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THE EFFICACY OF APPLYING SOME PLANTS AND HERBS IN CANCER THERAPY FOR HUMANS AND ANIMALS – A COMPREHENSIVE REVIEW

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Abstract

Cancer is a challenging ailment and represents the main reason for death worldwide for humans and animals. Although great developments have hindered cancer progression, several adverse effects are associated with modern chemotherapy. Natural remedies, such as the usage of medicinal plant or their products in cancer treatment, may decrease prejudicial side properties. Recently, the modern research scheme and innovative screening practices for herbs or plants have enabled phytochemical discovery for the prevention and treatment of cancer. This criticism highlights herbs such as acacia, basil, black seeds, cedar, castus, ficus, garlic, ginger, indigo, onion, pomegranate, quince, and thyme, promising anticancer effects. The present review also revealed the mode of action of each herb as anticancer effects at level *in vitro* and *in vivo* studies. The item also totalizes the vital mechanisms and signaling molecules involved in preventing cancer diseases. This will fill the investigation gap in the exploration of using natural molecules and encourage researchers in clinical trials of anticancer agents from herbs for humans and animals.

Key words: herbs, plants, anticancer, tumor, therapy, natural remedies

Most people (70–80%) in the developing world depend on complementary or alternative medicine (World Health Organization, 2000). The World Health Organization (WHO) outlines alternative medicine as the entirety of the knowledge, practices and skills, according to the experiences, theories, and views indigenous to various cultures, whether justifiable or not, applied in the maintenance of health as well as in the diagnosis, prevention, enhancement or therapy of mental and physical diseases. Traditional or alternative medicine differs significantly from culture to culture and region to region, as they are affected by many features including history, culture, personal attitudes, and philosophy (WHO, 2000). Based on the WHO reports, the market value of herbal medications has also augmented tremendously in the last few years (WHO, 2019). Reports documented that the annual world market of alternative herbal medications was valued at $90 billion in 2015, while it was $200 000 and 1 300 000 in 2007 and 2009, respectively (WHO, 2019). There are many traditional medicines used worldwide, from Islamic medicine and Tibbs Nabawi or medicine of the Prophet (AlRawi and Fetters, 2012), that include herbs and plants of various biological events that may be beneficial for human health. In the current review, we will discuss the anticancer activity of some herbs and plants declared in the holy Quran and prophetic Hadith.

Recently, several scientific interpretations mentioned that herbal remedy is an important alternative tactic in the therapy of cancer (Dhanjal et al., 2021; Rana et al., 2021). These significant properties of some herbs in can-

cer therapy might be associated with their anticancer profits and other related pharmacological events, which have established a prodigious deal of consideration for their health usefulness (Roy et al., 2010; Khan et al., 2022). Moreover, herbal therapy preserves individuals' fertility and health, cures diseases, and even evades, inhibits, or reduces cancer progress without bringing toxicity or side effects (Khan et al., 2022; Muhammad et al., 2022). Studies indicated that more than 60% of cancer patients used herbs in their cancer therapy protocols (Khan et al., 2022; Muhammad et al., 2022; Tan et al., 2022). So, the present review article hypothesizes that using certain plants, herbs or their derivatives has a positive role in modern cancer therapy. In this criticism, we deliberate the uses of some herbs in the embattled therapy of cancer disease in various kinds of tumor cells based on anti-apoptotic or antioxidant agents, as well as facts on their toxicity and safety.

Cancer cell apoptosis

Carcinogenesis is an imbalance between cell development and cell death that accelerates cancer cell proliferation. Cancer can be observed as the result of a sequence of genetic fluctuations during which a normal cell is converted into a malignant one, while evasion of cell death is one of the indispensable fluctuations in a cell that causes this malignant transmutation (Hanahan and Weinberg, 2000). Hence, inhibition of apoptosis or its resistance is vigorous in carcinogenesis progression. Caspases are fundamental agents in the machinery of apoptosis, as they are both the initiators and executioners. Specifically, caspase enzymes can be activated through three pathways. The two generally described initiation tracks are irrelevant (or death receptor) and intrinsic (or mitochondrial) tracks of apoptosis.

Consequently, both tracks ultimately lead to a communal track or the execution stage of the apoptosis process. The third track's less well-recognized initiation is the intrinsic endoplasmic reticulum pathway (O'Brien and Kirby, 2008). Generally, the mechanisms by which cancer cells evade apoptosis may be regarded as the interrupted equilibrium of pro-apoptotic and anti-apoptotic mediators, reduced caspase function and weakened death receptor signaling. This imbalance between pro-apoptotic and anti-apoptotic elements promoted the survival and proliferation of cancer cells (Taylor et al., 2008).

Anticancer activities of some herbs and plants

Acacia (Acacia seyal)

In sub-Saharan Africa, the traditional system of medicine *Acacia seyal* is used to treat several ailments such as dermatosis, infertility, and cancers. The stem is also widely used to treat fungal infections, mainly genital yeast infections and as chewing sticks with antimicrobial activity. A bark decoction is applied alongside leprosy and dysentery diseases; as a stimulant and purgative agent; as an aphrodisiac with cytotoxic activity; as a pharmaceutical constituent in making emulsions and torches and as a masking agent for bitter substances (Gebriel, 2011). As reported by Roothaert and Franzel (2001), the usage of root decoction incorporated with leaves of *Combretum glutinosum* and curdled milk presented strong diuresis. As reported by various researchers, the anticancer activities of *A. seyal* are presented in Table 1.

Table 1. The potentiality of anticancer activities of *Acacia seyal* based on the *in vivo* and *in vitro* studies

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
Hydroethanolic extract	*In vitro*	MCF-7 cells-breast cancer cells	↑Cytotoxicity	(Zingue et al., 2018)
Hydroethanolic extract	*In vivo*	7,12-dimethylbenza-anthraceneDMBA-induced breast hyperplasia	↓Tumor progression	(Zingue et al., 2018)
Lectin	*In vitro*	Hepatocellular carcinoma (HepG-2), HCT-116 (colorectal carcinoma) and MCF-7 (breast cancer)	↓Bcl-2, ↑P53	(Patel et al., 2014)
Methanolic extract of leaves and branches	*In vitro*	A549 (lung carcinoma) and HepG-2 (hepatocellular carcinoma)	↑Cytotoxicity	(El-Hallouty et al., 2015)

Zingue et al. (2018) evaluated the *in vivo* and *in vitro* anticancer properties of hydroethanolic extract of *A. seyal* on breast cancer. The cytotoxicity action of *A. seyal* stem bark extract was estimated via a resazurin reduction test in different cell lines. The *A. seyal* extract meaningfully decreased tumor incidence in rats by 62.1% and 65.8% for 150 mg and 300 mg/kg doses, respectively. They also reported that the *A. seyal* extract showed IC50 of 100 in MCF-7 cells after 24 h. Moreover, *A. seyal* showed substantial protection against DMBA-brought breast hyperplasia in rats, with an optimum result at 300 mg/kg level.

Likewise, the cytotoxicity of the recombinant lectin extracted from *A. sayel* was executed on MCF-7 (breast cancer), HepG-2 (hepatocellular carcinoma), HEP-2 (larynx cancer) and HCT-116 (colon cancer) as reported by Patel et al. (2014). The purified lectin displayed a noteworthy cytotoxic property on MCF-7 cells, with the IC_{50} values for 100 µg/ml and 250 µg/ml for HepG-2 cells and MCF-7, respectively. According to the previous work, the lectin isolated form *Acacia* has beneficial anticancer properties, especially at a high dose of 100 µg/ml. Some of the mechanisms involved are suppression of the Bcl-2 and decreased expression of P53. Hence, *A. sayel* established possible cytotoxic events on the cancer cells HCT-116 (colorectal carcinoma), MCF-7 (breast adenocarcinoma), A549 (lung carcinoma) and HepG2 (hepatocellular carci-

noma). El-Hallouty et al. (2015) also confirmed the anticancer activities of *A. sayel* at 1000 µg/ml against several cancer cells, although the authors reported low activities that were less than 75% cytotoxicity.

Basil: sweet basil (Ocimum basilicum) and holy basil (Ocimum sanctum)

Basil (family *Lamiae*) is a prevalent herb incorporated with countless varieties of food preparations in Mediterranean diets. For a long time, basil has been considered one of the main essential oils-producing species connected to the genus *Ocimum* (Mohammadi et al., 2014). Moreover, studies have shown that basil and its extracts are also applied in the industrial trade, including pharmaceutical and cosmetic products (Grayer et al., 2002). Many studies have been published on the biological activities, including antibacterial, anti-inflammatory and antioxidant actions of basil essential oils and its components (Liu et al., 2012; Mehana et al., 2020; Khafaga et al., 2019). Basil essential oils present several active components, such as eugenol, geraniol, linalool, methyl chavicol and thymol, showing several biological properties. Many investigated the antimicrobial action of eugenol with analgesic action for humans (Koeduka et al., 2006) and the antioxidant action of geraniol and linalool (Liu et al., 2012).

Others examined the usage of thymol, methyl chavicol, and linalool for skin protection alongside all causes of environmental skin aggressors and handling of different dermatological syndromes (Huang et al., 2015). Essential basil oils are also used in folklore medicine to manage various human disorders such as cardiovascular and diabetes diseases (Zeggwagh et al., 2007). Basil has antioxidant, antimicrobial and antitumor activities. Because basil is widespread worldwide, it is easy to discover the potential activity of its essential oils. These biological properties of basil or its essential oil might be attributed to its aromatic compounds and phenolic acids (Zeggwagh et al., 2007; Zarlaha et al., 2014).

Taie and Radwan (2010) studied the upshot of the essential oils of sweet basil obtained from Egypt, which are extracted by hydro-distillation of the basil leaves. Results showed the activity of the essential oils on a line of *Ehrlich ascites* carcinoma cells (EACC), where different doses of the essential oils highly influenced the viability of these cancer cell lines by measuring the % of dead cells. Mahmoud (2013) studied the anticancer activities of basil essential oils (*in vitro* and *in vivo*). The previous study exhibited that incubating NB4 and HL-60 cells with basil essential oils at levels of 25–200 µg/ml for 24 h decreased these cells' viability. It was indicated that the basil essential oil (200 µg/ml) induced the highest HL-60 dead cell (82.33%), as mentioned by Mahmoud (2013). Moreover, administration of EACC with basil essential oils at levels of 25–200 µg/ml for 12 h decreased the viability percentages of these cells. *In vivo* results showed that basil leaf extract chemo-preventive action was manifest from the deceased tumor burden (the average number of papillomas/mouse) and the deceased proportion of tumor-bearing mice (Zeggwagh et al., 2007; Zarlaha et al., 2014).

In an *in vitro* experiment, Karthikeyan et al. (1999) studied the anticancer activity of *O. sanctum* alongside HFS cells (human fibrosarcoma cells). They found that ethanolic extract of *O. sanctum* produced cytotoxicity impacts on HFS cells at 50 µg/ml levels. The cells exhibited shrunken cytoplasm, condensed nuclei, DNA fragmentation, augmented lipid peroxidation levels, and depleted intracellular glutathione for the cytological attributes. Moreover, treating mice bearing solid sarcoma tumors with ethanolic and aqueous extracts of *O. sanctum* interceded a substantial decrease in tumor volume and an augment in lifespan (Sridevi et al., 2016). Based on the potential previous effects, it is clear that *O. sanctum* extract has anticancer activity.

Sridevi et al. (2016) studied the properties of alcoholic root extract of *O. sanctum* in NCI-H460 (human non-small cell lung carcinoma cell) by the generation of ROS, cell viability assay, mitochondrial membrane potential and apoptotic morphological changes. Administration of NCI-H460 cells with 150 µg/ml of *O. sanctum* extracts showed the lowest cell viability. Moreover, the *O. sanctum* extract (25–100µg/ml) presented a substantial augment in ROS synthesis, inhibited cell viability, increased apoptotic cell, loss of mitochondrial membrane potential, and colony-making ability in NCI-H460 cells. It is interesting to note that *O. sanctum* triggered loss of NCI-H460 cell, which is the potentiality of its anticancer activity. In another experiment, Magesh et al. (2009) confirmed that *O. sanctum* brings apoptosis in A549 cells via a mitochondrial caspase-dependent way and hinders the *in vivo* (animal model) development of Lewis lung carcinoma, indicating that *O. sanctum* can be useful for treating lung carcinoma as a chemo-preventive agent. Additionally, the study implemented by Kwak et al. (2014) recommended that the anti-metastatic machinery of *O. sanctum* is interceded by repression of PI3K/Akt in osteopontin-treated lung cancer cells (NCI-H460). Table 2 lists *in vitro* and *in vivo* studies that show basil's anticancer activities (*O. basilicum*).

Several scientific experiments indicated that *O. basilicum* extract or its essential oils showed cytotoxicity effects on MCF-7 or MDA-MB-231 via induction of apoptosis pathways, including caspase-3, bax, bcl-2, and p53 genes, as well as induced anaphase/telophase stages along with F-actin aggregation (Arshad Qamar et al., 2010; Behbahani, 2014; Mohammadi et al., 2014). These consequences support the antiproliferative and anticancer activities of *O. basilicum* extract against numerous types of cancer cell lines. Zarlaha et al. (2014) examined the antiproliferative action of ethanolic extract and the essential oil of *O. basilicum* alongside four various cancer cell lines in humans: FemX cells (melanoma), HeLa cells (cervix adenocarcinoma), SKOV3 cells (human ovarian) and K562 cells (chronic myelogenous leu-

kemia). The dominant elements of the extract are caffeic and rosmarinic acids, while the most abundant elements in the essential oil are linalool, eugenol, and isoeugenol. Those phytochemicals displayed noteworthy cytotoxic action alongside human ovarian cancer (SKOV3) cell lines. Curiously, caffeic acid was reported to be in the identical choice with cisplatin alongside the four cell lines displaying substantial anticancer properties. At the same time, isoeugenol showed a higher cytotoxic effect than eugenol. Moreover, depending on the *in silico* modeling experiments, the isoeugenol molecule can efficiently constrain cyclooxygenase and lipoxygenase enzymatic action. Mechanisms of action of acacia and basil are illustrated in Figure 1.

Black seed *(Nigella sativa)*

Nigella sativa seed (black cumin or black seed) is an annual flowering herb found in many countries worldwide, such as southern Europe and the Middle Eastern Mediterranean (Khare, 2004). Seeds of *N. sativa* and their oil have been broadly applied for several culinary or therapeutic applications. *N. sativa* has biological and therapeutic activities as an antioxidant, antimicrobial, analgesic, anti-inflammatory, diuretic, renal protective, antihypertensive, antidiabetic, immunomodulatory, bronchodilating, gastroprotective, hepato-protective, and anticancer (El-Far, 2015; El-Far et al., 2017). Although they contain a complex mixture of several compounds, thymoquinone (TQ) is undoubtedly its major active ingredient (Hajhashemi et al., 2004). TQ has been described to possess potent anti-inflammatory effects, such as in cases of encephalomyelitis, edema, colitis, and arthritis via the reduction of inflammatory prostaglandins and leukotrienes (Hajhashemi et al., 2004), and anti-tumoral activity (El-Far, 2015) (Table 5).

