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Review Article

Evidence based Scientific Narrative Review on the Anticoagulant Mechanisms of *Allium sativum* (Garlic)

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Abstract

Introduction: Garlic (*Allium sativum*, Family: Amaryllidaceae) is a seasoning plant cultivated all over the world. Garlic contains a lot of bioactive compounds including organosulfur compounds, saponins, phenolic compounds, and polysaccharides. Anticoagulant activity is one of the pharmacological properties of Garlic. The aim of this study was to review the mechanism of the anticoagulant activity of garlic and summarise the potential evidence about the anticoagulant activity of garlic from past studies. Method: Literature searches were conducted on PubMed and Google Scholar databases. 44 full articles were reviewed in detail in this study. The findings were reviewed and potential evidence for the anticoagulant mechanisms of garlic was summarised. Results: Organosulfur compounds in garlic play a major role in the anticoagulant property of garlic. Garlic exhibits anticoagulant activity mainly through three mechanisms. Those are inhibiting platelet aggregation, retarding thrombin formation, and promoting fibrinolysis. The anticoagulant activity of garlic is proven by several human, animal and *in-vitro* studies. Garlic significantly inhibits adenosine diphosphate and epinephrine induced platelet aggregation in healthy subjects. Garlic administration inhibit the thrombus formation in rats. Aqueous and methanolic extracts of garlic prolong prothrombin time. Extension in clotting time is reported with increasing concentrations of garlic extract. Conclusions: Garlic has been reported as a medicinal plant showing anticoagulant activity by resisting platelet aggregation, inhibiting thrombin formation and enhancing fibrinolysis and this study suggests that garlic reduces the risk of thrombosis therefore cardiovascular complications.

Keywords: Anticoagulant Activity, Garlic, Thrombosis

Introduction

Garlic (*Allium sativum*, Family: Amaryllidaceae) is a seasoning plant cultivated all over the world. It produces bulbs, with five to ten cloves (Figure 1). It is utilized as a spice for flavouring food during the cooking process [1]. Several parts of garlic are used in traditional folk medicine. Leaves and cloves are mostly used for medicinal purposes [2]. Since ancient times, people use garlic to treat cardiac diseases, hypertension, arthritis, pulmonary complaints, respiratory infection, abdominal growth, cold, diarrhea, headache, bites, skin diseases, wounds, worms, influenza, ulcers and tumours [1,3,4].

Garlic contains many bioactive compounds including organosulfur compounds, saponins, phenolic compounds, and polysaccharides [5].

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Among them, organosulfur compounds are the major compounds found in garlic [2]. The four major organosulfur compounds found in garlic are alliin (S-allyl cysteine sulfoxide), S-allylcysteine (SAC), S-methylcysteine (SMC), and S-ethylcysteine (SEC) [5]. Allicin (Diallyl thiosulfinate) is the principal bioactive compound responsible for most activities of garlic, released by crushing or chopping garlic. Crushing of garlic releases an alliinase enzyme that catalyzes formation of allicin from alliin [6,7,8]. Allicin is a very unstable molecule. Allyl methyl disulfide (MADS), diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), E/Z-ajoene, and dithiins found in garlic are produced due to breakdown of allicin [7,8]. The characteristic odor of garlic is due to the presence of allicin and other oil soluble sulfur compounds [6,8].

Compounds in garlic have several pharmacological properties that are very useful in herbal medicine such as anticoagulant, antimicrobial, anti-inflammatory, anticancer, antioxidant, antidiabetic, anti-obesity, antihypertensive, hypolipidemic, hypoglycemic, and fibrinolytic activities [9-16].

The aim of this study is to find out the mechanisms of anticoagulant activity and evidence for the anticoagulant activity of garlic from existing literature.

Figure 1: Bulbs of garlic and cloves

Methods

To gather the needed information, literature searches were conducted using keywords on PubMed and Google Scholar databases. A total of 104 articles published between 1963 and 2020 were selected for this study. Duplicate articles, articles that have no specific information, and articles that cannot be accessed to full articles (abstract and conference presentations) were excluded. Finally, 44 full articles were included to review in detail in this study. The full text of each article was read by the authors and information related to anticoagulant mechanisms of garlic was extracted. Finally extracted information was analysed qualitatively and potential evidence for the anticoagulant mechanism of garlic was summarised.

