ThromboMAX: Collation of current literature

Date: 11 March 2022

Serra-peptidase:

- Information taken from main review paper: *Jadhav, et al., 2020*.

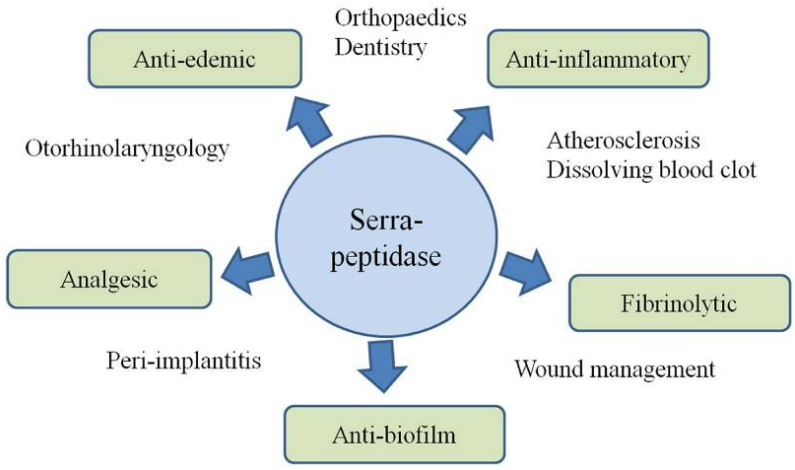

Figure 1.0 – Diagrammatic illustration of the ranging uses of serratiopeptidase, taken from Jadhav, et al., 2020.

Key Points of Interest (potential infographic use):

Mechanisms of action:

- *Wound healing:*

    - Serratiopeptidase can aid in drainage from inflamed and swollen areas by contributing to the thinning of fluids (Desser, et al., 1993).
    - Able to disband dead tissue that envelopes injured areas without harming living tissue (Desser, et al., 1993).
    - Aids in the reduction of swelling and decreases pain by hydrolysing bradykinin, histamine and serotonin (Desser, et al., 1993).

    - *Significance:*

        - Aids in the immune response to regions of swelling due to injury by increasing microcirculation, ensuring the delivery of white blood cells (immune response cells) and other appropriate constituents are delivered to the response sight.

- *Anti-Inflammatory Properties:*

    - Alters the adhesion factor of cell molecules, which are found to be involved within guided inflammatory response (Tiwari., 2017).
    - Aid in facilitating the repair and healing of wounds, as well as, homeostasis of skin temperature at sights of swelling (Tiwari., 2017).

    - *Significance:*
        - Allows for the inflammatory-response to be more accurately guided, allowing for an increased efficiency in the immune response.
        - Tries to maintain skin homeostasis at the sight of injury, possibly relieving discomfort but, more importantly, aiding in healthy microcirculation.

- *Fibrinolytic Properties:*

    - Aid in the degradation of fibrin and damaged tissue, thus, dissolving blood clots and atherosclerotic plaques (Santosh., 2018).
    - 'Arterial-cleaning effect': may dispose of cellular waste, cholesterol and other fat-based constituents from arteries (Santosh., 2018).
    - Thrombophlebitis, the risk of stroke, and thick blood are all complications that could possibly be alleviated by serratiopeptidase (Tiwari., 2017).

    - *Significance:*
        - Degradation of damaged tissue ensures no unhealthy cells are left to accumulate and possibly cause a blockage of arterial vessels.
        - Degradation of fibrin may help prevent unnecessary clotting of the blood.
        - Removal of LDL-cholesterol has been shown to be seen as a preventative measure in increasing heart health.

References:

