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Review Article

SAVOURING HEALTH: UNVEILING THE REMARKABLE ROLE OF SPICES IN PREVENTING CANCER

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Abstract

In recent years, the pursuit of natural and holistic approaches to disease prevention has gained substantial momentum. Among these, the exploration of the intricate relationship between diet and cancer prevention has emerged as a focal point of scientific inquiry. This comprehensive review delves into the captivating realm of Indian spices and their immense potential in hindering the onset and progression of cancer. Spices, renowned for their captivating flavours and aromatic profiles, have been treasured since ancient times for their culinary and medicinal value. However, it is their concealed prowess as reservoirs of bioactive compounds with potential anti-cancer properties that has ignited fervent research interest. Through an intricate interplay of various phytochemicals such as curcumin, capsaicin, gingerol, thymoquinone and many others; spices have demonstrated their ability to impede key processes in tumorigenesis, including uncontrolled cell proliferation, angiogenesis, metastasis, and inflammation. As the scientific community endeavours to unravel the intricate mechanisms behind the link between spices and cancer prevention, this review amalgamates current knowledge, highlights gaps in understanding, and underscores the necessity for multidisciplinary collaborations. The exploration of spices as agents of cancer prevention not only enriches the realm of culinary arts but also unveils an exciting frontier in the pursuit of innovative, complementary strategies to curtail the global burden of cancer.

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1. Introduction

Indian cuisine has a very prominent position among all the other cuisines. The main reason behind its prominence is the presence of spices. The Indian spices were considered with many philosophic concepts of improving health from time immemorial.

Cancer is one of the diseases that developed in a progressive manner involving many factors. The ultimate progression in some cases results in metastasis, spreading to other parts of the body. Cancer development can be defined using three critical steps – initiation, promotion, and progression. In some cases, cancer is asymptomatic making it challenging to diagnose. In a few cases, a person suffering from cancer is usually advised for radiotherapy, chemotherapy,

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gene therapy, and surgery. With the improvement in scientific health in India, the country aims the prevention of cancer. Preventive measures take time to improve the population's health, which prevents other deadly diseases such as diabetes and heart attack. The focus of cancer prevention in the 21st century is moving towards the improvement in the prediction of cancer risk, prevention of cancer, and personalized treatment. It also aims to increase the involvement of patients in taking the decision (Engineering Journal Publication of Research work, 2016).

Indian spices are well known for their role in improving health from ages. They are the prominent reason for making Indian cuisine to be loved across the globe. Indian spices are used in household kitchens regularly and are known to treat many diseases including flu and cancer prevention. They have the potential to inhibit the bioactivation of carcinogens, reduce the formation of free radicals and suppress cell division and promote apoptosis. Several spices are effective antioxidants and are important in decreasing the oxidative damage caused by environmental stress. Many historical events in India states the use of spices for several diseases. The continuous use of medicines has many side effects on the body. Recent research has shown that Indian spices possess several properties including anti-carcinogenic activity. Indian spices can also be used as dietary supplements. All the common properties of spices are shown in Table - 1.

Above all these properties, they are also known to have anti-microbial properties. The location at which spices show the anticancer effect varies based on the type. Few of the spices show the effect on the digestive system while other spices own the anticancer effect by various processes such as apoptosis, cell damage, and arrest of the cell cycle at the G2/M phase experimental studies have been done to show the role of different ingredients in cancer. All the mechanisms involved in the prevention of cancer by various spices are shown in this review.

2. Garlic

Garlic (*Allium sativum)* is one of the commonly used spices belonging to the "Amaryllidaceae " family which includes other vegetables such as onions, scallions, shallots, leeks, and chives. It is native to South Asia, Central Asia, and north-eastern Iran (Nicastro Ross and Milner 2015). Garlic has been used extensively in promoting cardiovascular health, maintaining cholesterol levels, and showing immunomodulatory effects (Jiang, 2019).

Garlic is highly abundant in organosulfur compounds such as S-allyl mercapto cysteine (SAMC), Diallyl- disulphide (DADS), Diallyl-trisulfide (DATS) and allicin which contributes to its flavour and odour (Omar and Al-Wabel, 2010). It serves various pharmacological properties such as antioxidant (scavenges oxidising agents), anti-inflammatory (limits the effects of pro-inflammatory cytokines), anti-mutagenic (inhibits cell division and induces apoptosis), antimicrobial (inhibits microbial growth) and anti-diabetic (stimulates insulin production and interferes glucose absorption) (Ansary *et al.*, 2020).

Anti-cancer effects of Garlic

Numerous studies have revealed that S-allyl mercapto cysteine (SAMC), Diallyl-disulphide (DADS), Diallyl- trisulfide (DATS) and allicin which are responsible for promoting the release of cytochrome c from mitochondria and activates the caspase family proteins such as caspase-3 and caspase-9 resulting in inducing Apoptosis (Yu *et al.*, 2012). These compounds are also involved in the p53 pathway which results in the decreased expression of Bcl-2 and increased expression of Bax (Xiao *et al.,* 2005).

Reactive oxygen species play a crucial role in signal transduction pathways. It leads to the activation of nuclear factor kappa B (NF Kappa B) which is involved in the regulation of gene transcription (Lichota and Gwozdzinski, 2018). It has been reported that the administration of allicin to mice results in low –ROS (Reactive Oxygen Species) production and prevents ROS - induced

cardiac hypertrophy through the inhibition of pro-inflammatory pathways such as Mitogen - Activated Protein Kinase (MAPK) and Phosphoinositide -3 kinase (PI3K) signalling pathways (Liu *et al.*, 2010). Several studies have revealed that garlic extract and one of its key components 'S-allyl cysteine ' inhibits nitric oxide production through the suppression of iNOS mRNA and protein expression in LPS and IF gamma-stimulated murine macrophage cell line RAW264.7 (Kim *et al.*, 2001).

Anti-angiogenic properties have been exhibited by various organo-sulphur compounds such as alliin, DATS and Ajoene (Powolny and Singh, 2008). In human breast cancer cells, DADS inhibits TNF- alpha-induced release of MCP-1, a chemokine involved in promoting tissue remodelling, angiogenesis and metastasis (Matsuura *et al.*, 2006). Alliin has shown prominent results in reducing Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor - 2 (FGF-2) induced tube formation and angiogenesis in HUVEC and *ex vivo* in CAM assay (Herman-Antosiewicz *et al.*, 2007). Various pharmacological studies have revealed that garlic-derived Organo-sulphur compounds (OSC) suppress the growth of cancer cells of different anatomical locations in relevance with the cell cycle arrest in the G2/M phase of the cell cycle.

The DATS-arrested mitotic cells express an accumulation of anaphase-promoting complex or cyclosome (APC/C) substrates cyclin A, cyclin B1 and hyperphosphorylation of securin (Herman-Antosiewicz *et al.*, 2007). The mechanism of the DATS-mediated cell cycle arrest in human gastric cancer cells is represented in Fig.1. Garlic is rich in antioxidant and anticancer properties which can trigger apoptosis (programmed cell death) that could help in preventing cancer. It also can inhibit the migration of breast cancer cells which can speed up the process of DNA repairing and can decelerate the proliferation of breast cancer cells.

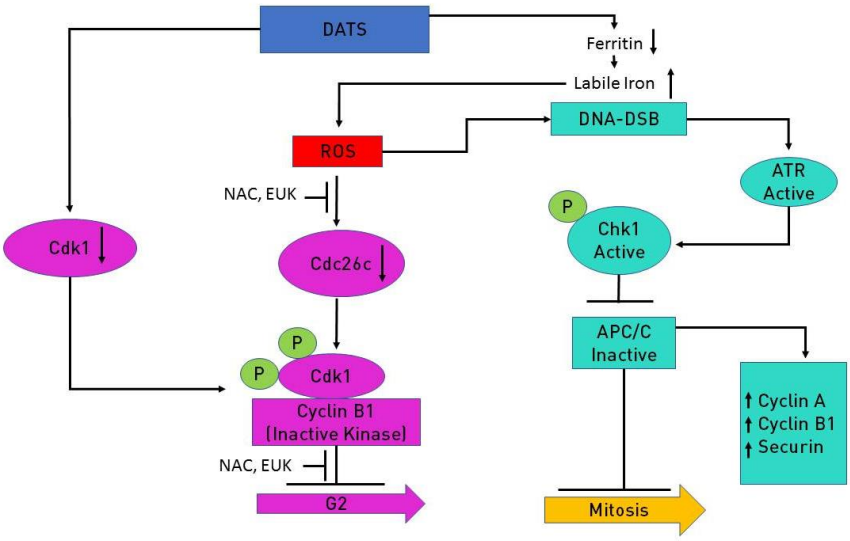

Figure - 1: Mechanism of DATS - mediated cell cycle arrest in prostate cancer cells