Results and discussion

Evidence for anticoagulant mechanisms of garlic, extracted from *in vitro*, animal, and human studies are given below.

Anticoagulant activity of garlic

Garlic shows anticoagulant activity by several mechanisms. Garlic enhances the anticoagulant activity of non-steroidal anti-inflammatory drugs and blood thinning medications. It recommends that a dosage of 4 g or 1-2 cloves of garlic per day is health beneficial [17].

Compounds in garlic responsible for its anticoagulant activity

There are several compounds that are responsible for anticoagulant activity in garlic. Organosulfur compounds in garlic play a major role in its anticoagulant property. Allicin, other thiosulfinates, allicin derivatives such as ajoene, diallyl trisulfide (DATS), diallyl disulfide (DADS), methyl allyl trisulfide (MATS), dithiins and adenosine in garlic are responsible for the antithrombotic effect of garlic. The most powerful antiaggregatory compound in raw garlic is allicin, but it cannot be identified in garlic extracts [18-

22]. Steroid saponins such as proto-isoeruboside-B and isoeruboside-B separated from garlic also affect blood coagulation therefore anticoagulant activity [23]. Saponin is a major non sulfur compound in garlic. It is not affected during the cooking process. It has the ability to inhibit the formation of clots (thrombus) [24]. Galactolipid and a phytosterol from garlic can affect adenosine diphosphate (ADP) induced platelet aggregation [25]. In addition to the above compounds, L-methionine, L-arginine and L-cysteine in aged garlic extract have been found to have antiaggregatory effects [26].

Mechanism of the anticoagulant activity of garlic

Garlic exhibits anticoagulant activity mainly through three mechanisms. Those are inhibiting platelet aggregation, retarding thrombin formation, and promoting fibrinolysis (Figure 2) [6]. Platelet aggregation and adhesion are significantly reduced by garlic [27]. Garlic shows anticoagulant effect by inhibiting collagen, adenosine diphosphate (ADP) and epinephrine induced platelet aggregation [28].

Platelet aggregation is a complex process that includes activation of cytosolic Ca^{2+}, thromboxane production, fibrinogen receptors, glycoprotein IIb/IIIa (GPIIb/IIIa) and other modulators like cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), lipoxygenase, protein kinase enzyme, and nitric oxide (NO). The rise in platelet aggregation can result in pathological thrombus formation. Some of the mechanisms said above are affected by garlic thus helping to reduce the risk of thrombosis, therefore, cardio associated death [7,29,30]. Platelet aggregation is inhibited by several mechanisms such as inhibition of cyclooxygenase enzyme, retardation of movement of calcium into platelets, and elevation of cAMP, and cGMP [31]. Diallyl trisulfide (DATS), a garlic component inhibits platelet aggregation induced by thrombin and collagen related peptides, and inhibition is increased with increasing concentration. DATS inhibits platelet aggregation without interfering the formation of cAMP, and cGMP [32].

Thromboxane production is retarded by garlic by the following mechanisms. DATS in garlic reduces the synthesis of thromboxane B_2 by repressing the signal transduction pathway, but not by retarding the cyclooxygenase [32]. Platelet lipooxygenase and cyclooxygenase enzymes are inhibited by allylpropyl disulfide, diallyl disulfide, and other sulfur compounds in garlic oil in order to prevent the synthesis of thromboxane B_2 (TXB_2) [19].

Platelet aggregation is inhibited through several mechanisms. Aged garlic, prepared by soaking raw garlic in 15-20% ethanol for 20 months [6] inhibits platelet aggregation through several mechanisms. It prevents the inflow of calcium ions by chelating calcium within cytosol or interfering with intracellular secondary messengers within the platelets [26]. Platelet aggregation is also retarded by blocking the synthesis of thromboxane A_2, changing the membrane fluidity and increasing the production of nitric oxide and cAMP [26,33]. It also induces disaggregation of platelets by resisting the fibrinogen to bind with glycoprotein IIb/IIIa receptor, increasing the bioavailability of nitric oxide, and decreasing the thromboxane production [34].

