The poor people in the rural areas and to treat various types of Mediterranean region. Leaves of **ABSTRACT**

Cancer is defined as an ailment in which anomalous cells in the body can grow uncontrollably. When we look into the statistics of cancer incidence and mortality in the last few years reported by IARC (International Agency for Research on Cancer), an estimated 14.1 million new cancer cases were registered and 8.2 million cancer-related deaths occurred in 2012 whereas in 2008, 12.7 million and 7.6 million were estimated respectively. In the population based study GLOBOCAN 2012 projects that the cancer incidence is high in urban population and developed countries but mortality due to cancer, was frequently found in rural population and under developed countries [1]. Since many years plants have been used as a remedy for the cancer treatment [2].

The uses of plants in the indigenous cultures particularly of developing countries, are numerous and diverse, forming an important socio-economic base including their use in cancer therapy [3]. The World Health Organisation (WHO) estimates that up to 80% of the world’s population in developing countries depends on locally available plant resources for their primary healthcare. A number of drugs have been isolated or derived from natural sources based on their use in traditional medicine as herbal remedies [4].

There are several books on Indian spices but a complete coverage on phytochemicals and pharmacological research about these spices are very important and highly demanded. The herbs which people use in daily food items are the best source for remedy or prevention of different ailments. Over 60% of the clinically used anticancer drugs are of natural origin and most of them are derived from higher plants [5]. In contrast, using whole herbal preparations has produced less effect on the human body because of the synergy of the plants which make up the preparations.

Moreover, ethnomedicinal plants used to treat cancer are considerably cheap and herbal drug treatment can be affordable to the poor people in the rural areas and to treat various types of cancers effectively. The current paper aims to systematically review the scientific literature and provide a comprehensive summary on the potential anticancer medicinal benefits of spices.

**Spice anticancer plant species**

**Bay leaf-Laurus nobilis** [6] (Family: Lauraceae)

*Laurus nobilis* L. is an aromatic evergreen tree native to the Mediterranean region. Leaves of *L. nobilis* are used as a spice and traditionally have been used as herbal medicine to treat many health complications. Leaves of this plant produce yellow oil known for many therapeutic indications [7,8]. *Laurus nobilis* essential oils were tested against some cancer cell lines, including breast, prostate and renal. This preliminary in vitro study showed that *Laurus nobilis* and other members of the same family demonstrated cytotoxicity and tumor growth inhibition [9]. A separate laboratory analysis demonstrated tumor suppression against leukemia cell lines [10]. A recent study results demonstrate that *Laurus nobilis* acetone extract strongly inhibited the proliferation of the cervical epithelial carcinoma (HeLa) cells [11]. Saab AM et al study results show that *Laurus nobilis* seed extract is suitable to kill multidrug-resistant P-glycoprotein expressing tumor cells [12]. Another *In vitro* study has indicated that 1, 8-cineole and hot-water-soluble sesquiterpenes purified from *Laurus nobilis* L. may have an inhibitory effect against human leukemia cells [13].

**Black pepper-Piper nigrum** [14] (Family: Piperaceae)

Black pepper (*Piper nigrum*) is a perennial climbing vine grown for its berries extensively used as spice and in medicine [15]. India is a leading producer, consumer and exporter of black pepper in the world. Peperine is an alkaloid found naturally in *Piper nigrum*, this alkaloid is responsible for the pungency of Black pepper. Manoharan *et al.* investigated the chemoprotective effect of piperine against 7, 12 dimethylnitrosamine induced buccal pouch carcinoma of Syrian golden hamsters [16]. They observed that piperine completely prevented the formation of oral carcinoma. El Hamss R *et al.* observed that 1-piperine was effective in immunomodulatory, antitumor activity and modulating lipid peroxidation and through the activation of antioxidative protection enzymes [22].