Table - 1: Common properties of spices

Properties	Description
Antioxidant	The ability to reduce or prevent the effect of free radicals. This helps in the prevention of delaying cell damage.
Anti-inflammatory	The ability to reduce the inflammation (swelling, redness, and pain) by blocking the inflammatory agent
Anti-microbial	The ability to reduce or prevent the spread of microorganisms in the body
Anti-diabetic	The property of a substance which involves in the treatment of diabetes by helping to control the blood sugar level
Anti-apoptotic	The ability to prevent the death of cells
Anti-cancer	The ability of the substance to treat malignant or benign tumours (usually cancerous)
Neuroprotective	The property helps in the prevention of neuronal death by inhibiting the cascade resulting in cell dysfunction
Cardioprotective	The ability to involve in the mechanisms preventing the myocardial damage

3. Turmeric

Turmeric (*Curcuma longa*) is a perennial herbaceous plant of the ginger family (Zingiberaceae) which is native to Southeast Asia (Fuloria *et al.*, 2022). It is rich in a yellow colour polyphenol compound called 'Curcumin' obtained from the rhizome of turmeric (Gupta *et al.*, 2012). Curcumin is a hydrophobic molecule that is insoluble in an aqueous phase of the digestive fluid, and it is eliminated from the digestive tract due to its poor bioavailability (Cas and Ghidoni, 2019). The turmeric rhizome is extraordinarily rich in vitamins c and E which enhances the antioxidative properties of curcumin through the neutralisation of the free radicals of the environmental carcinogens (Fabianowska-Majewska *et al.*, 2021). Numerous studies have also revealed that the Vitamin C participates in the hydroxylation of 5-methylcytosine to 5-hydroxymethylcytosine in DNA and is also involved in the modulation of epigenetic control of genome activity which results in the active demethylation of DNA (Minor *et al.*, 2013).

Anti-cancer effects of Turmeric

Several studies have revealed that curcumin may activate epigenetic remodelling in breast cancer cells resulting in Tissue - Specific Genes (TSGs) reactivation and oncogene downregulation. These changes in the expression of the gene-encoding proteins contribute to the regulation of intracellular oncogenic signalling pathways which may lead to the inhibition of Breast cancer cell proliferation through Cell cycle arrest and induce apoptosis (Fabianowska-Majewska *et al.*, 2021c).

Various pharmacological studies have revealed that curcumin targets multiple signalling pathways through its epigenetic anticancer activity. It results in the reactivation of numerous DNA -methylation-silenced Tissue-specific genes (TSGs) and the downregulation of oncogenes through promoter hypermethylation. It has also been implicated that curcumin modulates the activity of various transcription factors such as AP-1, NF-kB/ SP1 and TP53 binding sites which affects the DNMT1 (DNA methyltransferase) binding sites (Boyanapalli and Kong, 2015b). It has been found that curcumin inhibits the activity of various enzymes such as cyclooxygenase -2 (COX-2), lipoxygenase (LOX), inducible nitric oxide synthase (iNOS) and xanthine oxidoreductase (XOR) which activates ROS formation and promotes oxidative stress in cancer cells. Curcumin-mediated rapid generation of ROS induces apoptosis through the activation of caspases and alterations in the mitochondrial

membrane potential followed by the release of cytochrome C (Wang *et al.*, 2009).

Various *in vivo* and *in vitro* studies have revealed that curcumin down-regulates the expression of p53 as well as the survival genes such as EGR-1, c-myc and Bcl-XL in B cells (Khan *et al.*, 2012b). It inhibits the cell cycle progression of immortalised human umbilical vein endothelial cells through the expression of the CDK (cyclin-dependent kinases) inhibitors p21 WAF1/CIP1, p27KIP1 and p53 (Park *et al.*, 2002b).

In oestrogen – receptor negative breast cancer cell lines, curcumin inhibits angiogenesis factors such as VEGF and basic fibroblast growth factor (b-FGF) at the transcriptional level and has been shown to inhibit the phosphorylation of Akt within the MAPK/PI3K pathway resulting in pro-apoptosis (Farghadani and Naidu, 2021b). It has been observed that curcumin suppresses the proliferation of human vascular endothelial cells and eliminates the FGF-2-induced angiogenic response (Fu *et al.*, 2015b; Farghadani and Naidu, 2021b). The effect of curcumin on the regulation of factors involved in cancer is depicted in Figure - 2.

Curcuminoids have been recommended by the US Food and Drug Administration (FDA) as "Generally Recognized as Safe" (GRAS) for clinical use and assorted studies have revealed that curcumin particularly affects the cytochrome P450 enzymes (Gupta *et al.,* 2012b). The molecular targets of curcumin were depicted in Table - 2.

Table - 2: Molecular targets modulated by curcumin

Name of the Target molecule	Name of the Cell line	Effect
Nuclear factor kappa-B (NF-KB)	Breast cancer nude mouse model	Downregulation of NF-KB resulted in the suppressed expression of the cyclin D-1, COX-2, MMP-9 and pro-MMP 2
Growth-factor-induced signalling cascades	Prostate cancer cells	Suppression of EGFR signalling through inhibiting ligand-induced activation of EGFR and its intrinsic tyrosine activity
Cyclin D-1	Adenocarcinoma cells	Curcumin suppresses the proliferation through the inhibition of cyclin D-1 and Cyclin-dependent kinase
P53	In human renal carcinoma caki cells	Curcumin enhances dual PI3 kinase /Akt and mTOR inhibitor NVP-BEZ235-induced apoptosis through p53 - dependent Bcl-2 mRNA downregulation at the post-transcriptional level
Oncogenic kinase	In malignant glioma cells	Inhibits the PI3 kinase /Akt pathway and inhibits various kinases such as phosphorylase kinase, protein kinase C and protamine kinase
Nrf-2	In breast cancer cells	Inhibits breast cancer proliferation through Nrf-2 - mediated downregulation of FEN-1 expression
Peroxisome proliferator - associated receptor gamma	In Eker rat-derived uterine leiomyoma cell lines	Inhibits proliferation through activation of PPARy and curcumin acts as a PPARy ligand

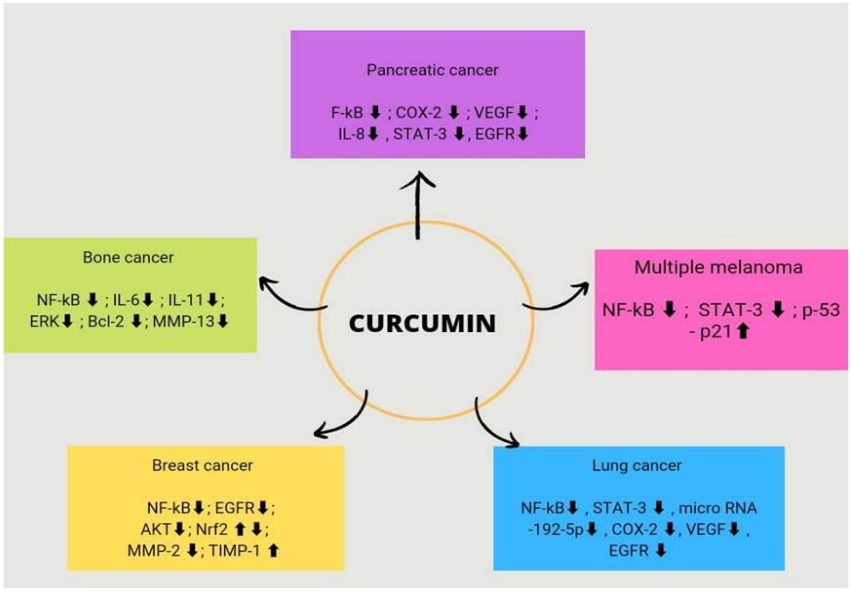

Figure - 2: The effect of Curcumin on the regulation of factors involved in Cancer

4. Rosemary

Rosemary is one of the evergreen herbs which belongs to the family " Lamiaceae" and it includes other herbs such as oregano, basil and lavender which are native to the Mediterranean region. It has been serving many culinary and medicinal benefits for an exceedingly long time and is well-known for making fragrant body perfumes (Moore *et al.,* 2016b). It is rich in a variety of polyphenolic compounds such as carnosol, carnosic acid, rosmarinic acid, Metalloproteinases (MMP-2, MMP-9) and alpha-tocopherol (Vitamin E) which are found in the extract of rosemary and are highly effective in treating cancer. It has been highly efficient in treating a wide range of health problems as it promotes brain health through the inhibition of acetylcholinesterase and butyrylcholinesterase, reduces diabetic complications by lowering blood glucose levels and increasing blood serum levels in diabetic patients and prevents skin damage (Allegra *et al.,* 2020b).

