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REVIEW ARTICLE

Effects of Caffeine on Hemostasis and Blood Coagulation: A Comprehensive Review

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Abstract

Caffeine is one of the most regularly taken behaviorally active drugs in the world. It is typically found in coffee, tea, kola nuts, numerous soft and energy drinks, and chocolate. High prevalence of caffeine consumption worldwide is due to its stimulatory effect in the central nervous system coupled with its widespread presence in foods such as coffee, tea, and chocolate. This review explains the roles of red blood cells, platelets, coagulation factors, anticoagulant systems, and fibrinolysis in maintaining hemostatic balance. Emphasis is placed particularly on laboratory assessment of coagulation using the following parameters; prothrombin time (PT), activated partial thromboplastin time (APTT), bleeding time, clotting time, fibrinogen levels, and platelet function tests. This review also covers the pharmacokinetics of caffeine, mechanism of action and physiological effects of caffeine including its interaction with adenosine receptors, cAMP pathways, and neurotransmitter systems. Moderate intake of caffeine may provide certain physiological and cognitive benefits and if taken in excess, caffeine can induce adverse cardiovascular, neurological and hematological effects. This review highlights the importance of understanding the relationship between caffeine consumption and hemostatic function to guide safe dietary practices amongst young adults.

Keywords: Caffeine, Hemostasis, Coagulation, Platelets, Prothrombin Time, Activated Partial Thromboplastin Time, Platelet Function, Blood Coagulation.

1. Introduction

Blood is a liquid that circulates under pressure via the vasculature. The total volume of blood inside the human body is around 8% of body weight (1). Blood is made up of two components: fluid (plasma) and cellular parts. The cellular component cover about 45 and 46 percent of the total blood. Humans have three different types of blood cells: red blood cells (RBCs), white blood cells (WBCs), and platelets. WBCs are immune cells and their major function is to provide defense or immunity to the body. Platelets also called thrombocytes are tiny anucleated blood cells

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regulating hemostasis. The major function of RBCs: Transportation of gases (oxygen and carbon dioxide). Plasma is the fluid component of blood comprising about 54 to 55% of total blood volume. It is a straw-yellow colored fluid primarily made of water and plasma proteins and a trace amount of other elements like nutrients, hormones, gases, ions, etc. Each of the components plays diverse responsibilities which in summation provide many activities of the blood including transportation of gases, nutrients, wastes, hormones, etc., defense against invading pathogens, maintenance of homeostasis, and distribution of heat (2).

Red blood cell (RBCs) were previously believed to be a passive participant in the coagulation cascade; however, they are now acknowledged as a critical and active component of the thrombotic process (3). In clinical observation, prolonged bleeding times are associated with lower RBC counts. These bleeding times are alleviated by RBC transfusion and the correction of iron deficiency. Five Nevertheless, the mechanistic insights that these clinical observations offer are restricted. Additionally, previous research has primarily concentrated on the prothrombotic properties of red blood cells (RBCs), including the release of adenosine 5′-diphosphate (ADP), direct RBC-platelet interaction, interaction with fibrinogen, and increased procoagulant activity from phosphatidylserine-exposed RBCs and derivative extracellular vesicles (EVs) (4). The influence of RBCs on hemostasis is often attributed to their hemorheologic function in facilitating platelet margination by pushing platelets toward the vessel wall (3).

RBCs interact with platelets in both a mechanical and biochemical fashion. Not only do RBCs enhance platelet margination by axial flow, but they also engage directly with platelets through the αIIbβ3-ICAM4 receptors (5). Moreover, RBCs can biochemically activate platelets by the export of ATP and ADP at high shear conditions, hypoxia, and acidosis (4). Platelet aggregation is also promoted by RBC export of thromboxane A2. Platelets triggered by RBC presence demonstrate higher P-selectin externalization and integrin αIIbβ3 activation which initiates a positive feedback loop during platelet activation (4). With RBC destruction (hemolysis), liberated hemoglobin molecules scavenge nitric oxide which leads to platelet disinhibition.

Following vascular injury, any escaping blood must swiftly be turned into a gel (“clot”) to cover the opening and reduce additional blood loss. The plasma fraction of blood comprises a variety of soluble proteins that function together in a cascade of enzyme activation events, culminating in the creation of a fibrin clot. Hemostasis is the normal process by which the clotting cascade closes up vascular damage to prevent blood loss following injury. It entails a complex equilibrium of the coagulation and fibrinolytic systems, together with platelets and endothelial cells, to reduce haemorrhage while concurrently averting excessive thrombus development and facilitating clot dissolution post-tissue regeneration (6). Thrombosis is a series of pathologic diseases in which the clotting cascade is activated inside the lumen of a blood vessel, leading to the production of a blood clot (known, in this case, as a “thrombus”) that can obstruct the flow of blood within a vessel. Severe thrombosis can block the flow of blood to a tissue, resulting to ischemia and tissue death. If patients require coagulation factors, plasma can be infused, and if the patient has thrombocytopenia, platelets can be transfused (1).

Haemostatic parameters are quantifiable indicators within the haemostatic system employed to evaluate the efficacy of an individual’s coagulation system, hence determining their health status or the presence of a problem. They include bleeding time, clotting time, thrombin test (TT), prothrombin time (PT), fibrinogen level, Activated partial thromboplastin time (APTT) among others (7).

2. Definition and Phases of Hemostasis

When a vessel is severed or ruptured, haemostasis is achieved through several mechanisms: vascular constriction, platelet plug formation, blood clot formation via coagulation, and subsequent fibrous tissue growth into the clot to permanently seal the vessel (8). Haemostasis is the initial stage of wound healing, which is the natural and physiological process of controlling blood loss after trauma by forming clots and slowing blood flow to afflicted sites while maintaining normal blood flow elsewhere in the circulation (9). It entails a complex equilibrium of the coagulation and fibrinolytic systems, together with platelets and endothelial cells, to reduce haemorrhage while concurrently averting excessive thrombus development and facilitating clot dissolution post-tissue regeneration (6). After a blood vessel wall is disrupted, the haemostatic response needs to be prompt, localised, and carefully controlled. When certain elements of these processes fail or are missing, abnormal bleeding or thrombosis (i.e., nonphysiologic blood clotting that is not required for haemostatic regulation) can occur (10). The cascade of events that occur immediately after injury to the blood vessels and preceding wound healing can be grouped into three main components: vasoconstriction, primary hemostasis, and secondary hemostasis. These events

occur simultaneously to cease blood loss from the injured vessel. Natural vasoconstrictor hormones such as epinephrine (a general vasoconstrictor hormone) and thromboxane (a localize vasoconstrictor hormone) are promptly released when a blood vessel ruptures.

Haemostasis relies on a complex network of interdependent activities to prevent spontaneous bleeding and control haemorrhage when vascular injury occurs. Although it is typically separated into primary and secondary for the sake of convenience and patient evaluation, both processes occur practically concurrently in vivo (6). Primary hemostasis involves the formation of the platelet plug. When an artery is wounded, endothelial cells retract and/or detach, exposing the procoagulant subendothelial matrix (which contains proteins such as collagen fibres). The subendothelial matrix proteins connect to receptors on the platelet surface, causing platelet adhesion, aggregation, and the release of intracellular granules, resulting in the creation of the platelet plug (figure 1) (11). Activated platelets and damaged endothelium release vWF and coagulation components from granules, resulting in platelet plug and fibrin production. Secondary haemostasis causes the synthesis of fibrin by coagulation proteins. Vessel wall injury causes tissue factor to be expressed on endothelial cells and subendothelium, which then binds to factor VIIa, activating factor X to Xa and initiating the coagulation cascade. Antithrombotic mechanisms carefully regulate these activities to restrict activation at the site of injury, while fibrinolysis dissolves the clot (11). Aberrant coagulation activation can result in intravascular clot formation, which is fundamental to pathological thrombotic diseases such as myocardial infarction, stroke, and venous thromboembolism (12). The key role in hemostasis plays the interaction of platelets and plasma coagulation factors with vascular endothelial cells and subendothelial tissues (13).

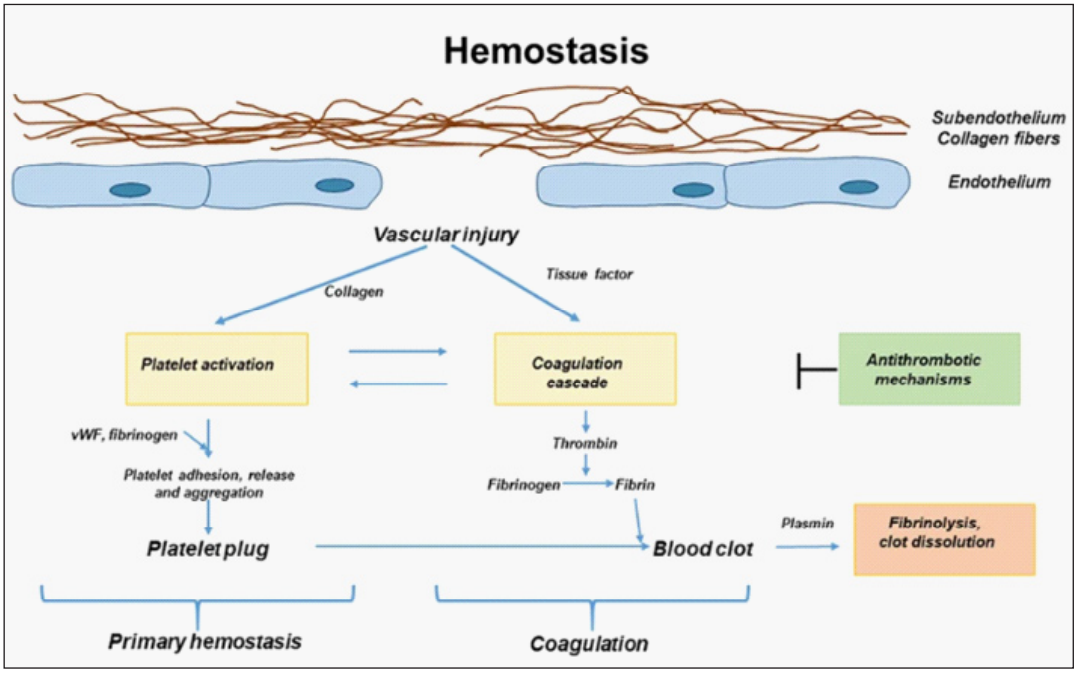

Figure 1. *Overview of hemostasis. Adopted from Noris & Galbusera, (11)*

3. Primary Hemostasis (Platelet Adhesion, Activation, Aggregation)

Primary hemostasis is the term used for the instantaneous plug formation upon injury of the vessel wall, which is achieved by vasoconstriction, platelet adhesion, and aggregation (14). The process is the result of intricate interactions between platelets, adhesive proteins, and the vessel wall, which result in the formation of an initial "platelet plug." The endothelial cells that line the vascular wall demonstrate antithrombotic qualities due to many factors, including negatively charged heparin-like glycosaminoglycans, neutral phospholipids, and the creation and secretion of platelet inhibitors, coagulation inhibitors, and fibrinolysis activators (15). Conversely, the subendothelial layer is markedly thrombogenic and comprises collagen, Von Willebrand factor (vWF), and other proteins like as laminin, thrombospondin, and vitronectin, which facilitate platelet attachment (16). Any vascular injury leads to arteriolar vasospasm, facilitated by reflex neurogenic mechanisms and the release of local mediators such as endothelin and platelet-derived thromboxane A2 (TxA2) (17).

