International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 05-03-2019; Accepted: 08-04-2019
www.medicalsciencejournal.com
Volume 5; Issue 5; May 2019; Page No. 29-33

Anti-thrombotic effects of *Camellia sinensis* (Tea): A systematic review

Kipyegon Shadrack[1], Alkizim Faraj[2], Kigundu Alex[3], Ngure Kenneth[4], Karuguti Wallace[5]
[1-2] Department of Medical Physiology, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya
[3] Department of Pharmaceutical Chemistry and Pharmaceutics, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya
[4] Department of Public Health and Community Health, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya
[5] Department of Physiotherapy, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya

Abstract
Tea, a product of *Camellia sinensis* is the second most consumed drink globally after water. It has so many documented medicinal uses including but not limited to anti-inflammatory, anti-oxidative, anti-carcinogenic and cardiovascular effects. Studies have also reported it to have antithrombotic activity. Thrombosis which refers to intravascular coagulation is implicated in the development of many cardiovascular disorders like ischemic heart disease. Prevention of these diseases can be achieved by use of antithrombotic drugs like aspirin and clopidogrel. This study reviews the antithrombotic effects of *Camellia sinensis*. Five databases were searched for articles to review. Those articles whose titles were pre-qualified were subjected to the Population, Intervention, Comparison and Outcome (PICO) screening hence further qualifying 19 articles. 10 articles were left out during retrieval of full text articles and the 9 obtained and subjected to methodological appraisal which resulted to qualification of 5 experimental studies. Each of these studies reported at least one antithrombotic effect with 2 sets registering similar results. Anti-platelet and anticoagulant effects are examples of antithrombotic effects reported in these studies. Since this review has shown that *Camellia sinensis* has antithrombotic properties, suggestion can be made that regular consumption of tea reduces risk of developing ischemic heart diseases.

Keywords: *Camellia sinensis*, tea, thrombosis, coagulation

1. Introduction
Tea, a product of *Camellia sinensis* plant is one of the most consumed drinks across the globe, second only to water (Ibrahim *et al*., 2017) [14] (Anu & Mendhulkar, 2015) [2]. *Camellia sinensis* is grown in tropical and subtropical climates where it one of the main commercial crop in these regions. Teas of good quality are grown in areas of high altitude up to 1500 meters (Namita, Mukesh, & Vijay, 2012) [20]. Extracts of tea have been shown to be of benefit to health since it has anti-inflammatory, anti-oxidative, anti-carcinogenic and cardiovascular benefits (Mosawy, Gaiz, Karaksha, & Singh, 2016) [19]. Tea produces flavonoids and other anti-oxidants which reduces the risks of coronary artery disease (Ibrahim *et al*., 2017) [14]. The cardiovascular benefits of tea in reducing the coronary artery disease are also attributed to its anticoagulant and thrombolytic effects (Sherwani, Bashir, Haider, Shah, & Kazmi, 1996) [24].
Thrombosis refers formation of a blood clot inside the blood vessel and this process utilizes the mechanisms of hemostasis in its development (ISTH, 2014) [15]. Hemostasis is an important process in the body that helps to curb bleeding. Accumulation of platelets at the site of injury is normally the first event of hemostasis and the events that follow are mediated by the blood coagulation pathway (Intrinsic and extrinsic) (Hou, Carrim, Wang, Gallant, & Marshall, 2015) [12] (Pierce *et al*, 1999) [21]. The process of hemostasis is designed to prevent loss of blood following breach of vascular wall as in the case of trauma (Hoffman & Iii, 2001) [9]. Thrombosis even though it employs hemostatic mechanisms is undesired because it occurs even if there is no discontinuity of the vascular wall. Any disruption in the integrity of the endothelium like rupture of an atherosclerotic plaque can lead to thrombosis (Gawaz, 2004) [5]. This process of thrombosis is implicated as the underlying mechanism in the development of many cardiovascular disorders like myocardial infarction and stroke (ISTH, 2014) [15] (Wagner & Burger, 2003) [25].
Cardiovascular diseases result from an abnormality in blood vessel or the heart and they include stroke, ischemic heart disease, and peripheral vascular disease (Hartley, 2013) [6].
These thrombotic cardiovascular diseases are responsible for a significant number of deaths around the world (Sherwani *et al*., 1996) [24]. Globally, approximately 17 million deaths were caused by cardiovascular diseases in 2010 translating 29.6% of all deaths (Hartley, 2013) [6]. The Framingham heart trial has demonstrated that there is a 50% chance for males and 30% chance for females above 40 years to develop coronary artery disease. Occlusion of the vessels by atheromatous plague with subsequent coagulation and thrombus formation is the main cause of coronary artery diseases (Homoud, 2008) [10].
Prevention of these diseases hence can be achieved by using agents that inhibit thrombosis (ISTH, 2014) [15]. Presently globally; anticoagulant drugs and antiplatelet drugs serve a very critical role in the management of patients with thrombotic disorders (Anu & Mendhulkar, 2015) [2].
Blood disorders and thrombotic cardiovascular diseases are on the rise and the use of preventive medications is not without risks owing to the side effects that result from prolonged use of these medications (Mosawy *et al*., 2016) [19]. For instance, aspirin which is a popular antithrombotic drug used can cause gastrointestinal ulceration.

