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Review article

Toxicity of anticancer drugs and its prevention with special reference to role of garlic constituents

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Abstract

Cancer is the leading cause of death globally. World Health Organisation (WHO) reported that 70% of death caused by cancer occurs in low or middle income countries which may be due to unavailability of correct treatment or delayed medical support. Despite of different therapies available to cure the cancer or to prolong the life of cancer survivors; chemotherapy is still central to cancer therapy. Administration of chemotherapeutic drugs either independently or in combination with other therapies such as irradiation or surgery provides relief to cancer patients. Nitrogen mustards were the first anticancer agents used in chemotherapy in 1940s. Their clinical use accelerated the development of different anticancers drugs. Due to the reports of toxicities of these anticancer drugs, herbal remedies for cancer treatment found notion of oncologists. A number of herbal extracts and natural products have shown the potential of anticancer activity. They also reduce the toxicity of synthetic anticancer drugs. Garlic (*Allium sativum* L.) is one of the herbal remedies with high anticancer potential and ability to mitigate the toxicities of anticancer drugs. The protective effects of garlic against the toxicities of anticancer drugs have been reported in a number of studies and it has also been reported that fresh garlic and aged garlic extract show considerable protective effects. Allicin (diallyl thiosulfinate) is the major pharmacological component of garlic which has attracted attention of the international medical field gradually due to its potential for disease prevention and treatment. The major unique organosulfur compounds in aged garlic extract such as water-soluble *S*-allyl cysteine (SAC) and *S*-allylmercaptocysteine (SAMC) have potent antioxidant activity. Many reports show the protective potential of these garlic constituents against anticancer drug-induced toxicities. Here, we present review of toxicities caused by anticancer drugs and their mechanism of action along with the efficacy of some plant extracts and natural products in reducing toxicity of anticancer drugs with special reference to of garlic constituents.

Keywords: Cancer, garlic, toxicity, anticancer drugs, chemotherapy

1. Introduction

Cancer is an uncontrolled growth of cell(s) which leads to a tumour of solid mass or liquid cancer such as blood or bone marrow related cancers. According to World Health Organization (WHO), cancer is the second leading cause of death globally and approximately 70% of death due to cancer occurs in low and middle income countries (WHO, 2006; Ferlay *et al.*, 2013). Cancers are of hundred types and are named after their tissue of origin; for example, breast cancer, lung cancer, colon cancer, *etc*. Anything that may cause the abrupt growth of normal cells of body, it can cause the cancer. The causative agent of cancer includes the human genetics, ionizing radiations, carcinogenic chemical exposure and some pathogens, *etc*. Stage of cancer is often determined by biopsy which helps in determining the type of cancer as well as stage of cancer. Treatment protocol varies according to type and stage of cancer. Most treatment includes surgery, chemotherapy, radiotherapy etc (Shewach and Kuchta, 2009).

The nitrogen mustards were the first compound used as chemotherapeutic agents for cancer in 1940s (Cheung-Ong *et al.*, 2013). Nitrogen mustards are powerful alkylating agents and antimetabolites. The low molecular weight drugs based on nitrogen mustards are mostly used in the chemotherapy which selectively kill the tumour cells or arrest their growth.

1.1 Anticancer drugs

On the basis of mechanism of action, anticancer drugs are classified as DNA interactive agents, molecular targeting agents, hormones, antitubulin agents, antimetabolites, monoclonal antibodies and other biological agents (Thurston, 2007).

1.1.1 Antimetabolites

Antimetabolites interact with essential biosynthesis pathways and with this mechanism of action, these are known as one of the oldest families of anticancer drugs (Peters, 2014; Loon and Chew, 1999). They masquerade as a purine or a pyrimidine and become the building blocks of DNA by incorporating into DNA during S phase and arresting the cell development and cell division. A typical example

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of pyrimidine includes 5-fluorouracil while a typical example of purine includes 6-mercaptopurine. Methotrexate represents another example of antimetabolites which interferes with essential enzymatic processes of metabolism (Wood and Wu, 2015).

1.1.2 DNA interactive agents

DNA is the foremost molecular target of many anticancer drugs acting through different mechanisms of action summarized as under (Basu and Lazo, 1990; Sissi *et al*., 2001).

- **Alkylating agents:** They cause the alkylation in either major or minor grooves of DNA, *e.g*., dacarbazine, procarbazine and temozolomide.
- **Cross-linking agents:** Most of the platinum complexes such as cisplatin, carboplatin, oxaliplatin and nitrogen mustards such as cyclophosphamide (CP) and ifosfamide cause the inter-strand or intra-strand cross linking of DNA.
- **Intercalating agents:** They bind between base pairs of DNA. Examples include actinomycin-D, mitoxantrone and anthracyclines (*e.g*., doxorubicin, epirubicin).
- **Topoisomerase inhibitors**: Some anticancer drugs such as irinotecan and etoposide compounds inhibit the topoisomerase enzyme which is responsible for cleavage, annealing, and topological state of DNA.
- **DNA-cleaving agents:** Anticancer drugs like bleomycin cause the strand scission of DNA.

1.1.3 Antitubulin agents

Taxanes and vinca alkaloids are the important antitubulin agents (Edelman, 2009; Cheetham and Petrylak, 2013). They cause the cell death through interacting with microtubule dyanamics and blocking the division of nucleus.

2. Types of cancer therapy

The ideal goal of cancer treatment is the complete removal of cancer without any single adverse effect to the body which is called achieving cure with near zero adverse effect. According to WHO guidelines, the main goal of cancer diagnosis and treatment programs is to cure or considerably prolong the life of patients and to ensure the best possible quality of life for cancer survivors (WHO, 2006). Keeping this in mind, a number of therapies and/or combination of therapies are used for cancer diagnosis and treatment including surgery, radiation, chemotherapy, hormonal therapy, targeted therapies, immunotherapy, angiogenesis inhibitors and synthetic lethality (Ramaswami *et al*., 2013; Neal and Sledge, 2014). Every cancer type requires a specific treatment regimen that encompasses one or more therapies which also include the propensity of cancers to damage the adjacent tissue or to spread to remote sites.

2.1 Surgery

Surgery is the oldest kind of cancer therapy and remains an effective treatment for different kind of cancers (Sudhakar, 2009). It is a general perception that cancers other than hematological cancer can be cured in case it is entirely removed by surgery. However, it is not always possible to remove cancerous tissue fully, as complete surgical excision is usually impossible due to metastasis nature of cancer. Surgery aims to either removal of only the tumor or the entire organ such as mastectomy for breast cancer and prostatectomy for prostate cancer (Matsen and Neumayer 2013; Bolenz *et al*., 2014). The purpose of surgery may vary. It is generally performed to diagnose the cancer, to remove all or some of a cancer tissue, to find the location of cancer, to check the metastasis of cancer, to restore the body's function and/or appearance and to relieve the side effects, *etc*.