Megakaryocytes produce disc-shaped, anucleate cellular pieces known as platelets. They play an important role in haemostasis by generating the initial haemostatic plug, which offers a surface for the assembly of active coagulation factors, resulting

in the creation of fibrin-stabilised platelet aggregates and subsequent clot retraction (18). Platelets include two types of granules:

- α granules contain P-selectin, fibrinogen, fibronectin, factor V, factor VIII, platelet factor IV, platelet-derived growth factor, and tumour growth factor-α (TGF-α).
- δ granules or dense granules contain ATP, ADP, Ca, serotonin, histamine, and epinephrine.

Normally, platelets do not adhere to intact vascular endothelium. Following arterial damage, platelets bind to collagen and vWF in the subendothelial tissue and undergo a morphological change, acquiring an uneven surface and generating many pseudopods, significantly increasing their surface area (16). The platelet plug is formed through a sequence of stages: Platelet adhesion, platelet secretion and platelet aggregation.

3.1 Platelet Adhesion and Activation

Platelet adherence to injured arterial walls is the initial step in haemostasis and thrombosis (19). Platelet adhesion occurs under flow circumstances, necessitating a distinct cell adhesion mechanism: platelet adhesion must occur quickly and withstand shear forces. This has resulted in the formation of a distinct set of ligands and receptors. Platelet-platelet interaction is facilitated by glycoproteins on the outer membrane and sticky proteins found in plasma, platelet a-granules, and the vessel wall.

Platelet attachment is followed by spreading and activation, which leads to the secretion of agranula and aggregation formation (figure 2). The severity of the platelet reaction is determined by the amount of the vessel wall damage and the relative reactivity of the components that have been exposed to the bloodstream. Platelets promote thrombus formation in arteries, leading to myocardial infarction, stroke, and angina. They also contribute to the progression of atherosclerosis (20).

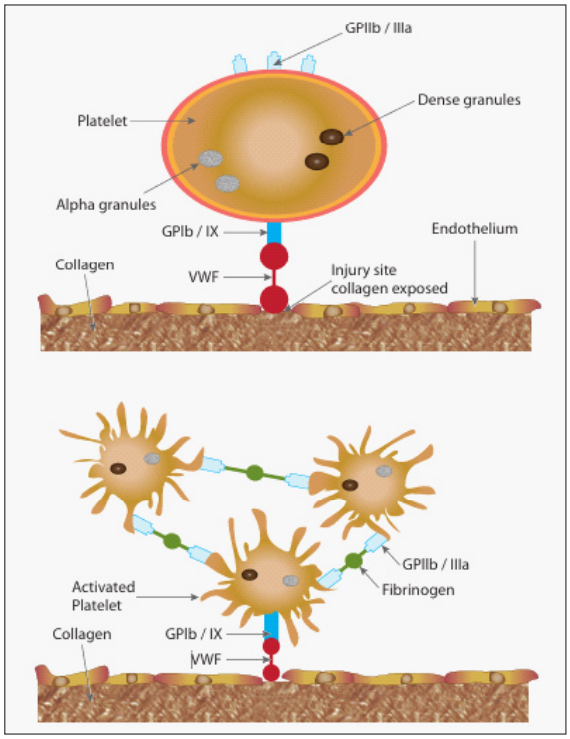

Figure 2. *Platelet adhesion and activation. Adopted from Black et.al., (21)*

3.2 Platelet Secretion

Following adhesion, both types of granules degranulate, resulting in the release of different substances. The release of calcium occurs here. Calcium binds to phospholipids that form during platelet activation and offers a surface for the assembly of numerous coagulation agents (15).

3.3 Platelet Aggregation

Activated platelets release thromboxane A2 (TxA2), which stimulates more platelet aggregation. TxA2 and adenosine diphosphate (ADP) increase the platelet aggregation, resulting in the creation of a platelet plug that temporarily closes off vascular damage. ADP interaction also promotes a conformational shift in GpIIb/IIIa receptors on the platelet surface, which leads to fibrinogen deposition (figure 3). Thrombin production also catalyses the conversion of fibrinogen to fibrin, which improves platelet plug stability and is now referred to as secondary haemostasis (22).

Prostacyclin suppresses platelet aggregation (platelet anti-aggregating action), and the balance of TxA2 and prostacyclin results in localised platelet aggregation, reducing clot extension and maintaining vessel lumen patency (15).

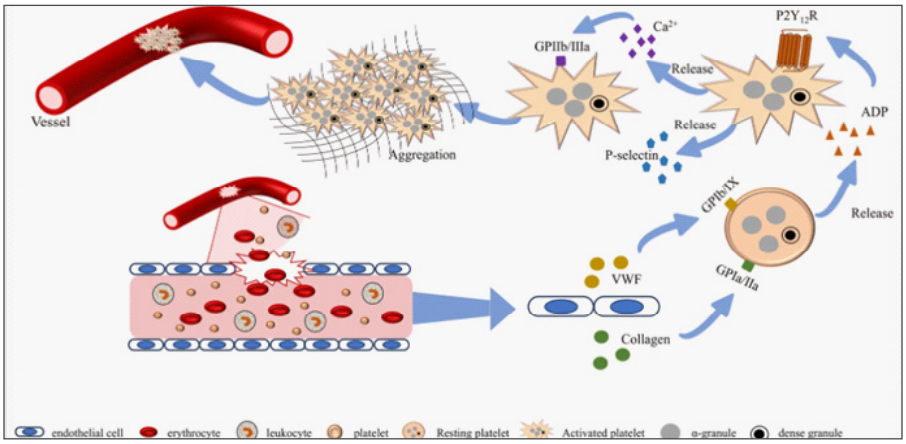

Figure 3. *Platelet aggregation. Adopted from Hou et.al., (22)*

3.4 Secondary Hemostasis (Coagulation Cascade)

Secondary haemostasis includes the two main coagulation pathways, intrinsic and extrinsic, that meet up at a point to form the common pathway (23). Secondary haemostasis occurs when coagulation is activated, reinforcing the platelet plug by forming a fibrin network from the soluble plasma protein fibrinogen. Endogenous inhibitors of blood coagulation prevent it from growing and forming clots (13). The conversion of fibrinogen, a soluble plasma protein, into a fibrin network, which strengthens the haemostatic platelet plug under thrombin's impact, is essential in the blood coagulation process. Table 1 lists different factors involved in coagulation, including plasma proteins, tissue factors, phospholipids, and calcium ions (14). The coagulation factors can be categorised into three groups:

1) The components of the prothrombinase complex include factors II, VII, IX, and X.
2) The elements influenced by thrombin include factors I, V, VIII, and XIII
3) The contact factors of haemostasis are XI, XII, prekallikrein, and high molecular weight kininogen (HMWK)

Some of the clotting factors are present in the plasma in the form of inactive proenzymes, also known as the zymogens. These are serine proteases, including FII (prothrombin), FVII (proconvertin), FIX (factor IX), FX (Stuart-Prower factor), FXI (factor XI), FXII (factor XII), and prekalikrein (13). Their transition into active forms is done by minimal proteolysis.

3.5 Fibrinolysis and Clot Dissolution

The fibrinolytic system dissolves the fibrin that forms the haemostatic clog, while the feeding cells remove the remaining components (Kosmalska *et.al.*, (13). Fibrinolysis refers to the dissolution of a blood clot within a blood vessel. It aids in the removal of clots from the lumen of the blood vessels. Plasmin, also known as fibrinolysin, is required for this procedure. Fibrinolysis occurs concurrently with coagulation and serves to avoid tissue ischaemia by maintaining the presence of fibrin clots. Several plasminogen activators function to produce plasmin, the primary fibrinolytic protein, from circulating plasminogen. Endothelial cells produce the majority of tissue plasminogen activator (tPA), and both tPA and plasminogen are highly fibrin-binding. Stasis upstream from an occluded vessel is the principal trigger for tPA release, and the clot's extra uptake of tPA shifts the haemostasis balance toward fibrinolysis.

An effective array of plasma antifibrinolytic proteins ensures that plasmin activities are localised to the fibrin clot. Plasminogen activator inhibitor (PAI) binds and inactivates tPA at physiological doses. PAI is primarily produced by endothelial cells, however platelet release during coagulation may play a significant role in preventing premature clot lysis.

α2-antiplasmin (AP) instantly inhibits plasmin activity in the bloodstream. During coagulation, AP competes with plasminogen for fibrin binding, preventing a typical clot from lysis on its own.

