



Received on 25 May 2021; received in revised form, 09 June 2021; accepted, 10 June 2021; published 01 July 2021

RECENT DEVELOPMENT IN THE FORMULATIONS OF GINGER FOR THERAPEUTIC APPLICATIONS AND AN OVERVIEW TOWARDS THE ACTION ON SARS-COV-2.

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Keywords:

Ginger, Chemical constituents, Therapeutic action, Novel formulations, SARS-CoV-2.

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ABSTRACT: Ginger or *Zingiber officinale*, Roscoe of the *Zingiberaceae* family is a rhizome that is widely found and most consumed in South east Asian countries; also used as a traditional remedy to treat various ailments like nausea, vomiting, pain, arthritis, indigestion, gastro reflux, cardiovascular disease, diabetes, obesity, microbes, cancer, inflammation, oxidation, and wounds to name some of its activity which is based on the various chemical constituents present in ginger as it is found to contain more than 400 different compounds which include sugar, protein, and fats. The major phenolic active constituents of ginger are 6-gingerol, 6-shogaol and 6-paradol; which are safe and showing only a few insignificant adversarial effects. Here, this review aims to summarize and discuss the ideas on how ginger is formulated and improve from conventional to novel formulations using novel techniques; to improve the pharmacological, biopharmaceutical and chemical properties of ginger extract and its compounds. Different novel formulations of ginger like a tablet, capsule, powder, cream, gel, transdermal patch, nanoparticles, liposomes and phytosomes along with its therapeutic actions that were developed in recent years. Future aspects in research are suggested for the advances in the novel formulation of ginger using each isolated compound and improving bioavailability, therapeutic effect, and delivery. Also, this article discusses the *in silico* studies that have been carried out for ginger and its phytochemicals that may be considered as potential agents in the treatment of SARS-CoV-2.

INTRODUCTION: Natural medicinal products or herbal medicines have been taken as supplements or as medicines, and they are considered to be an alternative medicine in treating or preventing diseases. The uses of natural therapies have been most preferred by consumers.

Though it is partially true, most people fallaciously believe that herbal products are superior, safe (no side effects) and much effective than allopathic medicines.

The secondary metabolites present in medicinal plants like phenolics, alkaloids, saponins, terpenes, lipids, and carbohydrates are substantially important in preventing the onset of many degenerative diseases like cancer, tumors¹ high-cholesterol, aging activities² and many others. Ginger or *Zingiber officinale*, Roscoe of the *Zingiberaceae* family, is a rhizome that is widely found and most consumed in Southeast Asian

<p>QUICK RESPONSE CODE</p> 	<p>DOI: 10.13040/IJPSR.0975-8232.12(7).3537-48</p> <hr/> <p>This article can be accessed online on www.ijpsr.com</p> <hr/> <p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(7).3537-48</p>
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countries, and it has been used in cooking as a spice for a very long time and also as a traditional remedy to treat various ailments such as nausea, vomiting, pain, arthritis, indigestion, gastro reflux, etc. In addition to these, several uses of ginger have found to be useful in treating, managing, or preventing diseases like cardiovascular disease, diabetes³, respiratory disease⁴, obesity⁵, nausea and vomiting induced by chemotherapy⁶ and in neurodegenerative diseases; it also in-holds some of the biological properties like antimicrobial⁷, anti-inflammation⁸, antioxidant⁹, anticancer¹⁰, and wound healing properties¹¹.

Apart from these many therapeutic activities, ginger may also be considered to be the plant that can treat or help the patient with SARS-CoV-2. Herbal products are obtainable in many different forms; the conventional forms are tablets, capsules, extracts, powders, oils, syrups, creams, ointments, and several others. The novel forms of the formulation are phytosome, niosome, liposomes, marinosome, phytosome, nanoparticles, and so on; novel formulations of herbal extracts overcome the limitations by helping in increasing the bioavailability, increase patient's compliance, and helps in reducing toxicity¹². Here, the aim is to summarize the different chemical constituents and formulations of ginger along with its applications, and also this article discusses the *in silico* studies that have been carried out for ginger and its phytochemicals that may be considered as potential agents for the treatment of SARS-CoV-2.