Surgery may be of following types depending on its objective.

- **Diagnostic:** A biopsy is the only way to make a definitive diagnosis for the most of the types of cancer. There are two main types of surgical biopsies.
  - **Incisional biopsy:** It is the removal of a piece of the suspicious area for examination.
  - **Excisional biopsy:** It is the removal of the entire suspicious area, such as an unusual mole or lump.
- **Staging:** It is performed to find out the size of the tumor and its metastasis, *i.e.*, where it has spread.
- **Primary or curative surgery:** This is the most common type of surgery and used to remove the tumor along with surrounding healthy tissue for margin.

2.2 Radiation therapy

Radiation therapy remains the important component of cancer treatment. It is also called as radio therapy or X-ray therapy or irradiation. The main goal of radiation therapy is to deprive cancer cells of their multiplication potential. Approximately, 50% of all cancer patients are receiving the radiation therapy around the globe, contributing to 40% of curative treatment of cancer (Baskar *et al*., 2012). Radiation is a physical agent which destroys the cells by forming the ions and depositing energy in the cells of tissues it is passing through. High-energy radiation damages, the genetic material of cells which arrests their ability of division (Jackson and Bartek 2009).

Radiation therapy is delivered in the fractionated regime based on the different radiobiological properties of cancer and surrounding normal tissues (Baskar *et al*., 2012). Fractionated regime is scheduled on the basis of total dose, number of fractions and overall time of treatment (Bernier *et al*., 2004). The advancement made to schedule the fractionated regime, suggested the more refined linear-quadratic formula which addresses the time-dose factors for individual tumor types and normal cells. Technological advances in the field of radiation theraphy include new imaging modalities, more powerful computers and software systems and new delivery systems such as 3D conformal radiotherapy (3DCRT), intensity modulated radiation therapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic body radiation therapy (SBRT).

Generally, two types of radiations are used to treat cancer including photon radiation (X-rays and gamma rays) and particle radiation (electron, proton and neutron beams). Particle radiation has higher linear transfer energy than photon with higher biological effectiveness (Schulz-Ertner and Tsujii, 2007). However, the equipment for production of particle radiation therapy is highly expensive (Ma and Maughan, 2006).

2.3 Chemotherapy

The treatment of cancer with anticancer drugs is called chemotherapy. Chemotherapeutic drugs generally act by their cytotoxic action. These drugs are of low molecular weight. They

selectively arrest the growth of tumor cells or devastate them. The side effects of many cytotoxic drugs include the hair lose, nausea, gastric lesions, bone marrow suppression and development of clinical resistance (MacDonald, 2009; Nussbaumer *et al*., 2011; Sak, 2012). Nitrogen mustards were the first anticancer agents which heralded the chemotherapy in 1940s (Cheung-Ong *et al*., 2013). Chemotherapeutic agents include strong alkylating agents and anti-metabolites. Early success of these anticancer agents propelled the development of a large number of anticancer agents (Shewach and Kuchta 2009). Some of the anticancer drugs are of natural origin obtained from the plants while a large majority is of synthetic kind. On the basis of mechanism of action, anticancer drugs are categorized as antimetabolites, antitubuline agents, DNA interacting agents, molecular targeting agents, monoclonal antibodies or hormons. (Thurston, 2007). Anticancer drugs are classified on the basis of their mechanism of action (Figure 1).

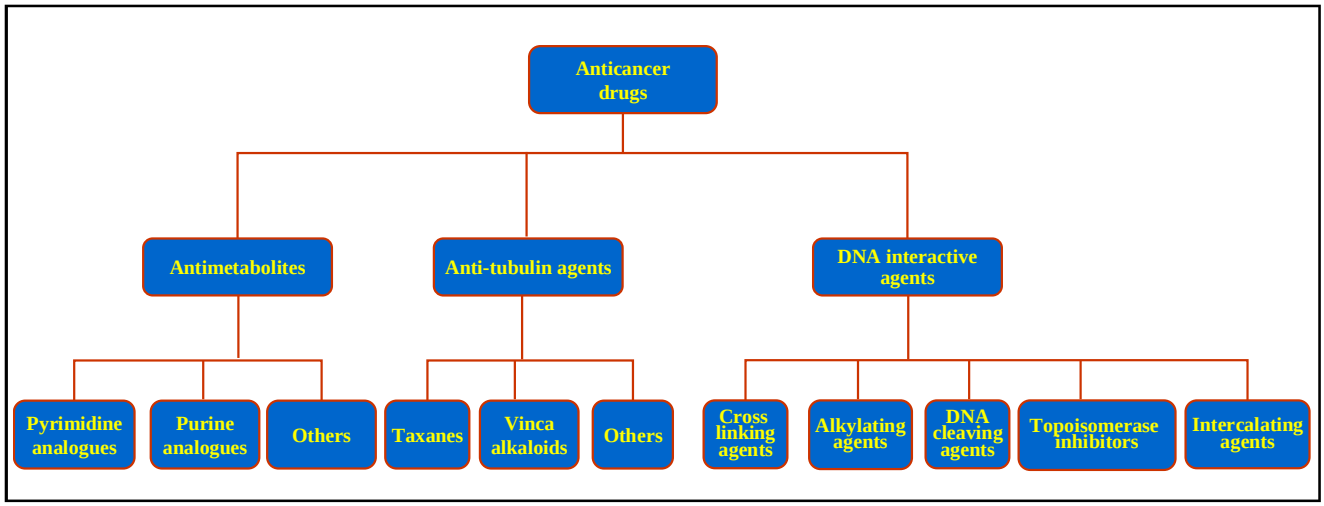


Figure 1: Classification of anticancer drugs on the basis of their mechanisms of action.

Most of the time, anticancer drugs are given intravenously. Drugs travel through the whole body to reach the cancer cells. In some situations, drugs are also delivered directly at the site of tumor (Bae and Park, 2011; Rodzinski *et al*., 2016). Other routes of administration of anticancer drugs include oral, intramuscular, intra-thecal, intra-peritoneal, intra-arterial and topical. The main goals of chemotherapy are to achieve the remission or cure, to help other treatments, to control cancers, to relieve the symptoms and to stop the cancer coming back (Liu *et al*., 2016).