When internal lysis alone cannot destroy a clot, as in the case of a heart attack or stroke, tPA is administered exogenously through a process known as external fibrinolysis (24). Modelling simulations of external fibrinolysis, supported by testing, demonstrated that the ratio of tPA and fibrin molecules (rather than the overall concentration of tPA present) is critical to the effectiveness of clot breakdown (24,25). The

composition of the clot may indicate the appropriate tPA drug dosage for patients in order to prevent excessive bleeding while simultaneously treating the patient within the optimal time window (25). However, this conclusion has only been reported for external lysis and has yet to be investigated for internal fibrinolysis. Gaining a deeper knowledge of the influence of relative protein concentrations and clot shape on the behaviour of internal lysis can inspire approaches to improve external lysis and clinical advancements (24).

4. Blood Coagulation Mechanism

4.1 Overview of Coagulation

Coagulation is a complex biological process that maintains the equilibrium between clot formation and haemorrhage by initiating a cascade of responses including the activation of coagulation factors and platelets (26). It involves a complex and dynamic interplay of platelets, plasma, and the endothelium of blood vessels. The vertebrate coagulation system is crucial for sustaining a closed high-pressure circulatory circulation. Proper activation of coagulation in response to vascular injury is essential for successful haemostasis, which enables the cessation of bleeding (27).

Blood coagulation is a crucial component of the haemostatic process and happens in three stages: Formation of prothrombin activator, conversion of prothrombin into thrombin, and conversion of fibrinogen into fibrin (28). Formation of prothrombin activator happens through two pathways: intrinsic pathway and extrinsic pathway (7). The intrinsic pathway, often assessed by activated partial thromboplastin time (APTT), is initiated by surface contact. The extrinsic pathway, often assessed using the prothrombin time (PT) test, is initiated by vascular damage. The conventional route to clot formation is initiated by the intrinsic and/or extrinsic pathway. Procoagulants or hemostatic agents are the substances which accelerate the process of blood coagulation e.g. thrombin, snake venom etc. (28). These tests detect most anomalies in haemostasis. If determined to be abnormal the patient is referred for conclusive tests which may be available only in specialized laboratories. The coagulation screening tests, including PT, APTT, thrombin time (TT), and fibrinogen, are essential for the fundamental evaluation of haemostasis (7). Blood clotting happens in a multi-step process known as the coagulation cascade (figure 4). The cascade is a chain reaction in which one step leads to the next. In general, each step produces a new protein which works as an enzyme, or catalyst, for the following phase. Moreover, in the following reactions, we are dealing with an amplification of the number of active substrate molecules. This is because more substrate molecules are hydrolysed by a tiny quantity of the enzyme. The enzyme-cofactor complex is regarded as the functional unit in the blood coagulation cascade (13).

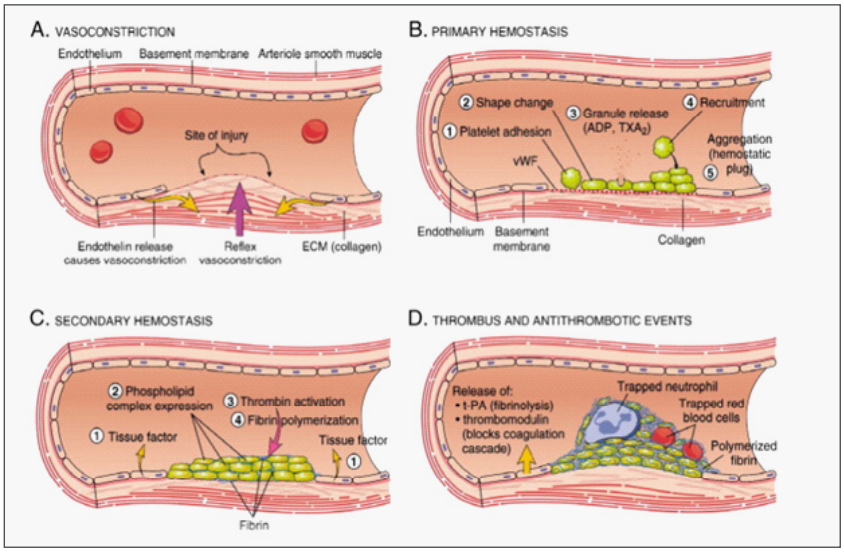

Figure 4. *Illustration of the blood clotting process showing the four main steps of hemostasis (vasoconstriction, primary hemostasis, secondary hemostasis and fibrinolysis). Adopted from Cito et.al., (29)*

4.2 Coagulation Factors and Their Functions

Coagulation factors are a family of heavily glycosylated plasma proteins. And most of them except (FI and FII) are available in extremely modest amounts. These factors, except tissue factor (TF) are attached to plasma membrane proteins and require a proteolytic activation step. Some of the coagulation factors are dependent on vitamin K and carboxylation happens in their glutamic acid side chains by enzymatic processes (28). Except for γ-carboxylation, other post-

translational modifications such as phosphorylation, sulfation and addition of β-hydroxyaspartic acid are present in other coagulation factors. Clotting factors are the most crucial and essential components of haemostasis. Haemostasis, the body's physiological response to vascular endothelial injury, triggers several processes that attempt to maintain blood in the vascular system by creating a clot (30). The nomenclature for coagulation proteins is somewhat intricate. The first four of the twelve components that were first discovered are commonly referred to as fibrinogen, prothrombin, tissue factor (TF), and calcium (31). The more recently discovered clotting factors, prekallikrein and high-molecular-weight kininogen, have not been assigned Roman numbers. Factors V and VIII are commonly referred to as the labile factors due to their transient coagulant activity in preserved blood (31).

Coagulation promotes haemostasis through a complex process involving multiple variables. The intrinsic route includes factors I, II, IX, X, XI, and XII. The following factors are named: fibrinogen, prothrombin, Christmas factor, Stuart-power factor, plasma thromboplastin, and Hageman factor. The extrinsic route includes factors I, II, VII, and X (23).

Table 1. *Clotting Factors in Blood and Their Synonyms. Adopted from Guyton & Hall, (14)*

CLOTTING FACTOR	SYNONYM(S)	Function
Fibrinogen	Factor I	Forms clot
Prothrombin	Factor II	IIa activates I, V, VII, VIII, XI, XIII, XIV, platelets
Tissue Factor	Factor III; tissue thromboplastin	Stored in sub-endothelium and in platelet core; VIIa's cofactor
Calcium	Factor IV	Cofactor for coagulation factors to bind to phospholipids
Factor V	Proaccelerin; labile factor; Ac- globulin (Ac- G)	X's cofactor with which it forms the prothrombinase complex
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor	Activates IX, X
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A	Cofactor of IX with which it forms a complex activating X
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B	See function of VIII
Factor X	Stuart factor; Stuart- Prower factor	Can be activated by IX, VII
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C	Activates IX; XI → XIa is triggered by XIIa, IIa and by itself
Factor XII	Hageman factor	Activates factor XI, VII, prekallikrein
Factor XIII	Fibrin-stablizing factor	Activated by IV, IIa; Crosslinks fibrin
Prekallikrein	Fletcher factor	Proenzyme
High- molecular-weight kininogen	Fitzgerald factor; high- molecular- weight kininogen (HMWK)	Cofactor
Platelets		

4.3 Intrinsic Pathway

This process is the lengthier pathway of secondary hemostasis. It begins with the activation of Factor XII (a zymogen, inactivated serine protease) which becomes Factor XIIa (activated serine protease) after exposure to endothelial collagen (figure 5). Endothelial collagen is only accessible when endothelial damage occurs. Factor XIIa works as a catalyst to activate factor XI to Factor XIa. Factor XIa then goes on to activate factor IX to factor IXA. Factor IXa goes on to serve as a catalyst for converting factor X into factor Xa. This is known as a cascade. When each factor is active, it continues on to activate many other factors in the next steps. As you travel further down the cascade, the concentration of that factor increases in the blood. For example, the concentration of factor IX is greater than that of factor XI. When factor II is engaged by either intrinsic or extrinsic pathway, it might reinforce the intrinsic pathway by sending positive feedback to factors V, VII, VIII, XI, XIII. This makes factor XII less necessary; patients can actually clot successfully without factor XII. The intrinsic route is clinically assessed as the partial thromboplastin time (PTT) (32).

Extrinsic Pathway

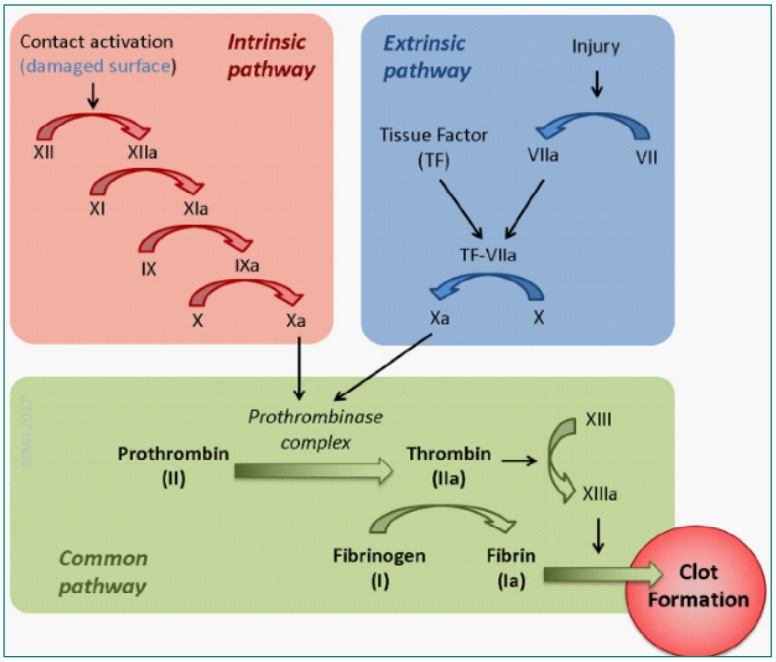

Figure 5. *The intrinsic, extrinsic and common pathways of the coagulation (clotting) cascade. Adopted from Robertson & Miller, (33)*

The extrinsic pathway is the shorter pathway of secondary hemostasis. Upon vascular injury, the endothelial cells release tissue factor and initiate the activation of factor VII to VIIa. Factor VIIa further activates factor X into factor Xa. At this stage, both the extrinsic and intrinsic pathways converge (figure 5). The extrinsic pathway is clinically assessed using the prothrombin time (PT) (34).

