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Ethnomedicinal uses of Indian spices used for cancer treatment: A treatise on structure-activity relationship and signaling pathways

Neetu Singh, Surender Singh Yadav *

Department of Botany, Maharshi Dayanand University, Rohtak, Haryana, 124001, India

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ABSTRACT

Cancer is among the major cause of demise worldwide. Though the array of anticancer chemical medications is available but unfortunately, they are also associated with negative health effects. The invaluable therapeutic potential of spices makes them an integral part of our daily diet. Therefore, the present work focuses on the traditional uses of 46 spices and the phytochemical analysis of 31 spices. Out of them, only 29 spices are explored for their cytotoxicity against different cancer cell lines. The pre-clinical and clinical anticancer studies of spices along with their toxicity, mechanism of actions like Wnt/β-catenin, phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), JAK/STAT, mitogen-activated protein kinase (MAPK), Notch-mediated pathways and Quantitative structure-activity relationship (QSAR) studies were also focused. Curcumin was found as one of the most explored bioactive in every aspect such as *in-vitro, in-vivo,* clinical as well as SAR anticancer studies while some other bioactive such as 1,8-Cineole, *trans*-Anethole, Diosgenin, Trigonelline are either unexplored or least explored for their clinical and SAR studies. In fact, traditional medicinal uses of spices also provide solid shreds of evidence for the new leads towards the invention of novel anticancer agents. Therefore, further research can be designed for the anticancer marketed formulation from spices after having their placebo and related toxicological data.

1. Introduction

Cancer is a dreadful disease and is one of the major deleterious causes of death all over the globe (Bhagat and Chaturvedi, 2016). According to World Health Organization (WHO)-Cancer report (2018), about 9.6 million deaths were reported to be caused by cancer. The disease is featured by unlimited cell division, growth, and distant migration. It is mainly caused by carcinogenic agents which can be categorized into two groups i.e., genotoxic agents and non-genotoxic agents. The genotoxic agents are those which directly interfere with the genetic material and induce the alteration in the cell cycle whereas the non-genotoxic agents indirectly induce cancer (Anwar et al., 2020). Though numerous conventional anticancer modalities such as surgery, radiation therapy, chemotherapy, immunotherapy, photodynamic therapy, cancer vaccinations, stem cell transformation, and combination thereof are often available but they are effectively used only for compromising the small-sized tumors and are also associated with several negative effects. Chemotherapy and radiotherapy lead to the damages of normal cells along with the tumor's cells. For instance;

* Corresponding author.
E-mail address: ssyadavindia@gmail.com (S.S. Yadav).

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Abbreviations

PCD	Programmed cell death
NF-κB	Nuclear factor kappa B
NEDD	Neural precursor cell expressed developmentally down-regulated protein
CSCs	Cancer stem cells
IL	Interleukin
MMP	Matrix metallopeptidases
VEGF	Vascular endothelial growth factor
IC	Inhibitory concentration
YAP	Yes-associated protein
TAZ	Transcriptional coactivator with PDZ-binding motif
TNF-α	Tumor necrosis factor-α
EGFR	Epidermal growth factor receptor
TRPV1	Transient receptor potential vanilloid type-1
Bcl-2	B-cell lymphoma 2
CRC	Colorectal cancer
OXA	Oxaliplatin
MNU	*N*-nitroso *N*-methyl Urea
PTEN	Phosphatase and tensin homolog
PARP	Poly ADP-ribose polymerase
ER-α	Estrogen receptor alpha
HDAC	Histone deacetylase
DMH	Dimethylhydrazine
DSS	Dextran sulphate sodium
GSK3β	Glycogen synthase kinase 3β
CK1α	Casein kinase 1α
DVL	Disheveled
TCF	T cell-specific factor
LEF	Lymphoid enhancer-binding factor
CBP	CREB binding protein
APC	Adenomatous polyposis coli gene
AXIN	Anti-Neurexin
PI3K	Phosphatidylinositol-3-kinase
mTOR	Mammalian target of rapamycin
PH	Pleckstrin-homology
MAPK	Mitogen-activated protein kinase
RTKs	Receptor tyrosine kinases
NICD	Notch intracellular domain
NEC	Notch extracellular subunit
NTM	Notch transmembrane fragment
NEXT	Notch extracellular truncated
CSL	C-protein binding factor 1/Suppressor of Hairless/Lag-1
GRAS	Generally recognized as safe
HNPMI	N-(2-hydroxy-5-nitrophenyl (4′-methylphenyl) methyl) indoline
NQO1,	NAD(P)H quinone oxidoreductase 1
Keap1	Kelch-like erythroid cell derived protein with CNC homology[ECH]-associated protein 1
Nrf2	[NF-E2]-related factor 2
QSAR	Quantitative structure-activity relationship
ISO	International Organization for Standardization

radiotherapy retards the bone and muscle growth in children suffering from cancer. Moreover, due to the continuous use of conventional anticancer therapies, many patients have also reported adverse effects like anemia, immunosuppression, diarrhea, cough, nausea, constipation, bleeding, hair loss, infection, vomiting, appetite loss, pain, drowsiness, irritability and sadness. These factors necessitate the requirement of natural and effective treatment of cancer with fewer adverse effects (Zheng et al., 2016; Mora et al., 2022).

Natural products are considered palliative over chemotherapy. There are numerous natural products with highly diversified structures and functions. They are also termed "secondary metabolites". The classification of these secondary metabolites is depicted in Fig. 1 (Das and Gezici, 2018). These products play a key role in drug development against cancer as well as other diseases too like cardiovascular disorders, pathogenic infections, digestive problems, neurological issues, and so on. They also regulate the endogenous defense system and interaction

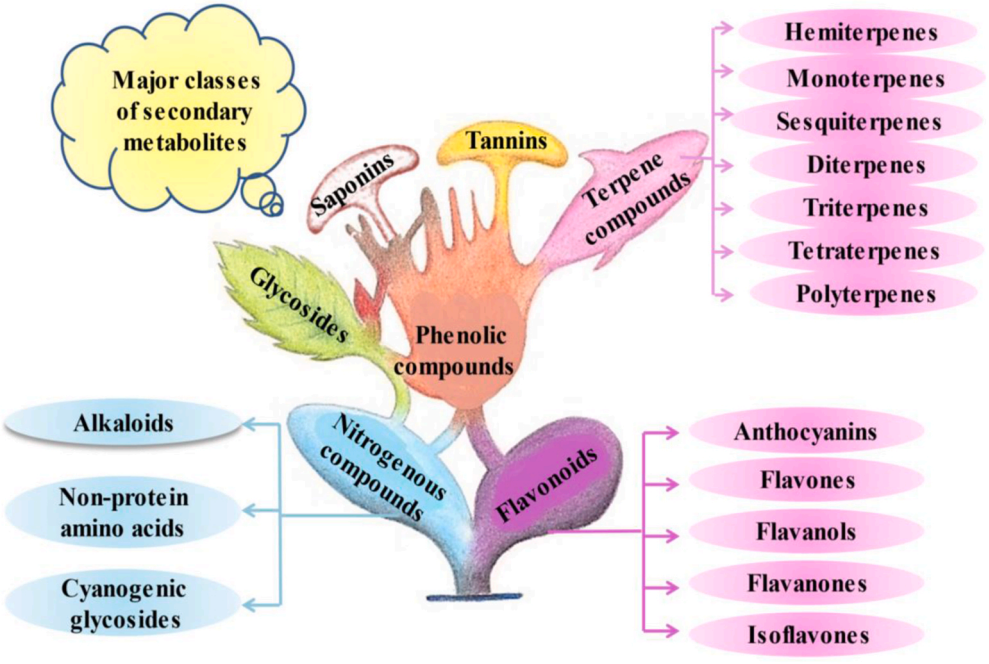

Fig. 1. Classification of natural products/secondary metabolites.

(in terms of the competition) with other organisms. They cover a wide pool of chemical space instead of synthetic compound libraries, thus, providing a great source of compounds that can be isolated and developed as a novel drug. Approximately, more than 70% of anticancer medications are developed from natural products. For instance, vincristine, vinblastine, paclitaxel, docetaxel, ellipticine, berberine, combretastatins, cephalotaxus, campothecin, curcumin and capsaicin are some of the most established examples of plant-derived natural products utilized for cancer prevention (Iqbal et al., 2017; Dallavalle et al., 2020; Atanasov et al., 2021). Besides, there are some factors that influence the frequent use of anticancer natural products. The major disadvantage is the scarcity of international standardization and documentation on the composition, quality, efficacy, safety, manufacturing practices, regulation, and approval processes of natural products. One another limitation that greatly affects the anticancer use of natural products is their poor solubility and bioavailability (Fridlender et al., 2015). Despite, these limitations, natural products are always preferable over chemical drugs due to their eco-friendly, less toxicity, and omnipresence properties.

Spices are also considered as one of the most promising anticancer agents due to their inverse relation with oncological incidences such as abnormal cell growth, irregular cell cycle, cell cycle arrest, abnormal apoptosis, damaging of healthy tissues, tumor inducing signaling pathways (Perez-Ortiz et al., 2020; Kammath et al., 2021). These are the naturally-fragmented dried plant parts including seeds, bark, roots, flowers, and fruits, especially used for flavoring, seasoning, coloring, and preserving food products (Singh et al., 2021a). Globally, thousands of spices are used for coloring, flavoring, and preserving food items. The use and preferences of these spices vary from region to region. Therefore, it seems difficult to enlist all the spices in a single shot. In India, under the act of parliament, a total of 52 spices are considered under the purview of Spices Board, however, 109 spices are mentioned in the International Organization for Standardization (ISO) list. Many spices are native to India; hence the country is aptly recognized as the land of spices. Generally, spices are used in minor quantities and especially used for preserving and imparting colour and taste to the food items but apart from this, they also possess tremendous health benefits (Kunnumakkara et al., 2018; Sachan et al., 2018). From millennia, several studies have ascertained the effectiveness of spices in the preparation of folkloric medicines for managing routine maladies and rejuvenating overall health. The pharmacological properties of spices are rendered by their active compounds (Sachan et al., 2018). They consist of alkaloids, flavonoids, terpenoids, phenols, phenylpropanoids, anthocyanins, fibers, sugar, fat, protein, ash, calcium, iron, vitamin B, vitamin C, carotene, gum, essential oils, and many more. They are rich source of sodium and fat and able to meet their dietary requirement. Thus, they exert beneficial health effects on salt and sugar reduction (Balasubramanian et al., 2016).

Spices are a rich reservoir of useful dietary bioactive and are popularly considered as the primary source of nutraceuticals (Srinivasan, 2017a). Many dietary spices have been well reported with numerous pharmacological effects such as antioxidant, antimicrobial, antidiabetic, wound healing, anti-inflammatory as well as immunomodulatory effect. All these pharmacological potentials are primarily being responsible for the anticancer efficacy of spices. Many spices such as *Curcuma longa* (Turmeric), *Cinnamomum verum* (Cinnamon), *Nigella sativa* (Black cumin), *Cuminum cyminum* (Cumin), *Zingiber officinale* (Ginger), *Trigonella foenum-graecum* (Fenugreek), *Allium sativum* (Garlic), *Crocus sativus* (Saffron), *Piper nigrum* (Black pepper) and *Capsicum annum* (Chilli powder) are well documented for their anticancer property (Zheng et al., 2016). Numerous bioactives from spices such as curcumin, sulfur compounds, 6-gingerol, thymoquinone, eugenol, and capsaicin are also well reported for their anticancer potential (Srinivasan, 2017a). Therefore, the present study summarizes the up-to-date information on the anticancer role of spices. The various ethnomedicinal uses of spices were described to indicate that a single plant can be used in treating other diseases too apart from cancer. Spices' bioactives were discussed to signify the role of a single phytocompound against several cancer types. The possible mechanism of action is depicted in figures to ease the understanding of signaling pathways. Structure-activity relationship (SAR) studies, pre-clinical and clinical studies are also well illustrated to strengthen the research going on cancer. Ultimately, the study provides solid pieces of evidences on the anticancer role of spices and baseline for the younger researchers particularly those working on the anticancer drug development from natural products.

2. Methodology

A comprehensive literature survey was conducted from 2015 to 2022 on the anticancer potential of species by referencing the major scientific databases such as Google Scholar, Science Direct, PubMed, Scopus, Web of Science and WHO. Spices listed under purview of Spices Board of India were only included for the current study. The reference articles were obtained via using the keywords like spices, anticancer potential, active compounds, anticancer potential of spice's bioactives, ethnomedicinal uses of spices and the SAR studies of spices bioactives to gather available information. Spices used for traditional uses were of primary concern to collect the valuable information, by adopting the comprehensive selection criteria. The articles dealing with the anticancer compound isolation were of primary focus. The articles related to spices but on different aspects like different kind of stress mitigation, stability issues, physiochemical and biochemical profiling, germination indices, genomic variations, packaging and adulteration were excluded. Chemical structures were drawn via ChemDraw ultra-8.0. Primarily, the current review focuses on the anticancer efficacy of ethnomedicinally used spices in India.