2.4 Targeted therapy

Agents of targeted therapy include specially designed anticancer drugs which interact with targeted molecules, mostly a protein. It is generally believed that this molecule is the key role player in carcinogenesis (Sawyers, 2004). Many exciting new targets for treating and/or preventing cancer have been offered by oncologists but classical chemotherapy and radiotherapy approaches remain the mainstay of cancer treatment for tumors that cannot be cured solely by surgical excision. The identification of appropriate targets of cancer therapy is based on a detailed understanding of the molecular changes in carcinogenesis. Some molecular target and their drugs are mentioned in Table 1.

2.5 Immunotherapy

There is a great progress made in the field of tumor immunology in past two decades (Mao and Wu, 2010). The rapid growth in the identification of molecular identities of many tumor associated antigens provided a major stimulus for the development of new immunotherapies for the treatment of patients with solid cancers. The effective treatment for a variety of heamatological and solid cancers comprises the passive transfer of anticancer monoclonal antibodies and donor T-cells (Mellman *et al*., 2011). Allogenic bone marrow transplantation and infusion of donor lymphocytes have shown a highly effective therapy for some leukaemias and lymphomas. Her2/neu, EGFR, VEGF, CD20, CD52 and CD33 are the cancer-associated proteins and nine monoclonal antibodies targeting these proteins are approved to treat solid and heamatological malignancies (Mellman *et al*., 2011).

Table 1: Molecular targets of drugs for different kind of cancers

Drug	Target molecule	Disease
Imatinib (Gleevec)	Abl Kit PDFGR	CML, GIST, HES, CMML and DFSP
Gefitinib (Iressa)	EGFR	Lung cancer
Bevacizamab (Avastin)	VEGF ligand	Colon cancer
CCI-779, RAD-001	mTOR	Various cancers
BMS-354825	Abl KIT	CML, GIST
PKC-412, MLN-518,	FLT3	AML
BAY 43-9006	VEGFR, RAF	Kidney cancer, melanoma
SU-011248	VEGFR	Kidney cancer

AML, acute myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; CML, Chronic myeloid leukemia; DFSP, dermatofibro sarcoma protuberans; GIST, Gastrointestinal stromal tumor; HES, hypereosinophilic syndrome.

2.6 Hormonal therapy

Hormonal therapy is one of the major modalities in medical oncology which provides the advantage over chemotherapy and targeted therapy as it includes no cytotoxic effects on normal cells (Prat and Baselga, 2008). It involves the manipulation of endocrine system by the administration of specific hormones such as steroids or drugs which inhibit the production of hormone or block the action of hormone. Hormone therapy is used for several type of cancers involving the hormonally active organs such as adrenal, breast, prostate and endometrium (King *et al*., 2013). The hormone therapy includes inhibitors of hormone synthesis such as aromatase inhibitors and GnRH analogues, hormone receptor antagonists such as selective estrogen receptor modulators and anti-androgens, and hormone supplementation such as progestogens, androgens, estrogens, and somatostatin analogues.

2.7 Angiogenesis inhibitors

Angiogenesis is the synthesis of new blood vessels and angiogenesis inhibitors arrest the growth of new blood vessels (angiogenesis). The angiogenesis inhibitors are endogenous that perform the normal function in body while others are obtained exogenously such as pharmaceutical drugs or diet (El-Kenawi and El-Remessy, 2013; Wang and Miao, 2013). Angiogenesis inhibitors have been applied to treat different kind of cancers but the limitations of their use have been shown in practice. Blood vessel growth in normal and cancerous cells is the product of stimulation of many factors but the anti-angiogenesis inhibitors target only one factor which limits their use. There are some other limitations of angiogenesis inhibitors which include the maintenance of stability and activity, route of exposure and tumour vasculature (Lin *et al*., 2016).

2.8 Synthetic lethality

When two or more genes are deficient in their expression and causing cell death while the deficiency of one of them does not cause cell death, it is called as synthetic lethality (McLornan *et al.*, 2014). There may be different causes of the synthetic lethality such as mutation, epigenetic alterations or suppression of any gene (Lord *et al*., 2015). Synthetic lethality is used for the purpose of molecular targeted therapy for cancer (Thompson *et al*., 2017). In 2016, FDA approved inactivated tumor suppressor gene (BRCA1 and BRCA2) as the first example of a molecular targeted therapy exploiting the synthetic lethality (Lord and Ashworth, 2013).

3. Mechanism of toxicity of anticancer drugs

The anticancer drugs of clinical importance show the malignant cell toxicity selectively (Paci *et al.*, 2014). Their toxicity is an additional burden on the patients undergoing chemotherapy (Kasetty *et al*., 2012). It not only is a body burden of a toxic drug but management of toxicity caused by the drug also incurs monetary burden. There are many regenerating tissues with high capacity of proliferation. These tissues include bone marrow, hair follicles and mucosa of gastrointestinal tract which have capability to compete with malignant tissues on the exposure to anticancer drugs. The immediate post therapy period is always crucial which leaves some acute toxic effects which may be usually reversible but some are long term toxic effects and may be irreversible in nature. Brenner and Stevens (2012) suggested that the common toxicities caused by anticancer drugs include pulmonary toxicity, gonadal toxicity, haematological, gastrointestinal, nervous system toxicity, local toxicity, metabolic abnormalities, skin and hair follicle toxicity, urinary tract toxicity, cardiac toxicity, hepatic toxicity, *etc*.

3.1 Haematological toxicity

Frequent dose limiting side effect of chemotherapy is peripheral cytopenia from bone marrow suppression which can manifest as acute and chronic marrow damage (Gupta *et al*., 2001). An important destructive effect of anticancer drugs is to damage the proliferating activity of haematopoietic precursor cells which leads to the deficiency of formed elements and life threatening haemorrhages along with infection (Hoagland, 1982; Gastineau and Hoagland, 1992).

3.2 Anaemia

There are many factors affecting the aetiology of anaemia in cancer patients such as marrow infiltration, absence of nutritional stores, blood loss and cytotoxic effects of anticancer drugs (Bomgaars *et al*., 2001; Seiter, 2005). The negative effects of mild and moderate anaemia include the diminished functional ability of the person and quality of life. Anticancer drugs causing anaemia are cisplatin, docetaxel, altretamine, cytarabine, topotecan and paclitaxel.