Anticancer properties of Rosemary

The Carnosic acid present in the rosemary extract induces apoptosis in human renal cancer cells by regulating the increase of sub-diploid DNA content and cleavage of PARP apoptotic fluid which activates various apoptotic fluid such as caspase-3 (Min *et al.,* 2014b). In kidney cancer cells, Carnosic acid stimulates programmed cell death through ROS-caused endoplasmic reticulum stress and triggers an increase in apoptotic markers such as ATF4 and caspase 3. It leads to an increase in TRAIL-mediated apoptosis in cake cells and other types of renal cell lines through a change in the endoplasmic reticulum stress-related proteins such as Bcl-2, COMP and OR5 (Jung *et al.,* 2015b). Many anticancer drugs face the severe problem of under and overdosing which leads to an elevated risk of treatment failure. Drug Metabolising Enzymes (DMEs) are highly responsible for drug responses in patients undergoing chemotherapy. Supercritical Fluid Rosemary Extract (SFRE) significantly increases the action of drugs such as tamoxifen, paclitaxel and trastuzumab and prolonged contact with elevated levels of carnosic acid causes excessive ROS generation which activates apoptosis of breast cancer cells through the stimulation of intrinsic and extrinsic apoptotic pathways (Posadas *et al.*, 2009b).

In Acute Myeloid Leukaemia (AML), combined administration of curcumin and carnosic acid could lead to synergistic growth inhibitory action and an increase in apoptosis through both extrinsic and intrinsic pathways (Pesakhov *et al.,* 2010b). Rosemary affects the activity of the human drug transporter p- glycoprotein (mdr1, abcb1) and multidrug resistance protein (mrp1 and abcc1) and in er-negative human breast cancer cells, carnosic acid at a low dosage increases the expression of three genes involved in glutathione synthesis (cyp4f3, GCC) and transport (slc7a11) (Nabekura, Yamaki, Hiroi, Ueno, & Kitagawa, 2010b).

5. Black pepper

Black pepper (*Piper nigrum*) also known as the "king of species" is a perennial climbing vine that is grown specifically for its berries. It is native to Malabar (a tropical region on the western coast of southern India) and is commonly used as medicine and spices. It is rich in an alkaloid dietary compound called piperine (1-piperoylpiperidine) which belongs to the species of the family Piperaceae (Takooree *et al.*, 2019b).

Piperine is one of the alkaloid compounds which contains a heterocyclic ring structure with a nitrogen atom (Stojanović-Radić *et al.,* 2019). Its structure consists of a Methylenedioxyphenyl (MDP) ring, a side chain with conjugated double bonds and a piperidine moiety attached through an amide linkage to the side chain as represented in Figure - 3. Several preclinical studies have revealed that black pepper serves many pharmacological properties such as anti-inflammatory, anti-tumour, antiparasitic, antioxidant and anti-cancer. It is extraordinarily rich in antioxidants which makes its best use in lowering cholesterol levels, and improving sugar levels and has enormous potential in treating cancer (Rather and Bhagat, 2018c).

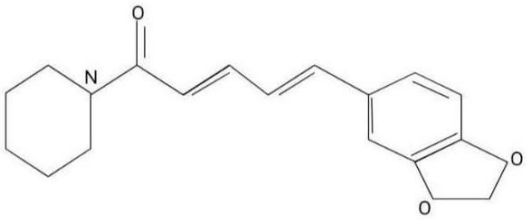

Figure - 3: Structure of Piperine

Anti-cancer effects of black pepper

Piperine inhibits proliferation, migration and tubule formation by umbilical vein endothelial cells and suppresses collagen-induced angiogenesis. It occurs by blocking Akt phosphorylation at Ser 473 and Thr 308 residues which leads to the inhibition of phosphoinositide - 3 kinase (a key regulator of angiogenesis) (Doucette *et al.,* 2013b). In Human oral squamous cells, piperine accelerates the generation of Reactive Oxygen Species (ROS) which eventually leads to the activation of caspases and cell cycle arrest (Siddiqui *et al.,* 2017d). Various research studies prove that piperine activates the Nrf-2 pathway which protects cells from extracellular as well as intracellular oxidation damage and maintains redox homeostasis by activating antioxidant response machinery mediatory such as HO-1, NRO-1GSH, GR and CAT. It scavenges Redox Oxygen Species (ROS) and decreases lipid peroxidation by blocking NF-kB and its associated downstream-signalling molecules such as Cox-2, PGE-2 and NO which play a crucial role in the survival and resistance of colon cancer cells (Rehman *et al.*, 2020b).

Piperine suppresses the proliferation of osteosarcoma cells by inducing G2/M cell cycle arrest and the migration and invasion of HOS and U20S cells through increased expression of TIMP-1/-2 and down regulation of MMP-2/-1 and is thereby considered an effective chemopreventive agent in the treatment of osteosarcoma (Zhang *et al.*, 2015b). Piperine has also shown great signs of effectiveness in various drugs such as Adriamycin (doxorubicin), Taxol (paclitaxel) and 5-FU chemotherapy and it can increase breast cancer

sensitivity to curcumin (a component of turmeric). Piperine is one of the dominant inhibitors of P-GP and MRP-1 which binds the consensus sequence and when the two analogues of piperine: Pip1 and Pip2 are co-administered with certain drugs such as vincristine, colchicine, and paclitaxel it leads to the reverse drug reaction in P-GP which leads to over expression of cervical and colon cancer (Lee *et al.,* 2017b). Piperine is one of the key components present in black pepper. It reduces proliferation, angiogenesis, and metastasis in cancer cells. It has been effective in reducing the growth of triple-negative breast cancer cells and thus acts as one of the effective chemopreventive agents in treating cancer.

6. Cumin

Cumin is an aromatic herb obtained from the dried seeds of the plant *Cuminum cyminum* L. which belongs to the family Apiaceae and is native to the eastern Mediterranean and South Asia (Singletary, 2021b). Cuminaldehyde is the prominent bioactive compound present in cumin with its other components such as p-cymene, γ-terpinene and β-pinene (Hb, 2013b).

Anti-cancer effects of Cumin

Cumin is involved in the reduction of oxidative stress, suppression of inflammatory marker expression and modulation of signalling pathways. Cumin oil has shown anti-inflammatory effects in LPS- stimulated RAW cells through the inhibition of NF-kB and mitogen-activated protein kinases. Cumin seeds are found to be effective in activating the activity of glutathione-S-transferase which is involved in eliminating carcinogens and it is found to inhibit the induction of gastric squamous cell carcinomas (Srinivasan, 2018). It has been also found that water soluble *C. cyminum* polysaccharides exhibit lower molecular weight and promote RAW264.7 and NK-92 cells to express the activity of interleukin (IL)-1β, IL-6, IL-12, and tumour necrosis factor (TNF)- α inflammatory cytokine and releases nitric oxide (Tabarsa *et al.*, 2020). Various independent studies have indicated that dietary cumin inhibits benzopyrene-induced tumorigenesis, 3-methylcholanthrene-induced uterine cervix tumorigenesis and 3-methyl-4-dimethylamino azobenzene-induced hepatomas in mice. This occurs due to the modulation of carcinogen metabolism through the carcinogen metabolizing phase I and phase II enzymes (Gagandeep *et al.,* 2003). It has been found that dietary supplementation of cumin inhibits the occurrence of rat colon cancer caused by a colon-specific carcinogen 1,2 - dimethyl hydrazine which resulted in the increased excretion of faecal matter and natural sterols. It leads to the decreased activity of the β-glucuronide and mucinase enzymes. β-glucuronide is responsible for increasing the hydrolysis of glucuronide conjugates and on the other hand, the increase in mucinase activity promotes the hydrolysis of the protective mucins in the colon (Nalini *et al.,* 2006).

7. Bhringraj

Bhringraj, scientifically known as *Eclipta alba* is a medicinal plant belonging to the family of Asteraceae. It is commonly known as “Ink plant” and “False daisy.” *Eclipta alba* is natively found in the tropical and sub-tropical regions of the world with characteristic white flowers. The major components present in *Eclipta alba* include the derivatives of thiophene, coumestan, phenolic acids, triterpenes, flavonoids, steroidal alkaloids, steroids, steroidal saponins, triterpene saponins and many more (Timalsina and Devkota, 2021). The Figure - 4 below represents some of the components present in Bhringraj. Bhringraj is considered a “Weed of Ethno-medical significance” (Jahan *et al.,* 2014). In the Indian subcontinent, Bhringraj is known in three forms of medical systems *viz.*, Unani, Ayurveda, and Siddha. Bhringraj is known widely for its medicinal properties to treat various ailments including spleen enlargement. The presence of a wide range of phytochemical components in the plant extract accounts for various properties such as anti-cancer, anti-microbial, anti-inflammatory, hepato-protective, anti-diabetic, antioxidant, snake venom neutralizing activities and many more (Jahan *et al.,* 2014).