Blood coagulation is suppressed by consumption of garlic which lowers fibrinogen level and promotes fibrinolysis [19]. In normal conditions, tissue type plasminogen activator (t-PA) produces plasmin from plasma precursor plasminogen and promotes fibrinolysis. Plasmin is a proteolytic enzyme which digests the stable fibrin clot to fibrinogen degradation products (FDP). Fibrinolysis is regulated by plasminogen activator inhibitor-1 and 2 (PAI-1 and PAI-2) [28]. Fibrinolysis is promoted by garlic. The

mechanism of improvement in fibrinolysis by garlic is due to enhancement in t-PA mediated plasminogen activation. Components in garlic function as a cofactor and increase the affinity of t-PA for plasminogen. Therefore, plasminogen is highly activated and produces a large amount of plasmin [14]. This enhancement depends on the concentration and duration of intake. It has also been found that the consumption of garlic with low concentration for a long time has the best effect on fibrinolysis [35]. There is no effect on platelet aggregation by steroid saponins, but they enhance fibrinolysis and inhibit blood clotting [23].

Anticoagulant activity is exhibited by DATS rich garlic oil by enhancing the activity of antithrombin III and protein C. Antithrombin III activates proteases which suppress the production and activity of thrombin. Protein C also inhibits the formation of thrombin [36]. The adenosine diphosphate (ADP) pathway is also suppressed by alcoholic garlic extract [37]. The description of the anticoagulant mechanisms of garlic is explained in Figure 2.