3.3 Gastrointestinal toxicity

After chemotherapy, anorexia, nausea and vomiting are frequently observed (Rittenberg, 2002). It is not a pathological process but rather a physiological process in which the body itself gets rid of toxic substances. This reaction is controlled by a reflex arc which involves multiple afferent limbs, a coordinating area (vomiting centre) and multiple efferent pathways that activate and coordinate the muscle group necessary for an emetic response. The multiple afferent limbs include:

- Chemoreceptor trigger zone pathway in which substances released into the cerebrospinal fluid and activate the trigger zone,
- The peripheral pathway initiated by neurotransmitter receptors *via* vagus nerve,
- Cortico-spinal pathway activated by learned association, and
- Vestibular pathway.

The patient can be distressed enough with nausea and vomiting that it can even leads to withdrawal from therapy.

3.4 Oral toxicity

The secondary target of chemotherapeutic drugs is mucosa and if once mucosa is ulcerated, it opens a window for a systemic infection (Main *et al*., 1984). It damages the proliferating epithelial lining of mucosa which causes the slower rate of renewal of mucosal lining. This leads to stomatitis, dysphagia, diarrhoea, oral ulceration, oesophagitis, and proctitis with pain and bleeding (Sharma *et al*., 2005). Drugs causing stomatitis are mitomycin, methotrexate, 5-flurouracil, cytarabine, dactinomycin, irinotecan, vincristine, doxorubicin, bleomycin, vinblastine and etoposide (Main *et al*., 1984; Dozono *et al*., 1989).

3.5 Nervous system toxicity

The neurotoxicity is associated with the weakening of blood brain barrier due to greater use of high dose chemotherapy and new drugs

(MacDonald, 1996; Magge and DeAngelis, 2015). Loss of deep tendon reflexes and weakness and paresthesia of hands and feet are common in almost all patients. Those chemotherapeutic agents that disrupt microtubules damages peripheral sensations and motor nerve axons at higher risk (Paulson and McClure, 1975). Autonomous nervous system (ANS) toxicities are chronic constipation, bowel obstruction, and orthostatic hypotension. In peripheral neuropathy, persisting numbness and tingling occur as a result of paraneoplastic effect (Hoekman *et al*., 1999). Carozzi *et al*. (2015) described the most significant mechanism of some chemotherapeutic drugs, by which they exert their toxic effect on peripheral nervous system.

Neurotoxicity associated with cytotoxic drugs (Magge and DeAngelis, 2015) can be categorized as under.

- **Autonomic neuropathy:** Cisplatin, vindesine, paclitaxel, vinblastine, procarbazine, vincristine.
- **Cranial nerve toxicity:** Vindesine, carmustine, vinblastine, cisplatin, vincristine, ifosamide.
- **Encephalopathy:** Carmustine, cytarabine, procarbazine, 5-flurouracil, cisplatin, ifosamide.
- **Peripheral Neuropathy:** Vincristine, carboplatin, vinblastine, procarbazine, vindesine, paclitaxel.

3.6 Hepatotoxicity

It is a common problem in cancer chemotherapy. The pattern of hepatotoxicity reactions may vary including fibrosis, parenchymal cell injury with necrosis, ductal injury with cholestasis, hepatic venoocclusive disease and steatosis (Costa, 1984; King and Perry, 1996; Bahirwani and Reddy, 2014). The pattern of hepatoxic injuries caused by chemotherapeutic agents is predictable as they adapt a direct mechanism or idiosyncratic mechanism. Cyclophosphamide, streptozocin, 5-flurouracil, methotrexate, 6-mercaptopurine and doxorubicin are known hepatotoxic drugs.

3.7 Urinary tract toxicity

Urinary tract toxicity includes the damage of renal tubule such as cisplatin-induced nephrotxicity and cyclophosphamide and methotrexate-induced heamorrhagic cystitis (Stillwell and Benson, 1988). Contact of toxic metabolites of CP such as acrolein with bladder wall produces mucosal erythema, inflammation, ulceration, necrosis and a reduced bladder capacity (Brock *et al*., 1979; Sigal *et al*., 1991; Batista *et al*., 2006).

3.8 Renal toxicity

Nephrotoxic chemotherapy drugs, age, nutritional status, exposure of nephrotoxic chemicals and pre-existing renal dysfunction are the major risk factors for renal toxicity (Paterson and Reams, 1992). Cisplatin, ifosamide, mitomycin, plicamycin and streptozotocin are the drugs causing renal toxicity (Kintzel and Dorr, 1995).

3.9 Cardiac toxicity

Due to free radical mediated injury, cardiomyopathy is the most common chemotherapy associated cardiac toxicity (Keizer *et al*., 1990). Bolus administration causes the acute effects within hours. Such effects include arrhythmia and sinus tachycardia. There is no dose related changes in ECG but they are transient. After the weeks to months or a year of therapy, sub-acute cardiomyopathy is observed. After one to five years of therapy, later effects of the cardiac toxicity occur (Hardy *et al*., 2010).

4. Prevention of toxicity of anticancer drugs

WHO has reported that even hundred years before the development of modern medicine, traditional medicines (TM) have been existing in therapeutic practice (WHO, 2013). Traditional medicine is the synthesis of the therapeutic experience of generations of practicing physicians of indigenous system of medicine. Herbal drugs comprise only those TM which mainly use medicinal plant preparations for therapy. It has been observed that traditional medicine shows advantages as an adjuvant therapy to enhance the anticancer effects over the modern synthetic drugs and offers a new window of options. Moreover, many studies indicated that the role of traditional drugs in the prevention and treatment of cancer is very essential in post-operational recovery stage as well as during chemotherapy or radiotherapy (Zhou *et al*., 2014).

4.1 Radix Ginseng

Radix Ginseng is the dried root of *Panax ginseng* C.A. Meyer (family Araliaceae). Radix Ginseng is known as the king of herbs and a very popular traditional medicine. It is being used since ancient times for various activities with mysterious powers as a tonic and prophylactic and restorative agent (Xiang *et al*., 2008). It has been shown in different studies that Radix Ginseng and its active constituents have various pharmacological activities including anti-ulcer, antiadhesive, anticancer, antioxidant, immunomodulatory, hypoglycemic and hepatoprotective activities (Sun, 2011). As an anticancer drug, it has been reported in animal models, cells and clinical samples that Radix Ginseng has chemopreventive effects on various kinds of cancer including colon cancer, lung cancer, gastric cancer, liver cancer and pancreatic cancer (Yun, 2003; Hofseth and Wargovich, 2007; Sun, 2011). Radio-protective activity and capability of Ginseng in reducing the toxic effects of radiotherapy in cancer patients has also been shown coupled with its immunomodulatory and anti-oxidation activities (Lee *et al*., 2005).

