



## Protective and therapeutic potential of spices and herbs in Cancer

Bee Ling Tan<sup>1</sup>, Rasha Babiker<sup>2,3\*</sup>, Monica Neagu<sup>4,5,6</sup>, Carolina Constantin<sup>4,5</sup> and Ayman El-Meghawry El-Kenawy<sup>7,8</sup>

<sup>1</sup>Department of Nutrition and Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia

<sup>2</sup>Department of Physiology, RAK Medical and Health Sciences University, Ras Al Khaimah, United Arab Emirates (UAE).

<sup>3</sup>Department of Physiology, Faculty of Medicine and Surgery, National University-Sudan, Sudan

<sup>4</sup>Victor Babes National Institute of Pathology, Immunology Dept., Bucharest, Romania

<sup>5</sup>Colentina University Hospital, Bucharest, Romania

<sup>6</sup>University of Bucharest, Bucharest, Romania

<sup>7</sup>Department of Pathology, College of Medicine, Taif University, Saudi Arabia

<sup>8</sup>Department of molecular biology, GEBRI, University of Sadat City. Egypt

\*Correspondence: [rashat33@yahoo.com](mailto:rashat33@yahoo.com) Received 06-06-2022, Revised: 03-08-2022, Accepted: 04-08-2022 e-Published: 06-08-2022

Based on a common belief, spices and herbs are commonly used by patients who seek conventional health care. Some spices and herbs have been extensively studied, but others are poorly understood. Spices and herbs with the least possible adverse outcomes should be centred on cancer care. Compelling evidence suggests that oxidative stress plays a predominant role in the development of chronic diseases including cancer. Oxidation damage depends on the acquired or inherited defects in enzymes mediated by their ox signalling pathway. Spices and herbs are rich in bioactive compounds and exert antioxidant activity, which is predominantly due to their red ox properties and their ability to inhibit the reactive oxygen species (ROS). In this review, we discussed the underlying molecular mechanisms of herbs and spices and its compounds in the modulation of cancer. The antibacterial, anti-diabetic, and antihypertensive activities of spices and herbs as well as their derived compounds were also discussed in this review. Collectively, a better understanding of the potential benefits of spices and herbs would provide a useful approach in the overall maintenance of health and prevention of cancer.

**Keywords:** Aantibacterial, diabetes, cancer, herbs, hypertension, oxidative stress, spices

### 1. INTRODUCTION

Cancer continues to escalate as a public health problem although tremendous efforts and pharmaceutical improvements have been made over the last few decades (Seyed et al. 2016). According to the World Health Organization (2021), cancer is the second leading cause of death globally, which is represented by 9.6 million deaths in 2018. Female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, followed by lung, colorectal, prostate and stomach cancers (Sung et al. 2021).

Despite the physiological role of inflammation, its role in the pathogenesis of several types of malignancies is recognized (Chen et al. 2018). Overexpression of inflammatory cytokines/chemokines, inflammatory enzymes, and adhesion molecules has been associated with chronic inflammation (Larsen, 2017). Chronic inflammation has been demonstrated in several age-related diseases including Alzheimer's disease, arthritis,

diabetes, cancer, and cardiovascular disease (Rea et al. 2018). Chronic inflammation can drive a series of steps in tumorigenesis such as metastasis, invasion, and proliferation (Savant et al. 2018). Inflammation is a risk factor for various types of cancer (Taniguchi and Karin, 2018, Neagu et al, 2019a). Increased apoptosis resistance is the predominant obstacle that needs to be overcome in clinical practice (Baumgartner et al. 2018, Neagu et al. 2019b). Further, most of the anticancer drugs exhibited a narrow therapeutic window with limited selectivity towards cancer cells (Shengquan and Sze Ngong, 2013). The optimal effect of treatment can reduce an adverse outcome, prolong survival time, and improve quality of life. Therefore, the concept of "survival with cancer" has emerged (Qi et al. 2015).

Substantial evidence shows that a high dietary intake of plant-based agents such as spices and herbs can prevent several chronic diseases including cancer (Kunnumakkara et al. 2018). The earliest utilization of

spices in humans is documented since 5,000 B.C., and numerous biological activities have been reported (Imran et al. 2017; Lin et al. 2017). Spices and herbs have been widely used in the day-to-day life of mankind as a means of preservative, flavouring agent, colouring agent, and remedies (Guldiken et al. 2018). Several studies suggest that bioactive compounds-derived from spices and herbs such as ginger, garlic, clove, and rosemary preventing chronic diseases via modulation of the inflammation pathways (Kunnumakkara et al. 2018). Several studies stated that spices and herbs have anticancer activity by inducing cell differentiation (Liu et al. 2016), improving the immune system (Abdollahi et al. 2018), inducing apoptosis of cancer cells (Liu et al. 2018), and suppressing telomerase activities (Sun and Wang, 2003). Given its pivotal role in modulating the inflammatory response; in this review, we highlighted the underlying molecular mechanisms of spices and herbs and its derived compounds in the modulation of cancer. The antihypertensive, antidiabetic, and antibacterial activities were also highlighted in this review. Overall, a better understanding of the benefits of herbs and spices would provide a useful approach in the overall maintenance of health and prevention of cancer.

### **Molecular mechanisms of oxidative stress-induced cancer**

Reactive oxygen species (ROS) are generated constantly in the body as one of the phagocytes activities within the immune system. ROS are also generated through mitochondrial bioenergetics and oxidative metabolism (Vakifahmetoglu-Norberg et al. 2017). Nonetheless, increased amounts of ROS may lead to an adverse outcome for health (Rahal et al. 2014). ROS such as hypochlorous acid, singlet oxygen, hypochlorite, superoxide anion, hydrogen peroxide, lipid peroxides, and hydroxyl radical are involved in the cells' growth, death, and differentiation (Rahal et al. 2014). It can bind to enzymes, proteins, nucleic acids, and membrane lipids (Rajendran and Nandakumar, 2014). Short-term postprandial mitochondrial oxidative stress may trigger nuclear factor-kappa B (NF- $\kappa$ B) signalling and thereby contribute to inflammation (Jung et al. 2009; Tan et al. 2018a).

Inflammation is a key immune response to infection or any injury and it sustains tissue homeostasis and further regeneration of the damaged tissue. (Xiao, 2017). In particular, chronic inflammation can lead to the development of cancer (Colotta et al. 2009; Qu et al. 2017; Neagu et al, 2019a). Inflammation and cancer are mediated via intrinsic and extrinsic pathways. Oncogene modulates the inflammatory microenvironment intrinsically; by contrast, the inflammatory microenvironment may contribute to the progression and development of cancer extrinsically (Raposo et al. 2015). About 15% of cancer cases are stimulated via infection and chronic inflammation (Mangino et al. 2016). Nuclear

factor-kappa B (NF- $\kappa$ B), a key mediator of inflammation, is constantly activated in most cancer cells such as breast, liver, pancreas, colon, and lung cancers upon response towards carcinogens including tobacco and alcohol (D'Ignazio et al. 2017).

Research evidence indicates that transcription factors such as signal transducer and activator of transcription 3 (STAT3) and NF- $\kappa$ B, inflammatory enzymes (for instance, cyclooxygenase-2 (COX-2) and matrix metalloproteinase-9 (MMP-9)) and inflammatory cytokines (for instance, tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukins (IL) - 8, -6, and -1) are the primary molecular mediators that induce inhibition of apoptosis and sustain the chronic status of inflammation, favouring cancer cell invasion, proliferation, metastasis, and neoangiogenesis (Kunnumakkara et al. 2018). Among these mediators, NF- $\kappa$ B modulates cell adhesion molecules and activates genes encoding cytokines/cytokine receptors (Mitchell and Carmody, 2018). NF- $\kappa$  Activity is regulated by modulating the I $\kappa$ B kinase (IKK) complex (Karin, 2008; Maniboban, 2018). NF- $\kappa$ B plays an important role in the activation of several proinflammatory cytokines in macrophages, T cells, and epithelial cells (Verma et al. 2018). Activation of NF- $\kappa$ B was shown to be linked to radio resistance and chemo resistance (Li et al. 2018). Therefore, anti-inflammatory agents that target NF- $\kappa$ B are potential to be used in the prevention and treatment of cancers.

Due to its close association with NF- $\kappa$ B, IL-6 is another candidate that activates carcinogenesis (Bromberg and Wang, 2009). For instance, colon cancer patients showed a high IL-6 expression (Guo et al. 2012). A study reported by Bromberg and Wang (2009) has demonstrated the critical roles of downstream effectors STAT3 and IL-6 families of proinflammatory cytokines in colitis-related colon cancer. High STAT3 expression was found in cancer patients, in which STAT3 signalling was positively associated with poor prognosis (Chang et al. 2017).

IL-6 is a vital NF- $\kappa$ B-dependent cytokine that induces the STAT3 pathway. STAT3 is a cytoplasm protein that triggers a myriad of immune-related processes and hence, inflammatory response (Kunnumakkara et al. 2018). The up regulation of STAT3 may lead to tyrosine phosphorylation, homodimerization, and nuclear translocation, where it interacts with DNA and mediates gene expression (Sung et al. 2012; Kim and Yoon, 2016). Furthermore, protein kinases such as Janus-activated kinase (JAK) 1, 2, and 3 also induce STAT3 phosphorylation and thereby promote nuclear translocation (Sung et al. 2012).

Increased TNF- $\alpha$  expression, the most potent proinflammatory cytokine, can induce neoplastic transformation via stimulation of NF- $\kappa$ B activity (Chung et al. 2017). Therefore, suppression of TNF- $\alpha$  might have potential in the prevention of metabolic ailments including cancer. Interleukins such as IL-6, IL-8, and IL-1 $\beta$  play a crucial role in the induction of proinflammatory response (Stanley et al. 2017). Inappropriate stimulation of IL-8, IL-

1 $\beta$ , TNF- $\alpha$ , and IL-6 and up regulation of iNOS and COX-2 activity triggers oxidative stress, thereby contributing to inflammation (Lee et al. 2017). Collectively, inappropriate stimulation of inflammation may be involved in the pathogenesis of cancer. Accordingly, numerous drugs have been developed in targeting the inflammatory pathway. A previous study stated that compounds derived from spices and herbs can suppress inflammatory signalling, hindering chronic inflammation (Xu et al. 2018), suggesting that spices and herbs may provide beneficial health effects by modulating proinflammatory processes.

### Bioactive compounds in spices and herbs

Mother Nature has bestowed us with abundant remedy sources to prevent and treat metabolic ailments. Photochemical, in both synthetic and natural forms, are utilized in treating several metabolic disorders (Carrera-Quintanar et al. 2018). In this regard, an emerging role of spices and herbs in relation to chronic diseases has been reported (Yashin et al. 2017). Spices and herbs not only provide taste and flavour to food but also demonstrated tremendous functional potentials. Research evidence revealed that the active compounds of spices and herbs are of benefit in preventing and combating cancer (Jaksevicius et al. 2017, Kammath et al. 2021).

Turmeric, rosemary, onion, ginger, garlic, fennel, clove, cinnamon, and black pepper have been used for culinary purpose, in which most of them exert multiple biological activities (Guldiken et al. 2018). Data gathered from *in vitro* and *in vivo* studies have demonstrated that dietary spices and herbs may protect against oxidative stress and chronic inflammation (Kumar et al. 2017). Indeed, spices and herbs contain numerous natural water-soluble phenolic acids, flavonoids (quercetin and caffeic acid), and lipid-soluble compounds (carotenoids, tocopherols, and sterols), which are involved in the scavenging of ROS and can protect against the geotaxis lipid per oxidation products (Tapsell et al. 2006; Darband et al. 2018).

