I-PREVENT℠

VACCINE INJURY

An approach to post-vaccine cardiovascular and cancer care

February 2023

FLCCC® ALLIANCE

Disclaimer

This document is primarily intended to assist healthcare professionals in providing appropriate medical care for patients who have received a COVID-19 vaccine. Patients should always consult a trusted healthcare provider before embarking on any new treatment.

There is very limited data on the clinical features, pathogenetic mechanisms, and pathological findings of patients who have had delayed complications related to the COVID-19 vaccine. In addition, there is no published guidance on how to avoid these complications. This guidance is, therefore, based on our assessment of the likely pathogenic mechanisms underlying these delayed complications (spike protein-related disease) and the limited available autopsy data.

Post-vaccine cardiovascular events and cancer

The vast majority of serious adverse events following vaccination occur in the two weeks immediately following a dose of the vaccine. We had, therefore, previously suggested that patients who had not developed any adverse events after 2-3 weeks post-vaccination had 'dodged a proverbial bullet' and did not require specific interventions to prevent vaccine injury.

However, evolving data suggests this approach may not be optimal, for two reasons. First, some patients who otherwise had no adverse events from the vaccine appear to have delayed acute cardiac events (often leading to sudden death). This appears to peak between 4 to 6 months after the vaccine but may extend for at least one year. Second, there has been evidence of an emergence of "turbo" and relapsed cancers in the months following vaccination.

The approach to preventing these serious disorders is unclear and the developers and manufacturers of these 'vaccines' obviously did not develop an 'antidote'. Nevertheless, we have developed this document to attempt to limit these complications and reassure those who have been vaccinated.

Essentially, both cardiac and cancer-related complications are related to the persistence of spike protein. Therefore, any intervention that reduces the persistence and the 'load' of spike protein will likely be beneficial.

Delayed cardiovascular complications are likely related to endothelial inflammation, endothelial damage, rupture of atheromatous plaques, and clotting leading to acute coronary events. In addition, a lymphocytic vasculitis with medial necrosis and dissection of large vessels (aorta, coronary artery) has been reported in an autopsy series (unpublished).

The cause of the increased risk of cancers is less clear, however spike protein-induced alteration in the function of tumor suppressor genes, immune depression, altered mitochondrial function, and other metabolic pathways may be involved.

Potential treatment approach

The primary approach to preventing delayed complications from vaccination is to enhance the body's ability to eliminate spike protein. This is best achieved by practicing intermittent fasting/time-restricted eating and with a supplement like resveratrol, which activates autophagy and encourages the removal of spike protein.

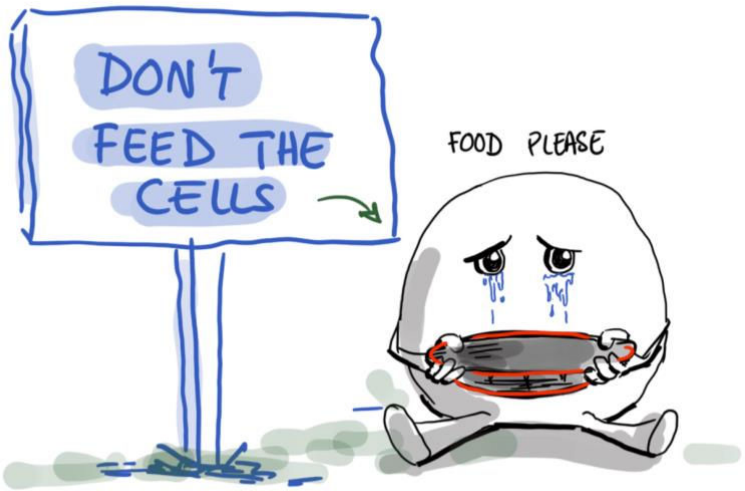
In addition, nattokinase, a naturally derived enzyme, breaks down extracellular spike protein and is a potent fibrinolytic agent, which breaks down blood clots.

Furthermore, treating hyperinsulinemia likely limits both endothelial inflammation and carcinogenesis.

We have added other interventions to this core treatment approach that likely have additional benefits. These include anti-platelet and fibrinolytic agents, which are central to the prevention of cardiovascular events following vaccination; the pharmacology, dosing, and precautions of these drugs are reviewed at the end of this document.

