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Research Article

In Vitro Anti-Clot Effects of Ginger Extract, Ginger-Derived Nanoparticles, and Alteplase on Human Blood

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Abstract
The result of clot weight show significant difference between treatment groups, in alteplase show the least value of clot weight 0.09 ±0.02 mg In lower concentration between treatment groups and in high concentration 0.02 ±0.00 mg , while in Ginger derived Nanoparticles show 0.14 ±0.02 mg in lower concentration between treatment groups and in high concentration 0.03 ±0.00 mg, and ginger extract show highest clot weight with 0.19 ±0.05 mg in lower concentration between treatment groups and in high 0.14 ±0.0 mg and the positive control at zero time with 0.20 ±0.04 mg. Hemoglobin quantity show significant difference post 30 min. and post 45 min. increase in post 45 min. and show significant difference between the treatment groups, in alteplase show the highest value of Hemoglobin quantity 0.620 ±0.10 mg/dl post 45 min. and 0.220 ±0.03 mg/dl post 30 min., while in Ginger derived Nanoparticles show o.400 ±0.10 mg/dl post 45 min. and 0.280 ±0.04 mg/dl post 30 min, and ginger extract show less with 0.380 ±0.09 mg/dl post 45 min. and 0.280 ±0.06 mg/dl post 30 min. and the least positive control with 0.040 ±0.02 mg/dl post 45 min. and 0.620 ±0.10 mg/dl post 30 min. Fibrinogen quantity show significant difference post 30 min. and post 45 min. decrease in post 45 min. and show significant difference between the treatment groups, in alteplase show the least value of Fibrinogen quantity 16.70 ±1.43 mg/dl post 45 min. and 18.36 ±1.14 mg/dl post 30 min., while in Ginger derived Nanoparticles show 17.65 ±1.17 mg/dl post 45 min. and 19.60 ±1.16 mg/dl post 30 min, and ginger extract show less with 22.62 ±1.01 mg/dl post 45 min. and 23.07 ±0.92 mg/dl post 30 min. and the highest positive control with 25.74 ±0.26 mg/dl post 45 min. and 26.06 ±0.24 mg/dl post 30 min. Fibrin quantity show significant difference post 30 min. and post 45 min. increase in post 45 min. and show significant difference between the treatment groups, in alteplase show the highest value of Fibrin quantity 82.49 ±3.82 mg/dl post 45 min. and 74.81 ±7.53 mg/dl post 30 min., while in Ginger derived Nanoparticles show 70.45 ±5.81 mg/dl post 45 min. and 62.36 ±4.74 mg/dl post 30 min, and ginger extract show less with 25.45 ±3.16 mg/dl post 45 min. and 21.72 ±2.35 mg/dl post 30 min. and the least positive control with 5.14 ±0.80 mg/dl post 45 min. and 5.59 ±0.63 mg/dl post 30 min.

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Introduction

Ginger (*Zingiber officinale*) has been used in traditional medicine for centuries due to its various pharmacological properties, including anti-inflammatory, antioxidant, and antiplatelet effects (AL-Bayaty, 2006; Al-Bayar, 2009; Nafia, 2012). there has been growing interest in beneficial effect of nanoparticles (Raheem and Hasan, 2021).) , as well as,

development of ginger-derived nanoparticles (GNPs) as a novel drug delivery system to enhance the therapeutic efficacy of ginger compounds,.

Alteplase, a recombinant tissue plasminogen activator, is a commonly used thrombolytic agent for the treatment of acute ischemic stroke and myocardial infarction. It works by activating the fibrinolytic system, leading to the dissolution of blood clots (Thiebaut *et al.*, 2018).
This study aims to investigate the *in vitro* anti-clot effects of ginger extract (Fawzi, 2009; Al-Saigh, 2012), GNPs, and alteplase on human blood (MustafaAl-Najjar *et al.*, 2016). This study provides evidence for the in vitro anti-clot effects of ginger extract and GNPs (JAAFAR *et al.*, 2020). These findings suggest that ginger-based therapies may have potential as natural anticoagulants (Al-Nimer *et al*., 2011). Further research is needed to evaluate the in vivo efficacy and safety of ginger extract and GNPs in animal models and human clinical trials (Sabino and Popat, 2020; Sabino *et al.*, 2019; Damodaran *et al.*, 2013).

Methodology

Evaluating Whole Blood anticlot *in vitro* on bio clot surfaces (Sabino and Popat, 2020)
blood taken from human 24 ml and distributed equally on four plate-well in 1 ml on each well without anticoagulant and let it until obtain clot, as in figure 1, weight it before treated, apportionment to four groups figure 2 below:

1. Group treated with Ginger extract in concentrations; 0.2%, 0.3%, 0.4%, 0.5%, 0.6% with self-control.
2. Group treated with Ginger-derived Nanoparticles (GDNPs) in concentrations; 0.2%, 0.3%, 0.4%, 0.5%, 0.6% with self-control.
3. Group treated with Alteplase in concentrations; 0.2%, 0.3%, 0.4%, 0.5%, 0.6% with self-control.
4. Group positive control with each group as control treated with normal saline.