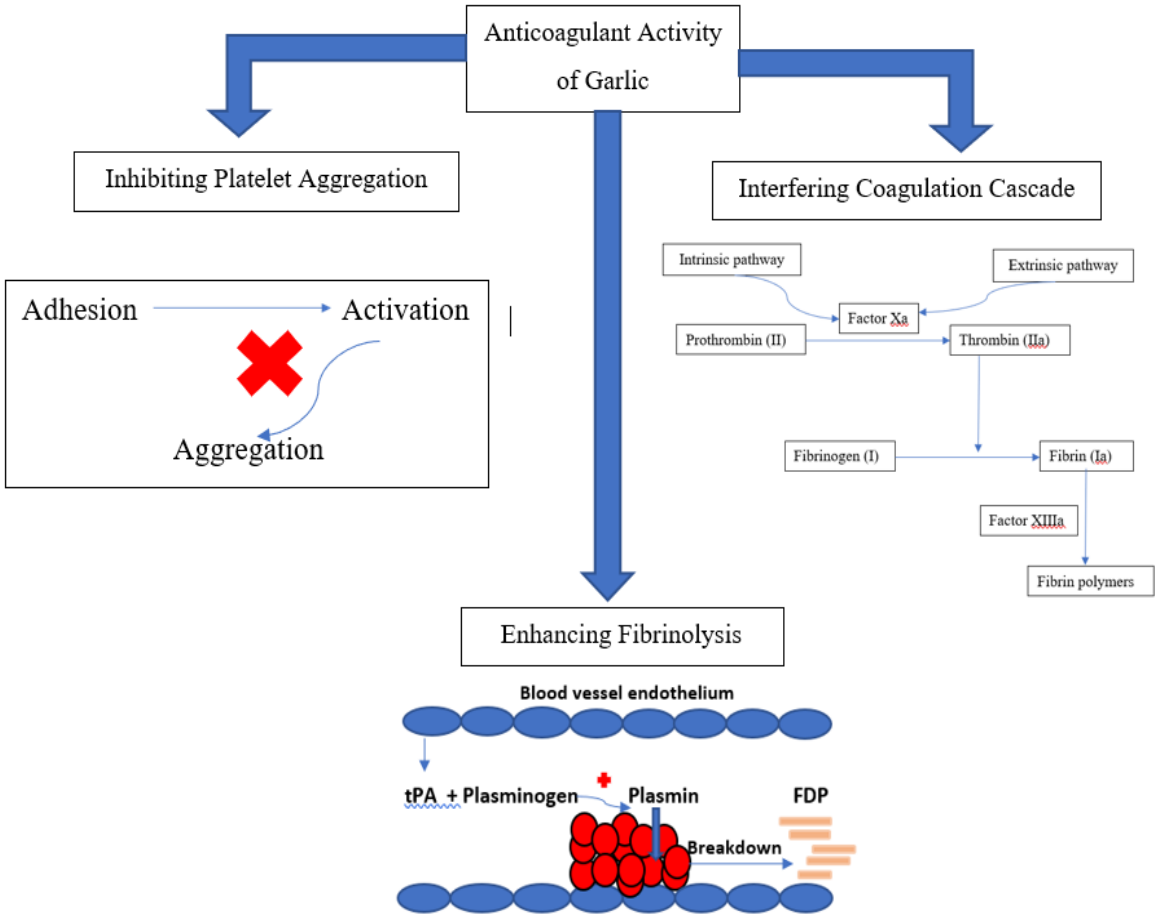

Figure 2: Description of the anticoagulant mechanisms of garlic

Evidence from in vitro studies

An *in vitro* study has been conducted by Reddy et al in 2017 to see the effect of raw garlic extract on blood coagulation and fibrinolysis. In this study, clotting time had been measured by capillary method before and after mixing blood with different volumes of garlic extract. It could be observed in this study that clotting time is increased with an increasing volume of extract. Fibrinolytic activity has been analysed by adding garlic extract after formation of a clot in tubes. The clot had partly dissolved with the addition of garlic extract [11].

Another study by Vaijayanthimala et al in 2017 has been conducted to see the in vitro anticoagulant activity of aqueous and methanolic *A. sativum* plant extracts using plasma of normal healthy individuals. This study had found that both aqueous and methanolic extracts of garlic prolong prothrombin time. Extension in clotting time had been observed with increasing concentration of extract [38].

The research by Song et al in 1993 had isolated an anticoagulant substance from garlic. In this study, prothrombin time and blood clotting time of garlic extract added plasma and potassium oxalate added plasma had been compared to see the antithrombotic, fibrinolytic activities. Prolongation of clotting time observed with garlic extract added plasma was higher than potassium oxalate added plasma [39].

Enhancement in fibrinolytic activity by odorless garlic has been proven in a study by Fukao et al in 2007, using fibrin film assay and chromogenic assay. It was found that, according to the fibrin film assay, t-PA activity had raised by 180% in the presence of garlic compared to the absence of garlic. In chromogenic assay plasmin had been used as a substrate and enzymatic activity had been measured calorimetrically. The results from the Lineweaver–Burk plot had reported that there is no effect in maximal reaction rate (V_{max}) by garlic, but Michaelis constant (Km) is reduced by garlic showing a high affinity of t-PA to plasminogen [14].

Another *in vitro* study by Hiyasat et al in 2009 has been conducted to see the antiplatelet activity of *A. sativum* and *A. ursinum*. In this study, *in vitro* platelet aggregation induced by ADP, collagen, A23187, epinephrine and arachidonic acid have been analysed in a four-channel aggregometer by measuring the amount of turbidity. Plasma pre-incubated with an alcoholic extract of *A. sativum* had shown a decrease in platelet aggregation as compared to normal (baseline) conditions. Furthermore, it was evident that alcoholic garlic extracts significantly reduce ADP induced platelet aggregation rather than other agonists [37].

A study on fibrinolytic activity of the blood clot in vitro has been carried out by Ansari et al in 2011. This study had been done by adding various volumes of ethanolic garlic extract into plasma followed by addition of fluorescent labeled clot into that mixture. Fluorescent intensity had been measured after adding labelled clots. A significant increase in fibrinolytic activity had been observed with garlic extracts than with control [35].

Evidence from animal studies

In an experimental study conducted on a group of albino rabbits by Singh et al in 2015, an alcoholic extract of garlic had been fed to albino rabbits for two weeks to analyse the anticoagulant and fibrinolytic activity of garlic. It has been reported in the study that blood coagulation time significantly increases by 61.9%, and prothrombin time by 15.2% after a week of administration of alcoholic garlic extract [40].

Another study by Fukao et al in 2007 has been performed to see the antithrombotic effect of odorless garlic in rat models. Thrombosis had been induced in rats by in situ loop operation (control).

Another group of rats had been administered odourless garlic powder with diet and also in situ loop operation had been done (test). At the end of the experiment, blood had been collected from the vena cava of anesthetized rats. According to the results, prothrombin time (PT), activated partial thrombin time (APTT), thrombin time (TT) and fibrinogen degradation products (FDP) had been analysed. PT, APTT, TT, and FDP had decreased in test rats as compared to control as coagulation factors were consumed in control group rather than the test group. Garlic administration had inhibited the thrombus formation in test rats [14].

