GARLIC: A SOURCE OF HERBAL MEDICINES FOR CANCER THERAPY

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ABSTRACT
Garlic (Allium sativum) is one of most powerful aromatic food plant which is used to alleviate a variety of health problems. Garlic derived sulfur compounds hold unique therapeutic potential which inhibit cell proliferation and oncogenesis by triggering cell cycle arrest or apoptosis in a variety of cancer cells. Garlic derivatives are antimutagenic which suppress tumor formation, finish neoplastic growth and prevent aberrant cell expansion by slowing progression of the cell cycle. Garlic based composite herbal nanomedicines/formulations can target oxidants or pro-oxidants and activate pro-apoptotic proteins. Garlic based herbal products and targeted molecules can be recommended for clinical management of various cancer types i.e. colon cancer, rectal cancer, stomach cancer, breast cancer, prostate cancer and lung cancer.

KEYWORDS: Garlic, cell cycle arrest, apoptosis, cancer therapy, traditional medicine

INTRODUCTION
Allium sativum, is commonly known as lahsun in Hindi (Garlic in English). It belongs to family Alliaceae and plant order liliales.[1] Garlic (Allium sativum) has been used for centuries as a nutraceutical, prophylactic and therapeutic medicinal agent. This is a perennial, erect, bulbous herb indigenous to Asia but it is commercially grown in many parts of the world. Plant prefers sunny dry spots in relatively arid climate. Both cultivated and wild species of garlic are available in different climatic regions. Its bulbs contain number of concentric bulblets that spread a characteristic strong alliaceous odor with persistent pungent acid taste. Among Allium species Allium sativum L. is an important aromatic plant that contains sulfur compounds and has multiple uses. [2] It possesses characteristic pungent flavor and medicinal properties. Other members of the garlic family include Allium cepa (onion),
Allium ascalanicum (shallot) and Allium porrum (Heeks). Garlic is a main combined foodstuff which is traditionally used as a medicine in India. It is a rich source of organo-sulfur compounds, which are thought to be responsible for its flavor and aroma, as well as its potential health benefits. It is one of the important Alliums that are used for both culinary and medicinal purposes by many cultures for centuries.

Garlic is a multi-component pioneer food that shows inhibition of oncogenesis, tumorigenesis, induction of cell cycle arrest and apoptosis, cancer cell proliferation and invasion can be used as a better tool in cancer treatment. Garlic and its components possess following anticancer activities. p63 and p73 are rarely associated with human cancer. This review aims to display an overview about recent researches done on apoptotic signaling pathways, cell cycle arrest, cytotoxicity and anti-invasive properties of garlic. This herbal medicine either induces or stops or inhibits main mechanisms by which cancer cells undergo programmed cell death. The green vegetable has enough potential to play a critical role in tumor suppression, repair of DNA damage, oncogene activation and telomerase erosion. Its sulfur components manage cell cycle arrest and induce apoptosis and exert cytotoxic activity involving activation of mitochondrial-dependent apoptosis through p53 and Bax/Bcl-2 pathways in human gastric cancer. Most important advancements can be done by understanding cancer biology and cancer genetics for induction of apoptosis and the genes that control malignancy.

Present review article describing use of garlic components for inducing apoptosis via small molecule drug treatments, death receptor ligation, and exposure to granule components of cytotoxic lymphocytes. Garlic based nanoformulations or nanomedicine could be used for induction of apoptosis by making changes in mitochondrial membrane potential, phosphatidylserine membrane localization, DNA content, and antigen cleavage. Garlic based nanoformulations can target oncogenic mutations which disrupt apoptosis, leading to tumor initiation, progression or metastasis or these may slow down oncogenic changes which promote apoptosis. By designing best possible targets against cancer progression and by producing selective pressure to override apoptosis and to finish multistage carcinogenesis new combinations of garlic components could be made. From biochemical researches it is now well documented that most of the garlic components are cytotoxic and anticancer agents which induce apoptosis. Hence, all intriguing possibilities that are responsible for defects in apoptotic pathways which contribute to treatment failure can be resolved by making
appropriate combinations. More often, defective or inefficient apoptosis is considered to be a hallmark of cancer cells. Therefore, a thorough understanding of apoptotic signaling pathways and insights into apoptosis resistance mechanisms are imperative to unravel novel drug targets for the design of more effective and target selective therapeutic strategies. Hence, there is an immense need to make conceptual framework that can link cancer genetics with cancer therapy by designing new strategies to exploit apoptosis for therapeutic benefits. For better cancer therapeutics oncogenes such as E1A and c-myc which induce apoptosis through p53-dependent and independent pathways, and pathways which facilitate cytochrome c release from mitochondria could be properly explored. In addition, new insights related to apoptotic signaling pathways, which are used by cancer cells to resist apoptotic insults, must be cleared with strong efforts to target the mitochondrion for restoring efficient cell death signaling in cancer cells.

Anticancer potential

Inhibition of carcinogenesis

Garlic is a multi-component pioneer food that prevents progression of cancer and chronic diseases. Garlic contains good nutraceutical which are highly protective to lung cancer and increase the life expectancy in cancer patients.[3][5][6] Dietary consumption of green garlic bulbs reduce all types of cancer risks,[7,6] stops invasion and progression of cervical cancer.[8] Homemade garlic ailments and preparations are used as herbal drug as complementary therapy of cancer. Garlic oil inhibits the proliferation of AsPC-1, PANC-1, and Mia PaCa-2 cells while garlic garlic tea shows strong therapeutic potential against lung and colorectal cancer.[9] Both black and green garlic extracts (BGE) check proliferation of lung[10] and colorectal cancer and inhibits other types of carcinoma.[11] It contains S-allylcysteine (SAC), one of the major water-soluble compounds significantly inhibit oncogenesis,[12] while, S-Allylmercaptocysteine (CySSA) is known to exhibit anti-cancer effects.[13]

Cyclic sulfoxides garlicnins B2, B3, B4, C2, and C3 isolated from Allium sativum are toxic to cancer cells.[14] DATS prevents tumor progression and promotes apoptosis in ectopic glioblastoma xenografts in SCID mice via HDAC inhibition[15] (Table 1). Allii, isolated from garlic (Allium sativum) prevents LPS-induced inflammation in 3T3-L1 adipocytes. Sodium 2-propenyl thiosulfate derived from garlic induces phase II detoxification enzymes in rat hepatoma H4IIE cells[16] while conjugates of daidzein-alliinase are used as a targeted pro-
drug enzyme system against ovarian carcinoma.\cite{17} Thiacremonone (2, 4-dihydroxy-2, 5-dimethyl-thiophene-3-one) is sulfur compound generated from high-temperature-high-pressure-treated garlic\cite{18} shows inhibition of NF-kappaB and cancer cell growth with IC(50) values about 100 microg/mL in colon cancer cells.\cite{19} Peroxiredoxin 6 (PRDX6) is a member of peroxidases, and has glutathione peroxidase and calcium-independent phospholipase A2 (iPLA2) activities. Garlic, silver bullets are used for carcinoma surveillance in upper endoscopy for Barrett's esophagus\cite{20} (Table 1).

**Induction of cell cycle arrest**

Among molecular anticancer mechanisms induction of apoptosis and cell cycle arrest are important events. However, experimental apoptosis can be achieved by the means of cell death through the effects on mitochondrial function after treatment of cancer cell lines with garlic sulfur compounds. AGE induce cytotoxic effects in various human cancer cell lines which can be established by enumerating cell morphological changes, determining percentage of viable cells and induction of apoptosis. Diallyl sulfide promotes cell-cycle arrest through the p53 expression and triggers induction of apoptosis via caspase- and mitochondria-dependent signaling pathways in human cervical cancer Ca Ski cells.\cite{21} It induces apoptosis in MCF7 human breast cancer cells\cite{22} and induce cell cycle arrest in prostate cancer cell line PC-3 and apoptosis induction in cancer cells\cite{23,24} It also controls unregulated cell division in human cancer cells and influence cell-cycle dysregulation\cite{25} and control signal transduction pathways. More often, garlic derived organosulfur compounds, mainly DATS, DADS, ajoene, and S-allylmercaptocysteine (SAMC) induce cell cycle arrest in cancer cells in culture experiments\cite{24,26,27} (Table 1). These compounds also induce specific programmed cell death or apoptosis that can be established by staining cell with DAPI stain in sub-G1 phase. Furthermore, flow cytometric assays are used to display AGE promoted the production of reactive oxygen species and nitric oxide. Further possibilities such as decrease in levels of mitochondrial membrane potential and promotion/activation of caspase-8 and -9 activities could be established.