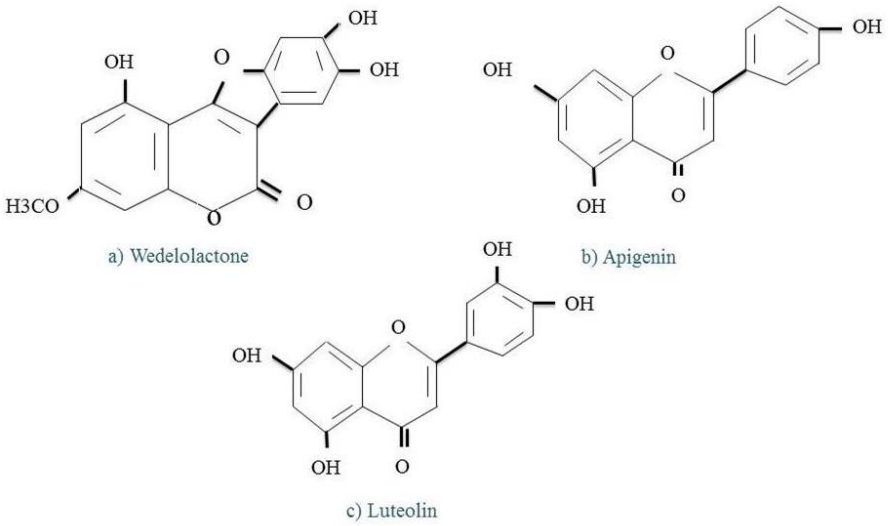

Figure 4: Components present in Bhringraj

Anti-cancer properties of Bhringraj

To evaluate the anticancer properties of Bhringraj, Nelson *et al.* (2020) conducted an experiment involving the treatment of methanolic extracts of Bhringraj on various cell lines such as human prostate cancer (PC-3), Michigan cancer foundation-breast cancer (MCF-7), human colorectal carcinoma (HCT-116) and renal cell carcinoma (RCC-45). An assay named MTT was conducted to figure out the action of Bhringraj extracts on the cell lines and the results inferred that the specificity of the Bhringraj extract was more against HCT-166 (colorectal carcinoma) when compared with other cell lines, meaning that Bhringraj had a more positive effect in killing the cancer cells from colorectal cell line than the other mentioned cell lines. The same study also checked for the impact of Bhringraj on normal human embryonic lung fibroblast cells (WI-38). The results suggested that the extracts have minimal or nontoxic effects on fibroblast cells (Nelson *et al.*, 2020). In another experiment conducted by Yadav *et al.* (2017) with alcoholic extracts of *Eclipta alba*, scientists recognized that the extract induced angiogenesis (programmed cell death) in human breast cancer cell line MCF 7 by causing DNA (deoxyribonucleic acid) damage and disrupting the mitochondrial membrane potential. The results also suggested that in a dose-dependent manner, alcoholic extracts of Eclipta alba also inhibited the migration of cancer cells to other parts of the body (Yadav *et al.*, 2017).

Chaudhary *et al.* (2014) conducted a study to figure out the anti-cancer and multi-drug resistance reversal properties of hydroalcoholic extracts of *Eclipta alba*. The study was done in a liver cancer-induced animal model. Usually, in the case of liver cancers, the ROS (Reactive Oxygen Species) levels are high and hence are also responsible for maintaining cancer. Increased levels of alfa fetoprotein were also observed which helps in the induction and progression of liver cancer. The hydroalcoholic extracts resulted in reduced ROS along with bringing down the alfa protein level to normal. Hence it can be inferred that the extracts from Bhringraj have a positive effect on tackling liver cancer cells (Chaudhary *et al.,* 2014).

8. Chili pepper

Capsicum is a tropical berry in the family Solanaceae, encompassing around 38 species. From the known species C. *pubescens*, C. *chinense*, C. *frutescenes*, C. *baccatum* and C. *annuum* are the 5 domesticated species. Since Chili pepper possesses many seeds bound to the pericarp of the fruit it is classified under berries.

They come in diverse colours (yellow, red, green, brown, and orange) and shapes (such as spherical, ovoid, fusiform, and elongated), both pungent and non-pungent varieties are available (Villa-Rivera and Ochoa-Alejo, 2021). Chili pepper has been in use for its medicinal properties and has culinary importance. Phytochemicals present in Chili pepper are vitamins C, pro-vitamin A, minerals (calcium, iron) carotenoids, flavonoids (anthocyanins) and the most important capsaicinoids such as capsaicin (represented in Figure - 5) and dihydrocapsaicin which are responsible for the pungency and medicinal properties (Villa-Rivera and Ochoa - Alejo, 2021; Chamikara *et al.,* 2016).

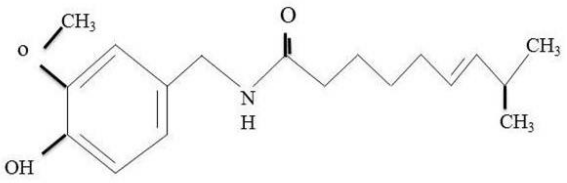

Figure - 5: Structural representation of Capsaicin

Anticancer properties of Chili pepper

In the last few years, scientists have tried to figure out the effects of phytochemicals present in various vegetables, fruits, teas, and whole grains. Capsaicin is one of the vital phytochemicals that possess anticancer properties. Capsaicin has been reported that affects several suppressor genes, multiple signalling pathways and oncogenes depending on the type of cancer (Clark and Lee, 2016).

Moriguchi *et al.* (2019) studied the effect of capsaicin on PEL (Primary Effusion Lymphoma) which is a rare B cell malignancy caused by KSHV (Kaposi's Sarcoma Associated Herpesvirus). PEL cells require pathways such as p38 MPK and ERK to grow and survive which were inhibited by capsaicin via phosphorylation. Phosphorylation of ERK and p38 MPK pathways affected the expression of hIL-6 (promotes tumour growth) which led to caspase 9-dependent apoptosis of PEL cells. The study also demonstrated that specific inhibitory signalling of p38 MPK and ERK pathways suppressed the hIL –6 expressions which also resulted in the attenuation of PEL cells (Moriguchi *et al.,* 2019). Another study conducted by Zhang *et al.* (2017) on three different human osteosarcoma cell lines namely, 143B, MG63 and HOS described capsaicin-induced apoptosis by affecting the mitochondrial apoptotic pathway. The study also revealed the positive effects of both higher and lower concentrations of capsaicin. Higher concentrations (250-300μM) were involved in apoptosis here as lower concentrations (50-200 μM, specifically 100 μM) induced G0/G1 cell cycle arrest, inhibited proliferation, and decreased colony formation. The study stated that the anticancer properties of capsaicin were majorly due to the involvement of various MAPK (Mitogen-Activated Protein Kinase) pathways such as the ERK1/2, JNK and p38 pathways. These pathways are usually involved in the activation of cellular activities which are involved in cancer progression (Zhang *et al.*, 2017). Bao *et al.* (2019) performed an experiment with capsaicin on MG63 (human osteosarcoma cell line) cells. The study inferred the activity of capsaicin on the cell *via* a dose-time manner. Capsaicin was observed to induce apoptosis and activate the TRPV1 receptor (Transient Receptor Potential receptor Valloniid 1). Capsaicin was observed to activate AMPK (Adenosine 5' monophosphate-activated protein kinase) JNK, p53 pathways. An antagonist to capsaicin named capsazepine was used to study the ion channels of TRPV. This helped the scientists to figure out that capsaicin affected the human osteosarcoma cell line MG63 via activation of both TRPV1-dependent and independent pathways. The TRPV1 independent pathway included the action of capsaicin on AMPK-p53 whereas the TRPV1 dependent pathway included the attenuation of capsaicin-induced apoptosis, overproduction of reactive oxygen species, JNK and mitochondrial dysfunction. Together capsaicin-induced cell death could be a potential agent for anti-osteosarcoma (Bao *et al.,* 2019).

Capsaicin was observed to act on cancer cells in a dose-dependent or dose-time-dependent manner. It can act as an excellent adjunct to already available cancer medications to help increase the efficiency of the available treatments (Zhang *et al.*, 2017; Bao *et al.,* 2019).

9. Tulsi

Ocimum sanctum L. (Holy Basil or Tulsi) belonging to the family Lamiaceae, and tribe Ocimeae, is considered a sacred plant in Indian culture. It originated in India and now is found in many other parts of the world. It is found in parts of China, Taiwan, Hainan Island, tropical Asia, and the eastern and northern parts of Africa (Cohen, 2014). Tulsi is an important ayurvedic herb that has been known to humankind from time immemorial. Scientific experiments conducted in recent decades have given substantial proof of its properties and can be considered a tonic for the mind, body and spirit that provides a wide range of solutions to today's health problems (Cohen, 2014).