Animal model studies have revealed that curcumin inhibits carcinogenesis and inflammation in cancers developed in colon, stomach, and breast (Hassanalilou et al. 2019). Another most commonly used spice or herb for preventing cancer is garlic. Garlic exerts anticancer, gastro protective, and anti-inflammatory properties. These effects are predominantly due to the bioactive constituents such as diallyl disulfides, diallyl sulfides, and S-allylcysteine (Srinivasan, 2014). A diet supplemented by organosulfur compounds such as diallyl disulfides, diallyl sulfides, and diallyl trisulfides inhibited several cancers induced by chemical carcinogens (Tan et al. 2018b). Likewise, feeding mice with a diet containing diallyl trisulphide inhibited the multiplicity of pulmonary metastasis and invasive carcinoma (Singh et al. 2008). Another spice that is widely used is red pepper (*Capsicum*), which contains various photochemical such as capsaicin, capsanthin, caffeic acid, zeaxanthin, and  $\beta$ -

carotene (Howard et al. 2000; Ilie et al. 2019). Due to their bioactive compounds, tremendous effort has been made to evaluate the effects of spices and herbs in alleviating oxidative stress. In this regard, the critical roles played by spices and herbs are worth study in-depth to elucidate the underlying pathophysiology pathways in cancer.

### Anticancer activity and mechanisms of spices and herbs in cancer

#### Preclinical and clinical approaches

Spices and herbs are viewed through a new lens as genuine helpers for cancer conventional therapies taking into account that various side effects associated with innovative therapies, and thus leading to the search of new approaches.

Hippocrates in 431 B.C. stated that "*let food be thy medicine and medicine be thy food*", hence at least 5,000 years of human civilization medicine relied on herbs and herbs extracts. Our ingested food contains ingredients with concealed pharmaceutical properties (Ganjre et al. 2015). Herbs and spices are mentioned in documents 1500 BC old, where anise, mustard, saffron, cinnamon, and cassia properties were documented (Leja and Czaczyk 2016). Compelling scientific evidences showed that spices and herbs hold important antioxidant, anti-inflammatory, antitumorigenic, anticarcinogenic, and several other properties. The bioactive constituents constitute a large array of molecular types, but the most important are sulfur-containing molecules, tannins, alkaloids, phenol diterpenes, vitamins, flavonoids, and polyphenols. Dietary consumption of foods for instance, chili pepper, cinnamon, ginger, black pepper, turmeric, fenugreek, rosemary, and garlic is linked to a lower risk of cancer death and cardio-respiratory diseases (Jiang 2019). A large array of compounds has anti-neoplastic effect (Table 1)

**Table 1: Bio-active compounds with proven anti-neoplastic activity**

Bio-active compound	Plant
curcumin and curcuminoids	Turmeric
limonene	Cardamom
allicin, allyl isothiocyanate	Garlic
cinnamic aldehyde, 2-hydroxycinnamaldehyde, eugenol	Cinnamon
gingerol, zingiberone, zingiberene	Ginger
dipropyl disulfides and quercetin	Onion
piperidine piperine, limonene, $\alpha$ - and $\beta$ -pinene	black pepper
crocetin, crocin and safranal	Saffron

#### Cinnamon

Among a myriad of spices, cinnamon's potential as a total extract or as an individual active compound was studied in cancer therapy. Hence, the antiproliferative action of cinnamon extract was evaluated using *in vitro* systems mimicking peripheral immune cells functionality such as Jurkat or U937 cell lines (Schoene et al. 2005) or

in solid cancers using SiHa cervical cancer cell line (Koppikar et al. 2010). In an *in vivo* study the anticancer effect of cinnamon in melanoma was evaluated. The study revealed that melanoma bearing mice treated with cinnamon extract for three weeks presented a decreased tumor size and reduced metastatic process (Kwon et al. 2009). Isolated single compounds from cinnamon have proved to be cytotoxic or antiproliferative against different cancer cell lines. For instance, *eugenol* as an individual compound or used in combination with conventional anticancer drugs such as gemcitabine significantly sensitized HeLa cells (Hussain et al. 2011). Furthermore, the cytotoxic effect of 2-methoxyestradiol could also be enhanced by *eugenol* against human prostate cancer PC-3 cell line (Ghosh et al. 2009). *Cinnamaldehyde* and  $\beta$ -*caryophyllene* are bioactive compounds of cinnamon displaying *antiproliferative* effects and having the potential to modulate various cellular intracellular pathways linked to tumour cell survival (Dutta et al. 2018). Treatment with cinnamon extract of melanoma cells decreased the expression of certain pro-angiogenic factors (epithelial growth factor- EGF, vascular endothelial growth factor - VEGF, and transforming growth factor-TGF- $\beta$ ) and thus inhibits angiogenesis. Moreover, certain major regulators of tumor progression (e.g., COX-2 or hypoxia inducible factor - HIF-1 $\alpha$ ) were modulated by cinnamon extract, leading to an increased CD8+ T lymphocytes cytotoxic activity, and moreover, through this process tumor progression was hindered (Kwon et al. 2009).

In a study published in 2015 on a large group of subjects with the uterine fibroid (myoma) registered in the Taiwanese National Health Insurance Research Database the effect of Chinese herbs was investigated. Thus, the study identified that Cinnamon Twig and Poria Pill (formula) and Rhizoma Sparganii (single herb) are the most used herbal remedies; moreover, subjects under 45 years have preferred herbal formulas instead of single herb. However, this approach still awaits confirmation in terms of its therapeutic effects and mechanisms and results regarding the effect of this therapy on a large sample still await confirmation in terms of its therapeutic effects and mechanisms (Yen et al. 2015).

Another work developed few years ago by The Ohio State University Center for Integrative Medicine is related to a specific nutrigenomic procedure for an integrated cancer care; besides other various compounds, this protocol contains Cinnamon extract that decrease serum glucose levels in patients as a part of relevant nutraceuticals (Varker et al. 2012). As recent evidences indicate glucose level as a risk factor for developing cancer (Neagu et al. 2020) the study highlighted the Cinnamon potency to lower serum glucose level and hence reduce cancer recurrence (Varker et al. 2012).

Standard therapies in cancer including chemo/radiotherapy are accompanied by various adverse effects. For instance, chemotherapy-induced peripheral neuropathy is frequently observed in patients subjected to

standard therapy in cancer (CIPN). Phyto-compounds can be appropriate candidates for alleviating CIPN. A study by Oveissi et al. (2019) evaluated adjuvant herbal products in five clinical trials of CIPN. Out of these plant products, chamomile (*Matricaria chamomilla* L.), sage (*Salvia officinalis* L.), and cinnamon (*Cinnamomum cassia* (L.) D. Don), and sweet flag (*Acorus calamus* L.) have shown the best effects and this could be attributed to the phytochemicals such as matrine, curcumin, and thioctic acid.

### Ginger

Among traditional medicinal herbs, ginger (rhizome of *Zingiber officinale*) could be exploited in pharmacological endeavors as a total extract, isolated compounds, or different parts of plant. Ginger has long been used as herbal medicine yet its anti-cancer properties and mechanisms of action are still to be revealed. Ginger leaf tested in cellular models reduced tumour cell viability and induced apoptosis in human colorectal cancer cell lines (HCT116, SW480, and LoVo cells) in a dose-dependent pattern. Based on evidence supporting the involvement of activating transcription factor 3 (ATF3) in cell growth inhibition and apoptosis induction in human colorectal cancer cells (Lee et al. 2013), the study suggests that the effects of ginger leaf may induce ATF3 gene promoter activation and thereby further increase the ATF3 expression via extracellular signal regulated kinase - ERK1/2 pathway activation in colon cancer (Park et al. 2014). In another study, the anticancer potential of ginger constituents including 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol or together named as ginger phenolics (GPs) has been evaluated in a prostate cancer mouse model. It has been demonstrated that after oral administration of the ginger extract, the free GPs form glucuronide conjugates accumulate in various tissues via systemic circulation. At the tissue level, these conjugates would release the free active GPs forms by the action of the  $\beta$ -glucuronidase, an enzyme that is highly expressed in tumor cells. This study suggested the possible mechanism of the pharmacological action of ginger extract in prostate cancer (Rao et al. 2018).

Ginger is one of the widely consumed spices and it has shown anti-inflammatory, antioxidant, antitumor, and antiulcer effect in human trials. In a systematic review regarding clinical trials performed on the use of ginger in gastrointestinal disease it has been underlined that a daily dose of 1500 mg ginger is a good nausea relief, a symptom currently experienced by most of the cancer patients (Nikkhah Bodagh et al. 2019).

### Garlic

According to epidemiological studies, consumption of *Allium* is related to a decreased risk of gastrointestinal tract cancers. Cancer-preventive properties of *Allium* rely on mechanistic studies related to individual sulfur-containing compounds and to various forms of *Allium*

extracts that affect carcinogenesis or modulate biologic processes underlying cancer risk (Nicastro et al. 2015). Isolated compounds from garlic were proven to exert antitumor properties. *Ajoene* is a phytochemical compound from garlic that has anti-metastatic potential by altering vimentin structure in cancer cells through S-thiolating at Cys-328 level. Vimentin, a normal major constituent of intermediate filament, when over-expressed is a driver of cancer progression leading to an invasive phenotype (Mendez et al. 2010). An *in vitro* model with garlic derivatives has shown that treating breast cancer (MDA-MB-231 cell line) and cervical cancer cells (HeLa cell line) with *ajoene* leads to vimentin condensation and disruption of vimentin filaments. *Ajoene*-treated tumor cells are less able to migrate and to invade the surrounding matrix compared to untreated cells. This antimetastatic property is related to the *ajoene* ability to affect vimentin, suggesting a role of *ajoene* as a natural dietary phyto-compound with anti-metastatic potential (Kaschula et al. 2019).

Several trials have shown an indirect link between the garlic diet and cancer. The studies analyzed ten populations and found that a diet with a high intake of garlic reduces gastric and colorectal cancers risk. European Prospective Investigation into Cancer and Nutrition (EPIC) has shown that the garlic diet is efficient in reducing colon cancer risk in men and women. Meanwhile, women that consume a higher amount of garlic reduces about 50% colon cancer incidences compared to those who consumed a low amount (Fleischauer and Arab 2001)

### Turmeric

The potential therapeutic effects of turmeric are mainly attributed to its main metabolite, namely curcumin. Curcumin is a polyphenolic compound with anticancer properties. There are numerous *in vitro* studies related to curcumin effects on various types of cancer cell lines such as lung, breast, liver, stomach, colorectum, cervix, and prostate cancer cells (Jie et al. 2016). In these cellular models it was shown that curcumin acts as an apoptosis inducer on small cell lung cancer NCI-H446 cell line by modulating the ROS-mediated mitochondrial pathway (Starok et al. 2015). Moreover, interferes tumor cell invasion and metastasis by modulating MMPs expression in MCF-7 breast cancer cells (Kim et al. 2012) or inhibits breast cancer stem cell migration through restoring E-cadherin expression that would ultimately suppress epithelial-mesenchymal transition process in breast cancer stem cell (Mukherjee et al. 2014). In addition, it was suggested that curcumin can be used as an adjuvant agent in chemotherapy with the addendum that curcumin has a low bioavailability, limiting the therapeutic potential of curcumin (Panda. et al. 2017).

### Onion

Onion is found in several regions in the world and is

being used for culinary and medicinal purposes. Onion contains various compounds with anticancer potential including quercetin, flavonoids, and specific organosulfur moieties like diallyl disulfide, S-allylcystein, and S-methylcysteine. As whole extract or isolated compounds, onion exhibits a broad range of benefits such as anticancer properties (Suleria et al. 2015). The extract of *Allium cepa* exerted antiproliferative activity and has proved its *in vitro* efficacy on the human breast cancer MDA-MB-231 cells. Specifically, the ethyl acetate fraction showed the best inhibition of cell viability and proved its efficiency in inhibiting FAS cell death receptor expression, suggesting that apoptosis induction in breast cancer cells by onion ethyl acetate fraction is modulating the process via FAS inhibition (Wang et al. 2012). The antiproliferative activity of *Allium cepa* was evaluated on human glioblastoma cell line-A1235A (Fredotović et al. 2017), human colorectal adenocarcinoma Caco-2 cell line (Yang et al. 2004), and human hepatocellular carcinoma cells HepG2 (Millet et al. 2012; Marrelli et al. 2018) and it has shown antiproliferative effect.

Moreover, distinct compounds isolated from onion such as quercetin has been shown to exhibit antiproliferative and growth-suppressing effects, senescence induction, apoptosis, and autophagy initiation along with anti-angiogenic activity corroborated with activation of immune system defense (Russo et al. 2012). Furthermore, an *in vitro* model showed that a high concentration of quercetin (70  $\mu$ M) blocked cellular proliferation and arrested cells in G1 phase in melanoma cells (OCM-1) (Casagrande et al. 2001). In human breast carcinoma (MCF-7) cell line, quercetin repressed cell cycle evolution through transient M phase accumulation and subsequent G2 arrest (Choi et al. 2001).

