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Review Article

SPICY ANTI-CANCER SPICES: A REVIEW

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ABSTRACT

The uses of ethnomedicinal dietary antimutagens and anticarcinogens for human healthcare still remain the most promising approach to the protection of human health and medication system in developing and under developing nations. The plant sources of India provide effective anticancer agents. Spice Herbs have a vital role in the prevention and treatment of cancer. Spices have been used for thousands of years and are known for their flavor, taste and color in the food. Moreover, ethnomedicinal spices used to treat cancer are considerably cheap. Herbal drug treatment can be given to poor people in the rural areas to treat different cancers effectively at an affordable cost. The article reveals the most recent studies on dietary ethnomedicinal spices and their families used to treat various types of cancer.

Keywords: Spices, Medicinal plants, Anti-cancer, Herbs.

INTRODUCTION

Cancer is defined as an ailment in which anomalous cells in the body 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 at 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 dimethylbenz [a]anthracene 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 when *Drosophila melanogaster* was exposed to mutation through promutagen ethyl carbamate, in such induced situation the *Piper nigrum* is effective to reduce mutational events [17]. Duessel *et al.* observed that piperine displayed an anti-proliferation effect at 24 h and statistically significant inhibition at 48 and 72 h at 100-200 µm concentration against cultured human colon cancer cells (DLD-1) [18].

Tharmalingam N *et al.* study demonstrated the inhibition of *H. pylori* growth and adhesion to gastric adenocarcinoma cells by a single compound, piperine [19]. The alcoholic extract of peppercorn and piperine was effective in immunomodulatory, antitumor activity and Dalton's lymphoma [20]. Wongpa *et al.* investigated the influence of piperine on chromosomes in rat bone marrow and they demonstrated that piperine at a dose of 100 mg*/kg, gave a statistically significant reduction in chromosomal aberrations [21]. Moreover, piperine from *Piper nigrum* reduced lung cancer by 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 phytomedicine, 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 suggests that caper essential oil and aqueous infusion contains 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 polyphenol mature fruit extract has antimitotic index against tested cell line [26]. Ji YB *et al.* demonstrated that *Capparis spinosa* N-butanol extract induces apoptosis through mitochondrial pathway [27].

Cumin-*Cuminum cyminum* [28] (Family: *Apaiaceae*)

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 oils such as 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. Amal A. I. *et al.* study showed cumin seed extracts activity against six tumor cell lines. They found antitumor effect of the EHP compound of *Cuminum cyminum* seeds against six cell lines (HEPG2; HELA; HCT116; CACO2; MCF7; HEP2) [29]. Aruna K *et al.* study showed cumin seeds (*Cuminum cyminum* Linn) significantly decreased the incidence of both B[a]P-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%, 31%, 28%, 27% against SF-295, Colon 502713, Colo-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 alliin, allicin, ajoene, diallyl trisulfide, sallylcysteine, vinyldithiines, allyl propyl disulfide, S- allylmercaptocystein and others. A number of studies have demonstrated the chemopreventive activity of garlic by using different garlic preparations including fresh garlic extract, aged garlic, garlic oil and a number of compounds derived from garlic. A study was performed to investigate the dose dependent effect of diallyl disulfide (DADS) on an androgen dependent prostate cancer cell line; results from the study suggest that DADS reduced the secretory activity of LNCaP cells with the gradual increase in dosage. DADS acts as a good antiproliferative agent, as confirmed by proliferation assay. DADS also induced apoptosis and nuclear segmentation in the higher doses [35]. A recent study found that sativum lectin 50 (ASL50, 50 kDa) isolated from aged *Allium sativum* was exhibited antiproliferative activity on oral carcinoma KB cells with an IC50 of 36 µg/ml after treatment for 48 h and induces the apoptosis of cancer cells by inducing 2.5-fold higher caspase enzyme activity than untreated cells [36]. Nkrumah-Elie *et al.* revealed mechanisms involved in DATS inhibition of BaP-induced carcinogenesis. This includes inhibition of cell proliferation, regulation of cell cycle, attenuation of ROS formation and inhibition of DNA damage. Thus, the investigators suggest that at the doses evaluated, DATS could be an 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 phases, as well as inducing cell 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 diallyl monosulfide 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 important active components 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 anticarcinogenic 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 34.8 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 decreased 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 neovasculature in human tumors. Therefore, [6]-gingerol may be useful for preventing or treating angiogenesis dependent human diseases such as cancer [46]. A recent study outcome observed that *Zingiber officinale* plant extract with 50% inhibitory concentration (IC_{50}) 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 widely accepted as one of the spices with the highest antioxidant activity [50]. Rosemary essential oil is also used as an anti bacterial, antifungal and anticancer agent [51, 52]. Essential oils from *Rosmarinus officinalis* can affect the pattern of bcl-2 and bax genes expressions, and this may increase the apoptosis of liver cancer cell line HepG2 [53]. A recent study outcome showed that supercritical fluid rosemary extract (SFRE) displays dose-dependent antitumor activities and exerts a synergistic effect in combination with 5-FU on colon cancer cells. Furthermore, SFRE sensitizes 5-FU-resistant cells to the therapeutic activity of this drug, constituting a beneficial agent against both 5-FU sensitive and resistant tumor cells. Gene expression analysis indicates that the enhancement of the effect of 5-FU by SFRE might be explained by the down regulation of TYMS and