Over the past two decades, experiments have been conducted to test the different properties of Tulsi. Everyday intake of Tulsi has said to tackle a wide range of diseases and promotes both mental and physical well-being. Many experiments have clearly shown different medicinal properties of Tulsi such as anti-microbial, anti-inflammatory, anti-diarrheal, anti-hypertensive, cardio-protective, neuro-protective, radio-protective, hepato-protective, anti-diabetic, anti-cancer, antioxidant, anti-asthmatic, anti-fertility, anti-spasmodic, anti-carcinogenic, anti-coagulant, anti-cataract, anti-stress, mosquito repellent and many more (Cohen, 2014; Baliga *et al.*, 2013; Bhattacharyya and Bishayee, 2013). There are different components of Tulsi including apigenin, luteolin, ursolic acid, oleanolic acid, eugenol, and vicenin. The components of Tulsi have been shown in Figure - 6.

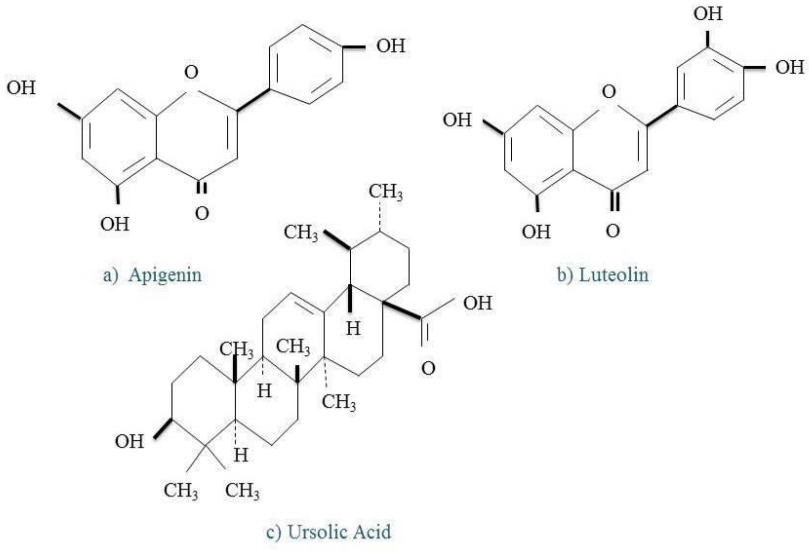

Figure 6: Components of Tulsi

Anticancer properties of Tulsi

A review of the literature has shown that experiments to know the effect of Tulsi is done on many cancerous cell lines. MDA-MD-435 is a breast cancer cell line, which when treated with Tulsi extracts has shown significant inhibition of TPA-induced increase in COX- levels. Inhibition of capillary tube formation and blood vessel formation was also observed. Eugenol, a component present in Tulsi demonstrated inhibition in the growth and proliferation of the

MCF-7 cell line (also a breast cancer cell line). Apigenin, another component present in Tulsi has been shown to induce apoptosis and inhibit cell growth in over-expressing breast cancer cell lines namely: SK-BR-3, MDA-MB-453, MCF-7, and HER2. Apigenin in the MDA-MD-435 cell line has displayed inhibition in tumour cell proliferation, invasion, migration, and induction of apoptosis. In liver cancer cell lines like HepG2, Hep3B, Huh7, HA22T, H22, and SMMC-7721, ursolic acid has been demonstrated to induce apoptosis and cell cytotoxicity. The angiogenic property of ursolic acid decreases the expression and production of IL-8 and VEGF. It also retains the GSH levels (Cohen, 2014). If human fibrosarcoma cells are considered then, HSF 1080 cell line was used, and these cells were treated with ethanolic extracts of Tulsi. This resulted in the observation of induced apoptosis alongside different processes such as the depletion of intracellular glutathione and an increase in the level of lipid peroxidation products. O6-alkylamines are potent mutagenic lesions that can be eliminated by increasing the levels of O6 Methylguanine DNA Methyl Transferase (MGMT). This increase of MGMT mRNA and proteins along with demethylation effects and increased levels of glutathione-S-transferase-pi (GSTP1) expression was observed in treated alcoholic extracts (Tulsi) of HT29 human colon cancer cell lines. In human non-small-cell lung carcinoma cell line A549, it was observed that the population of cells when treated with Tulsi extracts was more in the sub-G1 phase. Vicenin-2, a component present in Tulsi, when tested against prostate cancer cell lines like LNCaP (androgen-dependent), PC-3, and DU-145 (androgen-independent) showed anti-proliferative and anti-migratory effects. It was also observed that cancer cells when introduced with vicenin along with anti-cancer drugs increased the magnitude of anti-proliferation (Baliga *et al.*, 2013b).

Tulsi extracts have been shown to address the properties that help in tackling diverse types of cancers. One such study is focused on studying the effects of vicenin 2 (VCN-2) (a component present in Tulsi) on carcinoma of the prostate.VCN-2 was reported to possess pro-apoptotic, anti-angiogenic, and antiproliferative effects. VCN-2 inhibited various pathways such as EGFR, mTOR, and Akt. Additionally, it also increased the caspase 3 cleavage activity and decreased the colony formation of cancerous cells. VCN- also enhanced the levels of pro-apoptotic factor Bax and tumour suppressor E cadherin as shown in Figure - 7. Cells were also observed to be arrested in the G2/M phase of the cell cycle due to the decrease in CDK4 along with the decrease in cyclin B2 and cyclin D1. This cell cycle arrest was also observed in another component of Tulsi namely Apigenin. The study also evaluated the combined effects of Tulsi extract (vicenin 2) along with the already existing drug docetaxel (DTL). The observations inferred that the combination has a synergistic effect in the inhibition of the growth of the prostate in *in vivo* studies (Nagaprashantha *et al.*, 2011).

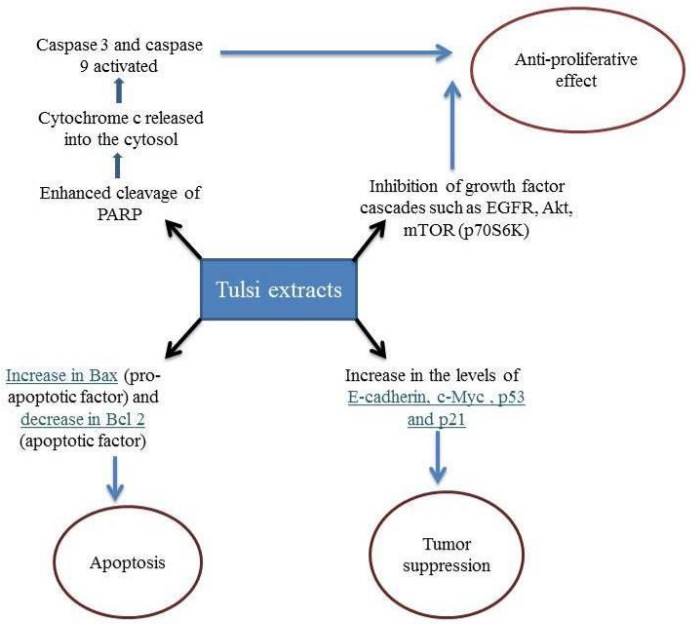

Figure - 7: Action of Tulsi extracts in cells

10. Black Cumin

Black cumin (*Nigella sativa*) belongs to the botanical family Ranunculaceae. It is an annual flowering plant grown all over the world but native to South and Southwest Asia, commonly found in Northern Africa, the Middle East, and Southern Europe (Khan *et al.*, 2011). N. sativa, also known as black seed, black caraway, fennel flower, or nutmeg flower is not only a common household spice but also known for its medicinal properties targeting cancer, diabetes, hypertension, and many others. One of its major components is Thymoquinone followed by p-cymene, Carvacrol, Thymohydroquinone (THQ), dihydro thymoquinone, dihydro-thymoquinone thymol, α-pinene, and γ-terpinene (Sahak *et al.*, 2016). Research suggests black cumin could be potentially used as an effective agent in controlling tumour growth, and metastasis either independently or in combination with other therapeutic drugs. This inference is because black cumin has anti-cancer properties such as pro-apoptotic, anti-proliferative, cytotoxic, and anti-metastatic, it also is an antioxidant in many primary cancer cells and cancer cell lines (Majdalawieh and Fayyad, 2016). The same has been represented in Figure - 8.

Anti-mutagenic effects

Nigella sativa promotes stimulation of detoxifying enzymes that degrade the mutagens. The chemical interaction with or absorption of mutagens (or their electrophilic degradation products), enhances the fidelity of DNA replication, and improves DNA repair. Such factors prevent or reduce chromosomal aberrations (Khader *et al.*, 2010).

The defensive effects of *Nigella sativa* against tumour generation and advancement have also been attributed to suppressing inflammation and exerting immune-boosting effects. *Nigella sativa* extracts therefore can potentially be utilized in the development of active therapeutic agents that can be employed in the regulation of several stages of tumorigenesis and the treatment of many types of cancer.

