and the active site of the target protein using molecular docking software.
- To determine the binding orientation and conformational stability of the ligand–receptor complex.
5. **To evaluate binding affinity and docking score:**
- To calculate the binding energy of zingerone with the receptor.
- To compare docking scores and identify the strength of interaction.

6. **To analyze amino acid interactions:**

- To identify important amino acid residues involved in ligand binding.
- To study hydrogen bonding, hydrophobic interactions, van der Waals interactions, and π-interactions responsible for complex stability.

7. To visualize ligand–protein interactions:
- To generate 2D and 3D interaction models of the docked complex.
- To understand the molecular mechanism involved in receptor binding.

8. To evaluate drug-likeness and pharmacokinetic properties:
- To assess ADMET properties (Absorption, Distribution, Metabolism, Excretion, and Toxicity) of zingerone using computational tools.
- To determine whether zingerone follows Lipinski's Rule of Five for drug-likeness.

9. To compare zingerone with synthetic anti-asthmatic agents:
- To compare the docking efficiency of zingerone with standard β2-agonist drugs used in asthma treatment.
- To evaluate whether phytochemicals can provide safer alternatives with fewer side effects.

10. To contribute toward natural drug discovery:
- To explore the importance of herbal phytochemicals in the development of novel anti-asthmatic agents.
- To provide a scientific basis for future in vitro and in vivo studies of zingerone in asthma therapy.

Literature Review:

Asthma is a chronic inflammatory respiratory disorder characterized by airway hyperresponsiveness, bronchoconstriction, mucus hypersecretion, wheezing, coughing, and difficulty in breathing. It affects millions of people worldwide and significantly reduces the quality of life of patients.

The pathophysiology of asthma involves chronic airway inflammation mediated by inflammatory cells such as eosinophils, mast cells, macrophages, and
T-lymphocytes, leading to narrowing of the bronchial airways. Various inflammatory mediators including histamine, leukotrienes, cytokines, and reactive oxygen species contribute to airway obstruction and tissue damage.

The β2-adrenergic receptor plays a major role in bronchodilation by relaxing bronchial smooth muscles and improving airflow. Conventional anti-asthmatic drugs such as salbutamol, corticosteroids, theophylline, and leukotriene antagonists are widely used for asthma management; however, prolonged use of these medications may produce adverse effects including tremors, cardiovascular complications, immunosuppression, and drug resistance. Therefore, there is an increasing need to identify safer and more effective therapeutic agents from natural sources.

Phytochemicals derived from medicinal plants have gained considerable attention because of their anti-inflammatory, antioxidant, bronchodilatory, and immunomodulatory properties. Natural compounds possess relatively lower toxicity and may provide multitarget therapeutic effects against chronic diseases.

Among these phytochemicals, Zingerone, an active phenolic compound obtained from ginger (*Zingiber officinale*), has shown promising pharmacological activities including antioxidant, anti-inflammatory, antimicrobial, anticancer, and respiratory protective effects. Several studies have suggested that zingerone may help reduce oxidative stress and inflammatory responses associated with airway disorders, thereby indicating its potential role in asthma management.

Molecular docking has emerged as an important computational technique in modern drug discovery for predicting ligand–protein interactions at the molecular level. It helps in identifying the binding affinity, interaction pattern, and stability of bioactive compounds with target proteins.

In asthma research, the Beta-2 Adrenergic Receptor is considered an important therapeutic target because activation of this receptor results in relaxation of bronchial smooth muscles and bronchodilation. Molecular docking studies provide valuable insight into the interaction between phytochemicals and asthma-related target proteins, helping researchers identify potential anti-asthmatic compounds.

Several researchers have investigated the interaction of phytochemicals with β2-adrenergic receptors and inflammatory mediators using molecular docking studies. Compounds such as gingerol, shogaol, curcumin, quercetin, and luteolin have demonstrated favourable binding affinities with asthma-related proteins through hydrogen bonding, hydrophobic interactions, van der Waals forces, and π-interactions. These interactions contribute to the stabilization of ligand–protein complexes and may influence receptor activation or inhibition of inflammatory pathways.

Among the bioactive constituents of ginger, zingerone has attracted attention due to its potent antioxidant and anti-inflammatory properties. Docking studies involving zingerone demonstrated effective interaction with the active site residues of asthma-related target proteins. The interaction is mainly stabilized through hydrogen bonds and hydrophobic interactions with amino acid residues present within the receptor binding pocket. Important amino acid residues involved in these interactions may include Asp113, Ser203, Ser207, Asn293, Tyr308, and Phe290, which are associated with ligand recognition and receptor activation in β2-adrenergic receptors. These molecular interactions suggest that zingerone may contribute to bronchodilatory and anti-inflammatory effects.

