https://doi.org/10.33472/AFJBS.6.6.2024.488-509

African Journal of Biological Sciences

Research Paper Open Access

Predictive Insights into the ADME and Toxicological Profiles of Allium Sativum Phytochemicals Using Swiss ADME and ProTox-II"

Manukonda Upender Kumar[1], Dr Ashish Srivastava[2] , Dr. Anandkumar K. Patel[3], Dr.Akshaykumar Harshadkumar Shah[4], Chennu MM PRASADA Rao[5], Rahit Paul[6], Dr PravinBadhe[7] , Prof.(Dr.) N. G. Raghavendra Rao[8]*

***Corresponding e mail raghavendra.rao@kiet.edu**

1 Research scholar, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana.

2 Associate Professor, PSIT-Pranveer Singh Institute of Technology (Pharmacy), NH-19, Bhauti Road Kanpur, UP

3 Professor, Saraswati Institute of Pharmaceutical Sciences, Gandhinagar

4 Professor & Head, Department of Pharmacy Practice Anand Pharmacy College Anand

5 Professor, School of Pharmacy Raffles university Neemrana 301705

6 Assistant professor, Department of Pharmaceutical chemistry, Brainware university, Kolkata - West Bengal, 700125

7 Associate Professor, Sinhgad College of Pharmacy, Swalife Biotech Ltd."

8 Professor, Dept of Pharmaceutics, KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Muradnagar, Ghaziabad-201206, UP.

Article History
Volume 6,Issue 6, 2024
Received:07 Mar 2024
Accepted : 31 Mar 2024
doi: 10.33472/AFJBS.6.6.2024.488-509

ABSTRACT

Background: The exploration of pharmacokinetic and toxicological properties of phytochemicals within traditional medicinal plants like *Allium sativum* (garlic) is crucial for their potential therapeutic application. The complex nature of phytochemical interactions necessitates advanced predictive analysis to optimize safety and efficacy.

Objective: This study aims to predict the ADME (absorption, distribution, metabolism, and excretion) properties and toxicological profiles of key phytochemicals in *Allium sativum* using the Swiss ADME and ProTox-II tools.

Method: Using canonical SMILES notations of compounds identified from *Allium sativum*, the Swiss ADME tool predicted pharmacokinetic properties, while ProTox-II provided insights into potential toxicities. Parameters analyzed included lipophilicity, solubility, blood-brain barrier permeability, carcinogenicity, and involvement in stress response pathways.

Results: Notable findings include the ability of alliin and diallyl disulphide to easily cross the blood-brain barrier. All examined compounds adhere to Lipinski's Rule of Five, suggesting good oral bioavailability. Ajoene and several diallyl compounds meet Muegge's criteria, indicating favorable pharmacological properties. However, diallyl disulphide, diallyl trisulphide, and diallyl sulphide are classified under varying classes of carcinogenic potential (III, III, and V, respectively). Stress response pathway activation was observed with diallyl disulphide, diallyl trisulphide, and diallyl tetrasulphide, specifically influencing the phosphoprotein p53. S-allylcysteine showed the highest solubility ([log S (E sol)] = 0.79), and diallyltetrasulphide exhibited the highest lipophilicity (2.8). The average bioavailability score across the compounds was 0.55. Molecular weight variations were significant, with diallyl tetrasulphide having the highest (210.40 g/mol) and allyl methyl sulphide the lowest (88.17 g/mol). Ajoene contained the highest number of rotatable bonds (8), indicating structural flexibility.

Conclusion: The study effectively utilizes in silico tools to delineate the ADME and toxicological profiles of *Allium sativum* phytochemicals, highlighting their potential in drug development. While offering promising pharmacokinetic attributes, some compounds exhibit significant toxicological risks that must be mitigated in drug design.

Keywords: Allium sativum, ADME, toxicology, Swiss ADME, ProTox-II, phytochemicals, pharmacokinetics, bioavailability, carcinogenicity.

INTRODUCTION-

The pharmacokinetic profile of bioactive compounds within medicinal plants remains a paramount area of study in the intersection of pharmacology and toxicology.[1] The quintessential nature of understanding absorption, distribution, metabolism, and excretion (ADME) properties, alongside the toxicological profiles of phytochemicals, serves as the bedrock for advancing herbal medicine into clinically viable therapeutics. [2] Allium sativum, commonly known as garlic, has been revered throughout history for its broad spectrum of biological and therapeutic effects. The phytochemical richness of Allium sativum positions it as a significant candidate for the development of novel drug leads and supplements. [3] However, the translation of its therapeutic potential into clinical settings necessitates a comprehensive evaluation of its ADME properties

and inherent toxicological profiles. In the traditional paradigm, the elucidation of ADME and toxicological attributes of phytochemicals was predominantly reliant on in vivo and in vitro methodologies. [4] These approaches, while comprehensive, are often marred by high costs, extensive time requirements, and ethical considerations pertaining to animal testing. In the light of these limitations, computational tools and predictive models have emerged as indispensable assets in the preliminary screening of bioactive compounds, offering a cost-effective, rapid, and ethically considerate alternative. [5]

Swiss ADME, a web-based tool offering a broad spectrum of predictions related to pharmacokinetics, drug-likeness, and medicinal chemistry friendliness, presents a formidable platform for the in-silico assessment of phytochemicals present in Allium sativum. Concurrently, ProTox-II, a web server designed for the prediction of toxicological profiles, facilitates an intricate understanding of the potential toxicities, including organ toxicities, cytotoxicity's, and systemic toxicities of these compounds. [6] The integration of these software tools into the evaluation process embodies a pioneering approach to demystify the ADME and toxicological landscapes of phytochemicals within Allium sativum. The paramount objective of this research is to harness the capabilities of Swiss ADME and ProTox-II in predicting the pharmacokinetic properties and toxicological profiles of selected phytochemicals present in Allium sativum. Through this computational exploration, we aim to delineate the therapeutic viability and safety profiles of these compounds, thereby paving the way for their translational potential from bench to bedside. [7] The endeavor not only stands to contribute valuable insights into the pharmacological prowess of Allium sativum but also underscores the utility of computational tools in the preliminary stages of drug discovery and development.