**Caper-Capparis spinosa** [23] (Family: Capparidaceae)

*Capparis spinosa* is one of the most common aromatic plants growing in wild in the dry regions around the west or central Asia
and the Mediterranean basin. The caper has been known for centuries in traditional phytotherapy, its properties made it to use for several purposes. Various parts of caper plant which can be used as drugs, cosmetics and foods are also used in different areas for landscaping, control of erosion or animal feeding [24]. A recent study suggested that two major essential oils (neurogenicol and sabinic acid) present in caper fruit extracts contain volatile and non-volatile compounds which potentially can play an important role in colon cancer prevention [25]. According to a recent study it was observed that there was no significant difference in its effect when they have tested on two different tumor cell lines, HeLa and Hep-2 cell lines. The cytogenetic study on HeLa cell line shows that polychromatophilic cell extract has antimutagenic index against tested cell line [26]. Ji Yi et al. demonstrated that Capparis spinosa N-butanol extract induces apoptosis through mitochondrial pathway [27].

Cumin-Cuminum cyminum [28] (Family: Apiaceae)

Cuminum cyminum L. is commonly known as cumin or jeera, the seeds of the plant are used to add flavour to spicy recipes. It is one of the old cultivated medicinal food herbs in Asia, Africa and Europe. Its seeds have been commonly used for culinary and flavoring purposes and folklore therapy since antiquity in various countries. Cumin seeds have been found to possess essential prostate cancer cuminaldehyde (4-isopropylbenzaldehyde), pyrazines, 2-methoxy-3-sec-butylpyrazine, 2 ethoxy-3-isopropylpyrazine, and 2-methoxy-3-methylpyrazine. Studies have shown that cumin seeds have also anti-carcinogenic properties. Aamal A. I. et al. study showed cumin seed extracts inhibits against some cell lines. They found antitumor effect of the EHP compound of Cuminum cyminum seeds against six cell lines (HEPG2; HELA; HCT116; CAO2; MCF7; HEP2) [29]. Aruna K et al. study showed cumin seeds (Cuminum cyminum Linn) significantly decreased the incidence of both BaP[α]-induced neoplasia and 3′MeDAB-induced hepatomas [30]. A recent in-vitro study evaluates cuminum cyminum ethanolic extract cytotoxic activity, and it was found to be 25%, 61%, 40%, 31%, 28%, 27% against SF-295, Colon 502713, Colon-205, Hep-2, A-549, OVCAR-5, PC-5 human cancer cell lines respectively. Cuminum cyminum extract showed 61% maximum activity against Colon 502713 cell line [31]. Gagandeep et al. analyzed the chemo preventive potentials of different doses of cumin seed-mixed diet on benzo [a] pyrene [B (a) P]-induced forestomach tumorigenesis and 3-methyl cholanthrene (MCA)-induced uterine cervix tumorigenesis. Results showed a significant inhibition of stomach tumor burden (tumors per mouse) by cumin. Results strongly suggest the cancer chemo preventive potentials of cumin seed and could be attributed to its ability to modulate carcinogen metabolism [32].

Garlic-Allium sativum [33] (Family: Alliaceae)

Allium sativum is a cultivated food highly regarded throughout the world. Originally from Central Asia, garlic is one of the earliest of cultivated plants [34]. Common food for flavor and spice, and has been traditionally popular with strong folkloric awareness. The use of garlic as a food and medicine dates back to prehistoric time. Garlic contains several potentially important agents such as alicin, allin, ajoene, diallyl trisulfide, sallylcysteine, vinyldithiines, allyl propyl disulfide. The cell cycle was arrested at G2/M phase, the cells with S-allylcysteine C may be a effective attenuator of BaP-induced breast carcinogenesis in vitro [37]. A recent study found that S-allylcysteine, a potent compound present in garlic, suppressed the proliferation of PC-3 cells and led to cell cycle arrest at the G0/G1 phase, as well as inducing apoptosis. This was accompanied by the decreased expression of Bcl-2 and increased expression of Bax and caspase 8. This study demonstrated the chemo preventive activity of S-allylcysteine in vitro, and that S-allylcysteine C may be a promising candidate for prostate cancer treatment. The cell growth was significantly suppressed by diallyl trisulfide, which is a major constituent of the garlic oil, but not by diallylpropyl and diallyl disulfide. The cell cycle was arrested at G2/M phase, the cells with sub-G1 DNA content, and the cells with caspase-3 activity were significantly increased by diallyl trisulfide treatment [38]. The anticancer effect of diallyl trisulfide was examined using human colon cancer cells HCT-15 and DLD-1 and observed that disrupted microtubule network formation of the cells [39].