TK1, enzymes related to 5-FU resistance [54]. Nabekura T *et al.* study results suggest that rosemary phyto chemicals, such as carnosic acid, have inhibitory effects on anticancer drug efflux transporter P-glycoprotein and may become useful to enhance the efficacy of cancer chemotherapy [55]. Petiwala 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 studys 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. Medicinal 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 Curcurmin 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 ethanomedicine, *M. koenigii* is used as a stimulant, antidysentric and for the management of diabetes mellitus, cancer [69]. A number of chemical constituents from every part of the plant have been extracted. The most important chemical constituents responsible for its intense characteristic aroma are P-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 EBV 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-and time-dependent antiproliferative activity in acute lymphoid (MOLT-3) and chronic myeloid (K562) leukemic cell lines and in the primary cells of leukemic and myeloid patients, with minimal effect on normal immune cells including CD34 (+) cells [73]. Koenoline isolated form root bark exhibited cytotoxic activity against the KB cell culture test system98. 9-formyl-3 methyl carbazole displayed weak cytotoxic activity against both mouse melanoma B 16 and adriamycin resistant P 388 mouse leukemia cell lines [74]. The effects of extracts of M. koenigii in in-vitro (short term incubation method and in-vivo (Dalton's ascitic lymphoma (DAL) anticancer models have been evaluated in male Swiss albino mice. DAL cells (106 cells) were injected into the mouse intraperitoneally [75]. According to Roy MK *et al.* study M*. koenigii* has been found to induce apoptosis in human myeloid cancer cell (HL-60). Results show that mahanine down-regulates cell survival factors by activation of caspase-3 through mitochondrion-dependent pathway, and disrupts cell cycle progression [76].

Cinnamon-*Cinnamomum zeylanicum* [77] (Family: *Lauraceae*)

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 Srilanka, south east of India. The *Cinnamon* has essential oils, resinous 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-stransferase (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'-hydroxycinnamaldehyde derived from cinnamaldehyde, can inhibit tumor growth. Overall, the antitumor 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 cinnamic aldehyde inhibits the activity of NF-κB 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