Furthermore, this research endeavors to bridge the gap between traditional herbal medicine and contemporary pharmacological applications. By systematically predicting the ADME profiles and toxicological implications of Allium sativum's phytochemicals, we advocate for a renewed perspective on the integration of herbal compounds in modern therapeutic regimes. In doing so, we reinforce the notion that traditional medicinal plants, through the lens of contemporary science, can offer a rich reservoir of pharmacologically active compounds, potentially leading to the development of novel pharmaceuticals and nutraceuticals. [8]

In conclusion, the application of Swiss ADME and ProTox-II in the prediction of ADME and toxicological profiles of phytochemicals in Allium sativum represents a significant stride towards elucidating the pharmacokinetic and safety parameters of these compounds. This research embodies a comprehensive effort to align the therapeutic promises of Allium sativum with the stringent requisites of drug development, heralding a new era in the integration of phytochemicals into the pharmacopeia. [9]

Materials and Methods

Chemical Compounds and Databases

The study focused on a comprehensive list of phytochemicals identified in Allium sativum, sourced from existing literature and phytochemical databases. Each compound's chemical structure was curated and verified using PubChem and ChemSpider databases to ensure accuracy in molecular identification. [10] The canonical SMILES (Simplified Molecular Input Line Entry System)

notations for these compounds were retrieved for subsequent computational analysis.

Computational Tools for ADME Prediction

Swiss ADME Tool: The Swiss ADME web tool, developed by the Swiss Institute of Bioinformatics, was utilized to predict the pharmacokinetic properties, including absorption, distribution, metabolism, and excretion (ADME) of the selected phytochemicals. The tool offers predictions on various parameters such as lipophilicity, water solubility, gastrointestinal absorption, blood-brain barrier permeability, and potential inhibitors or substrates for cytochrome P450 enzymes. The canonical SMILES notations of the phytochemicals served as input for the Swiss ADME tool, adhering to the guidelines and parameters set by the platform.

Toxicological Prediction Using ProTox-II

ProTox-II Tool: ProTox-II, a web server designed for the prediction of toxicological profiles, was employed to evaluate the potential toxicities of the phytochemicals. This included predictions on LD50 values, hepatotoxicity, carcinogenicity, immunotoxicity, and mutagenicity. Similar to the ADME predictions, the SMILES notations of the phytochemicals were input into ProTox-II, following the tool's specified parameters for toxicological assessment.

Data Analysis and Interpretation

The data generated from Swiss ADME and ProTox-II were compiled and analysed to identify the pharmacokinetic properties and toxicological profiles of the phytochemicals in Allium sativum. The analysis focused on evaluating the compounds' drug-likeness, potential for bioavailability, and safety profiles, aiming to identify phytochemicals with promising therapeutic potential and acceptable safety margins.

Ethical Considerations

This study, being computational and in silico in nature, did not involve human participants, animals, or biological samples, and therefore did not require ethical approval. However, all procedures were conducted in accordance with ethical standards for computational research.

Assesment of ADME of *In- Silico* Study of Natural Compound of Allivum Sativum

ALLICIN: Allicin, a sulfur-containing natural compound with many different biological properties is responsible for the typical smell and taste of freshly cut or crushed garlic.[11] The general, though not entirely accurate, perception of natural products as mild and largely harmless in comparison to their chemically synthesized counterparts, has been suggested as one of the reasons for their growing preference by consumers, as well as their increasingly popular use in medicine and agriculture[12].

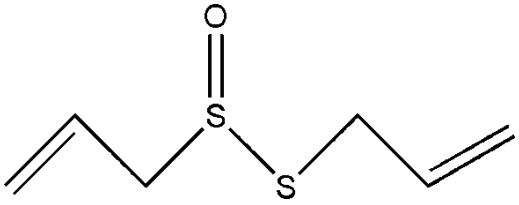


Fig-1 Structure of Allicin

The present investigation illustrates the in silico structure based drug design method to

identify the target bacterial proteins of diallyl thiosulfinate (allicin) and its inhibitory mode of action against the target proteins through molecular docking simulation.[13] As phytochemicals are continuously gaining attention for antimicrobial therapy against various infectious diseases, a stable, efficient and cost-effective herbal formulation that includes allicin should gain esteemed confidence in accordance to patient compliance in this modern world.[14] Zero violation was observed for Lipinski's rule of drug likeliness for allicin which proves that allicin can be used in herbal medicine formulations. Several bacterial growth promoting enzymes were found susceptible to allicin during in silico analysis.[15] Moreover, allicin has been shown to inhibit several proteins responsible for bacterial drug resistance by binding with their active site residues revealing the mode of action.[16]

ALLIN: Stoll and Seebeck discovered alliin (S-allyl cysteine sulfoxide) in 1947, and it has been considered the main specific principle of garlic since then. Alliin can be found in both intact and reduced garlic; S-allyl-cysteine, along with other derived organosulfur compounds, is the main component of aged garlic extract (AGE).[17] It is absorbed in the intestine via the amino acid transport for cysteine, has a hypoglycemic effect, increases blood insulin concentrations, and has been extensively studied for its antioxidant activity. Nonetheless, to the best of our knowledge, its anti-inflammatory potential has not been investigated.[18]

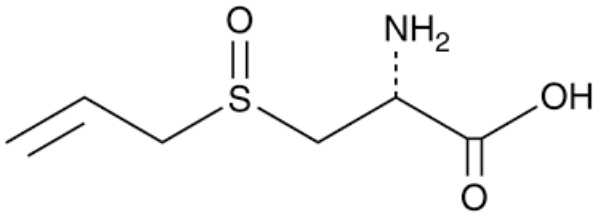


Fig-2 Structure of Allin

The most widely studied and widely available adipogenic cell line is mouse preadipocyte 3T3-L1. This cell line has proven to be extremely useful in identifying key molecular markers, transcription factors, and various interactions required for preadipocyte differentiation.[19] Furthermore, 3T3-L1 adipocytes respond to LPS via a fully intact innate immunity pathway, including the production and secretion of immunomodulatory (primarily proinflammatory) molecules such as IL-6, TNF-, and TLR-2 , as well as TLR-ligand-induced activation, which causes adipocytes to undergo proinflammatory and diabetic transformation[20].

AJOENE: Ajoene, thiosulfinates, and a variety of other organosulphurate compounds have been linked to the garlic properties. In terms of biochemical properties, ajoene [(E,Z)-4,5,9 Trithiadodeca 1,6,11 Triene 9-oxide] is stable in water and can be synthesised chemically.[21] There is evidence that some garlic constituents have a wide range of effects on various biological systems. Ajoene, on the other hand, is the garlic compound linked to more biological activities, as demonstrated in in vitro and in vivo systems. According to these

studies, ajoene has antithrombotic, antitumoral, antifungal, and antiparasitic properties.[22] This study looks at ajoene's recently discovered antifungal property and its potential use in clinical trials to treat a variety of fungal infections.[23]

