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Mechanistic Approach in the Management of Several Types of Cancer through Phytoconstituent of Garlic

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ABSTRACT

Background and aim: Garlic (Allium sativum) is a perennial bulb, it is cultivated many years ago worldwide. It has many phytoconstituents which have medicinal and therapeutic properties. from ancient times garlic has been used for the treatment of a wide variety of disorders including leprosy, diarrhea, constipation, asthma, fever, and infection. The present review aims to focus on the potential phytoconstituents that could be used in cancer treatment. **Materials and methods:** The extensive literature search was performed on Google scholar, Science direct, Springer, and other databases to collect the articles. In this article mechanism of anticancer activity of components of garlic, varieties of garlic, and distribution of garlic are reviewed. **Result:** One of the major health benefits of garlic is, it acts as an anticancer agent which is used in the treatment of many types of cancer such as gastric cancer, colorectal cancer, breast cancer, liver cancer, etc. Regular consumption of garlic in the diet promotes healthy status and decreases the chances of cancer. Several bioactive components which have anticancer properties are diallyl trisulfide, allicin, diallyl disulfide, diallyl sulfide, ajoene, Allin and allyl mercaptan, etc. **Conclusion:** The exact mechanism for anticancer activity of garlic is not known yet but researchers provide some evidence about mechanism like inducing apoptosis, suppression of expression of protein molecule, alteration in carcinogen-metabolozing enzyme, cell-cycle arrest etc.

1. INTRODUCTION

Garlic (*Allium sativum*) originates from central Asia, Siberia, and west of the Himalayas and now it is cultivated across the whole world. Garlic is a perennial bulb belonging to the genus, Allium. generally, the bulb part of the plant is used for medicinal purposes. It looks very similar to an onion, shallot, lee Breast cancer, Cervical cancer, Colorectal cancer, Garlic, Gastric cancerk, chive, etc. garlic is one of the herbs which is most commonly used in modern folkloric medicine. There are many sections present in the bulb part and each section is called clove[1]. In ancient times garlic has been used for the treatment of diseases or disorders like fever, asthma, constipation, diarrhea, leprosy, Alzheimer's, cold, and fungal disease. It is also useful in reducing or controlling blood pressure. Garlic also has an antimicrobial effect, it was used to treat the wound of soldiers during world war II. It is also used as a food flavoring agent and in traditional medicine as well. Garlic is one of the essential plants which is used in the treatment of disease. Medicinal uses of garlic have been proved in ancient medical texts from Egypt, Greece, Rome, China, and India. Father of medicine Hippocrates states that “let food be the medicine and let medicine be the food”. In support of this statement, Hippocrates suggests the use of garlic for a variety of conditions. Galen and hippocrates used garlic for the treatment of intestinal and extra-intestinal disease[2]. Labors are using a high amount of garlic for providing strength and increase work capacity. Several experiments and clinical investigations found a lot of effects shown by garlic e.g antimicrobial effect, anti-cancer effect, Antioxidant effect, anti-inflammatory effect, immune modulatory effect, anti-diabetic effect, anti-obesity effect, and antibacterial properties. etc. Current epidemiological studies show that intake of garlic is mostly associated with a reduction in the risk of cancer, particularly gastric and intestinal cancer. diethyl thiosulfinate, obtained from garlic is reported to inhibit sarcoma growth in S180-bearing mice[3]. many available laboratory data demonstrate that garlic has an effective component that kills the cancerous cell. An international organization like Garlic consumption as part of a healthy diet is advised by the National Cancer Institute (NCI), the American Institute of Cancer Research (AICR), and the World Health Organization (WHO). Garlic may affect cancer cells via modulating several mechanisms, including changes in the enzymes that metabolise carcinogens, cell cycle arrest, activation of apoptotic cell death, and suppression of oncogenic signal transduction pathways. due to their unpleasant smell and taste, many people are not able to ingest raw garlic, hence to enhance their taste and making a preparation that has no unpleasant taste is used without affecting their biological function. Many types of garlic