According to an animal study done by Miao et al in 2020 to find the anti-atherosclerotic property of total saponins of garlic in rats, administration of saponins extracted from garlic to rat models reduces the thromboxane B_2 (TXB_2) level and increases the 6-keto-prostaglandin F1α (6-keto-PGF1α). Both have the opposite effect on formation of atherosclerosis. TXB_2 enhances vasoconstriction and platelet aggregation while 6-keto-PGF1α relaxes blood vessels and inhibits platelet aggregation [24].

Evidence from human studies

A study has been done by Ali et al in 1995 to evaluate the effect of minimal intake of garlic on thromboxane synthesis. In this study, eight healthy male volunteers had been fed with one clove of fresh garlic daily for 16 weeks. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) had not been taken by subjects during the study period. It was found in this study that the intake of one clove of fresh garlic regularly for a long period decreases the level of TXB_2 [41].

Another study has been conducted by Bordia et al in 1996 to evaluate the effect of garlic on platelet aggregation in humans by administrating different numbers of capsules containing oil equivalent to 1g of raw garlic to healthy subjects and patients with coronary artery diseases (CAD). The study consisted of two parts to check the acute and long-term effects of garlic. It has been shown in this study that acute effect of garlic is dose related and epinephrine induced platelet aggregation is only inhibited by garlic. It has been found in long term effect studies that garlic significantly inhibits ADP, epinephrine induced platelet aggregation in healthy subjects and epinephrine induced platelet aggregation in patients with CAD. According to the results, there is no significant inhibition of ADP, collagen induced platelet aggregation by garlic in patients with CAD. The metabolism of arachidonic acid in washed platelets had also been studied in this study. It has been found that garlic oil affects the metabolism of arachidonic acid thus preventing the formation of thromboxane [42].

Another study by Bordia et al in 1998 has been conducted to see the effects of garlic on various factors. It had been done by administrating garlic oil to myocardial patients. It has been found that garlic oil significantly enhances fibrinolytic activity by 39.4% and 55.1% at 1.5 months and 3 months respectively, but there is no effect on fibrinogen level. Platelet aggregation induced by arachidonic acid, collagen, adrenaline, and calcium ionophore was also affected by garlic oil due to presence of DADS and DATS which inhibit thromboxane B_2 production [43].

A double-blind placebo controlled crossover study by Wojcikowski et al in 2007 has been conducted to see the effect of garlic oil on platelet aggregation. It has been proven in this study that adrenaline induced platelet aggregation is significantly reduced by garlic oil but, there is no significant effect on collagen and ADP induced platelet aggregation [44].

The summary of the evidence for anticoagulant mechanisms of garlic, extracted from in vitro, animal, and human studies are stated below in Table 1.

Table 1: Evidence of anticoagulant mechanisms of garlic extracted from previous studies

Type of study	Reference	Findings
In vitro study	Reddy *et al*. [11] 2017	Blood coagulation pathway is retarded and Fibrinolysis is enhanced by garlic extract.
	Vaijayanthimala *et al.* [38] 2017	Clotting time is prolonged with the addition of garlic extract and the prolongation is increased with increasing concentration of garlic extract.
	Song *et al.* [39] 1993	Prothrombin time and clotting time are prolonged with garlic extract added plasma than control.
	Fukao *et al.* [14] 2007	The affinity of tissue-type plasminogen activator (t-PA) to plasminogen is increased by garlic extract.
In vitro study	Hiyasat *et al.* [37] 2009	Garlic extracts significantly reduce adenosine diphosphate (ADP) induced platelet aggregation rather than other agonists.
	Ansari *et al.* [35] 2011	A significant increase in fibrinolytic activity exists with garlic extracts.
Animal study	Singh *et al.* [40] 2015	Blood coagulation time and prothrombin time significantly increase after an administration of alcoholic garlic extract.
	Fukao *et al.* [14] 2007	Garlic administration inhibits thrombus formation in rats.
	Miao *et al.* [24] 2020	Administration of saponins extracted from garlic to rat models reduces the thromboxane B_2 (TXB_2) level and increases the 6-keto-prostaglandin.
Human study	Ali *et al.* [41] 1995	Intake of one clove of fresh garlic regularly for a long period decreases the level of TXB_2.
	Bordia *et al.* [42] 1996	Garlic significantly inhibits ADP, epinephrine induced platelet aggregation.
	Bordia *et al.* [43] 1998	Garlic oil significantly enhances fibrinolytic activity and platelet aggregation induced by arachidonic acid, collagen, adrenaline, and calcium ionophore is also affected by garlic oil.
	Wojcikowski *et al.* [44] 2007	Adrenaline induced platelet aggregation is significantly reduced by garlic oil.