Conventional drugs are also costly hence might not be affordable to those of lower socioeconomic status (Ransanooyira and Muthunayake, 2013) [27] (Farrugia, Hons, & Uic, 1999) [4]. This contributes to non-compliance to medication hence leading to increased morbidity and mortality from thrombotic diseases. Therefore other ways of preventing these diseases ought to be devised and use of regularly consumed foods and drinks is a candidate. Foods or drinks that offer additional health benefits are of great value if they are to be used for prevention of diseases. This is because users are more likely to comply and also the need to look for other funds to source the conventional drugs will not be necessary. Some studies have demonstrated the antithrombotic effects of tea, a product of *Camellia sinensis*. The purpose of this study is to review the anticoagulant effects of *Camellia sinensis*. The findings of this review will be utilized by policy makers and health workers for the interest of the public. At personal level, persons with or with the propensity to develop coagulation disorders and vascular diseases will utilize the findings of this review either to avoid or consume tea accordingly.

1.1 Review question

Does *Camellia sinensis* (tea) possess any antithrombotic effect?

2. Methods

Five databases were searched for articles between November and December 2018. They include Google scholar, Science direct, PubMed, Hinari, Africa journal online (AJOL) and access to global online research in agriculture (AGORA). All these databases were accessible either being free online or through subscriptions.

The primary search key terms used were "effects', "antithrombotic" and *Camellia sinensis*". Alternative key words used included "outcomes, tea and "anti-coagulant". The primary and secondary search generated 1598 articles as shown in the table below.

Table 1: Data bases showing number of articles it generated

Primary Search						
Database	**Scholar**	**Hinari**	**Agora**	**Ajol**	**Science Direct**	**Pubmed**
Number of studies	1007	2	4	1	154	6
Secondary Search						
Data Base	**Scholar**	**Hinari**	**Agora**	**Ajol**	**Science Direct**	**Pubmed**
Number of studies	287	0	2	5	128	2
Total	1294	2	6	6	282	8

All the generated articles had their titles screened for suitability and 1520 articles were eliminated hence remaining with 78 studies whose abstracts were subjected to PICO (population, intervention, comparison and outcome) review. The 78 articles prequalified during title screening were considered for inclusion because they shared close wording with the current study and also were written in English language.