Diallyl sulfide induces cell cycle arrest and apoptosis in HeLa human cervical cancer cells through the p53, caspase- and mitochondria-dependent pathways.\cite{28} It also suppresses X-linked inhibitor of apoptosis protein in prostate cancer cells in culture and in vivo.\cite{29} Diallyl disulfide causes inhibition of matrix metalloproteinase activities and tightening of tight junctions by in AGS human gastric carcinoma cells \cite{30} while diallyl trisulfide inhibits
activation of signal transducer and activator of transcription 3 in prostate cancer cells in culture and in vivo.\[31\] Diallyl disulfide induces caspase-dependent apoptosis via mitochondria-mediated intrinsic pathway in B16F-10 melanoma cells by up-regulating p53, caspase-3 and down-regulating pro-inflammatory cytokines and nuclear factor-κβ-mediated Bcl-2 activation.\[32\] Similarly, S-benzyl-cysteine (SBC) a structural analog of SBC exerts cytotoxic activity involving activation of mitochondrial-dependent apoptosis through p53 and Bax/Bcl-2 pathways in human gastric cancer SGC-7901 cells \[33\] (Table 1). There remains a possibility that AGE may inhibit the level of Bcl-2 or promote the Bax level, and both proteins may lead to the release of cytochrome c from mitochondria to cytosol and activation of caspase-9 and -3, resulting in the apoptotic death which is mediated through the mitochondrial pathway. Collectively diallyl disulfide induces effective killing of cancerous cells via the ROS-promoted and mitochondria- and caspase-dependent apoptosis.\[32\]

**Induction of apoptosis**

Induction of apoptosis is indeed dependent on the redox-state of the cell, with anti-oxidants being able to prevent sulfide-induced apoptosis.\[34\] Furthermore, using cellular assays based on component susceptibility experiments can find out positive or negative effects which could be displayed by p53 gene mutations and its expression in cells mainly related to induction of apoptosis. However, both growth arrest and induction of apoptosis is associated with a considerable reduction of the level of cdc25C. As in normal tissues homeostasis is maintained by a highly regulated process of cellular differentiation balanced by cell death. It could be maintained in the state of disease or pathogenesis by right garlic components that are to be discovered. Garlic derived polysulfides lead to induction of apoptosis.\[34\] Oncogenes and tumor suppressor genes have been shown to play an important role in this process by regulating either cellular proliferation or cell death. Garlic derived organosulfur compounds can control cancer cell proliferation, angiogenesis and metastasis after identifying appropriate garlic based formulations. There is a possibility that garlic may restore all three different categories of cancer associated genes. First category of proto-oncogenes and their oncogenic counterparts encodes proteins that induce cellular proliferation. Some of these proteins function as growth factors or growth factor receptors. In normal cells the expression of growth factors and their receptors is carefully regulated. Garlic possesses apoptosis inducers which act on several apoptosis-related proteins to promote apoptotic cell death. Even its components bind to growth factor receptors and normalize any type of aberration related to gene function. A second category of genes called tumor suppressor genes or anti-oncogenes
encodes proteins that inhibit excessive cell proliferation. Inactivation of these genes results in unregulated proliferation. Garlic antioxidants and enzymatic inhibitors check unregulated cellular proliferation by making interference in metabolic pathways which synthesize cancer growth promoting factors.

Garlic induces caspase activity which halts or stalls mutation in p53 gene and thereby stop growth of lung, colon, and breast cancer. A third category of cancer associated genes encode and regulate programmed cell death. These genes encode proteins that either block or induce apoptosis, bcl-2 is an anti-apoptosis gene. DATS-induced apoptosis does down-regulation of Bcl-2, Akt and cyclin D1 protein levels, and up-regulation of Bax, Fas, p53 and cyclin B protein levels in Capan-2 cells[35] (Table 1). More specifically carcinogens and viruses might alter the regulated function of these genes and converting them into potent cancer causing genes. In such a condition garlic derived components mainly sulfur compounds, saponins and vitamins can evoke tumor suppressor gene and stop conversion of protooncogenes in to oncogenes. All this may occur due to mutations or due to genetic rearrangements of protooncogenes. Obviously, conversion of proto-oncogenes into oncogenes can involve mutation, resulting in production of qualitatively different gene products or DNA amplification or translocation, resulting in increased expression of gene products that may harm normal physiological metabolism of a normal cell. More specifically, viral integration into the host genome serves to convert a proto-oncogene into a transforming oncogene. Retroviruses have shown to integrate within the c-myc proto-oncogene. Such transformed or metastatic cells can be depleted by programmed cell death only through apoptosis induction pathways.

In normal cells growth occurs at regular interval through well controlled phases of mitotic cell division. Normally in the body old cells or defective cells are killed by apoptosis but to finish cancerous cells apoptosis is highly important event because it controls cell number and support healthy cells to live. Usually cancer cells display defective or inefficient or low apoptosis that is an important hallmark of these cells. Apoptosis is displayed mainly by cell shrinkage, blebbing of plasma membrane, maintenance of organelle integrity, condensation and fragmentation of DNA, followed by ordered removal of phagocytes.[36] It is operated like a suicide program to kill cancer cells and maintain minimal damage to surrounding tissues. Apoptosis is followed by two types of death pathways, namely, the extrinsic pathway and the mitochondria-mediated pathway. diallyl trisulfide-induce apoptosis of bladder cancer cells which is caspase-dependent and regulated by PI3K/Akt and JNK pathways.[37] These two
processes however, are not exclusive but these are linked and molecules in one pathway can influence the other.\[38\] Moreover, recent evidences support non-apoptotic roles for many effectors of the apoptotic signaling pathways. For instance, caspase 2, the most conserved member of the caspase family that also plays important role in cell cycle regulation, DNA repair, and tumor suppression\[39\]

Apoptosis is regulated by the Bcl-2 family of proteins which are called anti-apoptotic proteins. Bcl-2, Bcl-XL, and Mcl-1 are anti-apoptotic proteins that possess all the four domains (BH1-4). These proteins regulate apoptotic events and shares homology in any of the four common Bcl-2 homology (BH) domains. The second category of Bcl-2 family of proteins contains BH domains 1, 2 and 3. These proteins would include Bax and Bak. Bax is a pro-apoptotic protein that resides in the cytosol under physiological conditions. The third group of Bcl-2 family of proteins is the BH3-only proteins. The BH3-only family members include Bim, Bad, Bmf, Noxa and Puma. They act by neutralizing the anti-apoptotic proteins.\[40\] DADS induces apoptosis in the MCF-7 breast-cancer cell line through interfering with cell-cycle growth phases in a way that increases the sub-G(0) population and substantially halts DNA synthesis. DADS also induce phosphatidylinerine translocation from the inner to the outer leaflet of the plasma membrane and activate caspase-3 activity. Further studies revealed that DADS modulates the cellular levels of Bax, Bcl-2, Bcl-xL, and Bcl-w in a dose-dependent manner, suggesting the involvement of Bcl-2 family proteins in DADS induced apoptosis. Histone deacetylation inhibitors (HDACi) are known to suppress cancer growth and induce apoptosis in cancer cells. Here it is shown that DADS has HDACi properties in MCF-7 cells as it lowers the removal of an acetyl group from an acetylated substrate and induces histone-4 (H4) hyper-acetylation. There is a possibility that DADS may be responsible for the induction of apoptosis in breast cancer cells.\[41\]

Garlic components act upon two pathways of target cell apoptosis stimulated by CTLs. The Fas pathway in which ligation of trimeric Fas units by CTL borne Fas ligands leads to the association of death domains of Fas with FADD which in turn results in a series of reactions leading apoptosis of target cell. Second the parforin/granzyme pathway in which granule exocytosis relases garnzyme and perforin from the CTL into the space between the CTL and target cell. Granzyme B enters the target cell in two pathways via perforin generated pores or by binding to mannose 6 phosphate receptors that are subsequently endocytosed. Garnzyme is released into the cytoplasm in a perforin dependent process. Cleavage in procaspase 8 by
granzyme B activates a caspase cascade that results in the apoptotic death of the cell and interaction of Granzyme B with other targets can invoke mitochondrially mediated death pathways.

In normal cells, the cell cycle is tightly regulated to ensure faithful DNA replication and chromosomal segregation prior to cell division. Following DNA damage, the cell cycle can be transiently arrested to allow for DNA repair or activation of pathways leading to cell death (apoptosis). Apoptosis is induced in experimental systems through a variety of methods but there are two known methods biological induction and chemical induction. In biological induction activation of Fas or TNF receptors by their respective ligands, or by cross-linking with an agonist antibody, induces apoptosis of Fas- or TNF receptor-bearing cells. In chemical apoptosis inducers act on several apoptosis-related proteins to promote apoptotic cell death. Garlic oil induce programmed cell death, cell cycle arrest, and show pro-apoptosis effects on AsPC-1 cells\(^{[42]}\) and human pancreatic carcinoma cells.\(^{[42]}\) Depending on the agent selected and the concentrations used, apoptotic events can be detected between 8–72 h post-treatment. There are many more possibilities that different natural products may opt different pathway to maintain apoptosis in cancer cells. It is a potential therapeutic compound isolated from garlic derivative\(^{[43]}\) that suppresses proliferation and induces apoptosis in human ovarian cancer cells in vitro.\(^{[44]}\) S-allylcysteine is also used to enhance apoptosis in oral cancer by inducing cellular damage (Table 1). It also induces apoptosis in human breast cancer cells through ROS-mediated activation of JNK and AP-1.\(^{[45]}\)

Allyl sulfides inhibit cell growth of skin cancer cells through induction of DNA damage mediated G2/M arrest and apoptosis.\(^{[46]}\) Both allicin and allyl-mixed disulfides with proteins and small thiol molecules show good anticancer activity\(^{[47]}\) (Table 1). These organo-sulfur compounds from garlic are considered as safe botanicals\(^{[48]}\) which possess multiple therapeutic potential\(^{[49]}\) against different cancer types.\(^{[50]}\) These organosulfur compounds do induction of apoptosis in tumor cells.\(^{[51]}\) Alliin, isolated from garlic (Allium sativum) prevents LPS-induced inflammation in 3T3-L1 adipocytes\(^{[52]}\) while thiacremone shows anticancer activity and does down regulation of peroxiredoxin.\(^{[18]}\) Black garlic extract is strong inhibitor of lung cancer cell proliferation and radio sensitization\(^{[10]}\) (Table 1).