3. Ethnomedicinal uses of Indian spices

All across the globe, over 80 spices are grown and out of them near 50 spices are cultivated in India. It is the biggest producer of spices and that's why it is popular all over the world for its spices and traditional medicines (Balasubramanian et al., 2016). The history of the use of spices is as old as the history of mankind. The uses of spices are also well reported in "Epic of Gilgamesh" and the "Bhagavad Gita". In Ayurveda, spices are reported to be used in improving the state of mood and mind. They are a rich source of flavoring, coloring, and preserving agents. They not only improve the quality of food but also enhance the secretion of saliva as well as improve the digestive system. On the traditional medicinal scale, they are used to treat cold, influenza, nausea, stomach ache, and vomiting. Plenty of spices like cinnamon, black pepper, turmeric, and ginger have been used on a large scale during covid-19. These spices can also be used to cure other disorders. For instance; the long pepper can be traditionally used in curing respiratory disorders, gastric issues, tongue paralysis, diarrhea, fever, hepatitis, stomachache, cholera, cough, and tumors (Prasad and K Tyagi, 2016). Besides, they are also used for embalming mummies because of their flavoring properties (Gottardi et al., 2016). They also possess purgative, laxative, expectorant, carminative, and diuretic agents (Sachan et al., 2018). All these aforementioned studies provide scientific evidence to some extent for the effective use of spices in our daily diet, to improve human well-being. The various ethnomedicinal uses of some commonly used spices are summarized in Table 1.

Nowadays, there is the concept of repurposing the drug i.e., the drug that is already established against a particular type of disease is also explored for its therapeutics against other diseases, so that a single drug can be recruited against several disorders. Therefore, from Table 1, it can be inferred that the spices which possess immense pharmacology against several disorders can be further explored in novel drug development.

Table 1
Ethnomedicinal uses of Indian spices used for cancer treatment.

S. No.	Botanical Name	Family	Common Name	Plant part used	Prominent Ethnomedicinal use	Ref. (s)
1.	 *Piper nigrum* L.	Piperaceae	Black pepper	Fruit	• Gastric problems and diarrohea • Indigestion • Inflammation • Cold and fever • Worms and piles • Antihypertensive • Anti-asthmatic • Immunomodulatory • Anti-ulcer and analgesic	de Souza Grinevicius et al. (2016); Kunnumakkara et al. (2018); Perez-Ortiz et al. (2020)
2.	 *Syzygium aromaticum* (L.) Merr. & L.M. Perry	Myrtaceae	Cloves	Flower buds and essential oil	• Painkiller • Dental care • Oxidative stress and antiseptic • Prevent microbial infections • Vomiting and nausea • Flatulence • Liver, bowel and stomach disorders • Act as nerve stimulant • Microbial and protozoan infections	Sachan et al. (2018); Kello et al. (2020)
3.	 *Zingiber officinale* Roscoe	Zingiberaceae	Ginger	Rhizome	• Improve digestion and good for spleen and sore throats • Common cold and flu • Migraine pain and depression • Atherosclerosis and high cholesterol • Rheumatoid arthritis and ulcers • Painful menstrual periods • Cardiovascular disorders • Abdominal cramps • Respiratory disorders • Prevent inflammation • Antinausea remedy	Gottardi et al. (2016); Mansingh et al. (2020); Perez-Ortiz et al. (2020)
4.	 *Cinnamomum verum* J. Presl	Lauraceae	Cinnamon	Bark	• Improve digestion • Delays stomach emptying • Hepatoprotective • Good for spleen and sore throats • Pain • Antipyretic and antiseptic • Inflammation • Gastrointestinal disorders • Antimicrobial and antiviral properties	Gottardi et al. (2016); Srinivasan (2017b); Singh et al. (2021a)
5.	 *Curcuma caesia* Roxb.	Zingiberaceae	Black turmeric	Rhizome	• Cure injuries • Vomiting, toothache • Diarrhea and dysentery • Tumors and piles • Respiratory disorders and inflammation • Hemorrhoids • Menstrual problems, aphrodisiac • Different kind of discharges • Antihelminthic • Muscle relaxant and leprosy	Mukunthan et al. (2017)

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Table 1 (*continued*)

S. No.	Botanical Name	Family	Common Name	Plant part used	Prominent Ethnomedicinal use	Ref. (s)
6.	 *Curcuma longa* L.	Zingiberaceae	Turmeric	Rhizome	• Ceremonial purposes • Cough, cold and injuries • Liver disorders • Rheumatism and sinusitis • Stimulant and carminative • Sprains and swelling • Diuretic and laxative agent • Relief body pain • Prevention of liver disorders, diarrhea, stress and depression • Act as coloring agent	Perez-Ortiz et al. (2020)
7.	 *Myristica fragrans* Houtt.	Myristicaceae	Nutmeg/ Jaiphal	Seeds	• Improve digestion • Good for spleen and sore throats • Anti-allergic and analgesic • Insulin resistance • Prevent inflammation • Liver tonic, uterine tonic and cardiotonic • Sedative, aphrodiasic and hypolipidemic	Gottardi et al. (2016)
8.	 *Origanum majorana* L.	Lamiaceae	Marjoram	Leaves	• Chest pain • Wounds • Cold & cough • Sore throat • Rheumatic pain • Neurodisorders • Gastric issues • Heart diseases • Dermatological disorders • Helps soothe stomach muscles	Khaleel et al., 2016
9.	 *Capsicum annuum* L.	Solanaceae	Chili pepper	Fruit	• Asthma • Gastrointestinal problems • Pain, toothache and wounds • Ulcer • Headaches • Night blindness • Hypersensitivity • Arthritis and rheumatism • Can stop heart attack	Chamikara et al. (2016)
10.	 *Nigella sativa* L.	Ranunculaceae	Black seed	Seeds	• Arthritis and epilepsies • Asthma and ulcers • Hypertension • Inflammation, wounds and malaria • Analgesic • Gastroprotective • Hepatoprotective • Renoprotective • Used as nutritional supplement	Majeed et al. (2021)
11.	 Elettaria cardamomum *(L.) Maton*	Zingiberaceae	Small cardamom	Fruits	• Asthma and bronchitis • Cold and sore throat • Oral ailments, bad breath, vomiting and indigestion • Cataracts, nausea, diarrhea, constipation and stomach ache • Cardiac, digestive, bladder and kidney problems • Pulmonary disorders • Effective against snake and scorpion venom • Eyelid's irritations	Ashokkumar et al. (2020)

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Table 1 (*continued*)

S. No.	Botanical Name	Family	Common Name	Plant part used	Prominent Ethnomedicinal use	Ref. (s)
12.	 *Apium graveolens* L.	Apiaceae	Celery	Leaves	• Antihypertensive • Hypolipidemic • Empower brain and nerve • Colic pain and flatulence • Treat suppressed testicular functionality • Carminative	Perez-Ortiz et al. (2020)
13.	 *Foeniculum vulgare* Mill.	Apiaceae	Fennel	Seeds and fruits	• Digestive, reproductive, and respiratory disorders • Microbial infections • Can reduce bad breath and body odor • Glaucoma • Galactagogue • Improve eyesight • Flatulence of infants • Carminative and diuretic	Farid et al. (2020)
14.	 *Cuminum cyminum* L.	Apiaceae	Cumin	Seeds and fruits	• Carminative and hypertension • Gastro-protective • Antispasmodic • Hypertension, hypoglycemic and digestive stimulant • Anti-osteoporotic • Antioxidant • Dyspepsia and allergic rhinitis • Respiratory and metabolic disorders	Goodarzi et al. (2020); Perez-Ortiz et al. (2020); Singh et al. (2021b)
15.	 *Trigonella foenum-graecum* L.	Fabaceae	Fenugreek	Seeds and leaves	• Reduce sugar content • Socking seeds reported with increased antidiabetic potential • Stop liver disorders • Enhance kidney functions • Heart diseases • Prevent obesity • Hypocholesterolemic • Improve immune system • Prevent inflammation • Helps flush out harmful toxins	Mohamadi et al. (2018); Sanlier and Gencer (2020); Singh et al. (2022)
16.	 *Brassica juncea* L. Czern	Brassicaceae	Mustard	Seeds	• Cardio protective action • Used as emetic and diuretic agent • Prevent arthritis and rheumatism • Stop inflammation • Hyperglycemia, thyroids, hyperlipidemia and hypercholesterolemia	Kunnumakkara et al. (2018); Sanlier and Gencer (2020)
17.	 *Murraya koenigii* (L.) Spreng.	Rutaceae	Curry leaf	Leaf	• Prevent inflammation • Relief kidney pain • Stop vomiting • Used as antidiabetic agent • Increase glucose metabolism • Blood purifier • Prevent stomachache • Wound healing • Renal pain • Cure piles and leucoderma	Sanlier and Gencer (2020)

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Table 1 (*continued*)

S. No.	Botanical Name	Family	Common Name	Plant part used	Prominent Ethnomedicinal use	Ref. (s)
18.	 *Coriandrum sativum* L.	Apiaceae	Coriander	Whole plant	• Digestive and urinary disorders • Respiratory problems • Anti-inflammatory • Anti-diabetic • Insomnia, anxiety and convulsion • Cholesterol lowering effects • Carminative • Antiulcer	Sari et al. (2021)
19.	 *Pimpinella anisum* L.	Apiaceae	Aniseed	Seeds and fruits	• Gastro-protective • Analgesic in migraine • Hair and skin benefits • Hormonal imbalance in females • Anti-depressant • Disinfectant • Diuretic and carminative • Treatment of epilepsy, nightmare, melancholy and seizures	Sun et al. (2019)
20.	 *Trachyspermum ammi* (L.) Sprague	Apiaceae	Ajwain	Seeds and fruits	• Indigestion and dyspepsia • To cure asthma and colic pain • Skin infections • Common cold and migraine • Vomiting and mouth disorders • Hiccups and carminative • kidney and spleen diseases • Improves the cardiac health • Atonic dyspepsia • Astha and bronchial troubles • Abdominal pain, piles, amenorrhea and aphrodisiac	Chahal et al. (2017a)
21.	 *Carum carvi* L.	Apiaceae	Caraway	Fruits	• Anti-obesity • Anti-anxiety and analgesic • Anti-inflammatory • Hypothyroidism • Antispasmodic, carminative and immunomodulatory • Bowel diseases • Appetite-suppressing activity • Cure lower blood pressure • Antitubercular activity • Anticolitis activity	Miraj and Kiani (2016)
22.	 *Anethum graveolens* L.	Apiaceae	Dill	Seeds	• Bladder inflammation • Liver disorders • Insomnia, brain tonic and Cardio-protective • Hypolipidemic • Decrease blood cholesterol • Galactogogue and vomiting • Anticonvulsant and anticramp • Antispasmodic and anti-emetic agent	Chahal et al. (2017b)
23.	 *Allium sativum* L.	Alliaceae	Garlic	Bulb	• Performance enhancing • Snake and insect bites • Chronic cough • Antibiotic for infectious diseases and antidiabetic • Hypertension • Hypercholesterolemia • Arteriosclerosis • Cardio-protective	Gudalwar et al. (2021)

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Table 1 (*continued*)

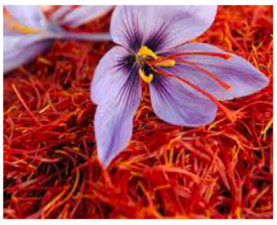
S. No.	Botanical Name	Family	Common Name	Plant part used	Prominent Ethnomedicinal use	Ref. (s)
24.	 *Garcinia indica* (Thouars) Choisy	Clusiaceae	Kokam	Fruit rind	• Anti-obesity and antidiabetic • Gastric problems • Anti-inflammatory • Dermatitis and wound healing • Rheumatic pain and diarrhea • Antihelmintic and skin ulcers • Cardioprotective • Skin elasticity and moisturiser • Dyspepsia and hyperplasia	Chate et al. (2019)
25.	 *Mentha piperita* L.	Lamiaceae	Mint	Leaf	• Fever and cold • Digestive disorders • Antifungal and antiviral • Oral mucosa and irritation • Throat inflammation • Digestive disorders • Larvicidal and antidiabetic • Radio-protective effect • Toothpaste preparation	Mahendran and Rahman, 2020
26.	 *Petroselinum crispum* (Mill.) Fuss	Apiaceae	Parsley	Seeds and leaf	• Kidney stones, amenorrhea, dieresis and blurred vision • Carminative and halitosis • Gastrotonic and astringent • Inflammation and dermatitis • Antiseptic, antimicrobial and antispasmodic • Sedative agent	Agyare et al. (2017)
27.	 *Punica granatum* L.	Punicaceae	Pomegranate	Seeds	• Peptic ulcers and dieresis • Atherosclerosis • Hyperlipidemia, chest pain, hypertension and diabetes • Cerebrovascular disease • Hunger headaches • Oral aphthae in behcet disease • Halitosis and bile disorders • Gingival bleeding • Jaundice and diarrhea	Ge et al. (2021)
28.	 *Crocus sativus* L.	Iridaceae	Saffron	Dried stigmas	• Depression, menstruation and painful urination • Weapon of seduction • Anti-inflammatory, anti-anxiety, diuretic and sedative • Asthma, cough, arthritis, • Dysmenorrhea, plague, chest pain, lung, liver and kidney function	Cardone et al. (2020)
29.	 *Vanilla planifolia* Jacks. Ex Andrews	Orchidaceae	Vanilla	Pod	• Relieve fever, gastric issues, overweight, ulcers, dental caries, cough, hysteria, dyspepsia and dysmenorrhea • Aphrodisiac properties • Aromatherapy, antimicrobial and antioxidant properties • Physiological and emotional health, menstruation regulation and promote arousal	Ahmad et al. (2020)
30.	 *Illicium verum* Hook.f.	Schisandraceae	Star anise	Fruit	• Stomachaches and vomiting • Rheumatic and colic pain • Skin inflammation • Dyspepsia and insomnia • Facial paralysis • Flatulence • Asthma and bronchitis • Antiseptic, antimicrobial and antioxidant activity	Rocha and Tietbohl (2016)

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Table 1 (*continued*)