preparation have been made. The synergistic effect of garlic shows with some antibiotics such as ciprofloxacin but in Ampicillin there is no effect shown. Extraction of garlic with ethanol used as an antibacterial against clinical pathogens. It can be used to prevent and treatment of drug resistance to microbial disease. Garlic has various bioactive compounds such as sulfides, saponins, phenol, and polysaccharides. Major active compounds are diallyl sulfides, diallyl disulfides, and diallyl trisulfide[4]. The present review aims to focus on the potential phytoconstituents that could be used in cancer treatment. In this article mechanism of anticancer activity of components of garlic, varieties of garlic, and distribution of garlic are reviewed.

1.1 Pharmacognostic details of Garlic

Biological or Medicinal Name- *Allium sativum*

Family- Liliaceae/ Alliaceae/Amaryllidaceae

Order- Asparagales

Kingdom- Plantae

Common name: Garlic (English), lahsun (Hindi), Rasonam & Lahsuna (Sanskrit), Taisan (Japan), Knoblauch (Ger), da suan (chin), Lobha (Nepalese). Garlic consists of two types of bulbs:- (1) white coloured bulbs and (2) Pink coloured bulbs. During the chopping of garlic, it has a pungent taste and order. But when it gets heated the allin is transformed into allicin further it is transformed into another compound called ajoene and the formed structure gives a sweet buttery flavor. **Figure 1** shows the representative image of Garlic.

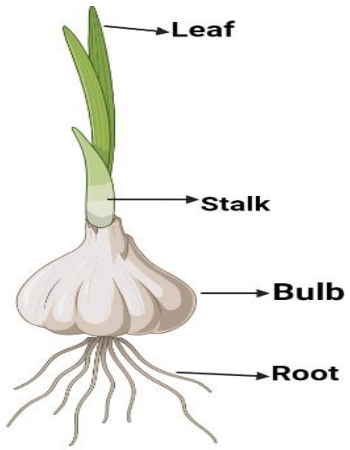

Figure 1. Allium Sativum

1.2 Geographical Source and components

Allium sativum is mostly grown in a temperate climate, similar to like central Asia. It is found to be grown in the north and south hemisphere[3]. The bulb of fresh garlic contains approximately ~65% water, ~28% carbohydrate, ~2% protein, ~1.2% Amino acid, ~1.5% fiber, fatty acid, phenols, etc. Approx ~2.3% sulfur-containing compound is found, it is converted into numbers then it contains approx. 33 in numbers. Allin is now considered the main sulfur-containing compound, it is derived from the amino acid cysteine. The pungent odor of garlic is due to the oil-soluble organosulfur compound(OSCs). Organosulfur compounds are divided into two categories (i) Oil-Soluble OSCs and (ii) water-soluble OSCs. Allin, Allicin, and ajoene are categorized under the oil-soluble organosulfur compound. Approx 8g/kg of allin is found in a garlic clove. Allinase enzyme is released when the garlic bulb is crushed or chopped. Allinase is responsible for the conversion of allin into allicin. In solvent extraction, Allicin is found to be a major constituent. Due to the unstable nature of allicin, it is rapidly degraded into a no. of compounds like ajoene, dithiins, allyl methyl trisulfide, diallyl sulfides (DAS), diallyl disulfides (DADS), Allyl methyl trisulfides (DATS). This conversion occurs within an hour at room temperature and within a minute during cooking. water-soluble organosulfur compounds are considered to be the main bioactive component in the prevention of cancer. components of water-soluble organosulfur compounds are S-allyl cysteine (SAC), S-Allylmercaptocysteine (SAMC), metabolite allyl mercaptan (AM), and allyl methyl sulfides (AMS). S-Allyl cysteine is stable in the blood. So, after oral intake of garlic, it can be detected in plasma, liver, and kidney. it is s marker of garlic consumption. oil-soluble organosulfur compounds are not detected in plasma or urine after the intake of larger amounts of garlic. In clinical studies, SAC has been found that it has anti-oxidant and cholesterol-lowering properties. NCI proved that SAC has lower toxicity approx. 30 folds than Allicin and DADS[5]. **Figure 2** shows the various components of the Garlic.