Table 2. The *in vitro* and *in vivo* studies showing the anticancer activities of basil (*Ocimum basilicum*)

Plant	Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
Sweet Basil (*Ocimum basilicum*)	Essential oils (crude)	*In vitro*	A line Ehrlich ascites carcinoma cells (EACC)	↓Cell viability	(Taie and Radwan, 2010)
	Essential oils (crude)	*In vitro* and *in vivo*	Human promyelocytic leukemia cell lines (HL-60 and NB4) and Ehrlich ascites carcinoma cells, EACC (animal model cancer cells)	*In vitro*: ↑cytotoxicity *In vivo*: ↓Tumor development and tumor volume of mice	(Mahmoud, 2013)
	Methanolic extract and active compound (ursolic acid)	*In vitro*	Human breast cancer cells (MCF-7 cell lines)	↑Apoptosis	(Arshad Qamar et al., 2010)
	Crude essential oils from leaves	*In vitro*	Human breast cancer cells (MCF-7 cell lines)	↑Apoptosis	(Mohammadi et al., 2014)
	Crude essential oils	*In vitro*	MCF-7 and MDA-MB-231 (breast cancer cell lines)	↑Apoptosis	(Behbahani, 2014)
	Ethanolic extract and the essential oil	*In vitro*	HeLa cells (cervix adenocarcinoma), FemX cells (melanoma), SKOV3 cells (human ovarian cancer) and K562 cells (chronic myelogenous leukemia)	↑Cytotoxic	(Zarlaha et al., 2014)
Holy Basil (*O. sanctum*)	Ethanolic and aqueous extract of the basil leaves	*In vitro* and *in vivo*	HFS cells (human fibrosarcoma cells) Sarcoma-180	*In vitro*: Morphologically the cells showed condensed nuclei and shrunken cytoplasm ↓intracellular GPx and increased ROS *In vivo*: ↓Tumor volume	(Karthikeyan et al., 1999)
	Ethanolic root extract	*In vitro*	NCI-H460 (non-small-cell lung cancer cell lines)	↓Cell viability ↓Colony forming capacity	(Sridevi et al., 2016)
	Ethanolic root extract	*In vitro*	A549 cells (adenocarcinomas' human alveolar basal epithelial cells)	↑Apoptosis	(Magesh et al., 2009)
	Ethanolic root extract	*In vitro*	NCI-H460 cell line	↓PI3K/Akt	(Kwak et al., 2014)

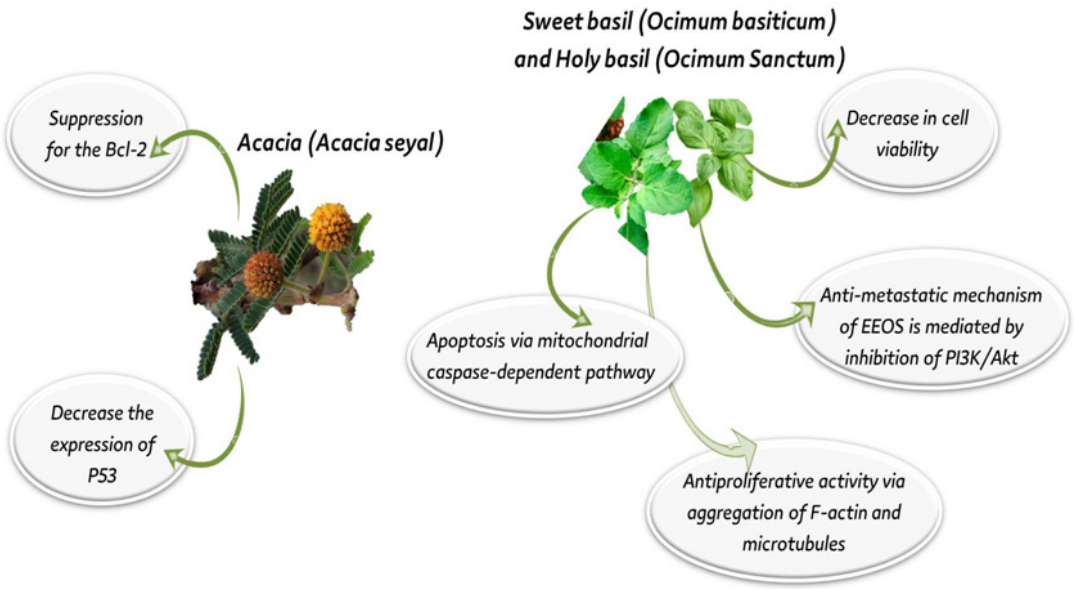


Figure 1. Anti-cancer mechanisms of action of acacia and basil

Table 5. Anticancer activities of *C. speciosus*

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
Diosgenin	*In vitro*	HepG2, HL-60, Saos-2 and MCF-7	Inhibition in the cell viability and induction of apoptosis	(Selim and Al Jaouni, 2016)
Dioscin	*In vitro*	Hela	Induction of apoptosis	(Selim and Al Jaouni, 2016)
Methanol and hexane extracts (leaves)	*In vitro*	HepG2, THP-1, and WI-38	Inhibition of cell proliferation	(Selim and Al Jaouni, 2015)
Costunolide	*In vitro* and *in silico*	MCF-7 and MDA-MB-231	Induction of apoptosis and Inhibition in the cell viability	(Pitchai et al., 2014) (Roy and Manikkam, 2015)
Methanol extract (leaves)	*In vitro*	HepG2	Cell proliferation inhibition using MTT	(Singh et al., 2016)

In breast tissue, it has promoted apoptosis via activation of the p38 phosphorylation MDA-MB-231 xenograft mice (Woo et al., 2013). Also, other molecular mechanisms, including the downregulation of Akt and XIAP that promoted the expression of caspase-3, Bax, apoptosis index factor (AIF), cytochrome c and p27 genes in MCF-7 and breast cancer (MDA-MB-231) cells (Rajput et al., 2013). Furthermore, *in vitro* results showed an elevated expression of PPAR-γ activity and lower expression of some related apoptosis genes, including *Bcl-2, Bcl-xL*, and survival in breast cancer cells (Woo et al., 2013). Other studies on lung cancer showed decreased expression of LPS-induced NF-B expression (Jafri et al., 2010). The bulk of scientific research on colon and colorectal cancers *in vivo* and *in vitro* has been recently addressed. In a study by Jrah-Harzallah et al. (2013) Wistar rats showed repressed DMH-induced oxidative stress and colon tumorigenesis, confirming the results from other studies in xenograft mice model of HCT-116 colon cancer cells (Shoieb et al., 2003; Gali-Muhtasib et al., 2008). in DLD-1 human colon cancer cells, TQ promoted the reduction in the generation of ROS and phosphorylation of JNK and ERK and elevated activity of caspase-3 and -7 (El-Najjar et al., 2010). Different animal models have been used to investigate the molecular mechanisms and potential therapeutic effects of TQ on hepatocellular carcinoma (HCC), such as rats, mice and rabbits (Nagi and Almakki, 2009; Sayed-Ahmed et al., 2010; El-Sayed, 2011; Elbarbry et al., 2012; Raghunandhakumar et al., 2013; Ashour et al., 2014). In Sprague Dawley rats, Al-Dalaen (2014), extensive studies have shown lowered activities of CYP1A1 and CYP2E1 in different tissues such as liver, lung and stomach tissues. Prostate cancer in vitro data showed a reduction in androgen receptors, E2F-1- and E2F-1-regulated proteins (Kaseb et al., 2007).

Hydroalcoholic extract, n-hexane, and ethyl acetate fraction in vitro recent research showed a lowered viability of the ACHN cell in a dose- and time-dependent manner without considerable cytotoxicity in the slandered renal epithelial cell (Shahraki et al., 2015, 2016). Other black seed preparations, such as the lipid fraction and aqueous extract, were cytotoxic to MCF-7 cells at low concentrations and improved the antitumor property of doxorubicin in breast cancer cells (MCF-7) (Mahmoud and Torchilin, 2013). Table 3 depicts different studies that demonstrated the potential anticancer activities of *Nigella sativa*.

Table 3. Anticancer activities of *Nigella sativa*

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
1	2	3	4	5
TQ	*In vivo*	MDA-MB-231 xenograft mice (breast cancer)	↑p38, ↑ROS	(Woo et al., 2013)
	In vivo	MCF-7 and MDA-MB-231 (xenograft breast cancer mice)	↓XIAP, ↓Akt , ↑p27, ↑caspase-3 ↑Bax, ↑cytochrome c, ↑AIF,	(Rajput et al., 2013)
	In vivo	Lung cancer	↓LPS-induced NF- B expression	(Jafri et al., 2010)
	In vivo	Colon cancer	↓DMH-brought ROS and colon tumorigenesis in Wistar rats	(Jrah-Harzallah, et al., 2013)
	In vivo	Mice model of HCT-116 colon cancer cells	↓growth of tumor cells	(Gali-Muhtasib et al., 2008)
	In vivo	Colon cancer	↓DMH-induced colon cancer promotion	(Jrah-Harzallah, et al., 2013)
	In vivo	Colorectal cancer (HCT-116) cells and osteosarcoma cells	↑p21 expression G1 phase cell cycle arrest	(Shoieb et al., 2003)
	In vivo	Hepatocellular carcinoma	↑expression of p21 ↓expression of cyclin D1, and E. ↓Cdk4, ↓Ki67, ↓PCNA in hepatic tissues of rat; ↓the cyclinD1, ↓cyclin E, ↓PCNA in NDEA-induced rats	(Raghunandhakumar et al., 2013)
	In vivo	Male Wistar albino rats	Restored DENA-induced depletion of glutathione, reduced hepatic enzyme activities including ↑CAT, ↑GPx, ↑GST, and down-regulation of some genes	(Sayed-Ahmed et al., 2010)
	In vivo	HepG2 cells	G2/M phase cell cycle arrest ↓p50, ↓p65, ↓IL-8, ↓CXCR1, and ↓CXCR2, ↑caspase-9, ↑caspase-3, ↑PARP, ↑TRAIL, ↓NF-B, ↓Bcl-2	(Ashour et al., 2014)
	In vivo	Sarcoma 80 xenograft mice	Mixture with diosgenin ↓tumor mass ↓volume and ↑apoptosis	(Das et al., 2012)
	In vitro	MCF-7, MDA-MB-231 and BT-474 (breast cancer cell lines)	↑apoptosis ↑caspases-8, ↑caspases-9, ↑caspases-7 ↑PPAR-γ, ↓Bcl-xL, ↓Bcl-2, and ↓survivin	(Woo et al., 2013)
	In vitro	HTLV-I-negative T-cell lymphomas	Induced mitochondrial-mediated apoptosis via generation of ↑ROS	(Dergarabetian et al., 2013)
	In vitro	NCI-H460 and NCI-H146 cells	Promoted apoptosis and suppressed the synthesis of ↓Gro-alpha and ↓ENA-78	(Jafri et al., 2010)
	In vitro	Primary effusion lymphoma	Induced mitochondrial-mediated apoptosis and TRAIL via deactivation of↑ROS and ↓Akt	(Hussain et al., 2011)
	In vitro	Prostate cancer	↓the development of G1 to S phase LNCaP prostate cancer cells ↓androgen receptors, ↓E2F-1, ↓E2F-1-regulated proteins such as cyclin A, Cdk-2, and Cdk-4	(Kaseb et al., 2007)
	In vitro	p53-null MG63 and p53-mutant MNNG/HOS (human osteosarcoma cells)	↑G2/M arrest ↑p21WAF1	(Roepke et al., 2007)

Table 3 – contd.

1	2	3	4	5
	In vitro	p53-null myeloblastic leukemia HL-60 cells	↑caspases-8,3,9, and ↑Bax/Bcl-2 ratio	(El-Mahdy et al., 2005)
	In vitro	Human colorectal cancer cells (HCT-116)	G0/G1 arrest ↑p53 ↑Bax/Bcl-2 ratio	(Gali-Muhtasib et al., 2004)
	In vitro	Mouse papilloma carcinoma cells (SP-1)	G0/G1 arrest, ↑p16, ↓cyclin D1 G2/M arrest, ↑p53, ↓cyclin B	(Gali-Muhtasib et al., 2008)
	In vitro	Colorectal cancer cells (p53-null HCT-116 cells)	↑apoptosis	(Gali-Muhtasib et al., 2008)
	In vitro	U266 multiple myeloma cells	↓STAT3 ↓cyclin D1, ↓Bcl-2, ↓Bcl-xl, and ↓survivin ↓Src, ↓Akt and ↓Jak2 ↓VEGF	(Li et al., 2010)
	In vitro	FG/COLO357 (pancreatic cancer cells)	↓migration of cancer cells ↓Mucin-4, and ↑JNK	(Torres et al., 2010)
	In vitro	KBM-5 human myeloid cells	↓NF-kB-regulated gene products and ↓NF-kB activation, ↓TNFα-induced expression of ↓VEGF, ↓expression of MMP-9, ↓transcripts of XIAP, Bcl-xl, Bcl-2, IAP2, IAP1, and survivin	(Sethi et al., 2008)
	In vitro	M059J and M059K glioblastoma cells	↓telomerase and caused telomere attrition	(Gurung et al., 2010)
	In vitro	DLD-1 human colon cancer cells	↓phosphorylation of ERK and JNK ↑activation of caspase-3, and -7 and ↑generation of ROS	(El-Najjar et al., 2010)
	In vitro	SiHa human cervical squamous carcinoma cells	↓expression of Bcl-2, ↑expression of p53; ↑Sub-G1 arrest	(Ng et al., 2011)
	In vitro	MCF-7 cells	↓mRNA expression of CYP 1A1 and UGT1A8	(Motaghed, et al., 2014) (Kundu et al., 2014) (Rajput et al., 2013)
	In vitro	HaCaT cells	↑Protein and mRNA expression of HO-1	(Kundu et al., 2014)
	In vitro	Breast cancer cells (T47D and MDA-MB-468)	↓expression of cyclin D1, E, Bcl-2 and survivin ↑expression of p27; ↑Bax, ↑cytoplasmic cytochrome c; ↑caspase 3 Induced G1 phase cell cycle arrest ↓phosphorylation of GSK3, PTEN, Akt, and PDK1	(Rajput et al., 2013)
	In vitro	PBD of Plk1; HeLa	Induction of mitotic arrest, ↓Polo box domain function, Plk1 activity. meddling with Plk1 localization to centrosomes	(Reindl et al., 2008)
	In vitro	Multiple myeloma cells	phosphorylation of STAT3, ↓expression of Bcl-2 and Bcl-xl. ↓F-actin polymerization	(El-Far et al., 2016)
	In vitro	HeLa cells	↓expression of NF-B. ↑pro-apoptotic genes, CASP1, BIK, FASL	(Sakalar et al., 2013)
	In vitro	A431 and Hep2 cells	↓phosphorylation of JNK and Akt ↑Sub-G1 arrest and TUNNEL positivity; ↑cytochrome c,↑Bax/Bcl-2 ratio, and activation of caspases	(Das et al., 2012)
	In vitro	Human neuroblastoma cells	↓XIAP and VEGF proteins, ↓expression of XIAP ↓mitochondrial membrane potential. ↑Bax/Bcl-2 ratio; ↑activation of caspase-9 and -3.	(Paramasivam et al., 2012)
	In vitro	Glioblastoma cells	↓Secretion and activity of MMP-9 and -2, ↓phosphorylation of ERK and↓FAK.	(Kolli-Bouhafs et al., 2012)

Table 3 – contd.

1	2	3	4	5
	In vitro	Pancreatic ductal adenocarcinoma (PDA) cells	↓histone deacetylase (HDAC) activity, PDA, MCP-1, ↓Cox-2, ↓TNF-alpha, and ↓interleukin (IL)-1beta. ↑histone hyperacetylation, ↑p21 WAF1 expression.	(Chehl et al., 2009)
	In vitro	Human HL-60 leukemia, 518A2 melanoma, multidrug-resistant KB-V1/Vbl cervix, and MCF-7/ Topo breast carcinomas, non-malignant human foreskin fibroblasts	↑ROS and ↑apoptosis related to DNA tearing, ↓MMP and	(Effenberger et al., 2010)
	In vitro and *in vivo*	Gastric cancer cells	↓Tumor growth in xenograft mice and ↑5-FU-induced apoptosis.	(Lei et al., 2012)
	In vitro and *in vivo*	SaOS-2 cells and mice	↓Expression of CD34, NF-B, and VEGF.	(Peng et al., 2013)
Lipid fraction and aqueous extract	*In vitro*	Human MCF-7 breast cancer cells	Cytotoxic to MCF-7 cells at low concentrations ↑Antitumor activity of doxorubicin	Mahmoud and (Torchilin, 2012)
Hydroalcoholic extract of *N. sativa*	*In vitro*	Human renal adenocarcinoma (ACHN) and normal renal epithelial (GP-293 cell lines)	↓Cell viability of ACHN. Apoptotic effect of total extract in ACHN cells compared with the GP-293 cells	(Shahraki et al., 2015)
Hydroalcoholic extract (30% distilled water and 70% alcohol)	*In vitro*	ACHN cell (normal renal epithelial).	↓ACHN cell viability and no cytotoxicity in GP-293 cells	(Shahraki et al., 2016)
Seeds of *N. sativa* in combination with *Smilax glabra* rhizome and *Hemidesmus indicus* root	*In vitro*	Hepatocarcinogenesis	↓liver cancer in male Wistar rats ↓number of cells/cm2 of the positive foci ↓DEN-induced GST-P positive foci	(Iddamaldeniya et al., 2003)
N. sativa plant extract	*In vitro*	Human hepatoma HepG2 cells	↓DNA synthesis induced cell apoptosis and/or necrosis	(Thabrew et al., 2005)
N. sativa extracts	*In vitro*	Human breast cancer MDA-MB-231 cell	↓the proliferation of human breast cancer cells through the induction of apoptosis	(Dilshad et al., 2012)
Aqueous and alcohol extracts	*In vitro*	MCF-7 breast cancer cells	↓the potency and survival	(Farah and Begum, 2003)
A crude gum, a fixed oil and two purified components of *N. sativa* seed, TQ, and dithymoquinone	*In vitro*	MDR (human tumor cell lines)	Cytotoxic effect through ↑cell accumulation	(Worthen et al., 1998)
N. sativa seed oil (NSO)	*In vivo*	Colon carcinogenesis in Fischer 344 rats	↓cell proliferation in the colonic mucosa	(Salim and Fukushima, 2003)
	In vitro	HEK293, MCF-7, A-549 and HepG2 cell lines	↓percentage cell viability of MCF-7, A-549, and HepG2 cells, ↓GSH, ↓MMP, ↓bcl-2 ↑ROS, LPO , ↑p53, caspase-3, 9, and bax.	(Al-Oqail et al., 2017)
	In vitro	Human fibrosarcoma cell line, HT1080	↓u-PA (urokinase-type plasminogen activator) ↓PAI-1 (plasminogen activator inhibitor type 1) ↓t-PA (type plasminogen activator)	(Awad, 2005)
	In vitro	Human monocyte and macrophages	↓cell growth and differentiation in monocyte and monocyte-derived macrophage	(Mat et al., 2011)

An experiment on male Wistar rats found that the mixture containing seeds of *Smilax glabra rhizome*, *N. sativa*, and *Hemidesmus indicus* root has repressed hepatocarcinogenesis (Iddamaldeniya et al., 2003). Another mixture containing crude gum (as a fixed oil) and both dithymoquinone and TQ of *N. sativa* seed produced a cytotoxic effect through increased cell accumulation in parental and multi-drug resistant (MDR) human tumor cell lines (Worthen et al., 1998). Finally, numerous *in vivo* and *in vitro* data promoted the high therapeutic

value of *N. sativa* seed oil in the induction of apoptosis and repression of cell proliferation in the colonic mucosa (Salim and Fukushima, 2003), HEK293, A-549, HepG2, and MCF-7 cell lines (Al-Oqail et al., 2017), human fibrosarcoma cell line, HT1080 (Awad, 2005), and human monocyte and macrophages (Mat et al., 2011).