4.2 Radix Astragali (Huang-Qi in Chinese)

Radix Astragali (*Astragalus propinquus* syn. *Astragalus membranaceus*; family Fabaceae) is a healthy food supplement used as a tonic (Liu and Li, 2012). It is also used as a herbal medicine. Like Ginseng, it is the dried root. Dried roots are used for medicinal and healthy food supplement purposes. The anticancer activity of Radix Astragali has been reported in cell lines, animal models and clinical samples for various kind of cancers including liver, gastric, colon, breast and lung cancers (Li *et al*., 2008; Lin and Chiang, 2008; Law *et al*., 2012). The mechanism of its anticancer activities has been reported to be through the inhibition of cell proliferation and angiogenesis as well as regulating immunity to reduce the toxic effects of chemotherapy (Li *et al*., 2008; Lin and Chiang, 2008; Law *et al*., 2012).

4.3 *Curcuma longa*

Curcuma longa belongs to the family of ginger. It is also commonly known as turmeric. In Asian countries, turmeric is used as a culinary spice as well as therapeutic agent for various diseases including jaundice, acne, dysmenorrheal, diabetes, atherosclerosis and cancer. The synergistic effect of curcumin against cancer in association with doxorubicin, cyclophosphamide and mitomycin has been

reported in various studies (Kumar *et al*., 2015). Various animal and cell culture studies have shown the potential anticancer activities of curcumin associated with different anticancer drugs such as paclitaxel, vincristine, doxorubicin, 5-flourouracil, oxaliplatin, etoposide, *etc*., for various kind of cancers including colon, pancreas, blood, liver, breast gastric, lungs, prostate and ovarian cancer (Goel and Aggarwal, 2010).

4.4 Shi-quan-da-bu-tang (Juzentaiho-to or TJ-48 in Japanese)

TJ-48 is a herbal formulation and well known in China for its medicinal value. It contains 10 herbs of different families including *Ligustici rhizome*, *Rehmanniae radix*, *Glycyrrhizae radix*, *Astragalus membranaeus*, *Atractylodis lanceae rhizoma*, *Cinnamomi cortex*, *Ginseng radix*, *Paeoniae radix*, *Angelicae radix* and *Poria* (Qi *et al*., 2010). TJ-48 has also been shown to attenuate the toxic effect of TS-1 which is an oral anticancer drug, causing the bone marrow suppression in mice (Ogawa *et al*., 2012). The breast cancer patients receiving the chemotherapy showed the reduced hematotoxicity without changing tumour marker (CEA and CA153) presentation in the short term (Huang *et al*., 2013).

4.5 *Solanum nigrum*

Solanum nigrum has been tested *in vitro* for its cytoprotection against gentamicin-induced toxicity on Vero cells. Cytotoxicity was attenuated significantly as assessed by the trypan blue dye exclusion assay and mitochondrial dehydrogenase activity (MTT) assay. Also, the test further showed its significant hydroxyl radical scavenging potential, thus suggesting its probable mechanism of cytoprotection (Kumar *et al*., 2001).

5. Garlic

Garlic (*Allium sativum* L.; family Liliaceae) has been a part of people's lives from ancient times either as a culinary spice, therapeutic agent against common diseases, cleansing aid or energy booster for athletes and sports enthusiasts. The major sulphur-containing compounds in garlic are *S*-allyl-L-cysteine sulfoxide (alliin) and γ-glutamyl-*S*-allyl-L-cysteine (GSAC) (Hirsch *et al*., 2000). Overall, various studies reveal that four main constituents of garlic, *viz*., allicin, alliin, diallyl sulfide and *S*-allyl cysteine (SAC) have been investigated extensively (Figure 2).

Figure 2: Four major constituents of garlic.

Alliin is a natural compound present in garlic which forms complexes with allinase, a lyase enzyme released from crushing, cutting and grinding of garlic bulb (Iciek *et al*., 2009). This complex is unstable and undergoes dehydration in the presence of a cofactor pyridoxal-phosphate, thereby, yielding a reactive intermediate, sulfenic acid and pyruvic acid and ammonia. Sulfenic acid, an unstable organic compound at room temperature undergoes self-condensation resulting in diallyl thiosulfinate (allicin) (Ilic *et al*., 2011). Similarly, allicin is also a highly unstable compound, and easily decomposes into dithiins, ajoenes and allyl sulfides (Iberl *et al*., 1990; Trio *et al*., 2014) (Figure 3).

Aged garlic extract (AGE) is prepared by soaking whole or sliced garlic into water and alcohol mixture for a certain period of time. It mostly contains water-soluble OSCs, such as *S*-allylcysteine (SAC) and *S*-allyl mercaptocysteine (SAMC). Diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), and diallyl tetrasulfide are lipid-soluble compounds in AGE.

Garlic has a wide range of biological activities including antioxidant, anti-inflammatory, antidiabetic and anticancer activities as shown based on population investigations and extensive studies from laboratory and animal models (Table 2). The mechanisms involved have been partially clarified as the ability of garlic to scavenge reactive oxygen species (ROS), inhibit lipoprotein oxidation, induce endogenous antioxidant enzyme expressions, suppress inflammation, lower glucose levels, inhibit tumor growth, promote apoptosis, and arrest cell cycle (Figures 4 and 5) (Ho *et al*., 2012; Trio *et al*., 2014).

5.1 Fresh garlic

Allicin (diallyl thiosulfinate) is the major pharmacological component of garlic (Rivlin, 2001) and has attracted attention of the international medical experts due to its potential for disease prevention and treatment. This compound is formed by the action of the enzyme alliinase on alliin in crushed fresh garlic cloves. It possesses antioxidant activity and is shown to cause a variety of actions potentially useful for human health (Hirsch *et al*., 2000; Tattelman, 2005; Jakubikova and Sedlak, 2006). Allicin exhibits hypolipidemic, antiplatelet, antibacterial, and antifungal effects, immunomodulatory, hypocholesterolemic, and hypotensive effects (Tattelman, 2005). It has been reported that allicin inhibits growth of various cancer cells demonstrating anticancer and chemopreventive activities (Hirsch *et al*., 2000; Jakubikova and Sedlak, 2006).

A study of Suddek (2014) revealed that the pre-treatment with allicin potentiates the antitumor effect of tamoxifen and protects animals against hepatic injury by preventing oxidative stress and lipid peroxidation, enhancing antioxidant enzyme activities and inhibiting hepatic inflammation.

5.2 Aged garlic extract

The major unique organosulfur compounds in AGE are water-soluble *S*-allyl cysteine and *S*-allyl mercaptocysteine having potent antioxidant activity (Imai *et al*., 1994; Ide and Lau, 1997; Amagase *et al*., 2001). The amount of SAC and SAMC in AGE is high as they are produced during the process of aging, thus providing AGE with higher antioxidant activity than fresh garlic and other commercial garlic supplements (Imai *et al*., 1994).