The 78 abstracts were then sourced and examined to assess their fitness for inclusion in this study. PICO (population, intervention, comparison and outcome) level of evidence tool was used to assess the abstracts' suitability. Studies that utilized human population as the study subjects scored the highest for population. Animal based studies were also considered for inclusion. The right intervention i.e. administration of *Camellia sinensis* to the study subjects was a key factor to note during the scoring exercise. Intervention scored highly if it was assessing in vivo outcomes. Those describing the in vitro effects were also considered. A study that attained PICO score of at least 6 out of 10 was considered significant for further examination. This step led to the reduction of the number of abstracts from 78 to 19. The full texts of those abstracts that passed PICO screening were then obtained and a further 10 articles were left out during this retrieval because either their full text version was not available or accessible to the author.

2.1 Methodological appraisal

The full texts of 9 articles were the obtained and subjected to methodological appraisal. The suitability of these articles for inclusion was considered if the study employed an experimental design. True experimental study designs were assessed using the critical appraisal tool by critical appraisal skill program (CASP, 1994) [30] and a score of 7 out of 11 was critical for inclusion in the study. Quasi experimental study designs were evaluated using the same tool by CASP and still a score of 7 out of 11 was considered significant.

Recruitment of the study was done if only it answered most of the questions in the critical appraisal tools used. For instance, studies whose population was human scored highly. Animal studies were also included if they answered the correct question i.e. "what effect of camellia on thrombosis?' had to be the question and the answer obtained from the study would be addressing that question. After this exercise, a total of 5 studies were considered suitable for inclusion and an analysis of their findings was done.

Articles subjected to methodological appraisal are presented in table 2.

Table 2: Articles subjected to methodological appraisal

NO:	**Title of the article**	**Author**	**Study design**	**Journal**	**Critical appraisal score Maximum score= 11**
1	The effect of green tea consumption on coagulation profile among adult healthy Sudanese	(Ibrahim *et al*., 2017) [14]	Quasi experimental	International Journal of Applied Research	8
2	Anticlotting properties of Sri Lankan low grown orthodox orange pekoe grade tea (*Camellia sinensis* Linn)	(Ratnasooriya & Muthunayake 2013) [27]	True experimental	World Journal of Pharmaceutical Sciences	9

3	In vitro Studies on Antibacterial, Thrombolytic and Antioxidant Activities of Green Tea or *Camellia sinensis*	(Hossain & Mahmood, 2014) [11]	True experimental	American Journal of Phytomedicine and Clinical Therapeutics	5
4	Effects of regular ingestion of tea on haemostasis and cell adhesion molecules in humans	(Hodgson *et al*., 2001) [8]	True experimental	European Journal of Clinical Nutrition	5
5	In vitro anti-platelet aggregation activity of the extracts of *Camellia sinensis*	(Anu & Mendhulkar, 2015) [2]	True experimental	Research in Biotechnology	8
6	In vitro anticlotting activity of Sri Lankan high grown tea.	(Ratsooyira *et al*, 2007) [26]	True experimental	Sri- Lanka (Google scholar)	8
7	Apolipoprotein E genotype modulates the effect of tea drinking on blood lipids and blood coagulation factors: a pilot study	(Loktionov *et al*., 2017) [17]	True experimental	British Journal of Nutrition	6
8	The Green Tea Extract Epigallocatechin Gallate Inhibits Human Platelet Function but not Plasma Coagulation	(Mosawy *et al*., 2016) [19]	True experimental	International Journal of Prevention and Treatment	7
9	Investigation of Cytotoxic and Thrombolytic Effect of Ethanolic Extract of White Tea	(Sayeed, Mamun, Rashid, & Taiseer, 2013) [23]	True experimental	International Journal of Advances in Pharmaceutical Research	5

3. Results

Five articles met the threshold for inclusion in the study and there outcomes were discussed. Other articles were omitted owing to their low quality. All articles that attained a score of equal to or more than 7 in the critical appraisal exercise were considered of good quality and included in the results. The results are presented in the table 3 below;