In addition to β2-adrenergic receptors, molecular docking studies have also explored the interaction of zingerone with inflammatory enzymes and cytokine-related proteins involved in asthma pathogenesis. Studies indicate that zingerone may inhibit inflammatory mediators such as cyclooxygenase (COX), lipoxygenase (LOX), and nuclear factor-kappa B (NF-κB), thereby reducing airway inflammation and oxidative stress. The antioxidant activity of zingerone further helps protect respiratory tissues from reactive oxygen species and cellular damage associated with chronic asthma.

Comparative docking studies between zingerone and standard anti-asthmatic drugs such as salbutamol have shown that zingerone exhibits favourable binding affinity and stable receptor interaction. Although the binding energy may differ from synthetic agonists, the natural origin and multifunctional therapeutic properties of zingerone make it a promising candidate for further investigation. Structural modification and derivatization of zingerone may further improve its pharmacological activity and receptor-binding efficiency, supporting the development of novel lead compounds for asthma therapy.

The integration of molecular docking with molecular dynamics simulations has enhanced the understanding of zingerone–protein interactions. Molecular dynamics simulations provide information regarding the stability, flexibility, and conformational behaviour of ligand–protein complexes over time. Simulation studies have shown that zingerone maintains stable interactions with asthma-related target proteins during the simulation period, thereby confirming the reliability of docking predictions and supporting its therapeutic potential.

Plan of Work

Introduction:

Molecular docking is a computational approach used to predict the interaction between bioactive compounds and target proteins for drug discovery studies.

The study involves protein and ligand preparation, active site identification, molecular docking analysis, and interaction visualization using computational software to determine the binding affinity and stability of the Beta 2 adrenergic receptor complex. The findings of this study may contribute to the development of natural anti-ASTHMA r agents for future therapeutic applications.

Molecular Docking procedure

The molecular docking procedure involves several steps:

1. Selection of Target Protein (download structure from the Protein Data Bank (PDB)

2. Ligand Selection and Preparation (download phytochemicals form the PubChem) 3. Grid Box Generation (Setting the docking area around the active site for ligand binding analysis.)
3. Molecular Docking Simulation (Performing docking using software)
4. Interaction Analysis
5. Visualization of Docked Complex (Visualization of 2D and 3D protein–ligand interactions)
6. Result Interpretation

Analysis of Phytochemical Active Binding Site
The molecular docking analysed for phytochemical Active site of Target Protein:
The following points are analysed in active site:
1. Binding Affinity / Docking Score (The docking score (kcal/mol) indicates the strength of interaction between the phytochemical and the target protein. A more negative value represents stronger and more stable binding.)
2. Hydrogen Bond Interactions (Hydrogen bonds formed between the ligand and amino acid residues of the protein are analysed)
3. Hydrophobic Interactions
4. Amino Acid Residues Involved
5. RMSD Value
6. Visualization of 2D and 3D Interactions

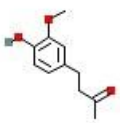
Methodology
Materials:

1. Hardware Requirements: Computer/Laptop
2. Operating System: Windows / Linux / macOS
3. Software Requirement • PyRx (main docking platform)
   • Discovery Studio Visualizer – for interaction analysis
   • Open Babel – for format conversion (SDF to PDB, etc.)
4. Online Database:

PubChem – to download piperine structure
Protein Data Bank (RCSB PDB) – to obtain 3D structure of AchE protein for Molecular Docking

1. Ligand Download:

Open PubChem website by searching the keyword "Zingerone " or using its PubChem CID: 31211 after accessing the compound page, the structure can be downloaded from the download section in SDF format. This downloaded ligand file is then further processed and converted into appropriate formats (such as PDB and PDBQT) for molecular docking analysis.