4.4 Common Pathway

The common pathway begins with the activation of factor X to factor Xa. The process of activating factor Xa is a sophisticated procedure mediated by a complex known as tenase. Tenase has 2 forms; extrinsic, consisting of factor VII, factor III (tissue factor), and Ca2+, or intrinsic, made up of cofactor factor VIII, factor IXA, a phospholipid, and Ca2+ (34). Once activated, factor Xa transforms factor II (prothrombin) to factor IIa (thrombin). In addition, factor Xa requires factor V as a cofactor to cleave prothrombin into thrombin. Factor IIa (thrombin) activates fibrinogen into fibrin. Thrombin also activates other factors in the intrinsic pathway (factor XI), cofactors V and VIII, and factor XIII. Fibrin subunits create fibrin strands, and factor XIII acts on fibrin strands to build a fibrin mesh (figure 6). This mesh serves to support the platelet plug (34).

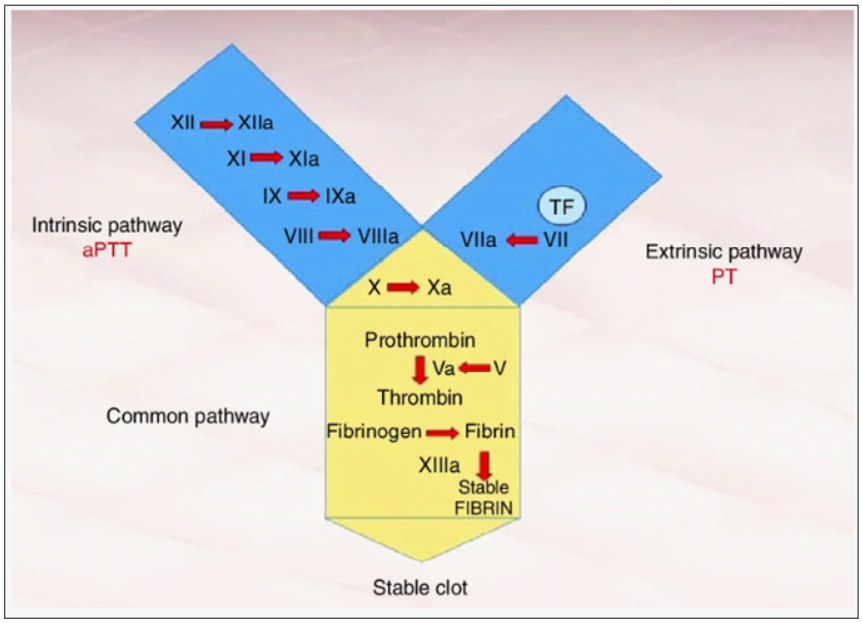

Figure 6. *The coagulation cascade with its intrinsic and extrinsic pathway leading to a common pathway and the formation of a stable fibrin clot. Sourced from Haddad et.al., (35)*

4.5 Regulation of Coagulation (Anticoagulants: Protein C, Protein S, Antithrombin)

The state of balance within the haemostatic system is essential in the pathophysiology of disorders associated with thrombosis, embolism, and haemorrhage (36). The disturbance of this dynamic equilibrium precipitates significant activation of the coagulation cascade, culminating in excessive thrombin production, the accumulation of thrombophilia indicators such as soluble fibrin (SF), soluble fibrin monomeric complexes (SFMCs), prothrombin fragment 1+2 (PF1+2), D-dimer, and a decrease in the levels of physiological blood coagulation inhibitors (37). The key mechanisms involved for natural anticoagulation include antithrombin (AT), tissue factor pathway inhibitor (TFPI), and the protein C (PC) pathway. AT is a highly potent inhibitor of serine proteases that are produced by the liver, transported in plasma, and found in trace amounts on the surface of platelets and endothelial cells (38). This compound is a selective inhibitor of thrombin and factor Xa (FXa), effectively binding to coagulation factors, including VIIa, IXa, XIa, and XIIa, rendering them inactive (38). Due to the minimal concentration of heparin in plasma, AT activation in the plasma is limited. However, binding AT with heparin sulfate on the surface of endothelial cells promotes their activation.

4.5.1 Protein C

Vitamin K-dependent protein C is the major component of an essential natural anticoagulant mechanism (38). The protein C system exerts its anticoagulant action by modulating the activities of FVIIIa and FVa, the cofactors in the tenase and prothrombinase complexes, respectively (Figure 1). The inhibition of FVIIIa and FVa mediated by the protein C system provides a highly efficient and specific regulation of blood coagulation (39). The physiological importance of the anticoagulant protein C system is most plainly demonstrated by the severe thrombotic disease, purpura fulminans, which affects neonates with homozygous protein C deficiency (40). In recent years, protein C has been shown not only to be anticoagulant but also to have antiinflammatory and antiapoptotic properties. The unique combination of anticoagulant, antiinflammatory, and antiapoptotic properties of APC has made it an attractive candidate as a therapeutic agent and administration of APC has proved beneficial in the handling of patients with severe sepsis. The protein C system has been carefully explored and insights into the 3-dimensional (3D) structure of the proteins and the intricate links between the structures and their functions have been gained. These novel insights are the focus of this review (39).

Activated protein C (APC) circulates in plasma as a light and heavy chain molecule linked together by a single disulfide bond. APC's N-terminal light chain consists of a non-catalytic γ-carboxyglutamic (Gla) domain, followed by two EGF-like domains. The catalytic domain of APC, with a trypsin-like primary specificity pocket, is found on the C-terminal heavy chain of the molecule (40). The Gla domain, with nine vitamin K-dependent γ-carboxylated Glu residues, facilitates the Ca2+-dependent interaction of APC with protein S on negatively charged membrane surfaces. Protein S is a vitamin K-dependent plasma cofactor which increases the anticoagulant function of APC in the proteolytic destruction of the procoagulant cofactors factors Va (FVa) and VIIIa (FVIIIa) (40). The APC cleavage of these procoagulant cofactors shuts down thrombin production through both intrinsic and extrinsic routes. Insight into the importance of the APC anticoagulant pathway in the regulation of blood coagulation can be gleaned from the observation that a heterozygous protein C deficiency is associated with a high risk of venous thrombosis and its homozygous deficiency causes purpura fulminans, which is fatal unless treated by protein C replacement therapy. A full protein C deficit in mice results in deadly neonatal consumptive coagulopathy, as revealed by the targeted gene disruption (40).

Protein S: Protein S is a crucial regulator of coagulation that works as a cofactor for the activated protein C (APC) and tissue factor pathway inhibitor (TFPI) pathways (38). It also has direct anticoagulant effects, blocking the intrinsic tenase and prothrombinase complexes. Through these roles, protein S modulates coagulation during both its beginning and its propagation phases. The role of protein S in hemostatic control is obvious from the substantial relationship between protein S deficits and higher risk for venous thrombosis (41). This is most likely because both APC and TFPIα are poor anticoagulants in the absence of any cofactors. The detailed molecular pathways involved in protein S cofactor functions have to be fully elucidated. However, recent breakthroughs in the science have substantially increased our understanding of these functions (38). Evidence suggests that protein S anticoagulant capabilities often depend on the presence of synergistic cofactors and the development of multicomponent complexes on negatively charged phospholipid surfaces. Their high affinity binding to negatively charged phospholipids helps bring the anticoagulant proteins to the membranes, resulting in

efficient and focused regulation of coagulation. In this review, we present an update on protein S and how it serves as a crucial hemostatic regulator (41). Protein S deficiency and dysfunction cause life-threatening thrombotic conditions, including neonatal purpura fulminans.

4.5.2 Antithrombin

Antithrombin (AT) is a natural anticoagulant pivotal in inactivating serine protease enzymes in the coagulation cascade, making it a potent inhibitor of blood clot formation (42). AT is a hepatic glycoprotein belonging to the serpin superfamily, a group of proteins with distinctive structural and inhibitory characteristics. Serine proteases activated (a) factor (f) II (thrombin), fXa, fIXa, fXIa, fXIIa, and fVIIa are all targeted and inhibited by AT. Heparin alone has no direct anticoagulant effect, but AT is necessary for therapeutic anticoagulation by heparin or low-molecular-weight heparin (LMWH), despite in vitro reports of heparin having AT-independent effects (43).

AT is released by the liver at a normal quantity of 0.125 to 0.160 mg/mL (80%-120%) 3 and is present in the plasma, vascular endothelium, and extravascular space (44). The regulating effect of AT is mediated via suppression of the production of thrombin and deactivation of numerous procoagulant serine proteases. The anticoagulant activity of AT is the reason behind the use of heparin in the treatment and prophylaxis of thrombosis, as the binding of heparin with AT generates a conformational shift that substantially improves the potency of AT to suppress the coagulation cascade. In addition to modifying coagulation, AT can also induce the release of chemicals that alleviate inflammation (42).

5. Effect of Caffeine on Haemostasis and Coagulation

Caffeine is believed to primarily exert its biological effects through adenosine receptors (ARs) (45). Caffeine may affect platelet function via adenosine A2A receptors (A2AR) and adenosine A2B receptors (A2BR), either enhancing or diminishing platelet reactivity based on dosage and ingestion frequency. Caffeine has been demonstrated to modify the sensitivity of adenosine receptors (ARs) to adenosine or other AR agonists; however, research on this subject is limited. The objective of this review is to analyse the impact of caffeine on blood platelets and the cardiovascular system through ARs (46). Coffee is regarded as the most abundant source of caffeine and the most popular caffeinated beverage globally. The relationship between caffeine and the cardiovascular system is significant due to the elevated mortality linked to cardiovascular disease (CVD) (46).

