

Indian spices: past, present and future challenges as the engine for bio-enhancement of drugs: impact of COVID-19

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Abstract

Spices are natural plant products enriched with the history of being used as herbal medicine for prevention of diseases. India is also known as the 'Land of Spices'. Out of 109 spices recognized by the International Organization for Standardization (ISO) more than 52–60 spice crops are grown in India. The major spices exported by India are turmeric, cumin, coriander, fenugreek, peppers, etc. The Indian spices are divided into three era viz. early period, middle age and early modern period. Spices are used in beverages, liquors, and pharmaceutical, cosmetic and perfumery products. The major issue with spices is their handling and storage. This review article mainly focuses on two aspects: at the outset the handling and storage of the spices is an essential factor as spices are available in different forms like raw, processed, fresh, whole dried, or pre-ground dried. Therefore, the need of processing, packaging, storage and handling of the spices is important as the deterioration of spices can lead to the loss of therapeutic activity. Furthermore, many herbal constituents have the capability to enhance the bioavailability of drugs. Therefore, an attempt has been made to throw a light on the bioenhancer activity and therapeutic activity along with their mechanism of action of some Indian spices which are regularly used for cooking purpose on a daily basis to enhance the taste of food. The spices suggested by ministry of AYUSH which is relevant to its medicinal and biological property in treatment and prevention from COVID-19 are discussed.

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Keywords: Indian spices; handling; storage; bioenhancer activity; therapeutic activity; COVID-19

INTRODUCTION

Spices have an enriched history for being used as herbal medicine for prevention of diseases.¹ Spices are natural plant products that are a seed, fruit, root, bark, or other plant substance primarily used for flavouring, colouring or preserving food. Spices take an important place in common man's life right from the kitchen and medicinal uses in homes. As India is blessed with a varied climate each of its states produce some spice or other. India is also known as the 'Land of Spices'. The major spices exported by India are turmeric (10%), cumin (10%), coriander (9.5%), fenugreek (4.2%), peppers (4%) and others (19%).² In the present time, humans are concerned about immunity. Nature gave us food and medicine stores, but we could not use that gift today. In fact, food is the only medicine. According to Hindu scriptures, excellent and scientifically made food makes a healthy body. The food style or habit of people is changing to a greater extent as they are moving towards spicy food because of good taste and aroma. Indian food has traditionally been rich in spices. There is no food in which spices are not used. The use of spices has been practiced in the Indian subcontinent since time immemorial and is still relevant today due to the importance of the spice and its therapeutic properties. States like Kerala, Punjab, Gujarat, Manipur, Mizoram and Uttar Pradesh are considered as the hub for growing spices.³ Spices are the main ingredients of Ayurvedic formulation used for antipyretic purposes viz. Sudarshan Churna and many more.⁴

Spices have flourished in the food industry, and cosmetics and pharmaceutical industries. In the blind race of vitamins and nutrients, we gave preference to frozen fruits, while the truth was that seasonal fruits and vegetables have always been helpful in seasonal changes. Indian food and its traditional recipes have been considered the best for centuries.

HISTORY OF SPICES

The history of Indian spice is divided into three periods and they are early period, middle age and early modern period.⁵

Early period

The most primitive history about Indian spices is recorded in the 'Rig ved' around 6000 BC. Spices are an important group of agricultural commodities. They can be primarily defined as farm products used in various forms; fresh, ripe, dried, broken, powdered, etc. which contributes aroma, taste, flavour and colour to food.

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Middle period

Common spices were imported into Western Europe each year during the Late Middle Ages. Spices were among the most demanded and high-priced products available in Europe in the Middle Ages. Some common spices are pepper, cinnamon, cumin, nutmeg, ginger and cloves. The most exclusive was saffron.

Early modern period

The development kept the spice trade, with America as a late comer with its new seasonings, commercial into the 19th century. Spices are well known as appetizers or preservatives and many of them have prosperous medicinal properties and are used in pharmaceutical, perfumery, cosmetic products and religious rituals, etc.⁶

Mechanism of action of spices

Due to variety in cultivation, collection and processing of spices; their mechanism of action varies depending on its structural microscopic, macroscopic and physical and chemical properties of the constituents. The general mechanism of action of bioenhancers is as follows:

- Reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply.
- Inhibition of gastric intestinal transit (GIT), gastric emptying time and intestinal motility
- Modification in GIT epithelial cell membrane permeability
- Cholagogue effect, bioenergetics and thermogenic properties.
- Suppression of first metabolism and inhibition of drug metabolizing enzyme.

Classification of bioenhancer

Extensive literature is available about the classification and types of bioenhancers. Bioenhancers can belong to any of the classes based on their mechanism of action by which they increase the bioavailability. A general way of classification of bioenhancers is depicted in Fig. 1(A).⁷

PROCESSING AND PACKAGING OF SPICES

A spice may be available in several forms: fresh, whole dried, or pre-ground dried. The processing steps are summarized in Fig. 1(B).⁸ The steps involved in processing of spices are:

- (1) *Sorting and heating*: Sorting is the early step where the spices are sorted to remove the unnecessary parts like rotting or mouldy parts. For heating the spices are heated at an average of 80 to 90 °C during an average time of 5 min before being sun dried.⁸
- (2) *Sun drying*: Sun drying is one of the important steps of the processing of spices. In this technique sun drying reduces the water activity in the spices and prevents the development of micro-organism but also reduces the weight of the spices. The duration of sun drying can also control the active compound and colour.⁹ In addition the drying of spices on the ground can lead to chemical and microbiological contamination of spices which are unsuitable for consumption.¹⁰
- (3) *Milling*: Sun drying of spices is followed by the milling step.¹¹ Milling is performed by various methods such as the tradition milling method by the use of cemented millstone, built stone and mortars. Modern mills are also used and they are small mill, plate disc mill.