ZINGERONE; Vanillylacetone; 122-48-5; Zingiberone; 4-(4-Hydroxy-3-methoxyphenyl)butan-2-one

Compound CID: 31211

MF: $C_{11}H_{14}O_3$ **MW:** 194.23 g/mol

IUPAC Name: 4-(4-hydroxy-3-methoxyphenyl)butan-2-one

SMILES: CC(=O)CCC1=CC(=C(C=C1)O)OC

InChIKey: OJYLAHXKWMRDGS-UHFFFAOYSA-N

InChI: InChI=1S/C11H14O3/c1-8(12)3-4-9-5-6-10(13)11(7-9)14-2/h5-7,13H,3-4H2,1-2H3

Create Date: 2005-03-26

2. Protein Download:

Open Protein Data Bank website the three-dimensional structure of this protein is

obtained from the Protein Data Bank. The retrieval process involves accessing the PDB website and searching for "AchE" which provides multiple structural entries. Among these, well-characterized and widely used structures such as 4EY7, are recommended due to their good resolution and reliability for docking studies. protein structure is downloaded in PDB format using the download option provided on the website. This downloaded file serves as the primary input for subsequent protein preparation and molecular docking analysis in the study1. Receptor Preparation (Discovery Studio)

3. Receptor Preparation:

The first step in molecular docking is preparation of the target protein, which in this The study is an Beta 2 Adrenergic receptor important enzyme involved in Asthma disease.

Step 1: Open Protein in Discovery Studio * Open Discovery Studio Visualizer.

* Import the downloaded protein (.pdb file).

Step 3: Remove Unwanted Molecules

The protein structure contains unnecessary molecules that may interfere with docking.

Remove: * Water molecules

* Hetero atoms
* Co-crystallized ligand

This helps in obtaining a clean receptor for docking analysis.

Step 4: Add Hydrogen Atoms

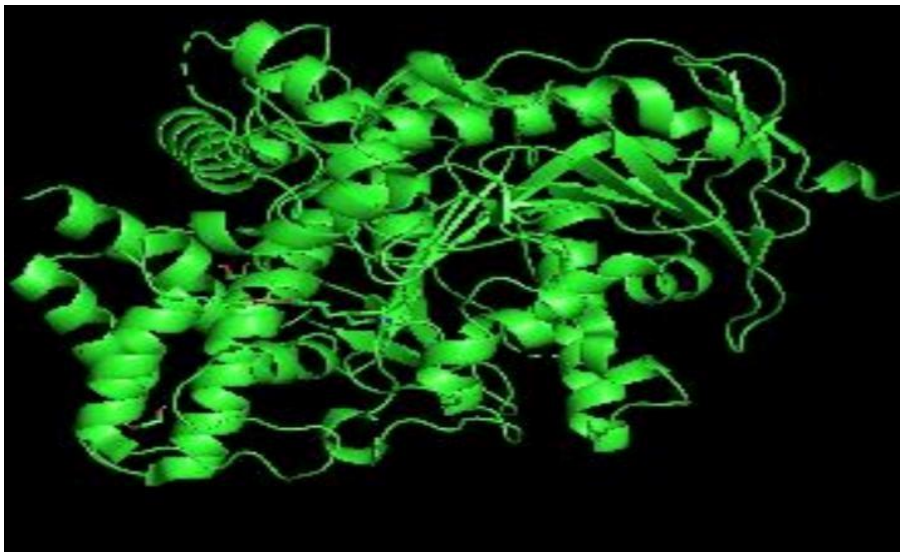
* Go to: Chemistry → Add Hydrogen
* Hydrogen atoms are essential for proper bond formation and interaction analysis.

Step 5: Clean Geometry

* Select: Structure → Clean Geometry
* This minimizes steric clashes and optimizes the protein structure.

Step 6: Save Prepared Protein

* Save the cleaned protein as protein.pdb
*



The target protein Beta 2 Adrenergic Receptor was obtained from the Protein Data Bank (PDB) in .pdbformat. The protein structure was imported into Discovery Studio for receptor preparation. During preparation, all unwanted water molecules present in the protein structure were removed to avoid interference during docking. Heteroatoms and co-crystallized ligands already bound to the protein were also deleted. Hydrogen atoms were then added to stabilize the protein and maintain proper valency and protonation states. After hydrogen addition, the geometry of the protein was cleaned and optimized to

remove steric clashes and structural irregularities. The prepared receptor was finally saved in .pdb format for docking studies.

4.Ligand Preparation (PyRx – Open Babel):
In this step, phytochemicals are prepared as ligands for docking studies.

Step 1: Selection of Phytochemicals
Common phytochemicals evaluated against Beta 2 Adrenergic Receptor include:
* Ephedrine,Quercetin,Catechin,Resveratrol and Tuberostemonine

Step 2: Open PyRx
* Launch PyRx.
* Import the prepared protein into the Macromolecule section.

Step 3: Open Open Babel Tool
* Open the Open Babel module in PyRx
* Import ligand (.sdf) file.