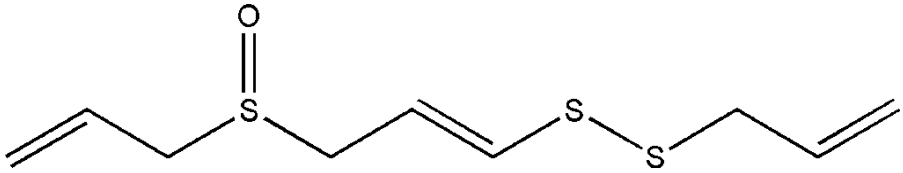


Fig-3 Structure of Ajoene

The research revealed that ajoene has antithrombotic, antitumoral, antifungal, and antiparasitic properties.[24] The topic of this study is ajoene's recently discovered antifungal capability and its potential clinical application in treating various fungal infections. In silico models have made it possible to estimate a number of ADME attributes by establishing a closer relationship between chemical structure and ADME characteristics.[25] As a result, several ajoene physical and chemical properties were calculated to ensure that they are within the acceptable range for a therapeutic molecule.[26]

DIALLYL DISULPHIDE: Garlic contains a number of water-and oil-soluble organosulfur compounds that have antimicrobial, antithrombotic, antiarthritic, and antitumor property.[27[When used to prevent or treat cancer, oil-soluble compounds such as diallyl sulphide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), and ajoene are more effective than water-soluble compounds. The primary components of garlic oil, which has a yellowish hue and is insoluble in water, are DADS and DATS[28]

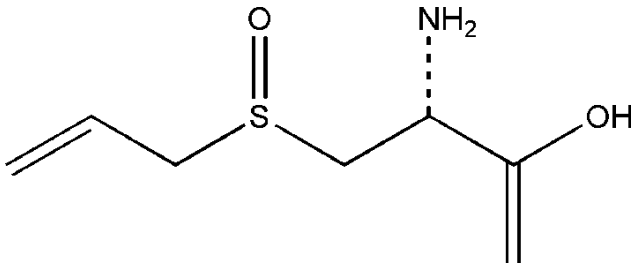


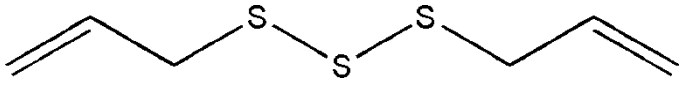
Fig-4 Structure of Diallyl disulphide

The ability of DADS to reduce the proportion of cells in the G1 and G2/M phases is related to its anti-proliferative properties. Furthermore, several studies have suggested that DADS may induce apoptosis in various types of cancer cells and act as a histone deacetylase inhibitor (3,4,9).[29] Previous research has suggested that the aforementioned abilities reduce cancer

cell proliferation, angiogenesis, invasion, and metastasis. A number of studies have demonstrated the chemopreventative properties of various garlic products and compounds, including fresh and aged garlic extract and garlic oil. Garlic oil's anti-cancer properties are attributed to the presence of organic sulphur compounds in garlic.[30]

Diallyl trisulphide: DATS has been shown to selectively kill cancerous cells while leaving healthy cells alone in the prostate and breast. This effect is attributed to an increase in reactive oxygen species (ROS) within cancer cells, an increase in the number of cells arresting in the G2 phase of mitosis, and a promotion of caspase-3 activity. These effects appear to contribute to cancer cell apoptosis and a decrease in cancer cell proliferation.[31]

Fig-5 Structure of Diallyl trisulphide



DATS can be converted to hydrogen sulphide by glutathione in red blood cells (H2S). This conversion occurs at a consistent rate over time, making DATS an excellent source of H2S. H2S is a cardioprotective agent with anti-inflammatory, antioxidant, and anti-apoptotic properties.The effect of hydrogen sulphide on reducing myocardial ischemia-reperfusion injury is a major research topic. Reperfusion injury is a serious threat to myocardial function that occurs when blood flow to the heart is restored after an ischemic episode.[32] Reperfusion causes an inflammatory response and frequently leads to oxidative damage. H2S reduces injury through a variety of mechanisms, including reduced oxidative stress, mitochondrial function maintenance, and increased eNOS (endothelial nitric oxide synthase) activation. eNOS is activated by H2S phosphorylation, which activates the PI3K/Akt pathway, increasing nitric oxide formation and bioavailability (NO). This has a negative impact on mitochondrial function. Through the opening of the ATP-sensitive K+ channel, the mitochondria have been shown to protect the heart from ischemic-reperfusion injury.[33]

Diallyl sulphide: DAS has been extensively studied for its anticancer activity and as a protective agent, there has been no comprehensive review of DAS in recent years. DAS can be justified as an adjuvant therapy for a variety of conditions based on its reported interactions with drug metabolising and anti-oxidant enzymes. To better understand the potential clinical applications of DAS, this review first summarises the reports on DAS's anti-cancer effects and its role as a protective agent. The review also focuses on DAS's ability to protect against alcohol, analgesic drugs, and other xenobiotic-mediated toxicity by targeting the cytochrome P450 2E1 (CYP2E1) enzyme. Because CYP2E1 has been linked to HIV, diabetes, and Parkinson's disease (PD).[34]However, recent research has revealed that the underlying mechanism for DAS's beneficial effects is a significant interaction with drug transporters and metabolic enzymes. DAS-induced changes in drug pharmacokinetic profiles are mediated by changes in effluxtransporter expression/activity and phase I/phase II drug metabolising enzymes.[35]

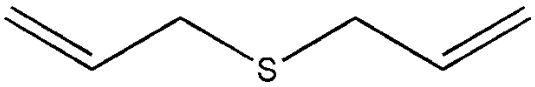


Fig-6 Structure of Diallyl sulphide

Allyl Methyl Sulphide: Allyl methyl sulphide (AMS) is a potential garlic-derived organosulfur compound with a wide range of beneficial effects in a variety of diseases.[36] The

purpose of this study was to look into the potential role of AMS in reducing the effects of oxidative stress and inflammation in the livers of streptozotocin (STZ)-induced experimental rats. A single intraperitoneal (i.p.) injection of STZ (40 mg/kg/b.w.) was used to induce diabetes. For 30 days, STZ-induced hyperglycemic rats were given intragastric doses of the AMS of 50, 100, and 200 mg/kg/b.w. AMS dietary intervention (100 mg/kg b.w) resulted in significant blood glucose reduction, expression of pro-inflammatory markers TNF-, IL-6, NF-B p65 unit, and significant elevation of plasma insulin level.[37]

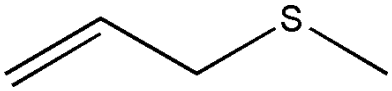


Fig-7 Structure of Allyl-methyl sulphide

Furthermore, AMS significantly increased the levels of hepatic tissue non-enzymatic antioxidants and the activities of enzymatic antioxidants in diabetic rats, with a significant decrease in lipid peroxides and hydroperoxides formation, serum biomarkers of liver damage, demonstrating AMS's protective efficacy in hyperglycemic states. The pathological abnormalities in diabetic rats' hepatic tissues were significantly improved by AMS supplementation, lending support to the biochemical findings.[64] These findings explain the potential application of AMS as a promising compound against glucotoxicity-mediated hepatic oxidative dysfunction in rats. However, clinical trials to validate this benefit for optimising AMS nutrition are required.[38]