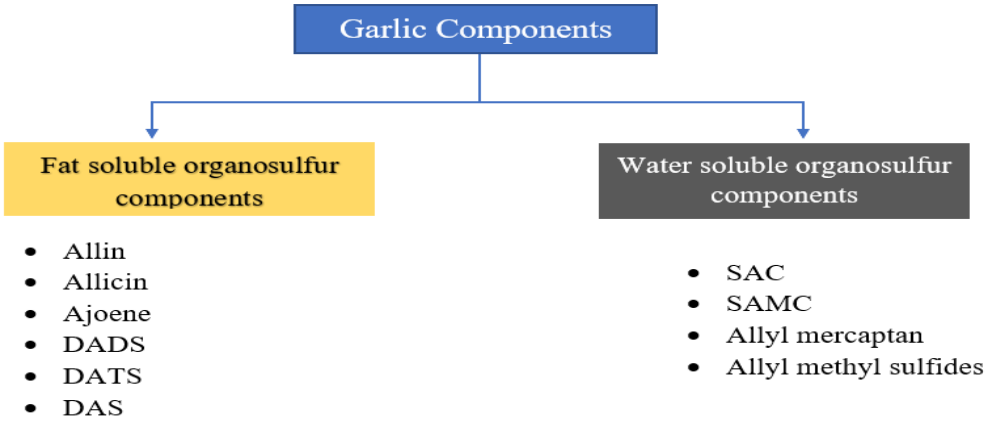

Figure 2: Various components of the Garlic

2. Different varieties of Garlic and their biological distribution

Garlic is one of the oldest known horticultural crops. Garlic has clear historical evidence that it is used for medicinal purposes since 5000 years ago. The garlic is Cultivated in a much larger region. This region where garlic has grown within the wild is referred to "center of origin". A wild region, where garlic plant grows without under care of humans, this point is referred to as "wild garlic". Wild garlic is not a true garlic. There are changes in species of garlic genus (e.g Allium vineale). Wild garlic (e.g Allium vineale) belongs to a wild family member of garlic& Mostly propagated in North America. There are two types of garlic, the hard neck, and the soft neck. In these 2 types, there are lots of varieties and types inside these categories. Climate can affect the taste and escape production of both this category[6].

2.1 Hard Neck Varieties

Biological name- *Allium sativum* varophioscorodon

A hard neck produces the edible flower stem called garlic scape. Hard neck varieties are often known as bolting or top-setting varieties. Varieties of hard neck garlic are-"rocambole"(it is a brownish colour with 12 cloves/bulb). "Purple stripe", "Marbled purple stripe", "Glazed purple stripe", "porcelain", "Asiatic", "creole", and "Turban". Hard necks produce 5-12 cloves per plant, roots and dry cloves are not stored after a few months. They can not be braided because of the hard flower stalk. Flowers are abort and form bulbilsm. Aerial Cloves of hard neck garlic are used for the propagation of the bulb. A single clove can produce a bulb of garlic.

2.2 Soft Neck Varieties

Biological Name- (*Allium sativum* var sativum)

Soft neck produces leaves, it does not produce scape. Mostly used for commercial propagation due to the production of the bulb and minimal flower stalk and bulbil production. It is more productive than a hard neck because all energy is used for producing a bulb. A partial flower stalk produces some soft neck varieties and bulbils form directly above the bulb. It has a longer shelf life. it can be stored for up to 6-8 months. it contains 10-40 cloves per plant. Soft neck typically grows in summer and starts in winter. Varieties of the soft neck are Blanco Piacenza, California early and late whites, silver, silver white, Corsican red, french red, Artichoke and silver skin.