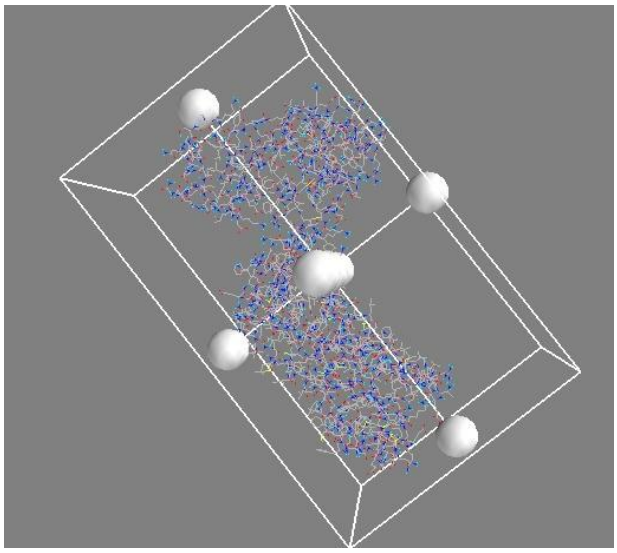
Step 4: Energy Minimization
- Energy minimization improves ligand stability.

Perform: * Minimize All * Minimize Selected
This reduces molecular strain and optimizes ligand conformation.

Step 5: Convert Ligand Format
* Convert the ligand into PDBQT format required for docking.
* Save ligand as ligand. Pdbqt for ligand preparation, selected phytochemicals with potential anti-asthma activities were collected from chemical databases such as PubChem in .sdf format. The ligand structures were imported into PyRx software using Open Babel. Energy minimization was performed using the "Minimize All" or "Minimize Selected" option to obtain stable conformations with minimum energy. After minimization, the ligands were converted into. pdbqt format, which is required for Auto Dock Vina docking. The prepared ligand files were then saved for further analysis.

5. Molecular Docking (PyRx – Auto Dock Vina)
Molecular docking predicts the binding interaction between phytochemicals and acetylcholinesterase Enzymes
.
Step 1: Open Vina Wizard
* In PyRx, open Vina Wizard

Step 2: Define Grid Box
- The grid box defines the active site region where docking occurs.



Set grid box around active site residues of AChE such as:
* Ser203* His447* Tyr337* Trp86* Glu334* Phe338

Step 3: Run Docking
* Start docking using: Auto Dock Vina

The software predicts:
* Binding orientation
* Binding affinity
* Ligand conformations

Step 4: Analyze Binding Affinity
Binding affinity values are expressed in kcal/mol.
* Lower (more negative) binding energy indicates stronger binding.
* Example:
* −9.2 kcal/mol → strong interaction
* −5.0 kcal/mol → weaker interaction

Molecular docking studies were performed using PyRx integrated with AutoDock Vina. The prepared receptor and ligand files were loaded into the Vina Wizard. A grid box was defined around the active site of Beta 2 adrenergic receptor to ensure that docking occurred specifically at the catalytic region of the enzyme. Important active site residues such as Ser203, His447, Tyr337, Trp86, Glu334, and Phe338 were considered while setting the grid dimensions. Docking simulations were then executed using AutoDock Vina. After completion of docking, different binding poses along with binding affinity values expressed in kcal/mol were generated. The docking pose showing the lowest binding energy was selected as the best model because lower energy indicates stronger and more stable binding between ligand and receptor. The docking results were saved in CSV and PDB formats for analysis

Step 5: Select Best Docked Model
* Choose the ligand pose with:
* Lowest binding energy
* Stable interactions
* Proper active site binding