Cedar (*Cedrus libani*)

Cedrus libani is one of the four *Cedrus* species (Pinaceae). *C. libani* and the other three naturally exist in the Mediterranean Sea area: *C. libani* in Turkey, Lebanon, and Syria, *C. atlantica* in Morocco and Algeria, and *C. deodara* in the Himalaya Mountains, while *C. brevifolia*, on Cyprus Island (Abd El-Hack et al., 2016, 2018, 2020, 2021). It is a perpetual tree with a thick branch extended horizontally, a short and wide trunk, and a broad corona with a pyramidal shape. The length of this plant reaches 20–40 m and up to 3 m in diameter, with glaucous blue-green leaves (8–25 mm), with a life as long as 1500–2000 years (Kurt et al., 2008). *C. libani* has been reported to have various biological activities; tar is obtained from its steam wood and resinous root, and it generally possesses antibacterial and insecticidal activities (Saeed et al., 2017, 2018; Abdel-Moneim et al., 2020; Reddy et al., 2016). Other studies revealed its antiulcerogenic properties (Yeşilada et al., 1999). Anticancer activities of *C. lebani* are summarized in Table 4.

It was reported by Saab et al. (2011) that *C. libani* ethanol and chloroform seed extract brought erythroid differentiation and growth restraint in K562 cells (human chronic myelogenous leukemia cells) with IC_{50} of 40.57 µg/mL and 69.20 µg/mL respectively. The essential oil of *C. libani* also persuaded erythroid differentiation and growth inhibition in K562 cells with IC_{50} of 23.38 µg/mL (Saab et al., 2012).

The 2-himchalene-7-ol (2HC7), a white crystalline solid (125 mg, 0.3%), was isolated from the oil of *C. libani* by Taleb et al. (2014). The isolated $2HC_7$ was then confirmed alongside colon (Caco-2) or brain (SF) cancer cells at different levels extending between 1 and 25 ug/mL. Results showed a noteworthy anti-proliferative property with IC99 values ranging between 11 and 13 ug/mL and IC50 values extending between 5 and 7 ug/mL (Taleb et al., 2014). Furthermore, the essential oil of *C. libani* was also cytotoxic alongside drug-sensitive CCRF/CEM acute lymphoblastic leukemia cells and their multidrug-resistant P-glycoprotein-expressing subline, CEM/ADR5000 (Saab et al., 2012).

Costus (*Costus speciosus*)

Costus speciosus (Family: Costaceae) is an important medicinal plant known as spiral ginger. *C. speciosus* is broadly applied as a folk medicine for treating various complaints (Pawar and Pawar, 2014). It is widespread in tropical and subtropical regions of Africa, the Americas, and Asia, particularly in India, Indonesia, Sri Lanka, and Malaysia (Specht and Stevenson, 2006; El-Far et al., 2016).

The rhizomes of the plant are characterized as bitter and astringent. Pharmacological studies showed that the rhizomes and root parts of *C. speciosus* possess antioxidant, anti-stress, antibacterial, antifungal, and anti-inflammatory properties (Selim and Al Jaouni, 2015). Otherwise, the leaf extract of *C. speciosus* was shown to have probable *in vitro* anticancer action concerning hepatic cancer (El-Far et al., 2016). Additionally, *C. speciosus* is a significant source of many molecules possessing different pharmacological incomes, such as saponins, B-sitosterol; diosgenin, dioscin, and prosapogenins A and B of dioscin, γ-tocopherol, among others. Moreover, the major compound of *C. speciosus* oil was found to be costunolide (Selim and Al Jaouni, 2015). The therapeutic properties of *C. speciosus* extracts may be accredited by using various ingredients such as flavonoids, alkaloids, sesquiterpenes, and saponins. All conceivable up-regulation of cellular apoptotic mediators as caspases, p21, p27, p53, reactive oxygen species generation and others, characteristic of the anticancer properties of *C. speciosus* toward the down-expression of the anti-apoptotic mediators (El-Far et al., 2016). As seen in Table 5, we summarized the potential anticancer activities of *C. speciosus* according to the *in vivo* and *in vitro* experiments.

Table 4. Anticancer activities of *C. lebani*

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
Ethanol and chloroform seed extract	*In vitro*	in K562 cells (human chronic myelogenous leukemia cells)	↓Cell growth	(Saab et al., 2011)
Essential oil	*In vitro*	in K562 cells (human chronic myelogenous leukemia cells)	↓Cell growth	(Saab et al., 2012)
Essential oil	*In vitro*	CCRF/CEM acute lymphoblastic leukemia cells and CEM/ADR5000 (multidrug-resistant P-glycoprotein-expressing subline)	↓Cytotoxicity effect	(Saab et al., 2012)
2-himachalene-7-ol	*In vitro*	SF (brain cancer cells) and Caco-2 (colon cancer cells)	↓Proliferation	(Taleb et al., 2014)

Diosgenin and dioscin have been reported to have anticancer activity and are considered of great interest to the pharmaceutical industry (Selim and Al Jaouni, 2016). Indeed, diosgenin induces apoptosis and inhibits cell viability in different cancerous cells (HepG2, HL-60, and MCF-7 and Saos-2) (Selim and Al Jaouni, 2015). Si milarly, the anticancer activity via apoptosis induction and cell viability inhibition was described for Costunolide in MDA-MB-231 and MCF-7 cells, shown in *in vivo* and *in silico* assays (Pitchai et al., 2014; Roy and Manikkam, 2015). On the other hand, dioscin – a derivative from diosgenin – was described to induce apoptosis in HeLa cells through cyclooxygenase activity in osteosarcoma cells (Selim and Al Jaouni, 2016). Methanol and hexane extracts of *C. speciosus* leaves were reported to have *in vitro* anti-proliferative effects on HepG2, WI-38, and THP-1 cells by inhibiting cell proliferation (Selim and Al Jaouni, 2015; Singh et al., 2016). The possible mechanisms of action of the black seed, *Cedrus libani*, and *Costus speciosus* are illustrated in Figure 2.

Ficus (*Ficus carica*)

Ficus (*Ficus carica*) is one of the copious kinds of medicinal plants comprised of about 800 species of shrubs, woody plants and trees mostly found in tropical and subtropical regions worldwide (Herre et al., 2008). Ficus represents one of the most common traditional Mediterranean plants in the Moraceae family. *F. carica* tree normally has 15–20 ft with several spreading branches and a trunk more than 7 ft in diameter (Chawla et al., 2012). The utmost imperative species of *Ficus* are *F. racemose, F. elastica*, *F. bengalensis,* and *F. carica*. Almost all plant portions, such as leaves, fruits, bark, shoots, latex and seeds, are medicinal. The *Ficus* is a beneficial health plant applied widely in different industrial and pharmaceutical uses. This feature is due to its richness in vitamins, micro and macro minerals, water, fats and various phytochemicals such as flavonoids, phenol, terpenoids, and other sources of calcium and fiber (Caliskan, 2015). Hence, the hepatoprotective, antioxidant, antidiabetic, anticancer, antiplatelet, anthelmintic, diuretic, hypolipidemia, and immunity activities of *Ficus* have been studied by various investigators (Singh et al., 2016).

Several studies have reported the anticancer activities of ficus (Table 6). The constituents of ficus comprise a combination of 6-O-acyl-beta-D-glucosyl-beta-sitosterols, the acyl moiety being mainly linoleyl and palmitoyl with minor amounts of oleyl and stearyl, displayed powerful cytotoxicity properties on various cell line cancer cells (Rubnov et al., 2001). The *F. carica* fruits and leaves latex also showed antiradical activity and antiproliferative activity against A375 (human melanoma cell line) after exposing to irradiation at a specific UVA at minimum IC50 values (Menichini et al., 2012). The anti-proliferative action of *F. carica* latex and *F. carica* latex-temozolomide mixture was examined in several cell lines, such as U-87 MG, T98G, and U-138 MG glioblastoma.

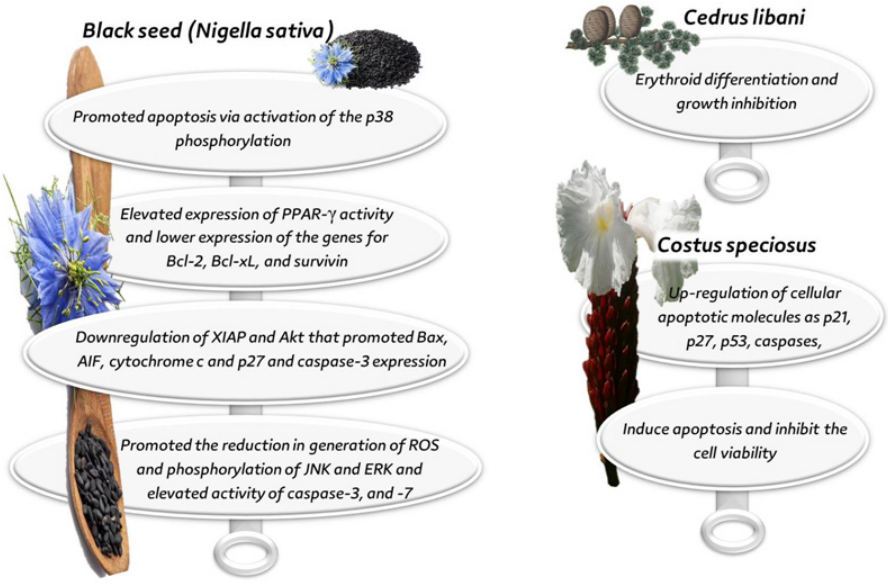


Figure 2. The possible mechanisms of action of black seed, *Cedrus libani* and *Costus speciosus*

Table 6. Anticancer activities of *Ficus*

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
6-O-acyl-beta-D-glucosyl-beta-Sitosterols	*In vitro*	Lymphoma cell (Raji Burkitt B), DU-145 prostate cancer and MCF-7 cells, Burkitt B cell lymphoma (DG-75), Jurkat T-cell leukemia	Not reported	(Rubnov et al., 2001)
Latex-temozolomide mixture	*In vitro*	U-138 MG, T98G, and U-87 MG glioblastoma	Cell death	(Tezcan et al., 2015)
Leaves, bark and wood extracts	*In vitro*	Human melanoma	↓proliferation	(Conforti et al., 2012)
Bergapten and psoralen from *F. carica* leaves	*In vitro*	Triple-negative breast cancer (MDA-MB-231 cells)	Not reported	(Zhang et al., 2018)
Ficutirucins A-I but ficutirucins A, B, C, F, G and I possessed anticancer effects	*In vitro*	MCF-7, HepG-2, and U2OS	↓Cytotoxicity effect	(Jing et al., 2015)

F. carica latex administration produced substantial cell death in glioblastoma multiforme cells with various responses to *F. carica* latex-temozolomide mixture (Tezcan et al., 2015). Khodarahmi et al. (2011) also affirmed the anticancer properties of *F. carica* latex on human cancer cells using HeLa cell line *in vitro* using the MTT assay. Leaves were revealed to have repression of peroxidation and the highest anti-radical action with IC_{50} values of 1.48 and 64 µg/ml, respectively. Conforti et al. (2012) found that the leaves had the maximum anti-proliferative action with an IC_{50} value of 3.92 µg/mL. Psoralen and bergapten are the dominant active molecules in *F. carica* leaves with general anticancer action on MDA-MB-231 (triple-negative breast cancer cells), representing that these two components might show imperative function in anticancer activities of *F. carica* leaves (Zhang et al., 2018). Likewise, the anticancer efficiency of ethanolic extract of pulverized fruit of *F. carica* was examined on breast cancer cell lines MCF-7. The extract presented robust anti-tumor actions at 85.5 and 89% suppression after 24 and 48 hours, respectively, at levels of 1000 µg/mL, while the low level showed the proportion inhibition was 76, 80.5 and 82.5% at 24, 48, and 72 hours, respectively (Jasmine et al., 2015). Jing et al. (2015) examined the cytotoxic activities of many molecules isolated from *F. carica* fruits, ficutirucins A-I, and these molecules exhibited moderate cytotoxic actions with IC_{50} values of 11.67–45.61 µM alongside many cancer cell lines in human such as U2OS, MCF-7, and HepG-2.

Garlic (*Allium sativum*)

Garlic (*Allium sativum* L.), originally from Asia, is a bulbous plant that can easily grow in mild climates. Garlic has played an important dietary role as a spice and food additive (Eja et al., 2007). Garlic can be consumed in the form of raw garlic, raw garlic homogenate, an aqueous extract of garlic, garlic oil, crushed or chopped garlic and aged garlic extract. The main compound present in intact garlic is alliin. Alliinase enzyme produces allicin from alliin when garlic is chopped or crushed. Also, other sulfur compounds such as diallyl disulphide, S-allylcysteine, and diallyl trisulfide contribute to some of the garlic effects (Lanzotti et al., 2012). Several medicinal and therapeutic effects of garlic or garlic preparations have been reported. These effects range from improving detoxification of foreign compounds and hepatoprotection or cardiovascular protection to antioxidant effect, antimicrobial effect, or even suppressing the risks of cancer (Colín-González et al., 2012). Table 7 summarizes studies of the anticancer activities of garlic.

The cancer-preventive effects of garlic or its preparations that contain allylsulfide derivatives have been extensively reported. Some studies on garlic anticancer action have shown that it can be established via the modulation of several molecular mechanisms responsible for carcinogenesis, including DNA adduct formation, mutagenesis, cell proliferation and angiogenesis (Capasso, 2013). Both rodent and human studies have reported that garlic or its preparations can suppress the development of chemically encouraged tumors in hepatic tissues (Kweon et al., 2003), esophagus (Chen et al., 2009), stomach (Turati et al., 2015), colorectum (Galeone et al., 2006), bladder (Turati et al., 2015), and prostate (Hsing et al., 2002). The possible mechanisms of action of fig and garlic are illustrated in Figure 3.

Ginger (*Zingiber officinale*)

Ginger (*Zingiber officinale*) is also a very prevalent plant that belongs to the family *Zingiberaceae*. It originated in South-East Asia and its rhizome is applied in numerous countries as a spice and food flavor (Park and Pezzuto, 2002). Several health-promoting perspectives of ginger are accredited to its rich polyphenols, such as gingerols (mainly in the fresh rhizome) and shogaols (dehydrated gingerol derivatives in dried rhizome) (Jolad et al., 2004; Jiang et al., 2006).

Using ginger can be considered safe, although further understanding of its mechanisms of action is needed. Ginger has several therapeutic uses, including degenerative and cardiovascular syndromes, vomiting, digestive health, diabetes mellitus, and even cancerogenic (Jiang et al., 2006; Patel et al., 2007). It also possesses anti-inflammatory, anti-oxidative properties and antimicrobial potential against gram-positive and gram-negative bacteria (Jiang et al., 2006; Patel et al., 2007; Singh et al., 2008). Evidence from both *in vivo* and *in vitro* studies (Table 8) recommends that ginger and its active components constrain the development of several cancer types, including breast, renal, cervical, colon, gastric, oral, pancreatic, prostate, hepatic, and brain cancer (Tuntiwechapikul et al., 2010; Kim et al., 2014; Wu et al., 2015). Shogaol suppresses the growth and brings apoptosis of non-small cell lung cancer cells (Kim et al., 2014; Wu et al., 2015) and enhances gemcitabine properties in human pancreatic cancer, such as BxPC-3 and PANC-1 (Gan et al., 2011).

Indigo (*Indigofera tinctoria*)

Indigofera tinctoria belongs to the family Fabaceae and is a widely distributed one- to two-meter height shrub found in several regions, Southeast Asia and the Indian subcontinent, Africa, and America (especially in tropical areas). The alcoholic extract of the leaves has an antihepatotoxic influence on carbon-tetrachloride and D-galactosamine-triggered hepatic damage (Sreepriya et al., 2001). Indigtone, an active constituent located in leaves has hepatoprotective activity (Singh et al., 2001). Moreover, *I. tinctoria* influences chronic myelogenous leukemia (Steriti, 2002). Indirubin showed noticeable repression of Walker carcinoma and Lewis lung carcinoma, signifying that *I. tinctoria* has considerable antineoplastic activity (Han, 1994). Another type of indigo called *Polygonum tinctorium* belongs to the family Polygonaceae. In its leaves, *P. tinctorium* stores large quantities of a colorless glycoside, indican (indoxyl beta-D-glucoside) (Selvius et al., 2011).