A study performed in three hospitals in China from 2009 to 2011 involving 800 cases of colorectal cancer patients has shown that individuals that consumed *Allium* vegetables such as garlic, garlic stalks, leek, onion, and spring onion, had a decreased colorectal cancer risk regardless of gender (Wu et al. 2019).

### Black cumin

*Nigella sativa* or known as black cumin has various bioactive compounds with anticancer properties such as thymoquinone, monoterpenes, p-cymene, and  $\alpha$ -piene. Thymoquinone was shown to inhibit cell proliferation, migration, and invasion in various cancer cell lines including breast, pancreatic, prostate, blood, oral, bone, head and neck, cervical, liver, and lung cancers. Thymoquinone induces apoptosis through down regulation of anti-apoptotic genes. It reduces metastatic capacity by lowering the phosphorylation of NF- $\kappa$ B and IKK $\alpha$ / $\beta$  (Inhibitor of Nuclear Factor Kappa B Kinase Subunit Beta) and reducing ERK1/2 and PI3K (Phosphoinositide 3-kinases) activities. Hence, this compound may be used as a diet-based therapy in several types of cancers (Imran et

al. 2018). The immunomodulatory and anti-inflammatory action of thymoquinone has also been reported. In this regard, it can increase the anti-tumoral cytotoxic activity of natural killer cells (NK) (Majdalawieh and Fayyad 2015).

#### 4.1.7. Piper nigrum

Piperine is the main bioactive compound in *Piper nigrum*. The pure piperine effect was evaluated in a double-blind experimental study. Supplementation of 120 mg coenzyme Q10 with piperine for 3-weeks increased its plasma levels and this could be probably due to the association with the thermotriener (Badmaev et al. 2000). Supplementation of 120 mg coenzyme Q10 with piperine for 3-week increased Q10 plasma levels in selected participant subjects and this effect could be probably due to the association with piperine (Badmaev et al. 2000). It was proposed that piperine may also be designated as a *thermotriener* because it enhances the gastro-intestinal absorption of certain nutrients and locally produces a thermogenic action (Chopra et al, 2016). It is known since the early '90s that coenzyme Q10 is a potent anti-oxidant and is associated with decreased recurrence of cancer (Lookwood et al. 1994) and thus the potentiation of piperine would be more so beneficial. Li et al. (2011) have shown that the anti-tumoral action of piperine is mediated through the multi-drug resistant receptor (MDR) and its associated processes, well known events in oncogenesis (Li et al. 2011).

#### Plants and herbs in cancer prevention

Since ancient times, herbs and spices have been used for health improvement. With the advent of increased toxicities of synthetic compounds, a new approach in pharmacology has emerged that uses specific natural products or extracted compounds. These natural compounds can suppress, reverse, or prevent neoplastic transformation. Natural agents have some important advantages such as low or no toxicity and high efficacy. These compounds should have a known mechanism of action and low cost compared to standard agents. Importantly, these plant/plant extracts have a large panel of biologically active phytochemicals such as polyphenols, flavonoids, carotenoids, and alkaloids. For example, carotenoids are potent antioxidants, in which  $\beta$ -carotene, lycopene, lutein, zeaxanthin, crocin, crocetin have other biological activities through inhibition of tumorigenesis and apoptosis induction (Festuccia et al. 2018).

Another issue in cancer is the tumor microenvironment, in which the interrelation between cancer cells and their neighboring cells is extremely important. The interrelation between cells can promote cancer cell growth, invasion, angiogenesis, and metastasis. The bystander cells surrounding the tumor's cell (for instance, endothelial cells, immune cells, and fibroblasts) could be anticancer therapy targets and their drug-regulation can participate to lowering the tumor recurrence. Active compounds from herbs and spices

inhibit carcinogenesis or reverse its complex stages towards cell differentiation as epithelial to mesenchymal transition is an important reversible process in cancer (Neagu et al, 2019c). Moreover, these compounds can also inhibit the self-renewal functions of cancer stem-like cells (Park and Surh 2017).

Mediterranean diets were linked to the reduction of oxidative stress thus populations that adopt this diet have a lower cancer incidence. Flavonoid such as e.g. quercetin, kaempferol, myricetin, apigenin, and luteolin and carotenoids were studied in relation to breast cancer risk and it was found that a diet based on these antioxidants lower the breast cancer risk. For instance, curcumin decreases oxidative stress and hence chronic inflammation (Griffiths et al. 2016). Although there are very few clinical trials regarding the direct influence of Mediterranean diet, in 2019, Zunica et al have shown in a breast cancer survival group that increasing anti-inflammatory foods, spices and herbs and decreasing consumption of proinflammatory food can lead to reduced risk of co morbidities and recurrence in breast cancer survival (Zuniga et al 2019).

In skin diseases, plant photochemoprotectives can be used to prevent skin cancer and photoaging. Several plant extracts were incorporated in creams and the efficacy was tested for a month in over 50 normal subjects (Table 2) (Saraf et al. 2012, Millsop et al. 2013).

**Table 2: Hydroalcoholic extracts of various plants incorporated in creams (1-5% w/w) and efficacy parameters (Saraf, 2012)**

Plant extracts	Efficacy parameters	
Curcuma caesia (rhizome)	biophysical characterization	viscoelasticity
		melanin content
Areca catechu (seeds)		hydration
		sebum determination
Centella asiatica (leaves)	psychometric evaluations	fragrance
		lathery feel
Cinnamon zeylanicum (dried bark)		softness
		irritation
Tamarindus indica (fruit pulp)		stickiness
		smoothness
		after effect on the skin

Among the plant extracts, the plant cream formulation (1% and 3% (w/w) extracts) showed the best photoprotective properties and passed all the safety tests. Cinnamon, Centella, and Tamarindus-based creams were the most effective as photoprotective (Saraf et al. 2012). Prevention and treatment of non-melanoma skin cancer using topical natural compounds could be attributed to the antioxidant, anti-inflammatory, and immunomodulatory

properties (Millsop et al. 2013).

Geranylgeranoic acid (GGA) is another potent antitumor retinoid found in the turmeric, basil, rosehip, and cinnamon (Shidoji and Ogawa 2004). Administering orally turmeric tablets in healthy subjects' increases plasma level of GGA 2 h after tablet intake and maintains its level for 4 h, suggesting an efficient bioavailability. This finding implies that GGA is absorbed in intact form from intestinal mucosa (Mitake et al. 2010). Herbs and spices are also rich in phytochemicals and were consumed for medical or dietary purposes. Importantly, as in all toxicological studies dose-dependent beneficial effect is to be evaluated so that the ratio between efficiency and toxicity tips toward higher efficacy and lower toxicity (Guldiken et al. 2018). In this regard, choosing between total plant extracts or selected bioactive compounds that can be used in the prevention and improving health care is still a matter of intense research.

### Other potential activities

#### Antibacterial activity

Plants are used since ancient times as sources of natural antimicrobial substances for the treatment of infectious diseases. Currently, in the food industry antimicrobial agents are used to increase the safety of food products by inhibiting pathogenic microorganisms. Moreover, in medicine, plants are expanding as antibiotics. The use of synthetic antibiotics in various domains has led to an increase in microbial resistance. Therefore, some herbs and plants such as cinnamon, ginger, turmeric, onion, and garlic possess various antibacterial activities against pathogenic bacteria, and, there is a great potential for some plants and spices to be developed into safe antimicrobial agents for human health.

Among spices, cinnamon is one of the most known and the oldest spices with antimicrobial activities bacteria (Tyagi and Malik 2011). The antimicrobial mechanism is due to the direct damage of microbial cell membrane by cinnamon and further due to the inhibition of nucleic acid synthesis (Cui et al. 2016; El-Hack et al. 2020). Cinnamon can be combined with classical antibiotics, such as streptomycin especially for the treatment of antibiotic-resistant bacterial infections and to decrease the adverse effects of the classical antibiotics by reducing the effective dose of the drugs (El Atki et al. 2019).

In garlic (*Allium sativum*), the allicin, a diallyl-thiosulfinate (2-propenyl-2-propenethiol sulfonate) is the active component in garlic (Shokrzadeh and Ebadi 2006). These components are responsible for antimicrobial activities such as *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*), by damaging mitochondria and cellular membranes and induction of genes differential expression. (El-Saber et al. 2020).

Ginger (*Zingiber officinale* Roscoe) has shown antibacterial activity against some common microorganisms (Yadufashije et al. 2020), and inhibits

*Pseudomonas gingivalis* (*P. gingivalis*) and *Enterococcal isolates* (*E. isolates*) (Abdel-Azeem et al. 2013; Jeena et al. 2013; Mostafa et al. 2018). The antibacterial mechanisms of action of ginger are unclear and thus more studies are needed.

Onion (*Allium cepa*) is extensively investigated for its antimicrobial effect. Different types and concentrations of onion were studied and most of these studies showed that different types of onions had inhibitory effects on bacterial growth, such as *methicillin-resistant Staphylococcus aureus*, *methicillin-sensitive Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella species*, and *Salmonella species*. (Kabrah et al. 2016).

Study conducted by Saxena and others in India had proven this antibacterial effect of onion (Saxena et al. 2010). The active components like sulfur which is found in onion, acts as an anti-inflammatory, thiosulfonates can also act as anti-thrombotic and superoxide-dismutase (SOD) which act as antioxidant (Barrett et al. 2000; Bora and Sharma 2009).

In turmeric molecule the main active component is curcumin ((1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione), and it has been investigated as a natural antibacterial, antiviral, and antifungal agent (Akram et al. 2010; Zorofchian et al. 2014; Sylvester et al. 2015; Kebede et al. 2021). The pathophysiological mechanism of turmeric inhibition to Gram-positive bacteria is caused by multiple targets that damage the cell wall or cell membrane, by interfering on cell by targeting DNA and proteins, bacterial quorum sensing inhibition (Zheng et al. 2020)

Moreover, turmeric affected the L-tryptophan metabolism in Gram-positive by producing lipid peroxidation, and increased DNA fragmentation but, no effect in Gram-negative, (Adeyemi et al. 2020). In general, Gram-positive bacteria limiting the diffusion of hydrophobic compounds by the rigid outer membrane, which consist of lipopolysaccharide, and more complex. This membrane is not dense in Gram-positive bacteria to resist small antimicrobial molecules, thus turmeric affected Gram-positive and, leads to cell death (Kwiatkowski et al. 2019).

Other study postulated that the small turmeric molecule can penetrate both Gram-positive and Gram-negative bacteria, and thereby leading to permanent damage of the membrane, which causes leakage and suppresses the bacterial cell proliferation (Tyagi et al. 2015).

The effect of turmeric on Gram-positive and Gram-negative bacteria is enhanced when turmeric is delivered with Neem (*Azadirachta indica* is a tree native to the Indian subcontinent utilized in traditional Asian medicine) in some studies, and it was found to be more effective than individual Neem against *E. coli* (Sunthar et al. 2020). As Neem is used in traditional medicine as well as in cleaning teeth, in endodontic study, it was found that turmeric as a root canal irrigates has antibacterial activity

against *E. faecalis* and *S. aureus* (Chaitanya et al. 2016).

Turmeric also has antibacterial activity against periodontopathic bacteria such as *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans*, and thereby may be an effective agent for preventing periodontal diseases (Bomdyal et al. 2017).

### Antidiabetic activity

Based on the World Health Organization report many people in developing countries believe and use plants as antidiabetic medicine. In Arab, the use of folk medicine is common, especially for the treatment of diabetes by herbs (Abdil Razzaq 2013). Diabetes is a metabolic dysregulation characterized by hyperglycemia resulting from deficient insulin secretion and impaired insulin action.