Figure 1: Clot formation pre lysis

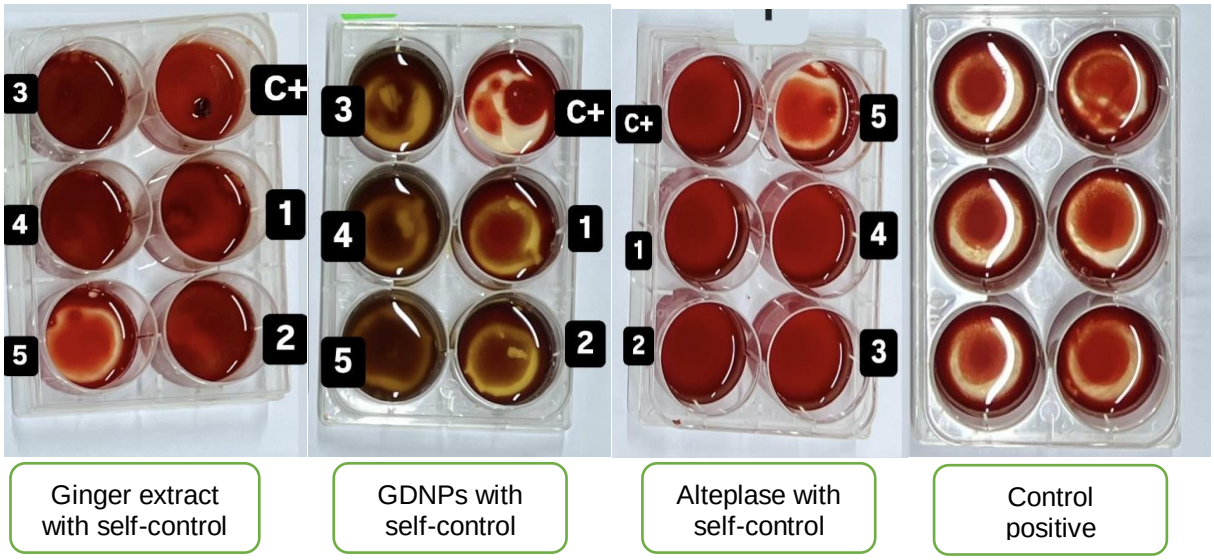

Figure 2: Clot lysis post 30 minutes, clot grouping and treatments, the sign C+ refer to self-control in all treated group and 1,2,3,4,5 refer to the concentration 0.2%, 0.3%, 0.4%, 0.5%, 0.6%in respectively.

Every 10 min. shaking the palate gently for 30 sec. in circling once to the left and once to the right (Sabino and Popat, 2020).

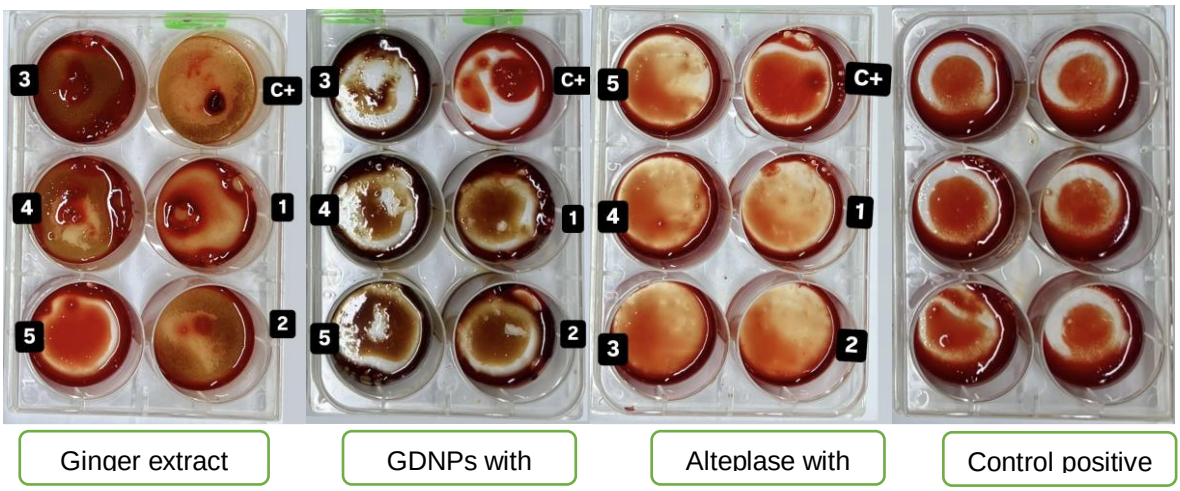

Figure 3: Clot lysis post 45 minutes, clot grouping and treatments, the sign C+ refer to self-control in all treated group and 1,2,3,4,5 refer to the concentration 0.2%, 0.3%, 0.4%, 0.5%, 0.6%in respectively.

Preparation of sample for experiment parameters

Evacuation a part of the solution everywhere the clot after 30 min. to evaluate the lysis of clot by accounting hemoglobin, platelet liberations, metabolomics and determine of fibrin and fibrinogen quantity (Sabino and Popat, 2020).

Evacuation another part of the solution everywhere the clot after 45 min. to evaluate the lysis of clot by accounting hemoglobin, platelet liberations, metabolomics and determine of fibrin and fibrinogen quantity (Sabino and Popat, 2020).

Take the residual clot in figure 3, for calculate the present of lysis by weighting it before and after treatment, using the following equation (Fernandez et al., 2019):

$$lysis\ percent = \frac{clot\ weight\ befor\ lysis\ - clot\ weight\ after\ lysis}{clot\ weight\ befor\ lysis} \times 100\%$$

Experiment parameters: by using autoanalyzer (hemolysis) device without using anticoagulant and using ELISA technique and fibrinogen, fibrin kit.