- Jadhav. S., Shah. N., Rathi. A., Rathi. V., and Rathi., A. Serratiopeptidase: Insights into the therapeutic applications. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7585045/> [Accessed 09 March 2022]
- Tiwari., M. The role of serratiopeptidase in the resolution of inflammation. *Asian J. Pharm. Sci.* 2017; 12:209-215. Available at: < https://www.sciencedirect.com/science/article/pii/S181808761630160X?via%3Dihub> [Accessed 09 March 2022]
- Santosh., K. The emerging role of serratiopeptidase in oral surgery: literature update. *Asian J. Clin. Pharm. Res.* 2018; 11(3):19-23. Available at: < https://scholar.google.com/scholar_lookup?journal=Asian+J.+Clin.+Pharm.+Res.&title=The+emerging+role+of+serratiopeptidase+in+oral+surgery:+literature+update&author=K.+Santhosh&volume=11&issue=3&publication_year=2018&pages=19-23&> [Accessed 09 March 2022].
- Desser. L., Rehberger. AA., Kokron. E., Paukovits. W., Cytokine synthesis in human peripheral blood mononuclear cells after oral administration of polyenzyme preparations. *Oncology*. 1993; 50:403-407. Available at: < https://scholar.google.com/scholar_lookup?journal=Oncology.&title=Cytokine+synthesis+in+human+peripheral+blood+mononuclear+cells+after+oral+administration+of+polyenzyme+preparations&author=L.+Desser&author=A.+Rehberger&author=E.+Kokron&author=W.+Paukovits&volume=50&publication_year=1993&pages=403-407&pmid=7694216&> [Accessed 09 march 2022].

1-Octasanol:

- Information taken from main review paper: Taylor, et al., 2003.

Key Points of Interest (potential infographic use):

Mechanisms of action:

- *Lipid-Lowering Properties:*
    - Serum cholesterol levels were found to be reduced significantly by those administered with policosanol (Hernandez, et al., 1992).
    - 20mg dosing found LDL levels to be lowered, while HDL concentrations were increased – this effect was profound and significant (Hernandez, et al., 1992).
    - Tolerance capabilities of all subjects was good (Hernandez, et al., 1992).
    - One study found that, when combined with a low-fat diet, policosanol proved to have: lowered LDL concentration, increased LDL:HDL ratio and total cholesterol : HDL ratio more successfully than pravastatin (Castano, et al., 1999).
    - Possible proposal to utilise policosanol in those with Type-2 Hypercholesterolemia and coronary risk – seeing as its effects aid in lowering risk factors associated with atherosclerosis (Castano, et al., 1999).
    - *Significance:*

        - The lowering of serum LDL-cholesterol levels, and the increase of serum HDL-cholesterol levels, have been linked to preventing cardiovascular disease (Blesso, et al., 2018).
        - Lowering LDL and increasing HDL helps reduce the formation of atherosclerotic plaques within arteries (Blesso, et al., 2018).

- *Anti-Aggregatory Properties:*

    - 20mg dose of policosanol found adenosine diphosphate (ADP)-, collagen- and epinephrine-induced platelet aggregation to be significantly reduced (Arruzazabala, et al., 1997).
    - Overdose of policosanol could lead to excessive thinning of the blood, and thus, provoke haemorrhage-based problems. Corollary, policosanol and anti-coagulation medication should not be taken synergistically.
    - A reduction in cardiac events within a twenty-month window – thought to be due to octasanol's ability to lower blood lipids, reduce arterial stiffness, and anti-aggregatory effects (Saint-John, et al., 1986)

    - *Significance:*

        - Aggregation is a component of the atherogenesis response. Platelet activation is stimulated via collagen-binding at the location of vesical injury – forming thromboxane-2 and ADP. These two constituents enhance the platelet response further. Sometimes this can either: be in excess or remain after injury. Both can result in clot formations occurring.

References:

- Arruzazabala ML, Valdes S, Mas R, et al. Compaative study of policosanol, aspirin and the combination therapy policosanol-aspirin on platelet aggregation in healthy volunteers. *Pharmacol Res*. 1997:36

- Taylor. J.C., Rapport. L., and Lockwood. B. Octacosanol in Human Health., 2003. *Nutrition*. 19(2):192-195. Available at: <https://www.sciencedirect.com/science/article/pii/S0899900702008699> [Accessed 09 March 2022].

- Saint-John M and McNaughton L. Octacosanol ingestion and its effects on metabolic responses to sub-maximal cycle ergometry, reaction time and chest and grip strength. *Int Clin Nutr Rev.* 1986;6:81

- Hernandez F, Illait J, Mas R, et al. Effect of policosanol on serum lipids and lipoproteins in healthy volunteers. *Curr Ther Res*. 1992;51:568

- Carbajal D, Molina V, Valdes S, et al. Anti-ulcer activity of higher primary alcohols of beeswax. *J Pharm Pharmacol*. 1995;47:731

- Castano G, Mas R, Arruzazabala M de L, et al. Effects of policosanol and pravastatin on lipid profile, platelet aggregation and endothelemia in older hypercholesterolemic patients. *Int J Clin Pharm Res.* 1999;4:105

- Blesso. C.N and Fernandez. M. L., 2018. Dietary cholesterol, Serum Lipids, ad Heart Disease: Are Eggs Working for or Against You? *Nutrients*. 10(4): 426. Available at: < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5946211/> [Accessed 11 March 2022].