Table 7. Anticancer activities of garlic

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
Garlic products	*In vivo* *In vitro*	Prostate cancer	↓prostate cancer risk.	(Hsing et al., 2002)
Fresh garlic	*In vivo*	Prostate cancer	↓ratio of prostate cancer by 30-50%.	(Hsing et al., 2002)
Garlic products	*In vivo*	Stomach cancer	↓Death ratio by 10-folds ↓risk of stomach cancer.	(Setiawan et al., 2005)
Fresh garlic	*In vivo*	Gastric cancer	↓nitrate-reducing bacteria and ↓nitrite formation.	(Turati et al., 2015)
Raw garlic	*In vitro*	Esophageal cancer	↓the risks of esophageal cancer.	(Galeone et al., 2006; Chen et al., 2009)
Garlic products	*In vitro*	Pancreatic cancer	↓risk of pancreatic cancer due to garlic use.	(Chan, 2005)
Garlic products	*In vitro*	Colorectal cancer	↓risk of colorectal cancer	(Galeone et al., 2006)

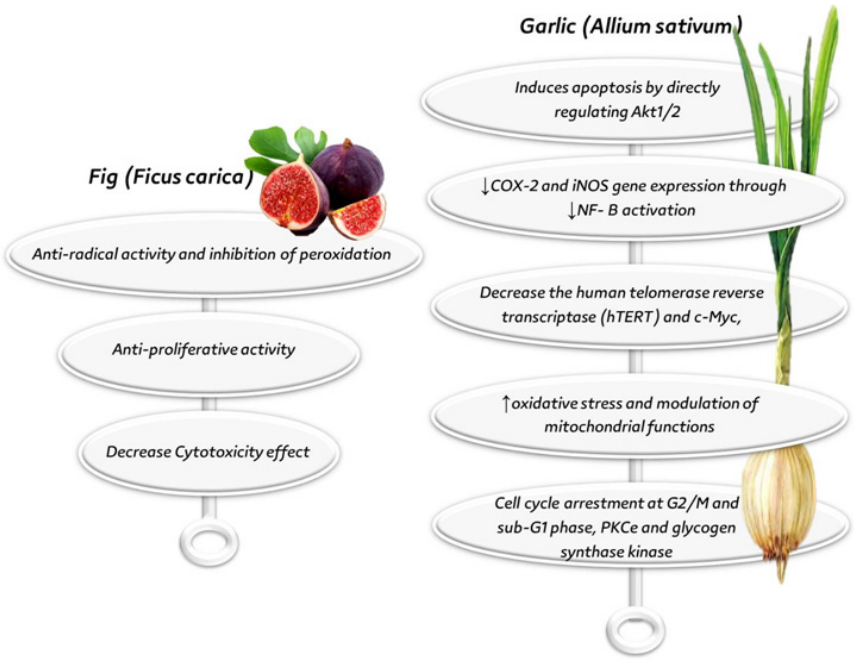


Figure 3. The possible mechanisms of action of fig and garlic

Table 8. Anticancer activities of ginger

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
Shogaols	*In vivo*	Lung cancer	↓tumorigenesis, ↓NF-B activation, ↓COX-2, and ↓iNOS, ↓development and apoptosis biomarkers of cancer cells via Akt1/2 pathway	(Kim et al., 2014)
Shogaols	*In vitro*	Pancreatic cancer	↓Bcl-2, MMP-9, cIAP-1, cyclinD1, surviving, XIAP, and Bcl-2. ↓Antitumor activity, ↓TLR4/NF- B signaling ↑PANC-1 and BxPC-3 ↓TLR4/NF- B, ↓formation of cancer cell colony.	(Gan et al., 2011)
Ethyl acetate	*In vitro*	Lung cancer (A549)	↑cell death, ↓hTERT (human telomerase reverse transcriptase) and c-Myc.	(Tuntiwechapikul et al., 2010)
Young *Zingiber officinale* and its essential oil	*In vitro*	MCF-7, and PC-3, A-549	↑cytotoxic effect against MCF-7, PC-3, and A-549 cancer cells; ↓risk of hepatic cancers	(Zu et al., 2010)
Ethanol extract	*In vitro*	Colon cancer	↓mTOR and Wnt/ catenin signaling pathways, ↑apoptosis in HT29 cells. ↓S-phase population in HT29 and HCT-116 cells.	(Abdullah et al., 2010)

The indigo plant has been used in medicine in Japan, China, and Korea for over a thousand years (Cooksey, 2012; Heo et al., 2012). The main bioactive substances in the indigo plant are mostly flavonoids, polyphenols, tannins, and flavonols (Heo et al., 2013). In addition, this plant's most beneficial active principles are indirubin, indigo, kaempferol, and tryptanthrin (Cooksey, 2012).

Kameswaran and Ramanibai (2008) explored indigo aerial parts' potential anticancer activity (against human non-small cell lung cancer cells A-549). Interestingly, flavonoid molecules isolated from the ethanolic extract of indigo considerably repressed the proliferation of A-549 cells. Flow cytometric analysis revealed that methanolic extract of *I. tinctoria* stopped cell cycle development in G0/G1 stage and boosted A-549 cell apoptosis. The authors suggested that flavonoid screening of methanolic extract of *I. tinctoria* action might contribute to its overall chemo-preventive impacts alongside lung cancer. They might probably be measured for upcoming therapeutic uses.

Oral administration of methanolic fraction of *I. tinctoria* at levels 100 and 200 mg/kg markedly lowered the increased level of uronic acid and hexosamine content compared to vehicle-treated control one. The *in vitro* cytotoxic action of methanolic extraction of *I. tinctoria* on melanoma cells (B16F10) was recorded at 24.8 µg/ml at IC50. Renukadevi and Sultana (2011) studied the cytotoxic, antioxidant and antibacterial activity of the leaf extract of *I. tinctoria*. The cytotoxic activity of leaf extract was determined on a lung cancer cell line. The phytochemical examination found several active molecules like saponins, flavonoids, steroidal terpenes, tannins, anthraquinone and phenols. The robust antioxidant activity of the indigo extract was detected at 250 µg mL^{-1} with an IC_{50} value of 51.66, which is more than that of standard ascorbic acid. The cytotoxic influence of leaf extract on NCI-H69 (lung cancer cell line) was found to be eminent by augmenting the level of leaf extract.

Heo et al. (2014) investigated the cytotoxic influences of the ethanol, water, and methanol extracts of leaves, flowers, seeds, and stems of indigo on HEK 293 (human renal cell line) and suppressor influences on the proliferation of MCF-7 (breast carcinoma cells), HeLa (cervical carcinoma cells), HCT-116 (colon cancer cell), Hep3B (liver carcinoma cells), SNU-1066 (laryngeal cancer cell) and SNU-601 (gastric cancer cell). The highest concentration of total polyphenols was detected in methanol extracts of flowers and leaves. However, the methanol extract of seeds, flowers and leaves has the highest proportion of flavonoids. The maximum antioxidant capacities were also detected in methanolic extracts of leaves and flowers. The highest relation between the survival rates and the antioxidant abilities was in methanol extracts of leaves on HeLa cells (Heo et al., 2014). So, *in vitro* studies showed that the indigo extracts were detected to be efficient in constraining the development of cancer cells (Table 9).

The use of naturally accessible fuels for nanoparticle solution combustion synthesis (SCS) has increased. Many studies reported that biofuels have harmless environmental effects, but their tactical recompenses for the synthesis of NPs have not been fully investigated. Prashanth et al. (2018) studied the usage of plant extracts as biofuels for the SCS of zinc oxide nanoparticles (ZnNPs). The authors carried out the combustion synthesis of ZnNPs by using aqueous and lactose leaf extracts of *Indigofera tinctoria, Melia azedarach, Abutilon indicum* as biofuels. A comparative analysis has been conducted to comprehend the benefits of using plant extracts over a biochemical as a combustion fuel for synthesizing ZnNPs.

Table 9. Anticancer activities of indigo

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
The methanolic extract of aerial parts of the plant	*In vitro*	Human non-small cell Lung cancer cells a-549.	Flavonoid fraction of methanolic extract of *I. tinctoria* prohibited cell cycle development in GO/G 1 Phase and induced a-549 cell apoptosis.	(Kameswaran and Ramanibai, 2008)
ZnNPs synthesized using lactose and aqueous leaf extracts	*In vitro*	DU-145 and Calu-6 cancer cells	The machinery of apoptosis in cancer cells due to ZnNPs still not being explored.	(Prashanth et al., 2018)
I. tinctoria leaf extract and the nanoparticles of gold and silver	*In vitro*	Lung cancer cell line A549	Induce reactive oxygen species by nanoparticles. It reasons reparations to the cellular constituent and leads to the cell death	(Vijayan et al., 2018)
Water, methanol and ethanol extracts of flowers, leaves, stems, and seeds from indigo (*P. tinctorium*)	*In vitro*	Hek 293, HEP3b, MCF-7 HCT-116, Hela, snu-1066, and snu-601.	Flavonoids and polyphenols in extracts of various parts of indigo.	(Heo et al., 2014)
Methanol and ethyl acetate from the indigo powder, seeds, or the prolipid.	*In vitro*	Calu-6 (human cancer cell lines) and SNU-601 (human gastric carcinoma)	Tryptanthrin and indirubin, both compounds originating from indican in the leaves of *P. tinctorium* are responsible for many of the biological activities of this Plant.	(Jang et al., 2012)

Moreover, the authors conducted antiproliferative evaluation against Calu-6 and DU-145 cancer cells and detected the higher anticancer action of ZnNPs ready utilization biofuels. The biocompatibility of ZnNPs at lower concentrations was detected by blood hemolysis. Further studies would be needed to validate the potential benefits of naturally offered fuel usage in SCS. Vijayan et al. (2018) reported the innovation of novel metal nanoparticles, explicitly gold (AgNPs) and silver (AuNPs), from their salt by using leaf extract of *I. tinctoria*. This leaf extract acts as a stabilizing and reducing mediator for the creation of nanoparticles. The antiproliferative influence of *I. tinctoria* leaf extract and the nanoparticles were investigated in A549 (lung cancer cell). It was detected that the elevating concentration reduces cell viability, and the pure leaf extract has a less toxic influence on cancer cells than nanoparticles. Studies have shown that the IC_{50} value of AgNPs, and AuNPs (biogenic synthesis) by *I. tinctoria* leaf extract are 56.62±0.86l g/ml, 59.33±0.57l g/ml and 71.92±0.76l g/ml, respectively. Moreover, the synthesized metal nanoparticles showed high antimicrobial actions.

Onion (*Allium cepa*)

Onion, a biennial plant, generally adapts to temperate environments with low water supplies. It is thought to have originated in central Asia (Zeng et al., 2015). Onion can be used in fresh, raw and processed forms. Besides its culinary uses, it is considered a good medicinal and therapeutic compound for many diseases (Nuutila et al., 2003; Vidyavati et al., 2010). Onions are rich in two bioactive ingredients, including flavonoids, such as anthocyanins and flavanols, such as quercetin, and the sulfur-containing compounds (alk(en)yl cysteine sulphoxides (ACSOs)) (Alagawany et al., 2014, 2016; Dosoky et al., 2021). The numerous reported health properties of onions *in vitro* and *in vivo* are due to their antioxidant, hypocholesterolemic, hypoglycemic, and thrombolytic or even anticarcinogenic effects (Vidyavati et al., 2010).

Onions may have anticarcinogenic properties, as reported in both animal and human trials against a wide range of cancer types, such as esophageal, gastric, colorectal, hepatic, renal, lung, bladder, breast, ovarian, and brain cancer (Fukushima et al., 1997; Hsing et al., 2002; Galeone et al., 2006; Millen et al., 2007). Table 10 shows the anticancer activities of onion. In breast cancer, the tetrasulfide compound naturally occurring in onion can inhibit the proliferation of both sensitive and resistant human breast carcinoma cells by targeting the enzymes involved in the cell cycle (Galeone et al., 2006; Millen et al., 2007). Several reports have concluded that onion or onion products can repress the growth of several human cancer cell lines, including stomach and colon cells (Setiawan et al., 2005; Turati et al., 2015). Also, onion intake has been consistently associated with decreasing the risk of colorectal cancer (Millen et al., 2007). A study by Hu et al. (1999) has described that dietary supplementation with onion products is associated with decreased brain cancer risk.

Pomegranate (*Punica granatum*)

Pomegranate is a long-lived and drought-tolerant small tree. It is mainly found throughout the Mediterranean, Iran, India, China, and the USA (Ercisli et al., 2011). The pomegranate consists of different compartments: seed, juice, peel, and leaf. The chemical composition of the fruits depends on several factors, including the growing region, climate, cultivation practice, and storage conditions (Fadavi et al., 2005). The peel contains important bioactive constituents like flavonoids, phenolics, proanthocyanidins, ellagitannins, and other significant minerals. The edible part of the pomegranate fruit is rich in several bioactive molecules such as flavonoids and phenolics, mainly anthocyanins (Viuda-Martos et al., 2010) that prevent lipid peroxidation of cells. Pomegranate seeds contain estrogenic compounds like estrone and estradiol (Kim and Choi, 2009). The seed cover of the fruit contains delphinidin-3,5-diglucoside, the primary anthocyanin in pomegranate juice (Elfalleh et al., 2012). Pomegranate juice, pomegranate extracts, and seed oil have interesting pharmacological activities. Extracts of all parts of the pomegranate fruit have numerous biomedical applications and therapeutic properties ranging from being utilized as a medication for dysentery, diarrhea, hemorrhage, acidosis, helminth infection, microbial infections, and respiratory pathologies (Kim and Choi, 2009) or even targeting a variety of ailments including cardiovascular syndromes, Alzheimer's disease, male infertility, aging, diabetes, and AIDS or even cancer (Lansky and Newman, 2007; Jurenka, 2008).

Recently, pomegranates have been reported for their wide range of anti-cancer properties, especially in breast and prostate cancers. Fermented pomegranate juice has doubled the pomegranate extracts' effect in constraining the development of MCF-7 (breast cancer cells) via stimulation of apoptosis (Mehta and Lansky, 2004; Jeune et al., 2005; Bassiri-Jahromi, 2018). Pomegranate fruit has been reported to inhibit cell growth, induce apoptosis of human prostate cancer, and prevent hepatocellular carcinoma in humans (Kaplan et al., 2001). Pomegranate extract has antiproliferative activity in non-small cell lung carcinoma cell lines both in a time- and dose-dependent manner (Khan et al., 2008; Husari et al., 2017; Sharma et al., 2017).

Pomegranate fruit extract can be used in human lung cancer therapy by inhibiting several signaling pathways such as mitogen-activated protein kinases (MAPK), PI3K/Akt, and NFκB (Khan et al., 2007). Pomegranate oil treatments have reduced tumor incidence and numbers in mice (Viuda-Martos et al., 2010; Elfalleh et al., 2012). The bulk of investigations showed that the pomegranate pulp extract exerts anti-skin tumor-encouraging action in CD-1 mice (Pacheco-Palencia et al., 2008). Additionally, pomegranate seed oil supplementation improved the expression of PPARα in the non-tumor mucosa and meaningfully reduced the occurrence of colonic adenocarcinomas (Kohno et al., 2004). The anticancer activities

of pomegranate were detected by several authors (Table 11). *In vitro* experiments have revealed that pomegranate juice possesses anti-inflammatory effects on the signaling proteins found in human colon cancer (HT-29 cell line) (Seeram et al., 2005). Several in vitro studies have reported potential machinery via which pomegranate can constrain the development of cancer cells such as lymphoid cell line (K562- 4), EJ cell – UBUC T24, glioma cells (U87MG), and J82 cell (Joseph et al., 2012; Dahlawi et al., 2013). The possible mechanisms of action of pomegranate and onion are illustrated in Figure 4.