3. Role of Garlic in Health

Garlic has healing power which can inhibit or kill bacteria, and fungi, and also contain anti-tumor properties. It has a major role as an immunity booster to fight against foreign particles and keep the body healthy. Garlic stimulates the lymphatic system which helps in flushing out the waste of the body. Garlic has over 200 surprising chemicals which can protect the human body from various disease[7].

3.1 Anticancer Activity of Garlic

Cancer is one of the leading causes of death in the world. Various natural products have anticancer properties such as berries, tomatoes, vegetables, and garlic. The major favorable action of garlic is the inhibition of the growth of the cancerous cell. Garlic can protect against various cancer like colorectal cancer, lung cancer, and gastric and bladder cancer because it contains a large no. of potent bioactive compounds with anti-tumor properties, largely allylsulfide derivatives. Take garlic with lemon to activate the immune system against breast cancer[8]. By stimulating the T-cells and natural killer cells garlic attribute the active prevention of disease. garlic modulate the immune response through a series of molecular mechanism in carcinogeneses, such as DNA adduct formation, mutagenesis, cell proliferation, and differentiation, and scavenging of free radicals. Various studies, epidemiological, clinical, and laboratory that Allium sativum plays a major role in the prevention of cancers, especially digestive tract cancer. Regular intake of garlic lowers the risk of esophageal cancer, stomach cancer, and colon cancer. In both rodents and humans, garlic and its constituents have been found to inhibit the development of chemically induced

tumors in livers, colon, and prostate. Allicin (which is the compound of garlic) has an antioxidant effect that inhibits the formation of carcinogenesis (also called oncogenesis or tumorigenesis) compound in the stomach and intestinal tract[9]. Cohort study of dutch research in the Netherland found that the chances of development of stomach cancer are low in those who consume garlic relatives of onion [(35)]. chances of development of prostate cancer in men are relatively low who intake allium vegetables >10.0g/day. ajoene and other garlic-derived natural compounds have been shown to introduce apoptosis in the human leukemic cell via stimulation of peroxide production, activation of caspase-3-like, and caspase-8 activity. Garlic promotes the activity of eicosapentaenoic acid (breast cancer suppressor) and affects the activity of linoleic acid (breast cancer enhancer).

3.2 Anticancer phytoconstituent of garlic

Here we only discuss the bioactive compounds of garlic which shows anticancer activity. The bioactive compound has 2 molecules (non-volatile organosulfur) such as ɤ-glutamyl-L-cysteine peptide and another L-cysteine sulfoxide (containing S-allyl-L-cysteine-sulfoxide)[10]. Further studied 80% of cysteine sulfoxide in garlic also known as allin. Allin is a derivative of amino acid cysteine, when a garlic clove is chopped, mashed, and crushed, the enzyme is produced. alliinase and enzyme allinase help to convert Allin into 2-propenesulfenic acid along with subsequent liberation of pyruvic acid and ammonia. Allin gets heated and then transformed into the volatile compound allicin found in allium sativum. Allicin is formed when 2-molecule of 2-propenesulfenic acid react with each other and also some quantity of water is liberated. when allicin is fermented with an organic solvent, it produces ajoene. S-allyl mercapto cysteine (SAMC) is formed when allicin is interact with L-cysteine in the body[11]. N-trans-feruloyl octopamine (Fo) was isolated from garlic skin, it is a derivative of hydroxycinnamic acid. Semethyl-L-selenocysteine (MseC) is a natural organo selenium molecule, it is a derivative of S-methylcysteine.ɤ-glutamyl-L-cysteine peptides which contain dipeptide- ɤ-glutamyl- S-allyl-L-cysteine, they produce 2 molecules i.e s-allyl-cysteine (SAC) and SAMC after long term fermentation of crushed garlic in an aqueous medium. S-benzyl-cysteine (SBC) is the structural analouge of SAC, it was isolated from aged garlic extract. S-proparyl-cysteine (SPRC) is a derivative of SAC and H_2S donor produced from garlic extract.