S. No.	Botanical Name	Family	Common Name	Plant part used	Prominent Ethnomedicinal use	Ref. (s)
31.	 *Acorus calamus* L.	Araceae	Sweet flag	Rhizome	• Hair loss • Arthritis and neuralgia • Sinusitis and eczema • Dyspepsia and diarrhea • Kidney and liver problems • Asthma, fever and bronchitis	Khwairakpam et al. (2018)
32.	 *Alpinia galangal* (L.) Willd.	Zingiberaceae	Greater galanga	Rhizome	• Kidney and liver troubles • Stomach and back pain • Rheumatism and dyspepsia • Enhance the appetite • Asthma, bronchitis, fever, diabetes and heart diseases • Cardiotonic lesions • Diuretic and irritations	Khairullah et al. (2020)
33.	 *Armoracia rusticana* P. Gaertn., B. Mey. & Scherb.	Brassicaceae	Horse Radish	Root	• Urinary tract infections • Asthma and bronchitis • Lung and heart problems • Treat wound, fever and pain • Headaches and hypertension • Nasal and sinus dysfunctions • Antiseptic and diaphroretic • Toothache and ulcers • Colic, scurvy and venereal diseases • Back pain and rheumatism	Yasmeen et al. (2020)
34.	 *Capparis spinosa* L.	Capparidaceae	Caper	Flower buds	• Liver and kidney disorders • Paralysis, diabetes and mental disorders • Splenomegaly • Tubercular glands • Rheumatoid arthritis and gout • Hemorrhoids and ulcers • Toothache and skin diseases • Convulsions • Menstruation	Zhang and Ma (2018)
35.	 *Ferula asafoetida* H. Karst.	Apiaceae	Asafoetida	Resins	• Muscle relaxant • Memory enhancer • Digestive disorders • Hypotensive and anthelmintic • Hepatoprotective • Antispasmodic • Treatment of unwanted abortion, unusual pain, sterility, leucorrhea, excessive menstruation, loose stools, flatulence	Upadhyay (2017)
36.	 *Hyssopus officinalis* L.	Lamiaceae	Hyssop	Leaf	• Cough suppressant • Gastrointestinal troubles • Epilepsy • Microbial infections • Ulcers and spasm • Antispasmodic • Expectorant	Tahir et al. (2018)
37.	 *Juniperus communis* L.	Cupressaceae	Juniper berry	Berry	• Antiseptic and antidiabetic • Diuretic • Gastrointestinal troubles • Rheumatic arthritis • Hypoglycemic • Hypolipidemic • Anti-inflammatory	Raina et al. (2019)

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Table 1 (*continued*)

S. No.	Botanical Name	Family	Common Name	Plant part used	Prominent Ethnomedicinal use	Ref. (s)
38.	 *Laurus nobilis* L.	Lauraceae	Bay leaf	Leaf	• Rheumatism and dermatitis • Epigastring blotting • Improper digestion • Flatulence, eructation and analgesic • Antidote in snake bite • Stomachache and migraine	Elkiran et al. (2018)
39.	 *Ocimum basilicum* L.	Lamiaceae	Basil	Leaf	• Haemostyptic in childbirth • Mentrual irregularties • Asthma and bronchitis • Microbial infections • Earache, fever, flu, cold, cough and malaria • Arthritis and anorexia • Diarrhea and influenza	Shahrajabian et al. (2020)
40.	 *Papaver somniferum* L.	Papaveraceae	Poppy seeds	Seeds	• Diarrhea • Dysentery • Cough and asthma • Used to remove dandruff • Insomnia • Analgesic, narcotic, sedative, stimulant and nutritive • Biliary colic • Headache	Raut and Ghotankar (2019)
41.	 *Rosmarinus officinalis* L.	Lamiaceae	Rosemary	Leaf	• Reliving muscle pain • Boost up the memory • Immunity enhancer • Promote the hair growth • Mild analgesic, diuretic • Carminative and expectorant • Treat wounds, rashes, headaches, dyspepsia, renal colic and circulation issues	Kompelly et al. (2019)
42.	 *Salvia officinalis* L.	Lamiaceae	Sage	Leaf	• Allergic swelling • Arthritis and rheumatism • Diarrhea, cold, cough, snake bite, sclerosis, respiratory, metabolic and mental sickness, heartburn, acidity • Excessive sweating, mouth and throat inflammation • Endocrine disorders and high blood pressure • Hypotensive, sedative and stimulant	Sharma et al. (2019)
43.	 *Thymus vulgaris* L.	Lamiaceae	Thyme	Leaf	• Whooping cough • Asthma and bronchitis • Prevent hardness of arteries • Urinary tract infections • Treat toothache • Enhance appetite by treating stomach and intestine infection • Dyspepsia and insomnia • Analgesic and antipyretic • Regulates the blood flow	Dauqan, and Abdullah (2017)
44.	 *Origanum vulgare* L.	Lamiaceae	Oregano	Leaf	• Stomachic troubles • Carminative • Menstrual related disorders • Expectorant • Relive from cough • Flatulence, hepatoprotective • Treat cramps • Emmenagogue	Oniga et al. (2018)

(*continued on next page*)

Table 1 (*continued*)

S. No.	Botanical Name	Family	Common Name	Plant part used	Prominent Ethnomedicinal use	Ref. (s)
45.	 *Artemisia dracunculus* L.	Asteraceae	Tarragon	Leaf	• Digestive disorders • Gingivitis and insomnia • Anaesthetic for toothache • Used to treat irritation, allergies, rashes, fever, intestinal cramps & worms • Gastritis, wound, cuts, ulcers and dyspepsia • Dermatitis and dysentery • Anti-epileptic • Immunostimulant	Ekiert et al. (2021)
46.	 *Tamarindus indica* L.	Caesalpiniaceae	Tamarind	Fruit	• Wound healing • Snake bite and analgesic • Abdominal pain • Cold, fever and inflammation • Diarrhea and hypolipidemic • Helminthes infection • Laxative effects	Menezes et al. (2016)

4. Phytochemistry of Indian anticancer dietary spices

Spices are the rich reservoir of many therapeutically active compounds *viz*. alkaloids, phenolic compounds, flavonoids, quinines, amino acids, polypeptides, terpenoids, vitamins etc. Approximately 180 chemical compounds from spices have been authenticated to be used against different degenerative diseases. Out of them, numerous bioactive are also being evidenced for cancer risk management. Cinnamaldehyde, allyl isothiocyanate, gingerol, *Ar*-tumerone, shagol, sulfur-containing compounds, zingiberene, anethole, estragole, ferulic acid, caryophyllene, 1,8-cineole, thymoquinone, eugenyl acetate, eugenol, limonene, sabinenecamphene, curcuminoids, curcumin, myrceneajoene, linalool, phenethyl isothiocynate, myristicin, allicin, alliin, methiin, trigonelline, cuminaldehyde, citral, safrole, quercetin, rutin, leutin, rosmarinic acid, capsaicin and many other compounds derived from spices play a pivotal role in cancer prevention (Mughal, 2019).

In a study by Vutakuri and Somara (2018), two bioactives *viz*. Diindolylmethane and indole-3-carbinol from *Elettaria cardamomum* (Cardamom) were reported for breast cancer treatment. But still many bioactives of spices are either unexplored or least explored for their anticancer potential hence herein we listed different bioactives derived from spices which are specifically used for cancer treatment. The list of anticancer bioactives from spices along with their structures and their anticancer specificity towards a particular type of cancer is summarized in Table 2.

Table 2 shows that some of the compounds were evaluated for their anticancer potential against more than one cancer while some of the compounds were reported only against one cancer type. Therefore, these compounds can be evaluated against other cancer types too. The anticancer efficacy of these compounds can be evaluated after the structural modification of these compounds. It is hypothesized that the structural modification is featured by enhanced functionalization. The same hypothesis can be applied on these bioactives too.

5. *In-vitro* cytotoxicity of Indian spices

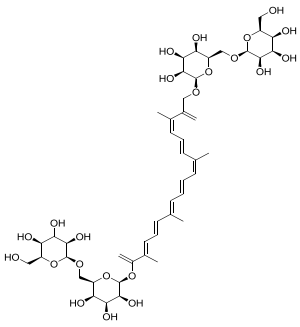
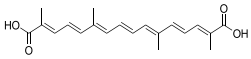
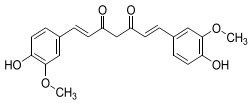
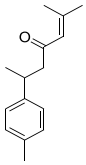
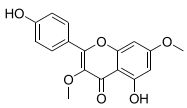
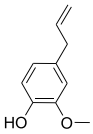
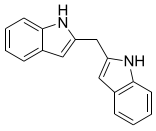
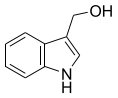
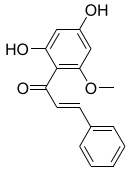
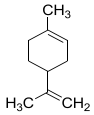
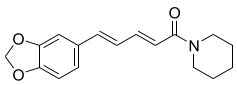
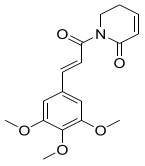
Being a multifactorial disease, it is difficult to tackle carcinogenesis with monodrug therapy. Sometimes monodrug therapy also exerts some negative effects which can be countered with adjuvant drugs (Geng et al., 2016). Due to such safety concerns, the plant bioactives are preferred to cure this deadly disease sophisticatedly as compared to the chemotherapy. Spices are the rich reservoir of many bioactives *viz*. alkaloids, terpenes, flavonoids, phenylpropanoids and anthocyanins which possess anticancer therapeutic potential. These bioactives have the potential to halt the excessive synthesis of reactive oxygen species (ROS) and nitrogen radicals which ultimately prevents the many metabolic disorders associated with them (Singh and Yadav, 2022). These bioactives also augments the endogenous antioxidant system. The suppression of oxidative stress ultimately reduces the risk of cancer initiation and progression (Bhagat and Chaturvedi, 2016).

Therefore, spices' derived bioactives can be used frequently for prevention of different kind of malignancies and for combating more than one cancer type such as breast, lung, fore stomach, liver, pancreas, colorectal and oral cancer (Srinivasan, 2017a). For instance, in a study by Ramaswamy et al. (2017), the antitumor potential of ginger, dalchini and ajwain decoctions was examined against lung cancer cell lines. It was observed that a concentration ranges from 25 to 50 μg/ml was effective in combating cancer cell proliferation while the concentration above 50 μg/ml was insignificant due to its intolerability. The significant anticancer effect of various spices and herbs was also screened against cancerous cells and their cyclooxygenase-2 (COX-2) inhibitory activity in HCA-7 cell lines of colorectal cancer (CRC) (Jaksevicius et al., 2017).

Numerous spices in the following order: turmeric, bay leaf, ginger, sage and rosemary have significantly suppressed the cell growth along with the down-regulation of COX-2 expression and activity. In another study by Saeed (2017), the synergistic anticarcinogenic activity of clove/dalchini water decoction was screened on HepG2 cell lines of liver carcinoma and it was found that the extract has exerted significant cytotoxicity as compared to the control. The anticancer efficacy of turmeric, ginger and garlic mixture on MCF-7, ZR-75 and MDA-MB 231 cell lines of breast cancer was carried out and it was found that the combined extract has induced apoptosis more profoundly in MCF-7 and ZR-75 cell lines followed by MDA-MB 231 cell lines (Vemuri et al., 2017). Thymoquinone from *Nigella sativa* can be used for the prevention of metastasis of tumor cells to the other body parts and phytoestrogen from red clove to stop breast cancer. Crocin, from saffron was also reported to downregulates the progression of cancer cell (Kammath et al., 2021). The *in-vitro* cytotoxicity studies of spice' derived extracts or a specific compound are summarized in Table 3.

From Table 3, it is observed that there is no specific bioactive that persist in all the spices for their anticancer effect. The anticancer therapeutic effects of these spices are mainly attributed to the presence of their unique bioactives that vary from spice to spice. For examples, curcumin from *Curcuma longa*, cinnamaldehyde from *Cinnamomum*

Table 2
Structure of novel anticancer compounds isolated from Indian spices.