Conclusions

Garlic has been reported as a medicinal plant showing anticoagulant activity. It shows anticoagulant activity by resisting platelet aggregation, inhibiting thrombin formation and enhancing fibrinolysis. Several compounds in garlic mainly organosulfur compounds are responsible for its anticoagulant activity. Anticoagulant activity of garlic is proven by several in vitro, animal and human studies. So, this study suggests the garlic to reduce the risk of thrombosis therefore cardiovascular complications.

References

1. Batiha, G.E., Beshbishy, A.M., Wasef, L.G., Elewa, Y.H., Al-Sagan A.A., El-Hack, A., et al. Chemical constituents and pharmacological activities of garlic (Allium sativum L.): A Review. Nutrients. 2020;12(3):872. DOI:https://doi.org/10.3390/nu12030872
2. Mikaili, P., Maadirad, S., Moloudizargari, M., Aghajanshakeri, S., and Sarahroodi, S. Therapeutic uses and pharmacological properties of garlic, shallot, and their biologically active compounds. Iranian Journal of Basic Medical Sciences. 2013;16:1031-48.
3. Rahman, M.S. Allicin and other functional active components in garlic: Health benefits and bioavailability. International Journal of Food Properties. 2007;10(2):245–68. DOI: https://doi.org/10.1080/10942910601113327
4. Amagase, H., Petesch, B.L., Matsuura, H., Kasuga, S., and Itakura, Y. Recent advances on the nutritional effects associated with the use of garlic as a supplement intake of garlic and its bioactive components. The Journal of Nitrition. 2001;131(3);955–62.
5. Zeng, Y., Li, Y., Yang, J., Pu, X., Du, J., Yang, X., et al. Therapeutic role of functional components in alliums for preventive chronic disease in human being. Evidance based Complementary and Alternative Medicine. 2017;2017(3):1-13. DOI: https://doi.org/10.1155/2017/9402849
6. Qidwai, W., and Ashfaq, T. Role of garlic usage in cardiovascular disease prevention : an evidence-based approach. Evidance based Complementary and Alternative Medicine. 2013;2013:1-9. DOI:
7. Butt, M.S., Sultan, M.T., Butt, M.S., and Iqbal, J. Garlic : Nature's protection against physiological threats. Critical Reviews in Food Science and Nutrition. 2009;49(6):538-51. DOI: https://doi.org/10.1080/10408390802145344
8. Pedisic, S., Miljanovic, A., Zoric, Z., Simic, D., Repagic, M., and Dragovic, V. Retention of bioactive compounds during domestic processing of croatian domestic garlic (Allium sativum L.). Food Technology and Biotechnology. 2018;56(4):590-596. DOI: https://doi.org/10.17113/ftb.56.04.18.5709
9. Shang, A., Cao, S.Y., Xu, X.Y., Gan, R.Y., Tang, G.Y., Corke, H., et al. Bioactive compounds and biological functions of garlic (Allium sativum L.). Foods. 2019;8(7):246.
10. Bungu, L., Van De Venter, M., and Frost, C. Evidence for an in vitro anticoagulant and antithrombotic activity in tulbaghia violacea. African Journal of Biotechnology. 2008;7(6):681–8.
11. Rama Narsimha Reddy, A., Srividya, L., Swamy, T.P., and Prasad, V.B. Effect of allium sativum (garlic) extract on blood coagulation and fibrinolysis. Advances in Pharmacology and Clinical Trials. 2017;2(1):000120.
12. Park, N-H., Jang, H-R., Lee, S-J., and Park, S-C. GC/MS analysis, antimicrobial and antioxidant effect of ethanol garlic extract. International Jounal of Phytomedicine. 2017;9(2):324-31. DOI: https://doi.org/10.5138/09750185.2087
13. Chen, C., Yang, F., Zhang, Q., Wang, F., Hu, Y., and Xia, Z. Natural products for antithrombosis. Evidance based Complementary and Alternative Medicine 2015;2015:1-17. DOI: http://dx.doi.org/10.1155/2015/876426
14. Fukao, H.F., Yoshida, H.Y., Tazawa, Y.T., and Hada, T.H. Antithrombotic effects of odorless garlic powder both in vitro and in vivo. Bioscience Biotechnology, and Biochemistry. 2007;71(1):84-90. DOI: https://doi.org/10.1271/ bbb.60380
15. Cordier, W., and Steenkamp, V. Herbal remedies affecting coagulation : A review. Pharmaceutical Biology. 2012;50(4):443-52.