3.3 Mechanism of Anticancer effect of garlic

Numerous in vitro tests and research investigations have demonstrated the anticancer properties of garlic. The anticancer effects of garlic are mediated by several mechanisms, including suppression of mutagenesis, scavenging of free radicals, control of enzyme activities, inhibition of protein production, and induction of apoptosis. It has been discovered that organic or aqueous garlic extract effectively inhibits the mutagenicity of bacteria such as Salmonella typhimurium and Escherichia coli that are induced to become mutagenic by various chemicals[11]. radical scavenging activities are shown by SAC & SMAC. Intake of garlic, reduce lipid peroxidation and increase antioxidant in the blood (antioxidant like vitamin E, superoxide dismutase, reduced glutathione, and glutathione peroxidase)[12]. These antioxidants increase the activity of the free radical scavenging enzyme to protect against oxidative damage[13]. garlic extract and its preparation also stimulate the carcinogen-detoxifying enzyme, such as glutathione S-transferase (GSTs) and cytochrome P450s (CYPs). DADS & DATS in original form prevents the enzymatic activity of arylamine N-acetyl-transferase (NAT)[14]. ajoene, compounds of garlic cause the accumulation of misfolded protein aggregate in cancer cells. In this context, we can see that garlic components work as blockers and regulators in the initiation and promotion stage of carcinogenesis.

3.4 Gastric Cancer

It is leading cancer the worldwide, in 2020 the new cases are estimated at 769,000 death and 4th position in a fatality. Environmental and genetic factors influence the etiology of this disease. The consumption of raw garlic or cooked garlic is used for the prevention of gastric cancer. cytotoxic activity in the human gastric cancer cell (SGC7901) shown by extract of mature black garlic through its antioxidant and immunomodulatory concentration-dependent apoptosis[15]. Allicin inhibits the proliferation of SGC-7901 gastric cancer cells by inducing apoptosis and release of it. C into the cytoplasm which subsequently activates caspase-3, caspase-8, and caspase-9Allicin putting down the rapid increase of gastric cancer cells (HGC27 and AGS) by triggering apoptosis[16].Allicin induces apoptosis through the induction of ROS and DNA damage Through the caspase-dependent/independent pathway and death receptor pathway(54). By actuate of apoptosis, allicin shows a similar anticancer activity[17]. It also exhibited inhibitory activity against the growth of carcinoma cell lines (MGC-803, BGC-823, SGC-7901) by inducing apoptosis and increasing the expressing level of p38, and cleaved caspase-3 associated with an increase in Bax expression level and decreased level of

Bcl-2, it also suppresses the p38 MAPK/caspase-3 signaling pathway[18]. DATS is a metabolite of garlic that inhibit the protein level sulfiredoxin (srx), MDA, and ROS in BGC823 gastric cancer cells. Increased srx in cancer that causes growth of cancer cell and tumor cell[19]. DATS inhibits the rapid cell growth of gastric cancer cells SGC-7901 by inducing cell cycle arrest at the G2/M phase. DATS leads to an increase in the causing factor of proapoptotic factor Bax and a decrease in the preventing factor of apoptosis (Bcl-2)[20]. Similarly, we observed, that induction of apoptosis inhibits the rapid cell growth of cancer and also inhibits the growth of tumor cells[21]. **Figure 3** demonstrate the DATS-induced anticancer effects of gastric cancer cell and **Figure 4** demonstrate the proposed pathway for SAMC-induced cell cycle arrest and activation of apoptosis in the gastric cancer cell.

