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Review

ALLICIN AND RELATED COMPOUNDS: BIOSYNTHESIS, SYNTHESIS AND PHARMACOLOGICAL ACTIVITY †

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Abstract. *In this review, the biosynthesis of allicin (allyl thiosulfinate) by enzymatic transformation of alliin and various methods of its synthesis with detailed investigation of mechanisms and kinetics are summarized. A convenient method is also described for determination of allicin stability and the utility of the inclusion complexes of this pharmacologically active agent with β-cyclodextrins in increasing its stability. Allicin is the initial precursor for the production of ajoene ((*E*)- and (*Z*)-4,5,9-trithiadodeca-1,6,11-triene 9-oxides) and vinyldithiin (2-vinyl-4H-1,3-dithiin, and 3-vinyl-4H-1,2-dithiin), which are more stable and show various pharmacological effects. The mechanisms of allicin transformations to these compounds are given in detail. Finally, the data on the pharmacological effects of allicin and its transformation products, ajoene and vinyldithiin, are presented.*

Key words: *allicin, ajoene, vinyldithiins, biosynthesis, synthesis, pharmacological activity*

1. ALLICIN (ALLYL THIOSULFINATE)

1.1. Biosynthesis of allicin

Under the influence of alliinase, allicin is produced by enzymatic transformation of alliin [(+)-(*S*)-allyl-L-cysteine-sulfoxide]. Alliin and alliinase are found in separate parts of garlic clove [1], therefore this chain reaction is initiated only after crushing the cells. The alliin complex with the enzyme alliinase is then formed in the presence of water. The unstable alliin-alliinase complex is further subjected to dehydration by pyridoxal phos-

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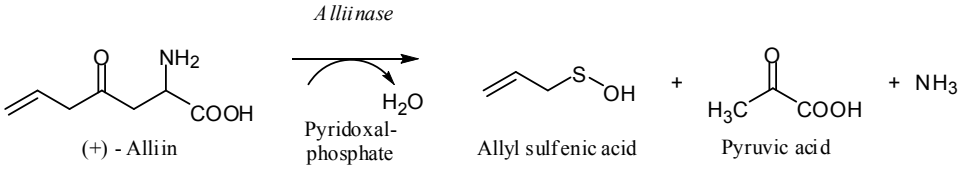
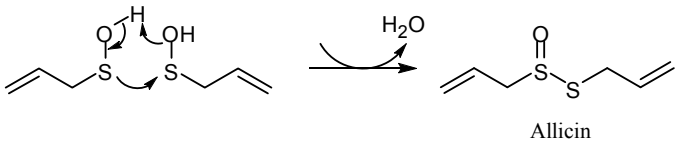
phate and transformed to allyl sulfenic acid, pyruvic acid and ammonia, as shown in Sheme 1 [2].



Sheme 1. Enzymatic transformation of alliin to allyl sulfenic acid

Allyl sulfenic acid is unstable and very reactive at room temperature. With the elimination of water, two molecules of allylsulfenic acid condense spontaneously to allicin (Sheme 2).



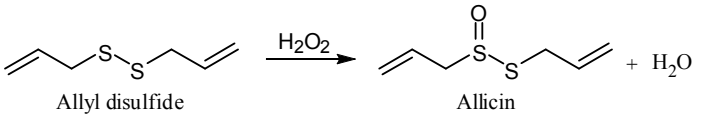
Sheme 2. Biosynthesis of allicin

At room temperature, these enzymatic transformations occur in 10-15 minutes. The optimal pH value for alliinase catalytic activity is 6.5, while the optimal temperature is 33 ^{o}C. The activation energy of allicin decomposition is 14.7 kJ/mol [3]. This enzyme is extremely sensitive to acids. By adding retinol (10 μmol/L) and hydroxylamine sulfate solution (50 μmol/L), the transformation of alliin into allicin by use of this enzyme can be inhibited up to 90%. It is assumed that retinol acts by blocking the flavin components of this enzyme.