Cinnamon is one of the main spices consumed daily by many people, and studies suggested that cinnamon has antioxidant, anti-inflammatory, and antidiabetic effects (Gruenwald et al. 2010). In clinical trials, intakes of cinnamon for 12 weeks reduce blood glucose and hemoglobin A1c in poorly controlled type 2 diabetes patients (Sahib 2016). The mechanisms of action may be attributed to the delay of gastric emptying (Hlebowicz et al. 2007), stimulation of glycogen synthesis, inhibition of gluconeogenesis, (Anand et al. 2010), inhibition of intestinal  $\alpha$ -glucosidase (Adisakwattana et al. 2011), increase of the expression of peroxisome proliferator-activated receptor (PPAR) and insulin sensitivity (Sheng et al. 2008). Clinical studies and animal models studies have demonstrated a significant effect of cinnamon in lowering of HbA1c (glycated hemoglobin) or plasma lipids (Mang et al. 2006) (Beji et al. 2018).

However, data obtained in clinical trials from an analysis of type 2 diabetes mellitus studies are sparse; half of clinical trials used cinnamon, blood glucose response has shown slight improvement to blood glucose and significant inconsistencies (Singletary 2019). Accordingly, randomized controlled trials are important to determine these effective doses and to further advise public health (Ranasinghe et al. 2013).

Garlic is a plant with protective effects on various diseases (Steiner and Li 2001). It exerts blood glucose-lowering effect in diabetic animal models (Anwar and Meki 2003), and has significant hypoglycemic and hypolipidemic effects when added with the standard antidiabetic agent (Ashraf et al. 2011).

The organosulfur is the effective biological compounds with therapeutic functions in garlic. It shows biological effects such as lowering of cholesterol and glucose, this effect is probably due to the increased of hepatic metabolism and/or increased release of insulin (Bever and Zahnd 1979). However, many studies have showed that the consumption of garlic significantly decreased fasting blood sugar levels (Sheela et al. 1995; Ohaeri 2001).

Several studies reported a significant hypoglycemic

effect of ginger juice in diabetic animal models (Sharma and Shukla 1977; Mascolo et al. 1989; Al-Amin et al. 2006; Al-Shathly et al. 2029; Ayuob et al. 2021).

This effect has been attributed to the serotonin receptor-blocking activity in rats (Akhani et al. 2004; Abdel-Aziz et al. 2005), stimulating glucose utilization by 3T3-L1 adipocytes and C2C12 myotubes this effects were attributed to the increase in 5 $\alpha$  adenosine monophosphate-activated protein kinase (AMPK) phosphorylation in 3T3-L1 adipocytes and consequently results in reduction of cholesterol, and body weight in high-fat diet-fed mice (Wei et al. 2017), and stimulate insulin secretion by the closure of KATP channels in pancreatic- $\beta$  cells (Nam et al. 2020).

A study by Islam et al. (2008) compared the antidiabetic effects of dietary ginger and garlic in 5-week-old rats. The study suggests that ginger and garlic increase insulin secretion rather than decrease blood glucose, while overall antidiabetic effect of ginger is better than those of garlic (Islam et al. 2008).

Many studies have shown the hypoglycemic action of onion in animal (Augusti 1974; Augusti et al. 1974; Jain and Vyas 1974; Karawya et al. 1984; Kumari et al. 1995) and it acts by different mechanisms against diabetes; including antioxidants, upregulation of adiponectin receptors,  $\alpha$ -glucosidase and  $\alpha$ -amylase inhibitory effect, reducing insulin resistance and glucose absorption from the intestine, elevation in the liver and muscle glycogen content, increasing insulin secretion and phosphorylation of AMPK (Galavi et al. 2021), insulin-mimetic actions and GLUT4 translocation in skeletal muscles (Gautam et al. 2015).

The antioxidant activity of onion peel (*Allium cepa*) and its active components (flavonoid compound) was found to prevent free radical generation as well as repair damaged cell, include pancreas and was able to decrease blood glucose level in normal rat compared to the combination of metformin and glibenclamide and combination of ethanol extract of garlic and onion peel (Lolok et al. 2019).

More interestingly, it was found that onion possess more enzymatic activity inhibition in the outer layer in comparison with the inner layer in smaller ones (Jaiswal and Rizvi 2017).

The onion extract reduces glucose transport into mouse jejunum (Schulze et al. 2015), but there is a few clinical-based evidence to support mechanism of onion diet on diabetes. Some clinical trials were performed on 84 adult diabetic patients, subjected to an intake of 100 g raw red onion. It was shown that oral glucose tolerance and fasting blood sugar were improved after 4 h (Eldin et al. 2010). In a study performed on Wistar male rats, three spices have been tested, namely turmeric, ginger, and garlic to determine the antidiabetic potential. The results concluded that turmeric, ginger, and garlic have potentiating antioxidant effects and potential health-promoting properties in experimental animals (Hester et

al. (2018).

### Antihypertensive activity

Hypertension is a chronic medical condition characterized by elevated arterial blood pressure (BP) (Carretero and Oparil 2000). A lot of efforts have been directed into researching plants with hypotensive and antihypertensive therapeutic values. Cinnamon was significantly decreased the mean ambulatory systolic blood pressure (SBP) and improved lipid profile in a double-blind, randomized, placebo-controlled trial in patients with stage 1 hypertension (Shirzad et al. 2021). In another cross-sectional study involving patients with uncontrolled hypertension, cinnamon was found to be effective in weight and blood pressure reduction. Weight loss, reduced waist circumference (WC), and waist to height ratio (WHR) was positively correlated with a reduction in SBP and diastolic blood pressure (DBP) (Patil and Patil 2021). Most studies concluded that cinnamon used in daily life and without any side effects, can be consumed as a medication to lower BP levels, particularly in patients with type 2 diabetes mellitus, although, so far, its mechanisms of action is unclear (Mahmoodnia et al. 2017). Thus, randomized clinical trial involving a larger number of patients is needed to determine the actual effect of cinnamon on BP among patients with type 2 diabetes mellitus (Akilen et al. 2013).

Garlic was found to decrease factors that induce the metabolic syndrome, which includes reduction in blood pressure, reduction in blood glucose, increased HDL after 4 weeks of consumption in patients with metabolic syndrome (Choudhary et al. 2018). In a meta-analysis, garlic was found to decrease BP in patients with increased SBP, but not in patients without increased SBP (Reinhart et al. 2008). Garlic are superior to placebo in reducing BP in individuals with hypertension (Ried et al. 2008), and the cardioprotective benefits of garlic in essential hypertension is undoubtedly (Dhawan and Jain 2005).

Another plant source that was found effective in reducing BP is ginger. It improves blood flow and relaxes muscles surrounding blood vessels through blockade of voltage-dependent calcium channels (Fugh-Berman 2000), or may partly involve the serotonergic antagonistic property (Ghayur and Gilani 2005). However, there was limited evidence of the human trials investigating the hypotensive effect of ginger used in a low dose, the trial obtaining inconclusive results (Nicoll and Henein 2009).

Vascular reactivity is an important factor for the treatment of cardiovascular diseases because it regulates blood flow and pressure. In seventy-two healthy overweight and obese participants that received onion peel extract, the data showed that a significant improvement of endothelial function, in term of flow-mediated dilation and circulation (Choi et al. 2015). It has been reported that turmeric lowers arterial blood pressure and heart rate in rats (Adaramoye and Medeiros 2008; Adaramoye et al. 2009), and in cellular models it induces

endothelium-independent vasorelaxation in isolated rat aorta (Sasaki et al. 2003).

Curcumin is the most important component of turmeric with biological activities, such as anti-hypertensive (Nakmareong et al. 2011), neuroprotective, anti-ischemic (de Alcântara et al. 2017), antiangiogenic (Dehghan et al. 2016), and vasorelaxation effects in isolated rabbit basilar artery (Ahn et al. 2009). Moreover, hypotensive and vasorelaxation effects were also obtained in isolated rat thoracic aorta (Moohammadaree et al. 2015). Therefore, many plants used in traditional medicine have been investigated for treating cardiovascular disease and hypertension, but more human trials for the hypotensive effects of herbal plants and spices are needed

### CONCLUSION

The anticancer potential of herbs and spices has been evaluated in *in vitro* and *in vivo* studies, but the clinical trials for assessing their anti-tumor effect are still scarce. High antioxidant activity in herbs and spices may alleviate malignancy and extend lifespan. Despite some spices and herbs were found to be cytotoxic and possess chemopreventive activity, further studies are warranted to access the benefit-risk profile of spices and herbs in large clinical trials. Phytochemicals with anti-proliferative potency hold great promising as adjuvants for standard chemotherapy in cancer. Collectively, this evidence would provide a useful strategy to combat cancer.

### CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

### ACKNOWLEDGEMENT

The authors declared that there is no acknowledgement.

### AUTHOR CONTRIBUTIONS

BLT, RB, MN, CC and AEE designed, wrote and revised the manuscript. All authors read and approved the final version.

---

### Copyrights: © 2022@ author (s).

This is an open access article distributed under the terms of the [Creative Commons Attribution License \(CC BY 4.0\)](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and source are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

---

### REFERENCES

- Abdel-Azeem, A. S., Hegazy, A. M., Ibrahim, K. S., Farrag, A. R. H., & El-Sayed, E. M. (2013). Hepatoprotective, antioxidant, and ameliorative effects of ginger (*Zingiber officinale* Roscoe) and

- vitamin E in acetaminophen treated rats. *Journal of dietary supplements*, 10(3), 195-209.
- Abdel-Aziz, H., Nahrstedt, A., Petereit, F., Windeck, T., Ploch, M., & Verspohl, E. J. (2005). 5-HT<sub>3</sub> receptor blocking activity of arylalkanes isolated from the rhizome of *Zingiber officinale*. *Planta medica*, 71(07), 609-616.
- Abdil Razzaq Mohammed Noori Aldallal, A. (2013). A potential role of Cinnamon in improvement of glycemic control in untreated diabetic patients. *karbala journal of pharmaceutical sciences*, 4(6), 85-91.
- Abdollahi, E., Momtazi, A.A., Johnston, T.P. and Sahebkar, A. (2018). Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-all-trades? *Journal of Cellular Physiology* 233(2): 830–848.
- Adaramoye, O. A., Anjos, R. M., Almeida, M. M., Veras, R. C., Silvia, D. F., Oliveira, F. A., ... & Medeiros, I. A. (2009). Hypotensive and endothelium-independent vasorelaxant effects of methanolic extract from *Curcuma longa* L. in rats. *Journal of Ethnopharmacology*, 124(3), 457-462.
- Adaramoye, O. A., & Medeiros, I. A. (2008). Involvement of Na<sup>+</sup>-Ca<sup>2+</sup> exchanger in the endothelium-independent vasorelaxation induced by *Curcuma longa* L. in isolated rat superior mesenteric arteries. *Journal of smooth muscle research*, 44(5), 151-158.
- Adeyemi, O.S., Obeme-Imom, J.I., Akpor, B.O., Rotimi, D., Batiha, G.E.S. and Owolabi, A., (2020). Altered redox status, DNA damage and modulation of L-tryptophan metabolism contribute to antimicrobial action of curcumin. *Heliyon*, 6(3), p.e03495.
- Adisakwattana, S., Lerdsuwankij, O., Poputtachai, U., Minipun, A., & Suparpprom, C. (2011). Inhibitory activity of cinnamon bark species and their combination effect with acarbose against intestinal  $\alpha$ -glucosidase and pancreatic  $\alpha$ -amylase. *Plant Foods for Human Nutrition*, 66(2), 143-148.
- Ahn, C. M., Park, B. G., Woo, H. B., Ham, J., Shin, W. S., & Lee, S. (2009). Synthesis of sulfonyl curcumin mimics exerting a vasodilatation effect on the basilar artery of rabbits. *Bioorganic & Medicinal Chemistry Letters*, 19(5), 1481-1483.
- Akhani, S. P., Vishwakarma, S. L., & Goyal, R. K. (2004). Anti-diabetic activity of *Zingiber officinale* in streptozotocin-induced type I diabetic rats. *Journal of pharmacy and Pharmacology*, 56(1), 101-105.
- Akilen, R., Pimlott, Z., Tsiami, A., & Robinson, N. (2013). Effect of short-term administration of cinnamon on blood pressure in patients with prediabetes and type 2 diabetes. *Nutrition*, 29(10), 1192-1196.
- Akram, M., Shahab-Uddin, A. A., Usmanghani, K. H. A. N., Hannan, A. B. D. U. L., Mohiuddin, E., & Asif, M. (2010). *Curcuma longa* and curcumin: a review
- Al-Amin, Z. M., Thomson, M., Al-Qattan, K. K., Peltonen-Shalaby, R., & Ali, M. (2006). Anti-diabetic and hypolipidaemic properties of ginger (*Zingiber officinale*) in streptozotocin-induced diabetic rats. *British journal of nutrition*, 96(4), 660-666.
- Al-Shathly, M.R., Ali, S.S. and Ayuob, N.N., (2020). *Zingiber officinale* preserves testicular structure and the expression of androgen receptors and proliferating cell nuclear antigen in diabetic rats. *Andrologia*, 52(3), p.e13528.
- Anand, P., Murali, K. Y., Tandon, V., Murthy, P. S., & Chandra, R. (2010). Insulinotropic effect of cinnamaldehyde on transcriptional regulation of pyruvate kinase, phosphoenolpyruvate carboxykinase, and GLUT4 translocation in experimental diabetic rats. *Chemico-biological interactions*, 186(1), 72-81.
- Anwar, M. M., & Meki, A. R. M. (2003). Oxidative stress in streptozotocin-induced diabetic rats: effects of garlic oil and melatonin. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology*, 135(4), 539-547.
- Ashraf, R., Khan, R. A., & Ashraf, I. (2011). Garlic (*Allium sativum*) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients. *Pak J Pharm Sci*, 24(4), 565-570.
- Augusti, K. T. (1974). Effect of alloxan diabetes of allyl propyl disulphide obtained from onion. *Die Naturwissenschaften*, 61(4), 172-173.
- Augusti, K. T., Roy, V. C. M., & Semple, M. (1974). Effect of allyl propyl disulphide isolated from onion (*Allium cepa* L.) on glucose tolerance of alloxan diabetic rabbits. *Experientia*, 30(10), 1119-1120.
- Ayuob, N., Al-Shathly, M. R., Bakhshwin, A., Al-Abbas, N. S., Shaer, N. A., Al Jaouni, S., & Hamed, W. H. (2021). p53 rather than  $\beta$ -catenin mediated the combined hypoglycemic effect of *Cinnamomum cassia* (L.) and *zingiber officinale* roscoe in the streptozotocin-induced diabetic model. *Frontiers in Pharmacology*, 1022.
- Badmaev, V., Majeed, M., & Prakash, L. (2000). Piperine derived from black pepper increases the plasma levels of coenzyme Q10 following oral supplementation. *The journal of nutritional biochemistry*, 11(2), 109-113.
- Barrett, B., Marchand, L., Scheder, J., Appelbaum, D., Chapman, M., Jacobs, C., ... & Clair, N. S. (2000). Bridging the gap between conventional and alternative medicine. *Journal of Family Practice*, 49(3), 234-239.
- Baumgartner, U., Berger, F., Gheinani, A.H., Burgerer, S.S., Monastyrskaya, K. and Vassella, E. (2018). miR-19b enhances proliferation and apoptosis resistance via the EGFR signaling pathway by targeting PP2A and BIM in non-small cell lung cancer. *Molecular Cancer* 17:44.
- Beji, R. S., Khemir, S., Wannes, W. A., Ayari, K., & Ksouri, R. (2018). Antidiabetic, antihyperlipidemic and antioxidant influences of the spice cinnamon