Nattokinase:

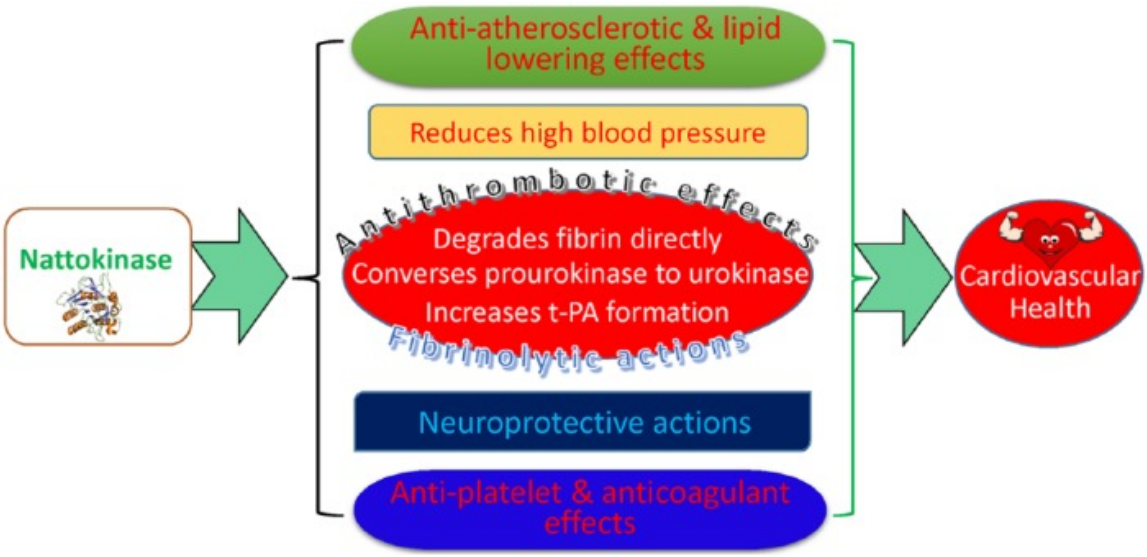

Figure 2.0 – Flow-diagram of the pharmacological effects of nattokinase taken from Chen, et al., 2018.

Key Points of Interest (Potential Infographic Use):

Mechanisms of action:

- *Fibrinolytic / Anti-thrombotic Properties:*
    - Nattokinase (NK) is involved in the direct degradation of fibrin (Fujita, et al., 1995).
    - NK results in the upregulated release of tissue plasminogen activator (tPA), which in turn, stimulates plasmin production (Yatagai, et al., 2008).
    - tPA is repressed by plasminogen activator inhibitor-1 (PAI-1) which, in turn, controls the fibrinolytic cascade (Tjarnlund, et al., 2012).
    - NK was found to prohibit and cleave PAI-1, thus, increasing the efficacy of fibrinolysis (Urano, et al., 2001).
    - The conversion of prourokinase to urokinase, by NK, was found to increase the efficacy of clot-dissolving properties (Fujita, et al., 1995 and Milner, et al., 2002).
    - NK shows an anti-aggregatory effect due to its ability to inhibit thromboxane synthesis – preventing the aggregation of platelets and mitigating the negative side-effect of bleeding (Jang, et al., 2013).
    - NK also lowers plasma euglobulin lysis time (ELT) – the time in which it takes for a clot to lyses (Sumi, et al., 1990).
    - Levels of factor VII, factor VIII and fibrinogen were all reduced two-months post-supplementation with NK – suggesting a strong usage for cardiovascular health (Hsia, et al., 2009).
    - The degradative products of blood fibrin were shown to be present post-oral consumption of NK at 2000 FU within four-hours ($p < 0.05$) – indicating an increased anti-coagulation effect was present (Kurosawa, et al., 2015).
    - *Significance:*
        - Degradation of fibrin may help prevent unnecessary clotting of the blood.
        - Plasmin is an enzyme that plays a role within fibrinolysis.
        - Fibrinolysis is a mechanism where fibrin is broken down enzymatically in blood clots.