Results

The clot weight, Clot lysis present, fibrin quantity and fibrinogen quantity profile of post-lysis and induced lysis via ginger extract, ginger derived nanoparticles, alteplase, in Figure: (4, 5, 6, 7, 8, 9, 10 and 11) respectively. post-lysis generally showed nonsignificant of normal values ($p<0.05$) and followed by inducing lysis via treated group the result show significantly ($p>0.05$) lysis in their present as compared with post-lysis present and control group.

Clot weight: The results of Clot weight were expensed as Log dose response curve displayed in figure 4, GE, GDNPs, and Alteplase show significant decrease in clot weight as compared to control group in all dosed concentration.

The GDNPs Showed significant ($p\leq0.05$) reduced the clot weight in dosed concentrations as compared to control and GE, but lower clot weight comparison with Alteplase except the Concentration (0.6%) was No significant ($p\leq0.05$) of clot weight as compared with Alteplase.

The figure 4.5 Shows the visual lysis of Bio whole Blood lysis, post 30 minutes treated as dose dependent with the lysis and- fragmented Clot showed detonation clot mass and stability and promised induced dissolution or break down in composition structure of clot integrity, show in figures

Clot lysis present: Clot lysis in figure 5 Showed significant ($p\leq0.05$) increase lysis percentage in GE, GDNPs and Alteplase as doses Concentrations dependent. The results of lysis percentage were expensed as Log dose response curve displayed in figure 5, GE, GDNPs, and Alteplase show significant increase in clot lysis percentage as compared to control group in all dosed concentration.

The GDNPs Showed significant ($p\leq0.05$) increase the clot lysis percentage in dosed concentrations as compared to control and GE, but more clot lysis percentage comparison with Alteplase except the Concentration (0.6%) was No significant ($p\leq0.05$) of clot lysis percentage as compared GE with Alteplase, figure 5:

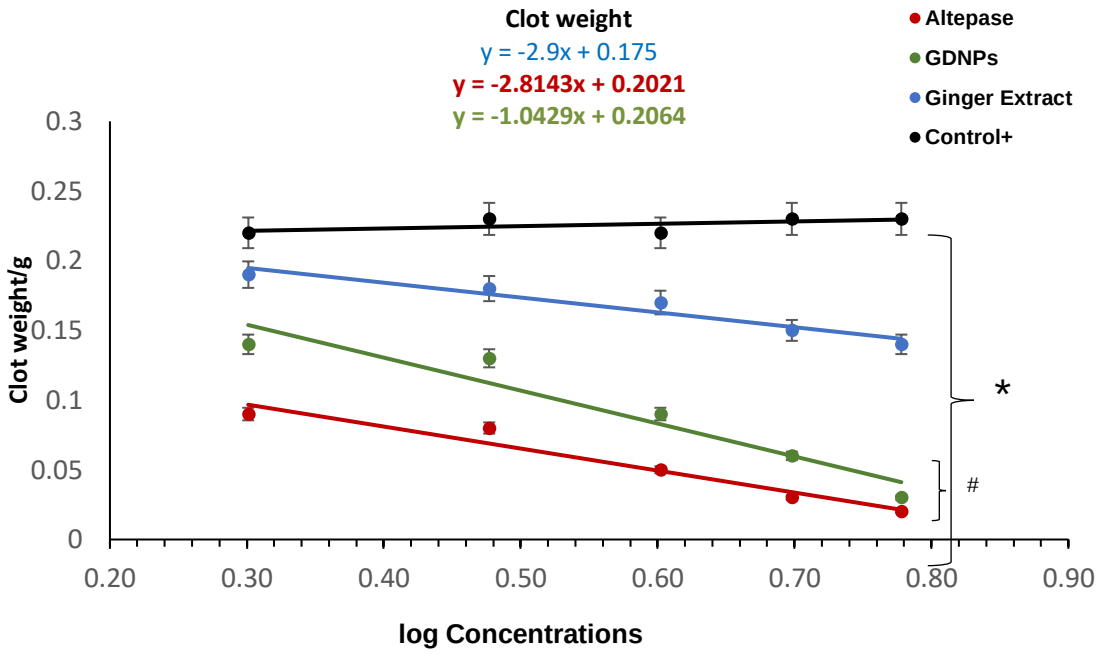

Figure 4: Clot weight indices after treated with Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 45 minutes. Clot weight/g after treated with Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 45 minutes, n =5, the data represented mean ± stander error, the star refer to significant references between treated groups significances (P≤0.05), # denoted non-significant (P>0.05) between groups.