Ginger-Zingiber officinale [40] (Family: Zingiberaceae)

Zingiber officinale is an herbaceous perennial, the rhizomes of which are used as a spice. India is a leading producer of ginger in the world. India produced 3.70 lakh tonnes of the spice from an area of 1.06 lakh hectares. The major active ingredients of Zingiber officinale root are thought to be pungent phenol compounds (such as gingerol and paradol) and volatile oils [41]. Zingiber officinale is widely used in Ayurveda, the traditional medical system of India. Population-based studies have shown a lower risk of colon, prostate, gastrointestinal [42] and other cancers in India compared to Western counterparts. Some phenolic substances in ginger have strong anti-oxidative and anti-inflammatory properties; consequently, they can possess significant anti-carcinogenic and anti-mutagenic activities [43]. Shahedur Rahman et al. study results showed that enriched ginger extract (rhizomes) exhibited the highest anticancer activity on MCF-7 cancer cells with IC50 values of 3.48 and 25.7 μg/ml [44]. The extract of ginger confined HCT 116 and HT 29 cells at G0/G1 and G2/M phases with consequent decrease in S-phase. This study suggests that ginger extract may bring to bear its antitumor effects on colon cancer cells by suppressing its growth, striking the G0/G1-phase, reducing DNA synthesis and inducing apoptosis [45]. Furthermore, [6]-Gingerol remarkably suppressed the endothelial cell proliferation induced by VEGF (Vascular Endothelial Growth Factor), the most important angiogenic factor associated with induction and maintenance of the neovascularization in human tumors. Therefore, [6]-gingerol may be useful for preventing or treating angiogenesis dependent human diseases such as cancer [46]. A recent study has observed that Zingiber officinale plant extract with 50% inhibitory concentration (IC50) values ranging between 1 and 28 μg/ml exposed cells showed cell cycle arrest, DNA damage and cytochrome c release, indicating that the mechanism of cytotoxicity could be via mitochondrial mediated apoptotic pathways [47].

Rosemary-Rosmarinus officinalis [48] (Family: Lamiaceae)

Rosmarinus officinalis L. is a small evergreen which grows wild in most Mediterranean countries, reaching a height of 1.5 m [49]. It is a spice and medicinal herb widely used around the world. The main active constituents are volatile oil which is constituted with camphene, camphor, cineol, borneol, resin, bitters matter, rosemary acid and flavonoids. Of the natural antioxidants, rosemary has been noted for its strong anti-oxidative and anti-inflammatory properties; consequently, they can possess significant anti-carcinogenic and anti-mutagenic activities [43]. Shahedur Rahman et al. study results showed that enriched ginger extract (rhizomes) exhibited the highest anticancer activity on MCF-7 cancer cells with IC50 values of 3.48 and 25.7 μg/ml [44]. The extract of ginger confined HCT 116 and HT 29 cells at G0/G1 and G2/M phases with consequent decrease in S-phase. This study suggests that ginger extract may bring to bear its antitumor effects on colon cancer cells by suppressing its growth, striking the G0/G1-phase, reducing DNA synthesis and inducing apoptosis [45]. Furthermore, [6]-Gingerol remarkably suppressed the endothelial cell proliferation induced by VEGF (Vascular Endothelial Growth Factor), the most important angiogenic factor associated with induction and maintenance of the neovascularization in human tumors. Therefore, [6]-gingerol may be useful for preventing or treating angiogenesis dependent human diseases such as cancer [46]. A recent study has observed that Zingiber officinale plant extract with 50% inhibitory concentration (IC50) values ranging between 1 and 28 μg/ml exposed cells showed cell cycle arrest, DNA damage and cytochrome c release, indicating that the mechanism of cytotoxicity could be via mitochondrial mediated apoptotic pathways [47].