Chemical Constituents of Ginger: Ginger being the most used spice worldwide contains more than 400 different compounds¹³, including sugar, protein, and fats. The major phenolic active constituents of ginger are 6-gingerol, 6-shogaol and 6-paradol¹⁴ where gingerols and shogaols are accountable for the pungent taste and are bioactive compounds of ginger rhizomes. In addition, gingerols are thermolabile and get converted to shogaols due to dehydration, and these shogaols are more pungent than gingerols. A part from the pungent compounds, ginger rhizome comprises compounds that are volatile and oily; detected by gas-chromatography/ mass spectroscopy (GC/MS). Three major classes of compounds found in the essential oils are sesquiterpenoids, monoterpenoids, and aldehydes, and from these, the following

constituents are identified, namely α -curcumene, α -farnesene, β -bisabolene, β -sequiphellandrene and zingiberene¹⁵. About 30% of Zingiberene contributes to the essential oil found in the ginger rhizome. With modern chemical excipients like GalenIQ 721, Kollidon K30, Neusilin UFL2, and calcium stearate were formulated by direct compression method, for the treatment of type 2 score (analysis to evaluate the effects of the supplement in the knee function) was obtained by significantly increasing the chances to be rated in the highest Lysholm' category in respect of combined lower ones diabetes Polysaccharides, organic acids, fibers and lipids are also found to contains in the rhizome¹⁶. Research in recent years suggested that the compounds present in ginger rhizome are very potent and useful in the cure and management of different diseases including cancer, tumors, allergic reaction, cough, and inflammation.

Different chemical constituents of ginger rhizome (*Zingiber officinale*) are described in **Fig. 1.** with different chemical structures of (a) Zinger one (4-(4-Hydroxy-3-methoxyphenyl)- 2- butanone), (b) Gingerol (5-hydroxydecan-3-one), (c) β -phell and rene ((5S)- 2-methyl- 5-propan- 2-ylcyclohexa-1,3-diene), (d) Zingiberene ((5R)-2-methyl-5-[(2S)-6-methylhept-5-en-2-yl]-cyclohexa-1,3-diene), (e) β -sesquiphellandrene (3-(6-methylhept-5-en-2-yl)-6-methylidencyclohexene), (f) 1, 4-cineol (1-methyl-4-propan-2-yl-7-oxabicyclo[2.2.1]heptane), (g) Shogaol ((E)-1-(4-hydroxy-3-methoxyphenyl) dec-4-en-3-one), (h) Farnesene ((3E,6E)-3,7,11-trimethyldodeca-1, 3 6, 10-tetraene), (i) Limonene (1- methyl- 4- prop- 1- en- 2-ylcyclohexene), (j) Geraniol ((2E)-3, 7-dimethylocta-2 ,6-dien-1-ol), (k) Citral ((2E)-3, 7-dimethylocta-2, 6-dienal), (l) Camphene (2, 2-dimethyl-3 -methylidenebicyclo [2.2.1]heptane), (m) α -terpineol (2-[(1S)-4-methyl cyclohex-3-en-1-yl]propan-2-ol), (n) 6-paradol (1-(4- hydroxy- 3-methoxyphenyl)decan- 3- one), (o) Curcumene (1-methyl- 4- (6- methylhept -5- en-2-yl)benzene), (p) Borneol (1, 7, 7-trimethylbicyclo [2.2.1] heptan-2-ol), (q) β -elemene ((1S, 2S, 4R)-1-etheny l- 1- methyl-2, 4-bis(prop-1-en-2-yl)cyclohexane), (r) *Zingiberenol* (1-methyl-4-(6-methylhept-5-en-2-yl) cyclohex-2-en-1-ol), (s) Linalool (3, 7-dimethylocta-1, 6-dien-3-ol), along with their biological or therapeutic activities that is described in **Table 1.**