A suggested theoretical approach to limit the long-term complications of spike protein

- **Intermittent fasting/time-restricted eating** (activates autophagy and removal of spike protein). [1,2] For more detail, see I-RECOVER: Post-Vaccine Syndrome and an FLCCC Guide to Intermittent Fasting. Fasting should be combined with a low-carbohydrate, high-fat diet (ketogenic diet), low in Omega-6 vegetable oils (improves insulin resistance).



Source: Dr. Mobeen Syed

- **Nattokinase**; 100-200 mg twice daily.

- **Resveratrol**; 500 mg daily. Resveratrol has cardioprotective, anti-inflammatory, and anti-coagulant properties and augments autophagy. [3-8] Resveratrol also binds to spike protein, likely promoting spike removal. Generally, the oral bioavailability of resveratrol is poor. [9] However, a bio-enhanced formulation containing trans-resveratrol from Japanese Knotweed Root appears to have improved bioavailability.

- **Aspirin (ASA)**; 81 mg daily (in those with low risk of bleeding).

- **Magnesium**; 100-400 mg daily. A starting dose of 100 to 200 mg daily is suggested, increasing the dose as tolerated up to 300 mg (females) to 400 mg (males) daily. Generally, organic salts of Mg have a higher solubility than inorganic salts and have greater bioavailability. [10] Magnesium Malate, Taurate, Glycinate, and L-threonate have good bioavailability. Magnesium deficiency is associated with serious cardiac arrhythmia and all-cause cardiovascular mortality. [11,12]

- **Omega-3 fatty acids**; 2-4 g daily. Omega-3 fatty acids have anti-inflammatory properties and have been demonstrated to improve endothelial function and reduce cardiovascular events. [13-15]

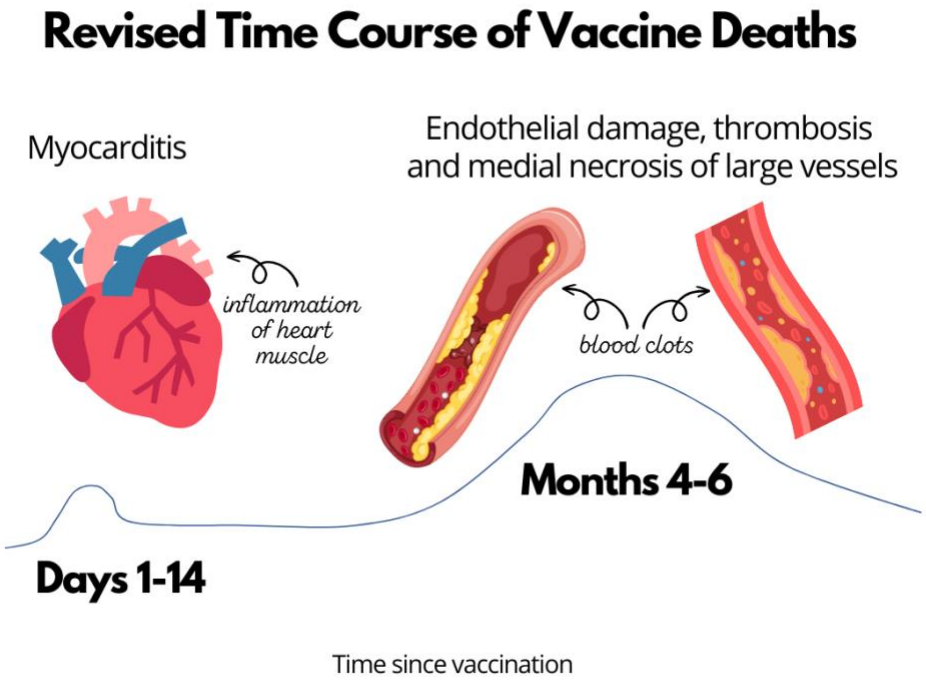
- **Co-enzyme Q (CoQ)**; 200-400 mg/day. CoQ has antioxidant, anti-inflammatory, and cardioprotective effects. [16-21]

- **Melatonin**; 3-10 mg at night (slow release/extended release). Melatonin has anti-inflammatory and antioxidant properties and is a powerful regulator of mitochondrial function with proven cardioprotective effects. [22-27]

- **Bromelain;** 500 mg twice daily +/- **N-acetyl cysteine (NAC)**; 600 mg twice daily. *In Vitro* studies have demonstrated that bromelain cleaves the spike protein. [28,29] This effect appears to be enhanced by the addition of NAC. [30]

- **Berberine**; 500-600 mg twice daily. Berberine has anti-cancer, anti-diabetic, antioxidant, and cardioprotective properties. [31-33] Avoid in patients taking cyclosporine and during pregnancy and breastfeeding. For more information see I-CARE: Insulin Resistance Treatment.