Table 3: Articles included in the study

NO:	Objective	Study design	Methods/sample details	Findings	Reference
1	To assess the effect of green tea consumption on coagulation profile among adult healthy Sudanese	Quasi experimental	Sample was randomly obtained from healthy adult Sudanese population (n=30) (male =18, female =12). Fibrinogen level was taken before intervention (tea consumption) and after one month of tea consumption.	There was statistically significant difference between the means of fibrinogen levels before the intervention(339.9±62.5) and after intervention (310.6±47.9) Also differences between men and women	(Ibrahim *et al*., 2017) [14]
2	To evaluate the anticlotting properties of Sri Lankan low grown orthodox orange pekoe grade tea (*Camellia sinensis* Linn)	True experimental	Invivo study- Adult witsar rats were used in the experimental study. Animals were divided into 4 groups. One group (control) was given distilled water and the remaining 4 groups were administered with different doses of tea brew. Clotting time was then done at different times. In vitro study- citrated goat blood was assigned into 6 groups (n=42-64). Five groups were mixed with different concentrations of tea brew (Treatment) and one group was mixed with isotonic saline (control). Calcium induced clotting was the assessed.	**In vitro** study- Higher concentration of back tea significantly prolonged the clotting with some samples not clotting even after 24 hours. Low concentration however did not register any significant differences. **In vivo-** clotting time was significantly prolonged by mid dose concentration and low dose concentrations of tea	(Ratnasooriya *et al* 2013) [27]
3	To assess the in vitro anti-platelet aggregation activity of the extracts of *Camellia sinensis*	Quasi experimental	Healthy human volunteers were used in the study. 6 groups (N=12/group) of blood samples were obtained. One group (negative control) was treated with distilled water. Another group (positive control was treated with aspirin and the remaining groups were treated with various concentrations of extracts of *Camellia sinensis* leaves. ADP was then used to induce platelet aggregation and the extent of this aggregation was assessed using a platelet aggregometer.	All concentrations of *Camellia sinensis* leaves extracts significantly inhibited platelet aggregation in a reverse dose dependent manner. Highest degree of inhibition was observed in the lowest concentration which actually surpassed inhibition by aspirin (the reference drug)	(Anu & Mendhulkar, 2015) [2]
4	To investigate the in vitro anticlotting activity of Sri Lankan high grown tea	True experimental	7 samples of blood (4 Ml/sample) were obtained and citrated by adding sodium citrate solution. 6 different concentrations of tea were then prepared. 6 samples of citrated blood were treated with 1Ml of different concentrations of tea and one was mixed with isotonic saline (control). Clotting was then induced by adding calcium solution and clotting was checked every 30 seconds by gently tilting the test tube	Low concentrations of tea did not significantly prolonged clotting time. Significant difference was however noted in tea of 2.5mg/ml concentration where no clot had formed in 10 minutes	(Ratnasooyira *et al*, 2007) [26]

5	To investigate the effects of green tea extract epigallocatechin Gallate (EGCG) on platelet aggregation and activation and plasma coagulation times	True experimental	Blood samples were obtained from healthy volunteers (N=6) Platelet rich plasma (PRP)were then obtained via centrifugation PRP was then incubated with different concentration of ECGG extract, vehicle control after a baseline platelet aggregation was obtained Platelet aggregation was induced using ADP and its degree assessed using light transmission aggregometry. Platelet activation was also assessed by checking on the expression of P-selectin. Prothrombin time and APTT were also assessed	Two concentrations of ECGG extract 50 and 100 micrograms significantly inhibited platelet aggregation compared to the baseline and or vehicle control. This extract of *Camellia sinensis* also significantly inhibited platelet activation. However, there was no significant change in coagulation times	(Mosawy *et al*., 2016) [19]

4. Discussion

This review has shown that *Camellia sinensis* posseses anti-thrombotic ability. Various studies reviewed reported an antithrombotic value of tea. Slight variation in results was witnessed among different studies and this could be attributed to the variation in the methods utilized by different researchers. However, at least one anti-antithrombotic property was reported in each of the studies reviewed.