The impact of coffee on platelet aggregation has been inadequately researched. While the primary physiological benefits of coffee consumption are typically attributed to caffeine, coffee is also a highly abundant source of phenolic acids, predominantly in the form of chlorogenic acid. The chlorogenic acid level in coffee closely resembles that of caffeine; a cup of American coffee has around 170 mg of chlorogenic acid and 180 mg of caffeine (47). The daily consumption of chlorogenic acid in coffee drinkers ranges from 0·5 to 1·0 g, and the presence of coffee phenolic acids in plasma after coffee drinking is well documented (47).Numerous epidemiological studies have indicated an inverse relationship between dietary polyphenol consumption and cardiovascular disease risk. The impact of dietary polyphenols on CVD has been linked to both their antioxidant activity in preventing LDL oxidation, and to their effect on the pathogenesis of thrombosis by interfering with platelet activation and function. Platelets play a significant function not only in the formation of acute thrombus and arteries blockage, but also in the development of atherosclerosis and CVD (48). Moreover, ex vivo platelet aggregation is associated to CVD mortality. Phenolic chemicals are capable of suppressing platelet aggregation both in vitro and in vivo. It has been demonstrated that phenolic-rich drinks, such as cocoa, tea and wine, can reduce platelet aggregation both in vitro and ex vivo (47).

6. Laboratory Assessment of Coagulation

Prothrombin time (PT) and activated partial thromboplastin time (APTT) are screening assays that are commonly used in tandem on citrate plasma to detect possible coagulation factor deficiencies (figure 7). The tests are functional bioassays that determine how long it takes for a clot to form in vitro in a reaction mixture that contains the test sample as the source of all coagulation components. The tests are designed using “trigger” reagents that differentially start coagulation through two different pathways, so that delays in clot formation signify deficiencies of one or more factors in that pathway (49). Different species have different clot formation kinetics and relative coagulation factor activities (50). To enable proper interpretation of patient values, the testing laboratory should ideally give species-specific reference intervals and same-species control values. Although published reference ranges can help with result interpretation, their

general application may be limited by test variables including reagent composition and endpoint detection technique. When species-specific reference intervals are not available, it is preferred to submit a paired sample from a healthy member of the same species in order to interpret test results (49).

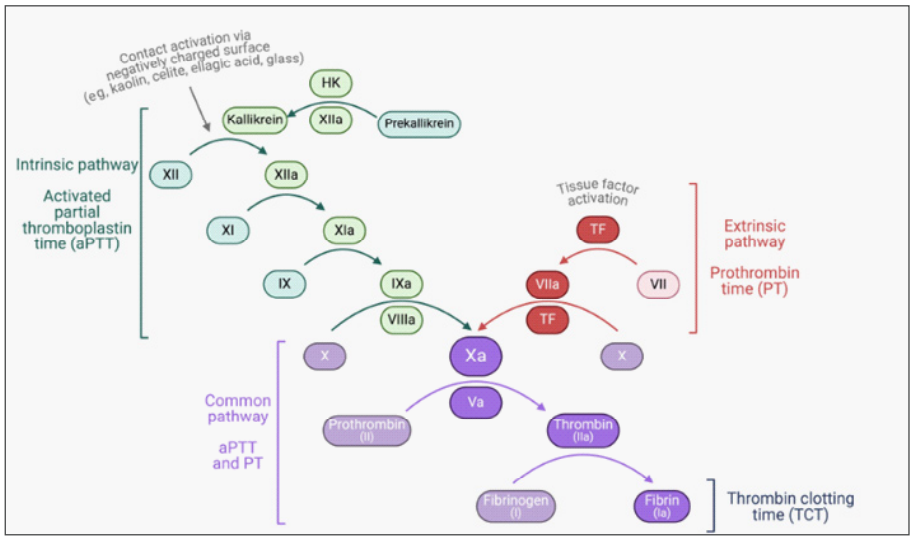

Figure 7. *Diagram of the coagulation cascade reactions demonstrating activation pathways and associated coagulation screening tests. Adopted from McKown et.al., (49)*

Coagulation factors are designated by roman numerals with "a" denoting the enzymatically active form of each procoagulant factor. The factors are shown in the order of activation from the top to the bottom of the Figure. The screening test color coding matches that of the pathway factors evaluated by each test: green/blue-green is activated partial thromboplastin time (contact, factor XII and intrinsic pathway, factors XI, IX, and VIII); red/pink is prothrombin time (extrinsic pathway and factor VII); purple/lavender is the common pathway (factors X, V, II, and fibrinogen); and black is thrombin clotting time (fibrinogen). HK = High–molecular-weight kininogen. TF = Tissue factor

6.1 Prothrombin Time (PT)

Prothrombin time (PT) is a laboratory screening test used to detect problems involving the activity of Factor I (Fibrinogen), Factor II (Prothrombin), Factor V (Proaccelerin), Factor VII (Proconvertin), and Factor X (Stuart factor) of the extrinsic and common pathways. The PT examines the function of Factor VII, Factor X, Factor V, Factor II (Prothrombin), and Factor I (Fibrinogen) after the addition of thromboplastin and calcium (51,52).The Factor VIIa/tissue factor combination activates Factor Xa and by the activity of prothrombinase complex, prothrombin is transformed to thrombin. The time in seconds for the conversion of fibrinogen to insoluble fibrin by thrombin is stated as PT (7). Activated partial thromboplastin time (APTT) is an assay used to screen for anomalies of the intrinsic and common clotting systems and to monitor the anticoagulant effect of circulating heparin. It assesses the activity of Factors I, II, V, VIII, IX, X, XI, and XII of the intrinsic and common routes (7).

The PT reagent includes large quantities of tissue factor and phospholipids that directly activate factor VII in the extrinsic route, followed by activation of the common pathway factors. A delay in the PT, therefore, implies a deficiency of factor VII and/or factors X, V, and II or fibrinogen. The APTT and PT are designed to identify factor deficiencies based on prolongation of clot formation durations and are insensitive to high factor concentrations or activities (34).

6.2 Activated Partial Thromboplastin Time (APTT)

Clot formation in the APTT is activated by a reagent that contains negatively charged particles and phospholipids (53). This reagent initiates coagulation through reciprocal activation of a set of hemostatic proteins referred to as the contact factors. These factors include prekallikrein, high–molecular-weight kininogen, and factor XII (49). Activated factor XII then promotes coagulation through the activation of the intrinsic route factors (factors XI, IX, and VIII) and common pathway factors (factors X, V, II, and fibrinogen).

6.3 Fibrinogen

The most extensively used measure of plasma fibrinogen is a functional test (Clauss Fibrinogen) that assesses the rate of clot formation after addition of excess thrombin to the test sample. Clotting timings are then translated to a concentration value of milligrams per liter or grams per liter by comparison to a calibration curve obtained from dilutions of a fibrinogen reference plasma (49). The choice of reference standard (human vs species specific) can alter fibrinogen results. Measurement of fibrinogen

can assist diagnose liver dysfunction disseminated intravascular coagulation, and hyperfibrinolysis diseases (54). Primary hypofibrinogenemia and dysfibrinogenemia can be identified by measurement of fibrinogen concentration, however hereditary fibrinogen diseases are rare (55). The thrombin time or thrombin clotting time (TCT) assay is another measure of plasma fibrinogen concentration based on the rate of thrombin-activated clot formation. The TCT assay findings are presented as clotting time in seconds with-out any data modification. In addition to its diagnostic usefulness, measurement of fibrinogen or TCT can also help identify fibrinogen-depleted samples arising from premature activation of coagulation during sample collection and processing (49). Many diagnostic facilities offer combined APTT and PT tests as a coagulation "panel" or "profile." Results of the APTT and PT screening tests are best understood in conjunction with the fibrinogen level of the test sample, since noticeably low or high fibrinogen will impact the time to clot endpoint formation in the assay reaction. If the fibrinogen concentration is normal, then the observation of prolonged APTT or PT implies a lack of one or more factors in the intrinsic or extrinsic pathways, respectively. The pattern of anomalies, together with the results of a fibrinogen determination, are diagnostic of certain illnesses and can guide patient management and selection of suitable ancillary testing (Figure 4) (50). On note, deficiencies of the contact factors prolong the APTT but are not related with clinical bleeding. For instance, factor XII deficiency is widespread in domestic cats and is typically diagnosed due to delayed APTT in pre-operative coagulation panels, while factor XII–deficient cats are clinically normal (49). In contrast, deficiencies of intrinsic and common route variables induce clinical bleeding disorders.

6.4 Clotting Time and Bleeding Time

Bleeding time (BT) is the time gap from seeping of blood following a cut or injury till arrest of bleeding. Puncture and the cessation of bleeding-the time in minutes which it takes for a standardized skin wound to cease bleeding. Significance: Cessation of bleeding from a minor wound as that inflicted during this treatment can be impacted by vascular spasm and production of platelet plugs. This test consequently examines the capillary and platelet activities in haemostasis. Normal: 1-5 minutes (using Duke's technique) (32).

Factors which alter the Bleeding Time:

1. Size and nature of the injury
2. Condition of the vessel wall
3. Number of platelets

Conditions when Bleeding Time is p6rolonged:

1. Decrease in the quantity of platelets-thrombocytopenic purpura
2. Functional platelet defect: a. Drugs like aspirin, penicillin b. von Willebrand's disease c. Uraemia, cirrhosis, leukaemia
3. Vessel wall defects: a. Prolonged therapy with corticosteroids b. Allergic purpuras c. Infections with haemolytic streptococci, bacterial endocarditis d. Deficiency of vitamin C e. Senile purpura.

6.5 Other Methods

1. In Duke's method, the edge of the ear lobe can also be used. Usually, it is determined by Duke method utilising blotting paper or filter paper method. Its normal duration is 3 to 6 minutes. It is prolonged in purpura (32).
2. Ivy's method: The cuff of the BP device is attached to the upperarm and the pressure is raised to 40 mm Hg. The front of the fore arm is employed. The normal bleeding time using this approach is up to 9 min (56).

Clotting time (CT) is the time period from seeping of blood following a cut or injury till the formation of clot. It is usually determined using capillary tube technique. Its normal duration is 3 to 8 minutes. It is prolonged in hemophilia. Clotting time is the time interval between the skin puncture and creation of fibrin thread. Significance: The clotting time is normally not influenced by lack of platelets as just few platelets are required to provide enough platelet factor 3 for normal coagulation (57). This test evaluates the intrinsic and common pathways of coagulation because the trigger for coagulation in this test is the surface activation of blood that comes into contact with the glass surface of the test tube (to ensure comparability, we should use standard size tubes and constant blood volumes). Normal range is 2-8 minutes (57).