Figure 1. *Time course of sudden death following vaccination*



Antiplatelet and Fibrinolytic Agents

Anticoagulants, anti-platelet drugs, and fibrinolytic agents are central to the prevention of cardiovascular events post-vaccine. The pharmacology of these agents is briefly reviewed below. The greatest risk with the use of anticoagulants, antiplatelet drugs, and fibrinolytics is clinically significant bleeding. A number of factors increase the risk of bleeding; [34-36] these include age (> 65 years; advanced age is a major risk factor for bleeding), hypertension, renal impairment, diabetes, previous stroke, a previous bleed, and male sex. Furthermore, the risk of bleeding increases exponentially as the number of anticoagulant/anti-platelet drugs is increased. [35,37] These risk factors need to be evaluated prior to embarking on any "anticoagulant" drug.

Antiplatelet drugs:

Aspirin (ASA): ASA produces a clinically relevant antiplatelet effect by irreversibly acetylating the active site of cyclooxygenase-1 (COX-1), which is required for the production of thromboxane A2, a powerful promoter of platelet aggregation. These effects are achieved by daily doses of 75 mg (and higher). The major adverse effect is bleeding. Bleeding most commonly occurs in the gastrointestinal tract and is rarely fatal. Bleeding also occurs at other sites, with intracranial bleeding being the rarest (approximately 4 per 10,000) but the most serious (with a 50% case fatality rate).

Clopidogrel (Plavix): Clopidogrel requires *in vivo* biotransformation to an active thiol metabolite. The active metabolite irreversibly blocks the ADP receptors on the platelet surface, which prevents

activation of the GPIIb/IIIa receptor complex, thereby reducing platelet aggregation. Similar to ASA, platelets blocked by clopidogrel are affected for the remainder of their lifespan (~7 to 10 days). The usual dose is 75 mg daily.

Oral Fibrinolytic agents:

Nattokinase: Nattokinase (NK) is a serine protease purified and extracted from natto, a traditional Japanese (cheese-like) food produced from the fermentation of soybeans with the bacterium, *Bacillus subtilis*. [38-40] Recent studies demonstrated that a high natto intake was associated with decreased risk of total cardiovascular disease mortality and, in particular, a decreased risk of mortality from ischemic heart diseases. [41]

Nattokinase has potent fibrinolytic, antithrombotic, and antiplatelet activity. [38,39,42-45] NK degrades fibrin directly and also increases the release of tPA with a subsequent increase in the formation of plasmin. [46] Furthermore, NK enhances fibrinolysis through cleavage and inactivation of PAI-1. [40,45]

In a study comparing the antiplatelet effects of NK and aspirin, NK was shown to display excellent antiplatelet aggregation and antithrombotic activities in vitro and in vivo, inhibiting thromboxane B2 formation from collagen-activated platelets. [47] In addition, in both animal and human studies, NK also has antihypertensive, anti-atherosclerotic, lipid-lowering, and neuroprotective actions. [39,45,48]

Of particular relevance to patients with spike-related clotting, nattokinase causes the proteolytic cleavage of both spike protein and amyloid proteins.[49,50] In a randomized study, NK proved to be more effective than statins (simvastatin) in reducing carotid artery atherosclerosis. [51]

Chen et al demonstrated that high dose NK (10 800 Fibrinolytic Units [FU]/day; ~ 500 mg/day) reduced the thickness of the carotid artery intima-media and the size of the carotid plaque. [52] The authors reported a synergistic effect between NK and aspirin/ASA. Studies indicate that an oral administration of NK can be absorbed by the intestinal tract. [48,53] NK, unlike most proteins, is more resistant to the highly acidic gastric fluids in the stomach and can be absorbed in the later sections of the digestive tract.

The optimal dose of nattokinase is unclear, however, a dose of 100-200 mg (2000-4000 FU/day) twice daily has been suggested.