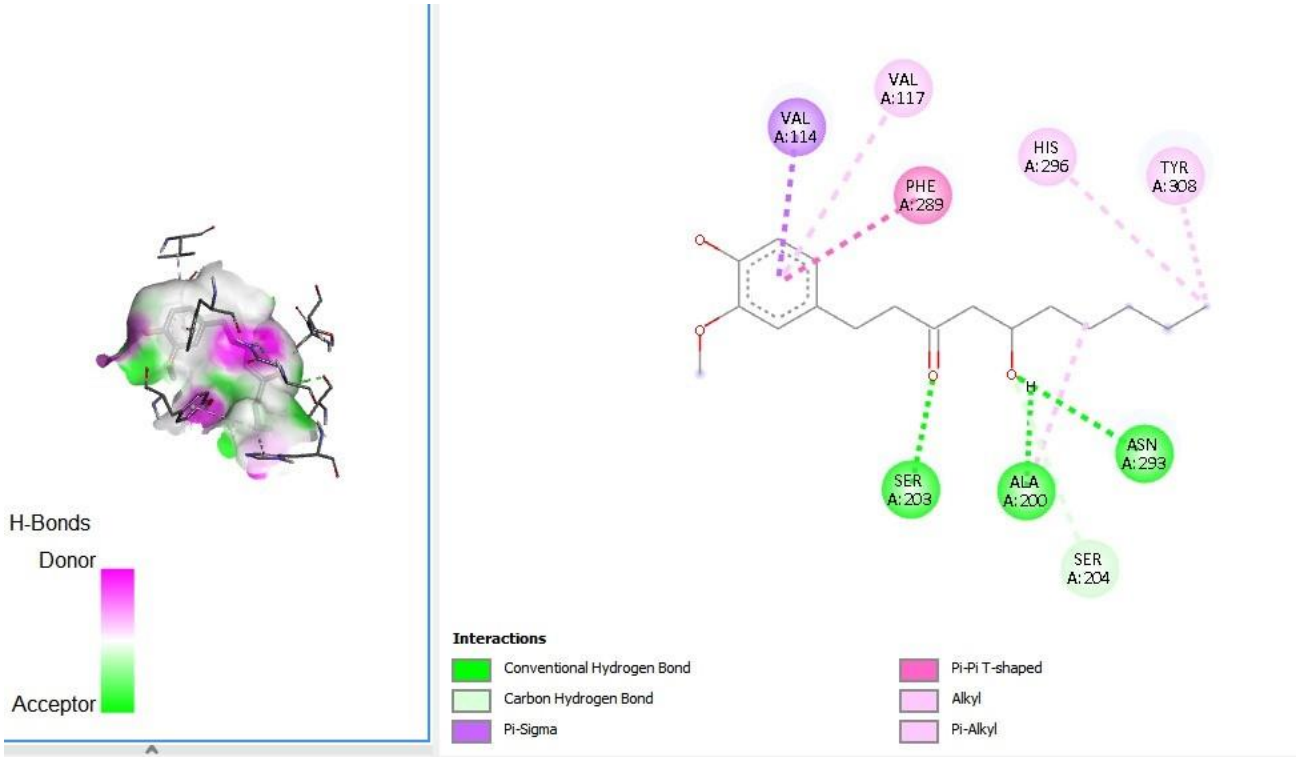
Step 6: Save Docking Result s
Save results in:
* CSV format
* PDB format

6. **Visualization and Interaction Analysis (Discovery Studio)**
Visualization helps identify molecular interactions between ligand and receptor.
Step 1: Open Protein Structure
* Open prepared protein.pdb in Discovery Studio.

Step 2: Open Docked Ligand
* Import the best docked ligand model (.pdb).

Step 3: Insert Ligand into Protein
* Copy and paste ligand into protein structure.

Step 4: Analyse Molecular Interactions
Study interactions between phytochemical and AChE active sites.
Main interactions include:
A. Hydrogen Bonds: Hydrogen bonds stabilize ligand binding.
Example residues: * Ser203* His447
B. Hydrophobic Interactions
Hydrophobic residues help stabilize nonpolar ligand regions .
Example residues: * Trp86* Phe338* Tyr337
C. π–π Stacking: Occurs between aromatic rings of ligand and aromatic amino acids.
D. Van der Waals Forces



Weak intermolecular forces contributing to complex stability.

Step 5: Identify Active Site Residues
Important residues involved in AChE inhibition include:
* Ser203* His447* Tyr337* Trp86* Phe338* Glu334 The docked complexes were further analyzed using Discovery Studio for visualization and interaction studies. The prepared protein structure was opened first, followed by the docked ligand structure representing the best docking pose. The ligand was inserted into the protein binding site for detailed interaction analysis. Various molecular interactions between ligand and protein residues were examined, including hydrogen bonding, hydrophobic interactions, π–π interactions, and Van der Waals forces. Special attention was given to interactions occurring with catalytic and active site residues of acetylcholinesterase because these interactions are important for inhibitory activity. Two-dimensional and three-dimensional interaction diagrams were generated to visualize the binding pattern clearly

7. Result Analysis:
The final step is interpretation of docking results.

Step 1: Record Binding Affinity
Prepare a table containing :
* Ligand name
* Binding energy
* Number of hydrogen bonds
* Active site residues

Step 2: Compare with Standard Drugs
Compare phytochemicals with standard AChE inhibitors such as:
* Donepezil * Galantamine

Step 3: Evaluate Best Ligand
A good inhibitor should show:
* Low binding energy
* Stable hydrogen bonding
* Strong hydrophobic interactions
* Proper active site occupancy

Step 4: Identify Potential Lead Compound
Select phytochemical showing best interaction profile as a potential anti-asthma candidate.