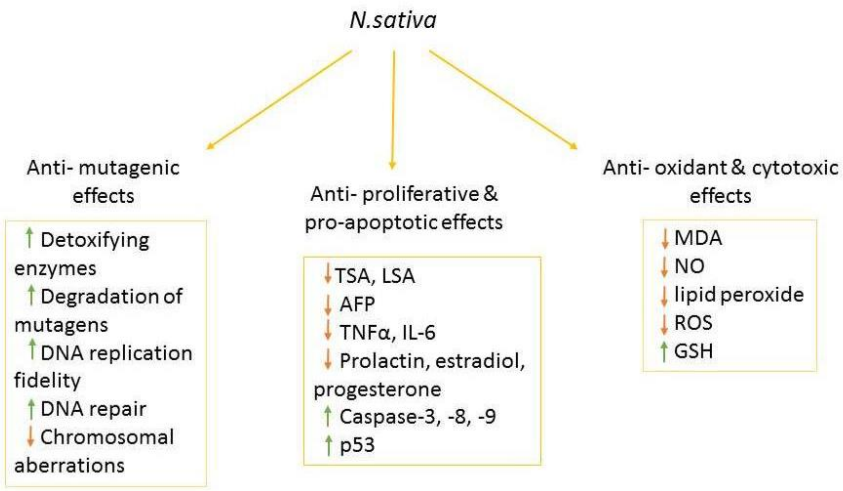

Figure - 8: Anti-cancer activity of *Nigella sativa*

11. Clove

Clove *(Syzygium aromaticum)* is one of the important spices which has several medicinal properties and is also used as a food preservative. It is most known as a traditional Chinese herb. It belongs to the Mitraceae family. Indonesia is the native of clove, but it is now cultivated in many places including Brazil. Clove has several phenolic components such as eugenol, eugenol acetate, and gallic acid. Thus, increasing its ability to be used in various industries such as the cosmetic, food, pharmaceutical and agricultural field. It is known to have high antioxidant and antimicrobial properties compared to other fruits and vegetables (Shu *et al.*, 2005). Clove consists of eugenol, eugenol, caryophyllene, naphthalene, methyl salicylate pinene, and other phenolic components.

Ethanol in clove and the aqueous extracts of clove have shown inhibition up to 95 %. It attributes to the hydrogen donating ability, metal chelating ability, scavenging of free radicals, hydrogen superoxide and hydrogen peroxide. The extracts of clove are used as food preservatives by improving the shelf-life period of the substances. The stability of encapsulated and unencapsulated clove was determined by testing with soybean oil (Chatterjee and Bhattacharjee, 2013). The antimicrobial activity of clove was tested by Sofia et al. and results showed that the aqueous extract of clove at 3 % was able to show the complete bactericidal effect against the *Escherichia coli*, *Staphylococcus aureus* and *Bacillus cereus* (Sofia *et al.*, 2007).

Clove was also known to have medicinal properties and it was observed that clove was being used as an analgesic for toothache, joint pain, and antispasmodic from the 13th century. It is known to have such medicinal properties due to the presence of eugenol. The antinociceptive properties of eugenol show its effects at doses of 50, 75, 100 mg/kg (Daniel *et al.*, 2009). The essential oil of clove is also used as an insecticide. Eamshobana *et al.* (2008) have stated that essential oil at 5 % possesses 100 % of repellent activity against *Leptotrombidium imphalu* which is safer compared to synthetic repellents (Eamsobhana *et al.*, 2008).

Anticancer activities of Clove

Eugenol in clove shows the properties of lipid peroxidation and is known as a strong oxygen scavenger. Clove helps in regulating the balance of cell proliferation and apoptosis by modulating the pattern of expression in proliferation and apoptosis by regulating the genes in tumour cells (Liu *et al.*, 2014). Clove constituents show the effect on pro and anti-apoptotic proteins along with the effect on caspase 3 expression and its activation. It also affects the cox-2 expression and expression of oncogenic proteins in the lungs (Liu *et al.*, 2014). The ethanol

effect of clove extract shows the effect of a 10 - fold enhancement of cell growth inhibition against the human cancer gene panel. The mechanisms in which clove is involved are depicted in Figure - 9.

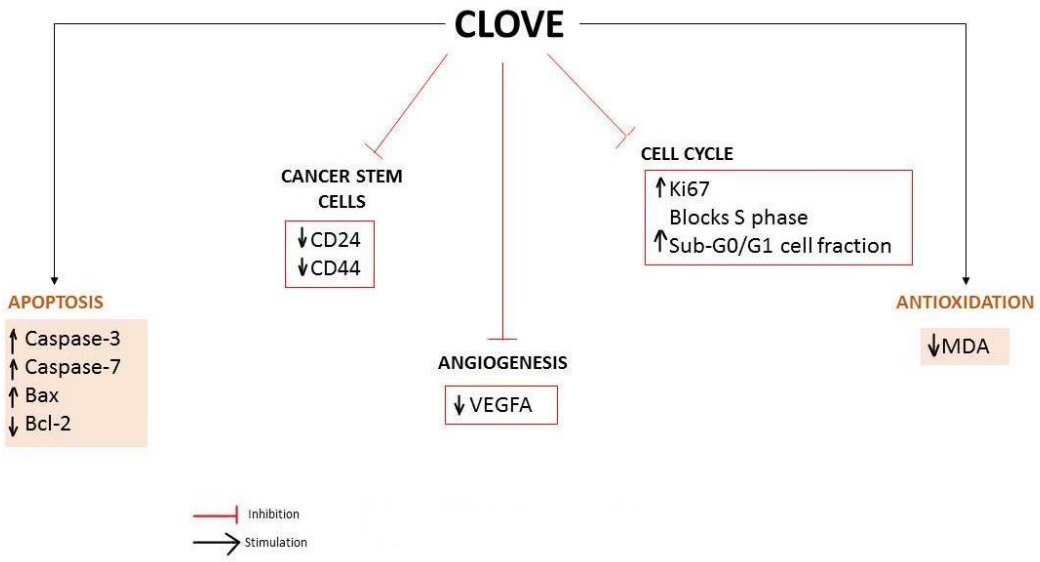

Figure - 9: Mechanisms in which Clove is involved

12. Green tea

Green tea is a product made from the Camellia sinensis plant and is commonly used as a beverage in many parts of the world (Chacko *et al.*, 2010). It originated in China and has spread to other countries in East Asia. It contains a huge quantity of Green Tea Catechins (GTCs) such as; epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epicatechin (EC), and many others (Shirakami and Shimizu, 2018). EGCG is one of the most abundant catechins, containing around 50 – 80 % of total catechins (Rahmani *et al.*, 2015). The chemical structural representations of these constituents are shown in Figure - 10. The anticancer role of these green tea catechins has been reported *via* modulation of signalling pathways and plays a role in the down regulation of protein expression involved in the invasiveness of cancer cells.

From antiquity, green tea and its constituents promote health management via the modulation of biological processes, inclusive of the molecular and biochemical pathways. Green tea has that ability due to its polyphenol content (Khan and Mukhtar, 2007), especially flavanols. Green tea holds beneficial properties such as Anti-inflammatory, antioxidant, anti-ageing, antiviral, antimicrobial, and anti-carcinogenic activities that help combat cancer. The other properties of green tea catechins are shown in Figure - 11.