1. Globocan. Available from: URL: http: //globocan.iarc.fr/ Pages/fact_sheets_cancer.aspx. [Last accessed on 02 Mar 2015]
2. Zohara Yaniv Bachrach. Contribution of selected medicinal plants for cancer prevention and therapy. Acta Fac Med 2012;29:117-23.
3. Abdel-Wahab SI, Ain NM, Abdul BA, Elhassan MM, Ibrahim TAT. Energy-dispersive x-ray microanalysis of elements? Content of medicinal plants used traditionally as anticancer cure. Res J Biol Sci 2009;4:547-9.
4. Butler MS. The role of natural product chemistry in drug discovery. J Nat Prod 2004;67:2141–53.
5. Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981–2002. J Nat Prod 2003;66:1022–37.
6. Peter KV. A handbook of herbs and spices. New Delhi: Woodhead Publishing Ltd; 2000.
7. Buto SK, Tsang TK, Sielaff GW, Gutstein LL, Meiselman MS. Bay leaf impaction in the esophagus and hypopharynx. Ann Intern Med 1990;113:82-3.
8. Santos FA, Rao. Antiinflammatory and antinociceptive effects of 1.8-cineole a terpenoid oxide present in many plant essential oils. Phytother Res 2000;14:240-4.
9. Loizzo MR. Cytotoxic ativity of essential oils from labiatae and Lauraceae families against *in vitro* human tumor models. Anticancer Res 2007;27:3293-9.
10. Moteki H, Hibasami H, Yamada Y, Katsuzaki H, Imai K, Komiya T. Specific induction of apoptosis by 1,8-cineole in two human leukemia cell lines, but not a in human stomach cancer cell line. Oncol Rep 2002;9:757-60.
11. Berrington D, Lall N. Anticancer activity of certain herbs and spices on the cervical epithelial carcinoma (HeLa) cell line. J Evidence-Based Complementary Altern Med 2012. doi.org/10.1155/2012/564927. [Article in Press]
12. Saab AM, Guerrini A, Zeino M, Wiench B, Rossi D, Gambari R, *et al*. *Laurus nobilis* L. seed extract reveals collateral sensitivity in multidrug-resistant p-glycoprotein-expressing tumor cells. Nutr Cancer 2015;67:664-75.
13. Komiya T, Yamada Y, Moteki H, Katsuzaki H, Imai K, Hibasami H. Hot water soluble sesquiterpenes [anhydroperoxy-costunolide and 3-oxoeudesma-1,4,11triene-12,6alpha-olide] isolated from laurel (*Laurus nobilis* L.) induce cell death and morphological change indicative of apoptotic chromatin condensation in leukemia cells. Oncol Rep 2004;11:85-8.
14. Menon KS, Nair MK, Sharma OP. Preliminary report on the performance of black pepper on non living standards. Indian Spices 1982;19:3-5.
15. Singh YN. Kava an overview. J Ethanopharmacol 1992;37:18-45.
16. Manoharan S, Balakrishnan S, Menon VP, Alias LM, Reena AR. Chemopreventive efficacy of curcumin and piperine during 7, 12 dimethylbenz[a]anthracene induced buccal pouch carcinogenesis. Singapore Med J 2006;50:139-46.
17. El Hamss R, Idaomar M, Alonso-Moraga A, Munoz-Serra A. Antimutagenic properties of bell and black peppers. Food Chem Toxicol 2003;41:41-7.
18. Duessel S, Heuertz RM, Ezekiel UR. Growth inhibition of human colon cancer cells by plants compounds. Clin Lab Sci 2008;21:151-7.
19. Tharmalingam N, Kim SH, Park M, Woo HJ, Kim HW, Yang JY, *et al*. Inhibitory effect of piperine on Helicobacter pylori growth and adhesion to gastric adenocarcinoma cells. Infect Agents Cancer 2014;16:43.