<u>*Cautions and contraindications*</u>: While NK appears to have an excellent safety profile, [52,54] bleeding has rarely been reported in patients with risk factors for bleeding (advanced age, renal failure, hypertension, concomitant ASA, etc). [55,56] High concentrations of vitamin K_2 in natto can reduce the INR when co-administered with warfarin; this may also occur with nattokinase supplements if vitamin K_2 is not removed during the production process. Information regarding safety and efficacy in pregnancy and lactation is lacking.

Lumbrokinase: Lumbrokinase derives from a group of enzymes extracted from earthworms. The enzymes are sourced mostly from the earthworm *Lumbricus rubellus*. Lumbrokinase has very similar pharmacodynamic properties to Nattokinase, i.e., it directly breaks down fibrin clots, inhibits PAI-1 activity, enhances t-PA activity, has antiplatelet activity, and proteolytically cleaves amyloid. [57-59]

The recommended dose is 300,000 to 600,000 IU/day (20-40 mg).

Lumbrokinase has been widely used for patients with acute ischemic stroke in China; however, because rigorously designed studies are lacking, the safety and efficacy of lumbrokinase remains largely unknown. [60]

As the pharmacology, clinical effectiveness, and safety of nattokinase has been assessed in a number of experimental and clinical studies, this agent is preferred over lumbrokinase.

References

1. Hannan A, Rahman A, Rahman S et al. Intermittent fasting, a possible priming tool for host defense against SARS-CoV-2 infection: Crosstalk among calorie restriction, autophagy and immune response. Immunology Letters 2020; 226:38-45.
2. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. N Engl J Med 2019; 381:2541-51.
3. Gligorijevic N, Stanic-Vucinic D, Radomirovic M et al. Role of resveratrol in prevention and control of cardiovascular disorders and cardiovascular complications related to COVID-19 disease: Mode of action and approaches explored to increase its bioavailability. Molecules 2021; 26:2834.
4. de Sa Coutinho D, Pacheco MT, Frozza RL et al. Anti-inflammatory effects of resveratrol: Mechanistic insights. International Journal of Molecular Sciences 2018; 19:1812.
5. Park D, Jeong H, Lee MN et al. Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition. Scientific Reports 2016; 6:21772.
6. Menezes-Rodrigues FS, Errante PR, Araujo EA et al. Cardioprotection stimulated by resveratrol and grape products prevents lethal cardiac arrhythmias in an animal model of ischemia and reperfusion. Acta Cirurgica Brasileira 2021; 36:e360306.
7. Kaur A, Tiwari R, Tiwari G et al. Resveratrol: A vital therapeutic agent with multiple health benefits. Drug Res 2022; 72:5-17.
8. Cheng CK, Luo JY, Lau CW et al. Pharmacological basis and new insights of resveratrol action in the cardiovascular system. Br J Pharmacol 2020; 177:1258-77.
9. Walle T. Bioavailability of resveratrol. Ann New York Acad Sci 2011; 1215:9-15.
10. Rylander R. Bioavailability of magnesium salts - A review. Journal of Pharmacy and Nutrition Sciences 2014; 4:57-59.
11. Liu M, Dudley SC. Magnesium, oxidative stress, inflammation and cardiovascular disease. Antioxidants 2020; 9:907.
12. Chrysant SG, Chrysant GS. Association of hypomagnesemia with cardiovascular diseases and hypertension. International Journal of Cardiology Hypertension 2019; 1:100005.
13. Hu Y, Hu FB, Manson JE. Marine omega-3 supplementation and cardiovascular disease: an updated meta-analysis of 13 randomized controlled trials involving 127 477 participants. J Am Heart Assoc 2019; 8:e013543.
14. Wang Q, Liang X, Wang L et al. Effect of omega-3 fatty acid supplementaion on endothelial function: A meta-analysis of randomized controlled trials. Atherosclerosis 2012; 221:536-43.
15. Zehr KR, Walker MK. Omega-3 polyunsaturated fatty acids improve endothelial funcion in humans at risk for atherosclerosis: A review. Prostaglandins & Other Lipid Mediators 2018; 134:131-40.
16. Yang YK. Coenzyme Q10 treatment of cardiovascular disorders of ageing including heart failure, hypertension and endothelial dysfunction. Clinica Chimica Acta 2015; 450:83-89.
17. Yuan S, Schmidt HM, Wood KC et al. CoenzymeQ in cellular redox regulaion and clinical heart failure. Free Radical Biology and Medicine 2021; 167:321-34.