S. No.	Spices used	Class of compound	Name of the compound	Structure of the compound	Cancer type	Ref (s)
1.	*Crocus sativus* L.	Carotenoid	Crocin (Pubchem CID: 17339399)		Breast, lung, leukemia, reproductive system and digestive system cancer	Zheng et al. (2016); Hire et al. (2017); Mir et al. (2020)
			Crocetin (Pubchem CID: 4444644)			
		Organic oxides	Safranal (Pubchem CID: 55000)			
2.	*Curcuma longa* L.	Polyphenol	Curcumin (Pubchem CID: 839564)		Pancreatic, lung, bladder, colon, breast, gastric, nasopharyngeal, hepatobiliary and prostate cancer	Basha et al. (2016); Zheng et al. (2016)
3.	*Curcuma aromatica* Salisb.	Sesquiterpenoid	Ar-tumerone (Pubchem CID: 485257)		breast cancer	Parida et al. (2020)
4.	*Syzygium aromaticum* (L.) Merr. & L.M. Perry	Flavonoid	Kumatakenin (Pubchem CID: 4477326)		Ovarian, cervical, oral squamous cell carcinoma, digestive system and breast cancer	Zheng et al. (2016); Woo et al. (2017); Das et al. (2018); Choudhury et al. (2020)
		Phenylpropanoid	Eugenol (Pubchem CID: 13876103)			
5.	*Elettaria cardamomum* (L.) Maton	Indoles	Diindolylmethane (Pubchem CID: 8928276)		Breast, lung, ovarian, prostate, colon, gastric and leukemia	Bhagat and Chaturvedi (2016); Vutakuri and Somara (2018); Nawaz et al. (2020); Yue et al. (2020)
		3-Alkylindoles	Indole-3-carbinol (Pubchem CID: 3581)			
		Chalconoid	Cardamonin (Pubchem CID: 557026)			
		Monoterpene	Limonene (Pubchem CID: 388386)			
6.	*Piper nigrum* L.	Piperamide	Piperine (Pubchem CID: 553590)		Breast, prostate colon cancer and osteosarcoma	de Souza Grinevicius et al. (2016)
		Alkaloid	Piperlongumine (Pubchem CID: 553441)		Lung, breast, ovarian, gastric and colon cancer	Prasad and K Tyagi, 2016; Tripathi and Biswal (2020)

(*continued on next page*)

Table 2 (*continued*)

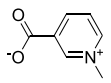
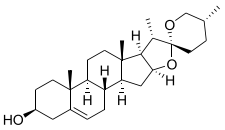
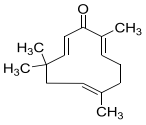
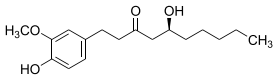
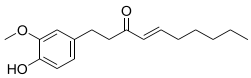
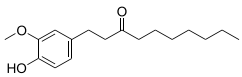
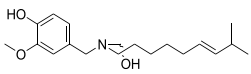
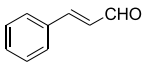
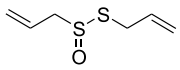
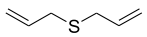
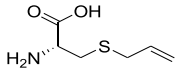
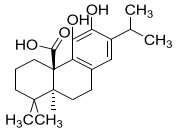
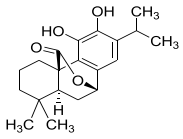
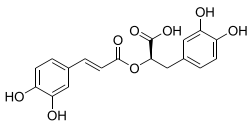
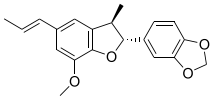
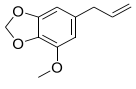
S. No.	Spices used	Class of compound	Name of the compound	Structure of the compound	Cancer type	Ref (s)
7.	*Trigonella foenum-graecum* L.	Alkaloid	Trigonelline (Pubchem CID: 5369)		Blood and breast cancer	Kunnumakkara et al. (2018); Mohamadi et al. (2018)
			Diosgenin (Pubchem CID: 89870)			
8.	*Zingiber zerumbet* (L.) Roscoe ex Sm.	Sesquiterpene	Zerumbone (Pubchem CID: 4580581)		Colorectal cancer	Sithara et al. (2018)
9.	*Zingiber officinale* Roscoe	Phenolics	6-Gingerol (Pubchem CID: 391126)		Breast, colorectal, prostate, lung cancer, melanoma and glioblastoma	Geng et al. (2016); Zheng et al. (2016); Kammath et al. (2021)
		Shogaols	Shogaol (Pubchem CID: 4445106)			
		Paradols	Paradol (Pubchem CID: 85173)			
10.	*Capsicum annuum* L.	Alkaloids	Capsaicin (Pubchem CID: 1265957)		Lung, colon, breast, cervical, prostate and tongue carcinoma	Geng et al. (2016); Kunnumakkara et al. (2018)
11.	*Nigella sativa* L.	Monoterpene	Thymoquinone (Pubchem CID: 9861)		Colon, bladder, lung, ovarian and gastric cancer	Zhang et al. (2016); Majeed et al. (2021)
12.	*Cinnamomum verum* J. Presl	Aldehyde	Cinnamaldehyde (Pubchem CID: 637511)		Leukemia, oral, liver, lung, prostate, breast and colon cancer	Singh et al. (2021a)
13.	*Cinnamomum tamala* (Buch.-Ham.) T. Nees & Eberm.	Monocyclic sesquiterpene	α-Caryophyllene (Pubchem CID: 4444853)		Lung, breast and brain cancer	Thanekar et al. (2016)
14.	*Allium sativum* L.	Organosulfur compound	Allicin (Pubchem CID: 58548)		Colon cancer	Perez-Ortiz et al. (2020)
			Diallyl sulphide (Pubchem CID: 11128)		Colon, skin, breast prostate and upper digestive tract cancer	Zheng et al. (2016); Kunnumakkara et al. (2018)
			S-Allyl-L-cysteine (Pubchem CID: 7969672)		Prostate cancer	Guldiken et al. (2018)
15.	*Rosmarinus officinalis* L.	Diterpenoids	Carnosic acid (Pubchem CID: 58635)		Lung, colorectal, breast, kidney, liver, prostate cancer and leukemia	Zheng et al. (2016); Kunnumakkara et al. (2018); Corveloni et al. (2020); Kammath et al. (2021)
			Carnosol (Pubchem CID: 390568)			
			Rosmarinic acid (Pubchem CID: 4445104)			
16.	*Myristica fragrans* Houtt.	Benzofurans	Licarin B (Pubchem CID: 4945284)		Skin carcinoma	Kunnumakkara et al. (2018); Perez-Ortiz et al. (2020)
		Phenylpropene	Myristicin (Pubchem CID: 4125)			

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Table 2 (*continued*)

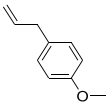
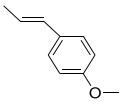
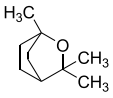
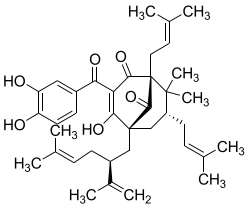
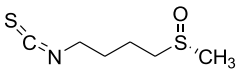
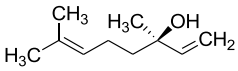
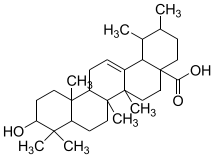
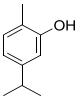
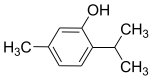
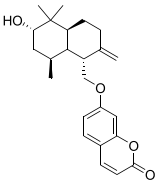
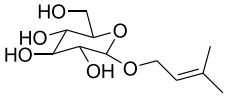
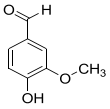
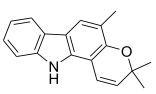
S. No.	Spices used	Class of compound	Name of the compound	Structure of the compound	Cancer type	Ref (s)
17.	*Illicium verum* Hook. f.	Phenylpropene	Estragole (Pubchem CID: 13850247)		Hepatocellular carcinoma	Kunnumakkara et al. (2018)
			trans-Anethole (Pubchem CID: 553166)		Osteosarcoma	Kunnumakkara et al. (2018)
18.	*Salvia officinalis* L.	Monoterpene cyclic ether	1,8-Cineole (Pubchem CID: 2656)		Hepatocellular and lung cancer	Kunnumakkara et al. (2018)
19.	*Garcinia indica* (Thouars) Choisy	Benzophenone	Garcinol (Pubchem CID: 10199485)		Breast, colon and squamous cell carcinoma	Duan et al. (2018); Kunnumakkara et al. (2018)
20.	*Brassica juncea* (L.) Czern.	Isothiocyanate	Sulforaphane (Pubchem CID: 7851806)		Lung, colorectal and bladder cancer	Kunnumakkara et al. (2018)
21.	*Coriandrum sativum* L.	Terpene alcohol	Linalool (Pubchem CID: 391430)		Breast cancer	Zheng et al. (2016)
22.	*Ocimum basilicum* L.	Triterpenoids	Ursolic acid (Pubchem CID: 191497)		Breast and colorectal cancer	Kunnumakkara et al. (2018)
23.	*Mentha piperita* L.	Triterpenoids	Carvone (Pubchem CID: 21106424)		Leukemia and skin cancer	Kunnumakkara et al. (2018)
24.	*Origanum vulgare*	Monoterpenoids	Carvacrol (Pubchem CID: 21105867)		Breast cancer	Baranauskaite et al. (2017)
25.	*Thymus vulgaris* L.	Monoterpenoids	Thymol (Pubchem CID: 21105998)		Colorectal cancer	Zeng et al. (2020)
26.	*Ferula asafoetida* H. Karst.	Sesquiterpene coumarins	Gummosin (Pubchem CID: 5442126)		Breast and prostate cancer	Iranshahy et al. (2019)
27.	*Capparis spinosa* L.	Glucopyranosides	3-methyl-2-buten-1-yl *β*-D-glucopyranoside (Pubchem CID: NR)		Breast cancer	Salih et al. (2020)
28.	*Vanilla planifolia* Jacks. Ex Andrews	Phenolic aldehyde	Vanillin (Pubchem CID: 1183)		Colorectal cancer	Xie et al. (2020)
29.	*Murraya koenigii* (L.) Spreng.	Carbazole alkaloid	Girinimbine (Pubchem: 87534)		Colon cancer	Iman et al. (2017)

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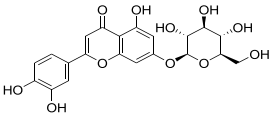
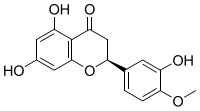
Table 2 (*continued*)

S. No.	Spices used	Class of compound	Name of the compound	Structure of the compound	Cancer type	Ref (s)
30.	*Cuminum cyminum* L.	Flavonoids	Luteolin-7-*O*-glucoside (Pubchem CID: 4444241)		Breast cancer	Goodarzi et al. (2020)
31.	*Origanum majorana* L.	Flavonoids	Hesperetin (Pubchem CID: 65234)		Brain and cervical cancer	Erenler et al. (2016)
		Benzenediol	Hydroquinone (Pubchem CID: 764)			

NR* = Not reported.

verum, cuminaldehyde from *Cuminum cyminum*, crocin from *Crocus sativus*, thymoquinone from *Nigella sativa*, eugenol from *Syzygium aromaticum*, cardamonin from *Elettaria cardamomum*, thymol from *Thymus vulgaris* and so on are specific to a particular spice for their anticancer effect. Sometimes, more than one bioactive from a single spice can also exhibit anticancer potential such as kumatakenin and eugenol are two different anticancer bioactive isolated from *Syzygium aromaticum*. Likewise, *Crocus sativus* possess two different anticancer bioactive including crocin and crocetin. On the contrary, a single bioactive can be reported from more than one spice but their therapeutic effects depend upon the yield of that particular bioactive. Hence, many bioactive compounds are responsible for the anticancerous activity of different spices.

Inflammatory tissues are one of the origins of cancer cells that increases the risk of carcinogenesis. Inefficient clearance of infected tissues during chronic inflammation leads to the tissue deterioration, ROS generation and ultimately DNA damage and mutation. Under these inflammatory conditions, the cells remain continuously proliferating in order to maintain homeostasis. This process becomes the major driving force for the development of initial tumor cells. Chronic inflammation is also the cause of overproduction of cytokines like TNF-α and IL-6. These cytokines trigger the malignancy and metastasis of cancerous cells. Therefore, the compound which exhibits anti-inflammatory potential can be precisely used to eliminate inflammation induced cancer pathology (Dupré and Malik, 2018).

Curcumin is a natural anti-inflammatory agent. It attenuates the production of pro-inflammatory and profibrotic cytokines by targeting the various inflammatory mediators like COX-2, inducible nitric oxide synthase and NF-κB, thus halts the excessive generation of free radicals. The whole mechanism will eventually aid to the amelioration of tissue toxicity. Curcumin anti-inflammatory efficacy induced NF-κB modulation and downregulation of it signaling cascade also help in reducing the angiogenesis, tumor progression and metastasis (Farhood et al., 2019). From Table 3, it can be inferred that curcumin is highly explored and a representative anticancer spice' bioactive. The compound alone or in combination with other drugs possesses significant anticancer efficacy against several types of cancers such as colon, pancreatic, breast, prostate, bladder, gastric and hepatocellular cancer. The compound exerts its anticancer effect via affecting the microtubule assembly that ultimately lead to the mitotic arrest. However, no treatment has yet been approved by the FDA. The reason behind this might be the non-specific action of curcumin which not only impacts the tumor cells but also imply its possible impact on normal cells. In addition, the poor bioavailability and insolubility of curcumin in water make it least absorbed in liver and intestinal walls (Fridlender et al., 2015). Therefore, further studies can be planned on the improvement of different physicochemical properties of curcumin and its disease-specific action. Inspire from curcumin and its anticancer efficacy, other spices and their bioactives can also be evaluated for their physicochemical properties, anticancer efficacy, toxicological evaluation and safety concern.

6. Structure-activity relationship (SAR)

Bioactives of spices (because of their active functional entities) gives a lead for designing the novel chemical compounds that consists of more than one compound that are linked via different bonding in a single structure, featured by improved therapeutics (Singh et al., 2021a). Various curcumin analogues were synthesized on the basis of its SAR studies to overcome its different limitations such as bioavailability, fastest metabolism, less solubility and absorption, which hinder its clinical efficacy (Gupta et al., 2017). They reported that introduction of a strong electron withdrawing group (acetone or cyclo-hexanone spacer, 4′-weak electrons donating and 2′-electron withdrawing groups) in curcumin will ultimately lead to its increased cytotoxicity due to its more electronegative character.

The SAR studies of cinnamaldehyde and eugenol was conducted to evaluate the compound's toxicity on human adipose-derived mesenchymal stem cells (HASCs). It was observed that both the compounds were non-toxic at their lower concentrations, easily biodegradable and can be metabolized through cytochrome-P450 (Absalan et al., 2017). The QSAR study of various derivatives of indole namely "*N*-(2-hydroxy-5-nitrophenyl (4′-methylphenyl) methyl) indoline (HNPMI)" has shown good anti breast cancer results, even better than cyclophosphamide (positive control). QSAR model revealed the presence of indole ring, aromaticity, nitrogen and oxygen like constituents, attributed to the biological efficacy of HNPMI (Palanivel et al., 2020). Various SAR studies of various spice's bioactives are clubbed in Table 4.

From Table 4, it can be inferred that curcumin is highly explored for SAR studies as compared to the other bioactives. Curcumin analogues were reported to possess significant anticancer activity after introducing the strong electron withdrawing group. The strong electron withdrawing group can also be introduced in other bioactives too, in order to enhance their anticancer efficacy.