20. Sunila ES, Kuttan G. Immunomodulatory and Antitumar activity of *piper longum* Linn. and piperine. J Ethnopharmacol 2004;90:339-46.
21. Wongpa S, Himakoun L, Soontornchai S, Temchargen P. Antimutagenic effects of piperine on cyclophosphamade induced chromosome aberrations in rat bone marrow cells. Asian Pac J Cancer Prev 2007;8:623-27.
22. Mona AM, Abo-Zeid, Ayman A, Farghaly. The anti-mutagenic activity of piperine against mitomycine C induced sister chromatid exchanges and chromosomal aberrations in mice. Nat Sci 2009;7:72-8.
23. SN Mishra, PC Tomar, N Lakra. Medicinal and food value of Capparis-a harsh terrain plant. Indian J Tradit Know 2007;6:230-8.
24. Özcan M, Akgül A. Influence of species, harvest date and size on composition of capers (Capparis spp.) flower buds. Nahrung 1998;42:102-5.
25. Kulisic-Bilusic T, Schmöller I, Schnäbele K, Siracusa L, Ruberto G. The anticarcinogenic potential of essential oil and aqueous infusion from caper (*Capparis spinosa L.*). Food Chem 2012;132:261–7.
26. Asaad Abdulwahed B AL-Asady, Khesar H Khalil, Sa'adi Saleh M Barwari. Cytotoxic and cytogenetics effects of aqueous, Methanolic and secondary metabolites extracts of *Capparis spinosa* on tumor cell lines *in vitro*. Jordan J Biol Sci 2012;5:15-30.
27. Ji YB, Yu L. N-butanol extract of *Capparis spinosa* L. induces apoptosis primarily through a mitochondrial pathway involving mPTP open, cytochrome C release and caspase activation. Asian Pac J Cancer Prev 2014;15:9153-7.
28. RK Johri. *Cuminum cyminum* and *Carum carvi*: an update. Pharmacogn Rev 2011;5:63–72.
29. Amal AI Mekawey, Mokhtar MM, Farrag RM. Antitumor and antibacterial activities of [1-(2-Ethyl, 6-Heptyl) Phenol] from Cyminum Seeds. J Appl Sci 2009;5:1881-8.
30. Aruna K, Sivaramakrishnan VM. Anticarcinogenic effects of some Indian plant products. Food Chem Toxicol 1992;30:953-6.
31. Prakash E, Gupta DK. Cytotoxic activity of ethanolic extract of *Cuminum cyminum* Linn against seven human cancer cell line. Univers J Agric Res 2014;2:27-30.
32. Gagandeep, Dhanalakshmi S, Méndiz E, Rao AR, Kale RK. Chemopreventive effects of *Cuminum cyminum* in chemically induced forestomach and uterine cervix tumors in murine model systems. Nutr Cancer 2003;47:171-80.
33. UP Singh, B Prilhiviraj, BK Sarma, Mandavi Singh, AB Rai. Role of garlic (*Allium sativum* L.) in human and plant diseases. Indian J Exp Biol 2001;39:310-22.
34. Londhe VP, Gavasane AT, Nipate SS, Bandawane DD, Chaudhari PD. Role of garlic (*Allium Sativum)* in various diseases: an overview. J Pharm Res Opin 2011;1:129-34.
35. Gunadharini DN, Arunkumar A, Krishnamoorthy G, Muthuvel R, Vijayababu MR, Kanagaraj P, *et al.* Antiproliferative effect of diallyl disulfide (DADS) on prostate cancer cell line LNCaP. Cell Biochem Funct 2006;24:407-12.
36. Kumar S, Jitendra K, Singh K, Kapoor V, Sinha M, Xess I, *et al*. Biological properties and characterization of ASL50 protein from aged allium sativum bulbs. Appl Biochem Biotechnol 2015;176:1914-27.
37. Nkrumah Elie YM, Reuben JS, Hudson A, Taka E, Badisa R, Ardley T, *et al.* Diallyl trisulfide as an inhibitor of benzo(a) pyrene-induced precancerous carcinogenesis in MCF-10A cells. Food Chem Toxicol 2012;50:2524-30.