Table 10. Anticancer activities of onion

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
Onion products - organo- sulphur compounds such as tetrasulfides	In vitro *In vivo*	Breast cancer	↓risk of breast cancer ↓the proliferation of sensitive and resistant human breast carcinoma cells by targeting the cell division cycle 25 phosphatases, crucial enzymes of the cell cycle	(Viry et al., 2011)
Fresh onion	*In vivo*	Gastric cancer	↓of nitrate-reducing bacteria and ↓nitrite formation.	(Turati et al., 2015)
Fresh onion	*In vivo*	Prostate cancer	↓risk of prostate cancer	(Hsing et al., 2002)
Onion products and derivatives	*In vivo*	Colorectal cancer	↓risk of colorectal cancer.	(Millen et al., 2007)
Onion products – quercetin and derivatives	*In vivo*	Lung cancer	↑anticancer properties as demonstrated in lung cancer	(Vijayababu et al., 2006)
Onion – quercetin and luteolin	*In vivo*	Skin cancer	↑anticancer properties as demonstrated in skin cancer. ↓UVB-induced skin tumorigenesis in SKH-1 hairless mice via ↓PKCε and c-Src kinase activity.	(Vijayababu et al., 2006)
Onion products – onion peel – total phenolics and flavonoids	*In vitro*	Stomach cancer	↓growth of several human cancer cell lines, including cells of the stomach and colon	(Setiawan et al., 2005; Turati et al., 2015)
Onion – quercetin and derivatives	*In vitro*	Liver cancer	↑anticancer properties as demonstrated in liver cancer	(Fukushima et al., 1997)

Table 11. Anticancer activities of pomegranate

Extract/active ingredient	*Study type*	Cancer cell type	Mechanisms of action	References
1	2	3	4	5
Juice, seed oil, fermented juice polyphenols, extract	*In vitro* *In vivo*	Breast (MCF-7- MCF-7aro)	↓Growth of MCF-7 through ↑apoptosis. ↓Expansion of new blood vessels.	(Jeune et al., , 2005; Bassiri-Jahromi, 2018)
Seed oil, fermented juice polyphenols, extract, juice	*In vitro*	Prostate (DU-145, PC-3)	Patients with prostate cancer, pomegranate juice has revealed substantial prolongation repetition time of prostate precise antigen.	(Seeram et al., 2005)
Fruit extract	*In vivo* *In vitro*	A549 lung carcinoma cells	↓H1299 cell survival by arresting cell cycle progression in G2/M phase. ↓HIF-1α and PHH3 expression. ↓cell proliferation, ↓pro survival pathways, ↓tumor growth in the nude mice, ↓formation of lung nodules.	(Khan et al., 2007; Khan, et al., 2008; Husari et al., 2017; Sharma et al., 2017)
Seed oil, fruit extract, pulp extract	*In vivo* *In vitro*	Skin	↑interleukin 1 (IL-1) and IL-1 beta from the cells in the mice and human's macrophages. ↑macrophages. Pomegranate pulp extract contains anti-skin tumor promoting activity in CD-1 mouse by ↓biomarkers of tetra decanoyl phorbol 13-acetate (TPA)-induced tumor promotion.	(Hora et al., 2003; Afaq et al., 2005; Pacheco-Palencia et al., 2008)
Seed-oil, juice	*In vivo* *In vitro*	Colon	↑PPARγ Pomegranate seed oil can↓azoxymethane-induced colon carcinogenesis.	(Kohno et al., 2004; Adams et al., 2006)
Pomegranate juice, total pomegranate ellagitannins; punicalagin, ellagic acid, pomegranate tannin extract	*In vitro*	Colorectal Cancer (HT-29, HCT-116, SW620-HT-29)	↓NF-kB response element, and PJ also ↓AKT stimulated by TNF-α. Punicalagin, EA, TPT and PJ ↑apoptosis, PJ, TPT and punicalagin ↓NF-α mediated COX-2 protein expression	(Seeram et al., 2005; Adams et al., 2006)

Table 11 – cont.

1	2	3	4	5
P. granatum peels extract-pomegranate juice, polyphenols	*In vitro*	Leukemia (K562- 4 lymphoid cell line)	↓development of K562 cell line through cell cycle arrest at G2/M phase, ↑apoptosis. ↓cellular proliferation	(Joseph et al., 2012; Dahlawi et al., 2013)
Pomegranate extract, Pomegranate juice, bioactive components, resveratrol	*In vitro*	Hepatocellular carcinoma	↓Lipid and protein oxidation in hepatic tissues. Prevention of hepatocellular ↓cell proliferation, control cell cycle development, and ↑apoptosis in rats.	(Kaplan et al., 2001)
Punicalagin as a polyphenol isolated from P. granatum	*In vitro*	Glioblastoma (U87MG glioma cells)	↓U87MG cell viability ↑Apoptosis, ↑AMPK/p27, ↑caspase-3 and 9, ADP-ribose ↑autophagy cell death via microtubule-associated protein light chain 3 II, LC3-II breakage.	(Wang et al., 2013)
Pomegranate extract, pomegranate polyphenols	*In vitro*	Bladder cancer (EJ cell – UBUC T24 and J82 cell)	↓bladder cancer cell EJ proliferation via p53/miR-34a axis, ↓mitochondrial image pathway ↑ER oxidative stress.	(Zhou et al., 2015)

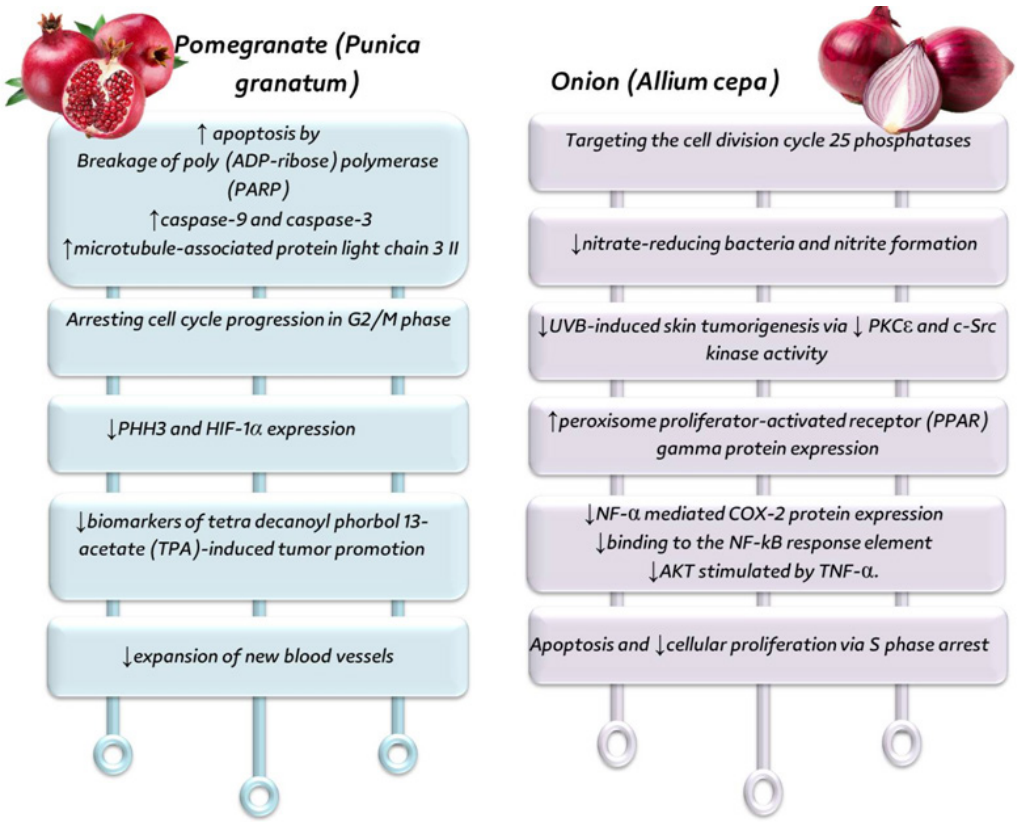


Figure 4. The possible mechanisms of action of pomegranate and onion

Quince (*Cydonia oblonga*)

Quince (*Cydonia oblonga)* is the only species in the genus Cydonia, which falls into the Pomoideae subfamily of the Rosaceae along with pear and apple. The yellow fruit may be apple- or pear-shaped and is considered a bright yellow, a highly astringent, acidulous, firm fruit flesh (Pacifico et al., 2012). Silva and Hussain (2017) conducted many investigations on *C. oblonga* Miller (also known as quince) in the past few years. They proved this plant is a low-cost, safe, and good natural source of various phenolic components, such as flavonol, flavone heterosides, and caffeoylquinic acids.

These compounds could provide the active principles of quince leaf and fruit in the treatment of cough, bronchial asthma, and hemorrhoids (Oliveira et al., 2007), cystitis (Sezik et al., 2001), constipation, and as a skin emollient (Pieroni et al., 2004). Quince fruit is considered a pivotal dietary source of health-promoting molecules due to its anti-ulcerative, antibacterial, anti-inflammatory, anti-obesity, and antioxidant properties (Oliveira et al., 2007; Pacifico et al., 2012). The leaf of quince has also been detected to have anti-hemolytic activity (Costa et al., 2009), in addition to its lipid-lowering activities (Pacifico et al., 2012). Quince fruit extracts have been mentioned to be efficient in inhibiting allergic ailments. Conclusively, a lipophilic quince extract was detected to have skin moisturizing activities.

The antiproliferative influence of pulp and peel polyphenolic extracts from *C. oblonga* fruit on both non-tumorigenic cells (HEK 293 and NIH 3T3) and human colon adenocarcinoma cells (LS174) was studied by Riahi-Chebbi et al. (2015). The same reported that the highest anticancer activity, without any toxic effect, was shown by aqueous acetone peel extract (IC50=5 μg/mL), explicitly on LS174 cells. Phenolic ingredients concentration in the pulp fraction is one-third lower than in the peel. Regarding the phytochemical screening of aqueous acetone peel, it was found that 13 phenolic compounds are the major active molecules, including rutin, quercetin, (−)-catechin, (+)-catechin, isoquercitrin, hyperin, cryptochlorogenic acid, chlorogenic acid, p-coumaric acid, neochlorogenic acid, kaempferol-3-O-glucoside, kaempferol and kaempferol-3-O-rutinoside (Fattouch et al., 2007). Carvalho et al. (2010) studied the phenolic screening and anticancer activity of quince fruit and leaf alongside colon cancer and human kidney cells. The 5-O-caffeoylquinic acid was the major component in the methanolic extracts of quince. The authors observed that quince fruit and leaf extracts revealed clear anticancer properties. This extract has potential anticancer effects on human colon cancer cells (IC50 = 239.7 (43.2 μg/mL), while no effects on human kidney cells were observed. The anticancer property of peel and pulp extracts was low in the range of extract levels. Therefore, the first study revealed that *C. oblonga* might be helpful as a cancer chemotherapeutic and/or chemopreventive agent.

Alesiani et al. (2010) isolated 59 active components from *Cydonia vulgaris* peels and categorized them based on their spectroscopic features. Among them, five metabolites have been isolated for the first time such as 3β-linoleoylurs-12-en-28-oic acid, 3β-(18-hydroxylinoleoyl)-28-hydroxyurs-12-ene, tiglic acid 1-O-β-d-glucopyranoside,3β-oleoyl-24-hydroxy-24-ethylcholesta-5,28(29)-diene, and 6,9-dihydroxymega-stigmasta-5,7-dien-3-one 9-O-β-d-gentiobioside. All the previous compounds were tested for their antioxidant and anticancer activity (especially murine B16-F1 melanoma cells). Pacifico et al. (2012) two complex preparations were in the focus of the present study, i.e., a lipophilic quince wax extract (QWE studied two complex preparations of quince phytochemicals, i.e., an aqueous fermented one (QAFE) and a lipophilic quince wax extract (QWE). The antiproliferative influence against human HeLa, A549, and HepG2 cell lines was investigated. QAFE was more active than QWE, but sometimes, its influences seemed to be strongly dependent on exposure time. Moreover, lipophilic and hydrophilic quince preparations are non-toxic and have health-promoting activities.

Table 12. Anticancer activities of quince

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
Methanolic extract from leaves and fruits	*In vitro*	Human renal (a-498 and 769-p) and colon (caco-2) cancer cell lines	Many phenolic compounds showed anticancer effects, such as flavone heterosides, flavonol and hydroxycinnamic acid.	(Carvalho et al., 2010)
Lipophilic quince wax extract and an aqueous fermented	*In vitro*	Human Hepg2, A549, and Hela cell lines	↑Apoptosis induction ↑Mitochondrial toxicity	(Pacifico et al., 2012)
Peel (Peph) and pulp polyphenolic extracts	*In vitro*	Human colon adenocarcinoma LS174 cells	↑Apoptosis induction ↑A cell cycle arrest in the G1/S phase, ↑ROS. ↓NF-κB and VEGF.	(Riahi-Chebbi et al., 2015)
Cydonia vulgaris peels	*In vitro*	Murine B16-F1 melanoma cells	Antioxidant activities of 3β-linoleoylurs-12-en-28-oic acid, 3β-(18-hydroxylinoleoyl)-28-hydroxyurs-12-ene, tiglic acid 1-*O*-β-d-glucopyranoside, 3β-oleoyl-24-hydroxy-24-ethylcholesta-5,28(29)-diene, and 6,9-dihydroxymegastigmasta-5,7-dien-3-one 9-*O*-β-d-gentiobioside	(Alesiani et al., 2010)

The development of substitute cancer-specific drugs is essential to overcome tumor resistance. Riahi-Chebbi et al. (2015) studied the antiproliferative effect of pulp and peel (Peph) polyphenolic extracts from the *C. oblonga* on both no-tumorigenic cells HEK 293 cells and NIH 3T3 fibroblasts and human colon adenocarcinoma LS174 cells. The Peph extract revealed the strongest anti-cancer influence, specifically on LS174 cells. On the other hand, each Peph phenolic component alone did not show any anti-cancer activity, indicating a synergistic influence of phenolic compounds. This influence was accompanied by an increase in the production of intracellular reactive oxygen species, caspase-independent apoptosis and a cell cycle arrest in the G1/S phase. Peel extract suppressed the pro-survival signaling pathway NFκB. It inhibited the expression of numerous cellular indicators that were significant in angiogenesis (vascular endothelial growth factor, VEGF) and cell cycling (cyclin D1). Interestingly, the chemotherapeutical agent 5-FU and the combination peel extract exhibited a synergistic inhibitory influence on cell viability. Table 12 shows the anticancer activities of quince.

Table 13. Anticancer activities of thyme

Extract/active ingredient	Study type	Cancer cell type	Mechanisms of action	References
Thyme essential oil	*In vivo*	PC-3, A-549 and MCF-7 cancer	↓growth in leukemia cells Displayed cytotoxic activity alongside MCF-7, A-549, and PC-3 cancer cells.	(Esmaeilbeig et al., 2015)
Thyme essential oil	*In vivo*	Oral cavity squamous cell carcinoma	↓human head and neck squamous cell carcinoma (HNSCC) cell growth.	(Sertel et al., 2011)
Thyme essential oil	*In vitro*	Human ovarian adenocarcinoma IGR-OV1 cell line	↑anticancer activity.	(Ismaili et al., 2002)
Thyme essential oil (carvacrol)	*In vitro*	Ovarian cancer	*in vitro* cytotoxic activity against tumor cells resistant to chemotherapy and a significant antitumor effect in mice.	(Ait M'barek et al., 2007)
Thyme extract	*In vivo*	Human lung cancer cell line (H460)	↑anti-inflammatory properties by ↓the NF-κB p65 and NF-κB p52 transcription factors protein levels followed by ↓pro-inflammatory cytokines (IL-1 beta and IL-8), and Muc5ac secretion in human normal bronchial and tracheal epithelial cells.	(Oliviero et al., 2016)
T. thymol, T. linalool, and T. thujanol.	*In vitro*	MCF-7 breast cancer cells- HeLa cervical cancer	↓HeLa cervical cancer and MCF-7 breast cancer cell viability by approximately 20% after 24 hours.	(Deering et al., 2017)

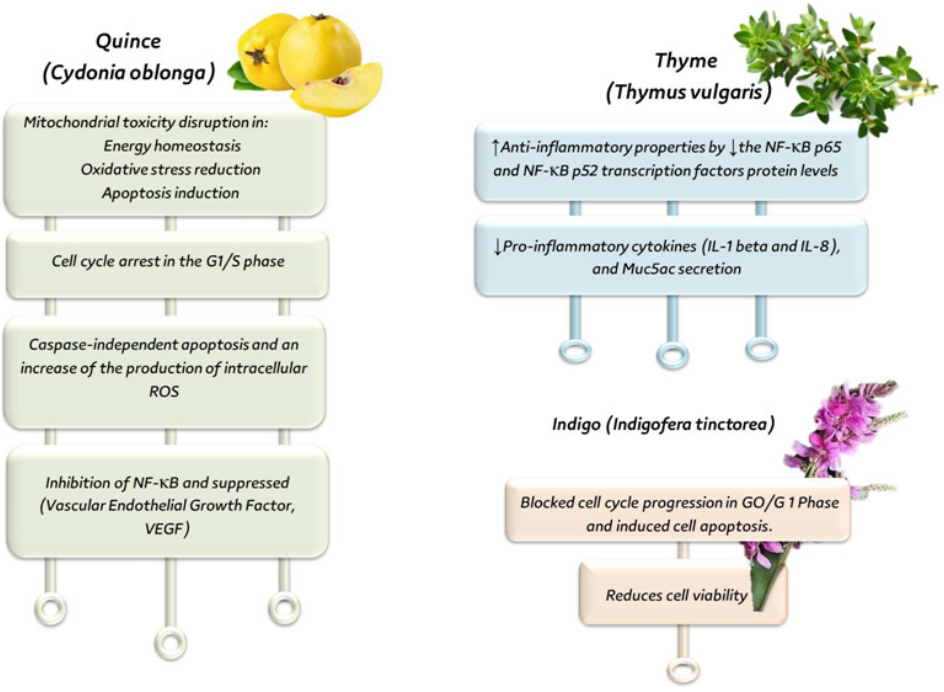


Figure 5. The possible mechanisms of action of thyme, quince and indigo

Thyme (*Thymus vulgaris*)

Thyme (*Thymus vulgaris* L.) is a Mediterranean aromatic herb. *T. vulgaris* is the most common variety. It is commonly used for ornamental, culinary, and medicinal purposes (De Martino et al., 2009). Thyme preparations are widely used in dried herbs, liquid extracts, tinctures, or elixirs. These thyme preparations' different effects should be carefully considered in their chemical composition. Thymol, carvacrol, eugenol, tannins, saponins, and luteolin are all active agents in thyme (Kluth et al., 2007). Most of the pharmacological effects of thyme are attributed to the presence of active agents carvacrol and thymol, the main ingredients of the essential oil of thyme, providing a high antioxidant activity (Kluth et al., 2007). Different thyme preparations are used for medicinal purposes, such as antitussive, expectorant, anthelminthic, antiseptic, spasmolytic, antimicrobial, antifungal, anti-inflammatory, analgesic, antipyretic, antidiabetic, antioxidative, carminative, sedative, and diaphoretic effects (Oliviero et al., 2016).