- (Cinnamomum zeylanicum) in experimental rats. *Brazilian Journal of Pharmaceutical Sciences*, 54.
- Bever, B. O., & Zahnd, G. R. (1979). Plants with oral hypoglycaemic action. *Quarterly Journal of Crude Drug Research*, 17(3-4), 139-196.
- Bomdyal, R. S., Shah, M. U., Doshi, Y. S., Shah, V. A., & Khirade, S. P. (2017). Antibacterial activity of curcumin (turmeric) against periopathogens-An in vitro evaluation. *Journal of Advanced Clinical and Research Insights*, 4(6), 175-180.
- Bora, K., & Sharma, A. (2009). Phytoconstituents and therapeutic potential of *Allium cepa* Linn.-A Review. *Pharmacognosy Reviews*, 3(5), 170.
- Bromberg, J. and Wang, T.C. (2009). Inflammation and cancer: IL-6 and STAT3 complete the link. *Cancer Cell* 15: 79–80.
- Carrera-Quintanar, L., López Roa, R.I., Quintero-Fabián, S., Sánchez- Sánchez, M.A., Vizmanos, B. and Ortuño-Sahagún, D. (2018). Phytochemicals that influence gut microbiota as prophylactics and for the treatment of obesity and inflammatory diseases. *Mediators of Inflammation* 2018, Article ID 9734845, 18 pages.
- Carretero, O. A., & Oparil, S. (2000). Essential hypertension: part I: definition and etiology. *Circulation*, 101(3), 329-335.
- Casagrande, F., & Darbon, J. M. (2001). Effects of structurally related flavonoids on cell cycle progression of human melanoma cells: regulation of cyclin-dependent kinases CDK2 and CDK1. *Biochemical pharmacology*, 61(10), 1205-1215.
- Chaitanya, B. V., Somisetty, K. V., Diwan, A., Pasha, S., Shetty, N., Reddy, Y., & Nadigar, S. (2016). Comparison of antibacterial efficacy of turmeric extract, morinda citrifolia and 3% sodium Hypochlorite on *Enterococcus faecalis*: An In-vitro Study. *Journal of clinical and diagnostic research: JCDR*, 10(10), ZC55.
- Chang, Y-C., Su, C-Y., Chen, M-H., Chen, W-S., Chen, C-L. and Hsiao, M. (2017). Secretory RAB GTPase 3C modulates IL6-STAT3 pathway to promote colon cancer metastasis and is associated with poor prognosis. *Molecular Cancer* 16: 135.
- Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X. and Zhao, L. (2018). Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget* 9(6): 7204–7218.
- Choi, E. Y., Lee, H., Woo, J. S., Jang, H. H., Hwang, S. J., Kim, H. S., ... & Kim, W. (2015). Effect of onion peel extract on endothelial function and endothelial progenitor cells in overweight and obese individuals. *Nutrition*, 31(9), 1131-1135.
- Choi, J. A., Kim, J. Y., Lee, J. Y., Kang, C. M., Kwon, H. J., Yoo, Y. D., ... & Lee, S. J. (2001). Induction of cell cycle arrest and apoptosis in human breast cancer cells by quercetin. *International journal of oncology*, 19(4), 837-844.
- Chopra, Bhawna & Dhingra, Ashwani & Kapoor, Ram & Prasad, Deo. (2016). Piperine and Its Various Physicochemical and Biological Aspects: A Review. *Open Chemistry Journal*. 3. 75-96. 10.2174/1874842201603010075
- Choudhary, P. R., Jani, R. D., & Sharma, M. S. (2018). Effect of raw crushed garlic (*Allium sativum* L.) on components of metabolic syndrome. *Journal of dietary supplements*, 15(4), 499-506.
- Chung, S.S., Wu, Y., Okobi, Q., Adekoya, D., Atefi, M., Clarke, O., Dutta, P. and Vadgama, J.V. (2017). Proinflammatory cytokines IL-6 and TNF- $\alpha$  increased telomerase activity through NF- $\kappa$ B/STAT1/STAT3 activation, and Withaferin A inhibited the signaling in colorectal cancer cells. *Mediators of Inflammation* 2017, Article ID 5958429, 11 pages
- Colotta, F., Allavena, P., Sica, A., Garlanda, C. and Mantovani, A. (2009). Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 30(7): 1073–1081.
- Cui, H. Y., Zhou, H., Lin, L., Zhao, C. T., Zhang, X. J., Xiao, Z. H., & Li, C. Z. (2016). Antibacterial activity and mechanism of cinnamon essential oil and its application in milk. *JAPS: Journal of Animal & Plant Sciences*, 26(2).
- D'Ignazio, L., Batie, M. and Rocha, S. (2017). Hypoxia and inflammation in cancer, focus on HIF and NF- $\kappa$ B. *Biomedicines* 5(2): 21.
- Darband, S.G., Kaviani, M., Yousefi, B., Sadighparvar, S., Pakdel, F.G., Attari, J.A., Mohebbi, I., Naderi, S. and Majidinia, M. (2018). Quercetin: A functional dietary flavonoid with potential chemopreventive properties in colorectal cancer. *Journal of Cellular Physiology* 233(9): 6544–6560.
- de Alcântara, G. F. T., Simões-Neto, E., da Cruz, G. M. P., Nobre, M. E. P., Neves, K. R. T., de Andrade, G. M., ... & de Barros Viana, G. S. (2017). Curcumin reverses neurochemical, histological and immunohistochemical alterations in the model of global brain ischemia. *Journal of traditional and complementary medicine*, 7(1), 14-23.
- Dehghan, M. H., Mirmiranpour, H., Faghihi-Kashani, S., Kabir, K., Larry, M., Zayerzadeh, E., & Salehi, S. (2016). Inhibitory effect of curcumin on angiogenesis in a streptozotocin-induced diabetic rat model: An aortic ring assay. *Journal of traditional and complementary medicine*, 6(4), 437-441.
- Dhawan, V., & Jain, S. (2005). Garlic supplementation prevents oxidative DNA damage in essential hypertension. *Molecular and cellular biochemistry*, 275(1), 85-94.
- Dutta, A., & Chakraborty, A. (2018). Cinnamon in anticancer armamentarium: a molecular approach. *Journal of toxicology*, 2018.
- El Atki, Y., Aouam, I., El Kamari, F., Taroq, A., Nayme, K., Timinouni, M., ... & Abdellaoui, A. (2019). Antibacterial activity of cinnamon essential oils and