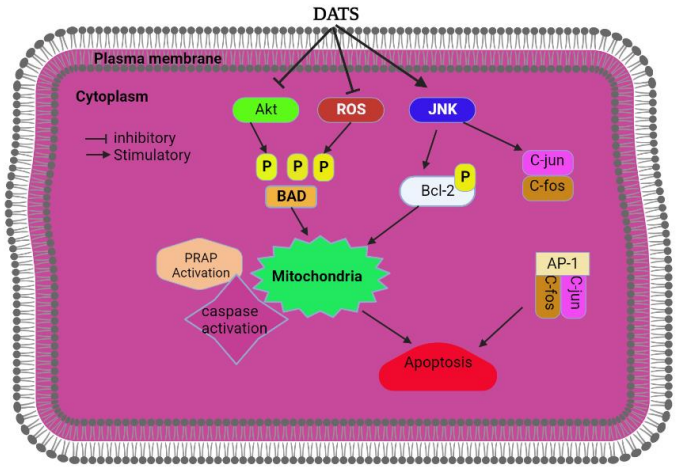

Figure 3. Diagrammatic representation demonstrates the DATS-induced anticancer effects of gastric cancer cell

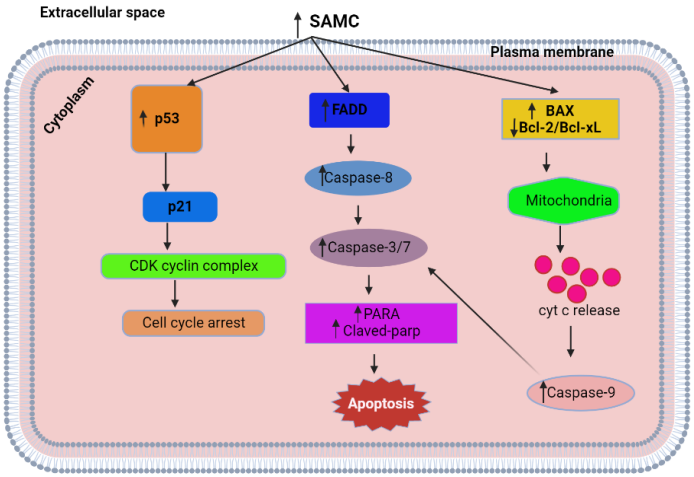

Figure 4. Diagrammatic representation demonstrates the proposed pathway for SAMC-induced cell cycle arrest and activation of apoptosis in the gastric cancer cell.

3.5 Liver Cancer

In 2020, new cases were estimated about 906,000, and the fatality rate was expected about 830,000. It is the sixth most frequently diagnosed cancer and a third major cause of mortality globally[22]. Several types of cancer can form in the liver but hepatocellular carcinoma (HCC) is the most common type of liver cancer[23]. FDA has approved the immunotherapy drug to treat a liver cancer patient. The natural plant shows a better effect on the liver, as garlic, and garlic shows their therapeutic action and protective action against liver cancer[24]. The combination of allicin and 5-fluorouracil inhibits the cell growth of HCC SK-HEP-1 and BEL-7402 cells[25]. DAS oppose the oxidation, reduction, and metabolism of diethylstilbestrol, which is responsible for increasing the carcinoma cells, hence they inhibit DNA formation and decrease the risk of liver cancer[26]. The rapid growth of HepG2 cells in the liver is inhibited by DATS due to the formation of H_2O_2 which lowered the thiol level and activated the caspase-3 activity[27]. In HepG2 cells, apoptosis is induced by SAMC, by promoting the TGF-β1, TβRII, p-smad2/3, smad4, and smad7 signal proteins. it increased the formation of BIM, Caspase-3, and Caspase-9 and lowered the formation of Bcl-2, because of that they activate the TGF-β-signaling pathway and inhibit the MAPK signaling pathway[28]. From the skin of garlic, an acid compound is separated, this acid is called hydroxycinnamic, it shows antiproliferative activity against Huh7 and HCCLM HCC cells by decreasing the phosphorylation expression levels of Akt and p38 MAPK[29]. Stimulation of NRF2 in HepG2 cells, by ajoene (ajoene transformed through allicin), Stimulated NRF2 shows the result of increased glutamate-cysteine ligase and GSH in cells and decreased the NRF2 interaction with kelch, and also ubiquitination of NRF2 get reduced[30]. From the extraction of garlic silver nanoparticles were produced which shows cytotoxicity against the human liver carcinoma cell[31]. Alginate-based black garlic nanoparticles show cytotoxicity against HepG2 cells[32.] Silver nanoparticles are responsible for the inhibition of the proliferation of HepG2 cell.