7. Anticancer mechanism of actions of Indian dietary spices and their principal bioactives

Spices can induce the PCD and halt the process of migration, invasion and proliferation of the tumour cells to combat cancer (Zheng et al., 2016). Different phytoconstituents of spices exerts different actions to suppress cancer cell growth. In a study by Mughal (2019), it was postulated that the phytoconstituents from spices have the ability to suppress the expression of cyt p450, isozymes like CYP-1A1, COX-2, signal transducer and activator of transcription-3 (STAT-3), which are crucial to tumourogenesis. The bioactives decelerates the process of carcinogenesis via the suppression of IL-6 receptors, epidermal growth

Table 3
Cytotoxicity of extracts derived from Indian spices (*in-vitro*).

S. No.	Botanical Name	Family	Common Name	Plant part	Active compound/extract	Cancer type	Cell line	Mechanism of action	Ref (s).
1.	*Zingiber zerumbet* (L.) Roscoe ex Sm.	Zingiberaceae	Ginger	Rhizome	Zerumbone	Colorectal cancer	SW480 cell line	Induced programmed cell death (PCD), cell cycle arrest and inhibited cell migration	Sithara et al. (2018)
2.	*Curcuma caesia* Roxb.	Zingiberaceae	Black turmeric	Rhizome	Hexane	liver Adenocarcinoma	HepG2 cell lines	Blockage of cell cycle at G2/M phase and finally induced PCD	Mukunthan et al. (2017)
3.	*Curcuma aromatica* Salisb.	Zingiberaceae	Wild turmeric	Rhizome EO	Ar-tumerone	Breast cancer	MCF7 cells	Inhibition of cancerous cell	Parida et al. (2020)
4.	*Curcuma longa* L.	Zingiberaceae	Turmeric	Rhizome	Curcumin	Pancreatic cancer	L3.6 pl and MIA PaCa-2 cells	DNA synthesis phase arrest, inhibit surviving expression, Increased PCD and halted nuclear factor kappa B (NF-κB) translocation	Basha et al. (2016)
							Patu8988 and Panc-1	Down regulation of neural precursor cell expressed developmentally downregulated protein-4 (NEDD-4) (oncoprotein)	Su et al. (2017)
							Patu8988 and Panc-1 cells	Inhibition of cell growth, invasion, migration and induction of PCD	Zhou et al. (2016)
						Bladder cancer stem cells	UM-UC-3 and EJ cells	Down regulation of cancer stem cell (CSC) markers, inhibited sonic hedgehog pathway, cell proliferation and induced PCD	Wang et al. (2017)
						Colon cancer	SW480 and SW620 cells	Decreased p53 level, cell proliferation and alteration in phosphoproteome	Sato et al. (2017)
						Colon carcinoma	CRC cells	Inhibition of Wnt/β-catenin & sonic hedgehog signalings	Luers (2018)
						Colorectal cancer	HT29 cells	Inhibit the tumor growth due to their anti-angiogenic effect	Yue et al. (2016)
						Colon cancer	HCT 116 cell line	Suppression of cellular protein synthesis, induced mitochondrial dysfunction, Inactivation of lysosomal activity and apoptosis	Wang et al. (2016)
						Gastric cancer	MGC-803 cell line	Decreased cell viability, colony formation, cell migration and caspases activation to induce PCD	He et al. (2017)
						Colon cancer	DLD-1, HCT116 and LoVo cells	High expression of Caspase-3 and -7, inhibited cell growth and ultimately lead to PCD	Montgomery et al. (2016)
						Breast canc Er	MCF-10F, MDA-MB-231 and Tumor-2 cells	Suppression of the expression of different proteins, cadherins (*E, N*) and catenins, vimentins, fibronectins, epithelial mesenchymal transition and cell proliferation	Gallardo and Calaf (2016)
							MDA-MB-231 cells	Inhibitory concentration $(IC)_{50} = 49 \pm 2.08$ μg/ml	Ahmad et al. (2016)
							MDA-MB-231 cells	Alteration of cellular cytoskeleton, morphology and cellular migration	Li et al. (2016)
							MCF-7 cells	Inhibition of LPA induced RhoA/ROCK/ matrix metallopeptidases (MMP) signaling, cell invasion	Sun et al. (2016)
								Regulation and inhibition of breast cancer promoting genes and tumour progression	Wang et al. (2018)
								Suppression the expression of phosphorylated protein p44/42 in MAP Kinase pathway, activation of p53, caspase-3, 9, B-cell lymphoma-2 (Bcl-2) and Bax activity	Bhuiyan (2020)
						Prostate cancer	PC3 cells	Halts the cell growth and finally lead to PCD	

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Table 3 (*continued*)

S. No.	Botanical Name	Family	Common Name	Plant part	Active compound/extract	Cancer type	Cell line	Mechanism of action	Ref (s).
									Irshad et al. (2017)
						Hepatocellular cancer	Hepa 1–6 cells	Reactivation of estrogen receptor alpha (ER-α) gene expression, Inhibition of cell growth and induced PCD	Sanaei et al. (2020)
					Curcumin along with silibinin B	Colorectal cancer	CRC cell line	Induced cell death by both PCD and autophagy	Horita et al. (2019)
					Curcumin analogues	Prostate cancer, colon cancer, lung cancer and pancreatic cancer	PC-3, HT-29, H1299 and BxPC-3 cells	Inhibition of cell growth, suppression of NF-κB and induced apoptosis	Zhang et al. (2016)
					WZ35 analogue	Gastric cancer	BGC-823 and SGC-7901 cells	Downregulation of yes-associated protein (YAP), activation of JNK and inhibition of glycolysis	Chen et al. (2020)
5.	*Piper nigrum* L.	Piperaceae	Black pepper	Fruit	Piperine	Breast and colon cancer	MCF-7 and HT-29 cells	DNA damage, decreased cell viability, cell proliferation, cell cycle arrest and induced apoptosis	de Souza Grinevicius et al. (2016)
						Prostate cancer	PC3 cells	Inhibition of cell growth and induction of apoptosis	Irshad et al. (2017)
6.	*Crocus sativus* L.	Iridaceae	Saffron	Dried red stigma	Crocin	Breast cancer	HCC70, HCC1806, HeLa and CCD1059sk cells	Depolymerization of microtubules, inhibit mitosis, tubulin assembly and cell proliferation	Hire et al. (2017)
				Leaf biowastes	Crocetin	Breast carcinoma	MCF-7 cells	Inhibition of ER-α and histone deacetylase 2 (HDAC2)	Mir et al. (2020)
7.	*Nigella sativa* L.	Ranunculaceae	Black cumin	Seed oil	Thymoquinone	Colon cancer	COLO205 and HCT116 cells	Inhibition of NF-κB	Zhang et al. (2016)
8.	*Allium sativum* L.	Amaryllidaceae	Garlic	Bulb	Thiosulfinate-enriched extract	Colon cancer	Caco-2 and HT-29 cells	Decreasing cell viability	Perez-Ortiz et al. (2020)
9.	*Syzygium aromaticum* (L.) Merr. & L.M. Perry	Myrtaceae	Clove	Flower bud	Kumatakenin	Ovarian cancer	SKOV3 and A2780 cells	Induced cytotoxicity, PCD, increased activity of caspase 3, 8, 9 and inhibition of interleukin (IL)-10, MMP-2/9 and vascular endothelial growth factor (VEGF)- Cancer promoting factors	Woo et al. (2017)
					Eugenol	Cervical cancer	HeLa cells	Modification of cellular morphology and ultimately induced PCD	Das et al. (2018)
						Esophageal cancer	TE-13 cells	Inhibition of cellular growth	Zheng et al. (2016)
						Breast cancer	MCF-7 cells	Downregulation of β-catenin and CSC markers	Choudhury et al. (2020)
								Induction of oxidative stress, DNA damage, alteration of Akt, p38 MAPK, JNK and Erk 1/2 signaling pathways and induced cell death	Kello et al. (2020)
10.	*Elettaria cardamomum* (L.) Maton	Zingiberaceae	Small cardamom	Fruits	Cardamonin	Human melanoma	M14 and A375 cell lines	Inhibited cell viability, reduced cell density, upregulation of BAX protein and induced apoptosis	Yue et al. (2020)
11.	*Cinnamomum tamala* (Buch.-Ham.) T. Nees & Eberm.	Lauraceae	Tejapatta	Leaves	Eugenol and α-caryophyllene	Lung, breast and brain cancer	A549, MCF-7 and U-87MG cells	Cell-specific cytotoxicity	Thanekar et al. (2016)
12.	*Cinnamomum zeylanicum* Blume	Lauraceae	Dalchini	Bark	Ethanolic extract	Breast carcinoma	MDA-MB-231 cells	IC_{50} = 25 μg/ml and DNA fragmentation	Husain et al. (2018)
13.	*Myristica fragrans* Houtt.	Myristicaceae	Mace	Outer aril	Dichloromethane	Oral cancer	Oral cancer cell lines	DNA fragmentation and genotoxicity	Cinthura et al. (2017)
14.		Alliaceae		Whole plant	Aqueous ethanol				

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Table 3 (*continued*)

S. No.	Botanical Name	Family	Common Name	Plant part	Active compound/extract	Cancer type	Cell line	Mechanism of action	Ref (s).
	Allium wallichii Kunth		Himalayan Onion			Prostate cancer, Breast Cancer and cervical cancer, Burkitt's lymphoma	PC3, MCF-7, HeLa and B-Lymphoma cell line	IC_{50} = 69.69 μg/ml (PC3), IC_{50} = 55.29 μg/ml (MCF-7), IC_{50} = 46.51 μg/ml (HeLa) and IC_{50} = 3.817 ± 1.99 mg/ml (B-Lymphoma)	Bhandari et al. (2017)
15.	*Origanum marjoran* L.	Lamiaceae	Marjoram	Aerial parts	Aqueous	Mammary adencarcinoma	AMN-3 cell line	Inhibition of cell growth	Khaleel et al. (2016)
					Hesperetin and hydroquinone	Rat brain tumor and cervical cancer	C6 and HeLa cells	Hesperetin IC_{50} = 64.38 μg/ml (C6 cells) Hydroquinone IC_{50} = NR	
16.	*Rosmarinus officinalis* L.	Lamiaceae	Rosemary	Leaves	Dimethyl sulfoxide	Breast cancer	MDA-MB-231 cell line	Inhibition of cell growth, cell survival and lead to PCD	Jaglanian and Tsiani (2020)
					Carnosic acid	Lung cancer	IMR-90 and NCI–H460 cell line	Blockage of cell cycle, inhibition of cellular proliferation and apoptosis	Corveloni et al. (2020)
17.	*Pimpinella anisum* L.	Apiaceae	Anise	Seeds	Aqueous	Oral cancer	KB cell line	Induced Cytotoxicity and Changes in cellular morphology	Mukunda et al. (2020)
18.	*Foeniculum vulgare* Mill.	Apiaceae	Fennel	Seeds	Protein fraction	Breast and pancreatic cancer	MCF-7 and AsPC-1 cells	Induced cytotoxicity in MCF-7 cells but no significant inhibition of AsPC-1 cell lines	Megeressa et al. (2020)
19.	*Coriandrum sativum* L.	Apiaceae	Coriander	Roots	Ethyl acetate extract	Breast carcinoma	MCF-7 cells	Halts the process of tumor cells migration	Zheng et al. (2016)
20.	*Origanum vulgare*	Lamiaceae	Oregano	Whole	Carvacrol	Breast carcinoma	MDA-MB-231 cells	IC_{50} = 199 μM	Baranauskaite et al. (2017)
21.	*Thymus vulgaris* L.	Lamiaceae	Thyme	Whole	Thymol	Colorectal cancer	HCT-116 and Lovo cells	Inhibition of cell growth and metastasis via downregulation of Wnt/β-catenin and activation of BAX/Bcl-2 signaling pathway	Zeng et al. (2020)
22.	*Ferula asafoetida* H. Karst.	Apiaceae	Asafoetida	Resin	Gummosin	Breast and prostate cancer	MCF-7 and PC-3 cells	IC_{50} = 32.1 μg/ml (MCF-7) and IC_{50} = 30 μg/ml (PC-3)	Iranshahy et al. (2019)
23.	*Capparis spinosa* L.	Capparidaceae	Caper	Fruit	3-Methyl-2-buten-1-yl β-D-glucopyranoside	Breast cancer	NR	Significantly declined the efficacy of the enzyme coenzyme colin estersase and killed the cancer cells	Salih et al. (2020)
24.	*Armoracia rusticana* P. Gaertn., B. Mey. & Scherb.	Brassicaceae	Horseradish	Above and underground parts	5-Phenylpentylisothiocyanate	Colon and cervical cancer	Caco-2 and HeLa cells	IC_{50} = 3.4 μg/ml (Caco-2) IC_{50} = 5.9 μg/ml (HeLa)	Dekić et al. (2017)
25.	*Alpinia galangal* (L.) Willd.	Zingiberaceae	Greater galanga	Rhizomes	Acetoxy Chavicol Acetate	Cervical, and breast cancer	HeLa, MCF-7 and T47D cells	Induction of apoptosis via the activation of Caspase-3 cascade	Suhendi et al. (2017)
26.	*Vanilla planifolia* Jacks. Ex Andrews	Orchidaceae	Vanilla	Beans	Vanillin	Colorectal cancer	HT-29 cells	Suppression of cell proliferation and Caspases induced apoptosis	Xie et al. (2020)
27.	*Garcinia indica* (Thouars) Choisy	Clusiaceae	Kokam	Fruit rind	Garcinol	Gallbladder cancer	GBC cells	Downregulation of mRNA levels to suppress the activity of MMP2 and MMP9	Duan et al. (2018)
28.	*Murraya koenigii* (L.) Spreng.	Rutaceae	Curry leaf	Leaf	Girinimbine	Colon cancer	HT-29 cells	Inhibition of inflammation and cell viability and finally induced apoptosis	Iman et al. (2017)
29.	*Cuminum cyminum* L.	Apiaceae	Cumin	Seeds and fruits	Luteolin-7 -*O*-glucoside	Breast cancer	MCF-7 cells	Selective cytotoxicity	Goodarzi et al. (2020)

NR* = Not reported.