- (4) *Packaging*: Spices are packed in different types of material such as glass bottles, plastic bottles, plastic bags and jute bags. The use of other packaging materials is also common, these include the use of cardboard boxes, multi-wall paper bags and plastic sacks that are utilized for enhanced preservation of spices.¹²

Storage for spices

Most herbs are marketed in the dried form as a high concentration of water will cause product deterioration over time. The changes in the volatiles depend on factors such as the drying method, the biological characteristics of the plants and their volatile composition. According to the World Health Organization (WHO), there are nearly about 119 plant derived pharmaceutical medicine and about 74% are used in modern medicine which for the same remedial value are used in traditional system of medicine. The major question is about safety, efficacy and quality of herbal drugs. Spices used as or in formulation should be identified and authenticated and be free from insect, pest, fungi and micro-organisms. In the store house there should be adequate space for testing, approving and rejecting herbs and an orderly placement of store herbs and spices with controlled temperature and humidity. The store house for storage of herbs and spices should be as per good manufacturing practices (GMP).¹³

Main factors that cause deterioration of foods during storage¹⁴

- (1) Climatic influences that cause physical and chemical changes (ultraviolet light, moisture vapour, oxygen and temperature changes)
- (2) Contamination (by micro-organisms, insects or soils)
- (3) Mechanical forces (damage caused by impact, vibration, compression or abrasion)
- (4) Tampering or adulteration

Packing of spices

There is no specified or standard procedure for proper storage of raw herbal material to date. It is only the proper handling, packaging and storage of herbs and spices which can conserve the safety, efficacy and quality of herbs and spices. Therefore, the choice of appropriate packaging material is important and depends upon the herbal material as shown in Table 1.¹³

Description of some of the commonly used Indian spices with their applications as bioenhancer

There are plenty of herbal spices that exist in various parts of India and possess broad spectrum of therapeutic and pharmacological action. A few of them are discussed here.

- (a) Black pepper
- (b) Cardamom
- (c) Cinnamon
- (d) Clove
- (e) Coriander
- (f) Star anise
- (g) Fenugreek
- (h) Turmeric

(a) Black pepper

Black pepper (*Piper nigrum* Linn.) is the world's most common spice and well-known as the 'King of Spices.' The word 'pepper'

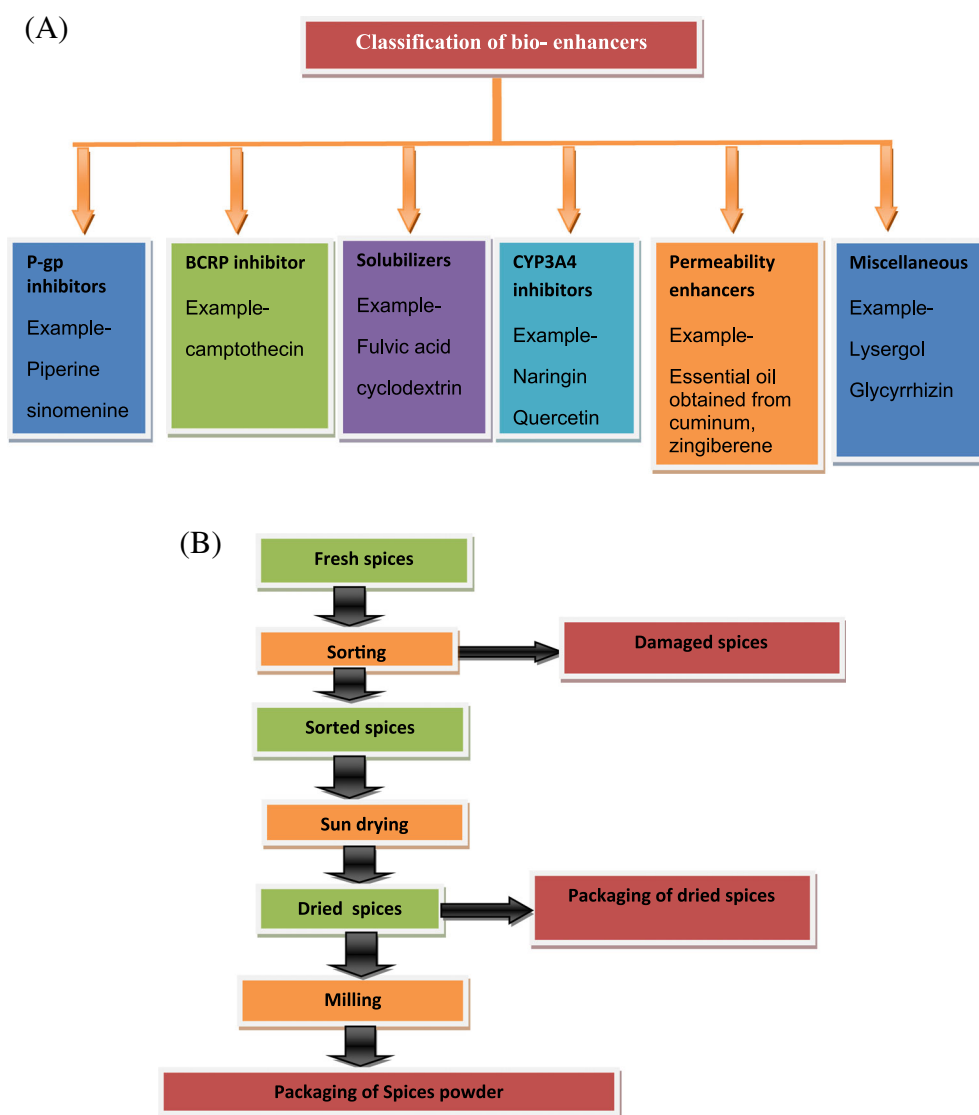


Figure 1. (A) Classification of bioenhancers. (B) Flow chart of processing of spices.

is derived from the Sanskrit *pippali*, the word for long pepper, via the Latin *piper*, which was used by the Romans. The English word for pepper is derived from the Old English 'pipor.' The Latin word is also the source of German *pfeffer*, French *poivre*, Dutch *peper*, and other similar forms.¹⁵ Pepper is a perennial climber and an inhabitant of south India mainly Kerala, Karnataka and Tamil Nadu and to a certain extent in Andaman and Nicobar Islands, Goa, Pondicherry and north-eastern states. In its dried form, the fruit is frequently referred to as peppercorns.¹⁶⁻¹⁹ Peppercorns, and the powdered pepper derived from grinding them, may be described as black pepper and their reported therapeutic activities are listed in Table 2.¹⁶⁻²⁵

Bioenhancer activity of black pepper. Piperine, the chief plant alkaloid present in *Piper nigrum* Linn. (Black pepper) and *Piper longum* Linn. (Long pepper), has bioavailability enhancing activity for some food substances and for some drugs. The bioenhancing dose of piperine is approximately 15 mg person⁻¹ d⁻¹ and no more than 20 mg d⁻¹ in divided doses, which corresponds to several thousands up to 40 000

times less than the median lethal dose (LD50) dose of piperine, as recognized in various experiments on rodents. The effective bioenhancing dose of piperine for drug compounds varies, but a dose of approximately 10% (w/w) of the active drug could be regarded as an appropriate bioenhancing dose for most drugs.²⁶ The mechanism of action of piperine as bioenhancer is shown in Fig. 2(A)²⁷ and some reported bioenhancer activity of piperine is shown in Table 3.