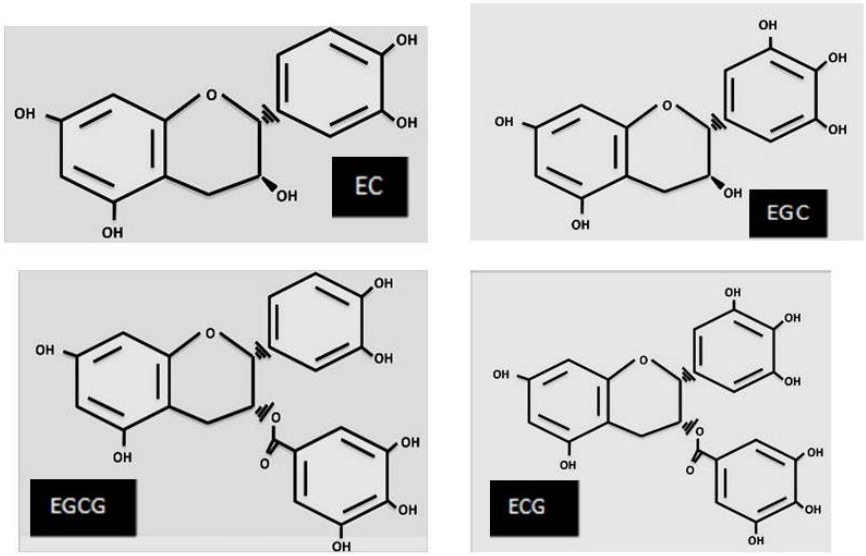

Figure - 10: Green tea catechins and their structures

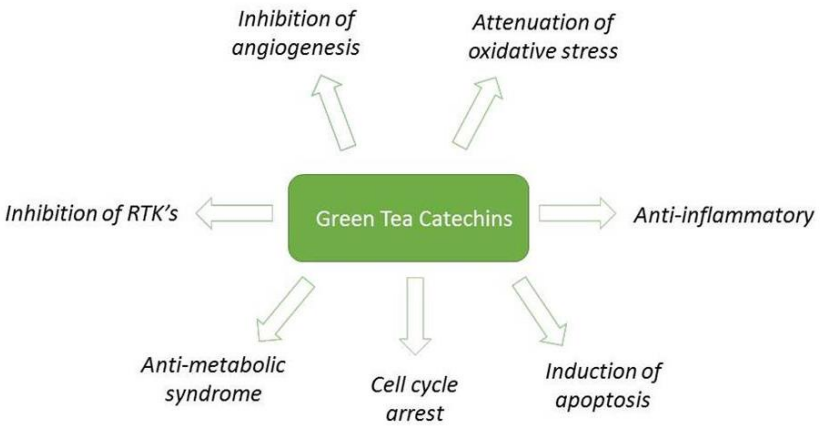

Figure - 11: Properties of Green tea catechins

Role of Green tea in cancer

Green tea catechins display their biological activity in cancer cells and malignancies through multiple mechanisms. GTCs or EGCG play a key role in the regulation of Tumour Suppressor Genes (p53). The modulation of various molecular pathways of genes is guarded by the p53 gene; altered expression/inactivation of which may give rise to tumours of several types. A study revealed that GTP and EGCG may lead to an increase in p53 transcriptional activity and acetylation by suppressing class I histone deacetylases whereas other studies showed EGCG-induced p53-dependent apoptosis in cancer cells. EGCG promotes the expression of p53 and its targets p21 and Bax in the cancerous cells i.e., prostate and breast cancer cells (Rahmani *et al.,* 2015b). The mechanisms were described in Table - 3.

Table - 3: Mechanisms of Green tea catechins on cancer

Activity of EGCG	Mechanism
Modulation of the Immune System (anti-inflammatory effect)	Studies indicate EGCG exerts inhibitory effects on cancers by suppressing IDO (indoleamine-2,3-dioxygenase) expression and function of suppressing effector T cell immunity, leading to immunomodulation against the malignancy of cancer
Anti-oxidant and Pro-oxidant activity	The presence of phenolic groups which are sensitive to oxidation generates quinine. The operation is further augmented due to the trihydroxyl structure in the D-ring.Catechins can provoke reactive oxygen species (ROS) required for the induction of apoptosis and routes to the obstruction of cancer-cell progression
Angiogenesis inhibition	Studies revealed treating nude mice with EGCG, resulted in detectable inhibition of growth, vascularity, and expansion of human colon cancer xenografts. EGCG also represses VEGF expression by hampering the activation of HIF-1α and NF-κB pathways, thereby obstructing tumor growth, proliferation, migration, and angiogenesis of breast cancer
Cell cycle arrest and apoptosis	ROS and caspase-3, -9 activations resulting from EGCG treatment induce apoptosis. This leads to cell-cycle arrest at the G1 phase *via* controlling expressions of cyclin D1, cdk4, and p21CIP1
Epigenetic alteration	EGCG alters epigenetics in cancer cells through histone modification and DNA methylation; EGCG suppresses DNA methyltransferase activation, leading to cytosine-phosphate-guanine demethylation and subsequent restoration of silenced tumor-suppressor genes, including retinoic acid receptor-β (RARβ), p16INK4a, and O6-methylguanine-DNA methyltransferase
Inhibition of Receptor Tyrosine Kinase Pathways (RTKs)	EGCG treatment has revealed suppressed VEGF production by inhibiting the activation of signal transducer and activator of transcription (STAT)-3 and NF-κB in human HNSCC and breast cancer cells

13. Ginger

Ginger (*Zingiber officinale*) is a rhizome that belongs to the Zingiberaceae family. Ginger originated from South-East Asia (currently North-East India) (Baliga *et al.*, 2003). It is widely used as a spice and condiment all over the world. It has a long history of medicinal activities and is used for the treatment of various diseases. Ginger contains numerous phytochemicals which are responsible for its therapeutic activities. The major volatile components of ginger include oleoresin which upon extraction and filtration gives Gingerols shogaols. The structures of gingerol and shogaols are given in Figure - 12. Gingerols ls are responsible for the pungent smell and the spicy flavour of ginger and are identified as 1-5-hydroxy alkane-2-ones. Shogaols are formed by the dehydration of gingerols but are more pungent than gingerols. These are present in low concentrations when compared to gingerols. the volatile fraction of ginger also consists of gingerols, gingediacetates, ginger-dione, gingernones, dehydrozongerone and zingerone which are responsible for the pungent smell of

ginger even present in low concentrations. The volatile fraction of ginger is composed of sesquiterpene derivatives which are responsible for the aroma. The concentration of these compounds is constant. Ginger also contains an exceptionally low concentration of essential oils which contain the derivatives of monoterpene (Peter, 2001; Vs, 1983).

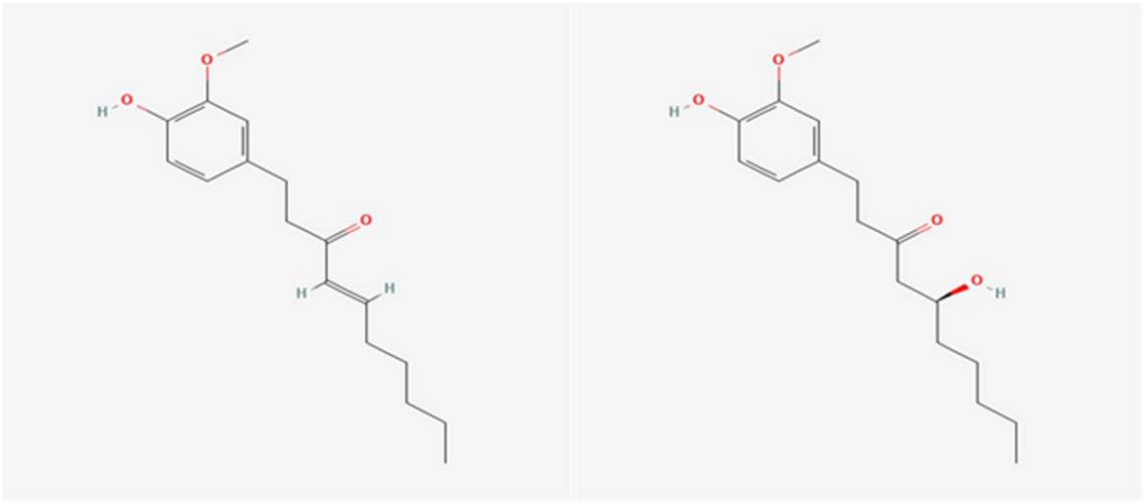

Figure - 12: Structures of (a) Gingerol and (b) Shogaols

The preclinical studies of ginger and its extract have shown various properties such as anti-inflammatory, antioxidant, antiviral, and antibacterial activities. It also plays a role in the dissolution of gallstone and acts as an antihyperlipidemic constituent. It has cardioprotective and neuroprotective activity along with the antiemetic and appetite-stimulating activity. Monoterpene components of ginger [Cineole, citral, limonene, linalool and pinene] will play a leading role in the anti-inflammatory response and are responsible for the antioxidant activities of the ginger. Sesquiterpene constituents of ginger contain amines and play a role in anticancer treatment along with phenolic compounds. Phenolic compounds play a key role in various properties exhibited by ginger. They show anticancer activity, anti-inflammatory, antiemetic, anti-angiogenesis and cardioprotective and neuroprotective properties. The role of ginger in the human body is shown in Figure - 13.

Role of Ginger on Cancer

Ginger and its derivatives participate in the cell cycle arrest by inhibiting the expression of the cyclin, CDKs (cyclin-dependent kinases) and the STAT3 level, NF-kB target genes. It also activates the cell cycle checkpoints and increases the p21 expression. The experimental studies of ginger had shown its chemopreventive mechanism by modulating the cell cycle progression. Ginger is also known to be involved in apoptosis. Apoptosis usually occurs in two ways: mitochondria-mediated intrinsic pathway and death receptor-mediated extrinsic pathway. It involves the members of Bcl-2 family proteins and the cysteine-aspartate proteases. The studies of Pashaei-Asl et al. have shown that an extract of ginger can be used for the treatment of ovarian cancer cell line SKOV-3 for 48hrs helps in the decrease of Bcl-2 gene expression and the subsequent p53-induced apoptosis (Pashaei-Asl *et al.*, 2017). The aqueous extract induces cellular apoptosis and the microtubules within human non-small lung epithelium cancer (NSCLC) A549 cell lines by increasing the Bax/Bcl-2 ratio and by acting as a mitochondrial death cascade (Choudhury *et al.*, 2010).