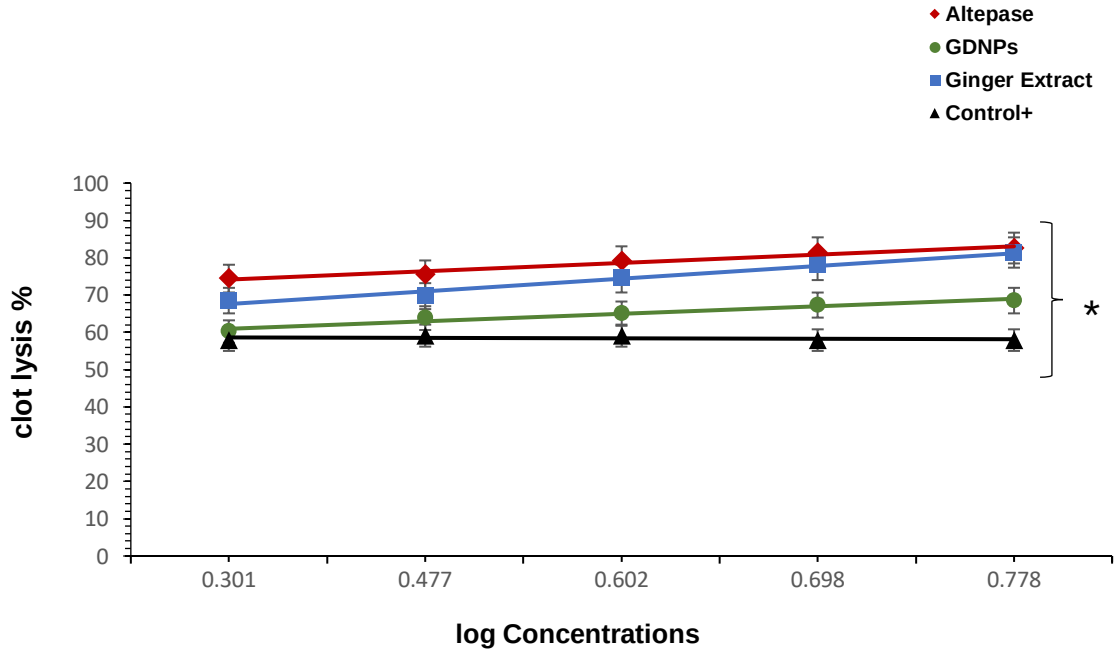

Figure 5: Clot lysis indices after treated with Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 45 minutes. Clot weight/g after treated with Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 45 minutes, n =5, the data represented mean ± stander error, the star refer to significant references between treated groups significances (P≤0.05), # denoted non-significant (P>0.05) between groups.

Hemoglobin quantity : The results of hemoglobin liberation were expensed as Log dose response curve, GE, GDNPs, and Alteplase show significant decrease in hemoglobin liberation as compared to control group in all dosed concentration.

The GDNPs Showed significant (p≤0.05) reduced the hemoglobin liberation in dosed concentrations as compared to control and GE, but lower hemoglobin liberation comparison with Alteplase except the Concentration (0.6%) was No significant (p≤0.05) of hemoglobin liberation as compared with Alteplase post 30 minutes, figure 6 and 7:

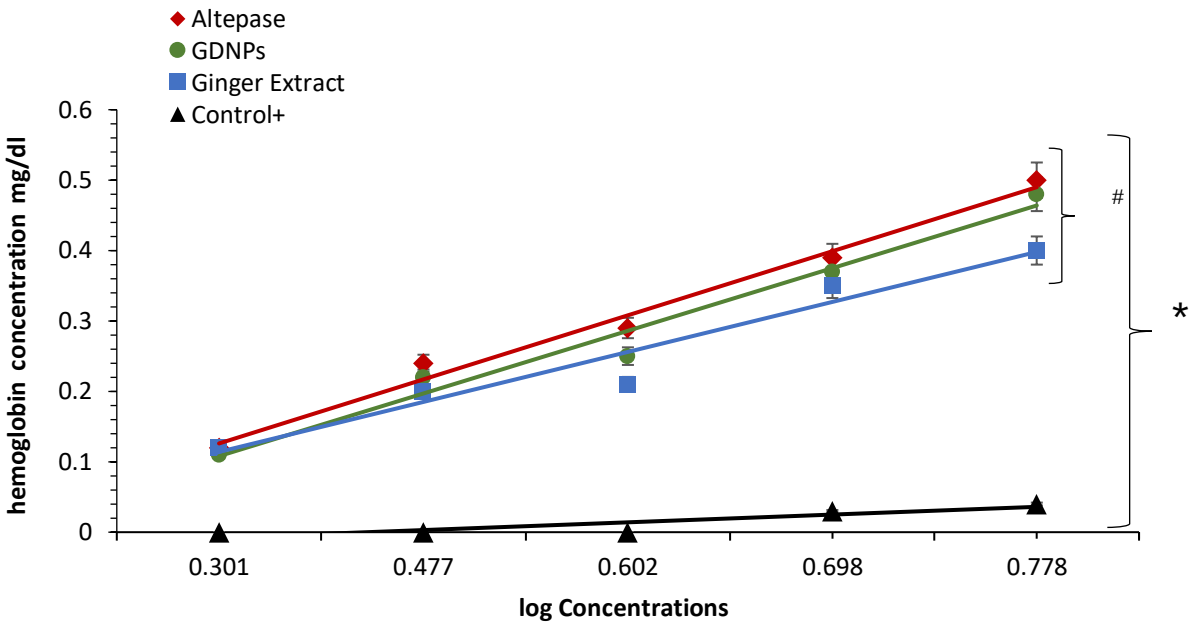

Figure 6: The Log dose response curve of Hemoglobin concentration post exposure of Ginger extract, Ginger Nanoparticles, Alteplase and control Post 30 minutes. Hemoglobin concentration after treated with Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 30 minutes, n =5, the data represented mean ± stander error, the star refer to significant references between treated groups significances (P ≤0.05), # denoted non-significant (P>0.05) between groups.