Table 4
Summary of QSAR studies and associated pharmacological effect of spice's bioactives.

S. No.	Active compound	Analogues	Conc./IC_{50} obtained	Pharmacological effects	Molecular targets	References
1.	Curcumin	Bisdemethoxycurcumin	10–40 μM	Cytotoxicity against ovarian cancer, CCL4-induced hepatotoxicity in rats, Colon cancer	COX-2, matrix metalloproteinase, STAT3 and Notch signaling, PI3K/Akt and Wnt/β-catenin pathway	Gupta et al. (2017)
		Demethoxycurcumin	20 μM	Combating lead-induced neurotoxicity in rats, proliferation of breast cancer cells		
		Tetrahydrocurcumin	34–112.5 μM	Suppression of COX-dependent arachidonic acid metabolism, intrinsic apoptosis pathway in breast cancer		
		Hydrazinocurcumin	NR	Inhibition of colon cancer via suppression the cell cycle		
2.	Cinnamaldehyde	End products obtained after cinnamaldehyde metabolism by cytochrome-P450	2.5 μM/ml	Non-genotoxic and low toxicity towards hASCs	May bind to DNA and proteins	Absalan et al. (2017)
3.	Eugenol	End products obtained after eugenol metabolism by cytochrome-P450	0.1 μg/ml	Non-genotoxic but carcinogenic and mutagenic and low-toxic in nature towards hASCs	May bind to DNA and proteins	Absalan et al. (2017)
		4-[(2S)-2,3-dihydroxypropyl]-2-methoxyphenyl 2-hydroxybenzoate	26.56 μmol/ml - 286.81 μmol/ml	Significantly inhibited Bcl-2 expression in HT29 colon cancer	Hydrophobic nature plays important role	Fadilah et al. (2020)
4.	Orientin	Fenofibryl glucuronide	100 μg/ml (202.389 μM)	Results showed 41% cell mortality of HepG2 cells after an exposure of 96 h	Due to its anti proliferative properties	Sharma et al. (2016)
5.	Indole	HNPMI	10–100 μM	Inducing anti-proliferative and PCD of breast cancer cells	Downregulation of PI3K/S6K1 genes via the upregulation of epidermal growth factor receptor (EGFR)	Palanivel et al. (2020)
6.	Ursolic acid	6r and 6q compounds	NR	Significant anticancer properties against T24 cell lines of bladder cancer	Down regulation of NF-κB signalings	Yadav et al. (2019)
7.	Sulforaphane	NR	NR	Upregulation of NAD(P)H: quinone oxidoreductase 1 (NQO1) (carcinogen detoxification enzyme)	Kelch-like erythroid cell derived protein with CNC homology [ECH]-associated protein-1 (Keap-1)-[NF-E2]-related factor-2 (Nrf-2) pathway	Vaghefinezhad et al. (2021)
8.	Different phytochemicals from Brassicaceae	Glucoraphanin	$pIC_{50} = 4.28$ μm	Prevent tumor inflammation	NF-κB inducing kinase	Devi et al. (2017)
9.	Myristicin	6-allyl-4-phenoxybenzo[d][1,3]dioxole (M_1)	Log P = 3.97	Antioxidant effect (Due to large number of electrons attributed to higher polarity)	More solubility in water as antioxidant drug due to its highest log P value	Muliadi et al. (2021)
10.	Piperic acid	2- (3,4-dihydroxyphenyl)ethyl ester	17 μM	Tumor specificity and cytotoxicity	Induced PCD and breakdown of caspase-3	Sakagami et al. (2017)
11.	Rosmarinic acid	Derivatives formed via the substitution of metal ions sodium with silver and amines with imidazole	$IC_{50} > 200$ μg/ml	Anti-glioblastoma	Upregulation of caspases 3,7,8 & 9, to induce PCD and modification of IL-17A downstream angiogenesis signalings	Khan et al. (2019)
12.	Capsazepine	*N-[2-(4-chlorophenyl)ethyl]-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-2-carbothioamide and* N-*benzyl-6,7-dihydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carbothioamide*	$IC_{50} < 15$ μM	HeLa cervical cancer	Target transient receptor potential vanilloid subtype 1 (TRPV1)	De et al. (2019)
13.	Cardamonin	Cu(II) complex of cardamonin: [Cu (C16H13O4)2(H2O)2]·2H2O	$IC_{50} = 13.2$ μM (A549 cell lines) $IC_{50} = 13.2$ μM (HK1 cells)	Anticancer activity against lung cancer and NPC cells	Caspases mediated DNA damage, cell cycle arrest and resulted PCD as well as suppression of mTOR signalings	Break et al. (2018)

NR* = Not reported.

factors (EGF), the protein involved in cell cycle and the suppression of Kappa-B. Spices active constituents have the potential to suppress ROS production, cell division and stimulate apoptosis. They have the potential to regulate inflammation and immunocompetence which ultimately contribute to their cancer treatment efficacy (Srinivasan, 2017a).

The anticancer mechanism of curcumin was performed in mice bearing colon cancer. The tumor proliferation was mediated via the dysregulation of Wnt/β-catenin pathways. Western blotting data revealed that curcumin treatment has downregulated the expression of β-catenin along with miR-130a and ultimately suppressed the Wnt/

β-catenin signaling pathway. MiR-130 expression was supposed to antagonize the anticancer effect of curcumin. Curcumin treated cells were noticed with decelerated cell viability and cell proliferation (Dou et al., 2017). In another study by Zhou et al. (2016), the anticancer mechanism of action of curcumin was assessed in treating pancreas cancer and it was suggested that curcumin treatment has significantly abolished the over expression of YAP and transcriptional co-activator with PDZ-binding motif (TAZ) and associated Notch-1 expression, which play critical role in pancreatic cancer cell proliferation and ultimately halted the cell proliferation and invasion.

The cancer treating mechanism of curcumin was evaluated in colon cancer bearing male Balb/c nude mice and it was reported that Sirtuin (silent mating type information regulation 2 homolog) 1 (SIRT1) (an NAD^+ -dependent histone/protein deacetylase) was overexpressed in colon cancer proliferation. The SIRT1 protein helps in viability and migration of human colon cancer cells. The tumor bearing mice were administrated with curcumin. Curcumin possesses the ability to suppress the expression of SIRT1 protein. It was noticed that curcumin treatment has significantly suppressed the SIRT1 protein expression without influencing its mRNA expression. Furthermore, post translational modification and proteasomal degradation of SIRT1 protein was also noticed. Moreover, it was also reported that curcumin bind to cysteine 67 domain of SIRT1 oncoprotein and replaced it with alanine (Lee et al., 2018). The anticancer mechanism of 6-gingerol and capsaicin (isolated from ginger and red chili, respectively) was investigated on lung carcinoma. Capsaicin exerted cancer promoting effect due to the enhanced level of EGFR level whereas reduced level of TRPV1. On contrary, 6-gingerol individually or synergistically with capsaicin, has significantly increased the TRPV1 content and ultimately reduced the EGFR, NF-κB and cyclin D1 level and finally decreased the pulmonary carcinoma metastasis (Geng et al., 2016). The anticancer mechanism of thymoquinone (TQ) was tested on COLO205 and HCT116 cell lines of colon cancer. TQ treatment resulted into the significant reduction of phosphorylated p65 level in the nucleus, VEGF, c-Myc and Bcl-2 factors which ultimately mediated the suppression of NF-κB and cell death (Zhang et al., 2016).

The antitumor mechanism of curcumin was studied in oxaliplatin (OXA) acquired resistant CRC cell lines. The OXA resistant CRC cells overexpressed the NF-κB transcription factor and associated CXC-chemokines (CXCL8, CXCL1 and CXCL2). It was observed that NF-κB signaling cascade can be inhibited through the curcumin alone or in combination with OXA. The compounds also made the CXCL8 and CXCL1 gene silencing via the suppression of the Akt/NF-κB pathway (Ruiz de Porras et al., 2016). Curcumin ability was examined for its cancer treating potential in pancreatic cancer. The compound was well demonstrated for its anticancer ability via deactivation the NEDD4 (oncoprotein) and stimulating the phosphatase and tensin homolog (PTEN) and p73 expression (Su et al., 2017). Cardamonin was also reported to exhibit the cell cycle blockage and PCD inducing potential in malignant cells (Nawaz et al., 2020). In a study by Manayi et al. (2018), the preclinical study was carried out on piperine alongwith its self-renewal, proliferation and survival inhibiting potential. It was also found that the compound possesses significant antimutagenic activity and can suppress the expression of multidrug resistance transporters such as P-gp and MRP-1 and exerts cancer cell specific cytotoxicity.

Eugenol was evaluated for its antitumor potency on CSC markers and its main regulator β-catenin in MCF-7 cell lines. It was observed that eugenol facilitated the N-terminal phosphorylation of Ser37 residue which mediated the suppression of β-catenin and CSC markers, these series of events play crucial role for exerting their anticancer potential (Choudhury et al., 2020). The mechanism of action of curcumin was examined in Hepa 1–6 cell lines of hepatocellular cancer. The compound treatment has exerted dose dependent cell growth inhibition, anti-proliferative and apoptotic effects mediated via the reactivation of estrogen receptor alpha (ERα) gene expression (Sanaei et al., 2020). Rosemary extract has significantly inhibited the phosphorylation/activation of Akt and mTOR signaling and increased the breakdown of poly ADP-ribose polymerase (PARP) apoptotic marker and ultimately induced PCD in triple-negative MDA-MB-231 cells of mammary cancer (Jaglanian and Tsiani, 2020). Curcumin can modulate the multiple pathways such as NF-κB, PI3K/AKT/mTOR, JAK/STAT, MAPK and notch signaling, as associated with cell proliferation, cell cycle regulation, senescence and PCD of breast cancer cells, therefore, the compound can be targeted for drug discovery against breast cancer (Banik et al., 2017). In a study by Kunnumakkara et al. (2018), the various signaling pathways including COX-2, TNF-α, NF-κB, PI3K/Akt/mTOR, MAPK and JAK/STAT mediated by spices bioactives to exert their anti-tumorigenic effect was reported therefore it can be inferred that these spice's bioactives can be effectively used to prevent various types of cancer. In this regard, the different anticancer mechanisms of actions mediated by spice's bioactives are described as follows:

7.1. Wnt/β-catenin signaling pathway

Upon activation of Wnt/β-catenin signalings, Wnt binds to their receptor (composed of frizzled proteins and LPR5/6) which in turn activates the cytoplasmic protein disheveled (DVL). The activated DVL protein will lead to the suppression of degradation complex as composed of adenomatous polyposis coli gene (APC), anti-neurexin (AXIN), glycogen synthase kinase 3β (GSK3β) and casein kinase 1α (CK1α). Subsequently, the phosphorylation and inhibition of GSK3β will increase the concentration of cytosolic β-catenin. The non-phosphorylated cytosolic β-catenin will move to the nucleus. In nucleus, it communicates with T cell-specific factor (TCF)/lymphoid enhancer-binding factor (LEF) and co-activators like CREB binding protein (CBP), in order to induce gene transcription. In case of Wnt off state or in the absence of Wnt, the destruction complex induces the phosphorylation of cytosolic β-catenin and subsequently its ubiquitin-mediated proteosomal degradation with no gene transcription (Zhang and Wang, 2020). The overall Wnt/β-catenin signaling pathway is depicted in Fig. 2.

7.2. PI3K/Akt/mTOR signaling pathway

The extracellular stimulus, such as growth factors, cytokines and hormones stimulate the dimerization of the p110 catalytic subunit with regulatory p85 subunit, to activate PI3K. Upon activation, PI3K stimulates the phosphorylation of PIP2 into PIP3 that recruits a subset of pleckstrin-homology (PH) or other lipid-binding domains of downstream targets which in response stimulates other signaling proteins, such as PDK1 and kinases AKT. The activated Akt impacts various downstream effectors, such as mTOR and finally activates the cell growth and cell survival pathways. PTEN deleted on chromosome 10 negatively regulates the PI3K signaling by dephosphorylating PIP3 to PIP2 and thus prevents the activation of downstream kinases (Kawade et al., 2018). The PI3K/Akt/mTOR signaling pathway is well presented in Fig. 3.

7.3. JAK/STAT signaling pathway

In noncanonical mode of signaling, JAK2 phosphorylates the histone 3 which ultimately transfers CBX5 from chromatin and associate with STAT5A to inhibit gene transcription. In canonical context, cytokines bind to receptor that induces the phosphorylation of JAK kinases. The activated JAK led to STAT phosphorylation and subsequently dimerises and translocates it to the nucleus. In nucleus, dimeric STAT associates with the sequence in the target gene promoters and resultantly activates gene transcription (Qureshy et al., 2020). The JAK/STAT signaling pathway is elucidated in Fig. 4.