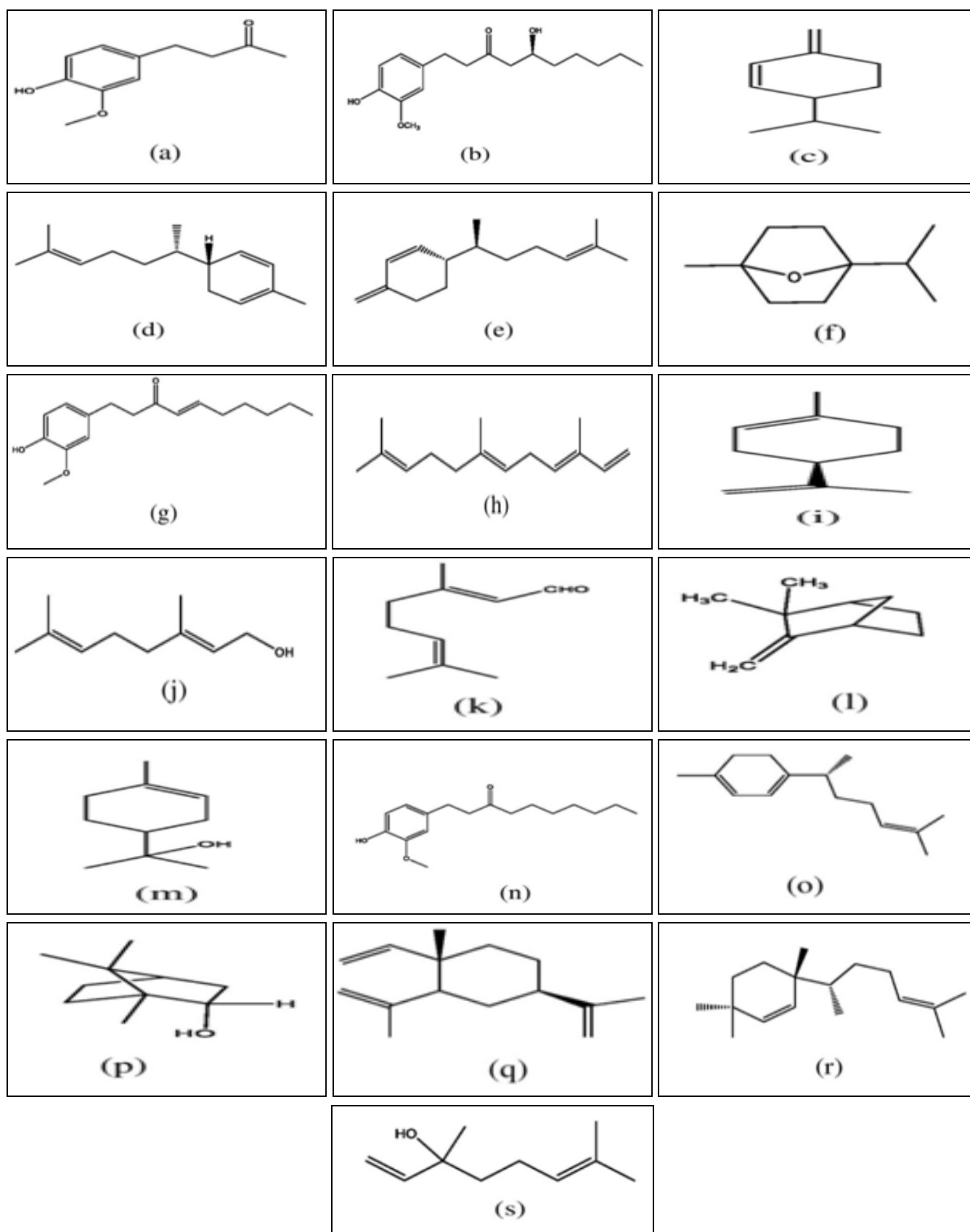


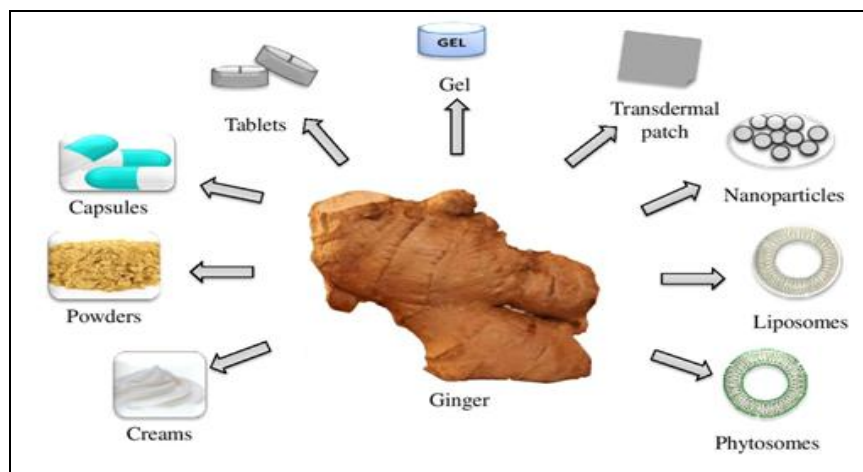
FIG. 1: DIFFERENT CHEMICAL STRUCTURES OF CHEMICAL CONSTITUENTS FOUND IN GINGER (*ZINGIBER OFFICINALE*). (A) ZINGERONE, (B) GINGEROL, (C) B-PHELLANDRENE, (D) ZINGIBERENE, (E) B-SESQUIPELLANDRENE, (F) 1,4-CINEOL, (G) SHOGAOL, (H) FARNESENE, (I) LIMONENE, (J) GERANIOL, (K) CITRAL, (L) CAMPHENE, (M) A-TERPINEOL, (N) 6-PARADOL, (O) CURCUMENE, (P) BORNEOL, (Q) B-ELEMENE, (R) ZINGIBERENOL, (S) LINALOOL