LLYL CYSTEINE: S-allyl cysteine (SAC) was tested in an acute liver injury model involving lipopolysaccharide/d-galactosamine (LPS/d-Gal) (ALI). LPS and d-Gal (50 g/kg and 400 mg/kg, respectively) were administered intraperitoneally to mimic ALI, and animals received SAC per os (25 or 100 mg/kg/d) for 3 days until 1 hour before LPS/d-Gal injection. SAC pretreatment of the LPS/d-Gal group reduced the activities of alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase and partially reversed inappropriate changes in hepatic oxidative stress- and inflammation-related biomarkers such as liver reactive oxygen species, malondialdehyde, and hepatic activity of the defensive enzyme superoxide dismutase, ferric reducing antioxidant power.[39]

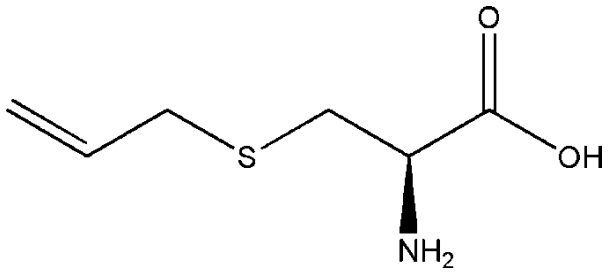


Fig-8 Structure of S-Allyl Cysteine

In-silico drug-likeness prediction, in conjunction with additional ADMET (absorption, distribution, metabolism, excretion, and toxicity) tools, present a plethora of opportunities that aid in the discovery of new anti-cancer candidates. To determine the drug-like properties, the title hybrids 9-12 were screened for their pharmacokinetic properties using opensource cheminformatics toolkits such as Molinspiration software (35) (for MW, rotatable bonds, and topographical polar surface area (PSA) descriptors, ALOGPS 2.1 algorithm from the Virtual

Computational Chemistry Laboratory (for: LogPo/w descriptor), Pre-ADMET 2.0 programme to predict various pharmacokinetic parameters, and These critical parameters define the drug molecule's absorption, permeability, motion, and action.Similarly, the Molinspiration web server was used to predict the potential interactions of novel compounds with the most common human receptors, which include G protein-coupled receptors (GPCR), ion channels, kinases, nuclear receptors, proteases, and enzymes. In addition, the OSIRIS Property Explorer (open source) was used to assess the overall drug-score.The most common human toxicity parameters, such as mutagenicity, tumorigenesis, irritant effect, and potential injuries, can all have an effect on the reproductive system.

Diallyl tetrasulphide: Dialyltetrasulfide is an organosulfur with anticancer, antioxidant, and antimicrobial properties. Dialyltetrasulfide induces mitotic arrest by increasing reactive oxygen species (ROS) and heme oxygenase-1 levels in vitro and inhibiting microtubule polymerization. Diallyl tetrasulfide has antibacterial and antifungal properties against a variety of microbes, including Staphylococcus aureus, methicillin-resistant Staphylococcus aureus (MRSA), and several Candida and Aspergillus species.[40] Furthermore, in several animal models, this compound reduces cadmium-mediated oxidative damage by increasing levels of superoxide dismutase, glutathione peroxidase, and other glutathione metabolising enzymes.[41]

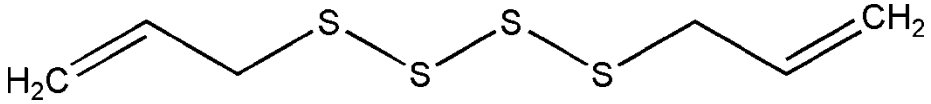


Fig-9 Structure of diallyl tetra sulphide

Allyl Propyl Disulphide: Allyl propyl disulfide has the chemical formula C3H5S2C3H7 and is an organosulfur compound. It has a strong odour and is a volatile pale-yellow liquid. It's a key ingredient in onion oil and is used in food additives and flavours. Garlic and onion contain this substance. When onion or garlic is sliced, the substance evaporates and irritates the eyes. [56] When garlic or onion is cooked, it evaporates, removing the spicy flavour and leaving a sweet flavour.[57]

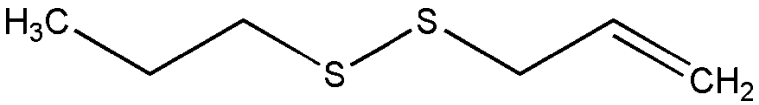


Fig-10 Structure of Allyl propyl disulphide

However, propyl allyl compounds are ineffective as CYP2E1 inhibitors. In terms of transcription and posttranscriptional activity, the lipophilic garlic compounds have no effect on mRNA levels; however, there is an effect on protein synthesis, suggesting a possible mechanism.[58]

Allyl Methyl Trisulphide: Allyl methyl sulphide is a chemical compound with the formula CH_2=$CHCH_2SCH_3$. An allyl (CH_2=$CHCH_2$) and a sulphide functional group are present in

the molecule. It is a colourless liquid with the strong odour of alkyl sulphides. It is a garlic metabolite, and its presence is associated with "garlic breath." It is made by combining allyl chloride, sodium hydroxide, and methanethiol.Allyl methyl sulphide (AMS) is a potential garlic-derived organosulfur compound with a wide range of beneficial effects in a variety of diseases.[59] The purpose of this study was to look into the potential role of AMS in reducing the effects of oxidative stress and inflammation in the livers of streptozotocin (STZ)-induced experimental rats. A single intraperitoneal (i.p.) injection of STZ (40 mg/kg/b.w.) was used to induce diabetes. For 30 days, STZ-induced hyperglycemic rats were given intragastric doses of the AMS of 50, 100, and 200 mg/kg/b.w. AMS dietary intervention (100 mg/kg b.w) resulted in significant blood glucose reduction, expression of pro-inflammatory markers TNF- , IL-6, NF-B p65 unit, and significant elevation of plasma insulin level.[60]