6.6 Platelet Count and Platelet Function Tests

Platelet function testing is a specialist test to assess how well platelets are operating in the blood clotting mechanism. Platelets are the cells in the blood responsible for initiating blood clotting. Platelet function testing is a key part of diagnosing platelet function disorders. Because there are many occupational domains in which platelet function is examined and the platelets show a myriad of roles, different approaches have been established. Indeed, the platelet methods are based on diverse operating

principles, and few assays are able to study "all in one device" platelet activation pathways (58). The numerous modalities of devices to operate may be based on the assessment of platelet adhesion and aggregation, on the submission of platelets under special shear circumstances, on the analysis of physical features of clot, and on the measurement of platelet compounds (Table 2). In addition to the large collection of assays and instruments for researching platelet function, because platelets are cells that may be easily triggered during the blood sampling, a number of preanalytical variables might induce platelet artifacts impacting the different platelet functions. Therefore, a high degree of experience and competence is necessary to execute and interpret PFT. In this regard, this review seeks to make a comparison of the various platelet function techniques on the basis of the same assumption that both are laboratory tests or POCT (59).

Table 2. *Different methodologies for assessment of platelet function. Adopted from Paniccia et.al., (2015)*

Method	Sample	Method Application	Method Principle
Bleeding Time	Native WB	Screening test (obsolete)	In vivo measurement of bleeding block
Tests based on platelet aggregation			
Light transmission platelet aggregation (LTA)	Citrated PRP	Screening tests for bleeding tendency	Photo-optical measurement of light transmission increase in relation to agonist-induced platelet aggregation
		Diagnostic for platelet defects	
		Monitoring antiplatelet treatment effect	
Impedance platelet aggregation	Citrated WB	Screening test for bleeding tendency	
		Diagnostic platelet defects	
		Monitoring antiplatelet treatment effect	
Lumiaggregometry	Citrated WB	Detection of storage/release disorders	LTA or WB aggregometry combined with luminescence
		Monitoring of the platelet response to antiplatelet agents	Platelet counting pre- and post-activation in whole blood
Tests based on platelet adhesion under sheer stress			
PFA-100; Innovative PFA -200	Citrated WB	Assessment of bleeding risk and drug effects searching severe platelet dysfunctions, revealing of VWD	Time evaluation of high sheer WB flow blocked by platelet plug into a hole in activated surface
Impact; Cone and Plate(let) Analyzer	Citrated WB	Screening of primary hemostasis	Shear-induced platelet adhesion-aggregation upon specific surface
Global Thrombosis Test (GTT)	Native WB	Evaluation of platelet function and thrombolysis	Measurement of time cessation of WB flow by high shear-dependent platelet plug formation
Platelet function methods combined with viscoelastic test			
TEG/platelet mapping system	Citrated WB	Assessment of global hemostasis plus monitoring antiplatelet treatments effect	Evaluation of rate of clot formation based on low shear-induced and agonist addition
ROTEM platelet	Citrated WB	Assessment of hemostasis plus diagnostic of platelet defects plus monitoring antiplatelet treatment effect	Measurement of electrical impedance increase in relation to agonist-induced platelet aggregation
Platelet analysis based on flow cytometry			
Flow cytometry	Citrated WB, PRP, W-PIt,	Cell counting, detection platelet activation by extent of expression of surface and/or cytoplasmic biomarkers	Engineering-laser based detection of suspending fluorescent label platelets in a flowing solution
Evaluation of Thromboxane metabolites			
Radio- or enzyme –linked immune assays	Serum, urine, citrated Pls	Measurement of TxA2 metabolites (and Beta- TG, PF4, soluble P-selectine)	Ligand-binding assays

Abbreviations: *Beta-TG, beta-thromboglobulin; Pls, plasma; PRP, platelet-rich-plasma; ROTEM, rotational thromboelastometry; TEG, thromboelastography; TxA2, thromboxane A2; WB, whole blood; W-Plt, washed platelets; VWD, Von Willebrand disease.*

7. Caffeine: An Overview

Research has already shown that caffeine stimulates the central nervous system by acting as an antagonist of A1 and A2 adenosine receptors, increases the levels of dopamine, noradrenalin, and glutamate, increases blood circulation and respiratory rate, mobilises intracellular calcium stores, and modifies the metabolism of fat and carbohydrates in the human body by stimulating lipolysis because it inhibits phosphodiesterase enzymes (60,61). In addition, coffee also enhances energy, alertness, excitement, and mood (62). According to the European Food Safety Authority (EFSA), a habitual daily use of caffeine up to 400 mg (5.7 mg/kg per day for a 70 kg adult) by adults, and 200mg by pregnant or breastfeeding women is regarded to be safe (63). Exceeding this dose or the quick termination of caffeine intake may produce anxiety, sleeplessness, hallucinations, hypertension and headache, gastrointestinal and sleep problems, diuresis, dehydration, tremors, palpitations, and heart arrhythmias given the stimulating effects of caffeine (63).

Caffeine's principal mode of action is its impact on adenosine receptors in the brain. Being both fat and water-soluble component, caffeine rapidly penetrates the blood-brain barrier and antagonizes all 4 adenosine receptor subtypes (A1, A2a, A2b, and A3). The antagonism of the A2a receptor is primarily responsible for caffeine's awake effects. Caffeine is a frequently used natural stimulant that plays a vital part in daily living across the globe. Belonging to the methylxanthine class, caffeine operates as a competitive antagonist of adenosine receptors, hence lowering weariness and improving alertness. It is typically found in plant-based sources such as coffee beans, tea leaves, cocoa, and kola nuts (64). In addition to natural sources, caffeine is often synthetically added into goods like soft drinks and energy beverages to boost energy and cognitive ability (65).

The recommended daily quantity of caffeine intake for adults is 400 mg (1-4 cups per day), according to the European Food Safety Authority (66). However, use of more than the prescribed quantity can cause caffeine intoxication, commonly known as caffeinism. This presents as anxiety, sleeplessness, and gastrointestinal problems (66). The typical caffeine intake is roughly 180 mg/day in the overall adult population, whereas college students consume around 268 mg/day. A high prevalence of mental health disorders, including depression, anxiety, and stress, has been found among college students in general. A study conducted at Taibah University indicated similar results for medical students (67). Other investigations conducted on the general population have indicated that ingestion of the recommended dosage of caffeine was related with a lower incidence of depression but an increase in anxiety symptoms.

7.1 Definition and Chemical Structure

Caffeine (1,3,7-trimethylxanthine) is a methylxanthine derivative with the chemical formula C8H10N4O2. It is classified as an alkaloid molecule due to its status as a byproduct of nitrogen metabolism (64). Caffeine is a heterocyclic chemical molecule characterised by a purine base. Figure 8 below illustrates the chemical structure of caffeine, with the purine base emphasised in a box. This structure closely resembles those of other metabolic chemicals, such as purines (64). The precise molecular structure of caffeine was verified in the late 19th century, following the isolation of pure caffeine in 1819 by Friedlieb Runge (64).

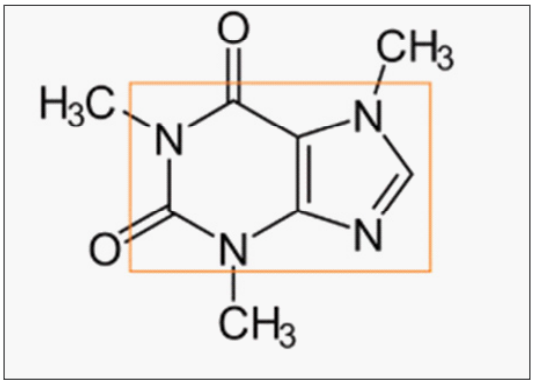

Figure 8. *Chemical structure of caffeine. Adopted from Reddy et.al., (64)*

7.2 Sources of Caffeine (Coffee, Tea, Energy Drinks, Cola)

Caffeine is a nitrogen-containing alkaloid that has been identified in over 60 plant species. The most prevalent sources include coffee beans, kola nuts, cocoa beans, and tea leaves. They are incorporated into numerous kinds of items such as americano, espresso, latte, cappuccino, tea, iced tea, soft drinks, energy drinks, chocolate, chocolate milk, cocoa powder, guarana, and caffeine supplements. However, evidence indicates

that chocolate often contains less caffeine compared to hot liquids such as coffee or tea (66). Their caffeine level varies greatly depending on the species of coffee bean. For example, Coffea canephora (Robusta) has a higher caffeine concentration than Coffea arabica (Arabica). Additionally, the serving size, manner of preparation, and quantity of coffee beans used also affect a beverage's total caffeine content. Natural caffeine is found in many plants, including coffee beans, cacao beans, and tea leaves. Around the world, many beverages, including coffee, tea, energy drinks, and some soft drinks, have this natural caffeine compound (68).

7.3 Pharmacokinetics of Caffeine (Absorption, Distribution, Metabolism, Excretion)

The way the body reacts to a medicine is explained by pharmacokinetics. It studies a substance's absorption, distribution, metabolism, and excretion (ADME) (69). Figure 9 gives a summary of caffeine pharmacokinetics. Caffeine belongs to the Biopharmaceutical Classification System (BCS) Class I medications since it is very water-soluble and permeable. The liver metabolizes the most active components or drug(s) before they are introduced into the bloodstream. But caffeine is rapidly absorbed. Hence, caffeine has little hepatic first-pass effects (the consequence of a drug's fast transformation when given orally and resulting in reduced bioavailability) (68) (Figure 9). Also, caffeine is absorbed independently of age, sex, and health, as well as the use of drug(s), alcohol, or nicotine because of little first-pass metabolism. Moreover, caffeine has a linear pharmacokinetic feature, because a rise in caffeine intake induces a commensurate rise in blood plasma levels (66).