TABLE 1: DIFFERENT CHEMICAL CONSTITUENTS FOUND IN GINGER WITH THEIR THERAPEUTIC ACTIVITIES

Compound name	Activity	References
Zingerone	Anti-inflammatory, anti-lipolytic, antidiabetic, antidiarrhoeic, antispasmodic, growth enhancement, immune stimulation, appetite stimulant, antithrombotic, antimicrobial, anxiolytic, inhibiting reactive nitrogen species in Alzheimer's, and radiation protection.	17
Gingerol	Anticancer, antioxidant, anti-inflammatory, anti-nausea, anti-vomiting, gastro-protective agent, anti-proliferation, antitumor, and many more.	18 19
Zingiberene	Antimicrobial, anti-dermophyte (effects on <i>A. flavus</i>), inhibits <i>Fusarium verticillioides</i> , an antioxidant, bronchodilator, anti-inflammatory, analgesic, anticancer (nucleosomal DNA fragmentation), anti-ulcer.	20
β -sesquiphellandrene	Antimicrobial, antioxidant, bronchodilator, anti-inflammatory, analgesic, anticancer (against HepG2 and HeLa cells), anti-ulcer.	20
Shogaol	Anticancer, antioxidant, anti-ulcer, antimicrobial, cardiovascular, neuroprotective substance, and many uncountable medicinal uses.	21
β -phellandrene	Antimicrobial, anti-inflammatory for arthritis.	22, 23
Farnesene	Anti-inflammatory.	24
1,4-cineol	CNS depressant and fumigant insecticide.	25
Citral	Precursor of Vitamin A, anti-mycobacterial, antioxidant, hypoglycaemic, anti-malarial, and anti-mutagenicity.	26
Camphene	Chronic obstructive pulmonary disease, hypolipidemic.	27
6-paradol	Anticancer, anti-hyperglycaemic.	28
Curcumene	Antimicrobial, anti-inflammatory, antioxidant.	29
α -terpineol	Anticancer, antiulcer, antioxidant, anticonvulsant, antinociceptive compound, antihypertensive.	30
Borneol	Treats bronchitis, cold, cough, reduces pain caused by sprains and rheumatism, reduces stress, and anti-inflammatory.	31
β -elemene	Anti-tumour, anticancer.	32, 33
Zingiberenol	Antifungal, antioxidant.	34
Limonene	Dissolve cholesterol-containing gallstones, relieve heartburn, neutralize gastric acid, and antimicrobial.	35
Geraniol	Antioxidant, anti-inflammatory, antimicrobial.	36
Linalool	Anti-inflammatory.	37

Different Types of Formulations: Different drug formulations given to a patient can be in various forms such as solid like tablets, capsules, powders, controlled-release tablets; semisolid like gels, creams, lotions, suppositories; or liquid-like drops, syrups, oils, parenteral. The type of formulation will depend up on different factors like the

condition of the patient, age, gender, rate of drug release, and health status of the patient, which is specific to specific routes of administration. Here in this review, different preparations concerning ginger as its constituents are being reviewed accordingly as shown in **Fig. 2**.

**FIG. 2: TYPES OF DIFFERENT FORMULATIONS OF GINGER (ZINGIBER OFFICINALE)**

Tablets: Ginger tablets are prepared by direct compressing the dry ginger extract and excipients into a tablet form along with a coating to mask the taste and improve the intake or patient's compliance. A study has been carried out recently on ginger tablets where dry ginger extract along with modern chemical excipients like Galen IQ 721, Kollidon K30, Neusilin UFL2, and calcium stearate were formulated by direct compression method, for the treatment of type 2 diabetes mellitus and showed a promising result³⁸. The ginger effervescent tablets formulated with citric acid along with tartaric acid at various levels were able to stop the vomiting³⁹ and were also able to treat common bacteria and fungi present in the oral cavity⁴⁰. With its main focus to improve the compliance of the aged people in taking tablets, oral disintegrating tablets were formulated, and a study was conducted where older adult volunteers were selected and performed the swallowing function test and reported a significant improvement in swallowing function⁴¹.