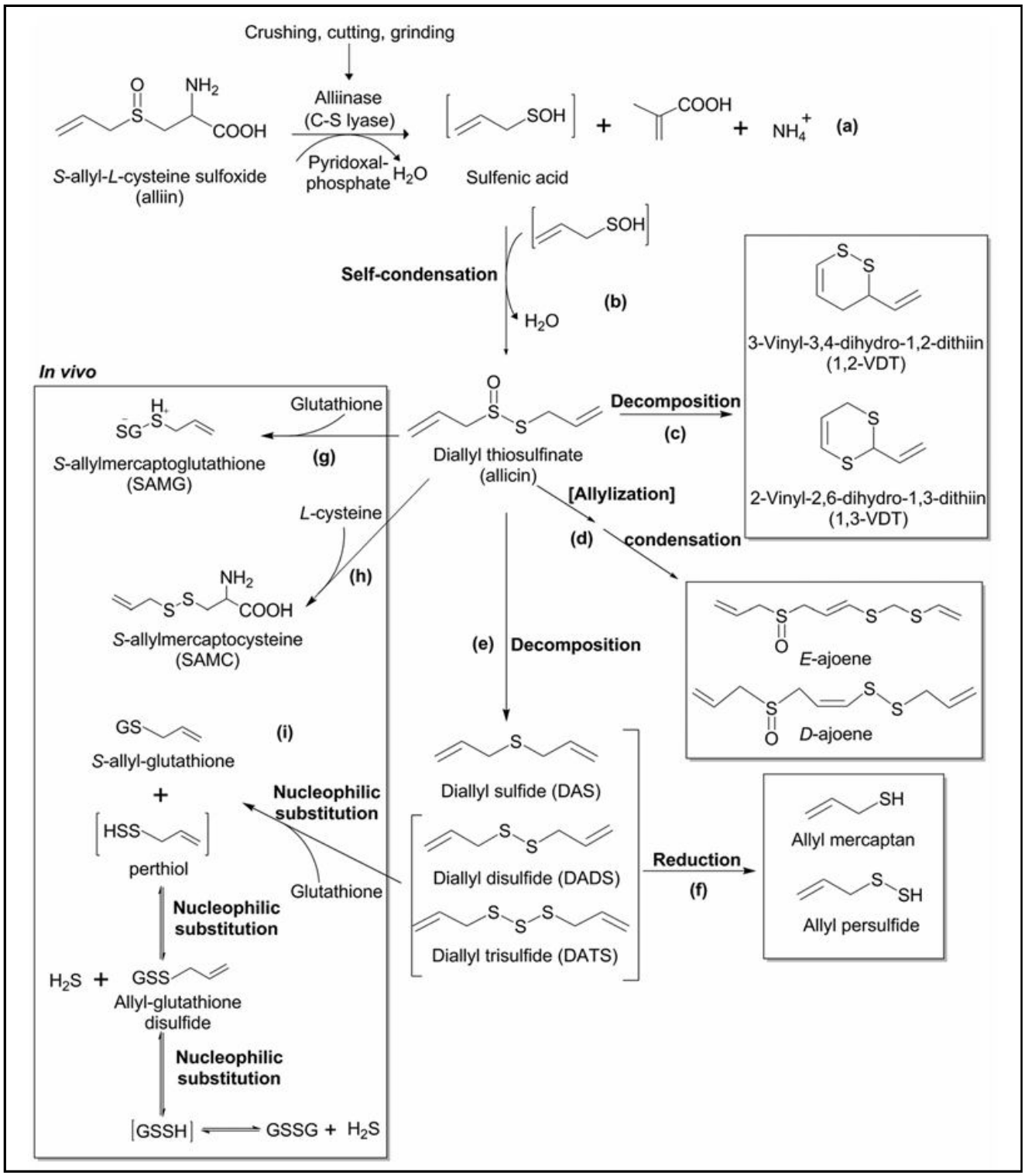


Figure 3: Biotransformation processes of alliin from garlic into different garlic OSCs. Alliin is a naturally present compound in garlic and forms complex with allinase, a lyase enzyme released from the crushing, cutting and grinding of the garlic bulb. As reacting with allinase, reactive intermediates including sulfenic acid, and pyruvic acid and ammonia are yielded (a). Sulfenic acid is an unstable organic compound which undergoes self-condensation resulting to allicin (b). Allicin is easily decomposes into dithiins (c), ajoenes (d) and allyl sulfides (e) which further reduce into allyl mercaptan and allyl persulfide (f). *In vivo*, alliin can react with reduced glutathione (GSH) to produce SAMG (g), or with L-cysteine to produce SAMC (h). Human red blood cells can convert garlic-derived DADS and DATS into hydrogen sulfide (H_2S) (i). **From Trio *et al.*, 2014 (with permission).**