18. Yin YJ, Zeng SL, Li YW et al. The effect of coenzyme Q10 plus trimetazidine on acute viral myocarditis treatment. Am J Transl Res 2021; 13:13854-61.
19. Gutierrez-Mariscal FM, de al Cruz-Ares S, Torres-Pena JD et al. Coenzyme Q10 and cardiovascular diseases. Antioxidants 2021; 10:906.
20. Kishimoto C, Tomioka N, Nakayama Y et al. Anti-oxidant effects of Coenzyme Q10 on experimental viral myocarditis in mice. J Cardiovasc Pharmacol 2003; 42:588-92.
21. Molyneux SL, Florkowski CM, George PM et al. Coenzyme Q10. An independent predictor of mortality in chronic heart failure. J Am Coll Cardiol 2008; 52:1435-41.
22. Molina-Carballo A, Palacios-Lopez R, Jerez-Calero A et al. Protective effect of melatonin administration against SARS-CoV-2 infection: A systematic review. Current Issues in Molecular Biology 2022; 44:31-45.
23. Hasan ZT, AlAtrakji MQ, Mehuaiden AK. The effect of melatonin on thrombosis, sepsis and mortality rate in COVID-19 patients. International Journal of Infectious Diseases 2022; 114:79-84.
24. Reiter RJ, Sharma R, Ma Q et al. Plasticity of glucose metabolism in activated immune cells: advantages for melatonin inhibition of COVID-19 disease. Melatonin Res 2020; 3:362-79.
25. Reiter RR, Sharma R, Castillo R et al. Coronavirus-19,Monocyte/Macrophage glycolysis and inhibition by melatonin. J SARS-CoV2 COVID 2021; 2:29-31.
26. Colunga Biancatelli RM, Berrill M, Mohammed YH et al. Melatonin for the treatment of sepsis: the scientific rationale. J Thorac Dis 2020; 12 (Suppl 1):S54-S65.
27. Dominguez-Rodriguez A, Abreu-Gonzales P, Baez-Ferrer N et al. Melatonin and carioprotection in humans: A systematic review and meta-analysis of randomized controlled trials. Front Cardiovasc Med 2021; 8:635083.
28. Reid PM, Borgstahl GE, Radhakrishnan P. Bromelain inhibits SARS-CoV-2 infection via targeting ACE-2, RMPRSS@, and spike protein. Clin Transl Med 2021; 11:e281.
29. Tallei TE, Yelnetty A, Idroes R et al. An analysis based on molecular docking and molecular dynamics simulation study of Bromelain as anti-SARS-CoV-2 variants. Front Pharmacol 2021; 12:717757.
30. Akhter J, Queromes G, Pillai K et al. The combination of bromelain and acetylcysteine (BromAc) synergistically inactivates SARS-CoV-2. Viruses 2021; 13:425.
31. Caliceti C, Franco P, Spinozzi S et al. Berberine: New insights from pharmacological aspects to clinical evidences in the management of metabolic disorders. Current Medicinal Chemistry 2016; 23:1460-1476.
32. Zamani M, Zarei M, Nikbaf-Shandiz M et al. The effects of berberine supplementation on cardiovascular risk factors in adults: A systematic review and dose response meta-analysis. Fronteirs in Nutrition 2022; 9:1013055.
33. Wang Y, Liu Y, Du X et al. The anti-cancer mechanisms of berberine: A review. Cancer Management and Research 2020; 12:695-702.
34. Decousus H, Tapson VF, Bergmann JF et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest 2011; 139:69-79.