In another study, highly standardized extracts of ginger and *Acmella oleracea* were formulated by using lecithin (a new food-grade) for the management of pain and inflammation in a group of volunteers with adequate knee osteoarthritis, and the results reported that a greater Lysholm score (analysis to evaluate the effects of the supplement in the knee function) was obtained by significantly increasing the chances to be rated in the highest Lysholm' category in respect of combined lower ones by a factor of the experiment and this formulation reported to be efficacious and safe⁴².

Capsules: Dried ginger was grounded into a fine powder of about 250 mg, 500 mg or less was then filled into the capsule shell. In one of the study, the action of ginger capsules 250 mg on nausea and vomiting induced by pregnancy demonstrated that there was a higher rate of development than placebo and lessened in vomiting times was also significantly greater than placebo and it has also been recommended that a daily dose of 1g of a ginger capsule will give more promising results⁴³. In another study, it was given to patients with non-alcoholic fatty liver ailment, and a randomized clinical trial was done to define the effectiveness of ginger capsule on lipid profiles like Low-density Lipoprotein cholesterol (LDL-C) and High-density

Lipoprotein cholesterol (HDL-C), liver enzymes like Serum Gamma-Glutamyl transferase (GGT) and Alanine Amino Transferase (ALT), inflammatory cytokines like High-sensitivity C-reactive protein (hsCRP), Fasting Blood Sugar (FBS) insulin resistance and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and antioxidant status like Total Antioxidant Capacity (TCA) and Tumour Necrosis Factor-Alpha (TNF- α). The results that came out from the study were the serum alanine aminotransferase (ALT) levels, total cholesterol, low-density lipoprotein (LDL-C), level of fasting blood sugar (FBS) and insulin resistance index (HOMA), C-reactive protein (hsCRP) and fetuin-A significantly decreased in the study group which received ginger capsule than compared to the control group. While the others, there were no significant changes between the treated group and the control group. A conclusion was drawn that consuming 1500 mg of ginger capsules daily can reduce inflammation, insulin resistance, and liver enzymes in patients suffering from non-alcoholic fatty liver disease and can be used as a supporting therapy to the current therapies for these ailments⁴⁴.

Women receiving Cisplatin and undergoing mastectomy usually show side effects like nausea and vomiting, and to treat it, a new study was conducted by a randomized clinical trial where cancer patients from the 10th day after receiving Cisplatin and one week before mastectomy were given a 500 mg ginger capsule twice daily. The result came out to be productive, where the intervention group that received ginger tablets showed a significant difference in terms of nausea severity and also significantly reduced vomiting and came to a conclusion that ginger capsule is effective in these certain conditions⁴⁵.

Powder: Ginger as an analgesic and anti-inflammatory substance can be used as a substituent for NSAIDs synthetic drugs like naproxen, diclofenac, ibuprofen, celecoxib, indomethacin, and many others. A recent study was performed in healthy volunteers with a chronic generalized period on titis and treated them with dried ginger powder and ibuprofen for three days and found that there were no significant differences amongst the groups in the Visual Analogue Scale (VAS) score and gingival inflammation which was

measured by using Modified Gingival Index (MGI) and concluded that ginger powder is similar to ibuprofen and henceforth it can be used as a substitute for NSAIDs in the cure of pain and gingival swelling caused by periodontal surgery⁴⁶. Another recent study showed that consumption of ginger powder for 14 days period reduces dysmenorrhea in overweight girls, but there was no effect on aerobic power capacity⁴⁷. Also, consumption of 1500 mg of ginger powder supplement daily for 12 weeks will decrease the rheumatoid arthritis symptoms by increasing Fox P3 gene expression and by reducing ROR γ t and T-bet gene expression, which is the immunity and inflammation intermediate factors in persons with rheumatoid arthritis⁴⁸.