(b) Cardamom

Elettaria cardamomum belongs to family Scitamineaceae locally known as 'elaichi' is a perennial herb and native to India cultivated in the states of Kerala, Karnataka and Tamil Nadu. It is also cultivated in Pakistan, Burma and Sri Lanka. In South Asia green cardamom is called 'elaichi' in Marathi, Hindi and Urdu. It is called elakkaay in Telugu and elam in Tamil.^{15,28-32} Therapeutic activity of cardamom is shown in Table 2.

Bioenhancer activity of cardamom. The essential oil obtained from cardamom acts as a bioenhancer by increasing the glutathione-S-

Table 1. Material for specific packaging and storage of raw herbs

Serial number	Part of plant and category	Packing material
1.	Woody in nature like stem, bark, etc.	Gunny bags and woven sacks
2.	Fleshy in nature like fruit, rhizomes, etc.	High gauge high-density high molecular (HDHM) bags, woven sac with Low density (LD) liner, wooden box
3.	Soft in nature like creepers, leaves, etc.	High gauge HDHM bags, woven sac with LD liner, high gauge polyethylene bags
4.	Flowers, anthers, stigma, petals, seeds, etc.	Corrugated box with polypropylene, woven sack, high-density poly ethylene (HDPE) container, fibers boards drums
5.	Herbal extracts and compounds	Air tight HDPE containers, corrugated box with polyethylene, woven sack and fiber boards drum with polyethylene bags
6.	Volatile content	Air tight HDPE containers, Air tight carboys, card board box with polyethylene liners

transferase (GST) and decreasing lipid per oxidation³³⁻³⁷ as shown in Fig. 2(B).³⁸ Some of the reported bioenhancer activity of cardamom is listed in Table 3.

(c) Cinnamon

Cinnamon is native to India, Sri Lanka, Bangladesh, and Nepal. The name 'cinnamon' comes from Greek *kinnámōmon*, itself ultimately from Phoenician. The botanical name for the spice, *Cinnamomum zeylanicum*, is derived from Sri Lanka's former (colonial) name, Ceylon. In sinhala (Sri Lanka), it is known as *kurundu*, Sanskrit as *tvak* or *da-rusita*-, Hindi as *dalchini*, and in Gujarati as *taj*. In Malayalam cinnamon is called *karuva* or *elavarngam*.¹⁵ It is mostly cultivated in the Western Ghats of Kerala and Tamil Nadu.³⁹⁻⁴² The therapeutic value of cinnamon is listed into Table 2.

Bioenhancer activity of cinnamon. Cinnamic acid obtained from cinnamon acts as a bioenhancer by inhibiting the enzyme P-gp used for drug biotransformation as shown in Fig. 2(C).⁴³⁻⁴⁵ Some of the reported bioenhancer activity of cardamom is listed in the Table 3.

(d) Clove

Cloves are native to Indonesia and are used as a spice in cuisine all over the world. The name derives from the French '*clou*,' meaning 'nail' as the buds vaguely resemble small irregular nails in shape. The spice is used in Ayurveda, Chinese medicine and Western herbalism.^{15,46-49} The medicinal property of clove is listed into Table 2.

Bioenhancer activity of clove. Clove oil enhances bioavailability by decreasing lipid per oxidation as shown in Fig. 2(D).⁴⁵ Some of the reported bioenhancer activity of clove is listed in the Table 3.

(e) Coriander

Coriandrum sativum belongs to family Umbelliferae. Coriander is native to south-western Asia and regions west to north Africa. The name 'coriander' derives from the French *coriander* through Latin *coriandrum*. It is an annual herb commonly used in Middle Eastern, Mediterranean, Indian, Latin American, African and Southeast Asian cuisine. Coriander leaves are referred to as cilantro (United States and Canada, from the Spanish name for the plant), *dhania* (Indian subcontinent, and increasingly in Britain), *kindza* (in Georgia), Chinese parsley or Mexican parsley.⁵⁰⁻⁵⁴ All parts of the plant are edible, but the fresh leaves and the dried

seeds are the most common parts used in cooking.¹⁴ The medicinal property of coriander is listed in Table 2.

Bioenhancer activity of coriander. According to the literature survey done bioenhancer activity is not reported for coriander.

(f) Star anise

Star anise (*Illicium verum*) belongs to the plant family Illiaceae.⁵⁵ The generic name *Illicium* comes from a Latin word, 'alluring' means – fragrance. The plant is known by different local names in different regions of the world like phoolchakri (Hindi), badiane (French), badian (Urdu), and star anise (English). The cutting of star anise fruit is done after ripening in summer season and then it is dried in sunlight. The flowering is observed from March to May, and its fruit become mature from September to October.⁵⁶ Star anise has been utilized frequently in Persian and Mughal Indian biryani rice dishes and curries. It was used as an alternative in commercial drinks for aniseed during the 17th century.⁵⁷ Star anise is a well-known source of carbohydrates, proteins, vitamin A and ascorbic acid. The aromatic odour of *Illicium verum* is because of the presence of essential oil which is 2.5–3.5% in the fresh fruit and 8–9% in dried material. This scented volatile oil mainly comprises of *trans*-anethol and shikimic acid (3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid). Other chemical constituents including sesquiterpenes, phenylpropanoids, lignans, flavonoids, palmitic acid are also present.⁵⁸⁻⁶⁰ The therapeutic activity of star anise is listed into Table 2.