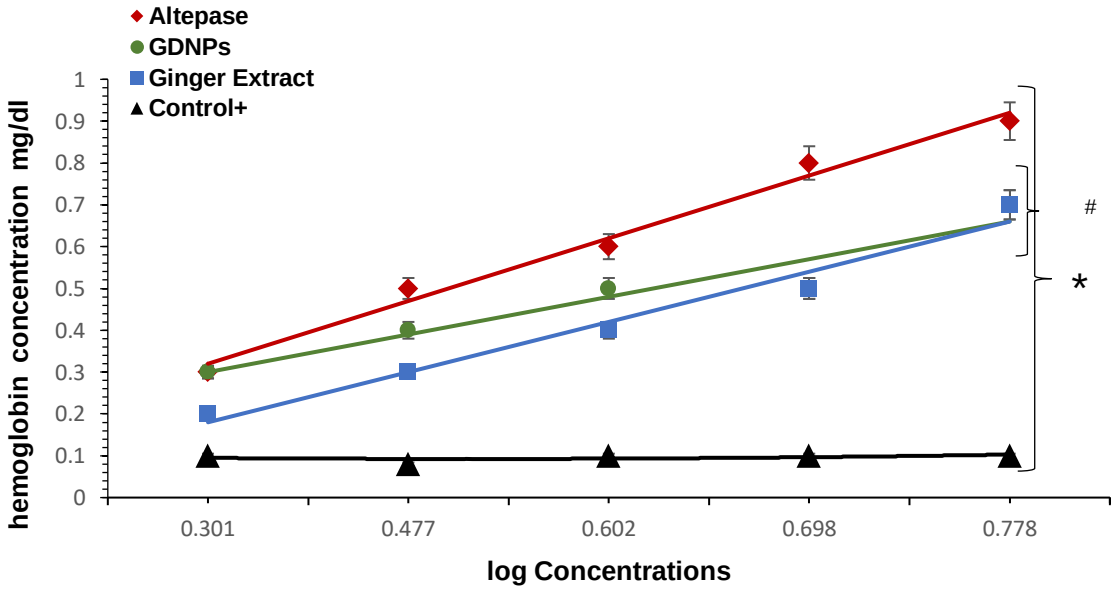

Figure 7: The Log dose response curve of Hemoglobin concentration post exposure of Ginger extract, Ginger Nanoparticles, Alteplase and control Post 45 minutes. Hemoglobin concentration after treated with Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 45 minutes, n =5, the data represented mean ± stander error, the star refer to significant references between treated groups significances (P ≤0.05).

Fibrinogen quantity: The results of fibrinogen quantity liberation were expensed as Log dose response curve displayed in figure 8 and 9, GE, GDNPs, and Alteplase show significant decrease in fibrinogen quantity liberation as compared to control group in all dosed concentration.

The GDNPs Showed significant (p≤0.05) reduced the fibrinogen quantity liberation in dosed concentrations as compared to control and GE, but lower fibrinogen quantity liberation comparison with Alteplase post 30 minutes and post 45 minutes except the Concentration (0.6%) was No significant (p≤0.05) of fibrinogen quantity liberation as compared with Alteplase post 30 minutes.

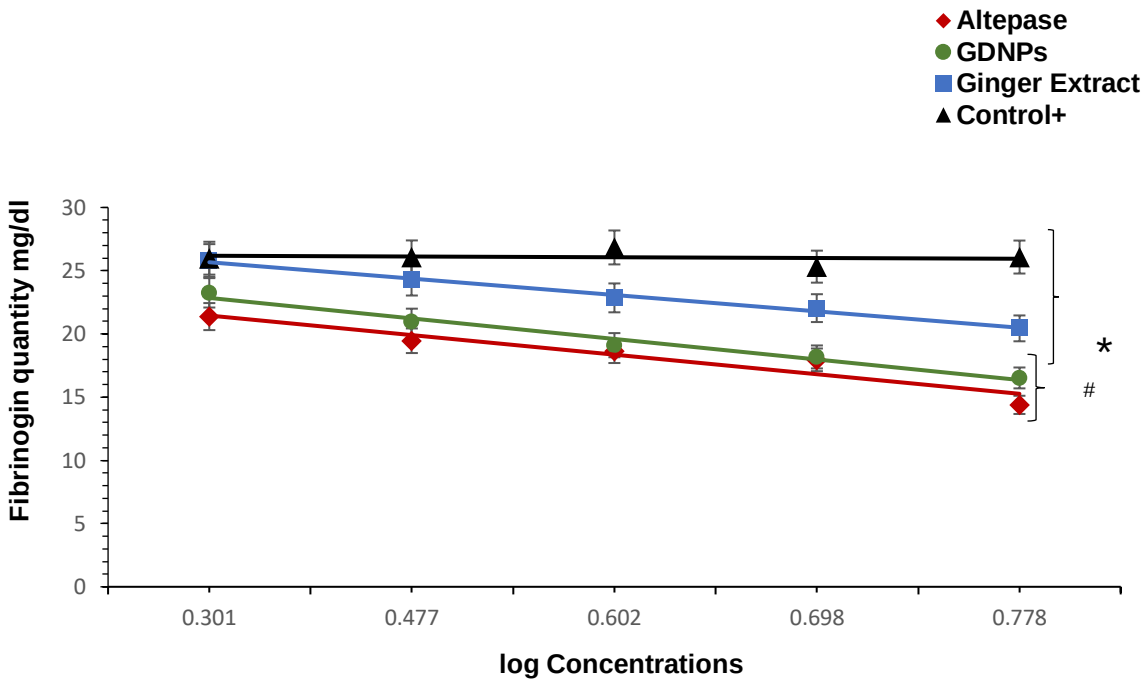

Figure 8: The Log dose response curve of fibrinogen quantity post exposure of Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 30 minutes. Fibrinogen quantity mg/dl after treated with Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 30 minutes, n =5, the data represented mean ± stander error, the star refer to significant references between treated groups Significances (P ≤0.05), # denoted non-significant (P>0.05) between groups.