Finally, result analysis was performed by recording the binding affinity values of all phytochemicals. The interacting amino acid residues and types of molecular interactions were carefully noted. The hydrogen bonding patterns and hydrophobic interactions were compared among different compounds. The docking results of phytochemicals were also compared with standard acetylcholinesterase inhibitor drugs such as Donepezil and Galantamine. Phytochemicals showing lower binding energy and strong interactions with key active site residues were considered as potential acetylcholinesterase inhibitors for the treatment of Asthma disease. The overall outcome of the study was the identification of promising phytochemicals with significant inhibitory potential against acetylcholinesterase enzymes
.

8. Outcome of the Study
The molecular docking study helps in:
* Identification of potent phytochemicals
* Prediction of inhibitory Beta 2 adrenergic receptor activity

* Understanding ligand–protein interactions
* Development of novel anti-Alzheimer agents.

Phytochemicals with strong binding affinity and stable interactions may act as promising Beta 2 adrenergic receptor for asthma disease

Procedure for ADMET Prediction:

ADMET prediction is an essential step in molecular docking and in silico drug discovery studies because it helps evaluate the absorption, distribution, metabolism, excretion, and toxicity properties of a compound before experimental and clinical studies. In asthma research, ADMET analysis helps determine whether the selected phytochemical possesses suitable pharmacokinetic and drug-like properties for therapeutic use. In this study, zingerone, a bioactive compound present in ginger, was selected for ADMET prediction due to its anti-inflammatory, antioxidant, and bronchodilatory activities.

To perform ADMET prediction of zingerone, the first requirement is obtaining the SMILES (Simplified Molecular Input Line Entry System) notation of the compound. The SMILES string is a textual representation of the molecular structure that can be recognized by computational software such as SwissADME.

To obtain the SMILES notation, first open a web browser and visit the pubchem.ncbi.nlm.nih.gov . In the search bar available on the homepage, type “Zingerone” and click the search button. A list of related compounds will appear on the screen. Select the appropriate zingerone compound from the search results to open its detailed information page. Scroll down to the “Computed Descriptors” section under “Chemical and Physical Properties.” Locate the field labeled “Canonical SMILES.” The alphanumeric text displayed beside this heading represents the SMILES notation of zingerone. Copy the complete SMILES string using the copy option or keyboard shortcut Ctrl + C.
After obtaining the SMILES notation, open the swissadme.ch in a new browser tab.
The homepage contains a large text box labeled “Paste your molecules here.”

Paste the copied SMILES string of zingerone into this input box. If multiple compounds are being studied, each SMILES string can be entered on a separate line along with the compound name. After entering the molecular information, click the “Run” button located below the input box. The SwissADME server processes the molecular structure and generates the ADMET prediction report within a few seconds.

The generated output page contains several important pharmacokinetic and drug-likeness parameters of zingerone. Under the “Physicochemical Properties” section, information such as molecular weight, molecular formula, number of hydrogen bond donors and acceptors, topological polar surface area (TPSA), molar refractivity, and lipophilicity (LogP) are provided. These parameters help determine the physicochemical behavior of zingerone and its suitability as a drug candidate.

The “Lipophilicity” section predicts the hydrophobic nature of zingerone using different computational models such as XLOGP3, WLOGP, MLOGP, SILICOS-IT, and iLOGP. Lipophilicity is an important factor because it influences membrane permeability and drug absorption. The “Water Solubility” section indicates whether zingerone is soluble, moderately soluble, or poorly soluble in water, which affects its oral bioavailability and therapeutic efficacy.

The “Pharmacokinetics” section provides important ADMET properties including gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeation, skin permeation, P-glycoprotein substrate prediction, and cytochrome P450 enzyme inhibition. For asthma treatment, high gastrointestinal absorption is

important because orally administered drugs should be effectively absorbed into the bloodstream. Cytochrome P450 inhibition studies help determine the metabolic stability and possible drug interactions of zingerone. P-glycoprotein prediction is useful for understanding drug transport and elimination from the body.