Allicin inhibits cell growth and induces apoptosis in U87MG human glioblastoma cells through an ERK-dependent pathway.\(^{[53]}\) It induces p53-mediated autophagy in Hep G2 human liver cancer cells\(^{[54]}\) and induces apoptosis in EL-4 cells in vitro by activation of
expression of caspase-3 and -12 and up-regulation of the ratio of Bax/Bcl-2.\textsuperscript{[55]} It also induces apoptosis in gastric cancer cells through activation of both extrinsic and intrinsic pathways.\textsuperscript{[56]} Allicin purified from fresh garlic cloves induces apoptosis in colon cancer cells via Nrf2\textsuperscript{[57]} while diallylpolysulfides induce growth arrest and apoptosis in cells.\textsuperscript{[34]} Allicin induce autophagic cell death in human HCC Hep G2 (p53(wild type)) cells, it may also induce apoptotic cell death through caspase-dependent and caspase-independent pathways by reactive oxygen species (ROS) overproduction in human HCC Hep 3B (p53(mutation)) cells. Moreover, in cell death mechanism p53 knocked down Hep G2, and silenced the p53 gene using siRNA-mediated silencing. However, allicin treatment induces apoptotic cell death in p53 knocked down Hep G2 cells similar to that of Hep 3B cells.\textsuperscript{[4]}

Similarly, di-allyl disulfide, a garlic component plays important role of in NF-κB mediated transient G2-M phase arrest and apoptosis in human leukemic cell-lines.\textsuperscript{[58]} Diallyl tetrasulfide induce mitotic arrest to apoptosis.\textsuperscript{[59]} It also induces apoptosis in human primary colorectal cancer cells\textsuperscript{[60]} and AGS gastric cancer cell line.\textsuperscript{[61]} Diallyl trisulfide sensitzes human melanoma cells to TRAIL-induced cell death by promoting endoplasmic reticulum-mediated apoptosis.\textsuperscript{[62]} It induces apoptosis and inhibits proliferation of A549 cells \textit{in vitro} and \textit{in vivo}.\textsuperscript{[63]} Allyl sulfides inhibit cell growth of skin cancer cells through induction of DNA damage mediated G2/M arrest and apoptosis.\textsuperscript{[13]} Similarly and S-alkenylmercaptocysteine (CySSR) with sodium selenite induce apoptosis in pancreatic cells.\textsuperscript{[65]} DATS-induced apoptosis is related with induction of pro-apoptotic Bax protein and p53 protein expression that was found upregulated and translocation to nucleus in MCF-7 cells.\textsuperscript{[22]} DATS inhibits phosphatidylinositol 3’-kinase/Akt activation that, in turn, results in modulation of Bcl-2 family proteins, leading to enhanced apoptosis of T24 cells.\textsuperscript{[13]} S-benzylcysteine mediate cell cycle arrest and apoptosis involving activation of mitochondrial-dependent caspase cascade through the p53 pathway in human gastric cancer SGC-7901 cells\textsuperscript{[66]} (Table 1). Thiacremonone inhibits lung cancer cell growth in a concentration dependent manner through induction of apoptotic cell death accompanied by induction of cleaved caspase-3, -8, -9, Bax, p21 and p53, but decrease of xIAP, cIAP and Bcl2 expression and inhibition of glutathione peroxidase activity of of PRDX6 through interaction.\textsuperscript{[18]}

The DATS-induced apoptosis in MDA-MB-231, MCF-7, and BRI-JM04 cells was associated with reactive oxygen species (ROS) production as evidenced by fluorescence microscopy and flow cytometry using a chemical probe (MitoSOX Red).\textsuperscript{[18]} However, over expression of
Cu,Zn-superoxide dismutase (Cu,Zn-SOD) as well as Mn-SOD conferred significant protection against DATS-induced ROS production and apoptotic cell death in MDA-MB-231 and MCF-7 cells. Activation of Bak, but not Bax, resulting from DATS treatment was markedly suppressed by overexpression of Mn-SOD. The DATS treatment caused ROS generation, but not activation of Bax or Bak, in MCF-10A cells. Furthermore, the DATS-mediated inhibition of cell migration was partially but significantly attenuated by Cu, Zn-SOD and Mn-SOD overexpression in association with changes in levels of proteins involved in epithelial-mesenchymal transition. The DATS-mediated induction of heme oxygenase-1 was partially attenuated by overexpression of Mn-SOD. There seems critical role for ROS in anticancer effects of DATS. S-Allylmercaptocysteine does cell cycle arrest at the G2/M and sub-G1 interphases. DAS-induced G0/G1 phase arrest is mediated through the increased expression of p21, p27, and p53 with a simultaneous decrease in CDK2, CDK6, and CHK2 expression. However, Ca Ski cells after exposure to DAS go under apoptosis, with significant morphological changes and DNA condensation, that also altered the ratio of Bax/Bcl-2 and sub-G1 phase. Furthermore, DAS induced mitochondrial dysfunction, leading to the release of cytochrome c for causing apoptosis in Ca Ski cells. Due to these properties DAS is considered a well know potential chemotherapeutic agent for the treatment of cervical cancer.

Cell cycle checks points
There are certain cell cycle check points such as late G2 check point controls progression of cell cycle from G2 to M phase. Here, active Cdk1 (cdc2) for formation of complex, cyclin B1 is required. In next step for regulation of the cdc-B1 complex inhibitory phosphatases are needed at a pair of amino acids in the roofs of the active site by Wee1 (Fig 1 and 2). After dephosphorylation of these sites by the phosphatase Cdc25C increases Cdk activity. At this stage DNA damage activates Chk1 which inactivates Cdc25C through phosphorylation of cdc25C. This results in the phosphorylation and activity of cdc2-B1 and G2-M arrest (1 and 2). More often G1/S is an important checkpoint that controls progression of cells through the restriction point (R) into the DNA synthesis S-phase (1 & 2). During G1 stage, the tumor suppressor Rb binds and inhibits transcription factor E2F. More specifically, diallyl trisulfide-induced G2/M phase cell cycle arrest in DU145 cells is associated with delayed nuclear translocation of cyclin-dependent kinase 1 while synthetic polysulfane derivatives induce cell cycle arrest and apoptotic cell death in human hematopoietic cancer cells (Table 1). DAS also induce G0/G1 cell cycle arrest and apoptosis in HeLa cells.
through caspase- and mitochondria and p53 pathways. It significantly inhibits the growth and induces apoptosis of human cervical cancer HeLa cells in vitro.\textsuperscript{[28]}