1.2. Synthesis of allicin

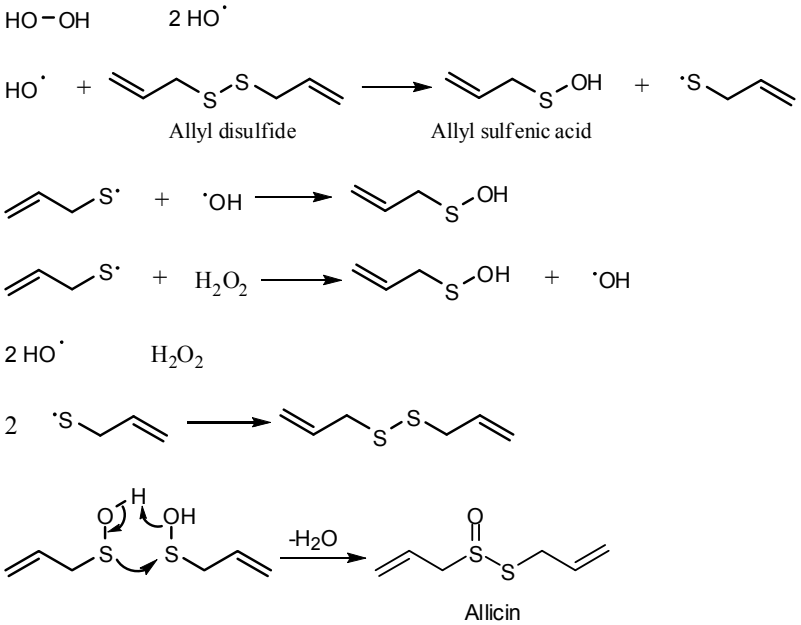
Allicin isolation, determination and standardization of allicin based products are made more difficult due to high instability and volatility. In recent decades its synthesis has become very relevant because pure allicin is hard to obtain commercially. The greatest part of methods of allicin synthesis refers to the oxidation of allyl sulfide by hydrogen peroxide in acid medium [4-8], oxidation of allyl disulfide with *m*-chloroperbenzoic acid in chloroform [9], and processing of dichloromethane solution of allyl disulfide by magnesium monoperoxy hydrate in the presence of ammonium-butyl sulfate [10]. All these methods are usually carried out at low temperatures (0 ^{o}C to room temperature), and depending on the method of synthesis and purification procedures, allicin of various grades of purity is obtained.

In a recent study a detailed investigation of the mechanism and kinetics of allicin synthesis from allyl disulfide and hydrogen peroxide in acid medium was carried out [8]. The general equation of this synthesis is show in Sheme 3.



Sheme 3. Synthesis of allicin from allyl disulfide

The mechanism of this radical-type reaction is given in the Sheme 4:



Sheme 4. The mechanism of synthesis of allicin from allyl disulfide

Since the dissociation energy of O-O bond in peroxide (200.9 kJ/mol) is lower than that of S-S bond in disulfide (301.39 kJ/mol), it favors formation of a hydroxyl-radical that attacks allyl disulfide molecule to produce thiyl-radical and allyl sulfenic acid [11]. The thiyl-radical can be further combined with hydroxyl-radical to give an unstable allyl sulfenic acid, or it can reacts with the non-degraded hydrogen peroxide to produce a new hydroxyl-radical and allyl sulfenic acid. Also, the recombination of two thiyl-radicals, which gives allyl sulfide (the initial substrate for allicin synthesis), can occur. Two molecules of allyl sulfenic acid, then react and give allicin and water molecule. The slowest stage in the allicin synthesis is the decomposition of the compound into radicals, whose concentration in the stationary state is constant, which indicates that the synthesis is a zero order reaction. Nikolic *et al*. [8] have investigated the kinetics of allicin synthesis, by using HPLC method, and confirmed that allicin synthesis reaction followed the kinetics of zero order. Additionally, described procedure is very convenient method for synthesis of allicin, as no significant amounts of byproducts are obtained [8].