- their synergistic potential with antibiotics. *Journal of Advanced Pharmaceutical Technology & Research*, 10(2), 63.
- Eldin, I. M. T., Ahmed, E. M., & Abd, E. H. (2010). Preliminary study of the clinical hypoglycemic effects of *Allium cepa* (red onion) in type 1 and type 2 diabetic patients. *Environmental health insights*, 4, EHI-S5540.
- El-Hack, A., Mohamed, E., Alagawany, M., Abdel-Moneim, A. M. E., Mohammed, N. G., Khafaga, A. F., ... & Elnesr, S. S. (2020). Cinnamon (*Cinnamomum zeylanicum*) oil as a potential alternative to antibiotics in poultry. *Antibiotics*, 9(5), 210.
- El-Saber Batiha, G., Magdy Beshbishy, A., G. Wasef, L., Elewa, Y. H., A. Al-Sagan, A., Abd El-Hack, M. E., ... & Prasad Devkota, H. (2020). Chemical constituents and pharmacological activities of garlic (*Allium sativum* L.): A review. *Nutrients*, 12(3), 872.
- Festuccia C, Colapietro A, Mancini A, D'alessandro (2018) A. Crocetin and crocin from saffron in cancer chemotherapy and chemoprevention. *Anticancer Agents Med Chem*. Dec 30.
- Fleischauer, A. T., & Arab, L. (2001). Garlic and cancer: a critical review of the epidemiologic literature. *The Journal of nutrition*, 131(3), 1032S-1040S.
- Fredotović, Ž., Šprung, M., Soldo, B., Ljubenkoy, I., Budić-Leto, I., Bilušić, T., ... & Puizina, J. (2017). Chemical composition and biological activity of *Allium cepa* L. and *Alliumx cornutum* (Clementi ex Visiani 1842) methanolic extracts. *Molecules*, 22(3), 448.
- Fugh-Berman, A. (2000). Herbs and dietary supplements in the prevention and treatment of cardiovascular disease. *Preventive Cardiology*, 3(1), 24-32.
- Galavi, A., Hosseinzadeh, H., & Razavi, B. M. (2021). The effects of *Allium cepa* L.(onion) and its active constituents on metabolic syndrome: A review. *Iranian Journal of Basic Medical Sciences*, 24(1), 3.
- Ganjre, A., Kathariya, R., Bagul, N., & Pawar, V. (2015). Anti-carcinogenic and anti-bacterial properties of selected spices: implications in oral health. *Clinical nutrition research*, 4(4), 209-215.
- Gautam, S., Pal, S., Maurya, R., & Srivastava, A. K. (2015). Ethanolic extract of *Allium cepa* stimulates glucose transporter typ 4-mediated glucose uptake by the activation of insulin signaling. *Planta Medica*, 81(03), 208-214.
- Ghayur, M. N., & Gilani, A. H. (2005). Ginger lowers blood pressure through blockade of voltage-dependent calcium channels. *Journal of cardiovascular pharmacology*, 45(1), 74-80.
- Ghosh, R., Ganapathy, M., Alworth, W. L., Chan, D. C., & Kumar, A. P. (2009). Combination of 2-methoxyestradiol (2-ME2) and eugenol for apoptosis induction synergistically in androgen independent prostate cancer cells. *The Journal of steroid biochemistry and molecular biology*, 113(1-2), 25-35.
- Griffiths, K., Aggarwal, B. B., Singh, R. B., Buttar, H. S., Wilson, D., & De Meester, F. (2016). Food antioxidants and their anti-inflammatory properties: a potential role in cardiovascular diseases and cancer prevention. *Diseases*, 4(3), 28.
- Gruenewald, J., Freder, J. and Armbruester, N., (2010). Cinnamon and health. *Critical reviews in food science and nutrition*, 50(9), pp.822-834.
- Guldiken, B., Ozkan, G., Catalkaya, G., Ceylan, F. D., Yalcinkaya, I. E., & Capanoglu, E. (2018). Phytochemicals of herbs and spices: Health versus toxicological effects. *Food and Chemical Toxicology*, 119, 37-49.
- Guo, Y.Q., Xu, F., Lu, T.H., Duan, Z.F. and Zhang, Z. (2012). Interleukin-6 signaling pathway in targeted therapy for cancer. *Cancer Treatment Reviews* 38: 904–910.
- Hassanalilou, T., Ghavamzadeh, S. and Khalili, L. (2019). Curcumin and gastric cancer: a review on mechanisms of action. *Journal of Gastrointestinal Cancer* 1–8.
- Hester, F., Verghese, M., Willis, S., Baldwin, A., Reid, M., Shackelford, L., ... & Walker, L. (2018). The Anti-Diabetic Potential of Thermally Treated Garlic, Turmeric, and Ginger in Pre-Diabetic Male Wistar Rat Model. *Food and Nutrition Sciences*, 9(04), 420.
- Hlebowicz, J., Darwiche, G., Björgell, O., & Almér, L. O. (2007). Effect of cinnamon on postprandial blood glucose, gastric emptying, and satiety in healthy subjects. *The American journal of clinical nutrition*, 85(6), 1552-1556.
- Howard, L.R., Talcott, S.T., Brenes, C.H. and Villalon, B. (2000). Changes in phytochemical and antioxidant activity of selected pepper cultivars (*Capsicum* species) as influenced by maturity. *Journal of Agricultural and Food Chemistry* 48: 1713–1720.
- Hussain A, Brahmhatt K, Priyani A, Ahmed M, Rizvi TA, and Sharma C, (2011) "Eugenol enhances the chemotherapeutic potential of gemcitabine and induces anticarcinogenic and anti-inflammatory activity in human cervical cancer cells," *Cancer Biotherapy and Radiopharmaceuticals*, vol. 26, no. 5, pp. 519–527.
- Ilie, M. A., Caruntu, C., Tampa, M., Georgescu, S. R., Matei, C., Negrei, C., ... & Boda, D. (2019). Capsaicin: Physicochemical properties, cutaneous reactions and potential applications in painful and inflammatory conditions. *Experimental and therapeutic medicine*, 18(2), 916-925.
- Imran, M., Nadeem, M., Saeed, F., Imran, A., Khan, M.R., Khan, M.A., Ahmed, S. and Rauf, A. (2017). Immunomodulatory perspectives of potential biological spices with special reference to cancer and diabetes. *Food and Agricultural Immunology* 28(4): 543–572.
- Imran, M., Rauf, A., Khan, I. A., Shahbaz, M., Qaisrani, T. B., Fatmawati, S., ... & Gondal, T. A. (2018). Thymoquinone: A novel strategy to combat cancer: A

- review. *Biomedicine & Pharmacotherapy*, 106, 390-402.
- Islam, M. S., & Choi, H. (2008). Comparative effects of dietary ginger (*Zingiber officinale*) and garlic (*Allium sativum*) investigated in a type 2 diabetes model of rats. *Journal of medicinal food*, 11(1), 152-159.
- Jain, R. C., & Vyas, C. R. (1974). Hypoglycaemia action of onion on rabbits. *British Medical Journal*, 2(5921), 730.
- Jaiswal, N., & Rizvi, S. I. (2017). Amylase inhibitory and metal chelating effects of different layers of onion (*Allium cepa* L.) at two different stages of maturation in vitro. *Ann Phytomed Int J*, 6, 45-50.
- Jaksevicus, A., Carew, M., Mistry, C., Modjtahedi, H. and Opara, E.I. (2017). Inhibitory effects of culinary herbs and spices on the growth of HCA-7 colorectal cancer cells and their COX-2 expression. *Nutrients* 9:1051.
- Jeena, K., Liju, V. B., & Kuttan, R. (2013). Antioxidant, anti-inflammatory and antinociceptive activities of essential oil from ginger. *Indian J Physiol Pharmacol*, 57(1), 51-62.
- Jiang TA. Health Benefits of Culinary Herbs and Spices. *J AOAC Int.* (2019) Mar 1;102(2):395-411. doi: 10.5740/jaoacint.18-0418. Epub 2019 Jan 16.
- Jie Zheng, Yue Zhou, Ya Li, Dong-Ping Xu, Sha Li, and Hua-Bin Li. Spices for Prevention and Treatment of Cancers. *Nutrients*. 2016 Aug; 8(8): 495.
- Jung, K.J., Lee, E.K., Kim, J.Y., Zou, Y., Sung, B., Heo, H.S., Kim, M.K., Lee, J., Kim, N.D., Yu, B.P. and Chung, H.Y. (2009). Effect of short term calorie restriction on pro-inflammatory NF-kB and AP-1 in aged rat kidney. *Inflammation Research* 58(3): 143–150.
- Kabrah, M. A. M., Faidah, H. S., Ashshi, A. M., & Turkistani, M. S. A. (2016). Antibacterial effect of onion. *Sch J App Med Sci*, 4, 4128-4133.
- Kammath, A. J., Nair, B., & Nath, L. R. (2021). Curry versus cancer: Potential of some selected culinary spices against cancer with in vitro, in vivo, and human trials evidences. *Journal of Food Biochemistry*, 45(3), e13285.
- Karawya, M. S., Wahab, S. A., El-Olemy, M. M., & Farrag, N. M. (1984). Diphenylamine, an antihyperglycemic agent from onion and tea. *Journal of Natural Products*, 47(5), 775-780.
- Karin, M. (2008). The IκB kinase- a bridge between inflammation and cancer. *Cell Research* 18(3): 334–342.
- Kaschula, C. H., Tuveri, R., Ngarande, E., Dzobo, K., Barnett, C., Kusza, D. A., ... & Schäfer, G. (2019). The garlic compound ajoene covalently binds vimentin, disrupts the vimentin network and exerts anti-metastatic activity in cancer cells. *BMC cancer*, 19(1), 1-16.
- Kebede, B. H., Forsido, S. F., Tola, Y. B., & Astatkie, T. (2021). Free radical scavenging capacity, antibacterial activity and essential oil composition of turmeric (*Curcuma domestica*) varieties grown in Ethiopia. *Heliyon*, 7(2), e06239.
- Kim, J. M., Noh, E. M., Kwon, K. B., Kim, J. S., You, Y. O., Hwang, J. K., ... & Lee, Y. R. (2012). Curcumin suppresses the TPA-induced invasion through inhibition of PKCα-dependent MMP-expression in MCF-7 human breast cancer cells. *Phytomedicine*, 19(12), 1085-1092.
- Kim, S.J. and Yoon, S. (2016). Activated Rac1 regulates the degradation of IκBα and the nuclear translocation of STAT3-NFκB complexes in starved cancer cells. *Experimental and Molecular Medicine* 48: e231.
- Koppikar, S. J., Choudhari, A. S., Suryavanshi, S. A., Kumari, S., Chattopadhyay, S., & Kaul-Ghanekar, R. (2010). Aqueous Cinnamon Extract (ACE-c) from the bark of *Cinnamomum cassiacauses* apoptosis in human cervical cancer cell line (SiHa) through loss of mitochondrial membrane potential. *BMC cancer*, 10(1), 1-12.
- Kumar, P., Barua, C.C., Sulakhiya, K. and Sharma, R.K. (2017). Curcumin ameliorates cisplatin-induced nephrotoxicity and potentiates its anticancer activity in SD rats: potential role of curcumin in breast cancer chemotherapy. *Frontiers in Pharmacology* 8:132.
- Kumari, K., & Augusti, K. T. (1995). Antidiabetic effects of S-methylcysteine sulphoxide on alloxan diabetes. *Planta medica*, 61(01), 72-74.
- Kunnumakkara, A. B., Sailo, B. L., Banik, K., Harsha, C., Prasad, S., Gupta, S. C., Bharti, A. C. and Aggarwal, B. B. (2018). Chronic diseases, inflammation, and spices: how are they linked? *Journal of Translational Medicine* 16:14.
- Kwiatkowski, P., Łopusiewicz, Ł., Kostek, M., Drożdowska, E., Pruss, A., Wojciuk, B., ... & Dołęgowska, B. (2019). The antibacterial activity of lavender essential oil alone and in combination with octenidine Dihydrochloride against MRSA strains. *Molecules*, 25(1), 95.
- Kwon, H. K., Jeon, W. K., Hwang, J. S., Lee, C. G., So, J. S., Park, J. A., ... & Im, S. H. (2009). Cinnamon extract suppresses tumor progression by modulating angiogenesis and the effector function of CD8+ T cells. *Cancer letters*, 278(2), 174-182.
- Larsen, J.M. (2017). The immune response to *Prevotella* bacteria in chronic inflammatory disease. *Immunology* 151(4): 363–374.
- Lee, H. A., Koh, E. K., Sung, J. E., Kim, J. E., Song, S. H., Kim, D. S., ... & Hwang, D. Y. (2017). Ethyl acetate extract from *Asparagus cochinchinensis* exerts anti-inflammatory effects in LPS-stimulated RAW264. 7 macrophage cells by regulating COX-2/iNOS, inflammatory cytokine expression, MAP kinase pathways, the cell cycle and anti-oxidant activity. *Molecular Medicine Reports*, 15(4), 1613-1623.
- Lee, S. H., Min, K. W., Zhang, X., & Baek, S. J. (2013). 3, 3'-diindolylmethane induces activating transcription factor 3 (ATF3) via ATF4 in human colorectal cancer