38. Liu Z, Li M, Chen K, Yang J, Chen R, Wang T, *et al.* S-allylcysteine induces cell cycle arrest and apoptosis in androgen independent human prostate cancer cells. Mol Med Report 2012;5:439-43.
39. Seki T, Hosono T, Hosono-Fukao T, Inada K, Tanaka R, Ogihara J, *et al.* Anticancer effects of diallyl trisulfide derived from garlic. Asia Pac J Clin Nutr 2008;17 Suppl 1:249-52.
40. S Adel, P Prakash. Chemical composition and antioxidant properties of ginger root (*Zingiber officinale*). J Med Plants Res 2010;4:2674-9.
41. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale* Roscoe): a review of recent research. Food Chem Toxicol 2008;46:409-20.
42. Prasad S, Tyagi AK. Ginger and its constituents: role in prevention and treatment of gastrointestinal cancer. Gastroenterol Res Pract 2015. doi.org/10.1155/2015/142979. [Article in Press]
43. Surh YJ, Park KK, Chun KS, Lee LJ, Lee E, Lee SS. Anti-tumor-promoting activities of selected pungent phenolic substances present in ginger. J Environ Pathol Toxicol Oncol 1999;18:131-9.
44. Rahman S, Salehin F, Iqbal A. *In vitro* antioxidant and anticancer activity of young *Zingiber officinale* against human breast carcinoma cell lines. BMC Complementary Altern Med 2011;11:76.
45. GC/MS investigation of the essential oils Rosmarinus officinalis L. Acta Pharm Hung 1987;57:159-69.
46. Peng Y, Yuan J, Liu Abdullah S, Abidin SAZ, Murad NA, Makpol S, *et al*. Ginger extract (Zingiber officinale) triggers apoptosis and G0/G1 cells arrest in HCT 116 and HT 29 colon cancer cell lines. Afr J Biochem Res 2010;4:134-42.
47. Bhargava S, Malhotra H, Rathore OS, Malhotra B, Sharma P, Batra A, *et al*. Anti-leukemic activities of alcoholic extracts of two traditional Indian medicinal plants. Leuk Lymphoma 2015;12:1-15.
48. Begum A, Sandhya S, Syed Shaffath A, Vinod KR, Swapna R, Banji D. An in-depth review on the medicinal flora *Rosmarinus officinalis* (Lamiaceae). Acta Sci Pol Technol Aliment 2013;12:61-73.
49. Kim EC, Min JK, Kim TY, Lee SJ, Yang HO, Han S, *et al.* [6]-Gingerol, a pungent ingredient of ginger, inhibits angiogenesis *in vitro* and *in vivo*. Biochem Biophys Res Commun 2005;335:300-8.
50. Héthhelyi E, Kaposi P, Domonkos J, Kernóczi ZS. GC/MS investigation of the essential oils Rosmarinus officinalis F, Ye J. Determination of active components in rosemary by capillary electrophoresis with electrochemical detection. J Pharm Biomed Anal 2005;39:431-7.
51. Oluwatuyi M, Kaatz GW, Gibbons S. Antibacterial and resistance modifying activity of *Rosmarinus officinalis*. Phytochemistry 2004;65:3249-54.
52. Leal PF, Braga MEM, Sato DN, Carvalho JE, Marques MOM, Meireles MAA. Functional properties of spice extracts obtained via supercritical fluid extraction. J Agric Food Chem 2003;51:2520-5.
53. Wei FX, Liu JX, Wang L, Li HZ, Luo JB. Expression of bcl-2 and bax genes in the liver cancer cell line HepG2 after apoptosis induced by essential oils from *Rosmarinus officinalis*. Zhongyaocai 2008;31:877-9.
54. González-Vallinas M, Molina S, Vicente G, de la Cueva A, Vargas T, Santoyo S, *et al.* Antitumor effect of 5-fluorouracil is enhanced by rosemary extract in both drug sensitive and resistant colon cancer cells. Pharmacol Res 2013;72:61-8.
55. Nabekura T, Yamaki T, Hiroi T, Ueno K, Kitagawa S. Inhibition of anticancer drug efflux transporter P-glycoprotein by rosemary phytochemicals. Pharmacol Res 2010;61:259-63.
56. Petiwala SM, Puthenveetil AG, Johnson JJ. Polyphenols from the Mediterranean herb rosemary (*Rosmarinus officinalis*) for prostate cancer. Front Pharmacol 2013;4:29.
57. Tai J, Cheung S, Wu M, Hasman D. Antiproliferation effect of Rosemary (Rosmarinus officinalis) on human ovarian cancer cells *in vitro*. Phytomedicine 2012;19:436-43.