1.3. Degradation of allicin

Allicin is an oily liquid, bright yellow in color, with a characteristic garlic odor [2], very unstable, thus its degradation occurs readily even at room temperature. Allicin can disintegrate under the influence of various factors. In our previous studies, the allicin degradation under the influence of temperature was monitored by FTIR spectrometry. A band in the IR spectrum originating from S=O valence vibrations at 1087 cm^{-1} (indicative of allicin) was chosen to monitor the allicin degradation [12].

The dependence of the peak area variation normalized with peak area maximum at 1087 cm^{-1} *i.e.* c_A / c_{A0} on the time of the allicin exposure to temperature of 70 and 80 °C represents an exponentially decreasing function and it is shown in Fig. 1 [12].

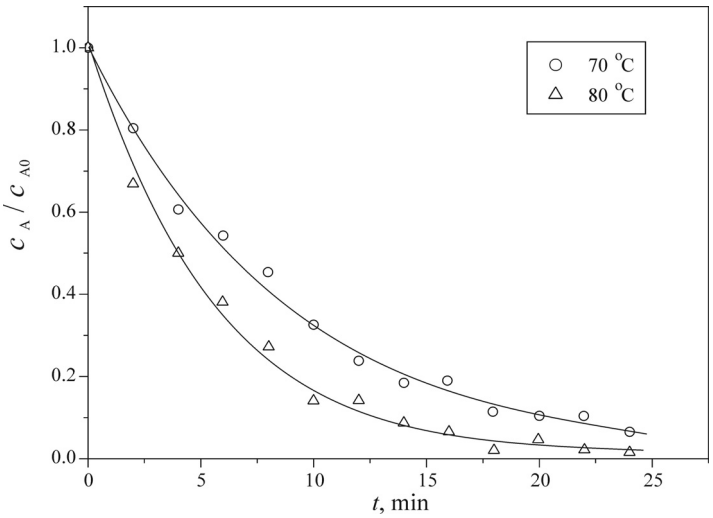


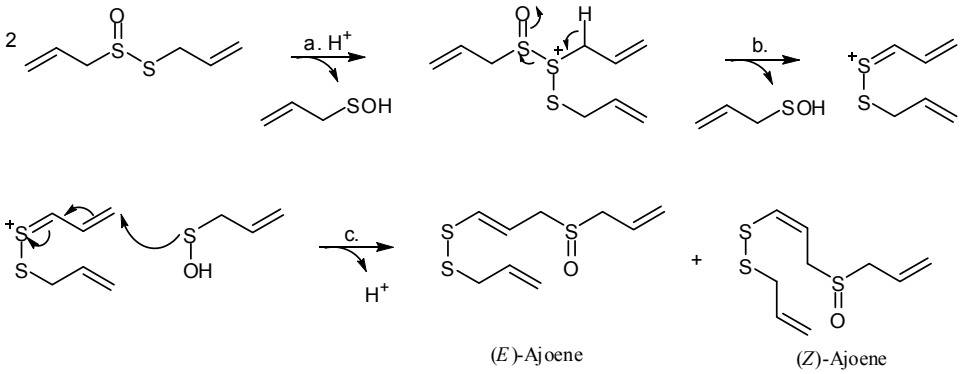
Fig. 1. Determination of the kinetic parameters of allicin degradation at 70 and 80 °C [12]

In order to increase the stability of this molecule, some reports have described processes of producing inclusion complexes with β-cyclodextrins [13] and carbamide [14], which preserved the pharmacological activity of allicin.

2. ALLICIN TRANSFORMATION PRODUCTS

Ajoenes ((*E*)- and (*Z*)-4,5,9-trithiadodeca-1,6,11-triene-9-oxides) are chemically more stable than allicin [15]. These degradation products of allicin are commonly found in chloroform and oil extracts of garlic, or in garlic powder mixed with water. They are found in form of (*E*) and (*Z*) isomers, whereby (*E*)-ajoene is usually present in twice as high quantities [16].