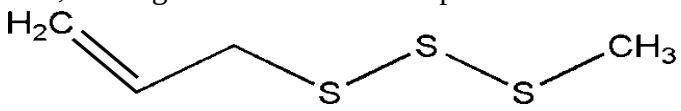


Fig-11 Structure of Allyl methyl trisulphide

In terms of water-soluble garlic compounds, structure-activity studies show that an allyl compound attached to sulphur with a methyl group is one of the most potent inhibitors of the CYP2E1 protein.[61]AMS significantly increased the levels of hepatic tissue non-enzymatic antioxidants and the activities of enzymatic antioxidants in diabetic rats, with a significant decrease in lipid peroxides and hydroperoxides formation, serum biomarkers of liver damage, indicating the protective efficacy of AMS in hyperglycemic state.[62] The pathological abnormalities in diabetic rats' hepatic tissues were significantly improved by AMS supplementation, lending support to the biochemical findings.[63]

Table 1: Compounds classified on basis of molecular formula, molecular weight and presence of heavy atom and rotatable bonds

S.no	Compounds	Molecular Formula	Molecular weight	No of rotatable atoms	No of H bond acceptor	No of H bond donor	Molar refractivity	TPSA
1	Allicin	$C_6H_{10}OS_2$	162.27 g/mol	5	1	O	45.88	61.58 Å²
2	Alliin	$C_6H_{11}NO_3S$	177.22 g/mol	5	4	2	43.24	99.60 Å²
3	Ajoene	$C_9H_{14}OS_3$	234.40 g/mol	8	1	0	67.41	86.88 Å²
4	Diallyl disulphide	$C_6H_{10}S_2$	146.27 g/mol	5	0	0	37.6	50.60 Å²
5	Diallyl trisulphide	$C_6H_{10}S_2$	146.27 g/mol	5	0	0	45.19	50.60 Å²
6	Diallyl sulphide	$C_6H_{10}S$	114.21 g/mol	4	0	0	37.6	25.30 Å²
7	Allyl methyl sulphide	C_4H_8S	88.17 g/mol	2	0	0	28.46	75.90 Å²
8	S - Allylcysteine	$C_6H_{11}NO_2S$	161.22 g/mol	5	3	2	42.55	88.62 Å²
9	Diallyl tetrasulphide	$C_6H_{10}S_4$	210.40 g/mol	7	0	0	60.37	101.20Å²
10	Allyl propyl disulphide	$C_6H_{12}S_2$	148.29 g/mol	5	0	0	45.66	50.60 Å²
11	Allyl methyl trisulphide	$C_4H_8S_3$	152.30 g/mol	4	0	0	43.64	75.90 Å²

According to Table 1 Diallyl Tetrasulphide have highest molecular weight of 210.40gm/mol and Allyl methyl sulphide have lowest molecular weight 88.17gm/mol. Ajoene have highest rotable atom of 8.

Table 2: Water Solubility, Druglikeness and Lypophilicity

		Water solubility		Druglikeness	Lypophilicity	
S.no	**Compound**	**Log S (ESOL)**	**Log S (SILICOS-IT)**	**Bioavailability Score**	**Log Po/w (iLOGP)**	**Log Po/w (SILICOS-IT)**
1	Allicin	-1.34	-1.7	0.55	1.95	0.96
2	Alliin	1.62	-0.21	0.55	0.55	-1
3	Ajoene	-1.84	-2.32	0.55	2.74	2.2
4	Diallyl disulphide	-1.64	-1.64	0.55	2.11	1.97
5	Diallyl trisulphide	-2.21	-1.91	0.55	2.65	2.38
6	Diallyl sulphide	-1.64	-1.64	0.55	2.11	1.97
7	Allyl methyl sulphide	-1.21	-1.13	0.55	1.77	1.14
8	S - Allylcysteine	0.79	-0.3	0.55	1.22	0.22
9	Diallyl tetrasulphide	-2.62	-2.03	0.55	2.8	2.59
10	Allyl propyl disulphide	-1.97	-2.13	0.55	2.54	2.18
11	Allyl methyl trisulphide	-1.77	-1.43	0.55	2.29	1.64

According to Table 2, S allylcysteine have highest [log S (E sol)] of 0.79 . Diallytetrasulphide have highest lipophilicity of 2.8. The bioavailiability of all the chemical constituent is 0.55.

TABLE 3: INSILICO STUDY ADME STUDIES

S.no	Compounds	Water solubility	GI absorption	BBB permeant	P-gp substrate	CYP3A4 inhibitor	Lipinski	Muegge
1	Allicin	Very soluble	High	High	No	No	Yes	No
2	Alliin	Very soluble	High	No	No	No	Yes	No
3	Ajoene	Very soluble	High	No	No	No	Yes	Yes
4	Diallyl disulphide	Very soluble	High	High	No	No	Yes	No
5	Diallyl trisulphide	Soluble	High	Yes	No	No	Yes	No
6	Diallyl sulphide	Very soluble	High	Yes	No	No	Yes	No
7	Allyl methyl sulphide	Very soluble	High	Yes	No	No	Yes	No
8	S - Allylcysteine	Very soluble	High	No	No	No	Yes	No
9	Diallyl tetrasulphide	Soluble	High	No	No	No	Yes	Yes
10	Allyl propyl disulphide	Very soluble	High	Yes	No	No	Yes	No
11	Allyl methyl trisulphide	Very soluble	High	Yes	No	No	Yes	No

According to Table 3, Allin, Diallyl disulphide can cross the blood brain barrier easily. All the chemical constituent follows Lipinski Rule. Muegge Rule followed by Ajoene and Diallyl Tetrasulphide.

TABLE 4: IN –SILICO TOXICITY PROFILE

S.no	Compounds	LD 50 DOSE	TOXICITY	CARCINOGENIC	IMMUNOTOXIC	Hepatotoxic	Tox21-Nuclear receptor signalling pathways	Tox21-Stress response pathways
1	Allicin	874mg/kg	Class IV	INACTIVE	INACTIVE	INACTIVE	INACTIVE	INACTIVE
2	Alliin	8000mg/kg	Class VI	INACTIVE	INACTIVE	INACTIVE	INACTIVE	INACTIVE
3	Ajoene	1600mg/kg	Class IV	INACTIVE	INACTIVE	INACTIVE	INACTIVE	INACTIVE
4	Diallyl disulphide	260mg/kg	Class III	ACTIVE	INNACTIVE	INACTIVE	INACTIVE	Phosphoprotein p53
5	Diallyl trisulphide	100mg/kg	Class III	ACTIVE	INACTIVE	INACTIVE	INACTIVE	Phosphoprotein p53
6	Diallyl sulphide	2980mg/kg	Class V	ACTIVE	INACTIVE	INACTIVE	INACTIVE	INACTIVE
7	Allyl methyl sulphide	1600mg/kg	Class IV	INACTIVE	INACTIVE	INACTIVE	INACTIVE	INACTIVE
8	S - Allylcysteine	4000mg/kg	Class V	INACTIVE	INACTIVE	INACTIVE	INACTIVE	INACTIVE
9	Diallyl tetrasulphide	260mg/kg	Class III	INACTIVE	INACTIVE	INACTIVE	INACTIVE	Phosphoprotein p53
10	Allyl propyl disulphide	2030mg/kg	Class V	INACTIVE	INACTIVE	INACTIVE	INACTIVE	INACTIVE
11	Allyl methyl trisulphide	260mg/kg	Class III	INACTIVE	INACTIVE	INACTIVE	INACTIVE	INACTIVE

According to Table 4, Diallyl disulphide, Diallyl trisulphide and Diallyl sulphide belongs to Class III,III and V are carcinogenic toxic. Diallyl disulphide, Diallyl trisulphide , Diallyl tetrasulphide is active in Tox 21- Stress Response pathway (Phosphoprotein (Tumor Supressor) p53).