58. Kim DH, Park KW, Chae IG, Kundu J, Kim EH, Kundu JK, *et al*. Carnosic acid inhibits STAT3 signaling and induces apoptosis through generation of ROS in human colon cancer HCT116 cells. Mol Carcinog 2015;8. doi: 10.1002/mc.22353. [Epub Ahead of Print]
59. Cattaneo L, Cicconi R, Mignogna G, Giorgi A, Mattei M, Graziani G, *et al*. Anti-proliferative effect of *Rosmarinus officinalis* L. Extract on human melanoma A375 Cells. PLoS One 2015;10:e0132439.
60. KC Velayudhan, N Dikshit, M Abdul Nizar. Ethnobotany of turmeric (*Curcuma longa* L.). Indian J Traditional Knowledge 2012;11:607-14.
61. Sasikumar B. Genetic resources of curcuma: diversity characterization and utilization. Plant Res 2005;3:230-51.
62. Wilken R. Curcumin: a review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Mol Cancer 2011;10:12.
63. Horie S. Chemoprevention of prostate cancer: soy isoflavones and curcumin. Korean J Urol 2012;53:665-72.
64. Balakrishna A, Kumar MH. Evaluation of synergetic anticancer activity of berberine and curcumin on different models of A549, Hep-G2, MCF-7, Jurkat, and K562 cell lines. Biomed Res Int 2015. doi.org/10.1155/2015/354614. [Article in Press]
65. Sa G, Das T. Anti cancer effects of curcumin: cycle of life and death. Cell Div 2008;3:14.
66. Ye M, Li Y, Yin H, Zhang J. Curcumin: updated molecular mechanisms and intervention targets in human lung cancer. Int J Mol Sci 2012;13:3959-78.
67. Shiri S, Alizadeh AM, Baradaran B, Farhanghi B, Shanehbandi D, Khodayari S, *et al*. Dendrosomal curcumin suppresses metastatic breast cancer in mice by changing m1/m2 macrophage balance in the tumor microenvironment. Asian Pac J Cancer Prev 2015;16:3917-22.
68. Shah Rajesh Kumar, Das Loveleena, Sangma Godwin. Medicinal property of murraya koenigii-a review. Int Res J Biological Sci 2013;2:80-3,
69. Xie JT, Chang WT, Wang CZ, Mehendale SR, Li J, Ambihaipahar R, *et al.* Curry leaf *Murraya koenigii* Spreng. reduces blood cholesterol and glucose levels in ob/ob mice. Am J Chin Med 2006;34:279-84.
70. Jain V, Momin M, Laddha K. *Murraya Koenigii:* an updated review. Int J Ayurvedic Herbal Med 2012;2:607-27.
71. Kok YY, Mooi LY, Ahmad K, Sukari MA, Mat N, Rahmani M, *et al.* Anti-tumour promoting activity and antioxidant properties of girinimbine isolated from the stem bark of *Murraya koenigii*. Molecules 2012;17:4651-60.
72. Mohan S, Abdelwahab SI, Cheah SC, Sukari MA, Syam S, Shamsuddin N, *et al*. Apoptosis effect of girinimbine isolated from murraya koenigii on lung cancer cells *in vitro*. J Evidence-Based Complementary Altern Med 2013. doi.org/10.1155/2013/689865. [Article in Press]
73. Bhattacharya K, Samanta SK, Tripathi R, Mallick A, Chandra S, Pal BC, *et al.* Apoptotic effects of mahanine on human leukemic cells are mediated through crosstalk between Apo-1/Fas signaling and the Bid protein and via mitochondrial pathways. Biochem Pharmacol 2010;79:361-72.
74. Chakraborty M, Nath AC, Khasnobis S, Chakraborty M, Konda Y, Harigaya Y, *et al*. Carbazole alkaloids from *Murraya koenigii*. Phytochemistry 1997;46:751-5.
75. Nutan MTH, Hasnat A, Rashid MA, Antibacterial and cytotoxic activities of *Murraya koenigii*. Fitoterapia 1998;69:173-5.
76. Roy MK, Thalang VN, Trakoontivakorn G, Nakahara K. Mechanism of mahanine-induced apoptosis in human leukemia cells (HL-60). Biochem Pharmacol 2004;67:41-51.
77. Vaibhavi Jakhetia, Rakesh Patel, Pankaj Khatri, Neeraj Pahuja, Sunil Garg, Anupriya Pandey, *et al.* Cinnamon: a pharmacological review. J Adv Sci Res 2010;1:19-23.
78. Leela NK. Cinnamon and cassia. In: Parthasarathy VA, Chempakam B, Zacharia TJ. Editors. Chemistry of spices. Cabi: Wallingford; 2008. p. 124-44.
79. Senanayake UM, Lee TH, Wills RBH. Volatile constituents of cinnamon (*Cinnamomum zeylanicum*) oils. J Agric Food Chem 1978;26:822–4.
80. Huang TC, Fu HY, Ho CT, Tan D, Huang YT, Pan MH. Induction of apoptosis by cinnamaldehyde from indigenous cinnamon *Cinnamomum osmophloeum* Kaneh through reactive oxygen