In patients with ulcerative colitis; oxidative stress is the main factor that initiates and worsens the ailment. As the dried ginger powder is identified to have antioxidant property, it helps in improving the treatment of patients with ulcer and reduces oxidative stress⁴⁹. It is also known to have beneficial effects on patients with metabolic syndromes (causing other chronic diseases like cardiovascular diseases, diabetes type-2, cancer, and renal diseases) by significantly improving the levels of triglyceride, fasting blood sugar and insulin resistance⁵⁰. Dried ginger rhizome has been known to treat gastrointestinal problems since a long time back, and a recent study proved that it can be used as an alternative drug in reducing functional dyspepsia affected by H. Pylori⁵¹.

Cream: Creams are semisolid emulsions, which are topically used and can be medicated or unmedicated. The medicated creams are used for wound healing, skin diseases, burns, antibacterial, antifungal, analgesic, and also a way of delivering drugs through specific sites, and many more. Certain bacteria and fungi have become resistant to certain antimicrobial drugs (creams, lotions, tablets, capsules, syrup, etc.) like *Candida albicans* to 'azoles' drugs due to the change in their genetic structure and chance of relapsing are high. Making a novel drug or modifications in the formulation is required. Some of the approaches are by incorporating herbal products and synthetic drugs to increase their activity. Ginger and clotrimazole cream was formulated as a vaginal cream for the treatment of vulvovaginal candidiasis in females,

and the results came out to be more in effect and useful than the usage of only clotrimazole alone⁵². Ginger and other plant extracts (*Harpagophytum procumbens*, *Boswellia serrate* and *escin*) in mixture with the sports cream resulted in a significant reduction in clinical symptoms and skin temperature in the cramped neck or shoulder pain⁵³.

Gel: Gels are cross-linked three-dimensional networks within the fluid that have a definite shape and soft. The main aim to formulate gels is due to its best cutaneous and percutaneous drug delivery to specific sites, avoid unwanted metabolism and topical route. Ginger is having a very short half-life so delivering the drug through the transdermal route is the best approach and gel formulation is one of them. Limited information on ginger gel formulation is there; one of the recent studies shows that ginger powder when formulated into a gel it is having good consistency, good skin feels, and homogeneity.

Though it has not been tested clinically; the *in-vitro* drug release is 99% after 2 h of application and it can be used in the treatment of rheumatoid arthritis⁵⁴ also on combining *Zingiber officinale* (ginger) with another plant like *Zingiber cassumunar* (plai) or with other drugs like NSAIDs in a gel form can be used to apply on osteoarthritis knees to reduce pain and inflammation which are common problematic symptoms of joint pain⁵⁵. In a recent study, ginger oil is used as a penetration enhancer to increase the permeation of the other plant extracts (polyherbal) which are combined to form an emulgel for use in the treatment of rheumatoid arthritis^{56,57}.

Transdermal Patch: A transdermal patch is an adhesive, medicated patch that is intended to bypass the first-pass effect and gastrointestinal disturbances or degradation by directly delivering the drug into the systemic blood circulation and provides a controlled release pattern but apart from these; skin is the main barrier to affect the drug delivery over this route and only minute and lipophilic drug molecule can easily pass through this barrier. Hence ginger is a suitable drug to be delivered by using this type of strategy. We know that ginger is having low molecular weight, is lipophilic but having a short half-life which might

denote a major drawback for the therapeutic use of ginger compositions. Formulating ginger into a transdermal patch will surmount the drawbacks of ginger by providing a long-lasting delivery and the maximal delivery percentage across rat skin was found to be more than 40% at 20 h and by this, it might provide scientific proof for the transdermal patch study of ginger⁵⁸.

Nanoparticles: Metal nanoparticles are some of the popular and a novel technique that is widely used in various fields of interest in materials chemistry like in pharmaceuticals, cosmetics, biomedical chemistry, water treatment and catalysis process. The plant-derived nanoparticles are non-immunogenic and non-toxic so they have been designed as targeting drug carriers. A study showed that a precise populace of nanoparticles derived from ginger was characterized and can be utilized in preventing inflammatory bowel disease (IBD) which includes Crohn's disease and targeting the ulcerative colitis-associated cancer; also provides management with an additional advantage of overcoming the drawbacks such as toxicity and common limitation faced with nanoparticles from synthetic polymers that are limited production scale⁸. Moreover, the ginger-derived nanoparticles were evaluated for toxicity in healthy mice and found that there was an induction of pro-inflammatory cytokines, no significant change in the colonic myeloperoxidase activity and also report to be safe in the reconstruction and surface decoration of nanoparticles derived from ginger⁵⁹.