RESULT and DISCUSSION

Lipinski's rule of five [molecular mass less than 500 dalton, high lipophilicity (log P value less than 5), less than 5 hydrogen bond donor, less than 10 hydrogen bond acceptor, molar refractive index 40-130]. All of the compounds discussed in this article adhere to the Lipinski rule of five. This means that these compounds can be used as medicines with only minor modifications to their structure.

Druglikeness is a qualitative concept used in drug design that describes how "druglike" a substance is in terms of factors such as bioavailability. Before the substance is even synthesised and tested, it is estimated from its molecular structure.

LogP is closely related to the drug's lipophilicity, which is a critical component of its solubility, absorption, membrane penetration, plasma protein binding, distribution, and tissue penetration. Because of the importance of medication lipophilicity, the Lipinski rule of five includes logP as a component. LogP is the partition coefficient of a molecule between the aqueous and lipophilic phases (typically octanol and water). Experiment with dissolving the substance in an immiscible biphasic solution of lipids and water to determine the amount of solute dissolved in each phase. The drug lipophilicity (Log p) of the compound must be less than 5, and all of these compounds are lipophilic.

All the chemical constituents of Allivum Satvum are “very soluble” but Diallyl trisulphide, Diallyl tetrasulphide are “soluble”. All the compounds are highly absorbed by GI. The 1st and 4th compound can easily cross blood bran barrier. CYP3A4 inhibitor , it is the most common mechanism for drug-drug interaction.

Muegge rule, which is based on simple structural rules, employs a pharmacophore point filter to distinguish between drug-like and nondrug-like compounds. A candidate drug should have two to seven pharmacophore points to pass the filtering. According to table 3 , Muegge rule followed by 3rd and 9 th compound.

Toxicity is the extent to which a chemical substance or a specific mixture of chemicals can harm an organism.In toxicity study of compound 1-10 via PROTOX II softwere shows compound 5, 7 carcinogenic toxicity. The compound 4,5,9 is active in Tox 21- Stress Response pathway (Phosphoprotein (Tumor Supressor) p53).

Our goal in writing this paper was to demonstrate the traditional use and previously confirmed pharmacological effects of garlic. Garlic has a wide range of pharmacological effects, including antimicrobial, cardiovascular, anti-inflammatory, anticancer, and immunomodulatory activity, as demonstrated in this study.

The most important contents in garlic are organosulfur compounds, which are responsible for the majority of their pharmacological effects. Allicin, allyl methyl sulphide, DTS, and ajoene have been identified as the main responsible compounds for garlic's antifungal, antibacterial,

antiprotozoal, and antiviral effects, respectively. This study shows that A. sativum is only toxic at high doses and that there have been few reports of intoxication caused by garlic consumption. When garlic is crushed or chopped, an enzyme called alliinase is released, which catalyses the formation of allicin from S-allyl-L-cysteine sulfoxide (Allin). Allicin degrades quickly into a variety of organosulfur compounds. However, scientists and clinicians should exercise caution when using this plant for therapeutic purposes until adequate studies confirm the plant's safety and quality.

CONCLUSION-

The present study effectively employed the Swiss ADME and ProTox-II computational tools to predict the pharmacokinetic and toxicological profiles of key phytochemicals found in *Allium sativum*. Our findings offer a profound insight into the ADME characteristics and potential toxicological hazards associated with these compounds, setting the stage for further experimental validation and therapeutic development.

Our analysis confirmed that all the studied phytochemicals, including alliin and diallyl disulphide, adhere to Lipinski's Rule of Five, indicating favorable oral bioavailability. Notably, alliin and diallyl disulphide demonstrated the capacity to readily cross the blood-brain barrier, suggesting potential uses in neurological conditions. Additionally, compounds such as S-allylcysteine and diallyltetrasulphide exhibited exceptional solubility and lipophilicity, respectively, which are desirable traits in drug candidates.

However, the study also brought to light significant toxicological concerns. Diallyl disulphide, diallyl trisulphide, and diallyl sulphide were identified as having varying classes of carcinogenic potential. Such findings necessitate cautious consideration in the development of these compounds as therapeutic agents. The activation of stress response pathways through the modulation of the p53 protein by certain compounds underscores the complex bioactivity of *Allium sativum* extracts and their potential impacts on cellular mechanisms.

This research validates the utility of in silico tools in the initial screening of phytochemicals for drug development, providing cost-effective and time-efficient insights. It also highlights the importance of integrating computational predictions with empirical data to refine the therapeutic profiles of natural compounds.

Future research should focus on detailed experimental studies to verify these computational predictions and assess the clinical relevance of these phytochemicals. Investigations into the mechanisms of action, dose-response relationships, and long-term safety profiles will be crucial for advancing these compounds into clinical trials.

In conclusion, while the phytochemicals in *Allium sativum* show promising pharmacological potentials, they also pose significant toxicological risks that must be carefully managed. This dual aspect underscores the critical need for a balanced approach in the development of these natural compounds as therapeutic agents, ensuring safety and efficacy for potential clinical use.