The degradation mechanism of allicin to (*E*)- and (*Z*)-ajoene was described by Block *et al.* [9], Sheme 5.



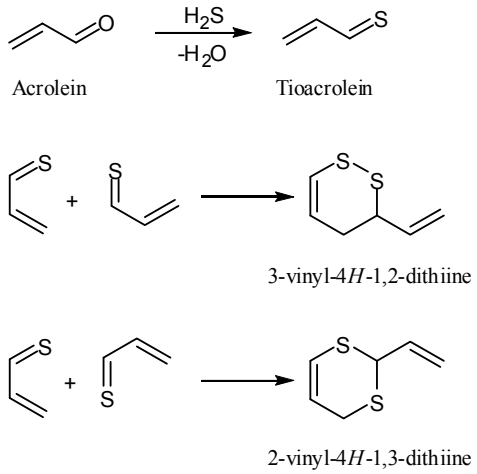
Sheme 5. The transformation of allicin to (*E*)- and (*Z*)- ajoene in low polar solvents

The process of allicin transformation into geometric isomers of ajoene is completed in three stages:

1. thioallylization of allicin in acid medium (a),
2. elimination (b),
3. condensation (c) leading to both (*Z*)- and (*E*)-ajoene isomers [9].

2.1. Allicin transformation in non-polar solvents

In non-polar organic solvents (most often *n*-hexane) or in oil, allicin and other thiosulfinates could be transformed to corresponding vinyldithiins (*ca.* 70%, the main products) and dialk(ene)yl-sulfides (up to 18%, by-products) [9].



Sheme 6. Synthesis of vinyldithiine regioisomers

Vinyldithiins are six-membered ring heterocyclic molecules containing two S-atoms. They occur as regioisomers, such as 2-vinyl-4*H*-1,3-dithiin (the main product) and 3-

vinyl-4*H*-1,2-dithiin (by-product). They represent pharmacologically active substances that are more stable than allicin [2]. Block *et al.* [9] suggested a mechanism of decomposition of allicin to vinyldithiins in oil and non-polar organic solvents, at slightly elevated temperatures.

According to the Besllin [17], vinyldithiins can also be obtained from acrolein and hydrogen sulfide (Sheme 6).

It was shown by both this standard synthesis procedure and allicin transformation in non-polar medium that 2-vinyl-4*H*-1,3-dithiin is predominant in the reaction mixture, while 3-vinyl-4*H*-1,2-dithiin is less evident.

3. PHARMACOLOGICAL EFFECTS OF ALLICIN

Allicin manifests a wide spectrum of antibacterial activity against numerous Gram positive and Gram negative bacteria, such as *Escherichia coli* [11-13, 18-21], *Salmonella enterica* [20-22], *Shigella (Shigella boydii*, *Shigella flexneri*, *Shigella sonnei)* [19-21], *Enterococcus faecalis* [20-23], *Staphylococcus aureus* [12-14, 20-22], *Streptococcus* (*Streptococcus faecalis*, *Streptococcus mutans*, *Streptococcus pyogenes*) [20-22], *Klebsiella aerogenes* [20-22], *Pseudomonas aeruginosa* [12-14], *Proteus vulgaris* [20-22]. Fungi susceptible to allicin are *Candida albicans* and *Aspergillus niger* [12-14].

The aim of one of our previous studies was to investigate the antimicrobial activities of pure allicin and allicin incorporated in Carbopol 940 gel (poly(acrylic acid)) by disc diffusion method, and the obtained results are given in the Table 1. It was found that pure allicin and allicin incorporated in gel showed the same activity against the tested microbes [12].