Several reports have explored the anti-cancer effects of thyme essential oil or its active ingredients (Table 13). These reports have demonstrated that thyme essential oil has inhibited the growth of cancer cells such as in head and neck squamous cell carcinoma (HNSCC), leukemia cell lines, and human head and cell (Sertel et al., 2011; Esmaeilbeig et al., 2015). Moreover, thyme extract induced cell cytotoxicity and reduced inflammatory cell signals in the H460 lung cancer cell line (Oliviero et al., 2016). The possible mechanisms of action of thyme, quince, and indigo are illustrated in Figure 5.

Conclusion

With the advancement of chemotherapy for different cancers, investigators have reported anticancer drugs are expensive and have side effects. Keeping in mind these weaknesses, we examined many publications on the use of herbs or the derivatives of important active molecules for cancer therapy. As we highlighted, most anticancer molecules belong to flavonoids and alkaloids classes. The active molecules isolated from herbs or some plants indicated in this review have a significant function as an apoptosis induction for cancer cells, destroying cancer cells by apoptosis signaling. In this sense, there is an excellent chance to try these molecules in clinical trials and disclose some plant-based drugs that regulate the elevated distribution of cancers. Henceforth, apoptosis induction mediators or autophagy signaling through herbs could show probability in decreasing the risk of influences connected with cancer development.

Conflicts of Interest

All authors declare that they have no conflicts of interest that could inappropriately influence this manuscript.

Author contribution

All authors contributed equally to writing this review article. All authors read and approved the final version of this manuscript.

Data Availability Statement

No data are available.

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References

Abd El-Hack M.E., Alagawany M., Farag M.R., Tiwari R., Karthik K., Dhama K. (2016). Nutritional, healthical and therapeutic efficacy of black cumin (*Nigella sativa*) in animals, poultry and humans. Int. J. Pharmacol, 12: 232–248.

Abd El-Hack M.E., Alagawany M., Arif M., Emam M., Saeed M., Arain M.A., Khan R.U. (2018). The uses of microbial phytase as a feed additive in poultry nutrition – a review. Ann. Anim. Sci., 18: 639–658.

Abd El-Hack M.E., Shafi M.E., Alghamdi W.Y., Abdelnour S.A., Shehata A.M., Ragni M. (2020). Black soldier fly (*Hermetia illucens*) meal as a promising feed ingredient for poultry: A comprehensive review. Agriculture, 10: 339.

Abd El-Hack M.E., El-Saadony M.T., Shehata A.M., Arif M., Paswan V.K., Elbestawy A.R. (2021). Approaches to prevent and control *Campylobacter* spp. colonization in broiler chickens: a review. Environ. Sci. Poll. Res., 28: 4989–5004.

Abdel-Moneim A.M.E., Shehata A.M., Alzahrani S.O., Shafi M.E., Mesalam N.M., Taha A. E., Abd El-Hack M.E. (2020). The role of polyphenols in poultry nutrition. J. Anim. Physiol. Anim. Nutr., 104: 1851–1866.

Alagawany M., Abd El-Hack M.E., Laudadio V., Tufarelli V. (2014). Effect of low-protein diets with crystalline amino acid supplementation on egg production, blood parameters and nitrogen balance in laying Japanese quails. Avian Biol. Res., 7: 235–243.

Alagawany M., Abd El-Hack M.E., El-Kholy M.S. (2016). Productive performance, egg quality, blood constituents, immune functions, and antioxidant parameters in laying hens fed diets with different levels of *Yucca schidigera* extract. Environ. Sci. Poll. Res., 23: 6774–6782.

Al-Dalaen S. (2014). Carcinogen metabolizing enzymes: modulation of their activities in liver, lung and stomach by thymoquinone. European J. Med. Plants., 4: 383–393.

Alesiani D., Canini A., D'Abrosca B., DellaGreca M., Fiorentino A., Mastellone C., Pacifico S. (2010). Antioxidant and antiproliferative activities of phytochemicals from Quince (*Cydonia vulgaris*) peels. Food Chem., Elsevier, 118: 199–207.

Al-Oqail M.M., Al-Sheddi E.S., Al-Massarani S.M., Siddiqui M.A., Ahmad J., Musarrat J., Farshori N. (2017). *Nigella sativa* seed oil suppresses cell proliferation and induces ROS dependent mitochondrial apoptosis through p53 pathway in hepatocellular carcinoma cells. South African J. Botany, 112: 70–78.

AlRawi S.N., Fetters M.D. (2012). Traditional Arabic & Islamic medicine: a conceptual model for clinicians and researchers. Glob. J. Health Sci., 4: 164–169.

Arshad Qamar K., Dar A., Siddiqui B., Kabir N., Aslam H., Ahmed S., Begum S. (2010). Anticancer activity of *Ocimum basilicum* and the effect of ursolic acid on the cytoskeleton of MCF-7 human breast cancer cells. Lett. Drug Des. Dis., 7: 726–736.

Ashour A.E., Abd-Allah A.R., Korashy H.M., Attia S.M., Alzahrani A.Z., Saquib Q., Rishi A.K. (2014). Thymoquinone suppression of the human hepatocellular carcinoma cell growth involves inhibition of IL-8 expression, elevated levels of TRAIL receptors, oxidative stress and apoptosis. Mol. Cell. Biochem. 389: 85–98.

Awad E.M. (2005). *In vitro* decreases of the fibrinolytic potential of cultured human fibrosarcoma cell line, HT1080, by *Nigella sativa* oil. Phytomedicine, 12: 100–107.

Bassiri-Jahromi S. (2018). *Punica granatum* (Pomegranate) activity in health promotion and cancer prevention. Oncology Rev.,12: 345.

Behbahan M. (2014). Evaluation of *in vitro* anticancer activity of *Ocimum basilicum*, *Alhagi maurorum*, *Calendula officinalis* and their parasite *Cuscuta campestris*. PLoS One, 9(12): e116049.

Caliskan O. (2015). Mediterranean figs (*Ficus carica* L.) functional food properties. The Mediterranean Diet. Academic Press, pp. 629–637.

Capasso A. (2013). Antioxidant action and therapeutic efficacy of *Allium sativum* L. Molecules, 18: 690–700.

Carvalho M., Silva B.M., Silva R., Valentao P., Andrade P.B., Bastos M.L. (2010). First report on *Cydonia oblonga* miller anticancer potential: differential antiproliferative effect against human kidney and colon cancer cells. J. Agric. Food Chem., 58: 3366–3370.

Chan J.M. (2005). Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco Bay area. Cancer Epidemiol. Biomar. Preven., 14: 2093–2097.

Chawla A., Kaur R., Sharma A. (2012). *Ficus carica* Linn: A review on its pharmacognostic, phytochemical and pharmacological aspects. Inter. J. Pharm. Phytopharmacol. Res., 1: 215–232.

Chehl N., Chipitsyna G., Gong Q., Yeo C.J., Arafat H.A. (2009). Anti-inflammatory effects of the *Nigella sativa* seed extract, thymoquinone, in pancreatic cancer cells. Hpb, 11: 373–381.

Chen Y.K., Lee C.H., Wu I.C., Liu J.S., Wu D.C., Lee J.M., Wu M.T. (2009). Food intake and the occurrence of squamous cell carcinoma in different sections of the esophagus in Taiwanese men. Nutrition, 25: 753–761.

Colín-González A.L., Santana R.A., Silva-Islas C.A., Chánez-Cárdenas M.E., Santamaría A., Maldonado P.D. (2012). The antioxidant mechanisms underlying the aged garlic extract- and S-allylcysteine-induced protection. Oxidative Med. Cell. Long., 2012: 907162.

Conforti F., Menichini G., Zanfini L., Tundis R., Statti G.A., Provenzano E., Alfano C. (2012). Evaluation of phototoxic potential of aerial components of the fig tree against human melanoma. Cell Prolifer., 45: 279–285.

Cooksey C. (2012). An annotated bibliography of recent significant publications on indigo and related compounds. Biotech. Histochem., 87: 439–463.

Costa R.M., Magalhães A.S., Pereira J.A., Andrade P.B., Valentão P., Carvalho M., Silva B. M. (2009). Evaluation of free radical-scavenging and antihemolytic activities of quince (*Cydonia oblonga*) leaf: a comparative study with green tea (*Camellia sinensis*). Food Chem. Toxicol., 47: 860–865.

Dahlawi H., Jordan-Mahy N., Clench M., McDougall G.J., Le Maitre C.L. (2013). Polyphenols are responsible for the proapoptotic properties of pomegranate juice on leukemia cell lines. Food Sci. Nutr., 1: 196–208.

Deering K., Nethery W., Averill C., Esposito E. (2017). Effects of Thyme essential oil chemotypes on breast and cervical cancer cell lineages. Ann. Pharmacol. Pharmacother., 2: 1–3.

Dhanjal D.S., Chopra C., Singh R. (2021). Himalayan herbal medicine for cancer. In: Modern cancer therapies and traditional medicine: an integrative approach to combat cancers, 268.

Dilshad A., Abulkhair O., Nemenqani D., Tamimi W. (2012). Antiproliferative properties of methanolic extract of *Nigella sativa* against the MDA-MB-231 cancer cell line. Asian. Pac. J. Cancer Prev., 13: 5839–5842.

Dosoky W.M., Zeweil H.S., Ahmed M.H., Zahran S.M., Shaalan M.M., Abdelsalam N.R., Abdel-Moneim E.A., Taha A.E., El-Tarabily K.A., Abd El-Hack M.E. (2021). Impacts of onion and cinnamon supplementation as natural additives on the performance, egg quality, and immunity in laying Japanese quail. Poultry Sci., 100: 101482.

Effenberger K., Breyer S., Schobert R. (2010). Terpene conjugates of the *Nigella sativa* seed-oil constituent thymoquinone with enhanced efficacy in cancer cells. Chem. Biodivers., 7: 129–139.

Eja M.E., Asikong B.E., Abriba C., Arikpo G.E., Anwan E.E., Enyi-Idoh K.H. (2007). A comparative assessment of the antimicrobial effects of garlic (*Allium sativum*) and antibiotics on diarrheagenic organisms. Southeast Asian J. Trop. Med. Public Health., 38: 343.

Elbarbry F., Ragheb A., Marfleet T., Shoker A. (2012). Modulation of hepatic drug metabolizing enzymes by dietary doses of thymoquinone in female New Zealand White rabbits. Phytother. Res., 26: 1726–1730.

Elfalleh W., Yahia N., Ferchichi A. (2012). Main pomegranate phytochemicals and their contribution to the antioxidant potencies of pomegranate juice. Proc. II International Symposium on the Pomegranate. CIHEAM/Universidad Miguel Hernández, Zaragoza, Spain, pp. 325–329.

El-Far H.A. (2015). Thymoquinone anticancer discovery: possible mechanisms. Curr. Drug Discov. Technol., 12: 80–89.

El-Far H.A., Badria A.F., Shaheen M.H. (2016). Possible anticancer mechanisms of some *Costus speciosus* active ingredients concerning drug discovery. Curr. Drug Discov. Technol., 13: 123–143.

El-Far A.H., Korshom M.A., Mandour A.A., El-Bessoumy A.A., El-Sayed Y.S. (2017). Hepatoprotective efficacy of *Nigella sativa* seeds dietary supplementation against lead acetate-induced oxidative damage in rabbit–purification and characterization of glutathione peroxidase. Biomed. Pharmacother., 89: 711–718.

El-Hallouty S.M., Fayad W., Meky N.H., EL-Menshawi B.S., Wassel G.M., Hasabo A.A. (2015). *In vitro* anticancer activity of some Egyptian plant extracts against different human cancer cell lines. Int. J. Pharm. Tech. Res., 8: 267–272.

El-Najjar N., Chatila M., Moukadem H., Vuorela H., Ocker M., Gandesiri M., Schneider-Stock R., Gali-Muhtasib H. (2010). Reactive oxygen species mediate thymoquinone-induced apoptosis and activate *ERK* and *JNK* signaling. Apoptosis, 15: 183–195.

El-Sayed W.M. (2011). Upregulation of chemoprotective enzymes and glutathione by *Nigella sativa* (black seed) and thymoquinone in CCl4-intoxicated rats. Int. J. Toxicol., 30: 707–714.

Ercisli S., Gadze J., Agar G., Yildirim N., Hizarci Y. (2011). Genetic relationships among wild pomegranate (*Punica granatum*) genotypes from Coruh Valley in Turkey. Genet. Mol. Res., 10: 459–464.

Esmaeilbeig M., Kouhpayeh S.A., Amirghofran Z. (2015). An investigation of the growth inhibitory capacity of several medicinal plants from Iran on tumor cell lines. Iran. J. Cancer Prev., 8: e4032.

Fadavi A., Barzegar M., Azizi M.H., Bayat M. (2005). Note. Physicochemical composition of ten pomegranate cultivars (*Punica granatum* L.) grown in Iran. Food Sci. Tech. Inter., 11: 113–119.

Farah I.O., Begum R.A. (2003). Effect of *Nigella sativa* (*N. sativa* L.) and oxidative stress on the survival pattern of MCF-7 breast cancer cells. Biomed. Sci. Instrum., 39: 359–364.

Fattouch S., Caboni P., Coroneo V., Tuberoso C.I., Angioni A., Dessi S., Marzouki N., Cabras P. (2007). Antimicrobial activity of Tunisian quince (*Cydonia oblonga* Miller) pulp and peel polyphenolic extracts. J. Agric. Food Chem., 55: 963–969.

Fukushima S., Takada N., Hori T., Wanibuchi H. (1997). Cancer prevention by organosulfur compounds from garlic and onion. J. Cell Biochem. Suppl., 27: 100–105.

Galeone C., Pelucchi C., Levi F., Negri E., Franceschi S., Talamini R., Giacosa A., La Vecchia C. (2006). Onion and garlic use and human cancer. Am. J. Clin. Nutr., 84: 1027–1032.

Gali-Muhtasib H., Diab-Assaf M., Boltze C., Al-Hmaira J., Hartig R., Roessner A., Schneider-Stock R. (2004). Thymoquinone extracted from black seed triggers apoptotic cell death in human colorectal cancer cells via a *p53*-dependent mechanism. Int. J. Oncol., 25: 857–866.

Gali-Muhtasib H., Kuester D., Mawrin C., Bajbouj K., Diestel A., Ocker M., Habold C., Foltzer-Jourdainne C., Schoenfeld P., Peters B., Diab-Assaf M., Pommrich U., Itani W., Lippert H., Roessner A., Schneider-Stock R. (2008). Thymoquinone triggers inactivation of the stress response pathway sensor *CHEK1* and contributes to apoptosis in colorectal cancer cells. Cancer Res., 68: 5609–5618.

Gan F.F., Nagle A.A., Ang X., Ho O.H., Tan S.H., Yang H., Chew E.H. (2011). Shogaols at proapoptotic concentrations induce G2/M arrest and aberrant mitotic cell death associated with tubulin aggregation. Apoptosis, 16: 856–867.

Gebriel W. (2011). International Institute for Science, Technology and Education (IISTE). Available at: https://www.iiste.org/Journals/index.php/JBAH/article/view/15162 (Accessed: 28 November 2018).

Grayer R.J., Kite G.C., Veitch N.C., Eckert M.R., Marin P.D., Senanayake P., Paton A.J. (2002). Leaf flavonoid glycosides as che-

mosystematic characters in *Ocimum*. Biochem. Syst. Ecol., 30: 327–342.

Gurung R.L., Lim S.N., Khaw A.K., Soon J.F.F., Shenoy K., Mohamed A.S., Jayapal M., Sethu S., Baskar R., Hande M.P. (2010). Thymoquinone induces telomere shortening, DNA damage and apoptosis in human glioblastoma cells. PloS one, 5(8) :e12124.

Hajhashemi V., Ghannadi A., Jafarabadi H. (2004). Black cumin seed essential oil, as a potent analgesic and antiinflammatory drug. Phytoth. Res., 18: 195–199.

Han R. (1994). Highlight on the studies of anticancer drugs derived from plants in China. Stem cells, 12: 53–63.

Hanahan D.,Weinberg R.A. (2000). The hallmarks of cancer. Cell, 100: 57–70.

Heo B.G., Park Y.J., Lee S.J., Kim K.S., Cho J.Y., Boo H.O. (2012). Antioxidant enzyme activity and antimicrobial activity of *Isatis tinctoria* extract. Korean J. Plant Res., 25: 543–549.

Heo B.G., Jang H.G., Cho J.Y., Namiesnik J., Jastrzebski Z., Vearasilp K., González-Águilar G. A., Martinez-Ayala A.L., Suhaj M., Gorinstein S. (2013). Partial characterization of indigo (*Polygonum tinctorium Ait*.) plant seeds and leaves. Ind. Crops Prod., 42: 429–439.

Heo B.G., Park Y.J., Park Y.S., Bae J.H., Cho J.Y., Park K., Jastrzebski Z., Gorinstein S. (2014). Anticancer and antioxidant effects of extracts from different parts of indigo plant. Ind. Crops Prod., 56: 9–16.

Herre E.A., Jandér K.C., Machado C.A. (2008). Evolutionary ecology of figs and their associates: recent progress and outstanding puzzles. Annu. Rev. Ecol. Evol., 39: 439–458.