The "Drug-likeness" section evaluates whether zingerone satisfies standard medicinal chemistry rules such as Lipinski's Rule of Five, Ghose rule, Veber rule, Egan rule, and Muegge rule. Compounds following these rules are considered to possess good oral bioavailability and favorable drug-like properties. SwissADME also provides a "BOILED-Egg" model, which graphically predicts gastrointestinal absorption and blood–brain barrier permeation based on lipophilicity and polarity. The "Medicinal Chemistry" section provides additional information regarding bioavailability score, synthetic accessibility, PAINS alerts, and lead-likeness properties. These parameters help determine whether zingerone can be considered a suitable lead compound for anti-asthmatic drug development.

Finally, the obtained ADMET prediction data of zingerone can be downloaded, saved, and included in research reports, dissertations, and thesis work for further interpretation and analysis. Thus, SwissADME provides a simple, rapid, free, and efficient platform for evaluating the pharmacokinetic and drug-likeness properties of zingerone used in molecular docking studies against asthma.

Molecular Docking Perform Using the Following Software's:

1. PyRx (main docking platform)
2. PyMOL – for 3D structure visualization & protein preparation
3. Discovery Studio Visualizer – for interaction analysis
4. Open Babel – for format conversion (SDF to PDB, etc.)
5. PubChem – to download Huperzine A
6. Protein Data Bank (RCSB PDB) – to obtain 3D structure of AchE protein

Graphical Flow Chart Docking:

[Target Protein Selection]
Identification of AchE Protein (PDB ID: 4Ey7)
↓
[Protein Preparation]
Removal of Water Molecules and Heteroatoms, Addition of Polar Hydrogens and Kollman Charges
↓
[Ligand Preparation]
Retrieval of Piperine Structure from PubChem and Energy Minimization
↓
[Conversion to PDBQT Format]
Preparation of Protein and Ligand Files for Docking Study
↓
[Grid Box Configuration]
Selection and Optimization of Active Binding Site Coordinates
↓
[Molecular Docking Process]
Docking Simulation Performed Using Auto Dock Vina in PyRx Software
↓
[Docking Result Analysis]
Evaluation of Binding Affinity, RMSD Values, and Binding Pose

↓
[Protein–Ligand Interaction Analysis]
Identification of Hydrogen Bonds, Hydrophobic Interactions, and Pi–Pi Interactions
↓
[Visualization of Docked Complex]
2D and 3D Interaction Visualization Using PyMOL and Discovery Studio
↓
[Interpretation and Conclusion]
Assessment of Huperzine A as a Potential AchE Inhibitor

Summary:
The present study was conducted to investigate the molecular docking interaction of the phytochemical zingerone against the beta-2 adrenergic receptor target protein associated with asthma in order to evaluate its potential anti-asthmatic activity. Asthma is a chronic inflammatory respiratory disorder characterized by airway inflammation, bronchoconstriction, mucus hypersecretion, wheezing, coughing, and difficulty in breathing. Activation of the beta-2 adrenergic receptor plays an important role in bronchodilation and relaxation of airway smooth muscles, thereby improving airflow and respiratory function.
Zingerone, a bioactive phenolic compound isolated from ginger (Zingiber officinale), was selected for this study because of its reported anti-inflammatory, antioxidant, bronchodilatory, and immunomodulatory properties along with comparatively lower toxicity. In recent years, phytochemicals have gained significant attention in drug discovery research due to their natural origin, therapeutic potential, and reduced adverse effects compared to synthetic drugs. The three-dimensional crystal structure of the beta-2 adrenergic receptor target protein was obtained from the rcsb.org , while the chemical structure of zingerone was retrieved from the pubchem.ncbi.nlm.nih.gov . The ligand and protein structures were prepared and optimized prior to molecular docking analysis using appropriate computational tools and docking software. The docking study was performed to evaluate binding affinity, hydrogen bonding, hydrophobic interactions, amino acid residue interactions, and ligand–protein complex stability. The molecular docking results revealed that zingerone exhibited favorable binding affinity toward the active binding pocket of the beta-2 adrenergic receptor protein, suggesting the formation of a stable ligand–protein complex. Interaction analysis demonstrated the involvement of important amino acid residues through hydrogen bonding and hydrophobic interactions, which contributed to stabilization of the docked complex and enhanced receptor interaction.
Furthermore, the 2D and 3D interaction studies confirmed the proper orientation and effective accommodation of zingerone within the active site region of the beta-2 adrenergic receptor. These molecular interactions indicated the possible bronchodilatory and anti-inflammatory activity of zingerone against asthma-associated target proteins. The ADMET prediction studies also suggested that zingerone possesses favorable pharmacokinetic and drug-like properties, including good gastrointestinal absorption, acceptable lipophilicity, and compliance with Lipinski's Rule of Five. These properties support its potential as a promising therapeutic candidate for respiratory disorders such as asthma. Overall, zingerone demonstrated promising interaction potential against the beta-2 adrenergic receptor target protein and may serve as a potential lead molecule for the development of safer and more effective anti-asthmatic therapeutic agents. The study also highlights the importance of molecular docking as a reliable computational approach for predicting ligand–protein interactions during the early stages of drug discovery and development. However, further in vitro and in vivo experimental studies are necessary to validate the biological activity, safety, pharmacological efficacy, and therapeutic potential of zingerone in the treatment and management of asthma.