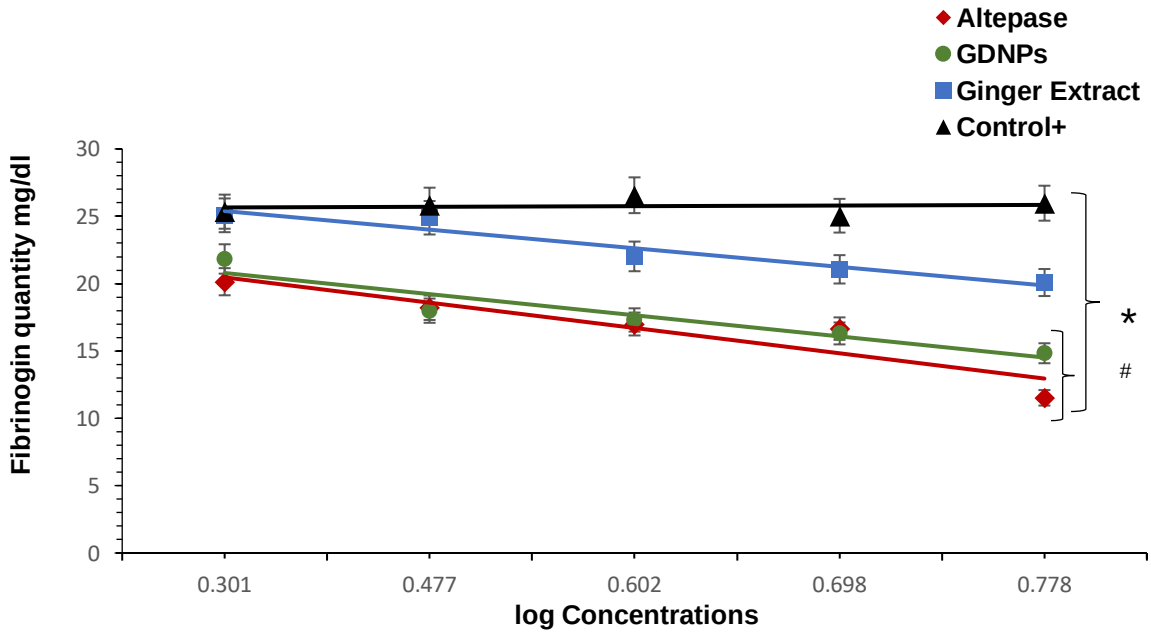

Figure 9: The Log dose response curve of fibrinogen quantity post exposure of Ginger extract, Ginger derived Nanoparticles, Alteplase and control post 45 minutes. Fibrinogen quantity mg/dl after treated with Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 30 minutes, n =5, the data represented mean ± stander error, the star refer to significant references between treated groups Significances (P≤0.05).

Fibrin quantity: The results of fibrin liberation from clot were expensed as Log dose response curve displayed in figure 10 and 11, GE, GDNPs, and Alteplase show significant increase in fibrin liberation from clot as compared to control group in all dosed concentration.

The GDNPs showed significant (p≤0.05) reduced the fibrin liberation from clot in dosed concentrations as compared to control and GE, but high fibrin liberation from clot comparison with Alteplase post 30 minutes and post 45 minutes except the Concentration (0.6%) was No significant (p≤0.05) of fi fibrin liberation as compared with Alteplase post 30 minutes.

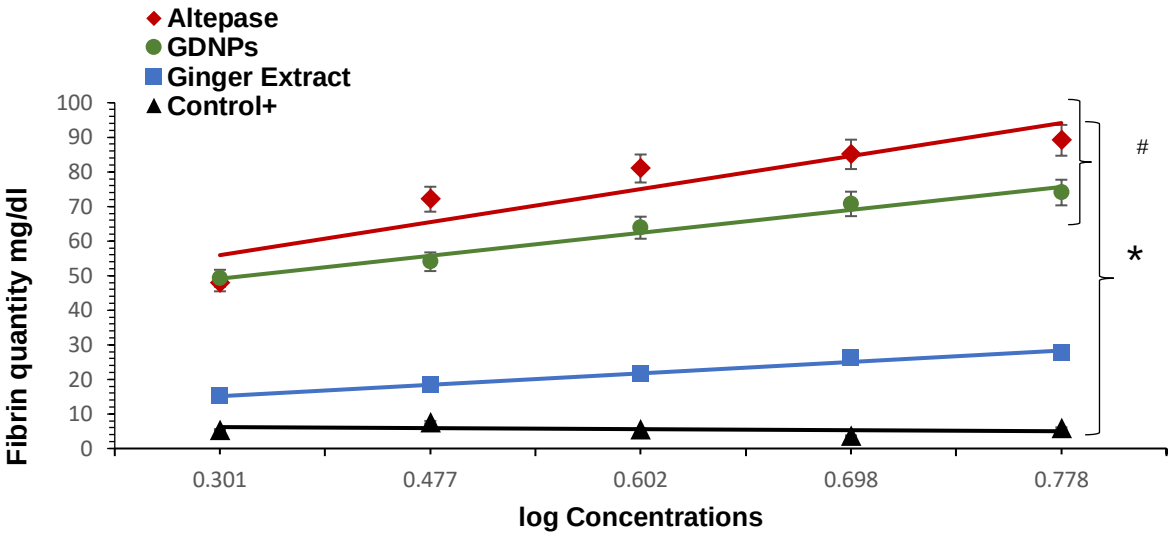

Figure 9: The Log dose response curve of fibrin concentration post exposure of Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 30 minutes. Fibrin quantity mg/dl after treated with Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 30 minutes, n =5, the data represented mean ± stander error, the star refer to significant references between treated groups Significances (P ≤0.05).