7.4. MAPK signaling pathway

MAPKs activation plays a critical role in inflammation-associated

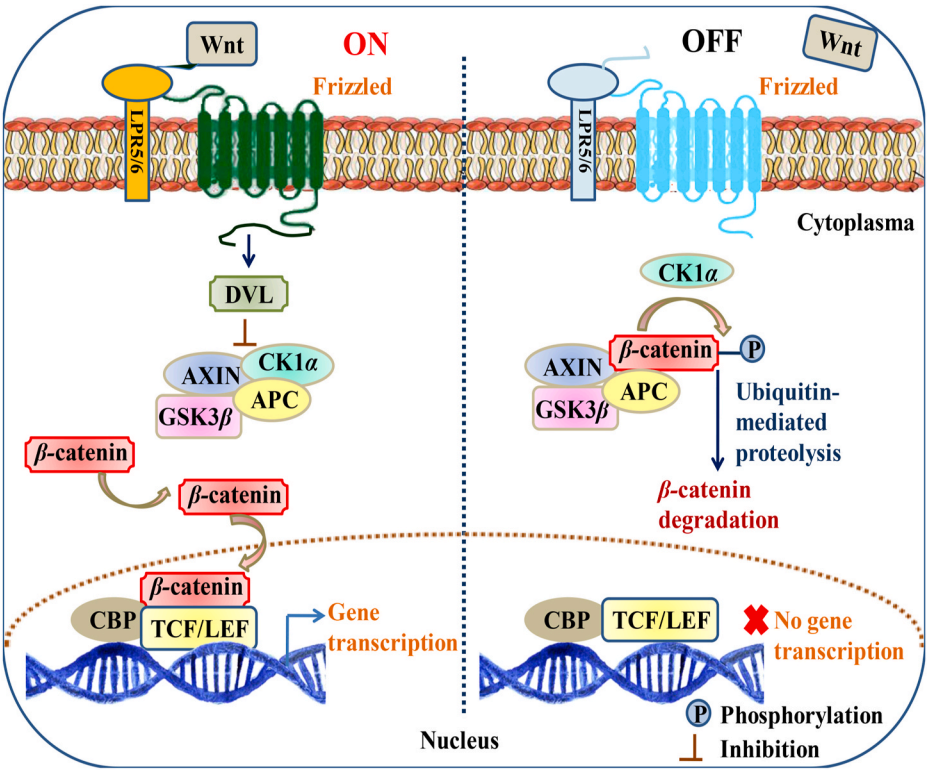

Fig. 2. Overview of Wnt/β-catenin signaling pathway.

cancer proliferation. Neoplastic transformation is facilitated by the active mutations of Ras-Raf-MEK-ERK. ERK regulates the inflammatory cytokines that promotes the inflammation-associated cancer. The phosphorylated ERK was also detected predominantly in pancreatic cancer. The Ras activation induces the local inflammation by enhancing the level of CXCL-8 and IL-8 that finally promotes neo-vascularization and cancer progression, therefore, MAPKs pathway can be a suitable target for treating cancer. The signaling cascade of MAPK kinase is described as follows:

Upon ligand binding, receptor tyrosine kinases (RTKs) stimulate guanine exchange factors, Sos proteins, which transfers GTP to Ras GTPases. Downstream activation of RAS/RAF and MEK subsequently activates the ERK1/2 transcription factor activator which further phosphorylates a number of downstream effectors. The activation of

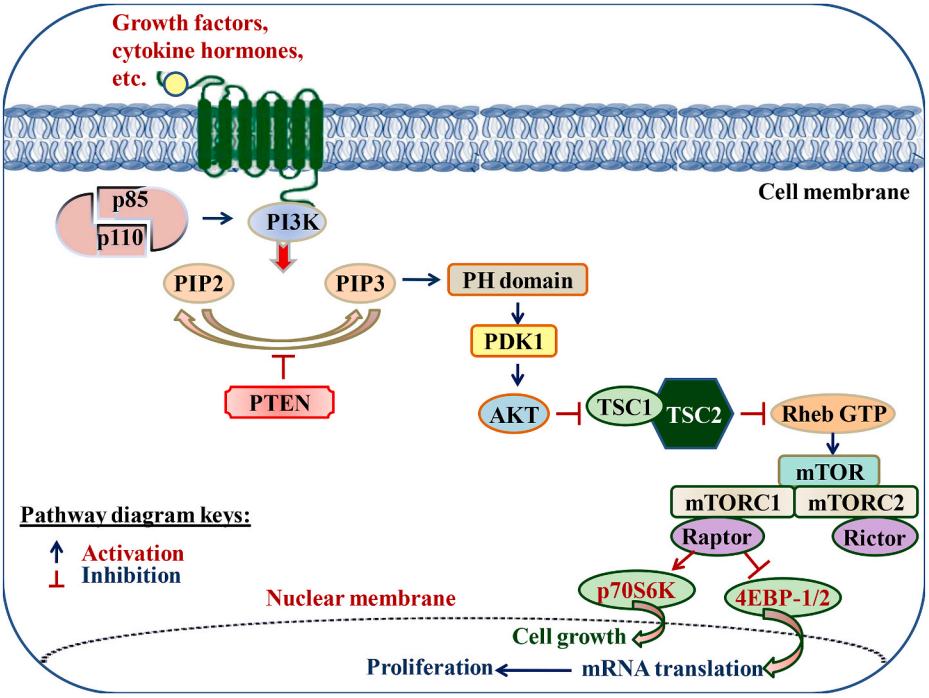

Fig. 3. Overview of PI3K/Akt/mTOR signaling pathway.

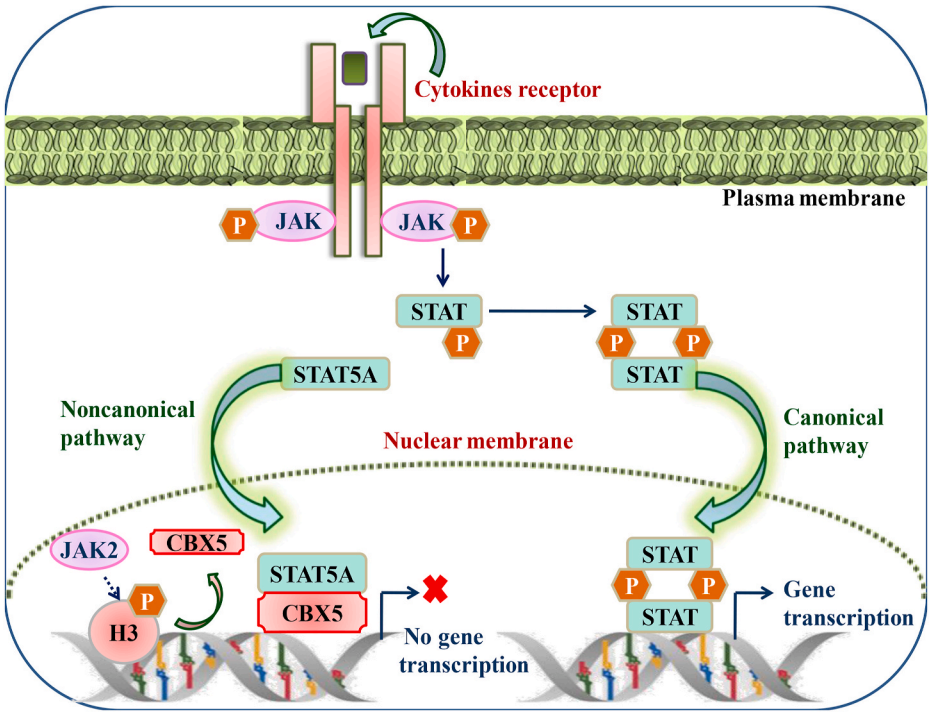

Fig. 4. Overview of JAK/STAT signaling pathway.

ERK signaling play significant role in cell death, proliferation and cytoskeletal remodeling (Yuan et al., 2020). The MAPK signaling pathway is shown in Fig. 5.

7.5. Notch signaling pathway

Upon ligand interaction with notch receptor, a two step proteolytic cleavage is stimulated by ADAM family proteases and γ-secretase, to release notch intracellular domain (NICD), which subsequently moves to nucleus and bind with C-protein binding factor 1/Suppressor of Hairless/Lag-1 (CSL) and finally lead to the conversion of repressor complex of notch target genes to activator complex (Venkatesh et al., 2018). The Notch signaling pathway is represented in Fig. 6.

8. Supremacy of natural products over synthetic anticancer medications

Despite the availability of enormous conventional anticancer

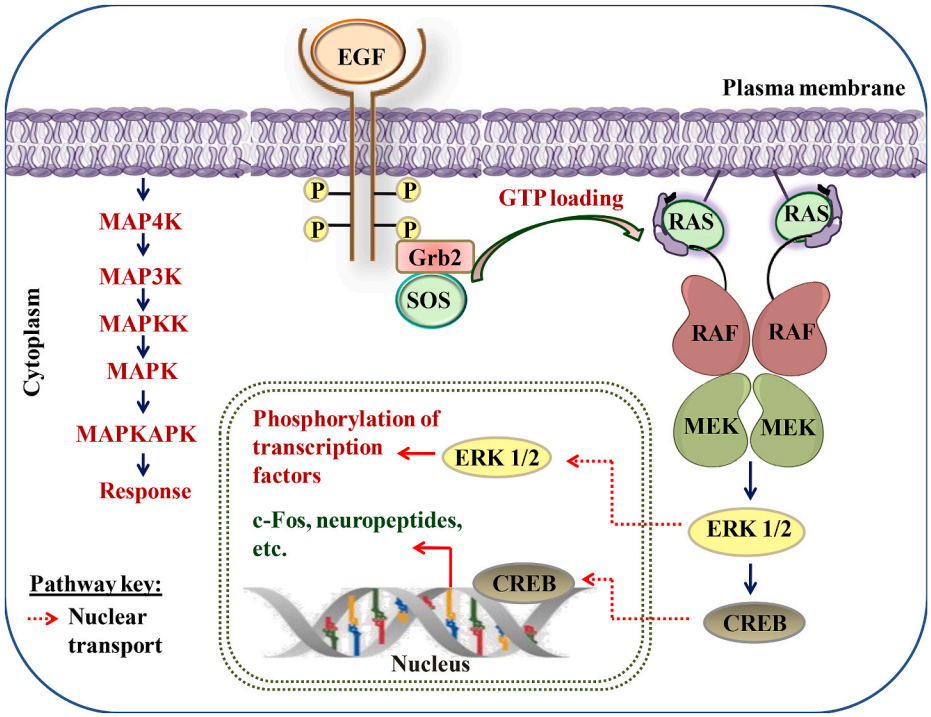

Fig. 5. Overview of MAPK signaling pathway.

medications, the researchers have always remained engaged in searching new therapeutic agents from natural resources. The main reason behind this is the efficacy and safety of natural products over synthetic drugs. The synthetic drugs work in action orientation manner for a particular disease. Moreover, the efficacy of synthetic medicines is time-bounded and non-curative. On contrary, natural entities play their action synergistically and offer a holistic treatment approach. Hence natural compounds can be used safely to cure more than one ailment at a single time at optimum concentration (Singh et al., 2021a). Some of the natural products derived from spices like capsaicin (red pepper); curcumin (turmeric); cyanidin glycosides (red onion); gingerol (ginger); crocin, crocetin and safranal (saffron) are most renowned anticancer agents that also possess other therapeutic effects too. Therefore, these phytocompounds can be used to treat other body ailments along with cancer at minimum risk. These bioactives can target heterogenous populations of cancer cells at a single time. They also have the ability to regulate several key pathways involved in carcinogenesis whereas the synthetic medicines lack this efficacy (Turrini et al., 2020). Along with, the synthetic medicines are associated with several adverse effects. For example; irinotecan (adverse effects: diarrhea, sensory neuropathy, neutropenia), melphalan, cisplatin, cyclophosphamide, oxaliplatin, carboplatin (adverse effects: toxicity of pulmonary, cardiovascular, hematological, gastrointestinal and renal system), doxorubicin (adverse effects: cardiotoxicity) (Iqbal et al., 2017). Hence, it is always preferable to cure several health issues with natural products instead of synthetic medicines.

9. Synergistic anticancer effect of spices

As we discussed in section 8 that spices and their bioactives follow a synergistic approach for their therapeutic action. These bioactives can stimulate more than one signaling pathway involved in different types of cancer, so a single spice's bioactive can be used to treat more than one cancer type. They induce their anticancer effect by the activation of tumor suppressing genes, apoptosis, deacceleration of tumor angiogenesis, cell cycle arrest and so on. From Table 3, it can be inferred that curcumin can be used to treat multiple cancer types such as pancreatic, breast, bladder, gastric and colon cancer. Likewise, piperine was also reported to be used for curing breast, colon, and prostate cancer (Turrini et al., 2020). The multiple cancer treating effect of a single bioactive can also be supported by Table 2. However, the clinical evidences on their multiple cancer treating effect are lacking. Therefore, future clinical studies can be planned to explore the bioavailability, bioefficacy, biosafety, mechanism of action and optimum dose of spice' bioactives needed for combating various cancer types (Almatroodi et al., 2021).