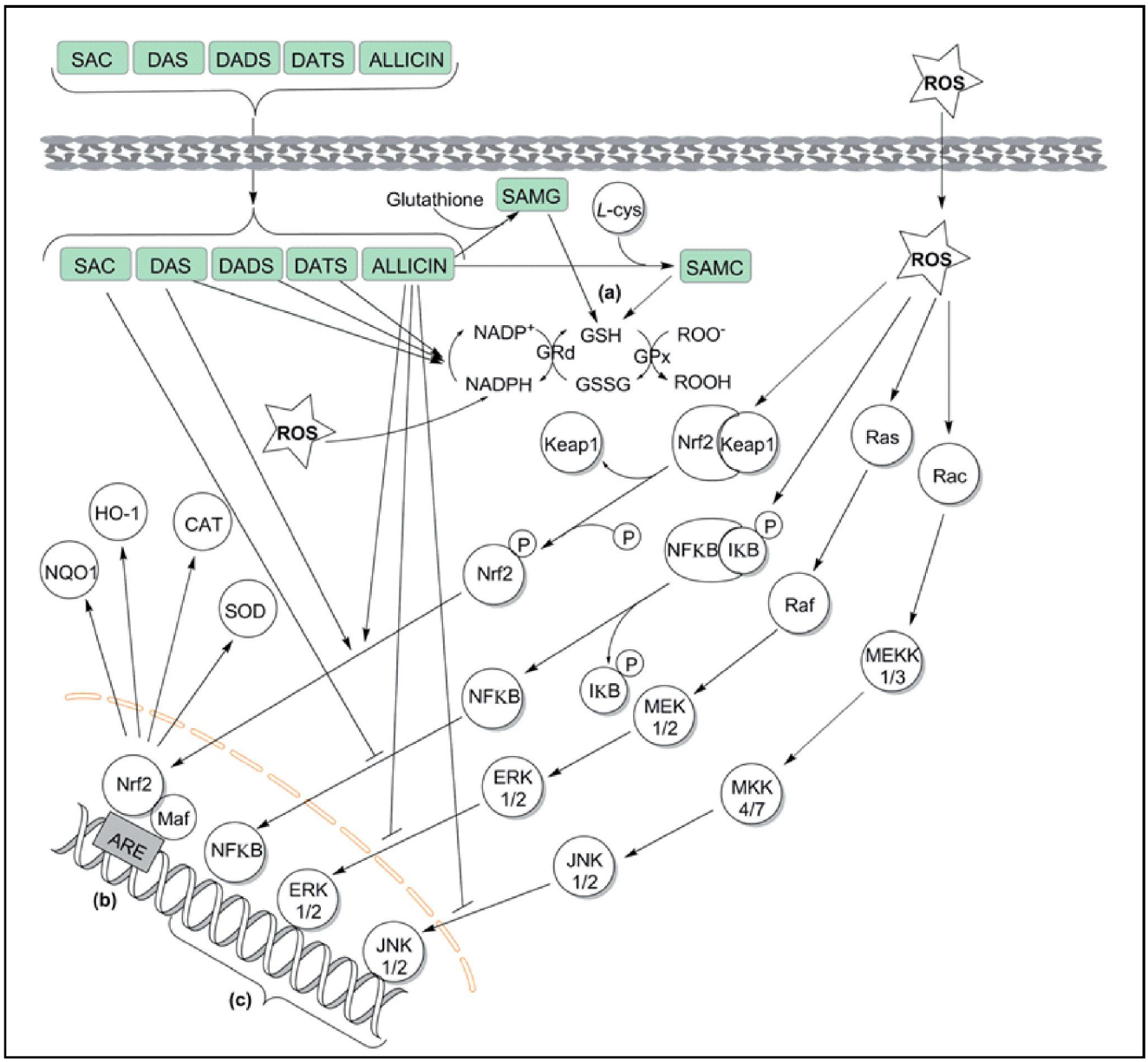


Figure 4: The schematic mechanisms of the antioxidative activities of garlic OSCs. The mechanisms at least involve OSCs reacting with intracellular glutathione to produce the thiol derivative, GSSA, since allicin could easily penetrate the cellular membrane and it readily reacts with the most abundant non-protein thiol in the mammalian system (a). OSCs modulate Nrf2-ARE pathway to enhance the expressions of antioxidative enzymes or protein genes (b), and also downregulate ROS-induced NF-κB and MAPK signalings to exert the crosstalk with anti-inflammatory activity (c). **From Trio *et al*., 2014 (with permission).**

Previous studies have shown that SAMC is very effective againt oxidative stress and inflammation (Pedraza-Chaverri *et al*., 2004; Wang *et al*., 2016). Therefore, it has been presumed that SAMC might be responsible for the protective effect of AGE in several experimental models associated with oxidative stress (Imai *et al*., 1994; Maldonado *et al*., 2003). Moreover, it has been shown that SAMC treatment could ameliorate gentamicin-induced oxidative and nitrosative stress and renal damage *in vivo* (Pedraza-Chaverri *et al*., 2004).

A study showed that cisplatin activates the NF-κB pathway depending on the degradation of IκB, which could increase a series of inflammatory cytokines including TNF-α, IL-1β and TGF1β (Peres and Da-Cunha, 2013). Pro-inflammatory cytokines could in turn initiate the degradation of IκB (inhibitor of NF-κB) (Hayden and Ghosh, 2004). Also, renal COX-2 expression increases concomitantly with kidney injury, renal inflammation and oxidative stress in rats treated with cisplatin (Fernandez-Martinez *et al*., 2016). However, SAMC was shown to markedly suppress the cisplatin-induced elevation in the level of inflammation cytokines including TNF-α, IL-1β, TGFβ1, COX-2 and iNOS clearly indicating that SAMC exerted an anti-inflammatory effect in cisplatin-induced renal injury as well as hepatotoxicity in rat model (Xiao *et al*., 2013; Zhu *et al*., 2017).

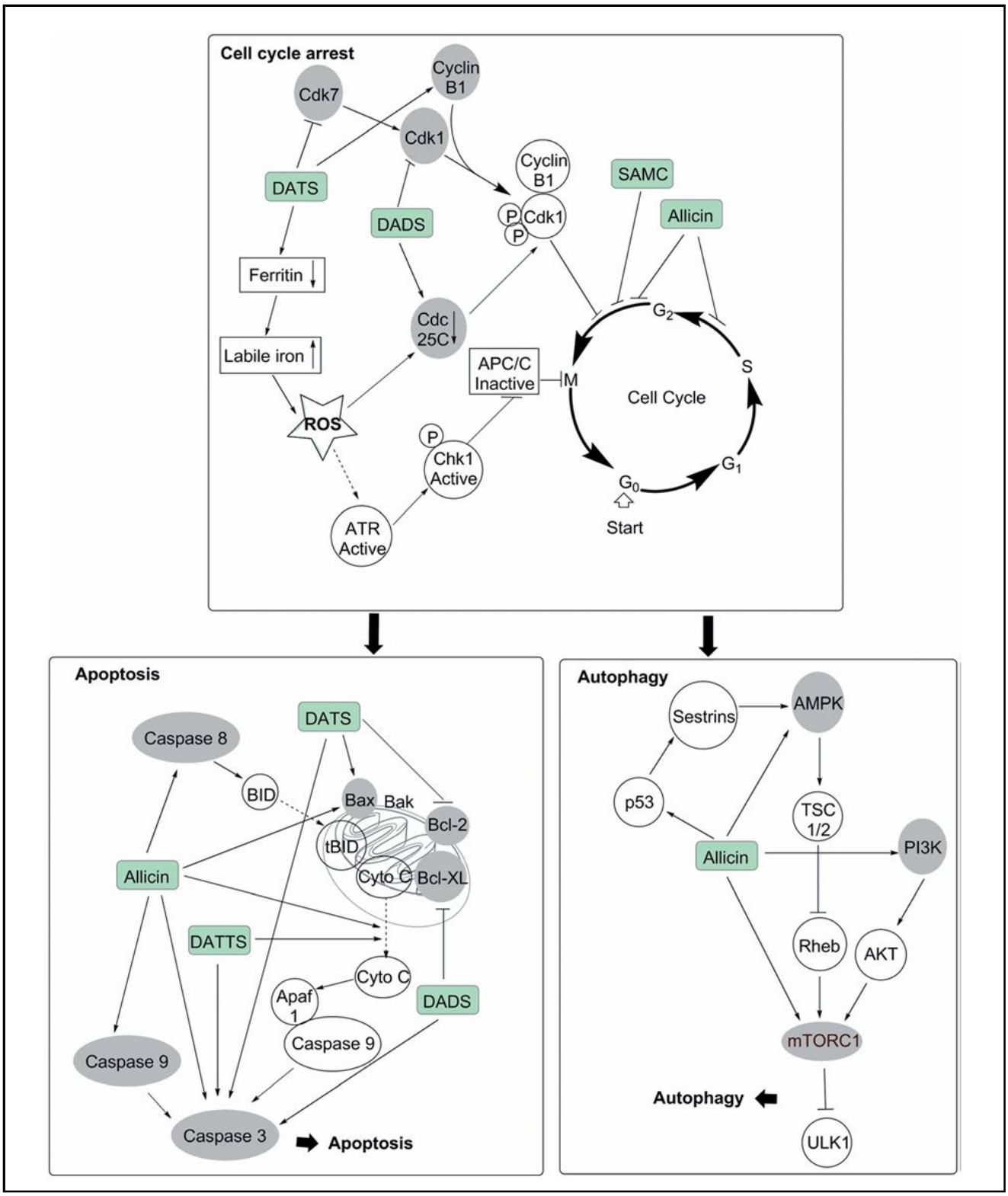
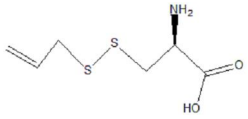
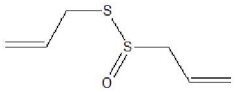
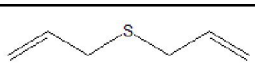
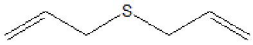
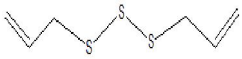
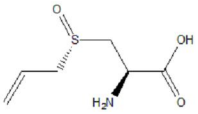
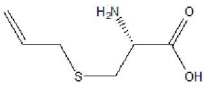