Diallyl disulphide, a beneficial component of garlic oil, causes a redistribution of cell-cycle growth phases, induces apoptosis, and enhances butyrate-induced apoptosis in colorectal adenocarcinoma cells (HT-29).\textsuperscript{[41]} Garlic sulfur components may activate phosphorylation of Rb by cyclin-bound cyclin dependent kinases (CDK) in late G1 induces dissociation of Rb and permits E2F-mediated transcription of S-phase-promoting genes.\textsuperscript{[68]} Responding to upstream signals, INK4 and Kip/Cip family inhibitors control CDK activity and prevent entry into S-phase. ). DNA damage activates response pathways through ATM/ ATR and Chk1/2 kinases to block CDK activity\textsuperscript{[69]}, leading to cell cycle arrest and DNA repair or cell death.\textsuperscript{[70]} DATS suppressed the viability of cultured human pancreatic cancer cells (Capan-2) by increasing the proportion of cells in the G2/M phase and induced apoptotic cell death. DATS enhanced the expression of Fas, p21, p53 and cyclin B1, but down regulated the expression of Akt, cyclin D1, MDM2 and Bcl-2.\textsuperscript{[64]} DATS induces cell cycle inhibition and elevated levels of cyclin B1 and p21, and reduced levels of cyclin D1 in Capan-2 cells and H6C7 cells.\textsuperscript{[64]} DATS reduced mitosis in tumors, decreased HDAC activity, increased acetylation of H3 and H4, inhibited cell cycle progression, decreased pro-tumor markers (e.g., survivin, Bcl-2, c-Myc, mTOR, EGFR, VEGF), promoted apoptotic factors (e.g., bax, mcalpian, active caspase-3), and induced DNA fragmentation. There also occurs an increase in p21Waf1 expression, which correlated with increased p53 expression and MDM2 degradation following DATS treatment.\textsuperscript{[15]} DATS suppressed the viability of cultured human pancreatic cancer cells (Capan-2) by increasing the proportion of cells in the G2/M phase and induced apoptotic cell death. In Western blot analysis DATS was found to enhance the expression of Fas, p21, p53 and cyclin B1, but down regulated the expression of Akt, cyclin D1, MDM2 and Bcl-2.\textsuperscript{[15]} DATS induced cell cycle inhibition which was correlated with elevated levels of cyclin B1 and p21, and reduced levels of cyclin D1 in Capan-2 cells and H6C7 cells.\textsuperscript{[64]} a DATS causes cytotoxicity which is mediated by the generation of ROS and subsequent activation of the ASK1-JNK-Bim signal transduction pathway in human breast carcinoma MDA-MB-231 cells.\textsuperscript{[61]} S-benzyl-cystein also mediate cell cycle arrest and operate apoptosis that involves activation of mitochondrial-dependent caspase cascade through the p53 pathway in human gastric cancer SGC-7901 cells.\textsuperscript{[33]} Tumor cells packing p53 may continue to replicate damaged DNA and do not undergo apoptosis. Finally, cell cycle stalls in the cells with the damaged DNA.
Cells treated with different concentrations of DAS also showed changes typical of apoptosis such as morphological changes, DNA damage and fragmentation, dysfunction of mitochondria. It also induce cytochrome c release and increase expression of pro-caspase-3 and -9. DAS also promote the release of AIF and Endo G from mitochondria in HeLa cells.\textsuperscript{[28]} In fact G2/M checkpoint prevents cells containing damaged DNA from entering mitosis (M). Activated CDK1 (cdc2) bound to cyclin B promotes entry into M-phase. Wee1 and Mit1 kinases and cdc25 phosphatase competitively regulate CDK1 activity; Wee1 and Mit1 inhibit CDK1 and prevent entry into M-phase, while cdc25 removes inhibitory phosphates. DNA damage activates multiple kinases activity\textsuperscript{[71]} phosphorylate kinases Chk1/2 and tumor suppressor protein p53. Chk1/2 kinases stimulate Wee1 activity and inhibit cdc25C, preventing entry into M-phase.\textsuperscript{[72]}

Phosphorylation of p53 promotes dissociation between p53 and MDM2 and allows binding of the transcription factor to DNA (Fig 1 and 2). SFN Sulforaphane (SFN) and NaHS activated p38 mitogen-activated protein kinases (MAPK) and c-Jun N-terminal kinase (JNK).\textsuperscript{[73]} Pretreatment of PC-3 cells with methemoglobin decreased SFN-stimulated MAPK activities. DATS inhibits phosphatidylinositol 3'-kinase/Akt activation that, in turn, results in modulation of Bcl-2 family proteins, leading to enhanced apoptosis of T24 cells.\textsuperscript{[74]} Crushed garlic inhibit the proliferation of tumour cells by inducing G(2)/M cell cycle arrest and apoptosis.\textsuperscript{[75]} Similarly, ajoene also inhibit WHCO1 cell growth, inducing G(2)/M cell cycle arrest and apoptosis by caspase-3 activation. Here, vinyl group serves to enhance the anti-proliferation activity manifold.\textsuperscript{[75]}

DADS inhibit the activation and nuclear translocation of p65, p50, and c-Rel subunits of nuclear factor (NF)-B and other transcription factors, such as c-fos, activated transcription factor-2, and cyclic adenosine monophosphate response element-binding protein, in B16F-10 melanoma cells.\textsuperscript{[32]} The pro-inflammatory cytokine production and gene expression of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF) were down-regulated in DADS-treated cells compared with control B16F-10 metastatic melanoma cells. DADS induces caspase-dependent apoptosis through a mitochondria-mediated intrinsic pathway in B16F-10 melanoma cells by activating p53 and caspase-3 gene expression and suppressing pro-inflammatory cytokines and NF-B-mediated Bcl-2 activation.\textsuperscript{[32]} DADS treatment of colonic adenocarcinoma cells (HT-29) initiates a cascade of molecular events characteristic of apoptosis. These include a decrease in
cellular proliferation, translocation of phosphatidylserine to the plasma-membrane outer-layer, activation of caspase-3 and -9, genomic DNA fragmentation, and G(2)/M phase cell-cycle arrest.\[^77\] Short-chain fatty acids (SCFAs), particularly butyrate (abundantly produced in the gut by bacterial fermentation of dietary polysaccharides), enhance colonic cell integrity but, in contrast, inhibit colonic cancer cell growth.\[^77\] Combining DADS with butyrate augmented the apoptotic effect of butyrate on HT-29 cells. More likely, anticancerous properties of DADS are of greater benefit when supplied with other favorable dietary factors (short chain fatty acids/polysaccharides) that likewise reduce colonic tumor development.\[^77\]

More specifically, DATS-mediated G2/M phase cell cycle arrest was found to be independent of reduced complex formation between cdk1 and cyclin B1, but it is correlated with delayed nuclear translocation of cdk1. Moreover, this DATS-mediated G2/M phase cell cycle arrest in DU145 cells results from differential kinetics of nuclear localization of cdk1 and cyclin B1.\[^67\] DAS treatment increased the accumulation of sub-G1 DNA and concomitant accumulation of cells in the G2/M phase in a dose-dependent manner. In addition, DAS-induced apoptosis shows a decrease in the level of Bcl-2 expression and an increase in the level of Bax expression, and cytochrome c was remarkably released from mitochondrial into the cytosol by DAS. Furthermore, caspase-9 and caspase-3 were activated by DAS, and DAS cleaved PARP. DAS decreases cell proliferation and induce apoptosis via mitochondrial signaling pathway in ATC cells.\[^78\] Here, both p38MAPK and caspase-3 are seems to be involved in the process of DADS-induced apoptosis in human HepG2 cells and interact with each other.\[^79\] Diallyl trisulfide inhibits phorbol ester-induced tumor promotion, activation of AP-1, and expression of COX-2 in mouse skin by blocking JNK and Akt signaling.\[^80\]

DADS treatment causes significant transcriptional induction of p21 in early hours of treatment, which is due to increased nuclear translocation of NF-κB and its specific binding to p21 promoter. It also induce transient G2/M phase arrest, which in later hours is lost leading to apoptosis via intrinsic mitochondria-mediated pathway through generation of reactive oxygen species followed by changes in mitochondrial membrane potential.\[^58\] Western blots indicate release of cytochrome-c, activation of caspase-3, cleavage of PARP1, and finally decrease in bcl-2 levels. In addition, inactivation of NF-κB by its inhibitor BAY 11-7085 causes early onset of apoptosis without any transient G2/M arrest. DADS induces reversible G2/M arrest through NF-κB mediated pathway in human leukemic cell lines, like U937, K562 and Jurkat, lacking wild type p53. However, G2/M arrest is lost owing to the
incapability of the damage repair system that leads to apoptosis.\textsuperscript{[58]} Similarly, BGE and radiotherapy combination significantly induce Lewis cells' apoptosis in G2/M stage which decreases the expression of bcl-2, and up-regulated the expression of bax.\textsuperscript{[10]} BGE could sensitize the lung cancer Lewis cells to ionizing irradiation. This effect might be probably caused by changing the cell cycles and affecting expressions of bax and bcl-2.\textsuperscript{[10]}

Spindle check points\textsuperscript{[81]} are important to repair DNA damage and cancer therapy\textsuperscript{[82]} (Fig 1 and 2). The spindle checkpoint ensures proper chromatid attachment prior to progression from metaphase to anaphase. The SCF and APC/C protein complexes play prominent roles, with APC-cdc20 initiating the entry into anaphase by promoting ubiquitin-mediated degradation of multiple substrates, including cyclin B.\textsuperscript{[83]} This is clearly showing regulatory protein have important role and follow a long strategy to repair DNA level defects and occurrence of mutation induced changes in stressed and cancer prone cells. It is true that proteins like SCF and APC/C ubiquitin ligases also control cell growth.\textsuperscript{[84]} There occurs a mutual regulation between the spindle check point and APC/C.\textsuperscript{[29]} Possibly di-allyl disulfide causes inhibition of histone deacetylation may also an important check point.\textsuperscript{[41]} Organosulfur compounds modulate the activity of several metabolizing enzymes that activate (cytochrome P450s) or detoxify (glutathione S-transferases) carcinogens and inhibit the formation of DNA adducts in several target tissues.\textsuperscript{[50]}