REFRENCE

1. Takagi, H. "Garlic Allium sativum L." *Onions and allied crops*. CRC press, 2020. 109-146.2
2. Londhe, V. P., et al. "Role of garlic (Allium sativum) in various diseases: A overview." angiogenesis 12 (2011): 13.4Gruhlke, Martin CH, et al. "The effects of allicin, a reactive sulfur species from garlic, on a selection of mammalian cell lines." *Antioxidants* 6.1 (2016):1.
3. Bhattacharya, Souptik, Dwaipayan Sen, and Chiranjib Bhattacharjee. "Inhibition mechanism study for diallyl thiosulfinate (allicin) against crucial bacterial proteins through in silico molecular docking simulation." *Process Biochemistry* 122 (2022): 110-119.
4. Ghaneian, M., et al. "The study of the stability, toxicity and antimicrobial effect of allicin solution." *Tolooebehdasht* 14.5 (2016): 141-150.
5. 5Ledezma E, Apitz-Castro R. Ajoene, el principal compuestoactivoderivado del ajo (Allium sativum), un nuevo agenteantifúngico [Ajoene the main active compound of garlic (Allium sativum): a new antifungal agent]. Rev Iberoam Micol. 2006 Jun;23(2):75-80.
6. Kumar S. Dual inhibition of acetylcholinesterase and butyrylcholinesterase enzymes by allicin. Indian J Pharmacol2015;47:444-6
7. Rehman F, Mairaj S. Antimicrobial studies of allicin and ajoene. Int J Pharm Bio Sci 2013;4:B1095-105.
8. 0. Yamada N, Hattori A, Hayashi T, Nishikawa T, Fukuda H, Fujino T, et al. Improvement of scopolamine-induced memory impairment by Z-ajoene in the water maze in mice. PharmacolBiochemBehav2004;78:787-91
9. O'Gara, J. E., J. D. Portmess, and K. B. Wagener. "Acyclic diene metathesis (ADMET) polymerization. Synthesis of unsaturated polythioethers." *Macromolecules* 26.11 (1993): 2837-2841.
10. Takeyama H, Hoon D, Saxton R, Morton D, Irie R. Growth inhibition and modulation of cell markers of melanoma by S-allyl cysteine. *Oncology*. 1993;50:63–
    9.
11. González-Trujano ME, Uribe-Figueroa G, Hidalgo-Figueroa S, Martínez AL, Déciga-Campos M, Navarrete-Vazquez G. Synthesis and antinociceptive evaluation of bioisosteres and hybrids of naproxen, ibuprofen and paracetamol. *Biomed. Pharmacother*. . 2018;101:553–62.
12. Meunier B. Hybrid molecules with a dual mode of action: dream or reality? Acc. *Chem. Res*. . 2008;41:69–77.
13. Takeyama H, Hoon D, Saxton R, Morton D, Irie R. Growth inhibition and modulation of cell markers of melanoma by S-allyl cysteine. *Oncology*. . 1993;50:63–

9.

14. Fatmawaty, Fatmawaty, et al. "Skrining in silico potensisenyawa allicin dari allium sativum sebagaiantiplasmodium." *Jurnal Kimia Terapan Indonesia* 17.2 (2015): 175-184.
15. Humadi, Suhad Sami, et al. "Design, synthesis, ADME, biological evaluation and molecular dynamic studies of natural and synthetic remedy of Herpes simplex virus type-1." *Pakistan Journal of Pharmaceutical Sciences* 35.4 (Special) (2022): 1181-1190.
16. Bhattacharya, Souptik, Dwaipayan Sen, and Chiranjib Bhattacharjee. "Inhibition mechanism study for diallyl thiosulfinate (allicin) against crucial bacterial proteins through in silico molecular docking simulation." *Process Biochemistry* 122 (2022): 110-119.
17. Fatmawaty, Fatmawaty, et al. "In Silico Screening of Potential Allicin Compound From Allium Sativum as Antiplasmodium." *Indonesian Journal of Applied Chemistry* 17.2: 106209.
18. Zhang, Feng-xiang, Zi-ling Tang, and Zuo-cheng Qiu. "A novel strategy for exploring food originated anti-adipogenesis substances and mechanism by structural similarity evaluation, ADME prediction, network pharmacology and experimental validation." *Food & Function* 12.15 (2021): 7081-7091.
19. Chang, Zhenglin, et al. "Allicin suppressed Escherichia coli-induced urinary tract infections by a novel MALT1/NF-κB pathway." *Food & Function* 13.6 (2022): 3495-3511.
20. Chung, Lip Yong. "The antioxidant properties of garlic compounds: allyl cysteine, alliin, allicin, and allyl disulfide." *Journal of medicinal food* 9.2 (2006): 205-213.
21. Iberl, Bernhard, et al. "Quantitative determination of allicin and alliin from garlic by HPLC." *Planta medica* 56.03 (1990): 320-326.
22. Salman, Hertzel, et al. "Effect of a garlic derivative (alliin) on peripheral blood cell immune responses." *International Journal of Immunopharmacology* 21.9 (1999): 589-597.
23. Kourounakis, P. N., and E. A. Rekka. "Effect on active oxygen species of alliin and Allium sativum (garlic) powder." *Research communications in chemical pathology and pharmacology* 74, no. 2 (1991): 249-252.
24. Ellmore, G. S., & Feldberg, R. S. (1994). Alliin lyase localization in bundle sheaths of the garlic clove (Allium sativum). *American Journal of Botany*, *81*(1), 89-94.
25. Izzo AA. Interactions between Herbs and Conventional Drugs: Overview of the Clinical Data. ed Princ Pract. 2012;21:405.

1. Quintero-Fabián, Saray, et al. "Alliin, a garlic (Allium sativum) compound, prevents LPS-induced inflammation in 3T3-L1 adipocytes." Mediators ofinflammation 2013 (2013).
2. Hassan, Hassan T. "Ajoene (natural garlic compound): a new anti-leukaemia agent for AML therapy." Leukemia research 28.7 (2004): 667-671.

3. Ledezma, Eliades, and Rafael Apitz-Castro. "Ajoene the main active compound of garlic (Allium sativum): a new antifungal agent." Revistaiberoamericana de micologia 23.2 (2006): 75-80.
4. Yoshida, Susumu, et al. "Antifungal activity of ajoene derived from garlic." Applied and Environmental Microbiology 53.3 (1987): 615-617.
5. Naganawa, Rie, et al. "Inhibition of microbial growth by ajoene, a sulfur-containing compound derived from garlic." Applied and environmental microbiology 62.11 (1996): 4238-4242.
6. Kuruvilla M, Gurk-turner C. A review of warfarin dosing and monitoring. Bumc. 2001;14:305–06.
7. Ahmed, N., L. Laverick, J. Sammons, H. Zhang, D. J. Maslin, and H. T. Hassan. "Ajoene, a garlic-derived natural compound, enhances chemotherapy-induced apoptosis in human myeloid leukaemia CD34-positive resistant cells." Anticancer research 21, no. 5 (2001): 3519-3523.
8. Li, M., Ciu, J. R., Ye, Y., Min, J. M., Zhang, L. H., Wang, K., ... & Leung-Tack, J. (2002). Antitumor activity of Z-ajoene, a natural compound purified from garlic: antimitotic and microtubule-interaction properties. Carcinogenesis, 23(4), 573-579
9. Ferri, N., Yokoyama, K., Sadilek, M., Paoletti, R., Apitz-Castro, R., Gelb, M. H., & Corsini, A. (2003). Ajoene, a garlic compound, inhibits protein prenylation and arterial smooth muscle cell proliferation. British journal of pharmacology, 138(5), 811-818.
10. Germain, Emmanuelle, Jacques Auger, Christian Ginies, M-H. Siess, and Caroline Teyssier. "In vivo metabolism of diallyl disulphide in the rat: identification of two new metabolites." Xenobiotica 32, no. 12 (2002): 1127-1138.
11. Tyson, J. L., R. A. Fullerton, G. S. Elliott, and P. J. Reynolds. "Use of diallyl disulphide for the commercial control of Sclerotium cepivorum." New Zealand Plant Protection 53 (2000): 393-397.