3.6 Breast Cancer

Breast cancer was found more rapidly growing neoplasm in females. This has been seen in both developing and developed countries worldwide. In 2020, it is estimated that a total of 2,261,419 new female breast cancer case was identified, and approx. 684,996 cancer death occur[33]. garlic component and aqueous extracts like allicin, allin, DADS, and others are very useful in the inhibition of the proliferation of MCF-7 human breast cancer cells. They inhibit

the growth of these cells in their G_0/G_1 or G_2/M phase of the cell cycle[34]. Allin and allicin inhibit the viability of luminal A MCF-70 and triple-negative HCC70 breast cancer cells. Allicin possesses more cytotoxicity and antiproliferative activity by inducing apoptosis, decreasing mitochondrial membrane potential, and increasing the expression level of caspase-3, caspase-8, and caspase-9 in both cells. Levels of antiapoptotic protein (BCl-XL) are also decreased by allicin and proapoptotic protein (P21, Noxa, Bak) levels are increased. These activities suppress the growth of tumor cell[35]. growth of canine mammary tumor (CMT-13) cells is inhibited by the oil-soluble organosulfur compound found in garlic (DAS, DADS, & DATS). DAS, and DADS, are found to be cytostatic while DATS are cytotoxic in nature[36]. MDA-MB-231 cells are estrogen receptor-negative human breast cancer cells. The growth of these cells is inhibited by DADS and DAS in the G_1 phase of the cell cycle by inducing apoptosis and cell cycle arrest. MCF-7 cells are estrogen receptor-positive human breast cancer cells. DADS inhibit the proliferation of these cells by inducing apoptosis with an increase in caspase-3 and PARP cleavage[37]. DADS modulates the expression level of caspase-3, BAX, BCl-2 Bcl-xl, and Bcl-w by triggering the phosphatidyl serine translocation, this can ultimately lead to induced H4 histone hyperacetylation[38].MDA-MB-231, MDA-MB-468, and BT-549 cells are human triple breast cancer cells. DADS inhibit the growth and metastatic capacity by inhibiting β-catenin signaling pathways. It induced apoptosis and inhibit cell proliferation linked with an increase in expression of Bax, caspase-3, and caspase-9 and an increase in the protein expression level of Bcl_2, matrix Metallo proteinase-9 (MMP-9), and β-catenin siRNA[39]. **Figure 5** demonstrate the proposed pathways for DADS-induced cell cycle arrest in the breast cancer cell.

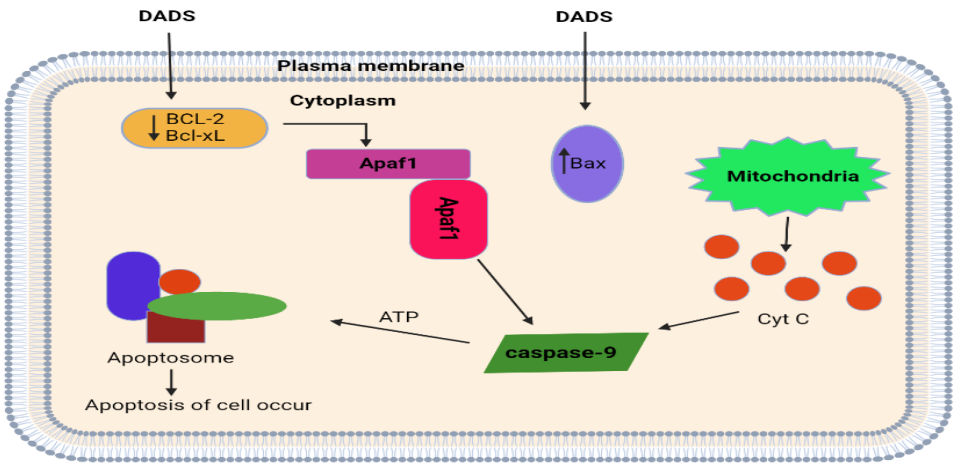

Figure 5. Diagrammatic representation demonstrates the proposed pathways for DADS-induced cell cycle arrest in the breast cancer cell.