DOI: https://doi.org/ 10.3109/13880209. 2011.611145

16. Elyasi, H., Rahimi, H., and Kiani, A.A. A review of medicinal herbs capable of preventing blood coagulation and platelet aggregation. Herbal Medicines Journal. 2017;2(4):158-65. DOI: https://doi.org/10.22087/hmj.v0i0.639
17. Stanger, M.J., Thompson, L.A., Young, A.J., and Lieberman, H.R. Anticoagulant activity of select dietary supplements. Nutrition Reviews. 2012;70(2):107–17. DOI: https://doi.org/10.1111/j.1753-4887.2011.00 444.x
18. Cavagnaro, P.A.F.C., Camargo, A.L.C., Galmarini, C.L.R.G., and Simon, P.H.W.S. Effect of Cooking on Garlic (Allium sativum L.) Antiplatelet activity and thiosulfinates content. Journal of Agricultural Food Chemistry. 2007;55(4):1280–8. DOI: https://doi.org/10.1021/jf062587s
19. Rajaram, S. The effect of Vegetarian diet, plant foods, and phytochemicals on hemostasis amd thrombosis. American Journal of Clinical Nutrition. 2003;78:552–8.
20. Agarwal, K.C. Therapeutic actions of garlic constituents. Medicinal Research Reviews 1996;16(1):111–24.
21. Apitz-castrol, R., Badimon, J.J., and Badimon, L. A garlic derivative , ajoene, inhibits platelet deposition on severely damaged vessel wall in an in vivo porcine experimental model. Thrombosis Research. 1994;75(3):243–9.
22. MacDonald, J.A., and Langler, R.F. Structure–activity relationships for selected sulfur-rich antithrombotic compounds. Biochemical and Biophysical Research Communications. 2000; 273:421–424.
23. Peng, J.P., Chen, H., Qiao, Y.Q., Ma, L.R., Narui, T., Suzuki, H., et al. Two new steroidal saponins from allium sativum and their inhibitory effects on blood coagulability. Acta Pharm. Sin. 1996;31(8):607–12.
24. Miao, Q., Wang, R., Bai, D., Xue, X., Xu, J., Sun, X., et al. Antiatherosclerosis properties of total saponins of garlic in rats. Evidance based Complementary and Alternative Medicine. 2020;2020:1-6. DOI: https://doi.org/10.1155/2020/3683659
25. Sabha, D., Hiyasat, B., Grotzinger, K., Henning L., Schlegel, F. et al. Allium ursinum L.:bioassay-guided isolation and identification of a galactolipid and a phytosterol exerting antiaggregatory effects. Pharmacology. 2012;89(5-6):260–269.
26. Allison, G.L., Lowe, G.M., and Rahman, K. Significance of garlic and its constituents in cancer and cardiovascular disease aged garlic extract and its constituents inhibit platelet aggregation through multiple mechanisms. The Journal of Nutrition. 2006;136(06):782–8.
27. Kisioglu, B., and Nergiz-unal, R. The powerful story against cardiovascular diseases : Dietary factors. Food Reviews International. 2018;34(8):713–45. DOI: https://doi.org/10.1080/87559129.2017.1410 172
28. Subramanian, S., Giri Nandagopal, M.S., Nordin, S.A., Karuppiah, T., and Joseph, N. Prevailing Knowledge on the Bioavailability and Biological Activities of Sulphur Compounds from Alliums : A Potential Drug Candidate. Molecules (Basel, Switzerland). 2020;25(18):1-15. DOI: https://doi.org/10.3390/molecules25184111
29. Khatua, T.N., Adela, R., and Banerjee, S.K. Garlic and cardioprotection : insights into the molecular mechanisms. Canadian Journal of Physiology and Pharmacology. 2013;91(3):448–58. DOI: https://dx.doi.org/10.1139/cjpp-2012-0315
30. Rahman, K. Review Effects of garlic on platelet biochemistry and physiology. Molecular Nutritio Food Research. 2007;51:1335–44. DOI: https://doi.org/10.1002/mnfr.200700058 335