Bioenhancer activity of star anise. According to the literature survey done bioenhancer activity is not reported for STAR Anis.

(g) Fenugreek

Fenugreek (*Trigonella foenum-graecum*) is commonly known as *maithray* (Bangla, Gujarati), *methi* or *mithi* (Hindi, Nepali, Marathi, Urdu and Sanskrit), *menthyada soppu* (Kannada), *ventayam* (Tamil), *menthulu* (Telugu), *hilbeh* (Arabic), *ulluva* (Malayalam) and *shambalileh* (Persian). The name 'fenugreek' or *foenum-graecum* is from Latin for 'Greek hay'.¹⁴ It is one of the most common vegetables grown throughout the country. The seeds can be lightly roasted and ground and used as flavouring, especially in curry dishes. Fresh seed can be sprouted to give tasty sprouts.⁶¹⁻⁶⁵ Fenugreek contains steroidal saponins, alkaloids (including trigonelline and gentianine), mucilage, protein, vitamins A, B, C and minerals. The therapeutic activity is listed in Table 2.

Table 2. List of some reported therapeutic activity of spices and their constituents

Species name (part used)	Scientific name	Activity	Mechanism of action	Reference		
Black pepper (fruits)	<i>Piper nigrum</i>	Gastrointestinal stimulatory activity	The anti-spasmodic activity of black pepper and piperine is mediated through activation of opioid receptor along with Ca ²⁺ channel blocking (CCB) effect.	16		
		Antibacterial activity	Bactericidal action of pepper appears by alteration of cell membrane permeability result in leakage of intracellular material might cause cell death.	17		
		Antihistamic activity	The inhibition of histamine release from the mast cells plays an important role in the mechanism of anti-allergic effect against type I allergy.	18		
		Analgesic and anti-inflammatory activity	Piperine possesses inhibition of prostaglandin synthesis and release.	19		
		Antidepressant	Inhibit monoamine oxidase activity, increase monoamine neurotransmitter levels, and thus produce antidepressant-like activity in various mouse models of behavioral despair.	20		
		Anti-asthmatic activity	H-1 receptor antagonism	21		
		Blood pressure lowering	Piperine mediates spasmolytic effect through calcium antagonism.	22		
		Antidiabetic activity	Enhancement of glucose utilization, so blood glucose levels were significantly decreased in glucose.	23		
		Hypolipidemic activity	Clearance of lipids from circulation may be due to reactivation of lipolytic enzymes.	24		
		Anticancer activity	Cytotoxic analysis revealed a dose-dependent response with maximum cellular inhibition	25		
		Cardamom (seed pods)	<i>Elettaria cardamomum</i>	Skin disorders (non-melanoma skin cancer)	Cardamom contains copper and manganese that are required for the activation of superoxide dismutase (SOD) enzyme, which in turn helps in the decrease in the process of lipid peroxidation. Thus, play anticarcinogenic role in preventing the progression of skin carcinogenesis in mice.	30
				Anticonvulsant activity	Cardamom extract increase the level of γ -aminobutyric acid (GABA) in the blood serum and shows the anticonvulsant activity	31
				Blood pressure lowering activity	Cardamom produced a dose-dependent fall in the arterial blood pressure. Partial blockade of hypotensive responses with atropine indicate that cardamom lowers blood pressure due to the presence of cholinergic and an additional (Ca ²⁺ antagonist) components, as identified in the gut preparations. Blood pressure is the product of peripheral resistance and cardiac output.	32
Diuresis	The diuretic effect of cardamom was confirmed, when it caused significant increase in the urine volume (diuresis) in rats, like furosemide, a standard diuretic. Cardamom also enhanced the urinary excretion of Na ⁺ and K ⁺ , similar to that caused by furosemide.			32		
Antioxidant activity	The extract showed protection against hydrogen peroxide (H ₂ O ₂) induced DNA damage and inhibited 2,2'-azobis (2-amidinopropane) dihydrochloride (AAPH) induced protein oxidation and lipid peroxidation. Cardamom also exhibited antioxidant effects.			33		
Anti-inflammatory and analgesic	Cardamom extract administration to rats at 50 and 100 mg kg ⁻¹ inhibited carrageenan-induced paw edema, and down-regulated cytokines such as COX-2, IL-6, and TNF- α and inhibited i-NOS mediated nitric oxide (NO) generation.			33		
Gastro- protective activity	A crude methanolic extract (TM), essential oil (EO), petroleum ether soluble (PS) and insoluble (PI) fractions of methanolic extract, were studied in rats at doses of 100–500, 12.5–50, 12.5–150 and 450 mg kg ⁻¹ , respectively for their ability to inhibit the gastric lesions induced by aspirin, ethanol and pylorus ligation. In addition their effects on wall mucus and gastric acid output were recorded. All fractions (TM, EO, PS and PI) significantly inhibited gastric lesions			34		