- cells. *The Journal of nutritional biochemistry*, 24(4), 664-671.
- Leja, K. B., & Czaczyk, K. (2016). The industrial potential of herbs and spices? A mini review. *Acta Scientiarum Polonorum Technologia Alimentaria*, 15(4), 353-365.
- Li, S., Lei, Y., Jia, Y., Li, N., Wink, M., & Ma, Y. (2011). Piperine, a piperidine alkaloid from *Piper nigrum* re-sensitizes P-gp, MRP1 and BCRP dependent multidrug resistant cancer cells. *Phytomedicine*, 19(1), 83-87.
- Li, Q., Yang, G., Feng, M., Zheng, S., Cao, Z., Qiu, J., You, L., Zheng, L., Hu, Y., Zhang, T. and Zhao, Y. (2018). NF- $\kappa$ B in pancreatic cancer: Its key role in chemoresistance. *Cancer Letters* 421: 127–134.
- Liu, F., Gao, S., Yang, Y., Zhao, X., Fan, Y., Ma, W., Yang, D., Yang, A. and Yu, Y. (2018). Antitumor activity of curcumin by modulation of apoptosis and autophagy in human lung cancer A549 cells through inhibiting PI3K/Akt/mTOR pathway. *Oncology Reports* 39(3): 1523–1531.
- Liu, H., Liu, A., Shi, C. and Li, B. (2016). Curcumin suppresses transforming growth factor- $\beta$ 1-induced cardiac fibroblast differentiation via inhibition of Smad-2 and p38 MAPK signaling pathways. *Experimental and Therapeutic Medicine* 11(3): 998–1004.
- Lockwood, K., Moesgaard, S., Hanioka, T., & Folkers, K. (1994). Apparent partial remission of breast cancer in 'high risk' patients supplemented with nutritional antioxidants, essential fatty acids and coenzyme Q10. *Molecular aspects of medicine*, 15, s231-s240.
- Lolok, N., Mashar, H. M., Annah, I., Saleh, A., Yuliasri, W. O., & Isrul, M. (2019). Antidiabetic effect of the combination of garlic peel extract (*Allium sativum*) and onion peel (*Allium cepa*) in rats with oral-glucose tolerance method. *Research Journal Pharmacy and Technology*, 12(5), 2153-2156.
- Mahmoodnia, L., Aghadavod, E., & Rafieian-Kopaei, M. (2017). Ameliorative impact of cinnamon against high blood pressure; an updated review. *Journal of Renal Injury Prevention*, 6(3), 171-176.
- Majdalawieh, A. F., & Fayyad, M. W. (2015). Immunomodulatory and anti-inflammatory action of *Nigella sativa* and thymoquinone: A comprehensive review. *International immunopharmacology*, 28(1), 295-304.
- Mang, B., Wolters, M., Schmitt, B., Kelb, K., Lichtinghagen, R., Stichtenoth, D. O., & Hahn, A. (2006). Effects of a cinnamon extract on plasma glucose, HbA1c, and serum lipids in diabetes mellitus type 2. *European journal of clinical investigation*, 36(5), 340-344.
- Mangino, G., Chiantore, M.V., Iuliano, M., Fiorucci, G. and Romeo, G. (2016). Inflammatory microenvironment and human papillomavirus-induced carcinogenesis. *Cytokine Growth Factor Rev* 30: 103–111.
- Mantovani, A. (2018). The inflammation-cancer connection. *The FEBS Journal* 285: 638–640.
- Marrelli, M., Amodeo, V., Statti, G., & Conforti, F. (2018). Biological properties and bioactive components of *Allium cepa* L.: Focus on potential benefits in the treatment of obesity and related comorbidities. *Molecules*, 24(1), 119.
- Mascolo, N., Jain, R., Jain, S. C., & Capasso, F. (1989). Ethnopharmacologic investigation of ginger (*Zingiber officinale*). *Journal of ethnopharmacology*, 27(1-2), 129-140.
- Mendez, M. G., Kojima, S. I., & Goldman, R. D. (2010). Vimentin induces changes in cell shape, motility, and adhesion during the epithelial to mesenchymal transition. *The FASEB Journal*, 24(6), 1838-1851.
- Millet, A., Lamy, E., Jonas, D., Stintzing, F., Mersch-Sundermann, V., & Merfort, I. (2012). Fermentation enhances the biological activity of *Allium cepa* bulb extracts. *Journal of agricultural and food chemistry*, 60(9), 2148-2156.
- Millsop, J. W., Sivamani, R. K., & Fazel, N. (2013). Botanical agents for the treatment of nonmelanoma skin cancer. *Dermatology Research and Practice*, 2013.
- Mitake, M., Ogawa, H., Uebaba, K., & Shidoji, Y. (2010). Increase in plasma concentrations of geranylgeranoic Acid after turmeric tablet intake by healthy volunteers. *Journal of Clinical Biochemistry and Nutrition*, 1004080012-1004080012.
- Mitchell, J. and Carmody, R.J. (2018). NF- $\kappa$ B and the transcriptional control of inflammation. In: Loos, F. (ed.) *Transcriptional gene regulation in health and disease. International Review of Cell and Molecular Biology* 335: 41–84.
- Mohammadaree, A., Changtam, C., Wicha, P., Suksamram, A., Tocharus, J., & Tocharus, C. (2015). Mechanisms of vasorelaxation induced by hexahydrocurcuminin isolated rat thoracic aorta. *Phytotherapy Research*, 29(11), 1806-1813.
- Mostafa, N. M. (2018). Antibacterial activity of ginger (*Zingiber officinale*) leaves essential oil nanoemulsion against the cariogenic *Streptococcus mutans*. *Journal of Applied Pharmaceutical Science*, 8(9), 034-041.
- Mukherjee, S., Mazumdar, M., Chakraborty, S., Manna, A., Saha, S., Khan, P., ... & Das, T. (2014). Curcumin inhibits breast cancer stem cell migration by amplifying the E-cadherin/ $\beta$ -catenin negative feedback loop. *Stem cell research & therapy*, 5(5), 1-19.
- Nakmareong, S., Kukongviriyapan, U., Pakdeechote, P., Donpunha, W., Kukongviriyapan, V., Kongyingoes, B., ... & Phisalaphong, C. (2011). Antioxidant and vascular protective effects of curcumin and tetrahydrocurcumin in rats with L-NAME-induced hypertension. *Naunyn-Schmiedeberg's archives of pharmacology*, 383(5), 519-529.
- Nam, Y. H., Hong, B. N., Rodriguez, I., Park, M. S., Jeong,

- S. Y., Lee, Y. G., ... & Kang, T. H. (2020). Steamed ginger may enhance insulin secretion through KATP channel closure in pancreatic  $\beta$ -cells potentially by increasing 1-dehydro-6-gingerdione content. *Nutrients*, 12(2), 324.
- Neagu, M. (2020). Metabolic traits in cutaneous melanoma. *Frontiers in oncology*, 10, 851.
- Neagu(a), M., Constantin, C., Caruntu, C., Dumitru, C., Surcel, M., & Zurac, S. (2019a). Inflammation: A key process in skin tumorigenesis. *Oncology Letters*, 17(5), 4068-4084.
- Neagu(b) Monica, Carolina Constantin, Iulia Dana Popescu, Donato Zipeto, George Tzanakakis, Dragana Nikitovic, Concettina Fenga, Constantine A. Stratakis, Demetrios A. Spandidos, Aristidis M. Tsatsakis, (2019b). Inflammation and metabolism in cancer cell – mitochondria key player, *Front Oncol*, 9:348, 2019b doi: 10.3389/fonc.2019.00348
- Neagu(c) Monica, Carolina Constantin, Marinela Bostan, Constantin Caruntu, Simona Rebeca Ignat, Sorina Dinescu, Marieta Costache (2019c) Proteomic Technology “Lens” for Epithelial-Mesenchymal Transition Process Identification in Oncology, October 2019, *Analytical Cellular Pathology* (Amsterdam) 2019:1-17, 2019 Oct 29;2019:3565970. doi: 10.1155/2019/3565970
- Nicastro, H. L., Ross, S. A., & Milner, J. A. Garlic and onions: their cancer prevention properties. *Cancer Prev Res (Phila)* 2015; 8: 181-9.
- Nicoll, R., & Henein, M. Y. (2009). Ginger (*Zingiber officinale* Roscoe): a hot remedy for cardiovascular disease?. *International journal of cardiology*, 131(3), 408-409.
- Nikkhah Bodagh, M., Maleki, I., & Hekmatdoost, A. (2019). Ginger in gastrointestinal disorders: A systematic review of clinical trials. *Food science & nutrition*, 7(1), 96-108.
- Ohaeri, O. C. (2001). Effect of garlic oil on the levels of various enzymes in the serum and tissue of streptozotocin diabetic rats. *Bioscience reports*, 21(1), 19-24.
- Panda, A. K., Chakraborty, D., Sarkar, I., Khan, T., & Sa, G. (2017). New insights into therapeutic activity and anticancer properties of curcumin. *Journal of experimental pharmacology*, 9, 31.
- Park, G. H., Park, J. H., Song, H. M., Eo, H. J., Kim, M. K., Lee, J. W., ... & Jeong, J. B. (2014). Anti-cancer activity of Ginger (*Zingiber officinale*) leaf through the expression of activating transcription factor 3 in human colorectal cancer cells. *BMC complementary and alternative medicine*, 14(1), 1-8.
- Park, S. A., & Surh, Y. J. (2017). Modulation of tumor microenvironment by chemopreventive natural products. *Annals of the New York Academy of Sciences*, 1401(1), 65-74.
- Patil, M., & Patil, V. (2021). EFFICACY OF CINNAMON CONSUMPTION FOR REDUCING BLOOD PRESSURE IN ADULT HYPERTENSIVE MALES. *Journal of Hypertension*, 39, e320.
- Qi, F., Zhao, L., Zhou, A., Zhang, B., Li, A., Wang, Z. and Han, J. (2015). The advantages of using traditional Chinese medicine as an adjunctive therapy in the whole course of cancer treatment instead of only terminal stage of cancer. *Bioscience Trends* 9: 16–34.
- Qu, D., Shen, L., Liu, S., Li, H., Ma, Y., Zhang, R., Wu, K., Yao, L., Li, J. and Zhang, J. (2017). Chronic inflammation confers to the metabolic reprogramming associated with tumorigenesis of colorectal cancer. *Cancer Biology and Therapy* 18(4): 237–244.
- Rahal, A., Kumar, A., Singh, V., Yadav, B., Tiwari, R., Chakraborty, S. and Dhama, K. (2014). Oxidative stress, prooxidants, and antioxidants: the interplay. *BioMed Research International* 2014, Article ID 761264, 19 pages.
- Rajendran, P., Nandakumar, N., T. Rengarajan, T., Palaniswami, R., Gnanadhas, E.N., Lakshminarasiah, U., Gopas, J. and Nishigaki, I. (2014). Antioxidants and human diseases. *Clinica Chimica Acta* 436: 332–347.
- Ranasinghe, P., Piger, S., Premakumara, G. A., Galappaththy, P., Constantine, G. R., & Katulanda, P. (2013). Medicinal properties of ‘true’cinnamon (*Cinnamomum zeylanicum*): a systematic review. *BMC complementary and alternative medicine*, 13(1), 1-10.
- Rao Mukkavilli, Chunhua Yang, Reenu Singh Tanwar, Roopali Saxena, Sushma R. Gundala, Yingyi Zhang, Ahmed Ghareeb, Stephan D. Floyd, Subrahmanyam Vangala, Wei-Wen Kuo, Padmashree C. G. Rida, and Ritu Aneja. (2018). Pharmacokinetic-pharmacodynamic correlations in the development of ginger extract as an anticancer agent. *Sci Rep*. 8(1), 1-10.
- Raposo, T.P., Beirão, B.C., Pang, L.Y., Queiroga, F.L. and Argyle, D.J. (2015). Inflammation and cancer: till death tears them apart. *The Veterinary Journal* 205(2): 161–174.
- Rea, I.M., Gibson, D.S., McGilligan, V., McNerlan, S.E., Denis Alexander, H. and Ross, O.A. (2018). Age and age-related diseases: role of inflammation triggers and cytokines. *Frontiers in Immunology* 9:586.
- Reinhart, K. M., Coleman, C. I., Teevan, C., Vachhani, P., & White, C. M. (2008). Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. *Annals of Pharmacotherapy*, 42(12), 1766-1771.
- Ried, K., Frank, O. R., Stocks, N. P., Fakler, P., & Sullivan, T. (2008). Effect of garlic on blood pressure: a systematic review and meta-analysis. *BMC cardiovascular disorders*, 8(1), 1-12.
- Russo, M., Spagnuolo, C., Tedesco, I., Bilotto, S., & Russo, G. L. (2012). The flavonoid quercetin in disease prevention and therapy: facts and fancies.