Table 1. Growth inhibition zone values for the microorganisms tested for pure allicin and allicin in gel [12]

Microorganisms	Growth inhibition zone values for the microorganisms [mm]	
Bacteria	Pure allicin	Allicin in gel
Staphylococcus aureus ATCC 6538	39	40
Escherichia coli ATCC 8739	37	38
Pseudomonas aeruginosa ATCC 9027	20	19
Fungi		
Candida albicans ATCC 10231	41	41
Aspergillus niger ATCC 16404	35	34

Another study has shown that the stability of allicin has been increased and its biological activity has been preserved after forming inclusion complexes with cyclodextrins. The results of this study are summarized in Table 2 [13]. The antimicrobial activities of pure allylthiosulfinate (ATS) and its complex with cyclodextrin (ATS:β-CD) were tested by disc diffusion method. ATS and ATS:β-CD were applied to the 12.7 mm diameter disk at 180 μg dose and tested against a panel of microorganisms including bacteria: *Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 9027, and fungi: *Candida albicans* ATCC 10231 and *Aspergillus*

niger ATCC 16404. Activity assays were repeated after 0, 8, 23, 40, 52 and 62 days after the complex preparation (both ATS and ATS:β-CD were kept under the same, controlled conditions).

Table 2. Microbiological activity of allylthiosulfinate and allylthiosulfinate:β-cyclodextrin complex [13]

t [day]	Inhibition zones [mm]									
	C. albicans		*A. niger*		*E. coli*		*S. aureus*		*P. aeruginosa*	
	ATS*	C†	ATS	C	ATS	C	ATS	C	ATS	C
0	45	45.5	29	29	29.5	30	30	31	14.9	15
8	35.6	42	23.5	27.5	27.5	29.5	27.5	31	14	14.8
23	26	36	14	22	14	22	20.5	23	12.8	13
40	18.8	24.5	14	18.5	14	18.5	17.6	19	-	-
52	15.4	19	-	15.7	-	15.5	14.1	15.3	-	-
62	-	18.5	-	15.5	-	15.3	-	15	-	-

*ATS - allylthiosulfinate
† C - complex ATS:β-CD

The results given in Table 2 indicate that the stability of allicin in the β-cyclodextrin complex is higher than that of pure allicin. The efficacy of complexed allicin activity against the tested microorganisms is extended to approximately 60 days and after that period of time the degradation of allicin and the decrease of microbiological activity occur.

In infections caused by *Mycobacterium tuberculosis,* an acid-resistant bacterium, the resistance to β-lactam antibiotics has been developed much faster and easier than to allicin, and, therefore, allicin is recommended as co-therapy for the above infections [24]. The observations of another study strengthen the idea that allicin should be tested in *in vivo* models to evaluate its therapeutic potential in the pathogenesis of tuberculosis [24].

Entamoeba histolytica, a gastrointestinal parasite, is proven to be very susceptible to allicin, and this substance in concentration of 30 μg/mL completely inhibits its growth, which indicates an expressed antihelminthic activity of allicin [22-25]. Its antifungal activity is stronger than that of nystatin and other antimycotics [23, 26]. More recently we have found that at lower concentrations (5 μg/mL), allicin inhibited by 90% the virulence of trophozoites of *E. histolytica* as determined by their inability to destroy monolayers of tissue-cultured mammalian cells *in vitro* [27].

Allicin show both *in vitro* and *in vivo* antiviral activities [23]. Among the viruses susceptible to allicin are *Herpes simplex* type 1 and 2, *Parainfluenza* virus type 3, human *Cytomegalo* virus, *Influenza B*, *Vaccinia* virus, *Vesicular stomatitis* virus and *Human rhinovirus* type 2 [23]. The main antimicrobial effect of allicin is due to its interaction with important thiol-containing enzymes. In the amoeba parasite, allicin was found to strongly inhibit the cysteine proteinases, alcohol dehydrogenases, as well as, the thioredoxin reductases which are critical for maintaining the correct redox state within the parasite [27]. Inhibition of these enzymes was observed at rather low concentrations (< 10 μg/mL). Allicin also irreversibly inhibited the well known thiol-protease papain, the $NADP^+$-dependent alcohol dehydrogenase from *Thermoanaerobium brockii*, and the NAD^+-dependent alcohol dehydrogenase from horse liver. Interestingly, all three enzymes could be reactivated with thiol-containing compounds such as DTT, mercap-

toethanol and glutathione [28]. At concentrations that are at least a log higher (> 100 μg/mL), allicin was also found to be toxic to tissue-cultured mammalian cells [27].