10. Bioavailability and bioefficacy of phytocompounds

Bioavailability is defined as the quantity of micronutrients and phytocompounds i.e., absorbed, distributed to its target organs/tissues where it metabolized and finally excreted. Though, it is not feasible to compute the précised amount of biologically available phytochemicals in humans because it needed *in-vivo* experimentations. This is the reason why several phytocompounds which show excellent potential in *in-vitro* experimentation fail to display the same potential during *in-vivo* evaluation. There are some factors that influence the bioavailability of a compound. These factors are categorized under two categories i.e., exogenous and endogenous. The exogenous factors include the complex nature of food matrix, chemical nature, amount and structure of the compounds co-ingested whereas the endogenous factors include the mucosal mass, duration to transit in intestine, metabolism, binding of proteins in blood/tissues, etc. However, some of the phytocompounds can be metabolized to make them biologically active whereas other phenolic extracts show a low bioavailability after ingestion. The polyphenolic compounds also interfere with the bioavailability and potential of the food that we eat. For instance; the ingestion of blueberries along with milk led to a deficit *in-vivo* antioxidant activity of blueberries. The association also decreased the absorption of caffeic acid. Moreover, bioaccessibility is essential for the bioavailability of a compound. It can

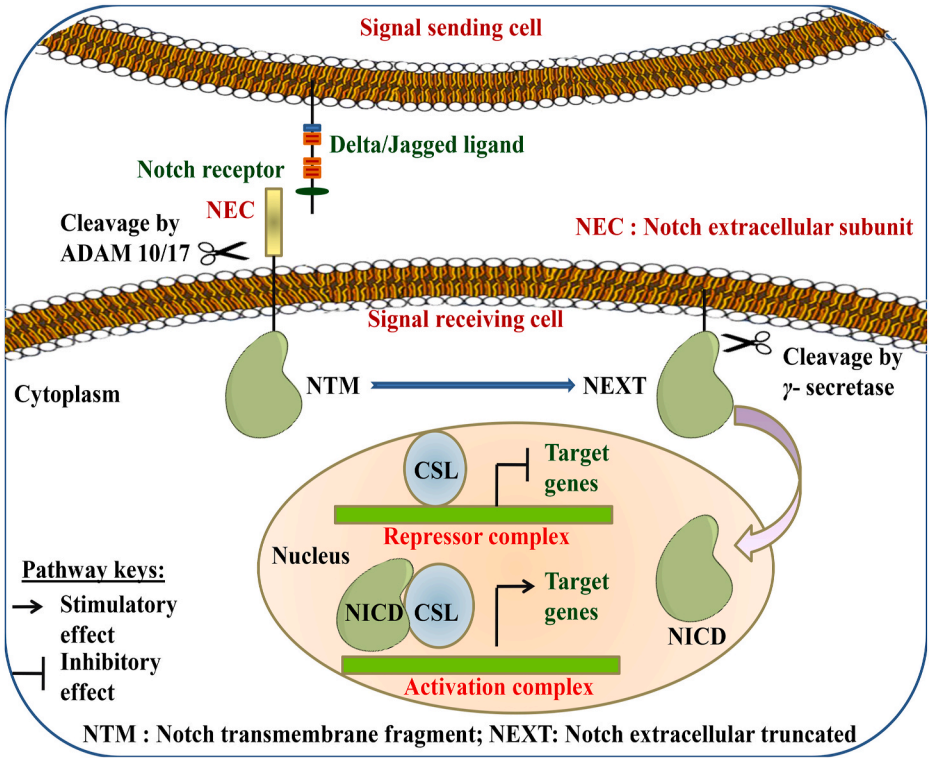

Fig. 6. Overview of Notch signaling pathway.

be described as the amount released from the food matrix into the lumen and absorbed in the intestine. Hence, bioavailability is directly proportional to the bioaccessibility of a compound. Bioaccessibility is affected by several factors including pH, temperature, texture, gut microbiota, plant cell wall composition, and so on. However, data were lacking on these two terms but a key was provided to understand the bioefficacy of phytocompounds being bioactive. Hence, phytocompounds are required to be biologically available in order to achieve their full potential (Anwar et al., 2021).

11. Bio-toxicity and bio-safety aspects of spices

Bio-toxicity of natural products can be defined as the toxic effects exerted by natural product on living organism. Spices are also considered as to exert toxic effects on living beings due to the presence of heavy metals (Pb, As, Cd), mycotoxins and especially aflatoxins. Some of the spices like red chillies, black pepper, nutmeg exert high aflatoxin risk whereas turmeric and ginger possess medium aflatoxin risk. Other spices including mace, cloves, cardamom, cinnamon, cumin, coriander and fennel are reported to possess low aflatoxin risk. The aflatoxin is carcinogenic (categorized as group 1 carcinogen by the International Agency for Research on Cancer), teratogenic, mutagenic, hepatotoxic, growth retardant and immunosuppressant in nature (Akhtar et al., 2020). Keeping in mind, the above-mentioned bio-toxicity of these spices, the bio-safety of these spices should be evaluated. Bio-safety of spices refers to the protection of living entities from the toxins released from the spices. As spices and their bioactives are basically considered safe, therefore, they are widely utilized in preparation of various cuisines at appropriate doses. They work in dose-dependent manner. Dose dependency refers to the change in effect on changing the dose of the drug. It helps in quantifying the drug effect at the level of molecule, cell, tissue, organ, organ system, and organism. It also helps in calculating the optimum dose at which the drug shows its maximal efficacy. Their isolated compounds also work in dose-dependent manner and are well documented for their therapeutic potentials especially for cancer preventing action without significant toxicity. For instance, Curcuminoids is categorized as "generally recognized as safe" (GRAS) by national cancer institute. Besides their anticancer approach, they are also noticed with some occasional toxic issues under some specific conditions. Curcumin is generally safe up to 12 gm daily doses, with minor adverse effects (Gupta et al., 2017). Curcumin was reported to possess DNA damaging effect in the presence of Cu^{2+} (both *in-vitro* and *in-vivo*). Safrole, a natural constituent of spices extracted essential oil was also noticed with some oncogenic effects but the content of safrole is reduced up to its safe level by high temperature during cooking. Apart from these toxicities, some anticancer compounds which show anti-platelet activities might induce over bleeding in patients suffering from bone marrow suppression (Zheng et al., 2016). In another study by Guldiken et al. (2018), it was opined that spices and herbs' bioactives safety is dose dependent. They are generally safe and health promoting at lower concentration whereas at high doses they cause health deteriorating symptoms. Some of the spices mediated toxicity is summarized in Table 5. Therefore, further studies are needed for the in-depth exploration of the bio-toxicity and bio-safety of spices and the derived anticancer compounds, so that their anticancer safe dose can be recommended.

12. *In-vivo* anticancer activity of Indian spices

The *in-vivo* anticancer efficacy of Indian spices can be evaluated by different studies like pre-clinical studies and clinical studies. The pre-clinical studies are those which are performed to evaluate the efficacy of a drug/medical treatment in animals. These studies provide preliminary data regarding the safety of new drug. On the basis of pre-clinical data, clinical studies can be performed. Clinical studies are those which are performed in people. The various *in-vivo* anticancer studies of Indian spices are discussed below:

12.1. Pre-clinical studies

A pre-clinical trial on colon cancer bearing male Balb/c nude mice was performed to evaluate the antitumor efficacy of turmeric ethanolic extract and curcumin. After 30 days of dose (75 mg/kg) administration, the mice were found with increased level of WBC, neutrophils and lymphocytes counts. The extract has also inhibited the tumor growth significantly (Yue et al., 2016). The potency of curcumin was tested for treating the colon carcinoma. The SW480 cells of colon cancer were introduced in to the female nude mice to generate the xenograft tumor model to study the curcumin effect. The mice were intraperitoneal injected with a dose of 200 mg/kg for 5 days and were observed daily. Curcumin treated mice were noticed with prolonged life span with suppressed proliferation of tumor cells (Dou et al., 2017). In another study by Lee et al. (2018), the colon cancer xenograft tumors were established by injecting HCT-116 colon cancer cells into the male Balb/c nude mice and were treated with curcumin dissolved in corn oil at a dose of 50 mg/kg and 100 mg/kg for 8 times/three weeks. The treatment has showed the significant silencing of SIRT1 protein and resultantly reduced the tumor volume.

The aqueous extract of ginger was examined on *N*-nitroso *N*-methyl Urea (MNU) caused gastric carcinoma in albino Wistar rats. The extract supplementation has significantly reduced the pathological changes associated with inflammation and oxidative stress and finally suppressed the tumor progression (Mansingh et al., 2020). The compound 6-gingerol and capsaicin, the main constituent of ginger and red chili, respectively were screened for their anticancer efficacy. The study was performed on urethane-induced lung adenocarcinoma in female ICR mice-model. The animals were supplemented with both ginger and red chili at a dose of 50 mg/kg, once a day for 20 weeks. Results revealed that both the constituents were antagonistic in nature and 6-gingerol significantly suppressed the lung carcinoma and also reversed the cancer-promoting effect of capsaicin (Geng et al., 2016).

The different extracts of *Cinnamomum tamala* was tested for their anticancer efficacy in fibrosarcoma-induced mouse tumor model. Among different extracts the petroleum ether fraction of methanol extract was the most potent anticancer agent. The fraction has significantly arrested the tumor growth and proliferation through the inhibition of topoisomerase-I enzyme activity (Thanekar et al., 2016). Eugenol, as one of the most common bioactive of many spices was examined in the breast tumor bearing Female Swiss Albino mice and it

Table 5
Toxicological effects of some spices.

Name of spice/ bioactives	Study type	Body part affected	Resulted adverse effects
Curcumin	*In-vitro* & *in-vivo*	Any	DNA damage
Chilli	Clinical study	Human stomach	Gastric cancer
		Gall bladder	Carcinogenic
Safrole from Areca nut		Human esophagus	
Star anise		CNS	Neutotoxic
Thyme oil	*In-vitro*	Human lymphocytes	Genotoxic
Carvacrol		Lung fibroblast cells	DNA damage, clastogenic
Allium sativum		Adipocytes cells	Cytotoxic
Saffron	*In-vivo*	Mice liver	Hepatotoxic
Chilli, coriander, fennel, ajwain, cardamom, cumin and dark pepper		Gastrointestinal part of albino rats	Gastrointestinal toxicity
Ginger		Mice	
	Clinical study	Human stomach	Gastric problems

Source: Guldiken et al. (2018).

was demonstrated that eugenol treatment has noticeably delayed the translocation of β-catenin to nucleus and promoted its cytoplasmic degradation which has ultimately reduced the mRNA expression and formation of enriched stemness of secondary mammosphere facilitated via the low level of $CD44^{+}/CD24^{-/low}$ population. All these alterations significantly reduced the volume of solid tumors and induced apoptosis of malignant cells (Choudhury et al., 2020).

A study was carried out on 5–6 weeks old male Balb/c mice to examine the piperlongumine (an alkaloid found in *Piper longum*) effect on 1,2-dimethylhydrazine (DMH)/dextran sulphate sodium (DSS) induced colon cancer. The compound treatment has noticeably suppressed the expression of Ras/PI3K/Akt/mTOR signaling that perform critical function during colon carcinogenesis and proliferation. The compound has also arrested the cell cycle growth at G2/M phase and restored the cell death (inhibited via the Ras proteins and PI3K/Akt signaling cascade) by down-regulating the expression of Bcl-2. The report of hepatic and renal toxicity declared that piperlongumine was safe, without any significant negative symptoms (Kumar and Agnihotri, 2019).

In a study by Jwaid et al. (2021), the different doses (500 mg/kg of body weight and 1000 mg/kg of body weight) of *A. dracunculus* L. extraction (extracted with 80% of ethanol) was tested against the proliferation of bone marrow and spleen cells of mice. Results revealed that the dose 500 mg/kg of body weight has significantly increased the mitotic index (i.e., 12.02 ± 1.16 and 10.48 ± 1.28 for bone marrow and spleen cells, respectively). On the contrary, the dose 1000 mg/kg of body weight has significantly decreased the mitotic index (i.e., 4.18 ± 0.73 and 3.76 ± 0.45 for bone marrow and spleen cells, respectively).

12.2. Clinical studies

A study by Farid et al. (2020), was carried out to evaluate the anti-mutagenic effect of *Foeniculum vulgare* seeds extract on human blood sample collected from 20 healthy persons (10 males and 10 females), who are not used to smoke. The samples were irradiated to induce elevated levels of cytokinines such as IL-1β, IL-6, IL-8, and Tumor necrosis factor-α (TNF-α). The fennel decoction has noticeably led to the reduction of cytokines levels and ameliorated negative effect caused by elevated cytokines.

The effect of ginger was tested on the complications associated with platinum-based adjuvant chemotherapy for ovarian cancer. The study was conducted on 49 patients, administrated with 2 gm of ginger capsules. Results revealed that ginger treatment has significantly prevented the nausea, vomiting, metabolic disorders, digestive problems, reproductive system problems, reduced the level of prostaglandins, stimulated appetite and alleviated the toxic effects of chemotherapy. Gingerol and shogaol from ginger was found to be responsible for such activities, so these compounds can be investigated further for their cancer preventive efficacy (Shokri et al., 2017). The above clinical data however, supports the clinical anticancer role of spice' bioactives but the data is not enough to substantiate their efficacy with commercially available anticancer drugs, therefore more clinically studies can be planned on anticancer efficacy of spice's bioactives.

13. Conclusion and future recommendations

Through this treatise, it is evident that the temptation towards spices is not only because of their aromatic and seasonings power but more importantly credited to their diverse medicinal attributes too. Within this context, the present study provides a clear understanding regarding the role of spices in cancer prevention, which has become the emperor of all maladies. More importantly, the review provides the ethnomedicinal basis for the reliable anticancer effectiveness of spices and their active constituents which otherwise always questioned due to the lack of enough scientific evidences. Overall, spices' bioactives have the ability to interact with multiple check points and also target various mediators to dysregulate or halt the various signaling pathways involved in cancer proliferation. Henceforth, in order to avoid inflating cost of advanced medication alongwith their associated fatal side issues, spices and their bioactives can be introduced as fresh lead for the development of cost-effective novel drugs. However, from the current study the anticancer role of spices is clear on traditional, pre-clinical and clinical scale to SAR studies to some extent but in-spite of these studies, sufficient placebo studies are also required to establish the anticancer role of spices on cancer patients. Future investigations are also needed on in-depth molecular mechanism of anticancer spices which can open new avenues for the better management of cancer patients.

Ethical approval

Not required.

CRediT authorship contribution statement

Neetu Singh: Writing – original draft, Conceptualization, Investigation, Data curation. **Surender Singh Yadav:** Conceptualization, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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