Table 2. Continued

Species name (part used)	Scientific name	Activity	Mechanism of action	Reference
		Asthma	The cardamom extract was then studied in isolated tracheal tissues, to elucidate the possible mode of bronchodilator action, where crude extract of cardamom caused relaxation of both carbachol and K ⁺ -induced contractions, like verapamil, a Ca ²⁺ antagonist.	35
		Insecticidal activity	The volatile oil from cardamom acts as a potential grain protectant by killing various life stages of the stored product insects attacking wheat, e.g. <i>Tribolium castaneum</i> and <i>Sitophilus zeamais</i> ; via contact and fumigant Action: Moreover, it also prevented eggs treated with the oil from developing to the adult stage. Cardamom oil dramatically suppressed egg hatching and larval survival of <i>Tribolium castaneum</i> , thus demonstrating its ovicidal properties.	36,37
Cinnamon (bark)	<i>Cinnamomum zeylanicum</i>	Anti-microbial activity	<i>Cinnamomum zeylanicum</i> extract demonstrated significant inhibition effect on <i>Staphylococcus aureus</i> , <i>Enterobacter cloacae</i> , <i>Acinetobacter baumannii</i> [minimum inhibitory concentration (MIC) 0.4 mg mL ⁻¹]	40
		Anti-diabetic activity	The effect of cinnamon extract on glycosylated hemoglobin A _{1c} and fasting blood glucose levels in patients with type 2 diabetes was analyzed. A total of 66 patients with type 2 diabetes were recruited and randomly divided into three groups: placebo and low-dose and high-dose supplementation with cinnamon extract at 120 and 360 mg d ⁻¹ , respectively. Both hemoglobin A _{1c} and fasting blood glucose levels were significantly reduced in patients in the low- and high-dose groups, whereas they were not changed in the placebo group. Thus, significantly improving blood glucose in patients with type 2 diabetes.	41
Cinnamon (bark)		Antioxidant activity	The volatile oil was screened for its potential as an antioxidant by using <i>in vitro</i> models, such as the β-carotene-linoleate and phosphomolybdenum complex method. The volatile oil showed 55.94% and 66.9% antioxidant activity at 100 and 200 ppm concentration, respectively. Also, the volatile oil showed good antioxidant capacity, using the formation of the phosphomolybdenum complex.	42
		Immuno-modulatory activity	Cinnamon at high dose increases both cell mediated and humoral immunity and at low dose shows effect only on humoral immunity. Cinnamaldehyde is reported to inhibit lymphocyte proliferation and NF-κ B stimulation. The results of the present study shows that cinnamon is a possible immune system booster.	43
		Wound healing activity	The ethanol extract of the bark of <i>C. zeylanicum</i> was evaluated for wound healing activity in Wistar rats. The extract was administered by the oral route at a dose of 250 mg kg ⁻¹ and 500 mg kg ⁻¹ body weight. The extract significantly enhanced the wound breaking strength in the case of incision wound, the rate of wound contraction and the period of epithelization in the case of excision wound.	44
Clove (flower buds)	<i>Syzygium aromaticum</i>	Antioxidant activity	The antioxidant potential of clove is evaluated against copper induced lipid peroxidant, 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging capability of methanol extract of clove is examined. The clove exhibited a concentration dependent antioxidant activity. Furthermore, 56% of DPPH free radicals were scavenged with extract equivalent to 100 µg clove.	46
		Antibacterial activity	Antibacterial susceptibility assay shows promising evidence for the antibacterial effect of clove methanolic and ethanolic extract against three foods associated with <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> and <i>Pseudomonas aeruginosa</i> . Methanolic extract of clove showed maximum zone of inhibition 24 mm against <i>Staphylococcus aureus</i> while minimum was 19 mm against <i>Pseudomonas aeruginosa</i> . Ethanolic extract of clove showed maximum zone of inhibition 20 mm against <i>Pseudomonas aeruginosa</i> while minimum was 18 mm against <i>Escherichia coli</i> .	47

Table 2. Continued

Species name (part used)	Scientific name	Activity	Mechanism of action	Reference
		Anti-inflammatory activity	The current study clearly demonstrated anti-inflammatory effect of clove essential oil <i>in vivo</i> , which equals to that of etodolac at 0.025 mL kg ⁻¹ and 0.100 mL kg ⁻¹ doses and to that of indomethacin at 0.050 mL kg ⁻¹ and 0.200 mL kg ⁻¹ doses.	48
		Hair growth enhancer	Formulation containing clove oil was clinically evaluated on rats back compared with minoxidil standard lotion as a positive control and distilled water as a negative control. The selected formulation was demonstrated to condition hair with grooming and enhanced hair growth with longer lag time compared with minoxidil but after one week the hair growth accelerated.	49
		Anti-cancer activity	Significant reduction in the number of proliferating cells and an increased number of apoptotic cells was noted in these blood pressure-induced lung lesions following clove treatment.	50
Coriander (dried seeds)	<i>Coriandrum sativum</i>	Antioxidant activity	Three different bioassays were used, namely scavenging of the DPPH radical method, inhibition of 15-lipoxygenase (15-LO) and inhibition of Fe ²⁺ induced porcine brain phospholipid peroxidation. Coriander leaves showed stronger antioxidant activity than the seeds, and in both parts of coriander, the ethyl acetate extract contributed to the strongest activity.	52
		Anti-diabetic activity	Coriander incorporated into the diet (62.5 g kg ⁻¹) and drinking water (2.5 g L ⁻¹ , prepared by 15 min decoction) reduced hyperglycaemia of streptozotocin-diabetic mice. Insulin secretion by hyperpolarized B-cells (16.7 mm-glucose, 25 mm-KCl) was further enhanced by the presence of extract.	53
		Anti-bacterial activity	Coriander oil exhibited bactericidal activity against almost all bacteria tested, due to membrane permeability with the exception of <i>Bacillus cereus</i> and <i>Enterococcus faecalis</i> .	54
Star anise (fruit)	<i>Illicium verum</i>	Anticancer activity	Diseases induced by free radicals and nicotine can be cured by star anise because it has anticarcinogenic agents. The anticancer action is because of flavonoids, resveratrol and curcumin. They additionally have exhibited remedial potential, including cell-defensive anti-inflammatory, and DNA protective properties. This spice also has positive effect on DNA damage, which can be a trigger for cancer, as well as on cancer cell migration.	58
		Insecticidal activity	Insecticidal activity of star anise, the direct contact methods were applied against fruit flies (<i>Drosophila melanogaster</i>). (<i>E</i>)-Anethole caused 80.3% mortality at 0.159 mg cm ⁻² at 1 and 3 days treatment in a filter paper diffusion method. Insecticidal properties have also been found in volatile oil of star anise against larva and adults of <i>Tribolium castaneum</i> , <i>Botrytis cinerea</i> and <i>Callosobruchus chinensis</i> .	59,60
		Anti-inflammatory activity	Star anise anti-inflammatory action was identified in mice by xylene-induced auricle edema. The star anise extracts of 10 and 20 mg rough drugs mL ⁻¹ , clearly decreased the contractility of mice intestinal smooth muscles in 15 min under the effect of acetylcholine and barium chloride. Therefore, it is concluded that aqueous extract of star anise has analgesic and anti-inflammatory effects on mice intestinal smooth muscles.	61
		Anti-fungal activity	The anti-fungal activity of star anise was tested against <i>Fusarium solani</i> and <i>F. graminearum</i> and <i>F. oxysporum</i> . Complete inhibition (100%) was examined by using 100 ppm concentration of star anise due to high antifungal action. The growth of <i>F. verticillioides</i> is also completely inhibited at 200 ppm concentration.	62