35. Pisters R, Lane DA, Nieuwlaat R et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138:1093-100.
36. Whitlock EP, Burda BU, Williams SB et al. Bleeding risks with aspirin use for primary prevention in adults: A systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2016; 164:826-35.
37. Dans AL, Connolly SJ, Wallentin L et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation 2013; 127:634-40.
38. Sumi H, Hamada H, Tsushima H et al. A novel fibrinolytic enzyme (nattokinase) in the vegetable cheese Natto; a typical and popular food in Japanese diet. Experientia 1987; 43:1110-1111.
39. Weng Y, Yao J, Sparks S et al. Nattokinase: An oral antitrombotic agent for the prevention of cardiovascular disease. Int J Mol Sci 2017; 18:523.
40. Dabbagh F, Negahdaripour M, Berenjian A et al. Nattokinase: production and application. Applied Microbiology and Biotechnology 2014; 98:9199-206.
41. Nagata C, Wada K, Tamura T et al. Dietary soy and natto intake and cardiovascular disease mortality in Japanese adults: the Takayama study. Am J Clin Nutr 2017; 105:426-631.
42. Sumi H, Hamada H, Nakanishi K et al. Enhancement of the fibrinolytic activity in plasma by oral administration of nattokinase. Acta Haematol 1990; 84:139-43.
43. Hsia CH, Shen MC, Lin JS et al. Nattokinase decreases plasma levels of fibrinogen, factor VII, and factor VIII in human subjects. Nutrition Research 2009; 29:190-196.
44. Kurosawa Y, Nirengi S, Homma T et al. A single-dose of oral nattokinase potentiates thrombolysis and anti-coagulation profiles. Scientific Reports 2015; 5:11601.
45. Chen H, McGowan EM, Ren N et al. Nattokinase: A promising alternative in prevention and treatment of cardiovascular diseases. Biomarker Insights 2018; 13:1-8.
46. Yatagai C, Maruyama M, Kawahara T et al. Nattokinase-promoted tissue plasminogen activator release form human cells. Pathoyphysiol Haemost Thromb 2009; 36:227-32.
47. Jang JY, Kim TS, Cai J et al. Nattokinase improves blood flow by inhibiting platelet aggregation and thrombus formation. Lab Anim Res 2013; 29:221-25.
48. Fujita M, Ohnishi K, Takaoka S et al. Antihypertensive effects of continuous oral administraion of nattokinase and its fragment in spontaneously hypertensive rats. Biol Pharm Bull 2011; 34:1696-701.
49. Tanikawa T, Kiba Y, Yu J et al. Degradative effect of Nattokinase on spike protein of SARS-CoV-2. Molecules 2022; 27:5405.
50. Oba M, Rongduo W, Saito A et al. Natto extract, a Japanese fermented soybean food, directly inhibits viral infections including SARS-CoV-2 in vitro. Biochemical and Biophysical Research Communications 2021; 570:21-25.
51. Ren NN, Chen HJ, Li Y et al. A clinical study on the effect of nattokinase on carotid artery atherosclerosis and hyperlipidemia [Chinese, Abstract in English]. Zhonghua Yi Vue Za Zhi 2017; 97:2038-42.

52. Chen H, Chen J, Zhang F et al. Effective management of atherosclerosis progress and hyperlipidemia with nattokinase: A clinical study with 1,1062 participants. Front Cardiovasc Med 2022; 9:964977.
53. Fujita M, Hong K, Ito Y et al. Transport of nattokinase across the rat intestinal tract. Biol Pharm Bull 1995; 18:1194-96.
54. Gallelli G, Di Mizio G, Palleria C et al. Data recorded in real life support the safety of Nattokinase in patients with vascular diseases. Nutrients 2021; 13:2031.
55. Ramachandran L, Aqeel A, Jafri A et al. Nattokinase-associated hemoperitoneum in an elderly woman. Cureus 2022; 13:-e20074.
56. Chnag YY, Liu JS, Lai SL et al. Cerebellar hemorrhage provoked by combinaed use of nattokinase and aspirin in a patient with cerebral microbleeds. Inter Med 2008; 47:467-69.
57. Metkar SK, Girigoswami A, Vijayashree R et al. Attenuation of subcutaneous insulin induced amyloid mass in vivo using lumbrokinase and serratiopeptidase. International Journal of Biological Macromolecules 2020; 163:128-34.
58. Metkar SK, Girigoswami A, Murugesan R et al. Lumbrokinase for degradation and reduction of amyloid fibriles associated with amyloidosis. Journal of Applied Biomedicine 2017; 15:96-104.
59. Metkar SK, Girigoswami A, Bondage DD et al. The potential of lumbrokinase and serratiopeptidase for the degradation of AB 1-42 peptide - an invitro and insilico approach. International Journal of Neuroscience 2022.
60. Chen Y, Liu Y, Zhang J et al. Efficacy and safety of lumbrokinase plus aspirin versus aspirin alone for acute ischemic stroke (LUCENT): study protocl for a multicenter randomized controlled trial. Trials 2022; 23:285.