12. Klevenhusen, F., Duval, S., Zeitz, J. O., Kreuzer, M., & Soliva, C. R. (2011). Diallyl disulphide and lovastatin: effects on energy and protein utilisation in, as well as methane emission from, sheep. Archives of Animal Nutrition, 65(4), 255- 266.
13. Tyson, J. L., et al. "Use of diallyl disulphide for the commercial control of Sclerotium cepivorum." New Zealand Plant Protection 53 (2000): 393-397.
14. Puccinelli, Michael T., and Silvia D. Stan. "Dietary bioactive diallyl trisulfide in cancer prevention and treatment." International journal of molecular sciences 18.8 (2017): 1645.
15. Powolny, Anna A., and Shivendra V. Singh. "Multitargeted prevention and therapy of cancer by diallyl trisulfide and related Allium vegetable-derived organosulfur compounds." Cancer letters 269.2 (2008): 305-314.
16. Liu, Cheng-Tzu, et al. "Effects of garlic oil and diallyl trisulfide on glycemic control in diabetic rats." European journal of pharmacology 516.2 (2005): 165-173.
17. Chan, Kung-chi, Mei-chin Yin, and Wan-ju Chao. "Effect of diallyl trisulfide-rich garlic oil on blood coagulation and plasma activity of anticoagulation factors in rats." Food and chemical toxicology 45.3 (2007): 502-507.
18. Tsao, Shyh-Ming, and Mei-Chin Yin. "In-vitro antimicrobial activity of four diallyl

sulphides occurring naturally in garlic and Chinese leek oils." Journal of medical microbiology 50.7 (2001): 646-649.
19. Lu, Xiaonan, et al. "Antimicrobial effect of diallyl sulphide on Campylobacter jejuni biofilms." Journal of antimicrobial chemotherapy 67.8 (2012): 1915-1926.
20. Tsao, Shyh-ming, Cheng-chin Hsu, and Mei-chin Yin. "Garlic extract and two diallyl sulphides inhibit methicillin-resistant Staphylococcus aureus infection in BALB/cA mice." Journal of Antimicrobial Chemotherapy 52.6 (2003): 974-980.
21. Abdel-Daim, M. M., Abushouk, A. I., Bungău, S. G., Bin-Jumah, M., El-Kott, A. F., Shati, A. A., ... &Alkahtani, S. (2020). Protective effects of thymoquinone and diallyl sulphide against malathion-induced toxicity in rats. Environmental Science and Pollution Research, 27(10), 10228-10235.
22. Katoch, Omika, et al. "Mitigation of hematopoietic radiation injury by diallyl

sulphide." Journal of Environmental Pathology, Toxicology and Oncology 31.4 (2012).
23. Colín-González, Ana L., et al. "The antioxidant mechanisms underlying the aged garlic extract-and S-allylcysteine-induced protection." Oxidative medicine and cellular longevity 2012 (2012).
24. Maldonado, Perla D., et al. "Antioxidant S-allylcysteine prevents gentamicin- induced oxidative stress and renal damage." Free Radical Biology and Medicine
35.3 (2003): 317-324.
25. Chuah, S. C., Moore, P. K., & Zhu, Y. Z. (2007). S-allylcysteine mediates cardioprotection in an acute myocardial infarction rat model via a hydrogen sulfide-mediated pathway. American Journal of Physiology-Heart and Circulatory Physiology, 293(5), H2693-H2701.
26. Pari, Leelavinothan, and Ponnusamy Murugavel. "Role of diallyl tetrasulfide in ameliorating the cadmium induced biochemical changes in rats." Environmental toxicology and pharmacology 20.3 (2005): 493-500.
27. Murugavel, Ponnusamy, et al. "Cadmium induced mitochondrial injury and apoptosis in vero cells: protective effect of diallyl tetrasufide from garlic." The International Journal of Biochemistry & Cell Biology 39.1 (2007): 161-170.
28. Oosthuizen, Carel, et al. "Diallyl polysulfides from Allium sativum as immunomodulators, hepatoprotectors, and antimycobacterial agents." Journal of medicinal food 20.7 (2017): 685-690.
29. Avula PR, Asdaq SM, Asad M. Effect of aged garlic extract and s-allyl cysteine and their interaction with atenolol during isoproterenol induced myocardial toxicity in rats. Indian J Pharmacol. 2014;46:94-9.
30. Reddy DG, Reddy GA, Rao SG, Haritha C, Jyothi k. Interaction on study on garlic and Atorvastatin with reference to Nephrotoxicity in Dyslipidaemic Rats. 2010;17:90-3.
31. Timmins GS, Dereti V. Mechanisms of action of isoniazid. Molecular Microbiology 2006;62:1220–27.
32. Satoshi M, Shigeo K. Mechanisms of action of cyclosporine. Immunopharmacology. 2000;47:119–25.

33. Bernhard, Richard A., et al. "Isolation and identification of allyl monosulfide and allyl

alcohol from Allium." Archives of Biochemistry and Biophysics 107.1 (1964): 137-140.
34. Mellitus, Insulin Dependent Diabetic. "allyl propyl disulfide allyl disulfide oxide."
35. Augusti, K. Thomas. "Therapeutic and medicinal values of onions and garlic." Onions and allied crops. CRC press, 2020. 93-108.
36. Boelens, Mans, et al. "Volatile flavor compounds from onion." Journal of Agricultural and Food Chemistry 19.5 (1971): 984-991.
37. Sparnins, Velta L., et al. "Effects of allyl methyl trisulfide on glutathione S-transferase activity and BP-induced neoplasia in the mouse." (1986): 211-215.
38. Zhao, Hui-Juan, et al. "Allyl methyl trisulfide protected against acetaminophen (paracetamol)-induced hepatotoxicity by suppressing CYP2E1 and activating Nrf2 in mouse liver." Food & function 10.4 (2019): 2244-2253.
39. Sujithra, Kathiroli, et al. "Allyl methyl sulfide, an organosulfur compound alleviates hyperglycemia mediated hepatic oxidative stress and inflammation in streptozotocin-induced experimental rats." Biomedicine & Pharmacotherapy 107 (2018): 292-302.