Table 2. Continued

Species name (part used)	Scientific name	Activity	Mechanism of action	Reference
Fenugreek (leaves and seeds)	<i>Trigonella foenum-graecum</i>	Anti-inflammatory and anti-arthritis activity	Anti-inflammatory activity was noted with linolenic acid in various acute models involving carrageenan, prostaglandin E2, leukotrienes, and arachidonic acid-induced inflammation signifying its ability to inhibit both cyclooxygenase and lipoxygenase pathways. Petroleum ether extract of fenugreek seeds show anti-inflammatory and anti-arthritis activities in all the models tested.	63
			Fenugreek seed extract attenuated hyperglycaemia was investigated <i>in vitro</i> . FSE stimulated glucose uptake in CHO-HIRC-mycGLUT4eGFP cells in a dose-dependent manner. This effect was shown to be mediated by the translocation of glucose transporter 4 (GLUT4) from the intracellular space to the plasma membrane.	64
			The seed extract exhibit scavenging of hydroxyl radical (OH [•]) and inhibition of H ₂ O ₂ induced lipid peroxidation in rat liver. The result shows that the extract of fenugreek seed contains antioxidant property.	65
			The effect of fenugreek seeds (<i>Trigonella foenum graecum</i>) compared to omeprazole was studied on ethanol-induced gastric ulcer. The soluble gel fraction derived from the seeds was more effective than omeprazole in preventing lesion formation.	66
Turmeric (rhizomes)	<i>Curcuma longa</i>	Anti-ulcer activity	An ethanol extract of turmeric was studied in rats for its ability to inhibit gastric secretion and to protect gastroduodenal mucosa against the injuries caused by pyloric ligation. An oral dose of 500 mg kg ⁻¹ of the extract produced significant anti-ulcerogenic activity in rats subjected to pyloric ligation.	68
		Anti-fungal activity	In the experimental animals, turmeric oil (dilution 1:80) was applied by dermal application on the seventh day following dermatophytosis induction with <i>Trichophyton rubrum</i> . An improvement in lesions was observed in 2–5 days and the lesions disappeared 6–7 days after the application of turmeric oil.	69
		Antioxidant, anti-inflammatory activity	Turmeric oil was found to have <i>in vitro</i> antioxidant activity and the half maximal inhibitory concentration (IC ₅₀) for scavenging superoxides, hydroxyl radicals, and lipid peroxidation were 135 µg mL ⁻¹ , 200 µg mL ⁻¹ , and 400 µg mL ⁻¹ , respectively. Turmeric oil showed significant reduction in paw thickness in carrageenan, dextran-induced acute inflammation, and formalin-induced chronic inflammation.	70

Bioenhancer activity of fenugreek. According to the literature survey done bioenhancer activity is not reported for fenugreek.

(h) Turmeric

Turmeric is derived from the rhizome of the plant *Curcuma longa* and has been used as a traditional medicine from ancient times in China and India.^{66,67} It is also known as *kunyit* (Indonesian and Malay), *besar* (Nepali) and *haldi* or *pasupu* in some Asian countries. In Assamese it is called *halodhi*.¹⁴ Turmeric is available in two seasons in India, i.e. February to May and August to October.^{6,68-70} India is the largest producer, consumer and exporter of turmeric in the world. The therapeutic activity of turmeric is listed into Table 2.

Bioenhancer activity of turmeric. Curcumin is obtained from *Curcuma longa* as it possesses the bioenhancer property with various drugs given in Table 3. It acts by suppressing drug metabolizing enzymes and by inhibition of P-gp as shown in Fig. 2(E).^{6,71,72}

Patenting of Indian spices has gained significance worldwide for their therapeutic potential in bioenhancing the activity of various synthetic drugs. Some of the recent findings are listed in Table 4.

ROLE OF SPICES IN TREATMENT OF CORONA

The Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy), Government of India, recently issued advice suggesting how to fight against the corona virus pandemic in India. While antiviral drugs and vaccines are still being developed, the traditional systems focus more on the initial immunity of the body and to provide a holistic result for the wellbeing of an individual as a synchronized strategy.⁷²⁻⁷⁴ The use of these traditional medicines not only helps cure symptoms but also helps progress immunity and reduces the risk of infections to a huge extent. The potential of these plant-based remedies in curing and preventing the