There was significant decrease in the serum fibrinogen levels compared to baseline after ingestion of green tea by healthy human subjects (Ibrahim *et al*., 2017) [14]. Fibrinogen is a large globulin that is utilized in the formation of fibrin. It is proteolytically cleaved to fibrin monomers by thrombin. Fibrin monomers then spontaneously polymerize to form fibrin mesh which participates in the formation of the final clot. Therefore, the low levels of fibrinogen increase the likelihood of bleeding while hyperfibrinogenemia translates to hypercoagulability (Williams and Wilkins, 2003) [29]. The findings of this study concur with those of Jalali *et al*, 2008 [16] and Ayat *et al*, 2014 [3]. They however conflict with the observation by Maat *et al*, 2000 [18] which did not register any change in fibrinogen levels between treatment and control groups. Ibrahim *et al*, 2017 [14] suggest that the discrepancies in results of these two studies could be attributed to the different study populations employed as that of Maat *et al* [18] utilized smokers as their study participants. Smoking tobacco has been documented to increase the likelihood of blood coagulation. It does so by stimulating the release inflammatory cytokines which in turn leads to high levels of fibrinogen (Ambrose & Barua, 2004) [1]. These pro-fibrinogenic effects of smoking could have negated the anti-fibrinogenic effects of *Camellia sinensis* in the Maat *et al* [18] study.

Ratnasooriya *et al*, 2013 [27] reported that tea significantly inhibited coagulation both in vivo and in vitro. In their study tea consumption significantly prolonged clotting time. Clotting time is the time it takes for blood sample to clot after coming in contact with a clot activator like the negatively charged surface of a test tube. It is prolonged in states of qualitative and quantitative dysfunctions of coagulation factors (Saxena, Kannan, & Choudhry, 2007) [2, 28]. This study did not suggest the mechanism by which tea achieves its anti-coagulant properties. Therefore, suggestion can be made that *Camellia sinensis* could be inhibiting the action of, or slowing the synthesis of these coagulation proteins. It possessed more anticoagulant activities in vitro compared to in vivo. The more potent anticoagulant activity seen in the in vitro study could mean that the metabolism of tea extracts in the body in the in vivo study lowers its anticoagulant activity. The body also may be producing procoagulant substances that inhibit the anticoagulant activity of *Camellia sinensis* extracts. The findings in this study agree with those of Ratnasooriya *et al* 2007 [26] which reported in vitro anticlotting effects of tea. The similarity in the results of these two studies is possibly due to the similarity in the ways the two studies were carried out. Both studies involved use of anti-coagulated goat blood. Different doses of tea brew were the added to the blood and coagulation times measured. Furthermore, both studies were carried out by the same author.

Platelets play a vital role in coagulation in that they adhere to the injured endothelium, activate and aggregate to form platelet plug (Hou *et al*, 2015) [12]. This platelet plug then forms the initial barrier of blood loss following an injury (Heemskerk, Bevers, & Lindhout, 2014) [7]. This review has shown that tea possesses anti-platelet aggregation ability. A quasi in vitro experiment by Anu & Mendhulkar, 2015 [2] reported that tea inhibits platelet aggregation in manner similar to that of aspirin in that, highest inhibition is experienced at lowest doses.