3.7 Cervical Cancer

Cervical cancer is predominantly found in women and it is the 4th most frequently diagnosed cancer. In 2020, an expected 604,00 new case was identified and 342,000 death was estimated globally[40]. Allicin suppresses the viability of human cervical squamous cell carcinoma cell lines (SiHa cells) by exhibiting anti-tumor activity. Inhibition of cell proliferation is done by induction of apoptosis through suppression of the expression level of nuclear factor erythroid-2 related factor 2 (nrf 2) and heme oxygenase 1. The phosphoinositide 3-kinase (PI3K) signaling pathway is also inhibited by allicin[41].

3.8 Colorectal Cancer

Obesity, lack of physical activity, red meat intake, alcohol intake, and use of tobacco are considered the primary cause of generating colorectal cancer. It is considered as 3rd most common cancer and in 2020, more than 1.9 million new cases arise and about 935,000 death was recorded[42]. dietary supplement of garlic may reduce the occurrence of colorectal cancer and is very helpful in the prevention of this disease[43]. The proliferation of HT29 colon cancer cells is inhibited by aged black garlic extract. It inhibits cell growth by inducing apoptosis and cell cycle arrest in G_o/G_1 phase through regulation of the PI 3K/AKT pathway[44].

3.9 Adverse Effect of Garlic Consumption

Various beneficial effects are shown by garlic and its constituent can be used in the treatment of many diseases. It is also mandatory to know about the possible adverse effect of garlic. Generally, garlic preparation is categorized into four main types, such as fresh garlic, garlic oil, garlic powder, and aged garlic extract. In these preparation various components of garlic are present, mainly allicin is known to exhibit toxic effects. When allicin was administered directly into the intestine of the rat, the intestinal microflora was affected. So, for this reason, enteric-coated preparation is given to compromise the intestinal epithelium[45, 46]. continuously use of garlic extract in large quantity act as a clastogenic or mutagenic agent. Red blood cell lysis also occurs when raw garlic is intake. Anemia and weight loss are seen due to excessive red blood cell lysis[47].

4. Applications, recommendations, and limitations of the study:

Garlic acts as an anticancer agent and is utilized in the treatment of several cancer types, including gastric cancer, colorectal cancer, breast cancer, liver cancer, and others. Garlic

regularly included in the diet improves health and lowers cancer risk. Diallyl trisulfide, allicin, diallyl disulfide, diallyl sulfide, ajoene, Allin, and allyl mercaptan are a few bioactive substances with anticancer effects. However, a detailed study of these phytoconstituents should be carried out in other forms of cancers and its potential could be evaluated at preclinical as well as clinical levels. So far exact anticancer mechanism of action is not fully understood. Some advanced molecular technologies need to be involved in the identification of the exact anticancer mechanism of action of Garlic and its phytoconstituents. Based on potent phytoconstituents utilized in cancer a stable, robust, and economical formulation should be launched in the market with proper clinical trials.

5. Conclusion

Garlic has been used for its therapeutic and medicinal properties for several years ago. It is used throughout the whole world as an herb for the prevention and management of several disease conditions, including cancer. Garlic contains several constituents such as SAC, SAMC, DAS, DADS, and DATS, which exhibit their significant antineoplastic activities against various types of cancer. These constituents exhibit their anticancer mechanism by apoptosis of cancer cells, arrest of the cell cycle, activation of angiogen cascasde, & blockage of expression of the protein molecule.

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