Hsing A.W., Chokkalingam A.P., Gao Y.T., Madigan M.P., Deng J., Gridley G., Fraumeni Jr J.F. (2002). Allium vegetables and risk of prostate cancer: a population-based study. J. Natl. Cancer Inst., 94: 1648–1651.

Huang H.C., Ho Y.C., Lim J.M., Chang T.Y., Ho C.L., Chang T.M. (2015). Investigation of the anti-melanogenic and antioxidant characteristics of *Eucalyptus camaldulensis* flower essential oil and determination of its chemical composition. Int. J. Mol. Sci.,16: 10470–10490.

Husari A., Hashem Y., Zaatari G., El Sabban M. (2017). Pomegranate juice prevents the formation of lung nodules secondary to chronic cigarette smoke exposure in an animal model. Oxid. Med. Cell. Longev., 2017: 6063201.

Iddamaldeniya S.S., Wickramasinghe N., Thabrew I., Ratnatunge N., Thammitiyagodage M.G. (2003). Protection against diethylnitrosoamine-induced hepatocarcinogenesis by an indigenous medicine comprised of *Nigella sativa*, *Hemidesmus indicus* and *Smilax glabra*: a preliminary study. J. Carcinog., 2: 6.

Ismaili H., Sosa S., Brkic D., Fkih-Tetouani S., Ilidrissi A., Touati D., Aquino R.P., Tubaro A. (2002). Topical anti-inflammatory activity of extracts and compounds from *Thymus broussonettii.* J. Pharm. Pharmacol., 54 :1137–1140.

Jafri S.H., Glass J., Shi R., Zhang S., Prince M., Kleiner-Hancock H. (2010). Thymoquinone and cisplatin as a therapeutic combination in lung cancer: *In vitro* and *in vivo*. J. Exp. Clin. Cancer Res., 29: 1–11.

Jang H.G., Heo B.G., Park Y.S., Namiesnik J., Barasch D., Katrich E., Vearasilp K., Trakhtenberg S., Gorinstein S. (2012). Chemical composition, antioxidant and anticancer effects of the seeds and leaves of indigo (*Polygonum tinctorium Ait.*) plant. Appl. Biochem, Biotechnol., 167: 1986–2004.

Jasmine R., Manikandan K., Karthikeyan K. (2015). Evaluating the antioxidant and anticancer property of *Ficus carica* fruits. Afr. J. Biotechnol., 14: 634–641.

Jeune M.A., Kumi-Diaka J., Brown J. (2005). Anticancer activities of pomegranate extracts and genistein in human breast cancer cells. J. Med. Food, 8: 469–475.

Jiang H., Xie Z., Koo H.J., McLaughlin S.P., Timmermann B.N., Gang D.R. (2006). Metabolic profiling and phylogenetic analysis of medicinal *Zingiber* species: Tools for authentication of ginger (*Zingiber officinale* Rosc.). Phytochemistry, 67: 1673–1685.

Jing L., Zhang Y.M., Luo J.G., Kong L.Y. (2015). Tirucallane-type triterpenoids from the fruit of *Ficus carica* and their cytotoxic activity. Chem. Pharm. Bull., 63: 237–243.

Jolad S.D., Lantz R.C., Solyom A.M., Chen G.J., Bates R.B., Timmermann B.N. (2004). Fresh organically grown ginger (*Zingiber officinale*): composition and effects on LPS-induced PGE_2 production. Phytochemistry, 65: 1937–1954.

Joseph M.M., Aravind S.R., Varghese S., Mini S., Sreelekha T.T. (2012). Evaluation of antioxidant, antitumor and immunomodulatory properties of polysaccharide isolated from fruit rind of *Punica granatum*. Mol. Med. Rep., 5: 489–496.

Jrah-Harzallah H., Ben-Hadj-Khalifa S., Maloul A., El-Ghali R., Mahjoub T. (2013). Thymoquinone effects on DMH-induced erythrocyte oxidative stress and haematological alterations during colon cancer promotion in rats. J. Funct. Foods, 5 1310–1316.

Jurenka J. (2008). Therapeutic applications of pomegranate (*Punica granatum* L.): a review. Altern. Med. Rev., 13 :128–144.

Kameswaran T.R., Ramanibai R. (2008). The antiproliferative activity of flavanoidal fraction of *Indigofera tinctoria* is through cell cycle arrest and apoptotic pathway in A-549 cells. J. Biol. Sci., 3: 584.

Kaplan M., Hayek T., Raz A., Coleman R., Dornfeld L., Vaya J., Aviram M. (2001). Pomegranate juice supplementation to atherosclerotic mice reduces macrophage lipid peroxidation, cellular cholesterol accumulation and development of atherosclerosis. J. Nutr., 131: 2082–2089.

Karthikeyan K., Gunasekaran P., Ramamurthy N., Govindasamy S. (1999). Anticancer activity of *Ocimum sanctum*. Pharm. Biol., 37: 285–290.

Kaseb A.O., Chinnakannu K., Chen D., Sivanandam A., Tejwani S., Menon M., Reddy G.P.V. (2007). Androgen receptor and E2F-1 targeted thymoquinone therapy for hormone-refractory prostate cancer. Cancer Res., 67: 7782–7788.

Khafaga A.F., Abd El-Hack M.E., Taha A.E., Elnesr S.S., Alagawan M. (2019). The potential modulatory role of herbal additives against Cd toxicity in human, animal, and poultry: a review. Environ. Sci. Pollut. Res., 26: 4588–4604.

Khan A.W., Farooq M., Haseeb M., Choi S. (2022). Role of plant-derived active constituents in cancer treatment and their mechanisms of action. Cells, 11: 1326.

Khan N., Hadi N., Afaq F., Syed D.N., Kweon M.H., Mukhtar H. (2007). Pomegranate fruit extract inhibits prosurvival pathways in human A549 lung carcinoma cells and tumor growth in athymic nude mice. Carcinogenesis, 28: 163–173.

Khan N., Afaq F., Mukhtar H. (2008). Cancer chemoprevention through dietary antioxidants: progress and promise. Antioxid. Redox Signal., 10: 475–510.

Khare C.P. (2004). Encyclopedia of Indian Medicinal Pplants. NewYork: Springes-Verlag Berlin Heidelberg.

Khodarahmi G.A., Ghasemi N., Hassanzadeh F., Safaie M. (2011). Cytotoxic effects of different extracts and latex of *Ficus carica* L. on HeLa cell line. ran. J. Pharm. Sci., 10: 273.

Kim M.O., Lee M.H., Oi N., Kim S.H., Bae K.B., Huang Z., Kim D.J., Reddy K., Lee S.Y., Park S.J., Kim J.Y., Xie H., Kundu J.K., Ryoo Z.Y., Bode A.M., Surh Y.J., Dong Z. (2014). [6]-Shogaol inhibits growth and induces apoptosis of non-small cell lung cancer cells by directly regulating *Ak*t1/2. Carcinogenesis, 35: 683–691.

Kim Y.H., Choi E.M. (2009). Stimulation of osteoblastic differentiation and inhibition of interleukin-6 and nitric oxide in MC3T3-E1 cells by pomegranate ethanol extract. Phytother. Res., 23: 737–739.

Kluth D., Banning A., Paur I., Blomhoff R., Brigelius-Flohé R. (2007). Modulation of pregnane X receptor-and electrophile responsive element-mediated gene expression by dietary polyphenolic compounds. Free Radic. Biol. Med., 42: 315–325.

Koeduka T., Fridman E., Gang D.R., Vassão D.G., Jackson B.L., Kish C.M., Orlova I., Spassova S.M., Lewis N.G., Noel J.P., Baiga T.J., Dudareva N., Pichersky E. (2006). Eugenol and isoeugenol, characteristic aromatic constituents of spices, are biosynthesized via reduction of a coniferyl alcohol ester. Proc. Nat. Acad. Sci., 103: 10128–10133.

Kohno H., Suzuki R., Yasui Y., Hosokawa M., Miyashita K., Tanaka T. (2004). Pomegranate seed oil rich in conjugated linolenic acid suppresses chemically induced colon carcinogenesis in rats. Cancer Sci., 95: 481–486.

Kolli-Bouhafs K., Boukhari A., Abusnina A., Velot E., Gies J. P., Lugnier C., Rondé P. (2012). Thymoquinone reduces migration

and invasion of human glioblastoma cells associated with *FAK, MMP-2* and *MMP-9* down-regulation. Clin. Drug Investig., 30: 2121–2131.

Kundu J., Kim D.H., Kundu J.K., Chun K.S. (2014). Thymoquinone induces heme oxygenase-1 expression in HaCaT cells via *Nrf2/ARE* activation: *Akt* and *AMPKα* as upstream targets. Food Chem. Toxicol., 65: 18–26.

Kurt Y., Kaya N., IŞik K. (2008). Isozyme variation in four natural populations of *Cedrus libani* A. Rich. in Turkey. Turk. J. Agric. For., 32: 137–145.

Kwak T.K., Sohn E.J., Kim S., Won G., Choi J.U., Jeong K., Kwon O.S., Kim S.H. (2014). Inhibitory effect of ethanol extract of *Ocimum sanctum* on osteopontin mediated metastasis of NCI-H460 non-small cell lung cancer cells. BMC Complement. Altern. Med., 14: 1–10.

Kweon S., Park K.A., Choi H. (2003). Chemopreventive effect of garlic powder diet in diethylnitrosamine-induced rat hepatocarcinogenesis. Life Sci., 73: 2515–2526.

Lansky E.P., Newman R.A. (2007). *Punica granatum* (pomegranate) and its potential for prevention and treatment of inflammation and cancer. J. Ethnopharmacol., 109: 177–206.

Lanzotti V., Barile E., Antignani V., Bonanomi G., Scala F. (2012). Antifungal saponins from bulbs of garlic, *Allium sativum* L. var. Voghiera. Phytochem., 78: 126–134.

Lei X., Lv X., Liu M., Yang Z., Ji M., Guo X., Dong W. (2012). Thymoquinone inhibits growth and augments 5-fluorouracil-induced apoptosis in gastric cancer cells both *in vitro* and *in vivo*. Biochem. Biophys. Res. Commun., 417: 864–868.

Li F., Rajendran P., Sethi G. (2010). Thymoquinone inhibits proliferation, induces apoptosis and chemosensitizes human multiple myeloma cells through suppression of signal transducer and activator of transcription 3 activation pathway. Br. J. Pharmacol., 161: 541–554.

Liu K., Chen Q., Liu Y., Zhou X., Wang X. (2012). Isolation and biological activities of decanal, linalool, valencene, and octanal from sweet orange oil. J. Food Sci., 77: C1156–C1161.

Magesh V., Lee J.C., Ahn K.S., Lee H.J., Lee H.J., Lee E.O., Shim B.S., Jung H.J., Kim J.S., Kim D.K., Choi S.H., Ahn K.S., Kim S.H. (2009). *Ocimum sanctum* induces apoptosis in A549 lung cancer cells and suppresses the *in vivo* growth of Lewis lung carcinoma cells. Phytother. Res., 23: 1385–1391.

Mahmoud G.I. (2013). Biological effects, antioxidant and anticancer activities of marigold and basil essential oils. J. Med. Plant Res., 7: 561–572.

Mahmoud S.S., Torchilin V.P. (2013). Hormetic/cytotoxic effects of *Nigella sativa* seed alcoholic and aqueous extracts on MCF-7 breast cancer cells alone or in combination with doxorubicin. Cell Biochem. Biophys., 66: 451–460.

Martino L. de., Bruno M., Formisano C., Feo V.D., Napolitano F., Rosselli S., Senatore F. (2009). Chemical composition and antimicrobial activity of the essential oils from two species of *Thymus* growing wild in southern Italy. Molecules, 14: 4614–4624.

Mat M.C., Mohamed A.S., Hamid S.S. (2011). Primary human monocyte differentiation regulated by *Nigella sativa* pressed oil. Lipids Health Dis., 10: 1–11.

Mehana E.S.E., Khafaga A.F., Elblehi S.S., Abd El-Hack M.E., Naiel M.A., Bin-Jumah M., Othman S.I., Allam A.A. (2020). Biomonitoring of heavy metal pollution using acanthocephalans parasite in ecosystem: An updated overview. Animals, 10: 811.

Mehta R., Lansky E.P. (2004). Breast cancer chemopreventive properties of pomegranate (*Punica granatum*) fruit extracts in a mouse mammary organ culture. Eur. J. Cancer Prev., 13: 345–348.

Menichini G., Alfano C., Provenzano E., Marrelli M., Statti G.A., Somma F., Menichini F., Conforti F. (2012). Fig latex (*Ficus carica* L. cultivar Dottato) in combination with UV irradiation decreases the viability of A375 melanoma cells *in vitro*. Anticancer Agents Med. Chem., 12: 959–965.

Millen A.E., Subar A.F., Graubard B.I., Peters U., Hayes R.B, Weissfeld J.L., Yokochi L.A., Ziegler R.G. (2007). PLCO Cancer Screening Trial Project Team. Fruit and vegetable intake and prevalence of colorectal adenoma in a cancer screening trial. Am. J. Clin. Nutr., 86:1754–1764.

Mohammadi M., Majd A., Nejadsattari T., Hashemi M. (2014). Antioxidant and anticancer activities of *Ocimum basilicum* L. cv. Dark Opal (Lamiaceae). Pharmacogn. Commun., 4: 48–58.

Motaghed M., Al-Hassan F.M., Hamid S.S. (2014). Thymoquinone regulates gene expression levels in the estrogen metabolic and interferon pathways in MCF7 breast cancer cells. Int. J. Mol. Med., 33: 8–16.

Muhammad N., Usmani D., Tarique M., Naz H., Ashraf M., Raliya R.,Tabrez S., Zughaibi T. A., Alsaieedi A., Hakeem I.J., Suhail M. (2022). The role of natural products and their multitargeted approach to treat solid cancer. Cells, 11: 2209.

Nagi M.N., Almakki H.A. (2009). Thymoquinone supplementation induces quinone reductase and glutathione transferase in mice liver: possible role in protection against chemical carcinogenesis and toxicity. Phytother. Res., 23: 1295–1298.

Nuutila A.M., Puupponen-Pimiä R., Aarni M., Oksman-Caldentey K.M. (2003). Comparison of antioxidant activities of onion and garlic extracts by inhibition of lipid peroxidation and radical scavenging activity. Food Chem., 81: 485–493.

O'Brien M.A., Kirby R. (2008). Apoptosis: A review of pro-apoptotic and anti-apoptotic pathways and dysregulation in disease. J. Vet. Emerg. Crit. Care, 18: 572–585.

Oliveira A.P., Pereira J.A., Andrade P.B., Valentão P., Seabra R.M., Silva B.M. (2007). Phenolic profile of *Cydonia oblonga* Miller leaves. J. Agric. Food Chem., 55: 7926–7930.

Oliviero M., Romilde I., Beatrice M.M., Matteo V., Giovanna N., Consuelo A., Claudio C., Giorgio S., Filippo M., Massimo N. (2016). Evaluations of thyme extract effects in human normal bronchial and tracheal epithelial cell lines and in human lung cancer cell line. Chem. Biol. Interact., 256: 125–133.

Pacheco-Palencia L.A., Noratto G., Hingorani L., Talcott S.T., Mertens-Talcott S.U. (2008). Protective effects of standardized pomegranate (*Punica granatum* L.) polyphenolic extract in ultraviolet-irradiated human skin fibroblasts. J. Agric. Food Chem., 56: 8434–8441.

Pacifico S., Gallicchio M., Fiorentino A., Fischer A., Meyer U., Stintzing F.C. (2012). Antioxidant properties and cytotoxic effects on human cancer cell lines of aqueous fermented and lipophilic quince (*Cydonia oblonga* Mill.) preparations. Food Chem. Toxicol., 50: 4130–4135.

Paramasivam A., Sambantham S., Shabnam J., Raghunandhakumar S., Anandan B., Rajiv R., Vijayashree P.J., Jayaraman G. (2012). Anti-cancer effects of thymoquinone in mouse neuroblastoma (Neuro-2a) cells through caspase-3 activation with down-regulation of XIAP. Toxicol. Lett., 213: 151–159.

Park J.E., Pezzuto J.M. (2002). Botanicals in cancer chemoprevention. Cancer Metastasis Rev., 21: 231–255.

Patel A., Hafez E., Elsaid F., Amanullah M. (2014). Anti-cancer action of a new recombinant lectin produced from *Acacia* species. Int. J. Med. Sci., 5: 1.

Patel B.P., Shah S.V., Shukla S.N., Shah P.M., Patel P.S. (2007). Clinical significance of MMP-2 and MMP-9 in patients with oral cancer. Head Neck., 29: 564–572.

Pawar V.A., Pawar P.R. (2014). *Costus speciosus*: an important medicinal plant. Int. J. Sci. Res., 3: 28–33.

Peng L., Liu A., Shen Y., Xu H.Z., Yang S.Z., Ying X.Z., Liao W., Liu H.X., Lin Z.Q., Chen Q.Y., Cheng S.W., Shen W.D. (2013). Antitumor and anti-angiogenesis effects of thymoquinone on osteosarcoma through the NF-κB pathway. Oncol. Rep., 29: 571–578.