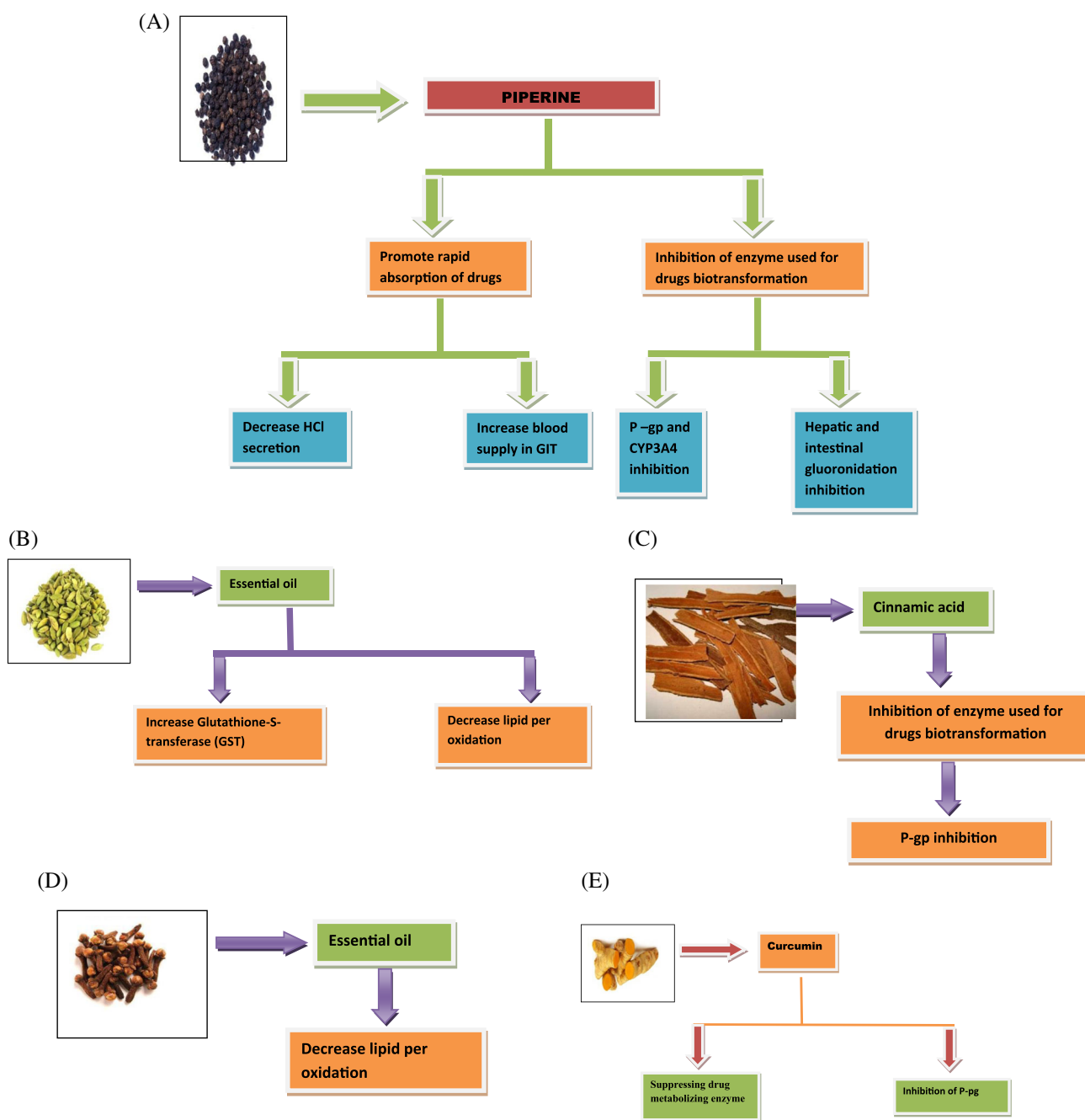


Figure 2. (A) Mechanism of action of black pepper as bioenhancer. (B) Mechanism of action for bioenhancer activity of cardamom. (C) Mechanism of action for bioenhancer activity of cinnamon. (D) Mechanism of action for bioenhancer activity of clove. (E) Mechanism of action of turmeric as bioenhancer.

COVID-19 infection must be broadly explored to develop globally satisfactory therapeutic remedies along with the modern medicines and vaccines.

Coronaviruses (CoVs) belonging to the family: Coronaviridae are enveloped viruses containing non-segmented, positive-stranded genomic RNA. The complete replication cycle takes place in the cytoplasm. Corona viruses can cause a number of diseases, including bronchitis, hepatitis, gastroenteritis, and even death in birds, humans, and other animals.⁷³ It has been found to assail all types of people, mostly elderly patients having diabetes, hypertension,

chronic bronchitis, cerebral infarction, chronic obstructive pulmonary disease, cardiovascular disease, and cancer. CoVs enter into the host cell through interaction between the S protein of the virus species and the receptor of the host cell. It binds with the angiotensin-converting enzyme 2 receptor from the host cell to create a suitable environment for viral replication.⁷⁴⁻⁷⁶

Some of recommended species by the AYUSH

AYUSH recommends the use of most herbal spices in the treatment of various diseases and dealing with coronal-like life

Table 3. Reported bioenhancer activity of some constituents of herbal spices

Herbal spices with drug	Bioenhancement activity	Reference
Piperine and resveratrol	Bioenhancer activity was studied on mice and the study demonstrated significant improvement in bioavailability of resveratrol.	27
Piperine and curcumin	The pharmacokinetic of curcumin with piperine was studied on animal and human volunteers. Piperine inhibit the hepatic and intestinal glucuronidation, thus extend the bioavailability of curcumin in both rat and human with no adverse effect.	28
Piperine and aflatoxin B1	10 mg dose of piperine enhance bioavailability of aflatoxin B1 in rat tissue	29
Cardamom and piroxicam	The penetration index of piroxicam after 1 h pretreatment with 10% cardamom oil was about 340.9-fold higher than that of non-pretreatment	38
Cardamom and indomethacin, diclofenac and piroxicam	The penetration index of piroxicam was extremely increased by 1% cardamom oil about 81.9-fold compared with that of indomethacin or diclofenac.	39
Cinnamon and saquinavir	It enhances bioavailability of saquinavir.	45
Clove oil and carvedilol	It enhances bioavailability of carvedilol.	51
Curcumin with celioprolol and midazolam	Curcumin suppresses drug metabolizing enzyme CYP3A4 in liver and increase AUC and Cmax of celioprolol and midazolam.	71

threatening viral infections which have no successful available treatment to date. However, to prevent all such infectious diseases herbal spices available in the kitchen is the best remedy.⁷⁸ Three such spices namely turmeric, ginger and holybasil are discussed here.

Turmeric

Curcumin, a natural polyphenolic compound, could be a potential treatment choice for patients with CoV disease. Curcumin has shown antiviral activities against a number of different viruses, could be a remedial option for the management of COVID-19 infection. Previous research has shown that curcumin interacts directly with around 30 proteins, including DNA polymerase, thioredoxin reductase, focal adhesion kinase (FAK), protein kinase (PK), tubulin, and lipoxygenase (LOX). Additionally, curcumin modulates intercellular signaling cascades which are crucial for competent virus replication such as attenuation of NF-κB and

PI3K/Akt signaling. It also affects cellular post-transcriptional and post-translational modifications, thereby preventing the viral multiplication by interfering with essential steps in their replication cycle, including genome replication, and viral attachment. A virus does not have all the enzymes needed for its replication as a single unit. The virus uses cellular mechanism for its metabolic processes and reproduction. The antiviral agents should stop the growth of viruses in infected cells without harming the healthy cells. The process of the replication of the viruses, including attachment, penetration, uncoating, genome replication and gene expression are potential therapeutic targets is listed in Table 5.

Challenges. Despite the possible beneficial effects and safety profile of curcumin against a range of diseases, the limited bioavailability of this turmeric-derived compound, especially via oral administration may be a challenging issue.