31. Rahman, K., and Billington, D. Human nutrition and metabolism dietary supplementation with aged garlic extract inhibits adp-induced platelet aggregation in humans. The Journal of Nutrition 2018;130(6):2662–5.
32. Qi, R., Liao, F., Inoue, K., Yatomi, Y., and Sato, K. Inhibition by diallyl trisulfide , a garlic component, of intracellular Ca 2^{+} mobilization without formation in activated platelets. Biochemical Pharmacology. 2000;60(10):1475–83.
33. Allison, G.L., Lowe, G.M., and Rahman, K. Significance of garlic and its constituents in cancer and cardiovascular disease aged garlic extract may inhibit aggregation in human platelets. The Journal of Nutrition 2006;136:789–92.
34. Allison, G.L., Lowe, G.M., and Rahman, K. Aged garlic extract inhibits platelet activation by increasing intracellular cAMP and reducing the interaction of GPIIb/IIIa receptor with fibrinogen. Life Sciences. 2012;9:1275–80.
35. Ansari, F., Soltan, N., Naderi, G., Sadegh, M., and Karimi, A. Study of garlic effect on fibrinolytic activity of the blood clot in vitro. Iranian Journal of Pediatric Hematology Oncology. 2011;1(2):48–52.
36. Chan, K., Yin, M., and Chao, W. Effect of diallyl trisulfide-rich garlic oil on blood coagulation and plasma activity of anticoagulation factors in rats. Food and Chemical Toxicology. 2007;45:502–7.
37. Hiyasat, B., Sabha, D., Grotzinger, K., Kempfert, J., Rauwald, J.W., Mohr, F.W., et al. Antiplatelet activity of allium ursinum and allium sativum. Pharmacology. 2009;83:197–204. DOI: https://doi.org/10.1159/000196811
38. Vaijayanthimala, P., Amutha, K., Anu, M., Archana, S., Bhuvaneshwari, S., Balamurugan, T.S., et al. Invitro anticoagulant activity of allium sativum plant extract. World Journal of Pharmacy Pharmaceutical Sciences. 2017;6(9):1256–61. DOI: https://doi.org/10.20959/wjpps20179-10017
39. Song, C.S., Kim, J.H., Kim, E.S., and Lee, P.H. A blood anticoagulant substance from garlic (allium sativum) l: its preparation and studies on its anticoagulant effect. Yonsei Medical Journal. 1963;4(11):17-20.
40. Singh, G., and Chaturvedi, G.N. Journal of Ayurveda Physicians & Surgeons (JAPS) Original Research Experimental study on anticoagulant and fibrinolysis activities of garlic (allium sativum). Journal of Ayuverda Physicians & Surgeons. 2015;2(4):85–8.
41. Ali, M., and Thomson, M. Consumption of a Garlic Clove a Day Could be Beneficial in Preventing Thrombosis. Prostaglandins Leukotrienes and Essential Fatty Acids. 1995;53(4):211–2.
42. Bordia, A., Verma, S.K., and Srivastava, K.C. Effect of garlic on platelet aggregation in humans : a study in healthy subjects and patients with coronary artery disease. Prostaglandins Leukotrienes and Essential Fatty Acids. 1996;55(3):201–5.
43. Bordia, A., Verma, S.K., and Srivastava, K.C. Effect of garlic (Allium sativum) on blood lipids , blood sugar , fibrinogen and fibrinolytic activity in patients with coronary artery disease. Prostaglandins Leukotrienes and Essential Fatty Acids. 1998;58(4):257–63.
44. Wojcikowski, K., Myers, S., and Brooks, L. Effects of garlic oil on platelet aggregation : A double blind placebo controlled crossover study controlled crossover study. Platelets. 2007;18(1):29-34.