Pieroni A., Quave C.L., Villanelli M.L., Mangino P., Sabbatini G., Santini L., Tomasi M. (2004). Ethnopharmacognostic survey on the natural ingredients used in folk cosmetics, cosmeceuticals and remedies for healing skin diseases in the inland Marches, Central-Eastern Italy. J. Ethnopharmacol., 91: 331–344.

Pitchai D., Roy A., Banu S. (2014). *In vitro* and *in silico* evaluation of *NF-κB* targeted costunolide action on estrogen receptor-negative breast cancer cells—a comparison with normal breast cells. Phytother. Res., 28: 1499–1505.

Prashanth G.K., Prashanth P.A., Nagabhushana B.M., Ananda S., Krishnaiah G.M., Nagendra H.G., Tejabhiram Y. (2018). Comparison of anticancer activity of biocompatible ZnO nanoparticles prepared by solution combustion synthesis using aqueous leaf ex-

tracts of *Abutilon indicum*, *Melia azedarach* and *Indigofera tinctoria* as biofuels. Artif. Cells Nanomed. Biotechnol., 46: 968–979.

Raghunandhakumar S., Paramasivam A., Senthilraja S., Naveenkumar C., Asokkumar S., Binuclara J., Devaki T. (2013). Thymoquinone inhibits cell proliferation through regulation of G1/S phase cell cycle transition in N-nitrosodiethylamine-induced experimental rat hepatocellular carcinoma. Toxicol. Lett., 223: 60–72.

Rajput S., Kumar B.P., Dey K.K., Pal I., Parekh A., Mandal M. (2013). Molecular targeting of Akt by thymoquinone promotes G1 arrest through translation inhibition of cyclin D1 and induces apoptosis in breast cancer cells. Life Sci., 93: 783–790.

Rana A., Anand J., Tyagi M., Rai N. (2021). Forest-based medicinal plants for cancer cure. In: Non-timber forest products, food, healthcare and industrial applications, Husen A., Bachheti R.K., Bachheti A. (eds). Springer, pp. 255–280.

Reddy S.E., Kirti Dolma S., Koundal R., Singh B. (2016). Chemical composition and insecticidal activities of essential oils against diamondback moth, *Plutella xylostella* (L.)(Lepidoptera: Yponomeutidae). Nat. Prod. Res., 30: 1834–1838.

Reindl W., Yuan J., Krämer A., Strebhardt K., Berg T. (2008). Inhibition of polo-like kinase 1 by blocking polo-box domain-dependent protein-protein interactions. Chem. Biol., 15: 459–466.

Renukadevi K.P., Sultana S.S. (2011). Determination of antibacterial, antioxidant and cytotoxicity effect of *Indigofera tinctoria* on lung cancer cell line NCI-h69. Int. J. Pharmacol., 7: 356–362.

Riahi-Chebbi I., Haoues M., Essafi M., Zakraoui O., Fattouch S., Karoui H., Essafi-Benkhadir K. (2015). Quince peel polyphenolic extract blocks human colon adenocarcinoma LS174 cell growth and potentiates 5-fluorouracil efficacy. Cancer Cell Int., 16: 1–15.

Roothaert R.L., Franzel S. (2001). Farmers' preferences and use of local fodder trees and shrubs in Kenya. Agrofor. Syst., 52: 239–252.

Roy A., Manikkam R. (2015). Cytotoxic impact of costunolide isolated from *Costus speciosus* on breast cancer via differential regulation of cell cycle–an *in-vitro* and in-silico approach. Phytother. Res., 29: 1532–1539.

Roy F., Boye J.I., Simpson B.K. (2010). Bioactive proteins and peptides in pulse crops: Pea, chickpea and lentil. Food Res. Int., 43: 432–442.

Rubnov S., Kashman Y., Rabinowitz R., Schlesinger M., Mechoulam R. (2001). Suppressors of cancer cell proliferation from fig (*Ficus carica*) resin: isolation and structure elucidation. Nat. Prod. Res., 64: 993–996.

Saab A.M., Lampronti I., Grandini A., Borgatti M., Finotti A., Sacchetti G., Guerrini A. (2011). Antiproliferative and erythroid differentiation activities of *Cedrus libani* seed extracts against K562 human chronic myelogenus leukemia cells. Int. J. Pharm. Biol. Arch., 2: 1744–1748.

Saab A.M., Guerrini A., Sacchetti G., Maietti S., Zeino M., Arend J., Efferth T. (2012). Phytochemical analysis and cytotoxicity towards multidrug-resistant leukemia cells of essential oils derived from Lebanese medicinal plants. Planta Med., 78: 1927–1931.

Saeed M., Abd El-Hack M.E., Alagawany M., Arain M.A., Arif M., Mirza M.A., Dhama K. (2017). Chicory (*Cichorium intybus*) herb: Chemical composition, pharmacology, nutritional and healthical applications. Int. J. Pharmacol., 13: 351–360.

Saeed M., Yatao X., Hassan F.U., Arain M.A., Abd El-Hack M.E., Noreldin A.E., Sun C. (2018). Influence of graded levels of l-theanine dietary supplementation on growth performance, carcass traits, meat quality, organs histomorphometry, blood chemistry and immune response of broiler chickens. Int. J. Mol. Sci., 19: 462.

Sakalar C., Yuruk M., Kaya T., Aytekin M., Kuk S., Canatan H. (2013). Pronounced transcriptional regulation of apoptotic and *TNF–NF*-kappa-B signaling genes during the course of thymoquinone mediated apoptosis in HeLa cells. Mol. Cell. Biochem., 383: 243–251.

Salim E.I., Fukushima S. (2003). Chemopreventive potential of volatile oil from black cumin (*Nigella sativa* L.) seeds against rat colon carcinogenesis. Nutr. Cancer., 45: 195–202.

Sayed-Ahmed M.M., Aleisa A.M., Al-Rejaie S.S., Al-Yahya A.A., Al-Shabanah O.A., Hafez M.M., Nagi M.N. (2010). Thymoquinone attenuates diethylnitrosamine induction of hepatic carcinogenesis through antioxidant signaling. Oxid. Med. Cell. Longev., 3: 254–261.

Seeram N.P., Adams L.S., Henning S.M., Niu Y., Zhang Y., Nair M.G., Heber D. (2005). *In vitro* antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. J. Nutr. Biochem., 16: 360–367.

Selim S., Al Jaouni S. (2015). Anticancer and apoptotic effects on cell proliferation of diosgenin isolated from *Costus speciosus* (Koen.) Sm. BMC Complement. Altern. Med., 15: 1–7.

Selim S., Al Jaouni S. (2016). Anti-inflammatory, antioxidant and antiangiogenic activities of diosgenin isolated from traditional medicinal plant, *Costus speciosus* (Koen ex. Retz.) Sm. Nat. Prod. Res., 30: 1830–1833.

Sertel S., Eichhorn T., Plinkert P.K., Efferth T. (2011). Cytotoxicity of *Thymus vulgaris* essential oil towards human oral cavity squamous cell carcinoma. Anticancer Res., 31: 81–87.

Sethi G., Ahn K.S., Aggarwal B.B. (2008). Targeting nuclear factor-κB activation pathway by thymoquinone: role in suppression of antiapoptotic gene products and enhancement of apoptosis. Mol. Cancer Res., 6: 1059–1070.

Setiawan V.W., Yu G.P., Lu Q.Y., Lu M.L., Yu S.Z., Mu L., Zhang Z.F. (2005). Allium vegetables and stomach cancer risk in China. Asian Pac. J. Cancer Prev., 6: 387.

Sezik E., Yeşilada E., Honda G., Takaishi Y., Takeda Y., Tanaka T. (2001). Traditional medicine in Turkey X. Folk medicine in central Anatolia. J. Ethnopharmacol., 75: 95–115.

Shahraki S., Mansouri-Torshizi H., Sadeghi M., Divsalar A., Saboury A.A. (2015). Novel Pt (II) complex and its Pd (II) aanalogue. Synthesis, characterization, cytotoxicity and DNA-interaction. Biomacromol. J., 1: 242–253.

Shahraki S., Khajavirad A., Shafei M.N., Mahmoudi M., Tabasi N.S. (2016). Effect of total hydroalcholic extract of *Nigella sativa* and its n-hexane and ethyl acetate fractions on ACHN and GP-293 cell lines. J. Tradit. Complement. Med., 6: 89–96.

Sharma P., McClees S.F., Afaq F. (2017). Pomegranate for prevention and treatment of cancer: an update. Molecules, 22: 177.

Shoieb A.M., Elgayyar M., Dudrick P.S., Bell J.L., Tithof P.K. (2003). *In vitro* inhibition of growth and induction of apoptosis in cancer cell lines by thymoquinone. Int. J. Oncol., 22: 107–113.

Silva J., Hussain A.I. (2017). *Citrullus colocynthis* (L.) Schrad. (colocynth): Biotechnological perspectives. Emir. J. Food Agric., 29: 83–90.

Singh B., Saxena A.K., Chandan B.K., Bhardwaj V., Gupta V.N., Suri O.P., Handa S.S. (2001). Hepatoprotective activity of indigtone – a bioactive fraction from *Indigofera tinctoria* Linn. Phytother. Res., 15: 294–297.

Singh G., Kapoor I.P.S., Singh P., de Heluani C.S., de Lampasona M.P., Catalan C.A. (2008). Chemistry, antioxidant and antimicrobial investigations on essential oil and oleoresins of *Zingiber officinale*. Food Chem. Toxicol., 46: 3295–3302.

Singh G., Passsari A.K., Leo V.V., Mishra V.K., Subbarayan S., Singh B.P., Nachimuthu S.K. (2016). Evaluation of phenolic content variability along with antioxidant, antimicrobial, and cytotoxic potential of selected traditional medicinal plants from India. Front. Plant Sci., 7: 407.

Specht C.D., Stevenson D.W. (2006). A new phylogeny-based generic classification of Costaceae (*Zingiberales*). Taxon, 55: 153–163.

Sreepriya M., Devaki T., Nayeem M. (2001). Protective effects of *Indigofera tinctoria* L. against D-galactosamine and carbon tetrachloride challenge on *'in situ'* perfused rat liver. Indian J. Physiol. Pharmacol., 45: 428–434.

Sridevi M., Bright J.O.H.N., Yamini K. (2016). Anti-cancer effect of *Ocimum-sanctum* ethanolic extract in non-small cell lung carcinoma cell line. Int. J. Pharm. Pharm. Sci., 8: 8–20.

Steriti R. (2002). Nutritional support for chronic myelogenous and other leukemias: a review of the scientific literature. Altern. Med. Rev., 7: 404–409.

Taie H.A.A., Radwan S. (2010). Potential activity of basil plants as a source of antioxidants and anticancer agents as affected by organic and bio-organic fertilization. Not. Bot. Horti. Agrobot., 38: 119–127.

Taleb R., El Hakim J., Elias A., Mroueh M., Daher C. (2014). Anticancer activity of 2-himachalen-7-ol isolated from *Cedrus libani*. Planta Med., 80: P1L27.

Tan W., Pan T., Wang S., Li P., Men Y., Tan R., Wang Y. (2022). Immunometabolism modulation, a new trick of edible and medicinal plants in cancer treatment. Food Chem., 131860.

Taylor R.C., Cullen S.P., Martin S.J. (2008). Apoptosis: controlled demolition at the cellular level. Nat. Rev. Mol., 9: 231–241.

Tezcan G., Tunca B., Bekar A., Yalcin M., Sahin S., Budak F., Bilir A. (2015). *Ficus carica* latex prevents invasion through induction of *let-7d* expression in GBM cell lines. Cell. Mol. Neurobiol., 35: 175–187.

Thabrew M.I., Mitry R.R., Morsy M.A., Hughes R.D. (2005). Cytotoxic effects of a decoction of *Nigella sativa*, *Hemidesmus indicus* and *Smilax glabra* on human hepatoma HepG2 cells. Life Sci., 77: 1319–1330.

Torres M.P., Ponnusamy M.P., Chakraborty S., Smith L.M., Das S., Arafat H.A., Batra S.K. (2010). Effects of thymoquinone in the expression of mucin 4 in pancreatic cancer cells: implications for the development of novel cancer therapies. Mol. Cancer Therap., 9: 1419–1431.

Tuntiwechapikul W., Taka T., Songsomboon C., Kaewtunjai N., Imsumran A., Makonkawkeyoon L., Pompimon W., Lee T.R. (2010). Ginger extract inhibits human telomerase reverse transcriptase and *c-Myc* expression in A549 lung cancer cells. J. Med. Food, 13: 1347–1354.

Turati F., Pelucchi C., Guercio V., Vecchia C.L., Galeone C. (2015). Allium vegetable intake and gastric cancer: A case–control study and meta-analysis. Mol. Nutr. Food Res., 59: 171–179.

Vidyavati H.G., Manjunatha H., Hemavathy J., Srinivasan K. (2010). Hypolipidemic and antioxidant efficacy of dehydrated onion in experimental rats. Food. Sci. Technol., 47: 55–60.

Vijayababu M.R., Arunkumar A., Kanagaraj P., Venkataraman P., Krishnamoorthy G., Arunakaran J. (2006). Quercetin downregulates matrix metalloproteinases 2 and 9 proteins expression in prostate cancer cells (PC-3). Mol. Cell. Biochem., 287: 109–116.

Vijayan R., Joseph S., Mathew B. (2018). *Indigofera tinctoria* leaf extract mediated green synthesis of silver and gold nanoparticles and assessment of their anticancer, antimicrobial, antioxidant and catalytic properties. Artif. Cells Nanomed. Biotechnol., 46: 861–871.

Viry E., Anwar A., Kirsch G., Jacob C., Diederich M., Bagrel D. (2011). Antiproliferative effect of natural tetrasulfides in human breast cancer cells is mediated through the inhibition of the cell division cycle 25 phosphatases. Int. J. Oncol., 38: 1103–1111.

Viuda-Martos M., Fernández-López J., Pérez-Álvarez J.A. (2010). Pomegranate and its many functional components as related to human health: a review. Compr. Rev. Food Sci. Food Saf., 9: 635–654.

Wang X., Bai H., Zhang X., Liu J., Cao P., Liao N., Zhang W., Wang Z., Hai C. (2013). Inhibitory effect of oleanolic acid on hepatocellular carcinoma via ERK–p53-mediated cell cycle arrest and mitochondrial-dependent apoptosis. Carcinogen., 34: 1323–1330.

Woo C.C., Hsu A., Kumar A.P., Sethi G., Tan K.H.B. (2013). Thymoquinone inhibits tumor growth and induces apoptosis in a breast cancer xenograft mouse model: the role of *p38 /MAPK* and ROS. PloS One, 8(10): e75356.

World Health Organization (2000). General guidelines for methodologies on research and evaluation of traditional medicine (No. WHO/EDM/TRM/2000.1). World Health Organization.

World Health Organization (2019). WHO global report on traditional and complementary medicine 2019. World Health Organization.

Worthen D.R., Ghosheh O.A., Crooks P.A. (1998). The *in vitro* anti-tumor activity of some crude and purified components of blackseed, *Nigella sativa* L. Anticancer Res., 18: 1527–1532.

Wu C., Wang M., Dong Y., Cheng Z., Meng H. (2015). Growth, bolting and yield of garlic (*Allium sativum* L.) in response to clove chilling treatment. Sci. Hortic., 194: 43–52.

Yeşilada E., Gürbüz İ., Shibata H. (1999). Screening of Turkish antiulcerogenic folk remedies for anti-*Helicobacter pylori* activity. J. Ethnopharmacol., 66: 289–293.

Zarlaha A., Kourkoumelis N., Stanojkovic T.P., Kovala-Demertzi D. (2014). Cytotoxic activity of essential oil and extracts of *Ocimum basilicum* against human carcinoma cells. Molecular docking study of isoeugenol as a potent cox and lox inhibitor. Dig. J. Nanomater. Biostructures., 9: 907–917.

Zeggwagh N.A., Sulpice T., Eddouks M. (2007). Anti-hyperglycaemic and hypolipidemic effects of *Ocimum basilicum* aqueous extract in diabetic rats. Am. J. Pharmacol. Toxicol., 2: 123–129.

Zeng Y.W., Du J., Pu X.Y., Yang J.Z., Yang T., Yang S.M., Yang X.M. (2015). Coevolution between human's anticancer activities and functional foods from crop origin center in the world. Asian. Pac. J. Cancer Prev., 16: 2119–2128.

Zhang Y., Wan Y., Huo B., Li B., Jin Y., Hu X. (2018). Extracts and components of *Ficus carica* leaves suppress survival, cell cycle, and migration of triple-negative breast cancer MDA-MB-231 cells. Onco Targets Ther., 11: 4377.

Zhou B., Yi H., Tan J., Wu Y., Liu G., Qiu Z. (2015). Anti-proliferative effects of polyphenols from pomegranate rind (*Punica granatum* L.) on EJ bladder cancer cells via regulation of *p53/miR-34a* Axis. Phytother. Res., 29: 415–422.

Zingue S., Njuh A.N., Tueche A.B., Tamsa J., Tchoupang E.N., Kakene S.D., Njamen D. (2018). *In vitro* cytotoxicity and *in vivo* antimammary tumor effects of the hydroethanolic extract of *Acacia seyal* (Mimosaceae) stem bark. BioMed Res. Int., 2018: 2024602.

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