Table 4. Recent patents of some bioenhancers

Name of bioenhancer	Patent number	Assignee	Date	Title
Piperine	US5744161A	Sabinsa Corporation	4 April 1998	Use of piperine as a bioavailability enhancer
Piperine	US005536506A	Sabinsa Corporation	16 July 1996	Use of piperine to increase the bioavailability of nutritional compounds
<i>Zingiber officinale</i>	WO2003049753A1	Council of Scientific and Industrial Research	19 June 2003	Bioavailability enhancing activity of <i>Zingiber officinale</i> Linn. and its extracts/fractions thereof
Cuminum Cyminum	WO2003075685A2	Council of Scientific and Industrial Research	18 September 2003	Bioavailability/bioefficacy enhancing activity of cuminum cyminum and extracts and fractions thereof
Fenugreek	US7338675B2	TSI Group Ltd Hong Kong	4 March 2008	Fenugreek seed bio-active compositions and methods for extracting same
Fenugreek	WO2005084323A2	Technical Sourcing International, Inc.	15 September 2005	Compositions of bio-active compounds from fenugreek seed and methods for producing same
Star anise	CN105713732B	Shandong Agricultural University	17 March 2020	Extraction method of star anise oil

Table 5. Mechanism of action of curcumin on virus replication process

Process	Mechanism of action	Reference
Viral attachment/penetration	Curcumin could alter the surface protein structure in viruses and block the entry of viruses to the cell. In addition, the positively charged curcumin on the surface is subjected to electrostatic interactions with porcine epidemic diarrhea virus (PEDV) or cell membranes and competing with the virus to bind with the cells. A molecular docking study indicated that curcumin possesses the better binding capability to the receptors and may inhibit the entry of COVID-19 virus.	75
Viral replication	The effects of curcumin on negative-strand RNA synthesis by using PEDV as a coronavirus model. They demonstrated that curcumin could inhibit PEDV at the replication step. This evidence supports the potential role of curcumin as a promising antiviral agent. The effect of curcumin on viral replication, by quantification of the number of spike proteins present in cultures of Vero E6 cells infected with SARS-CoV. Their result demonstrated that the inhibitory effect of curcumin in half maximal concentration (EC50) values was higher than 10 $\mu\text{mol L}^{-1}$ on SARS-CoV replication.	75,76
Potential inhibitory effect of curcumin on viral protease	The drugs that are at present tried for the management of COVID-19 are protease inhibitors that primarily act on the main protease curcumin that may have the potential to inhibit the COVID-19 infection by molecular docking. Curcumin showed relatively low binding energies and inhibition constants. They suggested that curcumin could have a potential inhibitory effect on COVID-19 and could potentially act as a therapeutic agent.	77
Potential effect of curcumin on interferons	Interferons play an essential role in the defense against coronavirus infection. These viruses could hinder the induction of interferon in humans. All types of interferons play a role in preventing viral infections. Treatment with cationic carbon dots based on curcumin can suppress PEDV model of coronavirus reproduction by stimulating the production of interferon-stimulating genes (ISGs) and the cytokines (IL8 and IL6) of Vero cells by triggering the innate immunity of the host.	78

Ginger (*Zingiber officinale*)

Gingerol exhibit the highest binding affinity ($-15.7591 \text{ kJ mol}^{-1}$) with 5R7Y COVID-19 main protease essential for replication and reproduction of SARS Cov-2. Corona viral protease 5R7Y residues such as His164, Glu166, Thr190 and Gln192 from hydrogen-bonded interaction with phyto compound gingerol, it also forms non-bonded interaction with the residues of His164, Met 165, Glu166, Leu167, Pro168, Arg188, Gln189 and Thr190.

Molecular interaction between COVID-19 viral RNA binding protein with gingerol makes hydrogen bonded interaction with Val42, Pro58, Ser60 and Thr68 residues and forms non-bonded interaction with Arg40, Phe41, Val42, Phe57, Pro58, Lys59, Ser60, Ile66, Thr68 and Ile92 residues of COVID-19 spike glycol protein. Furthermore, 6-gingerol possesses antiviral activities. The 6-gingerol binds with the COVID-19 main protease active sites. With this binding affinity gingerol possesses excellent drug likeliness parameters with zero violations of different rules and very good absorption, distribution, metabolism, and excretion (ADME) pharmacokinetic properties.⁷⁷ Finally, 6-gingerol proves anti-viral efficiency against SARS CoV-2 by showing the highest binding affinity and interaction with multiple targets of COVID-19 including viral proteases, RNA binding protein and spike protein.

Holybasil

The leaves of this plant are rich in phytonutrients such as anti-oxidant, flavanol, chlorophyll vitamins and minerals as well as Eugenol, a bioactive compound that has anti-microbial, antifungal and anti-bacterial properties and reduces stress and plasma glucose level. It is described as an adaptogenic helping the

body to adapt to new demands and stresses and has been used to treat colds, bronchitis, pleurisy, asthma, stress, insect bites and mouth ulcers. Immune response include increased natural killer and T-helper cell in the well adult and enhanced immune response to viral infection and aids asthmatic symptoms by rising vital capacity.⁷⁹

CONCLUSION

It can be concluded that various research studies are conducted on Indian spices across the world. Spices not only add taste and flavour to the food but also play an important role in maintaining health from various diseases. Many herbal compounds have the capability to enhance the bioavailability. The question is whether humans use spices as a medicine. Or are they were used for nutrient absorption and digestion. The mixing of spices in food not only makes it interesting but also ensures the effect on the body of that food. Therefore, an attempt has been made to compile the bioenhancer activity of Indian spices. In the present condition where the world is facing the COVID-19 pandemic the traditional Ayurvedic systems take longer to have an effect compared to modern medicines, but they also usually have the advantage of lesser side effects and being cost effective. Along with modern medicine, these systems could also be explored as possible treatment/prevention for COVID 19. This review provides scientific evidence which support the use of Indian spices in enhancing the activity of other drugs, prevent and relive from various health problem. Since it is not only necessary to eat the nutrients, it is also necessary for the nutrient to get to the right place. As we know, our immune system is strengthened by nutrients when the body absorbs nutrients properly.

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