A part from its therapeutic action, the ginger rhizome powder can be formulated into silver nanoparticles (which showed the best result than copper and nickel) where it can be used as a recoverable and reusable catalyst for the reductive hydrogenation of nitro-phenols and degradation of organic pollutants (azo dyes) that can cause harm to the surroundings⁶⁰. Several research works of plant-derived nano-vesicles (like ginger-derived nanoparticles) was considered as a novel form of nano-medicine in aspects of anti-cancer in ulcer-colitis⁶¹ anti-inflammation, modulating commensal microbiota by promoting *Lactobacillus rhamnosus* (LGG) growth in the gut⁶² tissue regeneration in case of alcohol-induced liver damage⁶³ and inhibiting *Porphyromonas gingivalis* in the oral cavity⁶⁴.

Liposomes: A liposome is a bilayer of lipid that is made of phospholipids and used as a vehicle for drug delivery of synthetic or herbal drugs and nutrients. Liposome-drug technology is not only used to encapsulate the bioactive compounds in lipid vesicles but also to carry the drug to a specific target site. Ginger can also be encapsulated into a liposome with the size of a nanoparticle (164.5 nm), which is also termed as nanoliposome; where it can be used as a natural antioxidant in foods, drugs, and in biological systems instead of synthetic preservatives which can cause chronic health complications⁶⁵. Also, a study was conducted where different natural antioxidant plants or spices were incorporated in phosphatidylcholine and found that ginger extract shows the greatest effect (24%) and also reported that complexation of the ginger extract-liposomes with a protein will decrease the antioxidant efficacy.

Knowing the effects of natural antioxidants and bio polymers on phosphatidylcholine-liposome properties can be used as a strategy in liposome-based systems for drug-targeting delivery and nutraceuticals⁶⁶. Lipids can be extracted from ginger nanoparticles and can be loaded with various components, like the siRNA-CD98 vector as a vehicle to target CD98 gene expression (which plays an important part in colitis and colitis-associated cancer) in the colon tissues⁶¹. Due to the lipophilicity of ginger constituents (6-shogaol), it makes the drug poorly or slightly soluble in the aqueous solution and shows low bioavailability. To overcome this problem, the active constituent (6-shogaol) was incorporated into liposomes coated with D- α -tocopheryl polyethylene glycol succinate (TPGS) a derivative of vitamin E (aqueous soluble) which intensively persist the half-life of the drug in the plasma to increase the oral bioavailability and making it a suitable carrier candidate for brain targeting⁶⁷. Another study showed that a novel proliposome was formulated to overcome the water insolubility of 6-gingerol, which enhanced the oral bioavailability and significantly improved the antitumor activity⁶⁸.

Phytosomes: A phytosome is a cell-like structure, an advanced herbal formulation that surrounds the plant extract by a layer of lipid increasing bioavailability and stability. Combined extract of

ginger rhizome along with mulberry fruit (1:1) was formulated together into a phytosome with phosphatidylcholine as an encapsulation matrix which improves the anti-inflammatory and antioxidant properties of the phytosome-combined extract than the conventional formulation. This phytosome can be used to target the adipose tissue to exhibit the antimetabolic syndrome effect but failed to show the dose-response study because of the involvement of multiple factors⁶⁹. In another study, gingerol is being formulated into phytosome (nanoparticle-based) and implemented in complexation with the chitosan approach. In this study, the phytosome was formulated by mixing ginger with soy lecithin in an organic solvent using an anti-solvent preference technique and loaded into an aqueous solution of chitosan, in which the phytosome associated with chitosan was formed. To optimize gingerol formulations, it was distinctive for entrapment efficiency percentage, drug loading, yield percentage physical studies, and particle size, and compatibility studies, etc. to demonstrate confirmation of the gingerol-phytosome complexation with chitosan and soy lecithin.

The study reported that the complexation of gingerol-phytosome has improved the bioavailability and the hematological correlation between rabbit blood and microorganisms were also performed and the prepared phytosome complex of gingerol is reported to be the best approach for its delivery where it showed a prolonged rate of oral absorption and a sustained-release of the drug to its site of action showing with potent antibacterial activity for the treatment of respiratory infection⁷⁰.