Garlic as a natural herbal medicine contains diverse sulfur components which target processes cancer cell formation and show therapeutic targets.\textsuperscript{[85]} Crude garlic extract exhibits inhibition of cell proliferation, induce cell cycle arrest and apoptosis in cancer cells.\textsuperscript{[86]} Effects of water garlic extracts on cell cycle and viability of HepG2 hepatoma cells.\textsuperscript{[87]} Cell cycle arrest and differential gene expression in HT-29 cells exposed to an aqueous garlic extract.\textsuperscript{[88]} Z-ajoene causes cell cycle arrest at G2/M and decrease of telomerase activity in HL-60 cells.\textsuperscript{[89]} Garlic derived allicin exhibit epigenic changes and removes of oxidative stress and cyclin dependent kinase inhibitor expression.\textsuperscript{[90]} Diallyl sulfide selectively causes checkpoint kinase -1 mediated G2/M arrest in human MGC808 gastric cancer cell line.\textsuperscript{[91]} It also promotes and promotes apoptosis through the p53/p21 and MEK-ERK pathways in human esophageal squamous cell carcinoma\textsuperscript{[92]} and in HCT-116 colon cancer cells.\textsuperscript{[93]} Natural tetrasulfides showed antiproliferative effect in human breast cancer cells is mediated through the inhibition of the cell division cycle 25 phosphatases.\textsuperscript{[94]} Diallyl sulfide induces apoptosis in Colo 320 DM human colon cancer cells: involvement of caspase-3, NF-kappaB,

4.0. Control of DNA Damage

There are so many extracellular agents such as ionizing radiation, UV light, environmental chemicals and alkylating agents which cause DNA damage in cells that finally induce carcinogenesis. Many potential therapies are used to target carcinogenesis through a series of alternatives including plant-derived pharmaceutical agents. A large number of these herbal remedies are particularly derived from garlic and are used to treat cancer patients mainly for inhibition of cancer cell proliferation and growth. DATS inhibits cell growth of human melanoma A375 cells and basal cell carcinoma (BCC) cells by increasing the levels of intracellular reactive oxygen species (ROS) and DNA damage. It also induce G2/M arrest, endoplasmic reticulum (ER) stress, and mitochondria-mediated apoptosis, including the caspase-dependent and -independent pathways. Diallyl trisulfide suppresses the proliferation and induces apoptosis of human colon cancer cells through oxidative modification of beta-tubulin. Similarly, DADS was found to be effective in inhibiting BaP-induced cell proliferation, cell cycle transitions, reactive oxygen species, and DNA damage in a normal cell line. It also inhibits environmentally induced breast cancer
Diallyl polysulfides play potential role as chemopreventive and therapeutic agents in cancer treatment due to their selective antiproliferative effects.

Some herbal medicines including garlic show potentially beneficial effects against cancer progression and ameliorate chemotherapy-induced toxicities. As most of the anticancer drugs undergo Phase I and/or II metabolism and are substrates of P-glycoprotein, breast cancer resistance protein, multidrug resistance associated proteins, and/or other transporters. Therefore, induction and inhibition of these enzymes seems to be essential and mechanism of action of transporters is important for herb-anticancer drug interactions and action. However, endogenous mechanisms causing DNA damage such as spontaneous chemical hydrolysis, intracellular interaction with reactive oxygen groups and errors in replication and recombination can be restored by identifying correct and appropriate bio-molecules from garlic in form of a formulation. In addition chemical carcinogen induced changes such as depurination, de-amination, and reactive oxygen species including superoxide anion (an ion and a free radical) formation can be controlled by highly permeable oxygen bearing molecules from garlic. These compounds conjugated with certain cofactors and vitamins can finish reactive oxygen species formed by the effect of ionizing radiation. Both garlic oil and sulfur rich compounds can minimize the formation of free radicals due to oxidant reactions with proteins and other biomolecules. Diallyl sulfide (DAS), one of the main active constituents of garlic, causes growth inhibition of cancer cells in vitro and promotes immune responses in vivo.

Moreover, garlic based drugs or crude extracts prepared green garlic cloves induce apoptosis through the generation of reactive oxygen species in Hep3B human hepatocarcinoma cells. These also target DNA repair mechanisms, and do restoration of a series of metabolic and signaling pathways. Temperature- and pressure-treated green garlic does inhibition of ENNG-induced pyloric stomach and small intestinal carcinogenesis in mice. DNA damage also occurs due to mistakes in DNA replication or recombination cause strand breaks to be left in DNA. An incorrect proof reading also results in incorporation of mismatched bases. When damage occurs due to effect of carcinogens it remain repairable but long term natural genetic changes cannot be reverted. Possible potential anti-cancer agents from garlic such as diallyl trisulfide can check these events in eukaryotic cells due by imposing external stress on “checkpoints” of cell cycle. Drug may target effectively on proper timing of cellular events that can stop cell cycle or delay it. Thus, passage of
anticarcinogenic effect through a checkpoint from one cell cycle phase will also require coordinated set of proteins that monitor cell growth and DNA integrity. Using natural products/molecules in a state of deficiency of transcription and translation of cell cycle proteins may activate DNA synthesis and protein translation. Garlic products can stop uncontrolled cell division or propagation of damaged DNA and save cells from genomic instability that give rise tumorigenesis (3).

Diallyl trisulfide does transcriptional repression and inhibition of nuclear translocation of androgen receptor in human prostate cancer cells.\[^{114}\] It also inhibits estrogen receptor-α activity in human breast cancer cells\[^{115}\] (Table 1). Thus garlic based herbal medicines have shown potentially beneficial effects on cancer progression and may ameliorate chemotherapy-induced toxicities.

DNA damage resulted in an impaired cellular response due to hypersensitivity generated by carcinogenic agents. If this DNA damage remains defective for longer period it results in mutations that lead to altered protein functions and generate impaired cellular responses. Normal cells react to DNA damage by stalling progress through the cell cycle at a check point until the damage has been repaired or triggering apoptosis if the damage remains un-reparable. All this is initiated by ATM protein briefly which sense DNA damage and relays the signal to the p53 protein which is synthesized under regulation of p53 gene that is known as the guardian of the genome.\[^{116}\] It plays a critical role in intrinsic tumor suppression via two mechanisms either through cell cycle arrest or by induction of apoptosis. A variety of triggers such as DNA damage, oncogene activation, and telomere erosion can lead to the activation of p53. An increase in p53 transcription inhibits cell cycling. Possibly p53 may be knocked out by mutation or by the action of an inhibitor such as the MDM2 gene product which binds p53 and targets for its degradation. S-Allylmercaptocysteine (CySSA) from garlic increases in phospho-p53, Bax and Bad levels which indicate that apoptosis occurs via the mitochondrial pathway.\[^{13}\] SAMC-induced apoptosis is associated with the Id-1 pathway and that the inactivation of Id-1 enhances the ability of SAMC to inhibit the survival, invasion and migration of bladder cancer cells.\[^{117}\]

DADS induces apoptosis in the MCF-7 breast-cancer cell line through interfering with cell-cycle growth phases in a way that increases the sub-G(0) population and substantially halts DNA synthesis.\[^{41}\] It also induces phosphatidylinerine translocation from the inner to the outer leaflet of the plasma membrane and activates caspase-3.\[^{41}\] It also modulates the cellular levels of Bax, Bcl-2, Bcl-xL, and Bcl-w in a dose-dependent manner, and show involvement.
of Bcl-2 family proteins in apoptosis). Diallyl trisulfide (DATS) induces apoptosis and inhibits the growth of many cancer cell lines. Mainly it induces apoptotic cell death in human primary colorectal cancer cells through a mitochondria-dependent caspase cascade signaling pathway through a significant decrease of the anti-apoptotic Bcl-2 that resulted in up-regulation of the ratio of Bax/Bcl-2 and the activity of caspase-3, -8, and -9. It also increases in the levels of cytochrome c, Apaf-1, AIF and caspase-3 and caspase-9 activity. Eventually, DATS induce the apoptosis and inhibit the cancer cell proliferation in a concentration- and time-dependent manner. Exposure to DATS additionally induced endogenous endoplasmic reticulum stress markers and intracellular Ca²⁺ mobilization, upregulation of Bip/GRP78 and CHOP/GADD153, and activation of caspase-4. It also makes an increase in reactive oxygen species (ROS) production in primary colorectal cancer cells but decrease in the level of ΔΨm was associated with an increase in the Bax/Bcl-2 ratio which led to activation of caspase-9 and -3. No doubt, DATS can offer protection against chemically-induced neoplasia as well as oncogene-driven spontaneous cancer development in experimental animals. DATS do alteration in carcinogen-metabolizing enzymes, operate cell cycle arrest, and impose induction of apoptotic cell death, suppression of oncogenic signal transduction pathways, and inhibition of neoangiogenesis. DATS did not affect the activity of sulfurtransferases and lowered sulfane sulfur level in HepG2 cells. But is possible that sulfane sulfur containing DATS may be bioreduced in cancer cells to hydroperthiol that leads to H(2)O(2) generation, thereby influencing transmission of signals regulating cell proliferation and apoptosis. Similarly, allicin also inhibit the cell viability of U87MG human glioma cells in a dose- and time-dependent manner. Allicin-induced inhibition of cell viability was due to apoptosis of cells. The mechanisms of apoptosis were found to involve the mitochondrial pathway of Bcl-2/Bax, the MAPK/ERK signaling pathway and antioxidant enzyme systems.