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TK1, enzymes related to 5-FU resistance [54]. Nabekura T et al. study results suggest that rosemary phyto chemicals, such as cncarnic acid, have inhibitory effects on anticancer drug efflux transporter P-glycoprotein and may become useful to enhance the efficacy of cancer chemotherapy [53]. Petiwal SM et al. findings suggest that rosemary polyphenols (carnosic acid and carnosol) target multiple signaling pathways involved in cell cycle modulation and apoptosis [56]. In 2012 one more study showed that rosemary extract inhibited the proliferation of ovarian cancer cell lines by affecting the cell cycle at multiple phases. It induced apoptosis by modifying the expression of multiple genes regulating apoptosis, and holds potential as an adjunct to cancer chemotherapy [57]. Two recent studies showed that main antioxidant compounds of Rosmarinus officinalis L were induced apoptosis in HCT116 cells and human melanoma A375 cell line via generation of ROS [58, 59].

**Turmeric-Curcuma longa [60] (Family: Zingiberaceae)**

*Curcuma longa* is a spice native to India. Historically, turmeric has been used throughout India, China and Indonesia as a spice and medicinal agent. India is the largest producer of turmeric in the world (93.7% of the total world production) and is cultivated in 150,000 hectares in India [61]. Turmeric is a mild spice that enhances the flavor of other spices and foods and is the base of most Indian curries. Several medical properties of turmeric are innumerable and the practices are very ancient. Curcumin is the principal curcuminoid of the turmeric it is main active constituent. Curcumin has been found to possess anticancer activities via its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis and metastasis. Curcumin has shown anti-proliferative effect in multiple cancers, and is an inhibitor of the transcription factor NF-B and downstream gene products [including c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF-a, interleukins and MMP-9]. In addition, curcumin affects a variety of growth factor receptors and cell adhesion molecules involved in tumor growth, angiogenesis and metastasis [62]. Curcumin activates the DNA damage response, providing an opportunity and rationale for the clinical application of these nutraceuticals in the chemoprevention of prostate cancer [63]. Balakrishna A et al. confirmed that the combination of Curcumin and Berberine synergistically generates anticancer effects in A549, Hep-G2, MCF-7, Jurkat, and K562 cells in vitro, possibly mediated by inducing apoptosis. With regard to A549, Hep-G2, MCF-7, Jurkat, and K562 Curcumin and Berberine are of extreme antitumor agents [64]. Sa G, Das T study shows that Curcumin asserts its anti-tumor activity in cancer cells by altering the deregulated cell cycle via (a) cyclin-dependent (b) p53-dependent and (c) p53-independent pathways. Such influences of curcumin upon key signal transduction pathways of cell cycle and effectiveness in animal model systems have qualified it as a multiple edged sword in combating the deadly disease-cancer [65]. Moreover, curcumin is well tolerated in humans. Therefore, EGFR-miRNA-autophagy and cancer stem cell-based therapy in the presence of curcumin might be promising mechanisms and targets in the therapeutic strategy of lung cancer [66]. Shiri S et al. study indicates the protective effects of a dendrosomal curcumin formulation on mice metastatic breast cancer, witnessed by increase in representation of M1 macrophages [confirmed by up-regulation of STAT4 and IL-12], and decrease in M2 macrophages [confirmed by down-regulation of STAT3 IL-10 and arginase I] in a typical animal model of metastatic breast cancer [67].

**Curry leaf-Murraya koenigii [68] (Family: Rutaceae)**

*Murraya koenigii*, a medicinally important herb, commonly known as curry-leaf tree, is a native of India, Sri Lanka and other south Asian countries. Widely used in Indian cookery for centuries because it has a versatile role to promote appetite and digestion. Based on ethnopharmacology, M. koenigii is used as a stimulant, antidysenteric and for fever. Medicinal properties of *Murraya koenigii* are numerous and chemical constituents from every part of the plant have been extracted. The most important chemical constituents responsible for its intense characteristic aroma are β-gurjunene, P-caryophyllene, P-elemene and O-phellandrene [70]. The presence of important phytochemicals make the plant useful for treating different ailments and have a potential of providing useful drugs of human use. In 2012 Girinimbine isolated from the stem bark of Murraya koenigii was studied, in this study in vitro anti-tumour promoting activity of girinimbine was determined by measuring the percentage inhibition of induced early antigen (EA) of BBV on the surface of Raji cells [71]. Girinimbine mediates its antiproliferative and apoptotic effects through up-and down regulation of apoptotic and antiapoptotic proteins. There was a significant involvement of both intrinsic and extrinsic pathways.