When caffeine is taken, around 10–30% of the caffeine gets reversibly linked with albumin and other plasma proteins. Quickly and broadly, the residual caffeine molecules are disseminated throughout the numerous tissues and organs. Following oral treatment, caffeine is absorbed fast with an absorption rate constant (K01) of around 0.33 min−1 in the small intestine. Owing to intra-individual variability and delayed gastric emptying, the time it takes to achieve the peak plasma concentration ranges from 15 min to 2 h. After absorption, caffeine is disseminated throughout all tissues, bodily fluids, and the developing fetus. Caffeine does not accumulate in any tissue, and its distribution is 0.5 to 0.75 L/kg. The peak plasma concentration (Cmax) level, which is similar to 8 to 10 mg/L, is attained by caffeine dosages of 5–8 mg/kg after roughly 30–75 min (tmax). In most situations, a cup of black coffee delivers a caffeine dosage of 0.4–2.5 mg/kg and a peak plasma concentration of 0.25–2 mg/L. After oral administration, it takes 45 min for the small intestine to absorb almost all of the caffeine, and it has a bioavailability of 99% with no significant first-pass effects (70). Caffeine is highly bioavailable and readily penetrates lipid membranes. After oral intake, peak plasma concentrations vary between 15 and 120 min, and due to rapid distribution and clearance rates, the half-life is within 3 to 5 h. This indicates that if caffeine is not ingested consistently, blood levels will not grow (Figure 9). Therefore, if needed for treatment or other health purposes, caffeine has the advantage of swiftly sustaining blood levels. Caffeine has been found to drastically increase cognitive function at modest dosages by speeding up reaction times and visual information processing. Numerous studies suggest that these benefits can be acquired at low dosages (beginning at 0.18 mg/kg), and that the dose–response curve for cognitive responses subsequently tends to be flat (68). Long-term caffeine tolerance is supported by the fact that chronic users show diminished or even nonexistent cognitive responses. Caffeine adverse effects may intensify with large dosages (9–13 mg/kg), but physical performance is unaffected (64). Higher doses (~10–13 mg/kg) created gastrointestinal side effects, mental confusion, agitation, difficulty in focusing, and difficulty in sleeping in certain subjects (71), but lower doses (7–10 mg/kg) caused chills, nausea, flushing, palpitations, headache, and tremors (68). When caffeine dosages were dropped to a moderate level (5–6 mg/kg), ergogenic benefits were maintained, and negative effects and physiological reactions were likewise reduced but not fully abolished (71). Doses of 200 mg or more of caffeine will cause toxicosis, which presents as uneasiness, insomnia, cramping in the muscles, and periods of extreme alertness (68). Caffeine is extensively metabolized via the microsomal cytochrome P450 enzyme in the liver Caffeine demethylation is facilitated by two of the cytochrome P450 isoenzymes, CYP1A2 and CYP2C9 (64). Approximately 90% of caffeine metabolism is done by the CYP1A2 isoenzyme. Before being excreted from the body, almost all caffeine is metabolised, largely in the liver. Caffeine and its metabolites are mostly removed by the kidneys in urine excretion. The body excretes less than 3% of caffeine unaltered, which is a relatively tiny amount (68). After glomerular filtration in the kidneys, reabsorption of the majority of caffeine molecules (98%) back by the renal tubules firmly into the circulation. This highlights how renal blood and urine flow are vital for the elimination of caffeine from the body. Caffeine undergoes oxidative

N-demethylation to yield primary mono-demethylated metabolites as theophylline, theobromine, and paraxanthine. The 3-demethylation of caffeine into paraxanthine is the key initial step in humans. Most of the caffeine follows this pathway and 80% of it is converted into paraxanthine, the major metabolite in humans. As illustrated in Figure 9, the remaining caffeine is metabolised to yield theophylline (~4%) and theobromine (~11%) (68).

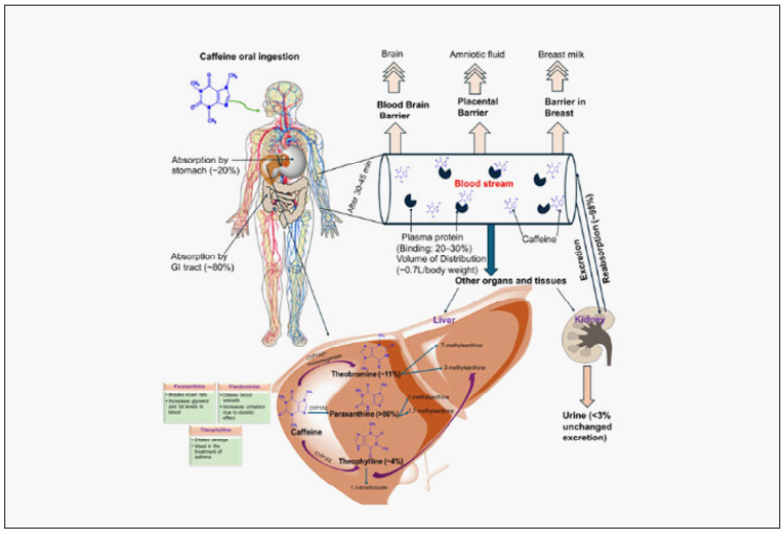

Figure 9. *Pharmacokinetics of Caffeine. Adopted from Song et.al., (68)*

7.4 Mechanism of Action (Adenosine Receptor Antagonism, cAMP Pathways)

Caffeine can effect cells by blocking adenosine receptors, releasing stored intracellular calcium and inhibiting phosphodiesterases (PDEs). It can block all adenosine receptors, in particular, A1R and A2AR (46). It is worth noting that whereas caffeine can inhibit adenosine receptors at low dosages, greater levels are needed for the two other processes. Caffeine can also stimulate calcium release from the endoplasmic reticulum by binding to ryanodine receptors (RyRs) (72); this also inhibits calcium reuptake. As a result of these processes, caffeine can improve contractility during submaximal contractions in both habitual and non-habitual coffee consumers. Finally, it is also a non-selective competitive inhibitor of phosphodiesterases, which can increase cellular cAMP concentration. The buildup of cAMP increases lipolysis and the release of numerous hormones, including as dopamine, adrenaline, and norepinephrine (46).

7.5 Physiological Effects of Caffeine

Caffeine influences the circulatory, neurological, immunological, pulmonary, renal, digestive, and musculoskeletal systems. Caffeine and its metabolites can alter lipid and glucose metabolism. Caffeine is known to impact the sympathetic nervous system resulting in the release of adrenaline and norepinephrine (46). Although caffeine can be found naturally or artificially in various goods, the most frequent include coffee, tea, soda, and chocolate (73). Low to moderate caffeine usage, is thought to have certain benefits, which may include, improved cognitive and behavioural impacts, higher mood, and potentially increased neuroprotection against certain disease (64). Caffeine also affects both stages of sleep: rapid eye movement (REM) and non-rapid eye movement (NREM), resulting in lower sleep quality and/or increased sleep latency (74). To make up for this sleep deficit, individuals may rely on coffee the next day to offset daytime sleepiness, leading to a cycle of caffeine usage and sleep deprivation. This is frequent in University students, with prior studies revealing over 48% of this demographic have short sleep time and 28% expressed daytime weariness (74). This could disturb the efficient mental and physical health essential for best academic success.

Caffeine predominantly affects sleep via the inhibition of adenosine receptors (A1 and A2). This receptor antagonism of caffeine affects the biological circadian rhythm and delays nocturnal sleep, so establishing a state of sleep debt characterized by cycles of insufficient sleep and daytime sleepiness. Due to caffeine's tendency to combat tiredness or lethargy and enhance wakefulness or alertness; a consumer can easily acquire caffeine dependence, and this could convert into caffeine misuse. Caffeine can cause sleep abnormalities as well inside the sleep-wake cycle. If coffee is consumed during mid-afternoon, it continues to operate as an anti-fatigue agent as well as a diuretic throughout the late evening. It can influence anywhere from 1-3 hours eaten before bedtime to up to 12 hours earlier, depending on the individual. In those persons prone to stress, interrupted sleep is even more probable (74).

Some studies have also indicated that students with low overall sleep quality likely to have worse Cumulative Grade Point Averages (CGPAs) compared to those who reported appropriate sleep quality. Although caffeine may be utilised to keep a student energized to accomplish academic obligations, its usage changes the sleep cycle, causing a drop in sleep quality which may lead to lower performance and reduced CGPAs (75). Although studies have shown an effect of caffeine on sleep and the importance of sleep on academic performance, there is a paucity of information evaluating the basis for the relationship between caffeine consumption, sleep, and daytime functioning among students in private tertiary institutions in Southern Nigeria (74,75).

Caffeine also activates the central nervous system and promotes hormonal production. It raises neurotransmitter levels in the brain, resulting in behavioural and neurochemical alterations (76) and has been proven to possess neuroprotective characteristics. Moreover, caffeine plays a critical role in inflammatory processes in a dose-dependent way. It suggests that modest caffeine levels could have detrimental effects, whereas greater quantities may diminish inflammatory biomarkers and also activate anti-inflammatory systems. Furthermore, experimental studies suggest that caffeine may have a role in the antioxidant effects of coffee (76).

The effects of caffeine on the heart are largely stimulatory and are accompanied with increased coronary blood flow. These effects are thought to be mediated not via an impact on adenosine receptors, but instead via phosphodiesterase inhibition. In the lungs caffeine can produce smooth muscle relaxation and bronchial dilation, potentially accounting for its antiasthmatic effects (77). However, the respective involvement of adenosine receptors and phosphodiesterase as mechanisms of caffeine's antiasthmatic activities remain disputed (46).

The effects of caffeine on the kidney diuresis, increased blood flow, and rennin secretion appear to be related to an action of caffeine at adenosine receptors. Caffeine's behavioral effects appear to be mediated both through adenosine receptors and phosphodiesterase actions and can readily be detected on neurochemically specific neurons (78). Caffeine's stimulatory activity on dopamine, norepinephrine, serotonin, acetylcholine, glutamate, and GABA neurons is theorised to derive from its capacity to prevent the action of adenosine, which generally suppresses neuronal function. Phosphodiesterase inhibition by xanthines may also account for some stimulatory effects. Interactions with other foods also characterize specific effects attributed to caffeine. Such interactions include those linked with aspirin, alcohol, nicotine, cocaine, certain other botanicals and other narcotics.