        - Thromboxane B2 formation occurs when collagen-bound platelets bind to the site of vessel wall injury – increasing aggregation and increasing risk of blood clotting. Therefore, NK inhibiting thromboxane may prove beneficial.

- *Anti-Atherosclerotic Properties:*
    - Daily consumption of NK has shown to hinder atherosclerotic effects within individuals who suffer from atherosclerotic plaques (Ren, et al., 2017).
    - 26-week follow up showed a reduction in common carotid artery intima-media thickness and the size of carotid plaques (Ren, et al., 2017).
    - *Significance:*
        - Reduced plaque size increases blood flow and reduces the hypertensive-induced state associated with blood clots.

- *Lipid-Lowering Properties:*
    - NK contributed to the lowering of LDL and total cholesterol, while increasing levels of HDL (Ren, et al., 2017).
    - In order for profound effects to be observable for lowering lipid-profiles, higher doses may be required.
    - *Significance:*
        - The lowering of serum LDL-cholesterol levels, and the increase of serum HDL-cholesterol levels, have been linked to preventing cardiovascular disease (Blesso, et al., 2018).
        - Lowering LDL and increasing HDL helps reduce the formation of atherosclerotic plaques within arteries (Blesso, et al., 2018).

- *Anti-Hypertensive Properties:*
    - NK has been found to impact the renin-angiotensin system by mitigating levels of angiotensin-converting enzyme (ACE) – an enzyme that synthesises angiotensin II (Okamoto, et al., 1995).
    - The consumption of NK orally, for an 8-week course, found both systolic and diastolic blood pressure levels to decreases – suggesting a use for NK as a preventative measure in hypertension (Kim, et al., 2008).

- Significance:
    - Angiotensin II raises blood pressure mainly by sympathetic nervous stimulation, vasoconstriction and renal actions. Therefore, by mitigating the synthesis of ACE, the formation of angiotensin II is reduced.

- *Anti-Platelet Properties:*
    - Collagen-activated platelets produce thromboxane B2, however, this has been shown to be inhibited by NK due to its anti-platelet and anti-thrombotic capabilities (Jang, et al., 2013).

    - *Significance:*
        - Thromboxane B2 formation occurs when collagen-bound platelets bind to the site of vessel wall injury – increasing aggregation and increasing risk of blood clotting. Therefore, NK inhibiting thromboxane may prove beneficial.

References:

- Fujita M, Hong K, Ito Y, Fujii R, Kariya K, Nishimuro S. Thrombolytic effect of nattokinase on a chemically induced thrombosis model in rat. *Biol Pharm Bull*. 1995;18:1387–1391. Available at: < https://scholar.google.com/scholar_lookup?journal=Biol+Pharm+Bull&title=Thrombolytic+effect+of+nattokinase+on+a+chemically+induced+thrombosis+model+in+rat&author=M+Fujita&author=K+Hong&author=Y+Ito&author=R+Fujii&author=K+Kariya&volume=18&publication_year=1995&pages=1387-1391&pmid=8593442&> [Accessed 10 March 2022].
- Tjarnlund-Wolf A, Brogren H, Lo EH, Wang X. Plasminogen activator inhibitor-1 and thrombotic cerebrovascular diseases. *Stroke*. 2012;43:2833–2839. Available at: < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3712849/> [Accessed 10 March 2022].
- Urano T, Ihara H, Umemura K, et al. The profibrinolytic enzyme subtilisin NAT purified from *Bacillus subtilis* cleaves and inactivates plasminogen activator inhibitor type 1. *J Biol Chem*. 2001;276:24690–24696. Available at: < https://scholar.google.com/scholar_lookup?journal=J+Biol+Chem&title=The+profibrinolytic+enzyme+subtilisin+NAT+purified+from+Bacillus+subtilis+cleaves+and+inactivates+plasminogen+activator+inhibitor+type+1&author=T+Urano&author=H+Ihara&author=K+Umemura&volume=276&publication_year=2001&pages=24690-24696&pmid=11325965&> [Accessed 10 March 2022].
- Milner M, Makise K. Natto and its active ingredient nattokinase: a potent and safe thrombolytic agent. *Alternat Complement Therap*. 2002;8:157–164. Available at: < https://scholar.google.com/scholar_lookup?journal=Alternat+Complement+Therap&title=Natto+and+its+active+ingredient+nattokinase:+a+potent+and+safe+thrombolytic+agent&author=M+Milner&author=K.+Makise&volume=8&publication_year=2002&pages=157-164&> [Accessed 10 March 2022].