DATS also exerts chemopreventive potential via ER stress and the mitochondrial pathway in BCC cells. DAS, DADS and DATS induce down regulation expression of PI3K, Ras, MEKK3, M KK7, ERK1/2, JNK1/2, and p38 and then lead to the inhibition of MMP-2, -7, and -9. DAS, DADS, and DATS inhibited NF-κB and COX-2 for leading to the inhibition of cell proliferation. DADS inhibit the activities of matrix metalloprotease (MMP)-2 and -9 in AGS cells in dose-dependent manner. It decreases expression of their mRNA and proteins and repressed the levels of claudin proteins (claudin-2, -3 and -4). In addition, both diallyl tri- and tetrasulfide are reported as strong inducers of an early mitotic arrest and subsequent...
apoptosis. Diallyl tetrasulfide acts independently of reactive oxygen species and tubulin represents one of its major cellular targets. Tubulin depolymerization prevents the formation of normal spindle microtubules, thereby leading to G2/M arrest. Moreover, c-jun N-terminal kinase, which is activated early in response to diallyl tetrasulfide treatment, mediates multisite phosphorylation and subsequent proteolysis of the anti-apoptotic protein B-cell lymphoma 2.

SAC suppress the proliferation of PC-3 cells and led to cell cycle arrest at the G0/G1 phases, as well as inducing cell apoptosis which was accompanied by the decreased expression of Bcl-2 and increased expression of Bax and caspase 8. This chemopreventive effect of SAC may be associated with the suppression of carcinogenesis factors such as N-methylpurine DNA glycosylase and OPN. SAC also significantly suppresses the phosphorylation of Akt, mammalian target of rapamycin, inhibitor of κBα and extracellular signal-regulated kinase 1/2 in tumour tissues. But SAC-mediated suppression of cyclin D1 protein was associated with an augmented expression of the cell-cycle inhibitor p16 (Ink4). SAC also inhibit expression of cyclo-oxygenase-2, vimentin and NF-κB p65 (RelA). In addition, both SFN Sulforaphane (SFN) and NaHS activate p38 mitogen-activate protein kinases (MAPK) and c-Jun N-terminal kinase (JNK). Thus, pretreatment of PC-3 cells with methemoglobin decreases SFN-stimulated MAPK activities. Suppression of both p38 MAPK and JNK reversed H(2)S- or SFN-reduced viability of PC-3 cells. H(2)S mediates the inhibitory effect of SFN on the proliferation of PC-3 cells. Therefore, H(2)S-releasing diet or drug might be beneficial in the treatment of prostate cancer. SAC also hinder the migration and invasion of MHCC97L cells corresponding with up-regulation of E-cadherin and down-regulation of VEGF. It also significantly induced apoptosis and necrosis of MHCC97L cells through suppressing Bcl-xL and Bcl-2 as well as activating caspase-3 and caspase-9. In addition, SAC could significantly induce the S phase arrest of MHCC97L cells together with down-regulation of cdc25c, cdc2 and cyclin B1. Similarly, phytoalexins show specific targets in cancer cells that include signal transduction pathways, transcription factors, cell cycle checkpoints, intrinsic and extrinsic apoptotic pathways, cell invasion and matrix metalloproteinase, nuclear receptors, and the phase II detoxification pathway. Thiacremonone inhibits tumor growth accompanied with the reduction of PRDX6 expression and glutathione peroxidase activity, but it shows an increase in expression of cleaved caspase-3, -8, -9, Bax, p21 and p53. Garlic extract induce cytotoxic and apoptotic effects in HL-60 cells that is mediated by oxidative stress,
phosphatidylserine externalization, caspase-3 activation, and nucleosomal DNA fragmentation and formation of MDA, a by-product of lipid peroxidation and biomarker of oxidative stress).\cite{127}

5.0. Inhibition of carcinogenesis
Diallyl trisulfide inhibits benzo(a)pyrene-induced precancerous carcinogenesis in MCF-10A cells\cite{128} and induce apoptosis in human basal cell carcinoma cells via endoplasmic reticulum stress and the mitochondrial pathway.\cite{55} Diallyl sulfide, diallyl disulfide and diallyl trisulfide affect drug resistant gene expression in colo 205 human colon cancer cells in vitro and in vivo\cite{120} (Table 1). Diallyl trisulfide (DATS) is used to prevent growth of pancreatic\cite{121} and prostate cancer cells PC-3 \cite{129} and HCT116 cells.\cite{143} Diallyl trisulfide (DATS) inhibits mouse colon tumor in mouse CT-26 cells allograft model in vivo.\cite{28} Diallyl disulfide inhibits the proliferation of HT-29 human colon cancer cells by inducing differentially expressed genes.\cite{130} Diallyl sulfide inhibits murine WEHI-3 leukemia cells in BALB/c mice in vitro and in vivo\cite{131} and induce molecular mechanisms which target cancer chemoprevention.\cite{132} It also induces Ca2+ mobilization in human colon cancer cell line SW480\cite{133} (Table 1).

Fresh garlic extract induces growth arrest and morphological differentiation of MCF7 Breast cancer cells.\cite{134} Sulfide compounds found in dietary garlic supplements\cite{135} increase C reactive protein concentration\cite{136} and enhance therapeutic potential against infectious agents\cite{137} (Barr et al., 2013). These effect cell proliferation, caspase 3 activities, thiol levels and anaerobic sulfur metabolism\cite{119} and modulate peroxisome proliferation activated receptor gamma co-activator 1 alpha in human hepatoblastoma HepG2 cells.\cite{57} Garlic oil shows protective effects on hepatocarcinoma induced by N-nitrosodiethylamine in rats.\cite{138} Similarly, S-allylcysteine (SAC), a garlic derivative suppresses proliferation and metastasis of hepatocellular carcinoma\cite{128} and induces cell cycle arrest and apoptosis in androgen-independent human prostate cancer cells.\cite{122} Oxidative species and S-glutathionyl conjugates aids in the apoptosis induction by allyl thiosulfate.\cite{139}

The aged garlic extract (AGE) contains S-allyl-L-cysteine (SAC) which is a potential therapeutic agents for Alzheimer's disease.\cite{140} It is a major water- soluble compound found in aged garlic exerts cytotoxic activity by involving activation of mitochondrial-dependent apoptosis through p53 and Bax/Bcl-2 pathways in human gastric cancer SGC-7901 cells.\cite{33} It inhibits tumor progression and the epithelial-mesenchymal transition in mouse xenograft model of oral cancer.\cite{123} It also shows ameliorating effects against Aβ-induced neurotoxicity
and cognitive impairment.\textsuperscript{141} It induces inhibition of gastric cancer cell growth \textit{in vitro} and \textit{in vivo}.\textsuperscript{39} Similarly, S-benzyl-cysteine (SBC) a structural analog of S-allylcysteine (SAC), mediates cell cycle arrest and apoptosis that involves activation of mitochondrial-dependent caspase cascade through the p53 pathway in human gastric cancer SGC-7901 cells.\textsuperscript{133} S-allylmercaptocysteine (SAMC) shows potent therapeutic effect on human cancer cells by causing apoptosis.\textsuperscript{142,10} Hydrogen sulfide mediates the anti-survival effect of sulforaphane on human prostate cancer cells.\textsuperscript{124} Garlic-derived allyl sulfides cause inhibition of skin cancer progression\textsuperscript{46} (Wang et al., 2012) and show modifying effect on colon carcinogenesis in C57BL/6J-ApcMin/+ mice.\textsuperscript{143}\textsuperscript{73}

However, intake of fruits and vegetable reduce the risk of gastric cancer\textsuperscript{144-145} and restore health and reduces the chances of occurrence of physiological diseases.\textsuperscript{146} Both garlic and garlic-derived organic sulfur compounds are used for controlling breast cancer.\textsuperscript{147,148} Besides, sulfur compounds garlic also contains saponins, flavonoids vitamins, minerals, hence daily consumption of garlic vegetables daily can lower down the risk of hematologic malignancies and other lifestyle diseases.\textsuperscript{149-151} Garlic dietary supplements also contain multivitamins and folic acid which show strong anticancer effects in breast cancer survivors.\textsuperscript{152} These lower down oxidative stress and induce apoptotic mechanisms in acute promyelocytic leukemia.\textsuperscript{127} Green garlic shows cardioprotective effects\textsuperscript{153} and is used as a complementary and alternative medicines for treatment of breast cancer.\textsuperscript{154} It shows potential beneficial effects in oncohematology\textsuperscript{155} (Table 1).