The repeated intake of caffeine does not modify its pharmacokinetics, yet in many cases development of tolerance does occur. Tolerance is not found for all effects of the medication, such as fat cell lipolysis, but is seen for specific behavioral actions, such as some of its stimulant qualities (increase in locomotor activity in rats) (76). Following the discontinuation of caffeine usage, withdrawal-like symptoms are sometimes noted in humans, such as headache, irritability, nervousness, and a drop in energy. The physiological underpinnings for these symptoms are not recognised. Although the development of withdrawal symptoms can indicate an addictive feature, caffeine does not exhibit a convincing profile as an addictive substance (79).

7.6 Effects on the Central Nervous System

Caffeine is one of the earliest central nervous system (CNS) stimulants that have maintained its pharmacological and commercial importance for decades. It is regarded an adenosine antagonist which acts through the competitive binding and subsequent blockage of adenosine receptors (majorly A1 and A2), hence inducing the secretions of numerous neurotransmitters such as dopamine, serotonin, and norepinephrine (74). Depending on the amount of caffeine ingested, it can generate a variety of effects on other organs of the body. In the central nervous system, more precisely in the autonomic nervous system, the neurotransmitter system based on the neurotransmitter adenosine functions as a reducer of heart rate, blood pressure and body temperature. Caffeine exerts an inhibitory impact on neurotransmitter adenosine receptors, found in nerve cells. Many of the physiological responses to caffeine administration are opposed to those of adenosine, thus there is a feeling of re-energizing, decreased sleep, and tiredness. Caffeine has an influence on the release of nerve cells and the release of several other neurotransmitters and hormones, such as adrenaline (64). The effects of caffeine on the body are various, so it is a stimulation of the central nervous system that boosts organic activity and streamlines mental and physiological and mental operations (73). In respect to intellectual performance, coffee drinking promotes short-term memory, facilitates the memorising process since it improves focus, helps preserve mental clarity and decreases cognitive degeneration in the elderly.

7.7 Effects on Sleep and Behaviour

Evening caffeine use often lowers the quantity and quality of future sleep. Experimental studies suggest that 100-600 mg of caffeine can considerably increase sleep onset latency (SOL) and wake after sleep onset (WASO) with reductions in total sleep duration (TST) and sleep efficiency (SE) (80–82). Additionally, caffeine doses ranging from 300-600mg increase the occurrence of non-rapid eye movement (NREM) stages 1 (N1) and 2 (N2) (i.e. light sleep) with reductions in the occurrence of NREM stage 3 (N3) (i.e. deep sleep), although this effect is not consistent when doses of 200 mg or less are consumed (82). Collectively, the available evidence supports a dose-dependent impact of caffeine on future sleep, whereby bigger dosages of caffeine may result in greater sleep disruptions.

The time of caffeine consumption is another crucial aspect when analysing the impact of caffeine on subsequent sleep. Sleep disruption is frequently observed when caffeine is eaten within 3 hours of bedtime, with inconsistent effects when caffeine is administered in the morning or afternoon (83). In accordance with the present research, sleep behavior recommendations generally encourage the avoidance of caffeine close to bedtime to reduce sleep disruption. Given evening caffeine consumption constitutes just a tiny fraction of daily caffeine intake, it is crucial to consider the normal patterns of regular users when analysing the effect of caffeine on future sleep. Additionally, there is substantial individual heterogeneity in the half-life and action of caffeine, mostly due to genetic predispositions, which should be addressed when evaluating the role of caffeine dose and time of administration on sleep (82).

7.8 Dose-Dependent Effects of Caffeine

Caffeine consumption has been reported to have adverse effects on human health such as palpitations, gastrointestinal disturbances, increased blood pressure, insomnia, iron deficiency anemia, higher risk of developing osteoporosis as well as problems in metal absorption, excretion, and reabsorption processes in intestine and kidney (84). It has also been observed that consumption of high quantities of caffeine used in energy drinks has been connected with seizures, abrupt cardiac arrests and strokes mainly in children and young adolescents. Nevertheless, caffeine consumption has been reported to enhance performance and endurance in athletes, increase alertness and reduce fatigue, potentiate postsynaptic neurotransmission in the sympathetic nervous system, increase secretion of gastric acid, and increase neuromuscular coordination (85).

The potential of caffeine to produce beneficial changes in alertness and cognitive performance contributes to its widespread use. Caffeine serves as an adenosine receptor antagonist to prevent the function of adenosine, a neuromodulator important in the homeostatic regulation of sleep and waking. Sleep pressure is proposed to rise in accordance with the accumulation of extracellular adenosine during wake and reduce with its dissipation during sleep (82). As such, caffeine can be adopted as a technique to offset excessive sleep pressure encountered during periods of insufficient sleep (86). It is estimated that up to 40% of the population fail to receive sufficient sleep, underlining the relevance of caffeine as a method to limit the adverse consequences associated with insufficient sleep. However, the ingestion of caffeine may interfere with subsequent sleep generating a potential cycle of poor sleep and reliance on caffeine (82).

8. Empirical Review

8.1 Global Consumption Trends of Caffeine

Caffeine is one of the most commonly used mood-altering substances (87). Caffeine's stimulatory properties, combined with its widespread presence in foods such as coffee, tea, and chocolate, help to explain the world's high caffeine intake rate (about 80%). In terms of caffeine sources, most European countries, with the exception of the United Kingdom and Ireland, have found coffee to be the most popular among adults (87).

According to the research, there has been a global increase in caffeine intake over the previous decade. In 2020/2021, consumers consumed around 166 million, 60 kg bags of coffee globally (88). Several explanations for caffeine usage have been previously examined in the literature. Its utilisation by surgeons to minimise fatigue, by sportsmen to boost their performance, and by students to improve focus and wakefulness (88). Drinking coffee has become a daily habit for many people, with Americans consuming around 517 million cups of coffee every day, the mean daily consumption per capita being two to three cups of coffee (46).

The main reasons stated for use of caffeine-containing products are mainly connected to the stimulant effects of caffeine, such to alleviate weariness, increase alertness or to boost athletic performance (89). Caffeine is the most popular of all sporting ergogenic aids, and it is consumed by 75% of athletes before or during the competition (90). The most well-established mechanism by which caffeine exerts its effects on sports

performance is its role as a competitive adenosine receptor antagonist. Due to these characteristics, caffeine has been considered, for a long period, a doping substance. Adolescents report they take caffeine to generate increased energy, for the taste of the product, and for visual improvement. University students reported using caffeine-containing products to increase mood and performance, or for a desire of alertness (89). Furthermore, in a supplementation study, university students thought that they were much more alert, awake, clear-minded, and able to concentrate after drinking low levels of caffeine, with such effects being beneficial for academic work (87).

In Africa, coffee consumption has surpassed global trends. As a result, global demand for coffee increased by 2.4% in the 2021/2022 period (Hamitri-Guerfi & Bachir-Bey, 2024). According to a survey of 442 young people in Nigeria, nearly three in five respondents consumed energy drinks (59.6%), with males being more likely to do so, and tea (71.7%) and coffee (69.2%) emerged as frequent caffeine sources; more than a third reported daily use, and many cited insomnia and palpitations, highlighting the health risks associated with high-caffeine products (92). Profiled caffeine use among 359 undergraduates at Madonna University and showed a predominance of soda, tea, chocolate, and energy drinks over brewed coffee; 57.1% were "high caffeine consumers" on a composite score, and motivations clustered around taste, alertness, and coping with study demands, while difficulty sleeping and nervousness were among the reported adverse effects (93).

8.2 Caffeine Consumption among Undergraduate Students

Adolescence is generally considered a healthy time of life for most people and a period of experimenting with various lifestyle choices. However, some harmful behaviors, including bad eating attitudes, imbibed at this period may remain for a long time with poor health repercussions. The school environment sometimes mistakenly promotes access to caffeinated drinks, while it should ideally be a space for health instruction and promotion (94). College and high school students are currently consuming caffeine in significant quantities. According to the AAP's 2014 report in the journal Paediatrics, 73% of kids drink caffeine every day (88). The majority of them consume large quantities of soft drinks, and although while these beverages contain sugar and other dangerous substances, caffeine alone can be harmful to their health. Numerous studies have documented the negative effects of caffeine on students, including panic episodes, sleeplessness, and persistent weariness.

Caffeine consumption has been documented in 75.5% of university students in Pakistan (95), while a study conducted among Bahrani university students determined that 98% of participants consumed caffeine on a regular basis (96). Similarly, a significant number of medical students (98.4%) in Jordan consume caffeinated products (97). In fact, it was discovered that the university lifestyle is conducive to the consumption of higher levels of caffeine in comparison to the general population (98). For example, college students who are either endeavouring to lose weight or experiencing disordered eating behaviours are more likely to consume high doses of caffeine. Additionally, the quality of sleep is negatively impacted by the excessive caffeine consumption of university students (99). A study conducted by Jun et al. discovered that high school students who consumed higher quantities of caffeine had a shortened sleep duration than those who consumed less (100). According to another study, the total sleep time and sleep efficiency are substantially impacted by the consumption of 200 mg of caffeine in the morning (Hamdan *et.al.*, 2025).

The data analysis of 254 students reveals that coffee consumption increases with both age and academic level, with the highest prevalence observed among students aged 16 to 20 years (91). Coffee has become an essential component of students' daily regimens, as it enhances alertness, promotes concentration, and alleviates fatigue. However, the prevalent excessive coffee consumption, often accompanied by high sugar intake 57% of students reported adding 2 to 6 teaspoons of sugar poses significant public health concerns (91). These emphasize the need for effective monitoring of coffee consumption patterns and for enhancing consumer awareness regarding the benefits of moderate intake and the potential adverse effects of excessive consumption.

9. Conclusion

Caffeine induces physiological changes in a dose dependent manner, therefore its consumption should be monitored to ensure safe use and to prevent undesirable effects on hemostatic and physiological functions.

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