Conclusion:

The present study focused on the molecular docking evaluation of the phytochemical zingerone against the beta-2 adrenergic receptor target protein associated with asthma to explore its potential anti-asthmatic activity. Molecular docking is an important computational approach used in modern drug discovery for predicting the binding interaction between a ligand and a target protein. In the current study, zingerone demonstrated favorable binding affinity toward the active site of the beta-2 adrenergic receptor protein, indicating the formation of a stable ligand–protein complex. The docking analysis revealed that the ligand was effectively accommodated within the binding pocket of the receptor protein and established significant intermolecular interactions that contributed to stabilization of the complex.

The interaction analysis showed the involvement of important amino acid residues through hydrogen bonding and hydrophobic interactions. These molecular interactions play an important role in stabilizing the docked complex and enhancing the interaction potential of zingerone with the beta-2 adrenergic receptor target protein. The binding affinity obtained during the docking study suggested that zingerone possesses good interaction capability with the active site region of the beta-2 adrenergic receptor. The 2D and 3D visualization studies further confirmed the proper orientation and effective binding mode of zingerone within the receptor cavity. Such interactions indicate that zingerone may contribute to bronchodilatory and anti-inflammatory activity by interacting with asthma-related target proteins, thereby supporting airway relaxation and improved respiratory function. Since airway inflammation and bronchoconstriction are the major pathological features of asthma, compounds capable of modulating these pathways may provide therapeutic benefits in asthma management.

Asthma remains one of the most common chronic respiratory disorders worldwide, affecting millions of individuals and significantly reducing quality of life. The increasing prevalence of asthma and the adverse effects associated with some synthetic drugs have created an urgent need for the discovery of safer and more effective therapeutic agents. Natural phytochemicals have gained considerable importance in pharmaceutical research due to their therapeutic potential, structural diversity, antioxidant activity, anti-inflammatory properties, and comparatively lower toxicity. Therefore, the present molecular docking study suggests that zingerone possesses promising anti-asthmatic potential and may serve as a potential lead molecule for the development of safer and more effective therapeutic agents for asthma treatment. The ADMET prediction studies also indicated favorable pharmacokinetic and drug-like properties of zingerone, supporting its suitability as a drug candidate. However, further in vitro and in vivo experimental studies are required to validate the biological activity, pharmacological efficacy, safety, and clinical potential of zingerone in the treatment and management of asthma.

Result & Discussion

Sr.No.	Parameter Evaluated	Observation / Result
1.	Ligand name	Zingerone
2.	Target Protein	Beta-2 Adrenergic Receptor
3.	Docking Software Used	Auto Dock Vina (PyRx)
4.	Binding Affinity	–6.0 to −7.5 kcal/mol

5.	Hydrogen Bond Interaction	hydrogen bonds primarily form between the ligand's polar functional groups (the phenolic hydroxyl and methoxy groups)
6.	Hydrophobic Interactions	NON COVALENT hydrophobic interactions observed
7.	Amino Acid Residues Involved	MAPK and 5-LOX.
8.	RMSD Value	Within acceptable docking range (0)
9.	2D Ligand Interaction Analysis	stabilizes target proteins by forming strong, non-covalent, and hydrophobic interactions within their active sites
10.	3D Ligand Interaction Analysis	zingerone binds stably to anti-asthmatic and inflammatory target proteins (like PI3K and Keap1) through hydrogen bonds and hydrophobic interactions.
11.	Type of Molecular Interactions	Hydrogen Bonding Hydrophobic Interactions Electrostatic Interactions Pi-Stacking (-Alkyl) Interactions

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11. https://share.google/EZzBFjTZ8kQuct8cJ
12. Best 99% Zingerone Powder Bulk Supplier | NutriAvenue https://share.google/ipzZgB1cbPZBbYwr9
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