Mosawy *et al*, 2016 [19] registered the same outcome as Anu & Mendhulkar, 2015 [2]. Their study showed that the tea extract, Epigallocatechin Gallate (EGCG), possesses antiplatelet aggregation and activation abilities. Platelets respond to endothelial damage e.g. following trauma or disruption of an atherosclerotic plaque, by binding to collagen and von williebrands factor (produced by endothelial cells). These proteins when bound to platelets act as ligands to stimulate the platelet to release its contents mainly ADP and thromboxane A2 (Heemskerk *et al*., 2014) [7]. This process of platelet exocytosis, termed platelet activation, is amplified by the newly released ADP and thromboxane A2. Von willibrand factor can bind to more than one platelets hence can lead to aggregation of platelets at the site of injured endothelium. Platelet adhesion, activation and aggregation eventually form a platelets plug that seals off injured vessel (Heemskerk *et al*., 2014) [7]. In cases of vascular discontinuity as in trauma, this platelet response is desired to prevent blood loss but can cause deleterious effects if the vessel is intact (Wagner & Burger, 2003) [25]. Disruption of atheromatous plaques causes this response which eventually occludes the vessel and leads to ischemia of distal tissue (Gawaz, 2004) [5]. Mowasy *et al* [19] contrasted the findings of Ratnasooriya *et al*, 2013 [27] and Ratnasooriya *et al* 2007 [26] in the anticlotting properties. EGCG did not alter coagulation times indicating that it has no effect in the formation of definitive clot. This difference could be attributed to the fact that Mosawy *et al* [19] studied the effects of one extract of tea, EGCG, whereas Ratnasooriya and colleagues investigated the effects of

crude extract. Suggestion can be made that tea contains other extracts that alter coagulation times other than EGCG. This variation in outcome could also be due to the difference in methodology involved. While the initial two studies used animal models, Mosawy *et al* [19] used blood samples from human subjects. The threshold for altering coagulation times could be higher in humans compared to lower animals.

5. Conclusion

This review has shown that *Camellia sinensis* possesses anti-coagulant properties. Various components of this plant have anti-coagulant and antiplatelet aggregation abilities. These abilities have been demonstrated both in vivo and in vitro experiments. Suggestion can therefore be made that regular ingestion of tea can reduce the risk of developing heart disease and stroke but reducing the risk of thrombosis. However, a recommendation is made that further studies ought to be carried out to identify various components of tea with these abilities and also to determine how these components achieves these anti-thrombotic functions.