Numerous *in vitro* and *in vivo* investigations of various garlic fractions and formulations prepared on its basis confirmed its extraordinary antioxidant potential. The antioxidant effect is related primarily to the presence of allicin in garlic; therefore, it exhibits strong antioxidant activity [12, 22, 25].

We found high antioxidant activity of allicin on the stable DPPH radical in our previous study (Fig. 2) [12]. EC_{50} value for allicin solution in methanol is 0.37 mg/mL.

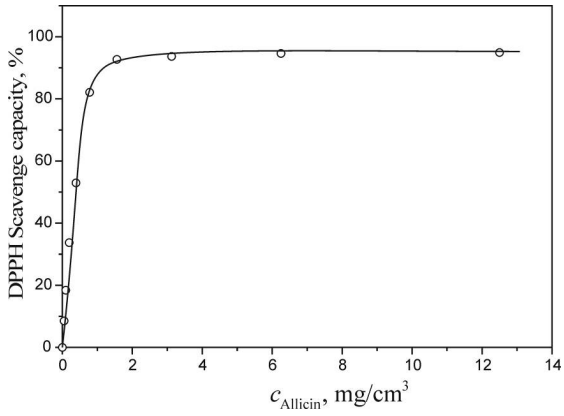


Fig. 2. Antioxidant activity of allicin methanol solutions [11]

Another test carried out on experimental animals show that in low concentrations allicin exhibits antioxidant effect, while in high concentrations its effect is pro-oxidative [20].

Favorable effects of allicin are also observed in cases of:

- stroke (has a protective role) [9],
- coronary thrombosis (diminishes the aggregation of thrombocytes) [9, 29, 30],
- atherosclerosis (diminishes build up of lipids, cholesterol, and calcium in large and medium arteries) [30, 31],
- hypertension (lowers high blood pressure) [30, 31],
- malignant diseases (inhibits growth of malignant cells and, in some cases, bring about their elimination) [30].

High doses of allicin can lead to complete hindering of growth, impairment of the function of the thyroid, hyperplasia (goiter), allergic reaction of the skin and mucous membrane. In patients with strong bleeding it aggravates hemorrhage [32].

There are also reports dealing with the interaction of allicin with other medicines. It is found that is especially dangerous to administer allicin to patients with disorders such as diabetes, irregular blood pressure, high level of cholesterol in blood, patients suffering from malignant diseases, and those with organic gastrointestinal tract disorder [32].

4. PHARMACOLOGICAL EFFECTS OF ALLICIN-DERIVED COMPPOUNDS

4.1. Pharmacological effects of ajoene

Ajoenes have antimicrobial effect (they affect a great number of bacteria, viruses, fungi and other parasites) [33, 34]. They participate in the inhibition of *in vitro* growth of *Helicobacter pylori*, a bacterium responsible for gastric diseases such as gastric ulcer and stomach cancer [35]. The mechanism is based on interaction with sulfhydryl group in microorganism's enzyme. The antifungal effect of ajoene was proven in both *in vivo* and *in vitro* conditions against many pathogen fungi. The mechanism of their effect as the antifungal agents has not yet been explained. It is considered to be related with a selective inhibition of phosphatidylcholine biosynthesis in lower eukaryotes [33].

Ajoenes are maximally efficient in the early process of HIV fusion. This fact suggests that ajoenes could be a promising agent for the treatment of HIV infections [36]. Results have shown that ajoene has indeed a direct virolytic effect on HIV (half-life about 4 h at > 250 μM); however, it seems extremely unlikely that lower concentrations (< 100-fold), that prevent fusion, are virolytic. In addition, the sole treatment of Molt-4 cells by ajoene has been found to be sufficient to prevent fusion [36].