Moreover, the upregulation of p53 as well as the cell proliferation repressor proteins, p27 and p21, and the significant role of insulin/IGF-1 signaling were also identified. Moreover the caspases 3 and 8 were found to be significantly activated [72]. Another study reported that mahanine, purified from the leaves of *M. koenigii*, has a dose-dependent time-dependent anti-proliferative activity [86]. In-vitro studies in animal model systems have demonstrated numerous beneficial health effects of Cinnamomum zeylanicum, such as anti-inflammatory properties, anti-microbial activity, reducing cardiovascular disease, boosting cognitive function and reducing risk of cancers [81].

Cinnamon is one of the oldest spices used by different cultures around the world for several centuries. Generally in India, *Cinnamomum zeylanicum* is cultivated in south India [78]. But it originates from the island of Sri Lanka, south east of India. The *Cinnamon* has essential oils, resinoid compounds. The active phytoconstituents of *Cinnamomum zeylanicum* are Cinnamaldehyde and Eugenol [79]. Cinnamon is mainly used in the aroma and essence industries due to its fragrance, which can be incorporated into different varieties of foodstuffs, perfumes, and medicinal products [80]. In-vitro and in-vivo studies in animals and humans from different parts of the world have demonstrated numerous beneficial health effects of *Cinnamomum zeylanicum*, such as anti-inflammatory properties, anti-microbial activity, reducing cardiovascular disease, boosting cognitive function and reducing risk of cancers [81].

Treatments with the aqueous extracts of cinnamon and cardamom augment the activities of the detoxifying and antioxidant enzyme glutathione-transferase (GST) with a concomitant reduction in lipid peroxidation levels in animals with colon cancer compared to controls [82]. Assadollahi V et al. study demonstrated that cell line samples that supplemented with 0.1 mg/ml *C. zeylanicum* aqueous extract enhanced induction of apoptosis in THP-1 cell line compared to samples that supplemented with 2, 1, and 0.01 mg/ml [83]. Jeong et al. reported that CB403, a chemical that can be synthesized from 2'-hydroxyxcinnamaldehyde derived from cinnamaldehyde, can inhibit tumor growth. Overall, the antioxidant and growth inhibitory properties of CB403 in animal-based studies as well as in cell culture-based studies indicate the potential of cinnamon to be used as an anticancer agent [84]. The aqueous extract and the fraction of cinnamon (procyanidins) from HPLC inhibit vascular endothelial growth factor subtype 2 (VEGFR2) kinase activities, thereby inhibiting angiogenesis involved in cancer. The results of the study revealed that cinnamon could potentially be used in cancer prevention [85]. Cinnamaldehydes have been synthesized and tested as inhibitors against angiogenesis [86]. Cabello et al. reported that cinnamaldehyde inhibits the activity of NF-kB and the production of tumor necrosis factor alpha (TNFα) induced interleukin-8 (IL-8) in A375 cells. This inhibition provides additional support to the existing unrecognized role of cinnamic acid as a potential anticancer agent [87].
CONCLUSION
In the recent years, traditional system of medicine emerged as a potential source to manage the growing rate of chronic, degenerative, environmental, lifestyle and stress related diseases. This study attempts to signify the role of spices and their constituents in therapeutic and pharmacological applications. From the description provided above, it is clear that spice-derived phytochemicals have an enormous potential in the prevention and treatment of cancer. They can induce apoptosis, suppress proliferation of tumor cells, and inhibit invasion and angiogenesis. Spice-derived phytochemicals may be safer to use, more number of animal studies and clinical trials are needed to prove the usefulness of these agents. The intervention or prevention of cancer by use of dietary ethnomedicinal spices may be considered as cheap herbal drug affordable to the rural and poor people and holds great promise in efforts to control cancers of various types. Dietary ethnomedicinal spices are likely to play a significant role in discovery of novel products for cancer treatment.

CONFLICT OF INTERESTS
Declared None

REFERENCES