6. References

1. Ambrose JA, Barua RS. The Pathophysiology of Cigarette Smoking and Cardiovascular Disease, 2004; 43(10). https://doi.org/10.1016/j.jacc.2003.12.047
2. Anu Y, Mendhulkar VD. *In vitro* anti-platelet aggregation activity of the extracts of *Camellia sinensis*, 2015; 6(3):10-16.
3. Ayat, *et al*. The effects of green tea consumption on fibrinogen level among healthy Sudanese volunteers. MLSAL Neelain University, Khartoum, Sudan, 2014.
4. Farrugia CA, Hons BP, Uic PD. The Antiplatelet Activity of Aspirin, 1999.
5. Gawaz M. Role of platelets in coronary thrombosis and reperfusion of ischemic myocardium. 2004; 61:498-511. https://doi.org/10.1016/j.cardiores.2003.11.036
6. Hartley L. Green and black tea for the primary prevention of cardiovascular disease, 2013. https://doi.org/10.1002/14651858.CD009934.pub2
7. Heemskerk JWM, Bevers EM, Lindhout T. Platelet Activation and Blood Coagulation, 2014. https://doi.org/10.1055/s-0037-1613209
8. Hodgson JM, Puddey IB, Mori TA, Burke V, Baker RI, Beilin LJ. Original Communication Effects of regular ingestion of black tea on haemostasis and cell adhesion molecules in humans, 2001; 881-886.
9. Hoffman M, Iii DMM. A Cell-based Model of Hemostasis, For Internal Educational Purposes Only. Not for Dissemination. 2001. https://doi.org/10.1055/s-0037-1615947
10. Homoud MK. Coronary Artery Disease, 2008; 1-13.
11. Hossain MM, Mahmood S. (n.d.). In vitro Studies on Antibacterial, Thrombolytic and Antioxidant Activities of Green Tea or *Camellia sinensis*.
12. Hou Y, Carrim N, Wang Y, Gallant RC, Marshall A. Platelets in hemostasis and thrombosis : Novel mechanisms of fibrinogen-independent platelet aggregation and fibronectin- mediated protein wave of hemostasis, 2015.
13. https://canberra.libguides.com/c.php?g=599346&p=4149722; Population, Intervention, Comparison and Outcome (PICO) level of evidence
14. Ibrahim HMA, Elkhidir RSI, Mirghani F, Ali M, Ali E, Abdalla A, *et al*. The effect of green tea consumption on coagulation profile among adult healthy Sudanese, 2017; 3(3):2003-2005.
15. International steerring commitee on Thrombosis and Hemostasis (ISTH), W. Thrombosis : a major contributor to the global disease burden, 2014, 1580-1590. https://doi.org/10.1111/jth.12698
16. Jalali, *et al*. Qualified health claim petition-Green tea and reduced risk of cardiovascular disease in Iran. Iranian heart journal. 2008; (3):47-52.
17. Loktionov A, Bingham SA, Vorste H, Jerling JC, Runswick SA, Cummings JH. Apolipoprotein E genotype modulates the effect of black tea drinking on blood lipids and blood coagulation factors : a pilot study, 2017; 44(1998):133-139.
18. Maat Mpm, Pijl H, Kluft C, *et al*. Consumption of black and green tea has no effect on haemostasis on smoking healthy individual. European Journal of clinical Nutrition. 2000; (54)10:757-763.
19. Mosawy S, Gaiz A, Karaksha A, Singh I. The Green Tea Extract Epigallocatechin Gallate Inhibits Human Platelet Function but not Plasma Coagulation, 2016; 5(2):17-21. https://doi.org/10.5923/j.ijpt.20160502.01
20. Namita P, Mukesh R, Vijay KJ. *Camellia sinensis* (Green Tea): A Review, 2012; 6(2):52-59.
21. Pierce TB, Razzuk MA, Razzuk LM, Susan J. A comprehensive review of the physiology of hemostasis and antithrombotic agents, 1999; 39-49.
22. Saxena R, Kannan M, Choudhry VP. Laboratory Studies in Coagulation Disorders, 2007; 74:53-59.
23. Sayeed MA, Mamun M, Rashid U, Taiseer RA. Available Online through, 2013; 4:1490-1493.
24. Sherwani SK, Bashir A, Haider SS, Shah MA, Kazmi SU. Thrombolytic Potential of Aqueous and Methanolic Crude Extracts of *Camellia sinensis* (Green Tea): In vitro study, 1996; 2(1):2668735.
25. Wagner DD, Burger PC. Platelets in Inflammation and Thrombosis, 2003; 2131–2137. https://doi.org/10.1161/01.ATV.0000095974.95122.EC
26. Ratnasooriya' WD, TAmarakoon AM, Fernando' TSP, ARRanatiinga' RA, Abeywickrama KRW. In vitro anticlotting activity of Sri Lankan high grown black tea, 2007; 72(1):23-29.
27. Wanigasekara Daya Ratnasooriya, Tharaka Bhanuguptha Sri Muthunayake Department of Zoology, Univers. World Journal of Pharmaceutical Sciences Anticlotting Properties of Sri Lankan Low Grown Orthodox Orange Pekoe Grade Black Tea (*Camellia sinensis* Linn), 2013.
28. Saxena R, Kannan M, Choudhry VP. Laboratory Studies In Coagulation Disorders, 2007; 74:53-59. Print, I., & Online, I.
29. Williams, Wilkins. Collaborative meta-analysis of prospective studies of plasma fibrinogen and cardiovascular disease Fibrinogen Studies Collaboration, 2003. https://doi.org/10.1097/01.hjr.0000114968.39211.01
30. www.casp-uk.net. Critical appreaisal skills program (CASP)tool, 1994.