- Biochemical pharmacology, 83(1), 6-15.
- Sahib, A. S. (2016). Anti-diabetic and antioxidant effect of cinnamon in poorly controlled type-2 diabetic Iraqi patients: A randomized, placebo-controlled clinical trial. *Journal of intercultural ethnopharmacology*, 5(2), 108.
- Saraf, S., Kour Chhabra, S., Deep Kaur, C., & Saraf, S. (2012). Development of photochemoprotective herbs containing cosmetic formulations for improving skin properties. *Journal of cosmetic science*, 63(2), 119.
- Sasaki, Y., Goto, H., Tohda, C., Hatanaka, F., Shibahara, N., Shimada, Y., ... & Komatsu, K. (2003). Effects of curcuma drugs on vasomotion in isolated rat aorta. *Biological and Pharmaceutical Bulletin*, 26(8), 1135-1143.
- Savant, S.S., Sriramkumar, S. and O'Hagan, H.M. (2018). The role of inflammation and inflammatory mediators in the development, progression, metastasis, and chemoresistance of epithelial ovarian cancer. *Cancers* 10(8):251.
- Saxena, A., Tripathi, R. M., & Singh, R. P. (2010). Biological synthesis of silver nanoparticles by using onion (*Allium cepa*) extract and their antibacterial activity. *Dig J Nanomater Bios*, 5(2), 427-432.
- Schoene, N. W., Kelly, M. A., Polansky, M. M., & Anderson, R. A. (2005). Water-soluble polymeric polyphenols from cinnamon inhibit proliferation and alter cell cycle distribution patterns of hematologic tumor cell lines. *Cancer letters*, 230(1), 134-140.
- Schulze, C., Bangert, A., Schwanck, B., Vollert, H., Blaschek, W., & Daniel, H. (2015). Extracts and flavonoids from onion inhibit the intestinal sodium-coupled glucose transporter 1 (SGLT1) in vitro but show no anti-hyperglycaemic effects in vivo in normoglycaemic mice and human volunteers. *Journal of Functional Foods*, 18, 117-128.
- Seyed, M. A., Jantan, I., Bukhari, S. N. A., and Vijayaraghavan, K. (2016). A comprehensive review on the chemotherapeutic potential of piceatannol for cancer treatment, with mechanistic insights. *Journal of Agricultural and Food Chemistry* 64: 725–737.
- Sharma, M., & Shukla, S. (1977). Hypoglycaemic effect of ginger. *Journal of Research in Indian Medicine, Yoga and Homeopathy*, 12(2), 127-130.
- Sheela, C. G., Kumud, K., & Augusti, K. T. (1995). Anti-diabetic effects of onion and garlic sulfoxide amino acids in rats. *Planta Medica*, 61(04), 356-357.
- Sheng, X., Zhang, Y., Gong, Z., Huang, C., & Zang, Y. Q. (2008). Improved insulin resistance and lipid metabolism by cinnamon extract through activation of peroxisome proliferator-activated receptors. *PPAR research*, 2008.
- Shengquan, L. and Sze Ngong, H.L. (2013). Design of low-molecular-weight prodrugs for targeted delivery of anticancer agents," in Proceedings of the 3<sup>rd</sup> International Conference and Exhibition on Pharmaceutics and Novel Drug Delivery Systems, Hilton, Chicago/Northbrook, USA.
- Shidoji, Y., & Ogawa, H. (2004). Natural occurrence of cancer-preventive geranylgeranoic acid in medicinal herbs. *Journal of lipid research*, 45(6), 1092-1103.
- Shirzad, F., Morovatdar, N., Rezaee, R., Tsarouhas, K., & Moghadam, A. A. (2021). Cinnamon effects on blood pressure and metabolic profile: A double-blind, randomized, placebo-controlled trial in patients with stage 1 hypertension. *Avicenna Journal of Phytomedicine*, 11(1), 91.
- Shokrzadeh, M., & Ebadi, A. G. (2006). Antibacterial effect of garlic (*Allium sativum* L.) on *Staphylococcus aureus*. *Pak. J. Biol. Sci*, 9(8), 1577-9.
- Singh, S. V., Powolny, A. A., Stan, S. D., Xiao, D., Arlotti, J. A., Warin, R., Hahm, E-R., Marynowski, S.W., Bommareddy, A., Potter, D.M. and Dhir, R. (2008). Garlic constituent diallyl trisulfide prevents development of poorly differentiated prostate cancer and pulmonary metastasis multiplicity in TRAMP mice. *Cancer Research* 68: 9503–9511.
- Singletary K. Cinnamon: Update of potential health benefits. *Nutrition Today*. (2019), Jan 1;54(1):42-52.
- Srinivasan, K. (2014). Antioxidant potential of spices and their active constituents. *Critical Reviews in Food Science and Nutrition* 54(3): 352–372.
- Stanley, J., Jua, C., Irene, K., Gordon, W., Mieko, T., Bonga, S. and Ashley, V. (2017). Interleukin-6, a cytokine critical to mediation of inflammation, autoimmunity and allograft rejection: therapeutic implications of IL-6 receptor blockade. *Transplantation* 101(1): 32–44.
- Starok, M., Preira, P., Vayssade, M., Haupt, K., Salome, L., & Rossi, C. (2015). EGFR inhibition by curcumin in cancer cells: a dual mode of action. *Biomacromolecules*, 16(5), 1634-1642.
- Steiner, M., & Li, W. (2001). Aged garlic extract, a modulator of cardiovascular risk factors: a dose-finding study on the effects of AGE on platelet functions. *The Journal of nutrition*, 131(3), 980S-984S.
- Suleria, H. A. R., Butt, M. S., Anjum, F. M., Saeed, F., & Khalid, N. (2015). Onion: Nature protection against physiological threats. *Critical reviews in food science and nutrition*, 55(1), 50-66.
- Sun, L. and Wang, X. (2003). Effects of allicin on both telomerase activity and apoptosis in gastric cancer SGC-7901 cells. *World Journal of Gastroenterology* 9(9): 1930–1934.
- Sung H, Ferlay J, Siegel RL et al (2021) Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71:209-249 Sunthar TP, Marin E, Boschetto F, Zanocco M, Sunahara H, Ramful R, Kamei K, Zhu W, Pezzotti G. Antibacterial and antifungal properties of composite polyethylene materials reinforced with Neem and Turmeric. *Antibiotics*. 2020 Dec;9(12):857.

- Sung, B., Prasad, S., Yadav, V.R. and Aggarwal, B.B. (2012). Cancer cell signaling pathways-targeted by spice-derived nutraceuticals. *Nutrition and Cancer* 64(2): 173–197.
- Sunthar, T. P., Marin, E., Boschetto, F., Zanocco, M., Sunahara, H., Ramful, R., ... & Pezzotti, G. (2020). Antibacterial and ANTIFUNGAL properties of composite POLYETHYLENE Materials reinforced with Neem and turmeric. *Antibiotics*, 9(12), 857.
- Sylvester, W. S., Son, R., Lew, K. F., & Rukayadi, Y. (2015). Antibacterial activity of Java turmeric (*Curcuma xanthorrhiza* Roxb.) extract against *Klebsiella pneumoniae* isolated from several vegetables. *International Food Research Journal*, 22(5).
- Tan, B.L., Norhaizan, M.E., and Liew, W-P-P. (2018a). Nutrients and oxidative stress: Friend or foe?. *Oxidative Medicine and Cellular Longevity* 2018, Article ID 9719584, 24 pages
- Tan, B.L., Norhaizan, M.E., Liew, W-P.P. and Rahman, H. S. (2018b). Antioxidant and oxidative stress: a mutual interplay in age-related diseases. *Frontiers in Pharmacology* 9: 1162.
- Taniguchi, K. and Karin, M. (2018). NF- $\kappa$ B, inflammation, immunity and cancer: coming of age. *Nature Reviews Immunology* 18: 309–324.
- Tapsell, L.C., Hemphill, I., Cobiac, L., Sullivan, D.R., Fenech, M., Patch, C.S., Roodenrys, S., Keogh, J.B., Clifton, P.M., Williams, P.G., Fazio, V.A. and Inge, K.E. (2006). Health benefits of herbs and spices: the past, the present, the future. *Medical Journal of Australia* 185(4): S1–S24.
- Tyagi, A. K., & Malik, A. (2011). Antimicrobial potential and chemical composition of *Eucalyptus globulus* oil in liquid and vapour phase against food spoilage microorganisms. *Food Chemistry*, 126(1), 228-235.
- Tyagi, P., Singh, M., Kumari, H., Kumari, A., & Mukhopadhyay, K. (2015). Bactericidal activity of curcumin I is associated with damaging of bacterial membrane. *PloS one*, 10(3), e0121313.
- Vakifahmetoglu-Norberg, H., Ouchida, A.T. and Norberg, E. (2017). The role of mitochondria in metabolism and cell death. *Biochemical and Biophysical Research Communications* 482(3): 426–431.
- Varker, K. A., Ansel, A., Aukerman, G., & Carson III, W. E. (2012). Review of complementary and alternative medicine and selected nutraceuticals: background for a pilot study on nutrigenomic intervention in patients with advanced cancer. *Alternative Therapies in Health & Medicine*, 18(2).
- Verma, A., Singh, D., Anwar, F., Bhatt, P.C., Al-Abbasi, F. and Kumar, V. (2018). Triterpenoids principle of *Wedelia calendulacea* attenuated diethylnitrosamine-induced hepatocellular carcinoma via down-regulating oxidative stress, inflammation and pathology via NF- $\kappa$ B pathway. *Inflammopharmacology* 26(1): 133–146.
- Wang, Y., Tian, W. X., & Ma, X. F. (2012). Inhibitory effects of onion (*Allium cepa* L.) extract on proliferation of cancer cells and adipocytes via inhibiting fatty acid synthase. *Asian Pacific Journal of Cancer Prevention*, 13(11), 5573-5579.
- Wei, C. K., Tsai, Y. H., Korinek, M., Hung, P. H., El-Shazly, M., Cheng, Y. B., ... & Chang, F. R. (2017). 6-paradol and 6-shogaol, the pungent compounds of ginger, promote glucose utilization in adipocytes and myotubes, and 6-paradol reduces blood glucose in high-fat diet-fed mice. *International journal of molecular sciences*, 18(1), 168.
- World Health Organization. (2021). Cancer. [https://www.who.int/health-topics/cancer#tab=tab\\_1](https://www.who.int/health-topics/cancer#tab=tab_1) [accessed on 18 October 2021]
- Wu, X., Shi, J., Fang, W. X., Guo, X. Y., Zhang, L. Y., Liu, Y. P., & Li, Z. (2019). *Allium* vegetables are associated with reduced risk of colorectal cancer: A hospital-based matched case-control study in China. *Asia-Pacific Journal of Clinical Oncology*, 15(5), e132-e141.
- Xiao, T.S. (2017). Innate immunity and inflammation. *Cellular and Molecular Immunology* 14: 1–3.
- Xu, C., Mathews, A.E., Rodrigues, C., Eudy, B.J., Rows, C.A., O'Donoghue, A. and Percival, S.S. (2018). Aged garlic extract supplementation modifies inflammation and immunity of adults with obesity: A randomized, double-blind, placebo-controlled clinical trial. *Clinical Nutrition ESPEN* 24: 148–155.
- Yadufashije, C., Niyonkuru, A., Munyeshyaka, E., Madjidi, S., & Mucumbitsi, J. (2020). Antibacterial activity of ginger extracts on bacteria isolated from digestive tract infection patients attended Muhoza Health Center. *Asian Journal of Medical Sciences*, 11(2), 35-41.
- Yang, J., Meyers, K. J., van der Heide, J., & Liu, R. H. (2004). Varietal differences in phenolic content and antioxidant and antiproliferative activities of onions. *Journal of agricultural and food chemistry*, 52(22), 6787-6793.
- Yashin, A., Yashin, Y., Xia, X. and Nemzer, B. (2017). Antioxidant activity of spices and their impact on human health: A review. *Antioxidants* 6(3):70.
- Yen, H. R., Chen, Y. Y., Huang, T. P., Chang, T. T., Tsao, J. Y., Chen, B. C., & Sun, M. F. (2015). Prescription patterns of Chinese herbal products for patients with uterine fibroid in Taiwan: a nationwide population-based study. *Journal of ethnopharmacology*, 171, 223-230.
- Zheng, D., Huang, C., Huang, H., Zhao, Y., Khan, M.R.U., Zhao, H. and Huang, L., (2020). Antibacterial mechanism of curcumin: A review. *Chemistry & Biodiversity*, 17(8), p.e2000171.
- Zorofchian Moghadamtousi, S., Abdul Kadir, H., Hassandarvish, P., Tajik, H., Abubakar, S., & Zandi, K. (2014). A review on antibacterial, antiviral, and antifungal activity of curcumin. *BioMed research*

international, 2014.

Zuniga, K. E., Parma, D. L., Muñoz, E., Spaniol, M., Wargovich, M., & Ramirez, A. G. (2019). Dietary intervention among breast cancer survivors increased adherence to a Mediterranean-style, anti-inflammatory dietary pattern: The Rx for Better Breast Health Randomized Controlled Trial. *Breast cancer research and treatment*, 173(1), 145-154.