species production, glutathione depletion, and caspase activation in human leukemia K562 cells. Food Chem 2007;103:434–43.

81. Jayaprakasha GK, Rao LJ. Chemistry, biogenesis, and biological activities of *cinnamomum zeylanicum*. Crit Rev Food Sci Nutr 2011;51:547–62.
82. Bhattacharjee S, Rana T, Sengupta A. Inhibition of lipid peroxidation and enhancement of GST activity by cardamom and cinnamon during chemically induced colon carcinogenesis in Swiss albino mice. Asian Pac J Cancer Prev 2007;8:578–82.
83. Assadollahi V, Gholami M, Zendedel A. *C. zeylanicum* aqueous extract induced apoptosis in the human myelocytic leukemia cell line (THP-1). Bratisl Lek Listy 2015;116:132-5.
84. Jeong HW, Han DC, Son KH, Han MY, Lim JS, Ha JH, *et al.* Antitumor effect of the cinnamaldehyde derivative CB403 through the arrest of cell cycle progression in the G2/M phase. Biochem Pharmacol 2003;65:1343–50.
85. Lu J, Zhang K, Nam S, Anderson RA, Jove R, Wen W. Novel angiogenesis inhibitor activity in cinnamon extract blocks VEGFR2 kinase and downstream signaling. Carcinogenesis 2010;31:481–8.
86. Kwon BM, Lee SH, Cho YK, Bok Seung SH, Youn MR, Chang SI. Synthesis and biological activity of cinnamaldehydes as angiogenesis inhibitors. Bioorg Med Chem Lett 1997;7:2473–6.
87. Cabello CM, Bair WB, Lamore SD, Ley S, Bause AS, Azimian S, *et al.* The cinnamon-derived Michael acceptor cinnamic aldehyde impairs melanoma cell proliferation, invasiveness, and tumor growth. Free Radical Biol Med 2009;46:220–31.