Consumption of s-allylcysteine inhibits the growth of human non-small-cell lung carcinoma in a mouse xenograft model.\textsuperscript{156} Similarly, S-allylmercaptocysteine effectively inhibits the proliferation of colorectal cancer cells under in vitro and in vivo conditions.\textsuperscript{157} S-allylmercapto-L-cysteine shows anticancer activity in implanted tumor of human gastric cancer cell\textsuperscript{61} (Table 1). S-allyl cysteine attenuates oxidative stress associated cognitive impairment and neurodegeneration in mouse model of streptozotocin-induced experimental dementia of Alzheimer's type.\textsuperscript{158} There occurs a relationship between lipophilicity and inhibitory activity against cancer cell growth of nine kinds of alk(en)yl trisulfides with different side chains\textsuperscript{159} (Table 1). Garlic oil suppressed the hematological disorders induced by chemotherapy and radiotherapy in tumor-bearing mice.\textsuperscript{160} Thiacremonone, a sulfur compound isolated from garlic, attenuates lipid accumulation partially mediated via AMPK activation in 3T3-L1 adipocytes.\textsuperscript{124} Artesunate combined with allicin shows
synergistic anticancer effect in osteosarcoma cell line in vitro and in vivo.\textsuperscript{161} Moreover, garlic components showed antioxidant activity\textsuperscript{172} inhibit fibrosarcoma tumor growth in BALB/c mice positive.\textsuperscript{163}

Oil-soluble compounds such as diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS) and ajoene are more effective than water-soluble compounds in protection against cancer. DADS, a major organosulfur compound derived from garlic, decrease carcinogen-induced cancers in experimental animals and inhibit the proliferation of various types of cancer cells. Its mechanisms of action include: the activation of metabolizing enzymes that detoxify carcinogens; suppression of the formation of DNA adducts; antioxidant effects; regulation of cell-cycle arrest; induction of apoptosis and differentiation; histone modification; and inhibition of angiogenesis and invasion.\textsuperscript{164} No doubt DAC inhibitory effects of garlic organosulfur compounds might play a role in primary cancer prevention at doses achievable by human diet.\textsuperscript{165} However, the decrease of the peripheral total white blood cells (WBCs) count induced by CTX/radiation was significantly suppressed by GO co-treatment. No doubt, GO consumption may benefit for the cancer patients receiving chemotherapy or radiotherapy.\textsuperscript{160}

5.1. Inhibition of cancer cell proliferation and invasion

Diallyl disulfide shows anti-invasive activity through tightening of tight junctions and display inhibition of matrix metalloproteinase activity in LNCaP prostate cancer cells.\textsuperscript{77} Diallyl trisulfide does inhibition of cell proliferation and migration in cancer cells and acts as chemopreventive drug.\textsuperscript{91} Similarly, natural tetrasulfides also show antiproliferative effect of in human breast cancer cells that is mediated through the inhibition of the cell division cycle 25 phosphatases.\textsuperscript{166} Garlic reduces the risk of colorectal polyps.\textsuperscript{167} and accelerates red blood cell turnover and splenic erythropoietic gene expression in mice.\textsuperscript{168} Boiled garlic does inhibition of 1, 2-dimethylhydrazine-induced mucin-depleted foci and O\textsubscript{6}-methylguanine DNA adducts in the rat colorectum\textsuperscript{169} while crude garlic extract and its fractions showed cytotoxic effect\textsuperscript{170} on malignant and nonmalignant cell lines.\textsuperscript{171} Garlic provides great protection against physiological threats\textsuperscript{172} and lower downs risk of gastric cancer.\textsuperscript{172,10} DAS also does growth inhibition and induce apoptosis in anaplastic thyroid cancer cells by mitochondrial signaling pathway\textsuperscript{74} while allyl sulfur compounds causes cellular detoxification of carcinogens and is used in cancer therapy.\textsuperscript{174} Garlic phytochemicals
counteract the cardiotoxic side effects of cancer chemotherapy\[^{[175]}\] 1. SAMC inhibit the survival, invasion and migration of bladder cancer cells.\[^{[117]}\]

5.2. Chemopreventive/antitumor effects

Garlic derived natural products showed chemopreventive effects and successfully prevent colorectal,\[^{[111]}\] and prostate cancer.\[^{[176]}\] These also show onco-cardiological prevention\[^{[177]}\] reduce the risk of invasive cervical \[^{[78,8]}\] and ovarian carcinoma.\[^{[17]}\] Diallyl trisulfide induces Bcl-2 and caspase-3-dependent apoptosis via downregulation of Akt phosphorylation in human T24 bladder cancer cells.\[^{[46]}\] Garlic powder supplemented diet shows chemopreventive effects in diethylnitrosamine-induced rat hepatocarcinogenesis\[^{[178]}\] (5a). It also shows chemoprotection against cyclophosphamide toxicity in mice\[^{[179]}\] and protects against adriamycin induced alterations in mouse red blood cells.\[^{[180]}\] Garlic inhibits methylcholanthrene-induced carcinogenesis in the uterine cervix of mice\[^{[181]}\] and shows prevention of 4-nitroquinoline 1-oxide-induced rat tongue\[^{[182]}\] and hamster cheek pouch carcinogenesis.\[^{[195]}\] It shows protective effects against bromobenzene toxicity to precision cut rat liver slices\[^{[183,184]}\] Diallyl disulfide shows prevention of chemically induced skin tumor development\[^{[185]}\] Organosulfur compounds from garlic and onions protect from benzo[a]pyrene-induced neoplasia and glutathione S-transferase activity in the mouse\[^{[186]}\] (Table 1). Onion and garlic oils and extracts inhibit tumor promotion in experimental animals.\[^{[187,188]}\] Diallyl sulfide, a flavor component of garlic (\textit{Allium sativum}), inhibits dimethylhydrazine-induced colon cancer.\[^{[189]}\]

A super antioxidant

Garlic chemical constituents showed very multiple therapeutic efficacy and are proved useful for preventing diseases associated with reactive oxygen species.\[^{[190,191]}\] Aged garlic extract scavenges superoxide radicals\[^{[190]}\] and induce apoptosis in cancer cells.\[^{[192,193]}\] Diallyl trisulfide does inhibition of cell proliferation and migration in cancer cells and acts as chemopreventive drug.\[^{[194]}\] DATS also increases reactive oxygen species (ROS) production in primary colorectal cancer cells.\[^{[60]}\] Diallyl tetralsulfide acts independently of reactive oxygen species and tubulin represents one of its major cellular.\[^{[59]}\] It induce production of reactive oxygen species (ROS) in normal cells similar to cancer cells in a time and dose dependent manner.\[^{[195]}\] This is the main reason that both garlic and its derivatives are used as conventional drug in many countries for clinical treatment of cancer.\[^{[196]}\]
Garlic derivatives such as ajoene, induces apoptosis in human promyeloleukemic cells, accompanied by generation of reactive oxygen species and activation of nuclear factor kappaB\cite{197} and show antiproliferative effects\cite{198}. Allicin a sulfur compound decompose at 30°C into diallyl disulfide (DADS) (66%), diallyl sulfide (DAS) (14%), diallyl trisulfide (9%), and sulfur dioxide \cite{199}. Allicin easily reacts with amino acids and proteins, creating a -SH group. It binds to protein and fatty acids in the plasma membrane, and is trapped before absorption. It cannot circulate in the blood stream\cite{200} and is not detected in the blood sample after the ingesting raw garlic or pure allicin.\cite{197} Allicin is metabolized into allyl methyl sulfoxide (AMS) and released into the breath after dietary intake.\cite{38} Allicin shows antitumoral activity in murine lymphoma L5178Y\cite{201} and induce apoptosis in human HepG2 cells\cite{79} (Table 1). Allicin acts as an antioxidant in the blood and remove out all reactive oxygen species generated due to metabolic stress.

Garlic-derived compound S-allylmercaptocysteine (SAMC) is associated with microtubule depolymerization and c-Jun NH(2)-terminal kinase 1 activation.\cite{202} These components also show induction of apoptosis in breast cancer cell lines,\cite{203} and did attenuation of cell migration and induction of cell death in rat sarcoma cells.\cite{204} The garlic-derived organosulfur component ajoene decreases basal cell carcinoma tumor size by inducing apoptosis.\cite{205} Z-ajoene, a natural compound purified from garlic shows antimitotic and microtubule-interaction properties.\cite{206} A protein fraction from aged garlic extract enhances cytotoxicity and proliferation of human lymphocytes mediated by interleukin-2 and concanavalin A.\cite{207} More specifically, garlic preparations were found active against human tumor cell proliferation\cite{208} and show antitumor and anti-cancer effects. Allium vegetables in the daily diet play important role in the prevention of cancer\cite{211} (Table 1).