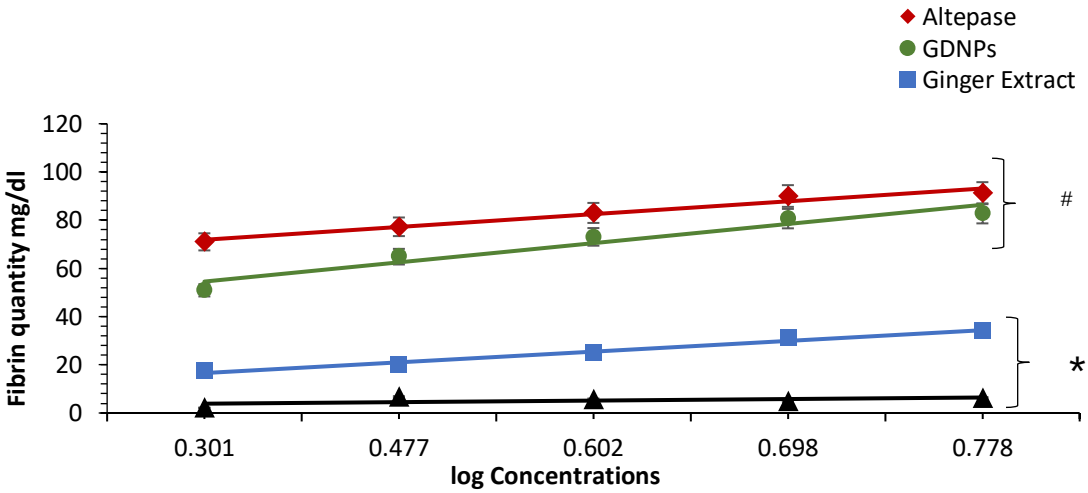

Figure 10: The Log dose response curve of fibrin concentration post exposure of Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 45 minutes. Fibrin quantity mg/dl after treated with Ginger extract, Ginger derived Nanoparticles, Alteplase and control Post 30 minutes, n =5, the data represented mean ± stander error, the star refer to significant references between treated groups significances (P ≤0.05), # denoted non-significant (P>0.05) between groups.

Discussion

Ginger Extract Compounds on Clot Formation:

While ginger extract itself may not directly interfere with the enzymatic cascade of fibrin formation, certain bioactive compounds within ginger, particularly phenolic compounds gingerols and shogaols, can exert indirect effects on clot formation through their anti-inflammatory and anti-platelet properties.

1. Anti-inflammatory Effects and Clot Formation: many facts may be endorsed on the forming clot inhibition by ginger active compounds

- Inhibition of Cyclooxygenase (COX) Enzymes: Gingerol and shogaol presumably have been shown to inhibit the activity of COX enzymes, particularly COX-2 (Srivastava, 2010). COX-2 plays a crucial role in the production of prostaglandins, such as thromboxane A2 (TXA2), which is a potent platelet aggregator and vasoconstrictor. By inhibiting COX-2, ginger compounds reduce TXA2 synthesis, leading to decreased platelet aggregation and potentially influencing clot stability and size (Tao, 2007).

- Inhibition of Leukotriene Synthesis: Ginger compounds also may be inhibiting lipoxygenase (LOX) enzymes, which are involved in the synthesis of leukotrienes. inflammatory mediators potent Leukotrienes, that contributing the aggregation of platelet, vasoconstriction, and vascular permeability increasing, all of which can affect clot formation and stability (Shah, 2023).

Ginger's Impact on Blood Clotting: Unpacking Its Anti-Platelet Actions

Ginger exhibits significant antiplatelet capabilities that can impede the development of blood clots. This is achi eved through multiple processes involving compounds i ncluding gingerol and shogaol (Koo *et al.*, 2001). Thes e active components function by initially decreasing the

activity of phospholipase A2.an enzyme that is crucial for the production of both prostaglandins and thromboxane (Nievergelt *et al.*, 2011). Moreover, ginger compounds can obstruct the activities of the GPIIb/IIIa receptor, necessary for platelet adhesi on and aggregation (Beura *et al*., 2023). Research indic ates that certain constituents of ginger may affect intrac ellular c.AMP levels, which leads to reduced platelet ac tivation as well as aggregation (Townsend *et al.*, 2014). This complete method underscores the essential role of ginger in inhibiting excessive blood clot formation.

Indirect Effects on Coagulation Factors:

Ginger's impact on blood clotting was not limited to just platelets; it seems it might also have an indirect effect on various coagulation factors. Although research is still in its early stages, some evidence suggests that ginger compounds could stimulus these influence factors. That was hypothesized that through their ability to reduce inflammation and platelet activation, the active ingredients in ginger can subtly alter the performance of coagulative factors involved in both the intrinsic and extrinsic pathways of the coagulation process. This implies that the effects of ginger on blood clotting may be more comprehensive (Phang, 2013).