Ginger as a Candidate to Treat SARS CoV-2:

Traditionally and commonly, people from time immemorial have been using spices and herbs like ginger, fenugreek, and onion as a therapy to cure a common cold and other viral or bacterial infections. Moreover, the effectiveness of herbal remedies for controlling infectious viral disease was demonstrated during the 2003 SARS-CoV outbreak, and the study predicts that the various types of compounds available in spices inhibit SARS-CoV-2 and will provide valuable information to the researchers and laypersons on the active constituents and spices that may be

effective against COVID-19. Lastly, based on the binding attachment of compounds with the main protease and spike receptor, spices have been reported for *in vitro* activity studies⁷¹. The essential oil of ginger acts as a bronchodilator acting on the airway system were reported and when the essential oil is combined with eucalyptus, citral, and camphor on the airways of rats. The effect of bronchodilation of ginger essential oil is related to that of citral and eucalyptol. The bronchodilation effect of ginger essential oil is inverted by propranolol, while no effect on the bronchodilator effects of ginger essential oil and citral with indomethacin and L-NAME. Ginger syrup has been prepared as the formulation to treat the bronchial effects of respiratory problems, the treatment of cough, and also as an adjuvant in SARS-CoV-2 management²⁰.

Gingerol a chemical constituent of ginger and other phytochemicals of other plants are identified as candidates that might play a role in inhibiting the replication of SARS-CoV-2 by binding to the Non-structural protein 15 (Nsp15) viral proteins. This Non-structural protein 15 is also known as uridylyate-specific endoribonuclease, and it has been known to be essential for the replication of the virus inside the host cells. These studies have been proved by conducting an *in-silico* method of study using docking Softwares like Auto dock and Swissdock with significant binding energy in comparison to chloroquine and hydroxy chloroquine to Nsp15 protein; even though further studies need to be carried out to confirm by *in vivo* and *in-vitro* studies⁷².

CONCLUSION: The papers reviewed provide ideas on how ginger is formulated and improve from conventional to novel formulations using novel techniques; to improve the pharmacological, biopharmaceutical, and chemical properties of ginger extract and its compounds. Based on the various chemical constituents present, ginger has a wide therapeutic range. The therapeutic actions of every constituent have been summarized along with their structures in **Table 1**. Varieties of novel formulations have been developed in recent years and many of them have demonstrated considerable improvement in the formulation using ginger as the active ingredient. Various developments in ginger tablets were taste masking, increase patient

compliance, better targeting, and improve absorption. In capsule form, it was used in treating nausea and vomiting induced by pregnancy and chemotherapy, in non-alcoholic fatty liver and the results came out to be productive and much more effective than ginger tablets. The powder form of ginger is used in different ailments where it shows good results as an analgesic, anti-inflammatory, antioxidant, also reducing dysmenorrhea, rheumatoid arthritis, ulcerative colitis, and dyspepsia.

The topical formulation of ginger includes creams, gels, and transdermal patches. In cream, it is used as potent anti-bacterial or anti-fungal, and as an analgesic when combined with other drugs. As a gel and transdermal patch, ginger can penetrate the cutaneous and percutaneous layers of the skin to treat rheumatoid arthritis and reduce joint pain.

These are the best approaches to overcome the drawbacks of ginger by the oral route. Novel techniques like nanoparticles, liposomes, and phytosomes are used to develop drug efficacy, drug targeting, and bioavailability.

These novel techniques can be used in tablets, capsules, gel, cream, oil, transdermal patch and many others. Ginger is a well-known and common spice that is used as herbal medicine in treating diseases or ailments which is safe and showing only a few insignificant adversarial effects. In the part of SARS-CoV-2, ginger and its phytochemical constituents show the promising effect as of the *in-silico* method of study and not to forget that there is a need to further investigate their actions towards SARS-CoV-2, for them to be considered as an adjuvant for prevention of coronavirus entry and replication by development into a different suitable form of formulations. Future research is suggested for the advances in the novel formulation of ginger using each isolated compound and improving bioavailability, therapeutic effect, and delivery.

ACKNOWLEDGMENT: The author would like to thank his guide Dr. Tapash Chakraborty and Ms. Asha Das, for their supervision and reviewing the manuscript; also very grateful to his colleagues Jakirul Islam, Saranga Shekhar Bordoloi, Bitopan Baishya, and Naimul Hasan for their help in writing the manuscript.

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest regarding this review.

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How to cite this article:

Rynjah D, Chakraborty T, Das A, Islam J, Bordoloi SS, Baishya B and Hasan N: Recent development in the formulations of ginger for therapeutic applications and an over view towards the action on SARS-COV-2. Int J Pharm Sci & Res 2021; 12(7): 3537-48. doi: 10.13040 IJPSR.0975-8232.12(7).3537-48.

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