Figure 5: Multiple molecular mechanisms of garlic OSCs towards anticancer activities. OSCs such as DATS, DADS and allicin can cause apoptosis in cancer cells by mitochondrial-mediated caspase activation pathways (a). Allicin, DATS and SAMC also can cause cell cycle arrest by downregulating cdc25B and cdc25C that results in the inactivation of Cdk1, and induces G2/M phase arrest (b). Allicin may induce p53-mediated autophagy by reducing cytoplasmic p53 and Bcl-2 levels, modulating the PI3K/mTOR signaling pathway and increasing the AMPK/TSC2 and Beclin-1 expression (c). **From Trio *et al.*, 2014 (with permission).**

Table 2: Major garlic constituents and their reported pharmacological activities

S.No.	Garlic compounds	Structure	Mol. wt. (g/mol)	Anticancer activity	Antitoxicity activity
1.	Alliin		161.22	Siegers *et al.*,1999	
2.	Diallyl thiosulfinate (Allicin)		162.26	Zheng *et al.*, 1997; Miron *et al.*, 2003; Zhang *et al.*, 2010; Chu *et al.*, 2012; Wang *et al.*, 2012; Lee *et al.*, 2013	Suddek, 2014
3.	Diallyl sulfide (DAS)		114.20	Kim *et al.*, 2012	
4.	Diallyl disulfide (DADS)		146.26	Nakagawa *et al.*, 2001; Arunkumar *et al.*, 2006; Ling *et al.*, 2010	
5.	Diallyl trisulfide (DATS)		178.33	Kim *et al.*, 2007; Nkrumah-Elie *et al.*, 2012	
6.	*S*-allylmercaptocysteine (SAMC)		193.28	Shirin *et al.*, 2001	Lee, 2008; Pedraza-Chaverri *et al.*, 2004; Xiao *et al.*, 2013; Zhu *et al.*, 2017
7.	*S*-allyl cysteine (SAC)		161.22	Demeule *et al.*, 2004	Bhatia *et al.*, 2008; Abdi *et al.*, 2016; Abdi *et al.*, 2018

A study on cyclophosphamide-induced toxicity suggests that SAC is more potent against CP-induced toxicity over other thiol compounds such as dially disulfide and *N*-acetyl-cysteine, as it is very less toxic than other garlic compounds and has a high bioavailability (Kodera *et al.*, 2002; Pérez-Severiano *et al.*, 2004). The presence of allyl group in SAC plays a major role in its various beneficial properties (Moriguchi *et al.*, 1997). SAC not only mitigates the CP-induced alterations of critical antioxidants in urinary bladder but also afforded protection at cellular level (Bhatia *et al.*, 2008). SAC has also been reported to ameliorate the CP-induced down-regulation of a vital transmembrane member of urothelium of urinary bladder, uroplakin (Abdi *et al.*, 2016; Abdi *et al.*, 2018). SAC being one of the nutritional constituents of garlic, its supplementation may be affordable in cancer patients under chemotherapy.

SAC has also shown to have modulatory effect on uroplakin IIIa, CCL11 and TNF-α. While TNF-α is a key mediator of inflammatory responses, CCL11 is an inflammatory chemokine contributing to patho-physiological development in diverse tissues. Modulation of these molecular inflammatory response markers indicates that SAC could offer a multi-faceted protection to urinary bladder from toxicity of cyclophosphamide. In fact, protection afforded by SAC was stronger than that afforded by mesna (mercaptoethane sulphonic acid) which is approved by the US-Food and Drug Administration (FDA) for treatment of CP-induced hemorrhagic cystitis (HC) (Abid *et al.*, 2016). SAC is one of the nutritional constituents of garlic. Its supplementation may be considered in cancer patients under chemotherapy.

6. Conclusion and future direction of research

Toxicity of anticancer drugs is a cause of great concern, as mechanism of action of these drugs is mostly based on their cytotoxic or cytostatic action. Non-target toxicity is bound to happen which limits clinical potential of these drugs. Use of herbal extracts and natural products to prevent such toxicity is validated by a number of studies. Among various natural products garlic constituents have shown promising results. Recently, study of molecular mechanism of action of some garlic constituents such as *S*-allyl cysteine has offered insight into therapeutic potential of garlic and its constituents. It is hoped that revelation of mechanism of action of other garlic constituents shall enhance our understanding of marvels of garlic which has been in use in traditional medicine and dietary supplementation for centuries.

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Conflict of interest

We declare that we have no conflict of interest.

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