Impact on Clot Stability:

The reduced platelet aggregation and modulation of inflammatory mediators by ginger compounds may lead to the formation of less stable clots. This could be beneficial in certain conditions, such as atherosclerosis, where excessive clot formation can lead to thrombosis. However, it is crucial to note that excessive inhibition of clot formation can increase the risk of bleeding (Asada *et al*., 2020).

Molecular attribution of how ginger extract compounds may inhibit clot and thrombus formation, Inhibition of Platelet Function by Ginger Compounds (Ahmad et al., 2022):

Ginger compounds, particularly gingerols and shogaols, have been shown to exert anti-platelet effects through various mechanisms:

Ginger compounds Inhibition of Platelet Aggregation:

Inhibition of Cyclooxygenase (COX) enzymes: Ginger compounds inhibit COX enzymes, particularly COX-1 and COX-2, leading to reduced thromboxane A2 (TXA2) production. TXA2 can potent platelet agonist which playing a crucial role in aggregation of platelet and vasoconstriction (Scridon, 2022).

Phospholipase A2 Inhibition: Ginger bioactive compounds can inhibit enzyme phospholipase A2, an enzyme which releases arachidonic acid, the prostaglandins precursor and thromboxanes (Tao, 2007).

Inhibition of GPIIb/IIIa receptor activation: Ginger compounds may interfere with the activation of the GPIIb/IIIa receptor, a crucial receptor involved in platelet adhesion and aggregation (Beura *et al*., 2023).

Ginger chemicals can alter intracellular signalling path ways associated with platelet activation, including the p rotein kinase C (PKC) and mitogen-activated protein kinase (MAPK) pathways. (Pázmándi *et al*., 2024).

Ginger compounds was documented the Modulation of Coagulation Factors: While less extensively studied, ginger compounds may also indirectly influence coagulation factors by modulating inflammatory responses (Fakhri *et al*., 2021).

The treated groups by Nano lipid drive ginger were share several superior result as thrombolytic and anti-clots with their belonging that generally attributed to nano-behavior which were approved the Nanolipid-Driven Delivery of Ginger Extracts: A Promising Approach It contains a plethora of bioactive compounds, including different phenolic compounds gingerols, shogaols, and paradols, and other compounds, which exhibit various pharmacological properties (MS and MR, 2024). However, the bioavailability and therapeutic efficacy of these compounds can be limited due to factors such as poor oral absorption, rapid metabolism, and low stability (Samota *et al*., 2024).

Nanolipid-based delivery systems offer a promising approach to overcome these limitations. These systems consist of lipid-based nanoparticles, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid emulsions, which can encapsulate and protect bioactive compounds, including ginger extracts.

Potential Advantages of Nanolipid-Driven Ginger Delivery:

Enhanced Bioavailability: Nanolipid carriers can significantly enhance the oral bioavailability of ginger compounds by improving their absorption across biological barriers, such as the intestinal epithelium. This can be achieved through various mechanisms, including:

Increased cellular uptake: Nanolipid carriers can interact with cell membranes more efficiently than free ginger compounds, facilitating their uptake by cells (Al-Ziyadi *et al.*, 2024).

Protection from degradation: The lipid matrix can protect encapsulated ginger compounds from degradation by enzymes and harsh environmental conditions in the gastrointestinal tract.

Targeted delivery: Nanolipid carriers can be engineered to target specific tissues or organs, such as the liver or inflammatory sites, thereby improving the delivery of ginger compounds to the desired site of action (Bahr *et al*., 2024).

Enhanced Stability: Nanolipid carriers are essential fo r safeguarding ginger compounds from oxidation and d egradation, hence improving their stability and prolongi ng its therapeutic effects. (Ekrami *et al.*, 2023).

Reducing Side Effects: Nanolipid carriers can considerably decrease systemic a dverse effects and enhance treatment outcomes by distri buting ginger components in a regulated and targeted m anner.

Sustained Release: Nano lipid carriers are engineered to release ginger com ponents in a controllable and sustained design, resulting in extended therapeutic advantages and reducing the nec essity for frequent administration. The clinical use of na no lipid carriers for the delivery of ginger extracts has s hown enhanced anti-inflammatory effects across various circumstances, parti cularly in enhancing anti

clot efficacy, as previously observed (Shazwani *et al*., 2 024). Nanolipid-
based delivery systems offer an efficacious solution to o vercome the constraints of traditional methods. Solid lip id nanoparticles (SLNs) and nanostructured carrier lipid (NLCs) encapsulate ginger extracts in a lipid matrix, en hancing their stability, bioavailability, and targeted deliv ery (Samota *et al.*, 2024). The administration of ginger e xtracts via nanolipid systems enhances their antithromb otic and anti-
clot properties through multiple mechanisms.

Enhanced Bioavailability: Nanolipid carriers enhance the oral bioavailability of gi nger components by safeguarding them from degradati on. The lipid matrix protects ginger components from e nzymatic degradation and adverse gastrointestinal symp toms (Gul *et al*., 2024).

Improved Absorption: Nanolipid carriers enhance the absorption of ginger co mponents through biological barriers, including the inte stinal epithelium, so improving their cellular uptake. Targeted Delivery: carriers of Nanolipid can be engineered to target specific tissues, such as the vascular endothelium, so enhancing the localised conce ntration of ginger components at the intended site of act ion (Ashfaq *et al.*, 2023).

Sustained Release: These carriers facilitate the sustained release of ginger i ngredients, ensuring therapeutic concentrations are pres erved in the bloodstream during an extended duration an d diminishing the frequency of delivery. (Quach *et al.*, 2022).

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