Synthetic ajoenes exhibit various inhibitory activities against immunodeficiency virus (HIV)-1. Anti-HIV activity of ajoene can be attributed to inhibition in early replications and particular viral adsorptions [37]. Results show that ajoene protected acutely infected Molt-4 cells against HIV-l and may block further destruction of CD4-T cells *in vitro*. It is not clear yet what is the exact nature and molecular mechanism responsible for the ajoene induced inhibition, but such effect suggests the possible therapeutic *in vivo* efficacy which remains to be established [37].

It has been proven that ajoenes are basic inhibitors of thrombocyte aggregation. Anti-thrombic activity is shown by disulfides directly bonded to phenyl ring, while their effect is enhanced by α-sulfonyl group [33, 38].

Moreover, anti-carcinogenic effect was investigated *in vitro* (on mice) and it was found that (*Z*)-ajoene was more active [33, 39]. Elimination of sulfide group from position 4 decreases ajoene activity by as much as twice. (*Z*)-Ajoene clearly shows the *in vitro* inhibition of carcinogenic cells, and in non-toxic concentrations [39]. Ajoenes have shown the ability to perform apoptosis (a form of programmed cell death) [39, 40]. Lately, more attention is also given to clinical effectiveness of ajoene in patients suffering from basal skin cancer [41].

Ajoenes are also utilized in the treatment of leukemia [38]. (*Z*)-Ajoenes are more efficient than (*E*)-ajoenes for the inhibition of growth of leukemic cells [39]. Futhermore, they possess the ability to lower the level of cholesterol in blood [42]. Another substantial characteristic of ajoene is its ability to enhance the effect of chemotherapeutic medicines, such as cytarabine and fludarabine [39, 43].

4.2. Pharmacological effects of vinyldithiin

Vinyldithiins are very biologically activite as they participate in the inhibition of thrombocyte aggregation, cyclooxygenase and 5-lipoxygenase, as well as, in regulation of systolic and diastolic blood pressure [44].

5. CONCLUSIONS

Allylthiosulfinate (allicin) and its derivatives, primarily ajoenes and vinyldithiins, represent important pharmacologically active components. These compounds display antimicrobial, antiviral, antioxidant and anti-carcinogenic effects. The negative aspect of allicin as a pharmacologically active agent is its high volatility and instability, which considerably limits its commercial use. Therefore, some previous studies dealt with its stabilization by complexation, i.e. by formation of inclusion complexes with cyclodextrins, which contributes to the conservation of allicin and its mictobiological activity for a period of 60 days. Moreover, it was demonstrated that allicin does not lose its antimicrobial activity when incorporated in a hydrophobic gel. The results of various methods of thermal degradation of allicin to corresponding transformation products are described. The mechanisms of allicin synthesis and its transformations are also presented.

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ALICIN I SRODNA JEDINJENJA: BIOSINTEZA, SINTEZA I FARMAKOLOŠKA AKTIVNOST

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*Ovaj pregled obuhvata detaljnan opis biosinteze alicina (aliltiosulfinata) enzimskom transformacijom alliina, kao i mehanizme i kinetiku različitih reakcija na kojima se zasniva njegova sinteza. Prikazana je i pogodna metoda za određivanje stabilnosti alicina. Pored toga, razmotren je postupak povećanja stabilnosti ovog farmakoški aktivnog agensa, kompleksiranjem sa β-ciklodekstinima. Alicin je prekursor za sintezu ajoena ((*E*)- i (Z)-4,5,9-tritiadodeka-1,6,11-trien-9-oksidi) i vinilditiina (2-vinil-4H-1,3-ditiin i 3-vinil-4H-1,2-ditiin), koji su od njega stabilniji i takođe farmakološki aktivni. Detaljno su opisani i mehanizmi reakcija kojima se ova jedinjenja dobijaju iz alicina. Pored toga, sumirani su i podaci vezani za farmakološko delovanje alicina i pomenutih transformacionih proizvoda.*

Ključne reči: *alicin, ajoeni, vinilditini, biosinteza, sinteza, farmakološka aktivnost*