- Jang JY, Kim TS, Cai J, et al. Nattokinase improves blood flow by inhibiting platelet aggregation and thrombus formation. *Lab Anim Res*. 2013;29:221–225. Available at: < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879341/> [Accessed 10 March 2022].
- Sumi H, Yanagisawa Y, Yatagai C, Saito J. Natto *Bacillus* as an oral fibrinolytic agent: nattokinase activity and the ingestion effect of *Bacillus subtilis natto*. *Food Sci Technol Res*. 2004;10:17–20. Available at: < https://scholar.google.com/scholar_lookup?journal=Food+Sci+Technol+Res&title=Natto+Bacillus+as+an+oral+fibrinolytic+agent:+nattokinase+activity+and+the+ingestion+effect+of+Bacillus+subtilis+natto&author=H+Sumi&author=Y+Yanagisawa&author=C+Yatagai&author=J.+Saito&volume=10&publication_year=2004&pages=17-20&> [Accessed 10 March 2022].
- Hsia C-H, Shen M-C, Lin J-S, et al. Nattokinase decreases plasma levels of fibrinogen, factor VII, and factor VIII in human subjects. *Nutr Res*. 2009;29:190–196. Available at: < https://www.ncbi.nlm.nih.gov/pubmed/19358933> [Accessed 10 March 2022].
- Kurosawa Y, Nirengi S, Homma T, et al. A single-dose of oral nattokinase potentiates thrombolysis and anti-coagulation profiles. *Sci Rep*. 2015;5:11601. Available at: < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4479826/> [Accessed 10 March 2022].
- Ren N, Chen H, Li Y, McGowan E, Lin Y. A clinical study on the effect of nattokinase on carotid artery atherosclerosis and hyperlipidaemia. *Nat Med J China*. 2017;97:2038–2042. Available at: < https://www.ncbi.nlm.nih.gov/pubmed/28763875> [Accessed 10 March 2022].
- Okamoto A, Hanagata H, Kawamura Y, Yanagida F. Anti-hypertensive substances in fermented soybean, natto. *Plant Foods Hum Nutr*. 1995;47:39–47. Available at: < https://www.ncbi.nlm.nih.gov/pubmed/7784396> [Accessed 10 March 2022].
- Kim JY, Gum SN, Paik JK, et al. Effects of nattokinase on blood pressure: a randomized, controlled trial. *Hypertens Res*. 2008;31:1583–1588. Available at: < https://www.ncbi.nlm.nih.gov/pubmed/18971533> [Accessed 10 March 2022].

- Jang JY, Kim TS, Cai J, et al. Nattokinase improves blood flow by inhibiting platelet aggregation and thrombus formation. *Lab Anim Res*. 2013;29:221–225. Available at: < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879341/> [Accessed 10 March 2022].

Pcynogenol:

Key Points of Interest (Potential Infographic Use):

Mechanisms of action:

- *Anti-oxidative Properties:*
    - May support cognitive function due to its ability to protect against oxidative stress by: being a free radical scavenger; preventing DNA from oxidative damage; upregulate enzymes with anti-oxidant properties; offer support to other endogenous antioxidants from oxidative stress (Packer, et al., 1999 and Rohdewald., 2002).

References:

- Rohdewald. P., 2002. A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. *Int J Clin Pharmacol Ther. 2002 Apr; 40(4):158-68.* Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11996210/> [Accessed 10 March 2022].
- Packer L, Rimbach G, Virgili F., 1999. Antioxidant activity and biologic properties of a procyanidin-rich extract from pine (Pinus maritima) bark, pycnogenol. *Free Radic Biol Med. 1999 Sep; 27(5-6):704-24.* Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10490291/> [Accessed 10 March 2022].