Relative Oxygen Species [ROS] involves a group of highly reactive molecules generated by mitochondria, NADPH oxidases, xanthine oxidase and uncoupled endothelial nitric oxide synthase, cyclooxygenase, CYP-P450s enzymes and oxygenase (Dröge, 2002; Bachi *et al.*, 2012; Grivennikova *et al.*, 2017). All cancers usually show an elevated ROS rate which is involved in the progression and development of tumours. They play a significant role in maintaining redox homeostasis, decreasing the quantity of ROS-induced tumour-promoting events can increase oxidative stress and provoke cell death.

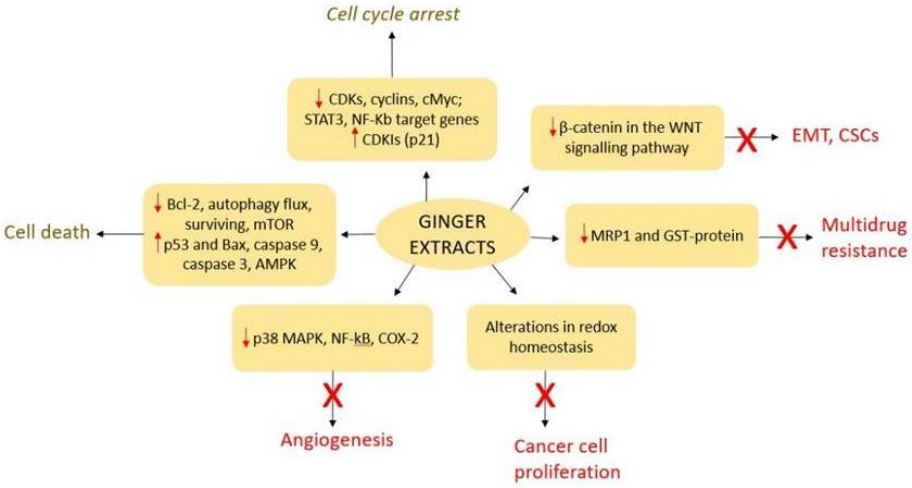

Figure - 13: Role of Ginger in the Human body

Chemopreventive activities of Ginger

The antineoplastic drugs doxorubicin and cisplatin had a positive effect on the treatment of cancer and are approved by FDA for their clinical use in the 1970s. But the usage of these drugs had led to various side effects such as nausea, vomiting and diarrhoea which must be treated as an immediate concern. The administration of ginger extract around 200 and 400 mg/kg before the doxorubicin administration has decreased the serum urea and creatinine levels creating a protective activity against the nephrotoxicity caused by doxorubicin (Ajith *et al.*, 2008). The oral feeding of ginger before and after the administration of cisplatin also decreased the serum creatinine levels, urea and lipid peroxides in the kidneys. The protection against cisplatin-induced testicular toxicity and renal toxicity and doxorubicin-induced cardiotoxicity and nephrotoxicity are obtained by inducing free radical scavenging, increase in total thiols, glutathione, antioxidant enzymes, superoxide dismutase, catalase, Glutathione S transferase and by decreasing the peroxidation of lipids.

The root powder of ginger plays a significant role in reducing the toxicity and severity caused by Chemotherapy-induced nausea and vomiting (CINV). The mechanisms for CINV prevention were given in Figure - 14. It is provided as an adjunct to ondansetron and dexamethasone in bone sarcoma patients who are treated with high emetogenic chemotherapy containing cisplatin/doxorubicin. Gingerol can also reverse the P-gp-mediated anticancer drug efflux, which gives additional significance to ginger. Chemotherapy usually kills the cells which are sensitive to drugs and leaves the drug-resistant cells behind. The accumulation of these drug-resistant cells will lead to the regrowth of the tumour cells which are resistant to chemotherapy. Thus, leading to the failure of response for chemotherapy. 6-gingerol, a component of ginger has an inhibiting activity that inhibits the efflux and can be used for the reversal of MDR (multidrug resistance) in cancer.

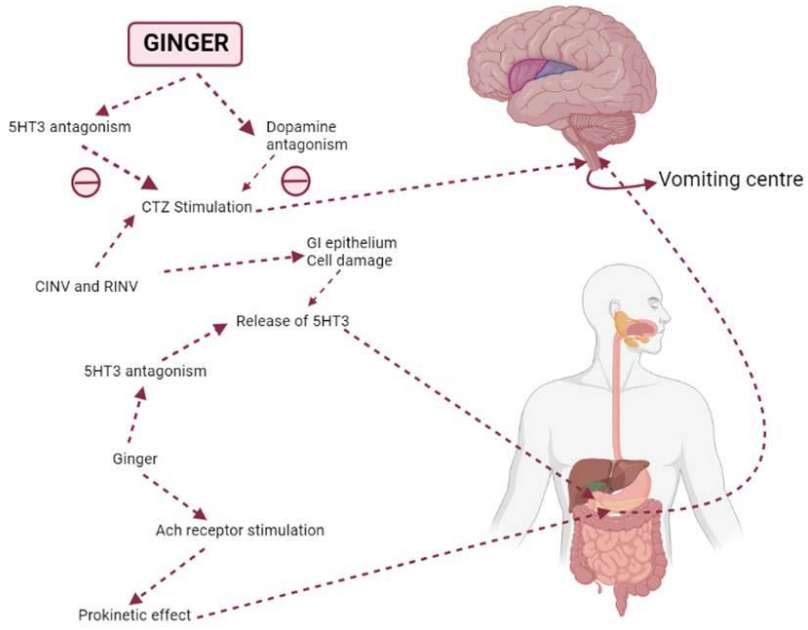

Figure 14: Mechanisms for CINV prevention

14. Cardamom

Cardamom (*Elettaria cardamomum*) commonly known as Maton, "Elaichi" belongs to the Zingiberaceae family whose fruits have been used extensively in traditional medicine. The botanical name for cardamom originated from Tamil in which Elettari means the seeds of cardamom. The cultivation of cardamom in India is usually observed in South Indian states having higher altitudes. In general cardamoms are dried capsules of various fruits of different genera belonging to the same Zingiberaceae family. It is considered as the "Queen of spices" for its taste and pleasant aroma, for which it is the third most expensive spice (Ashokkumar *et al.*, 2020).

Cardamom is used as a spice in regular households and is known to have various medicinal properties. It is commonly used for digestion, teeth, and gum infections, colds, coughs, and diuretics. It is known to control digestive and kidney disorders. Essential oils of cardamom are mostly composed of monoterpene constituents such as 1,8-cineole, α-pinene, α-terpineol, linalool, linalyl acetate and nerolidol and the ester constituent α-terpinyl acetate. All these constituents contribute to the therapeutic activity of cardamom. It includes antioxidant, anticancer, antidiabetic, and anti-inflammatory activities. Recent studies by Rathod et al have stated that alkaloids, flavonoids, terpenoids, anthocyanins and other phenolic compounds of cardamoms are responsible for controlling cardiovascular, lung, kidney, and pulmonary associated disorders.

Cardamom in Cancer

Cardamom is known for its effectiveness against colorectal cancer. The pro-apoptotic, anti-inflammatory and antiproliferative properties of cardamom decrease azoxymethane-induced colon carcinoma. It is also known for improving the antioxidant property of humans by 48%. The cineole and limonene phytochemicals present in cardamom have an anti-oncogenic effect and are known to reduce the risk of breast cancer. Cardamonin enhances the effect of chemotherapy drugs by reducing the tumour burden. A study on cardamom has found that the aqueous extracts of black pepper and cardamom improve the cytotoxic effect of natural killer cells against YAC-1 lymphoma cells (Majdalawieh and Carr, 2010). It also shows the antioxidative effects against non-

melanoma skin cancer by the modulation of signalling pathways.

Cardamonin, a chalcone derivative of cardamom play a significant role in cancer treatment, immune system modulation, inflammation and pathogens killing. It activates the cell death signal which induces the division of malignant cells. It is emerging as a promising novel experimental anticancer agent due to its potential activity against malignant cells. Cardamonin is a multi-target therapeutic agent which can target various signalling molecules such as cytokines and transcriptional factors. It also targets various enzymes such as mTOR, NF-kB, Akt, STAT3, Wnt and COX-2 (Kaskoos *et al.*, 2006). It is known to reduce Triple Negative Breast Cancer by inhibiting the binding of PDL1 to the PD-1 receptor. It thus inhibits the immune response of the host immune response against tumour cells.

Cardamom extract is known to prevent diethyl nitrosamine (DENA) - induced hepatocellular carcinoma by blocking oxidative stress and reducing pro-inflammatory cytokines. The delayed skin tumorigenesis was observed when the samples were ingested with cardamom by the activation of antioxidant enzymes, detoxifying enzymes, and decreased peroxidation of lipids. Cardamom containing anti-cancer activities is known to have very few side effects. However, investigations into its role in cancer treatment and prevention are still ongoing.

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