<table>
<thead>
<tr>
<th>Garlic component</th>
<th>Characteristics/attributes</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allicin</td>
<td>Multiple therapeutic agent</td>
<td>Found in raw garlic opens thermo-transient receptor potential channels that are responsible for the burning sense of heat in foods</td>
</tr>
<tr>
<td>Allicin derivatives</td>
<td>major contributors to the characteristic odor of garlic</td>
<td>Anti-mutagenic and anti-proliferative properties</td>
</tr>
<tr>
<td>Alliin</td>
<td>A sulfur-containing compound found in garlic</td>
<td>Flavor and aroma, as well as its potential health benefits, Prevents LPS-induced inflammation in 3T3-L1 adipocytes.</td>
</tr>
<tr>
<td>Vinyldithiins</td>
<td>A sulfur-containing compound</td>
<td>Strong antioxidant , control several</td>
</tr>
<tr>
<td>Compound</td>
<td>Type</td>
<td>Function</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Proteins, minerals, saponins, flavonoids, enzymes, B vitamins</td>
<td>Non sulfur compounds</td>
<td>Anticarcinogenic signaling pathways, including the inflammatory and apoptotic ones, inhibit matrix metalloproteinase activities and tightening tight junctions</td>
</tr>
<tr>
<td>Allixin mainly phytoalexin</td>
<td>A nonsulfur, with a γ-pyron skeleton structure</td>
<td>Antioxidant, show antimicrobial antitumor promoting effects, inhibition of aflatoxin B2 DNA binding, and neurotrophic effects, cancer prevention.</td>
</tr>
<tr>
<td>Allicin</td>
<td>Organosulfur compound</td>
<td>Strong odor a stinking rose, repellent action</td>
</tr>
<tr>
<td>Allyl methyl sulfide</td>
<td>After food intake garlic's strong-smelling sulfur compounds are metabolized, forming allyl methyl sulfide.</td>
<td>Abundant sulfur compounds in garlic responsible for turning garlic green or blue during pickling and cooking. Act as mosquito repellent.</td>
</tr>
<tr>
<td>Diallyl sulfide</td>
<td>A garlic-derived organosulfur compound is used to prevent growth of pancreatic cancer cells</td>
<td>Prevents tumor progression and promotes apoptosis in ectopic glioblastoma xenograft, prevent growth of pancreatic cancer cells, promotes cell-cycle arrest through the p53 expression. It also triggers induction of apoptosis via caspase- and mitochondria-dependent signaling pathways in human cervical cancer Ca Ski cells. It is found more toxic to prostate cancer cells PC-3, human retina pigment epithelial cells (ARPE-19) and HCT116 cells. It induces apoptosis in MCF7 human breast cancer cells.</td>
</tr>
<tr>
<td>diallyl trisulfide (DATS)</td>
<td>Cytotoxic to prostate cancer cells</td>
<td>Highly cytotoxic to prostate cancer cells, inhibits cell proliferation by triggering either cell cycle arrest or apoptosis, shows pro-apoptotic activity regulated by a caspase-dependent cascade through the activation of both intrinsic and extrinsic signaling pathways, or mediated through the blocking of PI3K/Akt and the activation of the JNK pathway</td>
</tr>
<tr>
<td>Diallylpolysulfides</td>
<td>Organosulfur compound</td>
<td>diallylpolysulfides induce growth arrest and apoptosis in cells</td>
</tr>
<tr>
<td>diallyltetrasulfide (DATTS)</td>
<td>Organosulfur compound</td>
<td>Induce mitotic arrest to apoptosis</td>
</tr>
<tr>
<td>gamma-glutamylcysteines, Allylcysteine sulfoxide (alliin)</td>
<td>Organosulfur compound</td>
<td>Generate hot odor</td>
</tr>
<tr>
<td>Allyl sulfides</td>
<td>Organosulfur compound</td>
<td>Inhibit cell growth of skin cancer cells</td>
</tr>
<tr>
<td>Organosulfur Compound</td>
<td>Description</td>
<td>Effects</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>S-allylmercaptocysteine</td>
<td>organosulfur compound</td>
<td>induce cell cycle arrest and reduce the risk of various types of human cancer.</td>
</tr>
<tr>
<td>S-alkenylmercaptocysteine</td>
<td>organosulfur compound</td>
<td>Induce apoptosis in pancreatic cells</td>
</tr>
<tr>
<td>Garlicinins B(1), C(1), and D</td>
<td>Sulfur containing compounds</td>
<td>Highly toxic to cancer cells</td>
</tr>
<tr>
<td>S-allylmercaptocysteine</td>
<td>active organosulfur compounds</td>
<td>Suppresses proliferation and induces apoptosis in human ovarian cancer cells in vitro. Reduced the migration of A2780 cells and decreases the protein expression of Wnt5a, p-AKT and e-Jun proteins which are involved in proliferation and metastasis.</td>
</tr>
<tr>
<td>S-allylcysteine, S-allylmercaptocysteine</td>
<td>active organosulfur compounds</td>
<td>Highly toxic to cancer cells</td>
</tr>
<tr>
<td>S-alkenylmercaptocysteine</td>
<td>active organosulfur compounds</td>
<td>Induce apoptosis in pancreatic cells</td>
</tr>
<tr>
<td>Polysulfanes</td>
<td>Sulfur containing compounds</td>
<td>Possess antimicrobial, chemopreventive and anticancer properties.</td>
</tr>
</tbody>
</table>

**Cell-cycle regulation/cell cycle arrest / apoptosis**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Description</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic oil</td>
<td>Steam distillation of garlic bulbs, leaf oil is also extracted</td>
<td>Inhibits the proliferation of AsPC-1, PANC-1, and Mia PaCa-2 cells and induced programmed cell death, cell cycle arrest, and show pro-apoptosis effects on AsPC-1 cells in a dose and time dependent manner in vitro</td>
</tr>
<tr>
<td>Garlic water extract</td>
<td>Maceration of garlic bulbs</td>
<td>Causes cell-cycle dysregulation and control signal transduction pathways leading to cell cycle arrest and apoptosis induction in cancer cells</td>
</tr>
<tr>
<td>Black garlic extracts (BGE)</td>
<td>Homogenization of garlic bulbs</td>
<td>Check proliferation of lung cancer while green garlic possesses enough potential to control colorectal cancer and other types of carcinoma</td>
</tr>
<tr>
<td>Aged black garlic extract (ABGE)</td>
<td>Long storage effect on garlic bulbs</td>
<td>Highly beneficial in preventing or inhibiting oncogenesis</td>
</tr>
<tr>
<td>S-benzyl-cysteine</td>
<td>Sulfur containing compounds</td>
<td>SBC exerts cytotoxic activity involving activation of mitochondrial-dependent apoptosis through p53 and Bax/Bcl-2 pathways in human gastric cancer SGC-7901 cells</td>
</tr>
<tr>
<td>DATS, DADS, ajoene, and S-allylmercaptocysteine (SAMC)</td>
<td>Sulfur containing compounds</td>
<td>Induce cell cycle arrest and apoptosis, regulating ion channels, modulating Akt signaling pathways, histone deacetylase inhibition, and cytochrome P450 inhibition</td>
</tr>
<tr>
<td>Ajoene</td>
<td>Sulfur containing compounds</td>
<td>Shows antimitotic and microtubule-interaction properties. Induces apoptosis in human promyeloleukemic cells,</td>
</tr>
</tbody>
</table>
CONCLUSION
Garlic is a multipurpose nutritional plant that possesses highly active chemical ingredients. It is widely used in Indian Traditional Medicine as a basic resource material. Garlic is one of most powerful food that is used for culinary and many home preparations for medicinal purpose. Garlic prepared foods mainly salads and vegetables, pickles and chutney induce cancer cell death by apoptosis, autophagy, or necrosis. Garlic not only induce apoptosis type-II programmed cell death but also autophagy in cancer cells. It is pioneer food and is used in complementary therapy in clinical cancer treatment and increase the life quality of cancer patients. Accumulating evidence indicates that aged black garlic extract (ABGE) may prove beneficial in preventing or inhibiting oncogenesis. Dietary garlic enhances immunity against diseases, removes off oxidants and induces free radical scavenging and anti-inflammatory activities that are helpful against cancer insurgence. Diallyl sulfide, diallyl disulfide, and daillyl trisulfide (DATS) are major volatile components of garlic oil which show very high potency in inducing antioxidant enzyme expression, and show strong anti-neoplastic and anti-inflammatory properties. Organosulfur compound isolated from garlic have been shown to have anticancer activity both in vitro and in vivo. These are also used as pharmaceuticals for treatment of acute and chronic diseases and are thought to be powerful instrument in maintaining health as medicine and nutraceutical. Garlic components can do make restoration of cell death pathways via the targeting of mitochondrial proteins. These can normalize the central pathway which can frequently impair cancer cells and contributes to the development of resistance to conventional chemotherapy. Garlic derived molecules can be formulated and designed to target oxidants or pro-oxidants and to activate pro-apoptotic proteins as well as to block these proteins. Garlic based herbal products and targeted molecules can find good solutions for clinical management of various cancer types. Today garlic based herbal medicines are attracting public health authorities, pharmaceutical industries because of its larger use in prevention and treatment of so many diseases and disorders. Garlic derived dietary supplements are highly demanded by nutritionists, physicians, food technologists and food chemists. No doubt garlic and its derived herbal products are providing optimal health and quality of life.

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